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Queensland Opioid Dependence Treatment Guidelines

2023

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Queensland Opioid Dependence Treatment Guidelines 2023

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An electronic version of this document is available at https://www.health.qld.gov.au/system-governance/policies-standards/guidelines

Acknowledgements

These clinical guidelines update the *Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines (2018)*, and the *Long-acting injection buprenorphine in the treatment of opioid dependence – Queensland Clinical Guidelines 2019*.

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Foreword

The *Queensland Opioid Dependence Treatment Guidelines 2022 (Queensland Health)* update the *Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines 2018* and the *Long-Acting Injection Buprenorphine in the Treatment of Opioid Dependence: Queensland Clinical Guidelines 2019*. The term 'medication-assisted' is not used since the treatment of opioid dependence, as with any other mental and behavioural disorders with evidence based pharmacological treatment, requires a comprehensive approach to care which includes medication treatment, specific psychological interventions and psychosocial support in combination.

These guidelines cannot provide detailed direction for managing every patient in every situation. Variation in practice from the guidelines should be carefully considered and the rationale clearly documented. Individual practitioners are responsible for decisions about the safety and effectiveness of treatment for each patient. The guidelines are not intended to replace professional judgement in individual cases. If further guidance is required in tailoring treatment to an individual patient, a second opinion or consultation with a medical addiction specialist is appropriate. If local AOD providers or medical addiction specialists are not accessible locally, the Alcohol and Drug Clinical Advisory Service (ADCAS) can provide advice and support – see Appendix 17.

All practitioners offering opioid dependence treatment should operate in a manner that is consistent with the Queensland Health Departmental Standard: Monitored medicines and complies with the Medicines and Poisons (Medicines) Regulation 2021.

Related documents

Queensland Health services providing opioid dependence treatment should also be aware of other relevant Queensland Health policies, standards, procedures, guidelines and protocols. The following is provided for reference but should not be considered an exhaustive list.

- Better Care Together
- Chief Psychiatrist Policy – Treatment and Care of Patients
- Comprehensive Care: Partnerships in Care and Communication
- Co-occurring substance use disorders and other mental health disorders: policy position statement for Mental Health Alcohol and Other Drugs Services 2021
- Queensland Multicultural Policy: Our story, our future
- Queensland Health Aboriginal and Torres Strait Islander Cultural Capability Framework 2010 – 2033
- Queensland Health Aboriginal and Torres Strait Islander Mental Health Strategy 2016 – 2021
- Queensland Health Guidelines - Information Sharing - Between mental health staff, consumers, family, carers, nominated support persons and others
- Working with parents: guidance for mental health alcohol and other drugs services

In addition, all services and health practitioners providing opioid dependence treatment may find the following links and resources helpful in understanding the policy landscape within which opioid dependence treatment is delivered:

- Equally Well – Improving the physical health and wellbeing of people living with mental illness in Australia, Australian Government, National Mental Health Commission

- Queensland Mental Health Commission: Changing attitudes, changing lives – options to reduce stigma and discrimination for people experiencing problematic alcohol and other drug use, March 2018
- Shifting minds: Queensland Mental Health, Alcohol and Other Drugs Strategic Plan 2018 – 2023
- The National Standards for Mental Health Services 2010, Australian Government Department of Health
- The National Safety and Quality Health Service Standards

Terminology and definitions

A note about language used in these guidelines. These guidelines seek to use language that is non-stigmatising and avoids reinforcing negative stereotypes about people who use opioids. This has resulted in moving away from some terms that are still in common use. This section attempts to clarify the change in terms and so potentially stigmatising terms which have been commonly used in the past may be used in this section alongside the term that will be used in the remainder of the document.

This document refers to the care of pregnant women who use opioids. The limitations of this language are acknowledged. These guidelines do not intend to offend or exclude people who do not wish to be associated with the term used.

In these guidelines the following terms are used as defined here.

Addiction medicine specialist: a medical practitioner with specialist registration as an addiction medicine specialist. This requires Fellowship of the Australasian Chapter of Addiction Medicine (FAChAM), Royal Australasian College of Physicians.

Addiction psychiatrist: a medical practitioner with specialist registration as a psychiatrist who is an accredited member of the Faculty of Addiction Psychiatry.

Administer: introduce a dose of a medication into the body of a person or give a dose of the medication to a person to be taken immediately as per the *Medicines and Poisons Act 2019*.

Buprenorphine: sublingual buprenorphine and long-acting injectable buprenorphine and sublingual buprenorphine/naloxone unless specifically stated.

Consultation with a medical addiction specialist: discussion of a person's care by the prescriber with a medical addiction specialist for advice in relation to some specific aspect of care. This may be sought by another medical addiction specialist or by other prescribers.

Delegate: non-prescriber clinicians functioning within their scope of practice acting as a prescriber's delegate in a health service providing opioid dependence treatment.

Dependence: an adaptive state in response to repeated exposure to a substance resulting in a withdrawal syndrome when the substance is withheld. It may be associated with both physical and psychological components. Dependence may be considered a substance use disorder if it meets criteria as outlined in a standardised diagnostic manual such as the *International Classification of Diseases* or the *Diagnostic and Statistical Manual of Mental Disorders*.

Dispense: sell a medication to a person on prescription, as per the *Medicines and Poisons Act 2019*.

Floating supervision: a medication regimen that allows for flexibility in meeting the patient's needs by specifying the number of supervised and self-administered doses per week but not specifying which day of the week that these must occur.

Long-acting injectable (LAI): a formulation of a medication that allows for slow release of the medicine over a long period of time.

Medical addiction specialist: an addiction medicine specialist and/or addiction psychiatrist.

Opioid dependence treatment (ODT): comprehensive treatment of opioid dependence, including opioid agonists (methadone, buprenorphine), psychosocial interventions and support.

Patient: a person engaged in treatment for opioid dependence.

Prescribe: direct a person, orally or in writing, to administer, dispense or give a treatment dose of a

medication, as per the *Medicines and Poisons Act 2019*.

Prescriber: medical and nurse practitioners approved and responsible for prescribing.

Queensland Opioid Treatment Program (QOTP): Queensland legislative and regulatory processes required with opioid dependence treatment.

QOTP service provider: a private prescriber or Queensland Health Alcohol and Other Drug (AOD) service prescriber who holds a QOTP approval to treat a patient with opioid medication as part of ODT. In Queensland Health AOD services, clinicians within the multi-disciplinary team may act as delegates of the prescriber when communicating with agencies.

QScript: the real-time prescription monitoring system for Queensland health practitioners to review patient's monitored medicines prescription history. It is a legislative requirement for all relevant prescribers to check QScript before prescribing a monitored medicine to a patient and all relevant pharmacists to upload monitored medicines dispensing events to QScript.

Scheduling: the national classification system that controls how medications are made available to the public. Medications are classified into schedules that determine the level of regulatory control over the availability of the medication.

Schedule 3 (S3): pharmacist only medicine

Schedule 4 (S4): prescription only medicine

Schedule 8 (S8): controlled drug.

Second opinion: a formal opinion from another prescriber. In general, another prescriber providing such an opinion should have at least a similar level of training and experience in ODT to the requesting prescriber. Another prescriber with less training and experience in ODT but with specific relevant expertise may provide a second opinion where it is sought for other reasons e.g. chronic pain or mental health disorders.

Self-administration: refers to medication dispensed by pharmacist for self-administration at a later time. Colloquially referred to as take away doses or TADS.

Split dosing: a prescribed daily dose of ODT medication given in two or more separate administration points of part-doses during a single day, which may be equal or different. It is also referred to as split daily doses.

Sublingual (SL): administration of ODT medication under the tongue. However, for the purpose of this guideline may also include buccal (inside the cheek) administration if required. An alternative single term for both sublingual and buccal administration is oral transmucosal, however sublingual is used here for consistency with typical prescribing nomenclature.

Supervised administration: refers to medication that is dispensed and administered by authorised persons with direct observation of patient's consumption of medication.

Supply: with respect to a regulated substance, as per the *Medicines and Poisons Act 2019*, is to sell or give the substance to a person. Does not include administering the substance.

Take Home Naloxone (THN): naloxone provided free-of-charge under the National THN program to patients engaged in ODT, their family, carers and/or friends.

Abbreviations and acronyms

Abbreviation	In full
ADCAS	Alcohol and Drug Clinical Advisory Service
AOD	Alcohol and other drug
BAL	Blood alcohol level
BBV	Blood borne virus
BPN	Buprenorphine
CBT	Cognitive Behavioural Therapy
CNS	Central nervous system
COWS	Clinical Opioid Withdrawal Scale
CYP	Cytochrome P450
DAA	Direct-acting antiviral
DDD	Defined daily dose
DDI	Drug-drug interaction
ECG	Electrocardiogram
ED	Emergency Department
GP	General Practitioner
HARU	Healthcare Approvals and Regulation Unit
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HSD	Highly Specialised Drugs
IM	Intramuscular
IV	Intravenous
LAI	Long-acting injectable
LAI BPN	Long-acting injectable buprenorphine
MAOI	Monoamine Oxidase Inhibitors
MET	Motivational Enhancement Therapy
MPA	Medicines and Poisons Act 2019
MPMR	Medicines and Poisons (Medicines) Regulation
NAS	Neonatal Abstinence Syndrome
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NOWS	Neonatal Opioid Withdrawal Syndrome
NX	Naloxone
ODT	Opioid Dependence Treatment
OME	Oral Morphine Equivalent

Abbreviation	In full
OOWS	Objective Opioid Withdrawal Scale
PBO Act	Pharmacy Business Ownership Act 2001
PBS	Pharmaceutical Benefits Scheme
PI	Protease inhibitor
QAS	Queensland Ambulance Service
QOTP	Queensland Opioid Treatment Program
QPS	Queensland Police Service
S3	Schedule 3 medication
S4	Schedule 4 medication
S8	Schedule 8 medication
SC	Subcutaneous
SIDS	Sudden Infant Death Syndrome
SL	Sublingual
SL BPN	Sublingual buprenorphine
SL BPN/NX	Sublingual buprenorphine/naloxone
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SOWS	Subjective Opioid Withdrawal Scale
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
THN	Take home naloxone
UDS	Urine drug screen

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1. Opioid dependence and its treatment

1.1 Opioid dependence

Opioid dependence is a disorder characterised by a loss of control over use of opioids with repeated or continuous use despite associated harms including in health and psychosocial function. Opioid dependence is often chronic with episodes of relapse. It involves:

- strong internal drive to use opioids manifested by:
  - an impaired ability to control use
  - an increasing priority over other activities
  - persistent use despite harm
- experience of urges and cravings
- physiological features including tolerance and withdrawal
- dependence usually evident over a period of 12 months but diagnosis can be made if opioid use is continuous (daily or almost daily) use after only one month[1].

Although low prevalence within the community, opioid dependence causes significant harms with health, economic and social costs such as:

- morbidity, including through co-occurring mental and behavioural disorders, transmission of blood borne viruses (BBV) including hepatitis C (HCV), hepatitis B(HBV) and human immunodeficiency virus (HIV)
- mortality, including due to overdose, with opioid-related deaths occurring at a much younger age than deaths attributed to alcohol or tobacco
- negative effects on function in relationships, employment, education, housing, parenting and finances
- need for health and social services, law enforcement and judicial systems.

Information about current opioid use and harmful use in Australia is available through the Australian Institute of Health and Welfare surveys in reports including the National drug strategy household survey, which provides information about non-medical use of pharmaceuticals and illicit drugs and the Alcohol, tobacco and other drugs in Australia Report. The Penington Institute publishes a report detailing overdose in Australia each year.

1.2 Opioid Dependence Treatment

Opioid Dependence Treatment (ODT) combines medication and psychosocial interventions and support, and requires multidisciplinary involvement from prescribers and pharmacists, supported by specialist AOD and other clinicians and other staff in various settings. While medication alone can bring about behavioural change[2, 3], it is prescribed within a holistic approach which identifies and addresses the person's needs for psychosocial intervention and support.

ODT is provided in a harm minimisation framework, working collaboratively with patients to achieve realistic individual treatment goals. While abstinence may be an important long-term goal, extended treatment with medication is the most effective approach.

An emphasis on abstinence and cessation of treatment may compromise the focus on broader functional and symptomatic outcomes. For most people, short-term achievable goals are important, such as:

- reducing higher risk behaviours, including
  - other harmful substance use
  - overdose
  - intravenous use
  - self-harm and suicide
  - non-adherence with medication and treatment goals
  - criminal behaviours.
- improving physical and mental health
- improving psychosocial functioning, including relationships and parenting, finances, and employment.

Medication regimens should be individually tailored, balancing patient autonomy and prescriber duty of care, minimising harms including diversion of medication. Decision making should consider specific indications for unsupervised medication administration and assess and manage risk of potential harms with prevention-oriented strategies.

1.2.1 Psychosocial support and psychotherapeutic intervention

Psychosocial interventions and support include the many ways in which the psychological health and social environment of people who use opioids can be supported to help improve quality of life[4]. As needed, access to formal welfare supports, together with encouragement from friends, partners, children, parents and other significant individuals, is commonly involved in the pathway through treatment[5, 6].

The stability afforded by long-term ODT provides an opportunity for any social problems and psychological difficulties to be addressed. An important consideration is to match treatment and counselling approaches to individual needs and circumstances[7]. A range of therapies have been demonstrated to support recovery, (e.g., Insight - Resources - Alcohol and Other Drugs Therapeutic Intervention Overview).

Private Queensland Opioid Treatment Program (QOTP) prescribers may provide psychological treatment as an integral part of their practice. If not, referral for psychological therapies under a Mental Health Treatment Plan should be considered. Public AOD service staff can deliver evidence based psychological interventions or facilitate treatment with an appropriate service provider.

1.2.2 Withdrawal intervention

Opioid withdrawal without continuing ODT is not recommended, since it rarely results in long-term changes in opioid use. If a person chooses to withdraw without continuing ODT, the loss of tolerance and consequent risk of overdose if the person relapses should be explained, along with the ongoing option of initiation of ODT during or after withdrawal treatment. Take Home Naloxone (THN) should also be provided. Refer to the Queensland Alcohol and Other Drug Withdrawal Guidelines for further information.

Overdose risk increases following withdrawal without initiation of ODT due to loss of tolerance.

1.2.3 Medication intervention

ODT medication

ODT medication refers to buprenorphine (BPN; long-acting injectable (LAI) or sublingual (SL)) or liquid methadone. These opioids are approved for ODT and are Schedule 8 (S8) medications subject to the Queensland Health Monitored Medicines Standard including the need to check QScript. See Appendices 1 and 4 for further details.

Naltrexone has been used rarely due to poor retention and potential for overdose after relapse and is not considered further in this guideline. ODT medications eliminate withdrawal, and control or eliminate cravings, and block the euphoric effect of opioid use[6].

> "*Buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials"*[8].
>
> *"Methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy"*[9].

Selection of ODT medication and delivery mode

Long-acting injectable buprenorphine (LAI BPN) is currently the recommended treatment due to regimen simplicity. LAI BPN increases flexibility for patients on ODT. Sublingual buprenorphine/naloxone (SL BUP/NX) is now the most prescribed ODT medication in Queensland because of improved safety profile and lower patient burden compared with methadone. In some circumstances, SL BPN mono may be necessary if a non-injectable mode of administration is required. If BPN in adequate doses is ineffective or produces significant side effects, it may be appropriate to consider a trial of methadone, recognising that longer-term side effects are more common with methadone[6].

Before commencing medication check contraindications listed in product information sheets (links to current PI in Appendix 11).

Table 1 Comparison of methadone and buprenorphine

	Methadone	Buprenorphine
Classification	Mu (μ) opioid receptor full agonist Used for ODT	Mu opioid receptor partial agonist (high affinity, lower intrinsic activity, and slow dissociation) Kappa (κ) opioid receptor antagonist Used for ODT or withdrawal treatment
Substitutes for opioids	+ + + Reduces craving for opioids	+ + Reduces craving for opioids
Attenuates effects of opioids	+ + Blocks at high doses (e.g., >60 mg)	+ + + + Blocks at high doses (e.g., >16 mg)
Side effects	Opioid like	Less sedating Can precipitate withdrawal Injection related side effects for LAI BPN

	Methadone	Buprenorphine
Withdrawal on cessation	+ + + Often severe and prolonged	+ + Less severe, but may be prolonged
Onset of effects	15-45 minutes	30–60 minutes
Peak effects	2.5-4 hours	1–4 hours
Duration of clinical effects	20-36 hours	Dose dependent 24–72 hours at high doses
Metabolism	Hepatic CYP450 (3A4) + + + affected by CYP3A4, CYP2D6 & CYP1A2 inducers/inhibitors	Hepatic CYP450 (3A4) and conjugation. Less clinical impact on liver metabolism
Mode of administration	Oral	Sublingual or subcutaneous injection
Drug interactions	Sedatives, opioid antagonists, inducers/inhibitors CYP450	Sedatives, opioid agonists and antagonists
QT Prolongation	Increased risk of QT prolongation with co-prescription of some selective serotonin reuptake inhibitors (SSRIs), some antipsychotics and a range of other medications (see Appendix 14.1.3)	

ODT medication requires an initial induction phase, with the dose progressively increased until it reaches a steady state in which the patient experiences the benefit of the medication with minimal side-effects.

Induction

Initially, more frequent reviews by a QOTP service provider are required to:

- titrate medication dose
- undertake more comprehensive assessment
- determine the level of treatment needs and support required
- discuss treatment and care plans[10].

When starting a patient on ODT, the goal is to safely achieve an adequate dose of medication, stabilise opioid use, and address co-existing conditions, with key objectives as follows:

- reduced withdrawal symptoms
- reduced cravings
- responding to continued substance use (of opioids and other drugs)
- patient satisfaction and engagement in treatment.

The pharmacological properties of BPN and methadone require different induction strategies. The partial agonist properties of BPN allow for more rapid induction including initiation using LAI BPN. Rapidly achieving an adequate dose of BPN (usually within three days) is associated with improved retention in treatment[6]. Because of the greater risk of opioid toxicity and overdose during methadone induction, a low starting dose and a slow rate of dose increase is required (usually over weeks in outpatient settings).

Stabilisation and maintenance

Doses should be individually tailored and adjusted, considering risks and potential harms:

- medication effects – intoxication/sedation or withdrawal
- side effects – many opioid side effects subside in the first 2–4 weeks of treatment, but if persistent may require dose adjustment
- continued drug use – an increasing opioid treatment dose is often appropriate in response to non-prescribed opioid use, but not in addressing use of other drugs (e.g., alcohol, cannabis, benzodiazepines, stimulants). If this is being considered following request by the patient or others, consultation with a medical addiction specialist is advised.
- patient report of dose adequacy and treatment goals
- adherence to medication regimen (attendance for supervised administration, method of administration)[10, 11]
- medication diversion[12].

Indicators for changes in medication dose are outlined in Table 2 below.

Table 2 Indicators for dose changes

Indicator	Decrease dose	Maintain dose	Increase dose
Treatment goals	No significant concerns regarding deterioration in clinical condition (e.g., substance use, physical or mental health symptoms) that may arise with a dose reduction	Achieving key treatment outcomes including no non-prescribed use of opioids	Not achieving desired treatment goals (e.g., persistent non-prescribed use of opioids) AND no significantly clinical safety concerns
Intoxication	Features of intoxication at peak effect times after administration		No features of intoxication particularly at peak effect times
Withdrawal		No features of withdrawal	Features of withdrawal over preceding 24 hours, increasing in the period immediately prior to the next dose
Cravings +/or opioid use		Few or no cravings for opioids	Intense cravings for opioids in the past 24 hours or opioid use to avert withdrawal
Side-effects and adverse events	Severe or intolerable side-effects (e.g., sedation or lethargy, persistent headaches, nausea, elevated liver enzymes)	Nil or mild and tolerable side-effects	Nil or mild and tolerable side-effects

Indicator	Decrease dose	Maintain dose	Increase dose
Patient experience	Patient reporting dose is too high, seeking to reduce dose, or attempt to discontinue ODT	Patient is satisfied with current dose and requesting the dose be maintained	Patient reporting dose is too low and they would like a dose increase

Dosage stability is when pharmacological equilibrium is reached and the patient no longer fluctuates between the physical states of withdrawal and intoxication.

Once stability is reached, there is greater flexibility for tailoring treatment to accommodate individual needs, such as increasing psychosocial support and other therapeutic interventions.

Medication administration and supervision

Requirements for administration of medication should vary with phase of treatment (induction, stabilisation or maintenance), the medication used and the route of administration, and associated risk assessment. Buprenorphine induction and stabilisation should vary with intended route of administration. Methadone requires a closely supervised regimen, with all doses initially supervised other than in special circumstances (e.g., necessary travel or usual dispensing site not being open 7 days a week).

Access to naloxone (NX) is especially pertinent when self-administration of methadone is commenced, or when ODT is ceased.

Risk assessment is an overall clinical judgement based on assessment of higher risk behaviours. See sections 1.2 and 4 together with appendix 3 for further information that may help guide risk assessment.

Table 3 Framework for administration and supervision of medication

Methadone		
Induction and stabilisation Usually first 3 months of treatment	Supervised medication administration, unless special circumstances	
Maintenance phase	Higher risk	3 to 7 supervised doses per week
	Lower risk	appropriate number of supervised doses per week to be determined on an individual basis (noting that a maximum of 7 days of diluted methadone can be provided at a time)
Buprenorphine (mono)		
Induction and stabilisation period Usually first 1–3 months of treatment	Supervised medication administration, unless special circumstances Consider second daily regimen to reduce burden. BPN mono should be considered primarily for allergy to NX.	

Maintenance phase	Higher risk	3 to 7 supervised doses per week
	Lower risk	3 or fewer supervised doses per week
Buprenorphine/naloxone		
Induction, stabilisation and maintenance phases	Higher risk	1 to 7 supervised doses per week
	Lower risk	Unsupervised (1 week-1 month dispensing interval)
Buprenorphine LAI		
Induction, stabilisation and maintenance phase	Injection administered by qualified clinician	

Floating supervision requirements

If supervised administration of medication is required to meet the treatment needs of a patient, but the patient's circumstances would benefit from flexibility in meeting these requirements, "floating supervision" could be arranged between the patient, prescriber and pharmacist. Direction for supervised administration of ODT medication should be included on the prescription. Floating supervision enables the pharmacist and the patient to determine which day is best suited for supervised administration of medication on a weekly basis, and the number of medication doses that are to be self-administered.

Floating supervision regimens are to be clearly documented including:

- the number of floating supervision medication administrations per week
- the designated days the week commences and finishes (e.g., Monday - Sunday)
- the maximum number of consecutive self-administered doses.

Medication supervision requirements are a decision of the prescriber.

Naloxone

Naloxone is an opioid antagonist used for the temporary reversal of the effects of acute opioid overdose. When assessing patients for opioid dependence, prescribers should consider prescribing NX or providing it free of charge under the THN program (see Take Home Naloxone Program Rules). Patients, family/carers and other relevant persons should be advised how to recognise and respond to an opioid overdose and how to use NX[13]. This initial contact may be the only time the patient is seen by the prescriber, and discussion about NX and how to administer it as part of an overdose response plan is an effective brief intervention[12].

Naloxone (solution for injection or nasal spray) is a Schedule 3 (S3) medicine when used for the treatment of opioid overdose (and a Schedule 4 (S4) medication when prescribed) and is available from a pharmacist, subsidised by the Pharmaceutical Benefits Scheme (PBS). NX is also available at no cost, without a prescription through the National Take Home Naloxone program available at some government and non-government services across the state including participating pharmacies. A list of participating service providers can be found online at Registered sites for Take Home Naloxone, using the search function to find one in a local suburb or postcode.

Any service supplying NX in ampoule form should check if the patient needs additional equipment to administer the injection (e.g., needle).

Further information and resources for health practitioners are available on the Insight website. The Penington Institute also offers NX training for services.

The patient should be directed to the following resources:

- contact QuIHN for NX training and access
- contact Adis for your local Queensland Health Alcohol and Drug Service - free call 1800 177 833

1.2.4 Discontinuation

Planning for discontinuation

The patient may discontinue treatment at any time; however, as with any chronic disorder, premature cessation of treatment can be associated with relapse and deterioration in the patient's health and wellbeing. This risk is particularly high for patients who discontinue treatment within the first year[12].

The issue of discontinuing ODT is important to many patients and should be discussed regularly throughout treatment. A collaborative approach about the timing and method of discontinuation/cessation can support reduction or tapering of ODT doses, which is generally more successful[7].

Understanding the predictors of successful cessation of ODT can provide a framework for patients and clinicians to plan for this process[12]. They include the following:

Patient factors:

- stability in alcohol and other substance use
- stable medical and psychiatric conditions (consider impacts of withdrawal on mental health or chronic pain disorders)
- stable social/personal conditions (housing, occupational and recreational activities, psychosocial supports such as family, friends, carers)[12].

Treatment process factors:

- patient centrally involved in decision making
- good patient understanding of process for withdrawal
- gradual ODT dose reduction over months
- regular review of progress and plans
- patient participation in psychosocial approaches to withdrawal management addressing coping strategies, risk behaviours and support systems[12].

Considerations when reducing

The aim is to support the ability of patients to discontinue ODT, while retaining their overall stability and minimising the risk of relapse into opioid use. Even at slow rates of reduction, it is common for patients to experience some withdrawal discomfort. While reducing, it may be appropriate to maintain a patient on a steady dose for some time[14, 15], to enable them to adjust to the physiological, behavioural and social changes that arise during this process and develop confidence in their ability to adapt[12].

Some patients remain on low doses of medication (<30 mg / day methadone or 2 mg / day BPN) for

extended periods. It is appropriate to discuss cessation strategies with the patient and address any concerns or fears. The key is stability: timing is important, and patients should be reassured that if they are stable and comfortable, there is no reason to push cessation of medication. Indeed, there are good reasons to maintain the medication. However, the use of such low doses as a means to facilitate additional substance use should be identified and any implications considered.

At any time, if relapse is likely or has occurred, further reductions in dose may need to be suspended, or an increase in dose considered.

Ensure that patients, family, carers and/or friends are provided THN – see section 1.2.3.

Withdrawal procedures

Withdrawal severity tends to increase as the dose approaches zero, with peak withdrawal discomfort usually described 1–4 weeks after cessation of ODT. Low severity symptoms (e.g., poor sleep, mood disturbances, and cravings) often persist for several months. As with any gradual withdrawal of medication, careful monitoring is required to identify a relapse or deterioration in the patient's condition and potential reconsideration of the treatment plan[12].

Role for ancillary medications

There may be a role for symptomatic medication to assist in the management of withdrawal symptoms such as nausea, aches and pains, and diarrhoea. Caution should be used in prescribing sedatives and other hypnotics due to the long-term nature of the sleep problems (weeks to months), and the high risk of dependence or misuse of such medication in people who use opioids. If it is considered appropriate to prescribe sedative or hypnotic medication, it should be at a low dose for a specified short duration (3–5 days). The patient should be made aware of the reason for its prescription, the associated risks of taking such medication and the intended short duration of this treatment.

Lapse and relapse

As with any chronic disorder, periods of remission and relapse are common. Stressors can trigger such changes - which may not necessarily result in return to opioid use but may result in use of other substances such as stimulants, benzodiazepines, gabapentinoids or alcohol. Risk management strategies such as review of treatment regimen are important to support return to stability[16].

Evidence for a need to review the treatment plan includes:

- self-report or clinical evidence of relapse to opioid or other significant substance use
- evidence of diversion
- recent injection marks
- deterioration in psychological, physical or social well-being[16].

Ongoing review of treatment plan should be based on assessment of risk.

Psychosocial support and psychotherapeutic intervention

The principles of effective psychosocial support for patients undergoing discontinuation from ODT are:

- patient information and engagement in treatment decision making[7]
- supportive care, including withdrawal counselling (maintaining motivation, coping strategies, identify risk behaviours), peer and self-help groups, community supports and stable living arrangements
- regular monitoring and increased frequency of reviews[12].

The period immediately following discontinuation or cessation of treatment is a time of considerable

relapse risk. Supportive care should be offered for at least three months following cessation of ODT medication, whether direct support from the ODT prescriber, other specialist AOD service provider or the General Practitioner (GP; where not the ODT prescriber), with transfer of care as appropriate[17]. Specific psychosocial support might include skills training (such as relapse prevention, problem-solving skills or vocational skills training), access to peer-based community organisations, or attending motivational counselling sessions.

The likelihood of maintaining abstinence after leaving treatment is increased where people have established drug-free social supports, are in stable family situations, employed, and with psychological strengths[18].

1.3 Queensland Opioid Treatment Program

The regulation of ODT in Queensland (including relevant approvals) is managed through the Queensland Opioid Treatment Program, by the Healthcare Approvals and Regulation Unit (HARU), Queensland Health. Contact details for relevant services are provided in Appendix 17.

Further information about the program and how to become a QOTP prescriber is available on the Queensland Health website. A general overview of QOTP procedures is in Appendix 4. Relevant communication related to QOTP should be directed to QOTP@health.qld.gov.au.

Opioid Dependence Treatment medication is primarily dispensed through community pharmacies. Some services treat patients directly during the induction period then transfer dispensing and administration responsibilities to community pharmacies. Pharmacists play a key role in delivering ODT, including by providing flexible, convenient treatment options. Their role includes assessing the patient for safety; dispensing and administration of ODT medication including administration of LAI BPN; and advising the QOTP prescriber of any concerns regarding the patient's clinical presentation.

2. Buprenorphine

2.1 Overview

Buprenorphine is a mu opioid receptor partial agonist with high receptor affinity. BPN has actions similar to full agonist drugs but with less efficacy due to lower intrinsic activity so that increases in dose have progressively less increase in effect. Doses beyond those required to saturate the majority of mu opioid receptors (usually 16mg) will cause a prolonged duration of action with additional full agonist opioids having little or no effect[6].

Buprenorphine can block the effects of other opioid agonists in a dose-dependent fashion. By reducing craving and attenuating the response to opioid drugs, BPN reduces illicit opioid use[6]. BPN also exhibits partial antagonist effects at kappa opioid receptors, which may contribute to an antidepressant action[19].

Buprenorphine exerts a degree of competitive blockade to the effects of full agonist opioids and also displaces agonists from opioid receptors. This may complicate the use of additional opioids for analgesia and means that BPN may precipitate opioid withdrawal one to four hours after a first dose[20], since in the short term, it may not produce sufficient agonist effects to compensate for the displaced full agonist opioid[6]. This can largely be avoided by appropriate dose induction procedures[20].

Buprenorphine is supplied in various forms however only the following are approved for ODT:

- long-acting injectable (LAI BPN: Buvidal® or Sublocade®)
- sublingual buprenorphine (SL BPN):
  - tablet (SL BPN: Subutex®)
  - buprenorphine/naloxone film in a 4:1 combination[13] (SL BPN: Suboxone®).

LAI BPN (Buvidal® or Sublocade®) is the preferred drug regimen, with alternatives planned only with specific rationale. SL BPN NX film (Suboxone®) is less likely to be used in a non-prescribed manner (e.g., injected) than BPN only tablets (Subutex®) and is easier to supervise administration. It is easier to supervise administration of the film preparation than BPN tablets (Subutex®)[6]. The less frequent need for administering LAI BPN formulations may require tailored approaches to structuring clinical reviews, psychosocial interventions and care planning. Broad options for consideration:

- Commence directly with weekly LAI BPN formulation (Buvidal® Weekly) (e.g., for the first two to four weeks) until the patient is stabilised and treatment needs clarified.
- Transfer to monthly BPN formulations (i.e., Buvidal® Monthly or Sublocade®) from SL BPN, or from LAI BPN Buvidal Weekly. Though intended for 4 weekly injection intervals, clinicians may schedule more frequent clinical reviews for patients initiating ODT or during periods of clinical instability, for assessment, care planning and psychosocial interventions.

Options should be discussed with patients when considering medication choices and developing treatment plans, emphasising that safe and effective ODT is more than the provision of medication, and that regular reviews, care planning and psychosocial interventions are important elements.

Table 4 Overview of buprenorphine products available for ODT in Australia[12]

	Sublingual (SL BPN)	Long-acting injectable (LAI BPN)	
Product name	Suboxone® and Subutex®	Buvidal® Weekly and Monthly	Sublocade®
Formulations	Suboxone® contains BPN and NX in 4:1 ratio 2/0.5mg and 8/2mg sublingual film Subutex® contains BPN in 0.4mg, 2mg and 8mg sublingual tablets	Buvidal® Weekly and Monthly uses FluidCrystal® LAI technology. Subcutaneous (SC) injections in prefilled syringes with 23-gauge needle. Administration via upper arm, thigh, abdomen or buttocks. Buvidal® Weekly: 8 mg/0.16 mL 16 mg/0.32 mL 24 mg/0.48 mL 32 mg/0.64 mL Buvidal® Monthly: 64 mg/0.18 mL 96 mg/0.27 mL	Sublocade® uses ATRIGEL® Delivery System SC injections in prefilled syringes with 19-gauge needle administered in abdomen. Monthly doses: 100mg/0.5mL 300mg/1.5mL

	Sublingual (SL BPN)	Long-acting injectable (LAI BPN)	
		128 mg/0.36 mL 160 mg/0.45 mL	
Storage Requirements	Suboxone: Store at room temperature (below 25ºC). Subutex: Store at room temperature (below 30ºC). Protect from prolonged exposure to light and protect from moisture.	Store at room temperature (below 25ºC) Do not refrigerate or freeze.	Cold storage requirements (2-8ºC). Do not freeze. May be stored at room temperature (below 25ºC) for up to 28 days before use. Remove from cold storage for at least 15 minutes prior to SC injection.
Clinical Pharmacology	Bioavailability 10-30%* Onset effects within 1 hour, with peak effects 2-4 hours after dose Duration effects usually 24 hours but dose dependent and can vary from 8 to 72 hours	Bioavailability = 100% Time to peak plasma level (tmax) • Buvidal® Weekly = 24hrs • Buvidal® Monthly = 6-10hrs Half life • Buvidal® Weekly = 3-5 days • Buvidal® Monthly = 19-25 days Steady-state equilibrium by 4th dose	Bioavailability = 100%. Time to peak plasma levels (tmax) = 24hrs. Half-life = 43 to 60 days. Steady-state equilibrium by 2nd (300/100mg) to 6th dose (300/300mg).
Frequency of medication administration	Daily or second or third daily doses	Buvidal® Weekly dose can be administered every 7±2 days (5-9 day schedule). Buvidal® Monthly dose can be administered every 4±1 weeks (3-5 week schedule).	Sublocade® administered every 4+2 weeks (26-42 day schedule).
Recommended treatment regimen	From heroin, pharmaceutical opioids: Commence 8mg Day 1 when patient in early / mild opioid withdrawal (usually >8-12hrs after last dose or use) Titrate upwards on daily basis as required From methadone: Initiate BPN when patient in moderately	Buvidal® Weekly dose can be initiated directly or, where transferring from SL BPN, be determined according to patient's SL BPN dose. If starting Buvidal directly the recommended starting dose is 16mg of Buvidal Weekly, with one or two additional 8 mg doses at least 1 day apart, to a target dose of 24 mg or 32	Initiate treatment with SL BPN (at least 8mg) for ≥7 days, then transfer to Sublocade®. May also transfer from Buvidal® Weekly. Recommended induction: 300mg monthly injections x 2 doses (8 weeks) then 100mg monthly doses (if patient 'stable' on initial 2 x 300mg doses) or 300mg monthly doses if require additional BPN effects (e.g., cravings, withdrawal, continued opioid use)

	Sublingual (SL BPN)	Long-acting injectable (LAI BPN)	
	severe withdrawal (e.g., COWS**≥12) (e.g., 1-2 days after last methadone dose) See also 2.2 Induction below. Day 1: 2mg + 6mg after 1-2 hrs, with additional 2-8mg doses every 2-4 hrs as required to alleviate opioid withdrawal to maximum dose of 32 mg. Day 2 onwards: titrate BPN dose daily as required	mg during the first treatment week. The recommended dose for the second treatment week is the total dose administered during the week of initiation. Titrate subsequent doses after clinical review Note increasing effects during first few doses (accumulation to steady state after about 4 doses)	Patients may be initiated with 100mg Sublocade® (after ≥7 days SL BPN treatment) doses if: safety concerns (e.g., severe hepatic disease) drug interaction concerns: e.g., overdose risk from polysubstance use
Maintenance phase	Adjust dose to achieve treatment goals (reduced use of other opioids, reduced withdrawal and cravings; blockade effects). Range 2-32mg daily; most patients require 12-24mg daily	Titrate dose to achieve treatment goals Adjust doses when transferring between weekly and monthly doses	Titrate dose to achieve treatment goals 100mg or 300mg monthly injections
Withdrawal phase	Gradually taper dose over several weeks-months (e.g., 2-4mg weekly reductions)	Gradually taper doses (reducing dose strengths every 1-2 injections). Peak withdrawal features may emerge 4-12 weeks after last Buvidal® Monthly dose, or 1-4 weeks after last Buvidal® Weekly dose.	Reduce dose to 100mg monthly injections prior to stopping. Peak withdrawal features may emerge 4-24 weeks after last 300mg dose or 4-12 weeks after last 100mg dose.
Key adverse events	BPN adverse events	Local injection site: Redness, pain, tenderness, swelling in approximately 5-10% patients Usually mild and transient and resolves spontaneously	

* bioavailability of BPN can vary significantly between individuals

** Clinical Opioid Withdrawal Scale (COWS)

Appendices 11 and 12 contains more detailed product and pharmacokinetic information, and up-to-date prescribing information can be found on MIMS Online:

- Buvidal® Weekly
- Buvidal® Monthly
- Sublocade®
- Suboxone®

- Subutex®

2.2 Induction

2.2.1 Transfer to buprenorphine from methadone and other opioids

When transferring patients to BPN from other opioids, there is a risk of precipitated withdrawal. This risk can be minimised by using a low dose BPN initiation schedule or moderated withdrawal methods of transfer or by initiation of LAI BPN (see section 2.2.2 Transfer to LAI BPN from SL BPN or from other opioids)[21]. Low dose BPN initiation or LAI BPN are increasingly the standard approaches.

1. ***Low dose BPN initiation***[22] schedule (also known as microdosing and the Bernese method) involves gradually increasing the BPN dose from a low starting dose in conjunction with the currently prescribed methadone over a period of 3 to 28 days. Evidence for safe transfer of patients using a low dose BPN initiation schedule is limited to multiple case series but is supported by expert opinion and clinical experience. This is now the recommended method of transfer because of the lower patient burden compared with moderated withdrawal[23]. This will require regular treatment reviews.
2. ***Moderated withdrawal*** requires entry into an early stage of withdrawal to prevent significant displacement of opioid agonists and begin substitution with BPN. This has been the most common method used to transfer patients from methadone to BPN; however, it is a challenge for patients, and has been a barrier for this treatment choice. Low dose BPN initiation is now likely to be preferred by patients, however, moderated withdrawal may remain preferable for practical and safety reasons (including where rapid transfer is necessary).

In general, transfer should occur within an ambulatory setting and will require informed consent following discussion of alternative options including potential risks and benefits, including risks of a higher dose transfer[11], leading to a documented and agreed decision about the planned approach.

Low dose BPN initiation

A range of low dose BPN initiation approaches have been trialed. As outlined in a review of methods[21], the key principle is bridging. The pharmacologic principle of bridging incorporates an as-slow-as-possible introduction of BPN onto the opioid receptors, facilitating a gentle loading of the high binding affinity and long half-life BPN, without significant displacement of the full agonist opioid.

Typically, over a period of 2 weeks while the patient's methadone dose is maintained SL BPN is commenced initially at 0.4 mg on day one, building gradually to about 4 mg twice daily by day 7 and 12 – 16 mg once daily by day 12 to 14, at which stage the methadone dose can be tapered (at perhaps 10 mg per day) or ceased altogether.

This method uses 0.4 mg SL BPN (Subutex®) tablets with a plan to shift to 2mg and 8mg doses, as above preferably as BPN/NX film, and with consideration of shift to LAI BPN.

This approach has facilitated the transfer to buprenorphine of patients on methadone who had never managed to lower their dose to a level which would allow a moderated withdrawal direct transfer. Consultation with a medical addiction specialist is recommended if prescribers are not familiar with this approach.

Consistent with the principle of bridging, Table 5 is intended as an example only. This is currently a

rapidly evolving area with varying initiation schedules in use[24-26].

Some patients may tolerate and prefer a once daily dose. If so, after a single 0.4 mg dose on day 1 the total daily doses can be given in a single dose for the remainder of the first week. Frequency of clinical review will need to be considered individually.

Table 5 Example low dose buprenorphine initiation schedule

Day	Buprenorphine	Opioid
1	0.4 mg daily	Maintain dose
2	0.4 mg twice daily	Maintain dose
3	0.8 mg twice daily	Maintain dose
4	1.2 mg twice daily	Maintain dose
5	1.6 mg twice daily	Maintain dose
6	2 mg twice daily	Maintain dose
7	4 mg daily	Maintain dose
If the patient is using both long- AND short-acting opioids, stop short-acting opioids here and maintain long-acting opioid dose. You may also choose to begin a taper of long-acting opioids at this point, though this may not be necessary.		
8	4.8 mg daily	Maintain dose
9	6 mg daily	Maintain dose
10	6 mg daily	Maintain dose
11	8 mg daily	Maintain dose
12	10 mg daily	Maintain dose
13	12 mg daily	Maintain dose
14	12 mg daily	Stop all remaining opioid therapy
Follow-up appointment at Day 7 to monitor progress and outline taper of long-acting opioid if you choose. See the patient on Day 14, after 12 mg of SL-BPN, and give another 2 mg every 1 hr until comfortable, to a max of 16 mg that day.		

Moderated withdrawal

Transferring to BPN from doses of methadone of 40 mg / 8 mL or less

Patients should be on a methadone dose of less than 40 mg / 8 mL for at least one week prior to first dose of BPN, which should be administered only in the presence of objective opioid withdrawal signs[10, 11]. The following conversion rates are a guide when changing from low-dose methadone to BPN.

Table 6 Guide to conversion rates - transfer from methadone to BPN

Last oral methadone dose	Initial buprenorphine dose	Day 2 buprenorphine dose
20–40 mg / 4–8 mL	4 mg–8 mg	8–12 mg
10–20 mg / 2–4 mL	4 mg–6 mg	4–10 mg
5–10 mg / 1–2 mL	2 mg	2–6 mg

The likelihood of precipitated withdrawal reduces as the time between the last methadone dose and the

first BPN dose increases.

Transferring to BPN from doses of methadone greater than 40 mg / 8 mL

Most patients on methadone require maintenance doses greater than 40mg / 8 mL and are unable to reduce their dose of methadone below 40 mg / 8 mL without considerable discomfort or relapsing to other opioid use. It is possible to transfer to BPN from methadone doses of 40–60 mg / 8–12 mL using a moderated withdrawal approach for willing patients. Reduce the methadone dose gradually until withdrawal is beginning within 24 hours (aiming for less than 40 mg / 8 mL if possible). If low dose BPN initiation is not possible or appropriate, inpatient care should be considered in settings of significant comorbidities, unstable and risky substance use, or high doses of methadone (>100 mg / 20 mL).

- Initiate BPN at least 24 hours after the last methadone dose or when the patient has significant, objective features of opioid withdrawal, which may be up to 96 hours after the last dose of methadone. Patients are encouraged to wait as long as possible between the last dose of methadone and the first dose of BPN to minimise the risk of precipitated withdrawal.
- Begin with a small test dose of BPN (2–4 mg) to reduce the risk of precipitated withdrawal. Ensure a total of at least 8 mg is given on the first day. Often 12 mg or more is required to manage withdrawal symptoms. Multiple smaller doses over the course of the day are less likely to precipitate withdrawal.
- Review frequently, titrate BPN and reassure patient.

Strategies to minimise the risk of precipitated withdrawal when transferring from methadone to BPN using a moderated withdrawal approach are summarised below.

Table 7 Key factors affecting precipitated withdrawal

Factor	Discussion	Recommended strategy
Dose of methadone	Doses greater than 40 mg / 8 mL of methadone are more often associated with precipitated withdrawal. Higher methadone dose is often associated with more severe withdrawal experience.	Attempt to transfer from less than 40 mg/8 mL where possible
Time between last methadone dose and first BPN dose	BPN should not be taken within 24 hours of last methadone dose. Increasing the interval between last dose of methadone and first dose of BPN reduces incidence and severity of precipitated withdrawal.	Cease methadone and delay the first dose of BPN until the patient is showing features of methadone withdrawal
Dose of BPN	Low doses of BPN (e.g., 2 mg) are generally inadequate as a substitute for methadone (unless methadone dose is very low). High first doses of BPN (e.g., 8mg or more) are more likely to precipitate withdrawal. This is a common mistake by inexperienced prescribers.	First dose of BPN should generally be 4mg, with review of the patient 2–4 hours later (or early the following day)

Factor	Discussion	Recommended strategy
Patient expectations	Patients who are not prepared for the possibility of precipitated withdrawal are more likely to be distressed and confused by its onset, with potential negative consequences (e.g., treatment dropout, misuse of other medications)	Inform patients fully (and carers where relevant). Provide written information. Prepare a contingency management plan for severe symptoms.

2.2.2 Transfer to LAI BPN from SL BPN or from other opioids

If patients commencing LAI BPN treatment are not already on SL BPN, they should either be started on LAI BPN (Buvidal® Weekly) or should have a short period (e.g., ≥7-days) of SL BPN (as Suboxone® or Subutex®) prior to transition, to:

- minimise risk of experiencing significant adverse events (e.g., headaches, nausea, sedation) when initiating BPN treatment
- minimise risk of precipitated withdrawal when initiating BPN treatment, particularly for those with recent methadone treatment
- ensure the patient is satisfied with BPN treatment choice.

Local guidelines should be followed when initiating SL BPN. Longer periods of SL BPN treatment may be required prior to initiating LAI BPN treatment in settings of adverse events or drug interactions, existing severe liver disease or difficulty stabilising dose of SL BPN. Transfers from methadone should generally occur via SL BPN, due to minimal relevant experience or research in transferring patients directly to LAI. Those with limited experience in providing ODT, wishing to transfer a patient from methadone directly to LAI BPN should first consult a medical addiction specialist.

Commencing treatment with Buvidal®

Patients may either be started on Buvidal® Weekly or if treated with SL BPN transferred directly to Buvidal® Weekly or Buvidal® Monthly starting on the day after the last daily SL treatment dose (see Table 8). Individual titration may be required on subsequent doses, recognising that the dose effects of the LAI are likely to increase with BPN accumulation until steady state equilibrium is achieved (usually after three to five doses). Factors that may lead to the clinician and patient choosing weekly over monthly treatment may include more frequent clinical review, or concomitant use of benzodiazepines, alcohol or other sedatives.

Table 8 SL and LAI Buvidal® Weekly and Buvidal® Monthly equivalent doses

Daily SL BPN dose	Buvidal® LAI weekly dose	Buvidal® LAI monthly dose
≤ 6mg	8 mg	No monthly equivalent
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg
24-32 mg	No weekly equivalent	160 mg

Titrating doses of Buvidal®

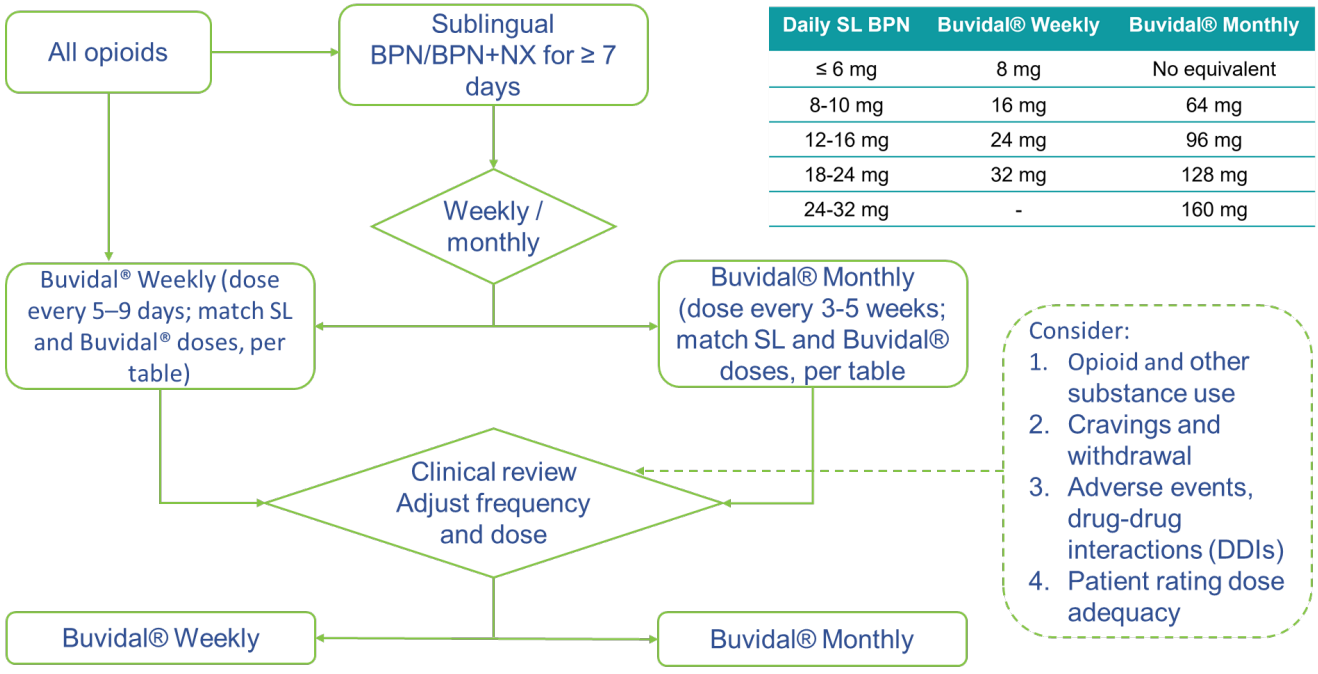
After selecting the appropriate weekly or monthly dose of Buvidal®, patients can usually continue on these doses without experiencing cravings, withdrawal symptoms or reporting significant non-prescribed opioid use. Four doses are usually required to achieve steady-state plasma levels (see product information and pharmacokinetic properties in Appendices 11 and 12).

However, titration of Buvidal® Weekly or Buvidal® Monthly may be required if patients present with significant opioid withdrawal during the first four doses of Buvidal®, while steady state plasma levels are being reached. In previous research[27] approximately 10-20% of patients adjusted their Buvidal® dose (up or down) in the subsequent doses following the initial Buvidal® dose.

Supplemental or 'top-up' BPN doses

'Top-up' or supplemental doses of Buvidal® may be given if the patient experiences opioid withdrawal, cravings or persistent continued opioid use. If clinically indicated 24 hours after a Buvidal® dose, patients may receive additional 8 mg Buvidal® Weekly injections. If the patient experiences opioid withdrawal or cravings, top up with supplemental doses of 8 mg Buvidal® Weekly (up to a maximum weekly dose of 32 mg, with at least one day between each supplemental 8mg injection) or consider administering Buvidal® Monthly every three weeks for the first 1-4 doses prior to reaching steady state.

There may be circumstances where top up or supplemental doses of BPN are required but Buvidal® Weekly 8 mg doses are not possible (e.g., travel away from regular service providers). Supplemental low doses of SL BPN (e.g., 4 mg or 8 mg daily) may be used for limited periods until the next LAI.



Dose conversion table

Daily SL BPN	Buvidal® Weekly	Buvidal® Monthly
≤ 6 mg	8 mg	No equivalent
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg
24-32 mg	-	160 mg

Figure 1 Overview of treatment schedules with Buvidal®[28]

Buvidal® flexible treatment schedules and missed doses

Patients may be switched from weekly to monthly injections or from monthly to weekly injections based

on the recommendations in Table 8 above. Patients switching from weekly to monthly injections will generally experience trough levels in the first few months. Monitor patients for increased withdrawal or craving symptoms or other signs of instability. Individual titration to higher or lower doses may be required.

While doses should be routinely scheduled to occur every 7 (Buvidal® Weekly) or 28 (Buvidal® Monthly) days, flexibility may be required to accommodate missed appointments, travel, public holidays, appointment availability etc. To avoid missed doses, the weekly dose may be administered up to 2 days before or after the weekly time point (days 5-9), and the monthly dose may be administered up to 1 week before or after the monthly time point (weeks 3-5).

If a dose is missed, the next dose should be administered as soon as practicable. If more than 10-14 days has occurred between doses of Buvidal® Weekly, re-induction may be required, with individual titration. If more than eight weeks between Buvidal® Monthly has elapsed, re-induction may be required, with individual titration.

Commencing treatment with Sublocade®

Sublocade® treatment is appropriate for patients who have undergone induction on another BPN product. Longer periods of SL BPN treatment prior to commencing Sublocade® may be required prior to initiating LAI BPN treatment if the patient reports BPN related adverse events or drug-drug interactions (DDI), has existing severe liver disease or is finding it difficult to stabilise on a dose of SL BPN.

The first Sublocade® dose should usually be administered approximately 24 hours after the last SL BPN dose. If a dose of SL BPN has been administered on the same day, the dose of Sublocade® does not need to be delayed. The recommended dose of Sublocade® for most patients upon initiation is 300 mg monthly for the first two months (two x monthly doses), reflecting ‘loading’ doses that elevate plasma BPN levels more rapidly in the initial treatment period.

There may be circumstances where treatment with Sublocade® may be initiated with 100mg (rather than 300 mg) doses, specifically where there are safety concerns arising from hepatic impairment or DDIs (e.g., concomitant use of other sedatives). This requires an informed decision by the patient who should be made aware that even 100 mg Sublocade® doses are significantly increasing plasma BPN levels, with treatment effects regularly monitored and the dose adjusted accordingly.

After the initial two monthly doses of Sublocade® treatment, doses are flexible with either 100 mg or 300 mg injections every four weeks, decided by the prescriber in consultation with the patient. For most patients, 100 mg monthly Sublocade® doses will be adequate, maintaining plasma levels (at steady state equilibrium) achieved with the first two 300 mg Sublocade® doses, and is likely to be associated with fewer concerns regarding high dose BPN-related adverse events. Maintenance of 300 mg doses should be considered for those patients who had previously stabilised on high dose SL BPN (e.g., 24 to 32 mg daily) or continue to experience cravings or non-prescribed opioid use during the first 2-month period of Sublocade® treatment.

Sublocade® flexible treatment schedules and missed doses

While doses should be routinely scheduled to occur every 28 days, flexibility may be required to accommodate missed appointments, travel, public holidays, appointment availability etc. To accommodate such scenarios, Sublocade® doses can be administered up to 2 days ahead of a scheduled dose (i.e., 26 days since the last injection), or up to 14 days after the 28-day interval (i.e., 42 days since the last injection) without dose adjustments.

Once steady state has been achieved (after two doses of 300 mg and four doses of 100 mg or after six 300 mg doses of Sublocade®), occasional delays in receiving the next dose of up to 4 weeks (i.e. 56

days since the last injection) after the last scheduled dose are not expected to have a clinically significant impact on treatment effect, and therapeutic BPN plasma levels are generally maintained for this period. The treatment schedule can usually be resumed without the need to alter the usual Sublocade® dose.

Delays in receiving the next scheduled dose of greater than 4 weeks (i.e. more than 56 days after last injection) may be associated with reduced plasma BPN levels and caution should be exercised in re-initiating treatment with Sublocade®. If there is any doubt regarding the patient's opioid tolerance (e.g., patient reports experiencing opiate withdrawal features), then a test dose of SL BPN (e.g., 8 mg) should be administered, and if there are no concerns (e.g., sedation), recommence the scheduled Sublocade® treatment (on the previous 100 mg or 300 mg dose) the following day.

A patient who has had no documented and confirmed BPN doses for more than 56 days after their last injection, or who has returned to regular use of other opioids since their last Sublocade® dose (with the attendant risk of precipitated withdrawal on recommencing BPN treatment), should be re-initiated to treatment with SL BPN for 7 or more days before recommencing Sublocade® treatment.

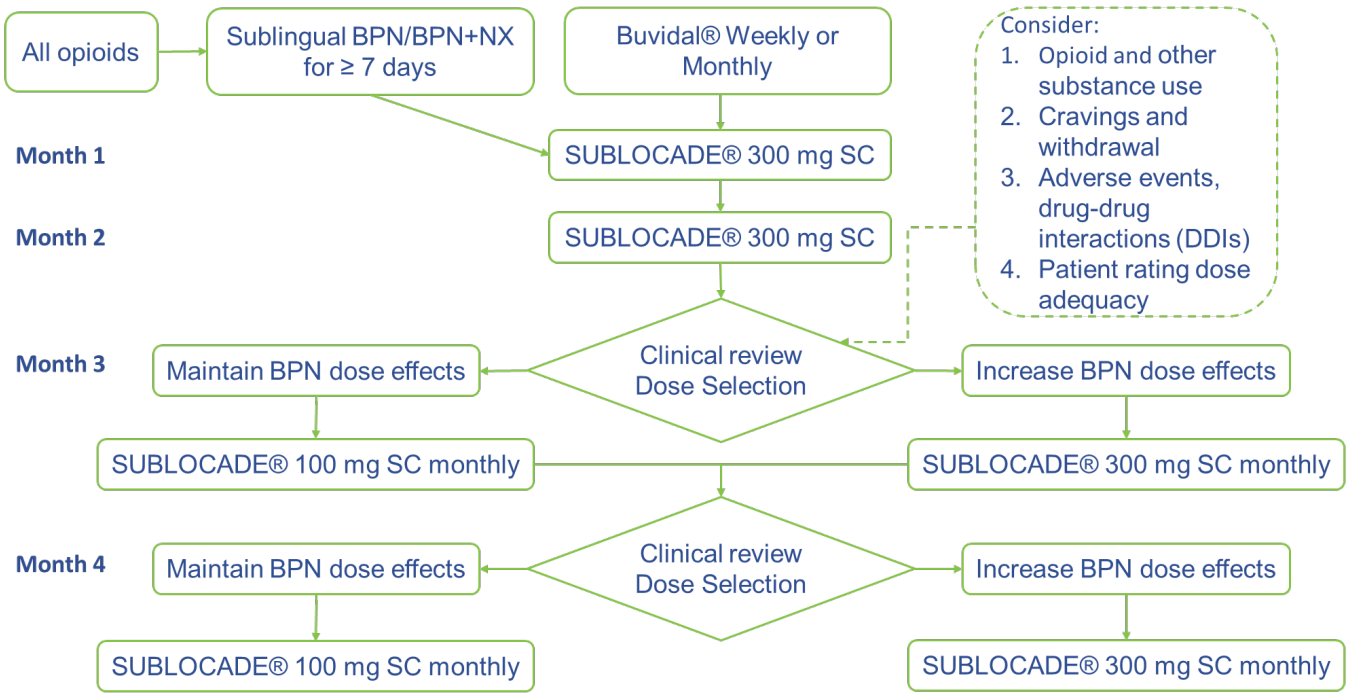


Figure 2 Overview treatment schedules with Sublocade®[28]

2.2.3 Transfer between Buvidal® and Sublocade®

There is no published data or clinical experience to provide recommendations on transfer between Buvidal® and Sublocade® products, so generally, transferring patients between Buvidal® and Sublocade® should be avoided. Note: treatment initiation is an exception where Sublocade® can be commenced after an induction on a BPN containing product (including Buvidal®).

However, situations may occur where it is not possible to continue one formulation, and transfer to the other LAI may be preferable to transferring back to SL BPN. Circumstances for which transfer between

Buvidal® and Sublocade® may be indicated include lack of availability of the required formulation at the treatment site (e.g. due to interrupted supply, or if the treatment site only stocks the alternative formulation).

If transfer between formulations does occur, in the absence of clinical studies on transfers between Buvidal® and Sublocade®, the following recommendations have been developed based on pharmacokinetic and clinical data (see Appendix 12).

Transfer from Buvidal® to Sublocade®

Patients on doses of Buvidal® Weekly higher than 8 mg weekly or on Buvidal® Monthly should be transferred to 300 mg Sublocade® to ensure continuation of steady state levels. This should be reviewed after each of the first two doses with consideration of reduction to 100 mg Sublocade® by the third monthly dose.

Transfer from Sublocade® to Buvidal®

Patients on stable Sublocade® 300 mg monthly doses for more than two months should transfer to Buvidal® Weekly 32 mg or Buvidal® Monthly 160 mg. Patients may experience a decrease in plasma BPN levels and develop opioid withdrawal and / or cravings following transfer to Buvidal®, although this is unlikely to occur given the long half-life of Sublocade®.

Patients on steady Sublocade® 100 mg monthly doses, or who have only received one or two Sublocade® 300 mg injections for initiation, should not experience a significant decrease in plasma BPN levels when transferring to Buvidal® Weekly or Buvidal® Monthly. Commence at Buvidal® Weekly 24 mg or Buvidal® Monthly 96 mg and titrate doses up or down as clinically indicated.

2.3 Maintenance

2.3.1 Maintenance of LAI BPN

Supplemental BPN administration

Treatment with LAI BPN should not routinely require additional or supplemental SL BPN. Wherever possible, LAI doses should be adjusted (either the dose or frequency of administration) to ensure effective and safe treatment.

However, supplemental doses of BPN may be required on an interim basis until the next ‘usual’ LAI BPN dose can be administered and should be prescribed in the standard manner. Common situations in which supplemental SL BPN may be considered include:

- During dose titration in the early stages of LAI treatment. LAI BPN doses are adjusted according to the patient’s prior SL dose; however, these transitional doses are a guide only, and subsequent dose adjustment may be required. Supplemental BPN doses may enable the patient to be held over until their next scheduled LAI dose.
- Following DDI – the commencement of another medication that induces hepatic metabolism of BPN (e.g. Cytochrome P450 (CYP) 3A4 inducer such as carbamazepine) may cause BPN plasma levels to be reduced – resulting in features of opioid withdrawal, cravings or non-prescribed drug use.
- Delayed or interrupted LAI BPN injection. Patients may miss routine dose of LAI BPN due to unforeseen circumstances. If a dose of LAI BPN cannot be arranged to suit the situation an interim period of SL BPN treatment may be organised instead.

- In response to other stressors or deterioration in psychological well-being. Some patients have a history of responding to a significant stressor by using substances. Patients may request an increase in their ODT medication to avoid other substance use or harmful behaviours (e.g. aggression, gambling). While there may not be a pharmacological basis for altering ODT doses under such circumstances, this can be a useful short-term measure to help patients through a difficult time, while supporting them to develop alternative healthy non-medication coping skills.

Patients should not routinely be maintained for more than 14 days on SL BPN treatment in addition to LAI BPN doses – adjustment of the next LAI BPN dose is recommended. If patients persistently describe their LAI BPN dose as not sufficient despite being on the maximum possible dose (e.g. 160 mg Buvidal® Monthly or 300 mg Sublocade®), then consider transferring to Buvidal® Weekly (the delivery system may make a difference), changing to alternative formulation or discontinuing LAI treatment and resuming SL BPN treatment.

Supplemental doses for patients treated with Buvidal®

The preferred approach to supplemental dosing for patients treated with Buvidal® is to use supplemental doses of Buvidal® (e.g. 8 mg weekly top-up doses) until their next scheduled regular dose, and then to adjust the next Buvidal® dose accordingly.

However, where supplemental LAI Buvidal® cannot be used (e.g. no access), then additional doses of SL BPN should be prescribed – either to add to (or 'top up') existing Buvidal® (in which case use up to 8 mg SL BPN per day); or SL BPN can be used 'instead of' Buvidal® (e.g. missed Buvidal® and SL BPN required until next Buvidal® can be administered – in which case SL BPN doses should be guided by 2.2.2Table 8).

Supplemental doses for patients treated with Sublocade®

While patients generally do not require additional BPN during treatment with Sublocade®, short term (up to 14 days) supplementary doses of SL BPN (SL BPN +/- NX tablets/film) of no more than 8 mg daily can be prescribed until the next scheduled Sublocade®.

In circumstances of a missed Sublocade® dose and where the patient is reporting features of opioid withdrawal or cravings, SL BPN may be used until Sublocade® can be administered (e.g. using 8 mg SL BPN per day and titrating the dose accordingly).

2.3.2 Maintenance of sublingual buprenorphine

Most SL BPN doses stabilise in a daily range 12-24 mg, although some patients may require higher (e.g., up to 32 mg) or lower (4-8 mg) doses for efficacy[6]. Retention in treatment can be effectively achieved with any dose above 2 mg/day[8]. Daily BPN doses of 12 mg or greater are more effective than lower doses in reducing non-prescribed opioid use and associated higher risk behaviours. Suppression of illicit opioid use is greatest when doses are 16 mg or higher[8]. BPN dose can be adjusted daily with increases of 2-8 mg/day.

Australian product information states the maximum daily dose of BPN is 32 mg. Prescribing above this level is beyond maximum dose recommended by the manufacturer. There is limited evidence regarding the safety of doses exceeding 32 mg, and risks may include associated dose-related adverse events such as hepatitis[12].

Rarely, a prescriber may consider a regular daily dose above 32 mg. Second opinion or consultation with a medical addiction specialist is recommended. Informed consent is required from the patient regarding the medication being prescribed outside the dose recommended by the manufacturer's Product

Information, the clinical basis for the decision, and the possible associated risks.

Reduced frequency SL BPN treatment regimens

Buprenorphine's pharmacokinetics allow a wide range of treatment regimens from several times daily (e.g., management of acute pain) to once every 2-3 days. For patients who are stable and identified as lower risk, reduced frequency of supervision is appropriate subject to patient preference and operational need, particularly limited pharmacy hours.

Transitioning patients to an LAI BPN formulation is the preferred option when indicated. If the treatment plan is to reduce the frequency of supervised administration, but maintain the patient on SL BPN formulations, double or triple dose regimens are possible. Consultation with a medical addiction specialist is recommended if the total dose to be administered is over 32 mg.

Multiple doses

Sometimes patients may benefit from multiple doses of BPN within one day, for example induction using a low dose initiation approach and treatment of acute pain.

Double dose regimen

Patients should be stabilised on a daily dose prior to alternate-day administration, when the daily (24 hour) BPN dose is usually doubled. The patient is reviewed following the first or second 48-hour dose. If there are no additional signs of withdrawal on the second day, including sleep pattern on the second night[12], the dose is adequate. Onset of withdrawal including cravings or sleep difficulties in the second day should lead to increased 48-hour dose. Excessive intoxication at time of peak effects (1-4 hours) should lead to reduced 48-hour dose.

Where the daily dose exceeds 16 mg it may still be appropriate to double dose, despite exceeding the 32 mg per day ceiling, based on individual assessment[12].

If a patient cannot be stabilised on double dose regimen, they should return to daily administration[12] or be trialed on an LAI BPN regimen. Patients on low doses of BPN may find that a double dose does not last for 48 hours. Patients reducing doses of BPN may need to switch to daily administration as the dose becomes lower (i.e., < 4 mg).

Triple dose regimen

A triple dose regimen is similar to double, with three times the 24-hour dose administered every three days and should only be trialled once a double dose regimen has been successful. The patient should be reviewed in the week following the first 72-hour dose, and the dose titrated accordingly. If the patient cannot be stabilised on a triple dose regimen, they can return to a double dose regimen.

Where the daily dose is 12 mg or higher it may still be appropriate to triple dose, despite exceeding the 32 mg per day ceiling.

2.4 Administration

2.4.1 Administering LAI BPN Injections

Buvidal® Weekly, Buvidal® Monthly and Sublocade® administrations are intended for subcutaneous (SC) use only. There should be sufficient subcutaneous tissue to allow for the injection. The area should be free of scarring, nodules or other lesions and not be inflamed, infected or bruised. A slow steady push should be used as slower injections are generally better tolerated. See the product information for

details. Injections should only be administered by an Australian Health Practitioner Regulation Agency (AHPRA) registered healthcare professional who has injection of S8 medications within their scope of practice.

LAI BPN should never be administered intramuscularly, intra-dermally, intravenously or intra-arterially. Serious health risks (including pulmonary thrombosis, infections, and tissue necrosis) may occur if LAI BPN is not injected as advised.

Administering Buvidal® injections

Buvidal® Weekly and Buvidal® Monthly should be injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Injection sites should be rotated. The injection sites may be alternated between the different injection areas i.e., the buttock, thigh, abdomen, or upper arm. The actual angle of injection will depend on the amount of subcutaneous tissue however Buvidal® should usually be administered at 90 degrees. For detailed instructions refer to product information (see Appendix 11).

Administering Sublocade® injections

Sublocade® should be injected subcutaneously in the abdominal region between the transpyloric (Addison's) and transtubercular planes. Injections should be given with the client laying down. Injection sites should be rotated. The actual angle of injection will depend on the amount of subcutaneous tissue however Sublocade® should usually be administered at 45 degrees. Sublocade® must be administered at room temperature. It may take 15 minutes after removing Sublocade® from refrigeration to achieve this temperature. For detailed instructions refer to product information (see Appendix 11).

2.4.2 Administering SL BPN

Diversion of supervised administration can be minimised when the following procedures are followed:

- administer medication to one patient at a time
- do not allow other people in the medication administration area while medication is being administered
- ask the patient to remove anything from their mouth prior to medication administration (e.g. chewing gum)
- observe the patient throughout the administration process, especially when the medication is placed in the mouth and immediately after
- once the medication is placed in the mouth ensure that the patient's hands are kept away from their mouth
- ensure the patient throws away (into a designated bin) or hands back any items used.

For BPN-mono tablets:

- offer the patient a drink of water prior to medication administration to moisten the mouth
- rough crumble the medication to large granule size (crushing to a fine powder tends to increase saliva, making it unpleasant for the patient and may prolong the dissolving process)
- dispense the medication in a disposable cup and instruct the patient to tip the granules from the cup under the tongue

- ask the patient to show the granules are in place, and advise the patient not to chew or swallow until the tablets are fully dissolved
- keep the patient in full view until the tablets are dissolved
- view and inspect the mouth cavity after the patient reports that the dose has been absorbed.

For BPN sublingual film:

- offer the patient a drink of water prior to medication administration to moisten the mouth
- ensure the patient's hands are clean and dry as the film may stick to wet fingers
- film must not be cut unless authorised by the prescriber
- open all film packages and offer the open packages to the patient. Ask the patient to remove the films from each package one at a time to place in their mouth. Alternatively, the pharmacist can remove each film from the package and place them in a dispensing container (e.g. disposable medication cup). Offer the container of films to the patient to place in their mouth one at a time.
- discourage the patient from overlapping films when placing them in their mouth. This impairs mucosal adherence and prolongs the time required for supervision.
- if multiple films are required, the first two are to be placed under the tongue either side of the frenulum, and the rest are placed inside the cheeks.
- advise the patient to refrain from attempts to move the films once they have been placed in the mouth
- advise the patient not to chew or swallow until the films have fully dissolved
- if films accidentally become stuck to teeth or top of tongue, reassure the patient that BPN will still be absorbed. The patient is to be advised to keep their mouth closed with mucosa in contact with the films as they dissolve
- the films adhere to the mucosa within seconds and are difficult to remove within 30-60 seconds, therefore supervise patient for one minute [13, 29, 30].

2.5 Disruptions in treatment

2.5.1 Missed doses

SL BPN

Missed 1 - 2 consecutive daily medication doses

Medication can be resumed as normal if there are no concerns regarding intoxication or other issues. Review by the prescriber (or delegate) may be required if any concerns prior to resumption of medication.

Missed 3 consecutive daily medication doses

The prescriber (or delegate) should review the patient prior to reinitiating ODT. If there are no specific concerns, regular medication can be resumed[6].

Missed 4 - 5 consecutive daily medication doses

Patients who recommence BPN after four or more consecutive missed medication doses are at risk of precipitated withdrawal if they have been using opioid agonists. The prescriber (or delegate) should

review the patient prior to reinitiating ODT. If there are obvious signs of withdrawal, resume normal medication treatment up to a maximum of 24 mg.

Missed 6 or more consecutive daily doses

The prescriber should reconsider the current medication choice, and if SL BPN is being reinitiated, treat the patient as a new induction.

LAI BPN

Patients who attend after more than 9 days from their last Buvidal® Weekly injection, more than 35 days from the last Buvidal® Monthly or more than 42 days from their last Sublocade® injection should be assessed for withdrawal symptoms and non-prescribed opioid use. The prescriber should then consider, mindful of the length of time since last injection, whether to give usual dose, a reduced dose or commence re-induction.

2.5.2 Vomited doses

Not applicable to LAI BPN treatment. SL BPN is absorbed sublingually within 2–3 minutes. Vomiting should make no difference to the absorbed dose[12].

2.6 Responding to overdose

2.6.1 Buprenorphine overdose

As part of an overdose plan, an effective brief intervention is to provide the patient with access to NX, and education about its use. See Section 1.2.3 for further information.

Treating BPN overdose usually requires inpatient hospitalisation, careful monitoring, NX administration and may require ventilatory support. Due to BPN's strong affinity for and slow dissociation from mu opioid receptors, higher doses and prolonged infusion of NX may be required to reverse BPN effects. Many BPN overdoses are reversed with usual NX doses:

- 0.4 to 2 mg intravenously every 2 to 3 minutes according to clinical effect up to a maximum dose of 15 mg
- 0.4 to 2 mg intramuscularly (IM), repeated according to clinical effect

OR

- 1.8 mg/0.2 mL nasal spray (1 spray into one nostril) repeated according to clinical effect.

However much higher doses (e.g., 10–30 mg / 70 kg) may be required. The long duration of action of BPN should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose[12].

While BPN alone is rarely associated with overdose in people with a dependence on opioids, overdose can occur in the context of polydrug use, specifically the use of other sedatives such as alcohol, benzodiazepines and gabapentinoids. Under such circumstances, emergency treatment is required with supportive care (oxygen therapy, assisted breathing and recovery position) and the use of NX. While laboratory studies (animal and receptor binding studies) suggest that very high doses of NX (e.g., 10 mg IM or intravenous (IV)) are required to reverse the effects of BPN (due to the comparable affinity of BPN and NX for the mu opioid receptor), in practice, polydrug overdoses in which BPN is implicated generally respond to 'routine' doses of NX (e.g., 1-2 mg IM/IV).

The specific potential risks of the LAI BPN product are the prolonged plasma levels of BPN, rather than higher plasma levels compared to SL medications. Hence, no greater risk of overdose is expected from LAI BPN formulations. However, the prolonged duration of BPN effects with LAI formulations requires patients to be clinically monitored for extended periods of time, until the patient has clinically recovered, and may require prolonged monitoring and a NX infusion in a hospital setting.

2.6.2 Incorrect administration

The risks associated with an incorrect dose of BPN will vary depending on the dose. If a higher than intended dose of LAI BPN is administered, a medical addiction specialist should be consulted with respect to management. In the event of an incorrect (excess) dose being administered:

- the dispensing staff should immediately notify the patient and the prescriber of the error
- the patient should be warned of the likely consequences (including increased sedation or drowsiness that may occur for several hours afterwards), warned against any additional drug use, and against driving or operating machinery for the rest of the day
- if any of the following circumstances apply, the patient should be monitored for at least six hours by a clinician or in a hospital emergency department (ED):
  - the patient is sedated following the dose (for any reason)
  - the patient is new to ODT (within the first two weeks of treatment)
  - the regular daily BPN dose is ≤4 mg and the patient was incorrectly administered a dose of ≥ 16 mg[30]
  - a BPN dose ≥ 64 mg was incorrectly administered (regardless of routine daily dose).

The prescriber should review the patient before the next dose of BPN

A lower dose, or no dose, may be required the following day (in effect, a two-day dose may have been administered).

2.7 Reduction for discontinuation

Various scenarios for discontinuing LAI BPN treatment are possible:

1. withdrawing off LAI BPN (with goal of opioid abstinence)
2. transferring to SL BPN
3. transferring to methadone / other opioid analgesics.

2.7.2 Withdrawing off LAI BPN (with goal of abstinence)

Many patients are keen to achieve abstinence, discontinue opioid treatment and withdraw from opioids. Unfortunately, most patients attempting withdrawal from ODT relapse to non-prescribed opioid use and are at increased risk of opioid overdose, with as few as 10% of patients successfully achieving opioid abstinence in the short to medium term. While some patients describe withdrawal from SL BPN treatment as ‘shorter’ and ‘easier’ than methadone withdrawal, there is little evidence to indicate greater

longer-term success rates with either medication.

Factors generally associated with successful withdrawal from ODT are considered above in Section 1.2.4. These are presumed to be relevant for withdrawal from LAI BPN.

There is little experience and no studies examining withdrawal from LAI BPN treatment, so the withdrawal time course and severity has not been characterised. The onset, peak and duration of withdrawal symptoms is likely to vary individually and with duration of prior LAI BPN treatment. Withdrawal syndrome from LAI BPN is expected to occur several weeks to several months after the last dose, persist for longer, and be of lower severity than withdrawal from SL BPN. Table 9 highlights the timeframe for plasma BPN levels to drop to sufficiently low levels for the emergence of significant withdrawal features following long-term (steady state) LAI BPN doses, although considerable individual variability may be expected. Clinical reviews are recommended at appropriate frequency to monitor symptoms and identify treatment options.

Table 9 Timeframe plasma BPN undetectable following discontinuation of long-term LAI BPN treatment

LAI BPN	Half-life (at repeated doses)	Likely timeframe for onset of withdrawal symptoms after last maintenance LAI dose
Sublocade® 100 mg doses	43-60 days	2-6 months
Sublocade® 300 mg doses		3-9 months
Buvidal® Weekly	3-5 days	Up to 2-3 weeks after last dose
Buvidal® Monthly	19-25 days	Up to 2-3 months after last dose

Patients who have been on treatment for long enough to achieve steady state plasma levels of LAI BPN are likely to have a longer time course of reduction of BPN levels and therefore longer time course of withdrawal symptoms than those on LAI BPN treatment for shorter periods.

Wherever possible, patients should consider reducing their LAI BPN dose prior to discontinuing treatment. However, there is no current evidence to guide the prescriber in assisting the patient to do this. An individualised approach will be required. Consistent with clinical care required for patients withdrawing from other ODT medication regimens, patients and treatment plans should be reviewed regularly, with additional psychosocial supports established to maintain motivation, and cope with cravings, withdrawal and the risk of relapse. There may be a role for symptomatic medication to assist with features of opioid withdrawal; however, extended use (beyond a few days) of sedatives or hypnotic medications should be avoided.

Patients who have withdrawn from LAI BPN should be strongly encouraged to access supplies of take-home NX.

2.7.3 Transfers to SL BPN

Given the variable excretion and clinical effects of LAI BPN products, there can be considerable individual variation in patient response to LAI BPN reduction or discontinuation. This will be affected by prior LAI dose (generally longer effects with higher doses), duration (generally longer effects with long-term LAI treatment), variation in hepatic function, age, and the patient's sensitivity to withdrawal symptoms, cravings and other stressors.

For Sublocade® to SL BPN

SL BPN should be initiated with low doses at approximately the time of the next scheduled LAI BPN injection – usually commencing with 8mg SL BPN four weeks after the last Sublocade® dose, and the dose titrated upwards subsequently according to clinical need (features of withdrawal, craving, intoxication, use of non-prescribed drugs) as LAI BPN concentrations gradually subside, aiming to achieve an effective SL dose.

For Buvidal® to SL BPN

Initiate SL BPN treatment at the time of the next scheduled injection (e.g. 5-9 days after Buvidal® Weekly, or 3-5 weeks after last Buvidal® Monthly injections). Dose conversion tables should be used to guide the initial SL BPN dose, with frequent clinical reviews in order to titrate the SL dose subsequently.

Table 10 SL and LAI Buvidal® Weekly and Buvidal® Monthly equivalent doses

Buvidal® Weekly LAI dose	Buvidal® Monthly LAI dose	Daily SL BPN dose*
8 mg	No monthly equivalent	≤6 mg
16 mg	64 mg	8-10 mg
24 mg	96 mg	12-16 mg
32 mg	128 mg	18-24 mg
-	160 mg	24-32 mg

* start at low end of range and titrate up as required.

2.7.4 Transfer to methadone or other opioid analgesics

There is little clinical experience and no published studies regarding transfer from LAI BPN to methadone. Given this, patients transferring from LAI BPN to methadone should transition via SL BPN (as described in previous section). Once stabilised on a dose of SL BPN for at least 1-2 weeks (for Buvidal® Weekly) and at least 4-8 weeks (for Buvidal® Monthly or Sublocade®), transition to methadone can occur, initiating at low doses 20-30 mg daily, reviewing regularly and titrating accordingly.

If a patient must discontinue all BPN treatment abruptly (e.g., due to a severe adverse event, or patient unwillingness to continue any BPN treatment), transition to methadone may be considered after consultation with a medical addiction specialist. The general principle is to recommence low dose methadone (e.g. 20 mg oral daily doses) at the time of the next proposed LAI dose, regularly monitor the patient (at least weekly), and carefully increase the dose (by no more than 5 mg intervals) after clinical reviews until the methadone dose and patient have stabilised, recognising that residual BPN from LAI BPN doses may be present for up to 4-6 months after long term treatment with Sublocade® 300 mg, or 2-3 months after 100 mg Sublocade® or Buvidal® Monthly treatment. See Section 3.3 for further information regarding methadone maintenance.

3. Methadone

3.1 Overview

Methadone is a potent synthetic opioid agonist that is well-absorbed orally and has a long, although variable, plasma half-life. Methadone is usually administered as an oral liquid (5 mg / mL) and is effective because its long half-life enables single dose daily administration to produce a steady state.

Two preparations are registered for ODT in Australia:

- methadone syrup: This formulation contains 5 mg / 1 mL methadone hydrochloride. A list of excipients can be found at MIMS online.
- Biodone Forte®: This formulation contains 5 mg / 1 mL methadone hydrochloride. A list of excipients can be found at MIMS online.

3.2 Induction

3.2.1 Initial methadone dose

The first dose of methadone is individualised based on assessment of severity of dependence and level of tolerance to opioids. Indicators for tolerance include history of opioid use (quantity, frequency and route of administration), and withdrawal symptoms, which should be supported by consistency of examination and investigation findings and collateral history, particularly if longitudinal. These indicators cannot predict tolerance with certainty[30]. Where there is doubt about the degree of dependence, a review with withdrawal symptoms may assist decision making about a safe starting dose.

When deciding on the initial dose, consider:

- time since last opioid use
- where administration of the medication is to occur
- availability of staff and facilities to observe and assess the patient before and after administration for signs of withdrawal/intoxication
- use of benzodiazepines, alcohol or other sedating agents (risk of overdose increases markedly when other central nervous system (CNS) depressants are also used).

The starting daily dose of methadone should be low. Usually **20 mg / 4 mL or less** is sufficient to modify withdrawal significantly, even for patients with severe opioid dependence. Occasionally higher doses may be justified however the **maximum starting daily dose should very rarely exceed 30 mg / 6 mL**.

This maximum dose should only be prescribed when there is substantial clinical evidence of a significant opioid dependence and unequivocal signs of more severe withdrawal. The dose should be reconsidered if signs of intoxication with opioids or other drugs such as benzodiazepines or alcohol. The following table should guide prescribers in determining the initial dose of methadone:

Table 11 Initial methadone doses

Situation	Initial daily dose
In general, start low. The dose can always be increased. Prescribe a lower dose for people with low or uncertain levels of opioid dependence, higher risk poly-substance use, or with severe other medical conditions[12].	5–20 mg / 1–4 mL methadone
Using opioids regularly for more than six months and in the past two weeks using twice a day or more and obvious needle track marks.	20–25 mg / 4–5 mL methadone
On methadone previously, long history of opioid dependence and using large amounts of opioids now.	25–30 mg / 5–6 mL methadone

Comparative strength opioid tables typically exclude methadone since calculating an equivalent dose of methadone is generally not possible. If not excluded, such tables should not be relied upon. It is also not possible to be certain of the accuracy of the patient's report.

The patient should be seen immediately before the initial dose of methadone to ensure that they are not intoxicated, and it is safe to administer methadone.

Supplementary dose

Upon review by the service provider, a supplementary dose can be considered for patients in severe withdrawal 4-6 hours after the induction dose[6]. This ensures safe titration of an initial daily dose for the patient, subject to the recommended maximum first day dose of 30 mg / 6 mL.

3.2.2 Transfer to methadone from other pharmacotherapies

Transferring to methadone from BPN

BPN to methadone transfer should be considered in the case of:

- intolerable side-effects from BPN
- inadequate response to BPN treatment
- transfer/travel to a setting where BPN is not available (e.g., overseas).

Methadone can be commenced 24 hours after the last dose of BPN. The initial methadone dose should not exceed 30 mg / 6 mL and patients transferring from lower doses of BPN (4mg or less) should be commenced on 20 mg / 4 mL or less of methadone. Care should be taken not to increase the dose of methadone too quickly.

Transferring to methadone from naltrexone

Where a patient on naltrexone is seeking ODT, it is recommended to consult with a medical addiction specialist due to low opioid tolerance and the increased risk of opioid overdose. Induction with low doses of methadone are likely to be required.

3.3 Maintenance

During stabilisation, dose increases should not exceed 5 mg/1 mL on any day except in extraordinary

circumstances. The daily dose should not exceed 40 mg / 8 mL in the first week (seven days) and should not increase by more than 20 mg / 4 mL in any single week. This is to prevent a dose that significantly overshoots the patient's opioid tolerance, with the risks of over-sedation and even death.

Methadone doses in the range 60-100 mg / 12-20 mL daily are usually required to achieve stabilisation and are appropriate for maintenance doses[6, 31]. A small proportion of patients may require higher doses (e.g., up to 150 mg / 30 mL daily) or lower (e.g., 30-40 mg / 6-8 mL daily) doses to achieve their treatment goals. Methadone in doses of 60 mg / 12 mL daily or greater is more effective than lower doses for retention in treatment, reduction in non-prescribed opioid use and associated higher risk behaviours[6, 32].

3.3.1 Dose in excess of methadone 100 mg / day

A standard upper dose limit for methadone maintenance is 100 mg / 20 mL daily. Doses of greater than 100 mg / 20 mL daily are generally associated with little additional benefit and may be associated with dose-related adverse events[12]. Caution is advised if considering a dose increase beyond this. A second opinion or consultation with a medical addiction specialist is appropriate. Within Queensland Health AOD services an ad hoc care review is appropriate. Electrocardiogram (ECG) monitoring is recommended at doses equal to or greater than 150 mg / 30 mL and could be considered at doses above 100 mg / 20 mL due to the risk of QT prolongation. When monitoring QT, the nomogram in Appendix 14.1.3 is the preferred method rather than QTc.

3.3.2 Dose adjustments

Dose changes should be considered only after the prescriber or delegate has reviewed the patient. Adjust doses 5-10 mg / 1–2 mL at a time, with at least three days between each dose adjustment.

Dose reductions should be made in consultation with the patient, unless due to safety concerns, such as the patient presenting intoxicated or sedated, when the methadone dose may be decreased or withheld.

3.3.3 Split doses

Sometimes patients may benefit from split doses of methadone within one day, for example:

- for effective management of persistent pain, typically administering medication every 8-12 hours (see Section 4.6)
- because of rapid metabolism of methadone due to genetic variation or interaction with medications that induce CYP enzymes
- in pregnancy, due to increased metabolism[6] (see Section 4.1).

For patients with rapid metabolism, there may be a role for therapeutic monitoring of methadone plasma levels. Consultation with a medical addiction specialist[12] is advised in this situation.

3.4 Administration

Diversion of supervised administration can be minimised when the following procedures are followed:

- administer medication to one patient at a time

- do not allow other people in the medication administration area while medication is being administered
- ask the patient to remove anything from their mouth prior to medication administration (e.g. chewing gum)
- observe the patient throughout the administration process, especially when the medication is placed in the mouth and immediately after
- once the medication is placed in the mouth ensure that the patient's hands are kept away from their mouth
- ensure the patient throws away (into a designated bin) or hands back any items used.

Conical measures are not accurate for measuring methadone. Syringes or cylindrical measures are recommended. Pumps and syringe units are available from wholesalers to ensure accurate measuring.

- use an individual disposable cup for each patient
- the medication should be presented to the patient undiluted. The patient may dilute with water themselves if desired
- do not pour methadone into another drink container
- view and inspect the mouth cavity after the patient reports that the medication has been swallowed
- offer the patient a drink of water after taking the medication

3.5 Disruptions in treatment

3.5.1 Missed doses

Missed 1 or 2 consecutive daily doses

The normal treatment schedule can be resumed if there are no concerns regarding intoxication or other issues. Review by the prescriber (or delegate) may be required if any concerns prior to resumption of medication.

Missed 3 consecutive daily doses

The prescriber (or delegate) should review the patient prior to administering medication. If there are no specific concerns, the regular dose can be resumed[6].

Missed 4-5 consecutive doses

Recommencing methadone after four or more consecutive missed doses poses a risk of overdose due to reduced opioid tolerance, particularly if other sedative drugs are used. The prescriber should review the patient prior to administering medication.

The initial prescribed dose should be equivalent to the lower dose of either half the regular daily methadone dose or 40 mg / 8 mL. Patients should be monitored on subsequent days, aiming to return to the regular dose within 5 to 7 days, usually in increments of up to 20 mg / 4 mL per day[6]. More rapid titration than at induction can occur given the prescriber's knowledge of the patient's opioid tolerance.

Missed 6 or more consecutive doses

The prescriber should reconsider the current medication choice and if methadone is being reinitiated

treat the patient as a new induction when reinstating the patient back onto a stable dose.

Regular missed doses

Poor attendance at medication appointments should lead to consideration of reasons and targeted strategies to enhance adherence such as changes in medication or regimen[12].

3.5.2 Vomited doses

Vomiting more than 10 minutes after ingestion should not prevent adequate absorption[12]. Vomiting less than 10 minutes after ingestion creates uncertainty about the amount absorbed and should lead to a prescriber review[12]. No extra methadone is to be given without prescriber review, ideally three to four hours after ingestion when plasma levels peak. If there is good evidence of opioid withdrawal at this time, a supplementary dose of half the usual dose (up to a maximum of 40 mg / 8 mL) may be considered, however caution is required.

Pregnant women and vomited doses

Extra care is required with pregnant patients as withdrawal symptoms can cause foetal distress. A medical review is required. If it is not possible to review the patient three to four hours after the medication has been administered, and vomiting was observed within ten minutes after ingestion, the prescriber may consider a supplementary dose of half the patient's usual dose, up to a maximum of 40 mg / 8 mL.

Patients with recurrent vomiting of doses

Patients who repeatedly vomit should be reviewed by their prescriber. Strategies to consider include:

- having a light meal or drink 10 minutes prior to administering the medication
- reconsideration of medication and formulation
- consuming the medication slowly
- an anti-emetic (e.g., metoclopramide 10 mg oral or IM) at least 30 minutes prior to administering the medication[12].

3.6 Responding to Overdose

As part of an overdose plan, an effective brief intervention is to provide the patient with access to NX, and education about its use. See Section 1.2.3 for further information.

Methadone related overdoses typically occur during the first 1–2 weeks of methadone treatment. Deaths commonly occur at home during sleep, many hours after blood methadone concentrations have peaked. Most overdose deaths involve other sedating drugs, particularly CNS depressants such as alcohol or benzodiazepines, and/or other psychotropic medications[12]. For information about recognising opioid overdose, please see the below resources.

- Insight - Toolkits - Take Home Naloxone
- Pharmaceutical Opioids - Adis
- Opioids - Alcohol and Drug Foundation

The long half-life of methadone means methadone overdose can be deceptive. Patients who may have

taken a methadone overdose require prolonged observation. Patients and their relatives should be warned that deep snoring during induction to methadone treatment may be a sign of dangerous respiratory depression, and relatives should be encouraged to seek urgent medical attention. Heavy snoring during maintenance treatment may be associated with sleep apnoea and should also be reported[15].

A single dose of NX acts for less than an hour so that patients can then lapse back into a coma due to the long-lasting effects of methadone[15]. Hospitalisation is usually required for at least 24 hours. Patients may require NX and mechanical ventilation. NX should be given as a continuous infusion for 48 hours when treating methadone overdose[12].

3.6.1 Incorrect administration

A patient who receives a methadone dose above that prescribed is at risk of overdose. Patients in the first two weeks of induction who receive an excess dose require observation for four hours, when the effects of peak serum levels are apparent. If signs of intoxication develop, more prolonged observation is required, which may require ED assessment[3].

Patients who have been on a dose of methadone >40 mg / 8 mL per day consistently for two months generally tolerate double their usual dose without significant symptoms. For an overdose greater than double the usual daily dose, the patient will require observation for at least four hours. If signs of intoxication are observed, prolonged observation must be maintained[6].

If a patient's level of tolerance is uncertain (e.g., dose < 40 mg / 8 mL per day or in treatment <2 months), they should be observed for at least four hours if given a dose greater than 50% higher than their usual dose[6].

The critical issues that determine how clinicians should respond to an accidental overdose are the patient's level of tolerance and the amount of methadone given in error.

The appropriate course of action, therefore, will depend on these variables.

Methadone excess dose

The dispensing staff should:

- Advise the patient of the excess dose. Carefully explain the consequences and warn against any additional drug use, and against driving or operating machinery.
- Notify the prescriber. If they cannot be contacted, consider consulting a medical addiction specialist.
- Inform the patient about signs and symptoms of overdose and advise the patient to go to an ED should any symptoms develop.
- If possible, a contact person nominated by the patient should be informed and advised of the event.
- Document the overdose event[6].

Methadone excess dose greater than 50 per cent of the normal dose

The dispensing staff should:

- Contact the prescriber immediately for consultation. If they cannot be contacted, a medical addiction specialist should be consulted.

- Inducing emesis is contraindicated, particularly if the patient has respiratory depression, an obstructed airway, is drowsy, or has other signs of symptoms of CNS depression. If there is concern about the amount of methadone consumed, it is best to be cautious and have the patient present to an ED without delay.

Emesis after the first 10 minutes does not prevent a methadone overdose.

If the prescriber decides that the patient should be assessed at the ED, this should be explained to the patient along with the need to attend ED. The situation should be explained to the triage nurse. If a patient refuses to present to the ED – despite being advised of the potential lethality of the dose consumed – try to ensure they understand the concerns of the prescriber and remain with another responsible adult over the next six hours. Give the patient information regarding methadone overdose and urge them to seek medical attention if symptoms of overdose appear. Importantly, warn the patient against any additional drug use, and against driving or operating machinery. Ensure the patient has access to, or is provided with, THN (see Section 1.2.3).

If the patient leaves before the mistake is realised, the prescriber and, in clinic settings, the senior registered nurse should be informed. Depending on the advice of the prescriber, all efforts must be made to contact the patient or anybody who may know their whereabouts. In attempting to locate a patient, confidentiality should be appropriately considered. If the patient cannot be contacted, the prescriber should consider contacting the Queensland Police Service (QPS) for a welfare check.

The prescriber should review the patient before the next dose of methadone.

3.7 Dose reduction

Most patients tolerate methadone dose reductions of 5–10% every 1 to 4 weeks (i.e., 5–10 mg / 1-2 mL reductions for doses >50 mg / 10 mL, 2.5–5 mg / 0.5-1 mL reductions for doses <50 mg / 10 mL). The rate of reduction may vary according to patient progress, planned time frame and the stability of the patient[12].

Some patients may reach a dose (often between 20-60 mg / 4-12 mL) where further dose reductions are not practicable e.g., due to intolerable withdrawal discomfort, increased use of other drugs, or deterioration in general health and wellbeing. Options include re-stabilising on a higher methadone dose or transfer to BPN, which may enable an easier withdrawal process[12].

4. Special populations and settings

When providing ODT service providers should consider the possible range of related matters for patients that could include health conditions (e.g. cognitive impairment, severe mental illness, poor mobility), social circumstances (e.g. child protection concerns, domestic and family violence, homelessness, poor literacy, social isolation, geographical remoteness) and different demographic and cultural backgrounds (e.g. Aboriginal and Torres Strait Islander peoples, people from culturally and linguistically diverse communities, women, people who identify as LGBTIQA+, people involved in the criminal justice system

including being incarcerated, older people). ODT should be trauma-informed, culturally safe and age and developmentally appropriate.

Where appropriate peer workers or advocate services should also be engaged to provide support where available and possible. Service providers and patients should collaboratively implement strategies that aim to enhance attendance for administering medication and clinical reviews and consider active follow-up strategies for patients who do not or are unable to attend for scheduled appointments.

4.1 Pregnancy

Effective opioid treatment during pregnancy is imperative to ensure positive outcomes for mother and baby. Untreated opioid dependence during pregnancy poses a particularly high risk of complications, due to a variety of possible factors, including:

- infrequent and inconsistent antenatal care
- repeated cycles of opioid intoxication and withdrawal with resultant significant risks to the foetus
- biological issues such as inadequate nutrition, BBV exposure and overdose
- psychological issues such as anxiety, depression, post-traumatic stress disorder
- social problems including domestic and family violence, financial, accommodation, relationship and legal problems, and exposure to criminality
- other substance use, including alcohol and tobacco[6, 33-36].

A range of obstetric complications may include:

- premature labour
- intrauterine growth restriction and low birth weight
- miscarriage
- intrauterine infection
- antepartum and postpartum haemorrhage
- intrauterine hypoxia or anoxia
- pre-eclampsia[36].

Neonatal complications may include Neonatal Opioid Withdrawal Syndrome (NOWS) and Sudden Infant Death Syndrome (SIDS).

The aims of treatment for pregnant women with opioid dependence are the same as for all pregnant women, specifically to minimise the likelihood of complications, and provide antenatal and postnatal care. Engagement in antenatal care improves outcomes for mother and infant, including women with continued substance use[37, 38].

It is important to support the pregnant woman with early referral for antenatal care, including specialist alcohol and drug antenatal services where available[7]. While referral is usually to local antenatal services, QOTP prescribers can contact CHAMP Clinic or Athena Clinic for telephone advice/consultation for any alcohol and drug antenatal issues.

Athena Clinic
(Alcohol and Drug Ante-natal care)
Athena Clinic Coordinator
Maternity Outpatients
Royal Brisbane and Women's Hospital
Butterfield Street, Herston Qld 4029
Phone: 07 3647 3957
Athena Clinic available each Monday
If Athena Clinic unavailable, contact:
Nurse Unit Manager, Maternity Outpatients
RBWH
Phone: 07 3647 3962 (Business hours)

CHAMP Clinic
(Alcohol and Drug Ante-natal care)
CHAMP Coordinator
Mater Mother's Hospital
Raymond Terrace, South Brisbane, Qld 4101
Phone: 07 3163 2417
Email: champ@mater.org.au

Antenatal and postnatal care should be managed in collaboration with a specialist obstetric service experienced in managing substance dependence during pregnancy.

4.1.1 Initial assessment

Most women are of child-bearing age when assessed for opioid dependence. It is therefore good practice to conduct a pregnancy test, to assist with treatment planning and medication choices. Assessment should also include, where applicable:

- plans about becoming pregnant and contraception
- plans regarding current pregnancy
- discussion about the effect of treatment on pregnancy and birth
- discussion about breastfeeding.

Assessment of opioid dependence during pregnancy

For pregnant women with a diagnosis of opioid dependence, ODT is the recommended treatment[39, 40] due to its capacity to:

- enhance access to antenatal care with improved health outcomes
- reduce illicit opioid and other drug use, and improve the health of pregnant women
- reduce maternal and infant deaths associated with opioid use
- reduce the spread of BBV communicable diseases associated with injecting drug use
- facilitate the improvement in social functioning of the mother[6].

Short term, low dose and less frequent use of opioids are less likely to be associated with dependence. Where there is uncertainty about the diagnosis of opioid dependence in a pregnant patient, careful assessment of the risks associated with continued drug use need to be considered, along with the risks involved with treatment with a dependence-forming opioid.

Pregnant women should be prioritised for ODT, along with their partner if opioid dependent, to help reduce non-prescribed opioid use[38]. Early stabilisation of ODT medication is paramount. Prescriber review should occur on a frequent and regular basis, particularly as the pregnancy progresses.

Other substances – in particular alcohol[41, 42], as well as nicotine[41], cannabis, benzodiazepines, amphetamines and cocaine - pose potential risks to pregnant women and their babies. Interventions to

reduce/cease substance use are a high priority, and targeted strategies may include counselling, relapse prevention and pharmacotherapy[43, 44].

Other prescribed medication

Opioid-dependent pregnant women may be prescribed additional medication such as anti-depressants. The risks to mother and foetus of untreated moderate to severe maternal major depression often outweigh the risks associated with antidepressants in pregnancy (information arising from low to moderate quality studies). However, concern remains about possible teratogenic effects and postnatal behavioural disorders as part of neonate withdrawals. Risks and benefits need to be weighed carefully and collaboratively in relation to specific medications and overall clinical situation. Specialist advice, including from perinatal mental health services, can be sought in relation to medications and treatment. Maintaining the mother's health during pregnancy will in turn promote the health of the unborn baby[45].

Consideration should also be given to analgesia options during labour. It is recommended that a medical addiction specialist is consulted to assist with planning for birth.

4.1.2 Opioid withdrawal management in pregnancy

Opioid withdrawal should be avoided during the first trimester due to risk of miscarriage and in the third trimester due to risk of foetal distress and premature labour. Any potential benefit from a planned withdrawal management program must also be balanced against the risk of relapse to uncontrolled substance use[12]. For a pregnant woman committed to participating in an opioid withdrawal program during pregnancy, obstetrics input is required[36, 46]. A structured attempt at withdrawal at some stage after pregnancy is preferred[12].

Overall, ODT is strongly recommended for opioid dependent women during pregnancy, with comprehensive obstetric care and psychosocial interventions[47].

Caution is advised in prescribing naltrexone to women who are pregnant or breastfeeding as naltrexone is classified as a B3 risk in pregnancy[48], and may precipitate withdrawal in the foetus. An exception to the avoidance of use of opioid antagonist medication in pregnancy is in case of opioid overdose, when the care of the pregnant woman will take precedence and NX may be indicated.

4.1.3 Medication selection

Sublingual BPN and methadone are both safe and effective treatments in pregnancy[39, 45, 49]. Before starting either medication, the patient's preference, prior experience in treatment, other drug use, risk behaviours and ability to access treatment should be considered[36, 49, 50]. BPN may have fewer drug interactions and has been associated with fewer maternal deaths attributable to overdose[50]. A Cochrane review reported that methadone and BPN were similar on treatment dropout and the number of newborns treated for NOWS, but that BPN may result in higher birthweight[51]. Other evidence points to some benefits of BPN over methadone with respect to reduced incidence of NOWS[52], lower risk of preterm birth, improved birth weight and increased head circumference[47, 52, 53]. However, the benefits of BPN do not outweigh the risk of transfer from methadone to BPN without sufficient clinical reason. BPN related precipitated withdrawal and the risk this may pose to the foetus are considerations, particularly during the induction/stabilisation period.

Since the absorption of NX is minimal when administered sublingually, pregnant and breastfeeding women may remain on BPN/NX[54] if stabilised on treatment prior to their pregnancy.

Pregnant women may choose to continue treatment with Buvidal® Weekly, Buvidal® Monthly or

Sublocade® during pregnancy and breastfeeding if the benefits outweigh the risks to them and their baby.

If continuation of LAI BPN is planned, the following points should be considered with the woman and documented:

- The safety of LAI BPN during pregnancy and breastfeeding is not yet established.
- The individual risks and benefits and rationale for their decision to continue LAI BPN.

Dose considerations

Physiological changes in later pregnancy (e.g., expanded plasma volume; an increase in plasma proteins which bind methadone; and placental metabolism of methadone) may reduce the bioavailability of methadone, making treatment at a given dose potentially less effective. These pharmacokinetic changes may necessitate significant dose increases to manage withdrawal symptoms, particularly in the second and third trimesters[45, 55, 56].

A proportion of patients on BPN will experience withdrawal symptoms when BPN is administered less frequently (e.g. double doses), therefore patients should be administered daily medication during pregnancy[45]. If a patient is on LAI BPN and experiences withdrawal symptoms, they may need an increased dose or supplemental Buvidal® Weekly 8 mg with continued monitoring. Alternatively, consider SL BPN supplementation and a daily SL BPN medication regimen. If increased dose or SL BPN supplementation is ineffective in managing withdrawal, LAI BPN should then be ceased, and the patient continue SL BPN until after the baby is delivered.

Pregnant women on SL BPN should receive medication daily.

Methadone treatment during pregnancy

Split doses

The half-life of methadone can decrease to as low as 8 hours in pregnant women, so split doses are occasionally considered as a treatment option[56]. Split doses can result in more sustained plasma levels, and therefore reduced withdrawal symptoms, cravings and risk of substance use in a pregnant patient[50]. In relation to the foetus, split doses may normalise foetal behaviour, (such as heart rate and motor activity), compared to single daily medication administration with its greater peak effects[56]. Stability of the patient needs to be carefully considered when assessing this option.

Medication dose reductions during pregnancy

Women should be maintained on BPN or methadone through pregnancy and beyond[6]; however, some pregnant women are determined to reduce and discontinue ODT. In this situation, any medication dose reductions should be undertaken only if the pregnancy is stable and only in the second trimester, which is considered the time of lowest risk for dose reductions[15]. It is recommended not to attempt to transfer from methadone to BPN during pregnancy because of the risk of precipitated withdrawal.

Methadone dose reductions of 5 mg / 1 mL per fortnight are likely to be safe for doses above 40 mg / 8 mL daily and reductions of 2.5 mg / 0.5 mL per fortnight are safe when the dose is 40 mg / 8 mL or less. Medication dose tapering should be flexible in collaboration with the patient. While it may be possible to undertake more frequent dose reductions, the severity of opioid withdrawal symptoms and the patient's capacity to cope must guide clinical decision-making[15]. Withdrawal symptoms should be avoided as far as possible as they may cause considerable distress to the foetus[45, 50].

If ODT dose reductions are planned, the second trimester is considered the least harmful period for an adverse obstetric event.

4.1.4 Review after giving birth

The ODT medication maintenance dose should be reviewed post-partum and regularly thereafter. The priority is to support and enhance the stability of the woman by ensuring her ODT medication dose is optimal, monitoring for:

- signs of withdrawal or intoxication
- risk of returning to or continued substance use.

For patients prescribed methadone, there is a risk of methadone toxicity immediately post-partum, particularly if the dose increased significantly during the third trimester. A suggested approach is to reduce methadone administration following birth to half the usual dose given mane, and then consideration of further doses administered four-hourly as required up to the previous maximum dose.

Effective liaison between relevant services including midwifery and obstetric, neonatal, child protection and AOD services is crucial in the postnatal period. Additional agencies might include Aboriginal and Torres Strait Islander Community Controlled Health Organisations or community mental health services.

4.1.5 Neonatal opioid withdrawal syndrome (NOWS)

Neonates born to women receiving ODT (or women regularly taking opioids during pregnancy) are at risk of developing NOWS from opioids[43]. NOWS may also be referred to in the literature as Neonatal Abstinence Syndrome (NAS) which is a broader syndrome which can occur from exposure to other substances. Queensland Health Maternity and Neonatal Clinical Guidelines include guidelines for NAS.

NOWS is a clinical diagnosis based on assessment of disturbances in the CNS, the gastrointestinal system and the respiratory system of opioid-exposed infants[37, 38]. All babies born to opioid-dependent mothers should be observed for developing signs of withdrawal, consistent with the guidelines[33, 34]. A validated scale may be used to assess the presence and severity of NOWS. Withdrawal symptoms can start from the first 24 hours following delivery, up to 10 days post-natal, depending on the substance or substances to which the baby was exposed in utero. Withdrawal from additional substances (for example benzodiazepines) may delay the onset of symptoms and prolong and complicate the withdrawal process[44, 45].

The incidence of NOWS may be less severe in neonates born to women stabilised on BPN rather than methadone[39, 57, 58]. There is minimal evidence of a relationship between maternal medication dose, with methadone or BPN, at delivery and the severity of NOWS[50, 59, 60]. Infants with NOWS should remain with their mother where possible. Refer to Queensland Maternity and Neonatal Clinical Guideline: Perinatal substance use: neonatal.

4.1.6 Breastfeeding while on methadone or buprenorphine

Breastfeeding promotes mother-child bonding and may decrease NOWS severity[44, 61]. There are no significant differences between opioid-dependent mothers treated with BPN or methadone and safety in breastfeeding. Concentrations of BPN and methadone in breast milk are low and remain stable over time[6, 35].

Women who are stable on BPN or methadone should be encouraged to breastfeed. The benefits of breastfeeding greatly outweigh potential harms of low concentrations of BPN or methadone present in breast milk[62].

Patients who use opioids in a 'one-off' pattern, should be advised against using substances when breastfeeding. If they choose to use opioids or other substances, they should be advised to express and discard breast milk for a 24-hour period afterwards, then return to breastfeeding. They should also be encouraged to have a 'safety plan' in place for the infant on occasions they use opioids[12].

Women who are unstable on ODT, continuing to use non-prescribed opioids, or use multiple substances, should be discouraged from breastfeeding, and support provided to help them stabilise their patterns of use[12].

The delay between delivery and appearance of NOWS reflects similar concentrations of BPN or methadone in the mother and neonate at birth, following which levels then gradually decline in the neonate. It is unclear if the effect of breastfeeding on NOWS is due to the beneficial effects of breastfeeding itself or because of the low concentrations of BPN or methadone present in breast milk mitigating withdrawal[62, 63].

4.1.7 Child Safety considerations

Some women may be reluctant to present for help with substance use during pregnancy due to stigma and concern regarding the involvement of child protection services. Similarly, those on ODT may be reluctant to advise other health practitioners about their pregnancy. Patients should be counselled about the importance of a partnership approach between the GP, the ODT prescriber where not the GP, obstetric and other service providers involved in the care of their pregnancy[38]. Women on ODT are more likely to retain custody of their infant when discharged from hospital compared with women who have opioid dependence but are not receiving treatment[37].

4.2 Patients under 18 years of age

If treating a patient under 18 years of age, the emphasis should be on culturally safe, age and developmentally appropriate psychosocial responses, harm reduction and family intervention approaches. If ODT is being considered caution is advised, and consultation with a medical addiction specialist or another practitioner with appropriate skills and experience, such as a child and adolescent psychiatrist or paediatrician, is recommended. The importance of this consultation increases the younger the patient is.

Pharmacotherapy should only be used:

- following careful assessment of the risks and benefits
- in the context of a comprehensive care plan embracing various psychosocial approaches
- after consideration of the patient's ability to consent to ODT.

If commencing ODT, BPN is preferable to methadone. Depending on their drug use history and social circumstances, adolescents may stabilise quickly enabling cessation of pharmacotherapy to be considered sooner than would be the case with adults[12].

4.3 Ageing patients

In 2015, 22% of patients receiving ODT in Australia were aged 50 years or over as compared to 8% in 2006[64]. This increase in ageing patients is predicted to continue.

In older patients, trauma and other factors accumulated from multi-morbidities including other substance use increase the likelihood of associated problems. Long-term use of high doses of opioids adversely impacts on the usual ageing process with osteoporosis and sex hormone deficiencies (particularly androgens in men), reduced cognition from repeated hypoxia, risk of falls, changes in pharmacokinetics and polypharmacy[12, 65] all more likely in this population. Care should address these multiple issues[12]. If any evidence of cognitive decline, consideration should be given to screening (e.g., with the Montreal Cognitive Assessment).

Older adults are likely to metabolise drugs at a slower rate, making lower opioid doses and slower dose titration of methadone advisable. Larger doses of methadone (>100 mg/day) may pose greater risks which should be reviewed with the patient[12].

Continued access to ODT can become problematic with reduced mobility, early onset cognitive impairment, and social isolation[65]. Ongoing communication between the prescriber, patient, family/carers and other health services involved in care is essential. Some patients require carer support to remain at home or may transition to a nursing home setting[66]. Appropriate management options should be identified. If patients are transitioning to a nursing home, careful consideration of continuing treatment needs and appropriate handover should occur, including any education necessary for nursing home staff, with involvement of the ODT prescriber and any other appropriate specialists.

4.4 Palliative care

When medical treatment transitions into palliative care for a patient receiving ODT, collaboration between the ODT prescriber, the palliative care team and other healthcare providers is essential. Treatment planning requires a flexible approach. ODT dose increases can assist with pain management, and flexible medication regimens can support quality of life for the patient.

Management will vary depending on the palliative care setting, and the patient's medical and social issues. Ongoing communication between all parties involved in care may assist in determining the right time for possible treatment options such as:

- authorisation of an agent to collect medication intended for self-administration
- where the GP is not the current prescriber, transferring ODT prescribing to the GP or palliative care. Substitution of ODT medication with other opioid medication may be considered.

4.5 Rural and remote

Access to QOTP service providers and pharmacies in rural and remote areas is often limited.[67, 68] Local AOD services or Adis (see Appendix 17) can advise about access to ODT. Strategies to manage access and capacity for ODT in regional areas vary but may include:

- GPs completing training to become QOTP prescribers, either *full*, BPN/NX + LAI BPN or *shared care*.
- reviews by prescriber conducted via videoconference or teleconference with a nurse present to assess the patient, with telemedicine an effective ODT review delivery mode[69, 70]

- transfer of patients to their GP for management of ODT under a shared care arrangement
- access to second opinion for QOTP prescribers is available from ADCAS (see Appendix 17)
- access to THN (via Adis or registered sites for Take Home Naloxone)
- ensuring care occurs in partnership with Aboriginal and Torres Strait Islander Community-Controlled Health Organisations for Aboriginal and Torres Strait Islander people who require ODT.

4.6 Persistent pain

Approximately 20% of the Australian population have persistent pain, with projections this will increase as the population ages[71-73]. It is commonly defined as non-cancer pain experienced daily for a minimum of three months[72, 74], with most patients rating their pain as mild to moderate in intensity[75].

Despite evidence about the limited benefit of opioids in treatment of persistent pain, supply of pharmaceutical opioids in this population has increased substantially in recent years[71, 76]. In Australia, the Defined Daily Dose (DDD) per 1,000 population/day of oxycodone dispensed in 2002 was 0.769, increasing to 2.157 in 2009, and 3.0 in 2016. Fentanyl increased from DDD of 0.212 to 0.9 over the same period[77, 78]. Morphine showed a consistent reduction from 1.801 to 0.7 DDD in that time. While the total supply of opioid medications increased forty-fold between 1990 and 2006[62, 73] (in Oral Morphine Equivalents (OME) per 1000 population), this appeared to stabilise over the period of 2012-13 to 2016-17[78].

Along with increased prescribing, there is growing evidence that long term opioid therapy may be associated with harms including opioid-induced hyperalgesia, opioid misuse, dependence, diversion and opioid toxicity, particularly with high dose opioid treatment (>100 mg OME)[79-82]. The risk of serious harms is dose dependent[79]. 10-25% of long term therapeutic opioid patients develop opioid use disorder, however its prevalence varies significantly[71, 83, 84]. In growing recognition of this harm and consideration of risk versus benefit for opioid use, the therapeutic ceiling OME dose has been reduced to 50-100mg per day.

Around 60% of patients being treated with methadone, and at least 33% of patients on BPN or BPN/NX, have persistent pain[80, 85-88]. While for many with persistent pain a ‘cure’ is not an appropriate treatment goal, a reduction in pain and improved function can be achieved with active self-management[72, 89].

Therapeutic opioid dependence may develop in the context of opioid treatment of a painful (non-malignant) medical condition, but poses diagnostic and management challenges[6]. Features consistent with diminished control over opioid use (e.g., multiple dose escalations, non-prescribed routes of administration, use for reasons other than pain, difficulties reducing opioid use) should be explored[6].

Comprehensive assessment and diagnostic review is necessary to decide on further opioid and pain management[7]. Comprehensive assessment should include collateral information from other current treating practitioners. Where appropriate, it should include multidisciplinary review, involving pain and medical addiction specialists.

Where opioid dependence occurs with treatment of persistent pain, the treating practitioner and patient should review their treatment plan, negotiating realistic goals, which may include cessation of opioids or review of the maintenance dose of opioid medication, which may be the most realistic option for patients on high dose opioids over extended periods.

Advice that the maximum dose not be increased, that lost or stolen doses should not be replaced, and staged dispensing may need to be implemented, may be warranted. Patients not adherent to the

treatment regimen, and whose predominant problem is judged to be opioid dependence, will generally need to be transferred to ODT, if appropriate under the shared care of the current treating practitioner. Multi-disciplinary team involvement is advised where non-pharmacological and psychosocial strategies can be incorporated. Short acting parenteral opioids are not appropriate for persistent pain management.

4.6.1 Persistent pain management in patients receiving ODT

A comprehensive initial assessment should consider history relating to pain including collateral information and prior assessment and treatment where possible. The priority in the initial treatment plan should be stabilising the patient's opioid dependence. The patient may be taking a higher or lower dose of opioids than prescribed[6]. Match induction dose to objective withdrawals, and then titrate to the point where no objective withdrawal signs are evident. It may then be timely to consider pain symptoms.

While prioritising management of opioid dependence, then considering pain, reassure the patient their ODT medication is a strong opioid which will provide analgesia while treating dependence. Once ODT medication is stabilised, pain is often effectively managed. For patients with continuing pain, it is important to assess the origin of the pain, distinguishing where possible between neuropathic and nociceptive pain. Interventions should be appropriately targeted.

Persistent pain should be managed with an emphasis on psychosocial and non-opioid pharmacological approaches. Non-pharmacological strategies can include patient education about healthy lifestyle modifications including a daily routine of structured activities incorporating sleep, nutrition, adequate exercise, social interaction, and rest. Patient education regarding the links between tobacco and pain may be indicated with discussion about tobacco cessation. Non-opioid pharmacological options might include simple analgesia and/or adjuvant medications, such as anticonvulsants and antidepressants prescribed according to clinical standards (e.g., these medications are not indicated for treatment of low back pain[90]) Benzodiazepines can exacerbate pain in the longer term and should only be considered for extremely short episodic use[91].

If the patient's GP is not the ODT prescriber, close collaboration with the GP is essential since they are assuming primary responsibility for coordinating and communicating often multiple, complex health care needs[7, 89], sometimes with input from other medical specialists involved in the care of the patient. Participation of a multi-disciplinary team may be indicated, including psychologist, physiotherapist and/or exercise physiologist, preferably experienced in pain management, under a Chronic Disease Management Plan[72].

When current ODT patients develop persistent pain, the same strategies apply. It is important to identify issues related to opioid dependence and those related to pain, and their overlap. ODT dose increase may be warranted, and for the very stable patient, split doses may be trialed. If another prescriber is seeking to prescribe another monitored medicine to a QOTP patient, they must develop a documented **joint prescribing plan** with the current QOTP prescriber. This is a requirement under the *Medicines and Poisons (Medicines) Regulation 2021* and a requirement for compliance with the *Monitored Medicines Standard*.

4.7 Patients with other co-occurring mental health disorders

Depression and anxiety, personality disorders and other substance use disorders are significantly more prevalent among people who use opioids than in the general population[78, 84]. The presence of a co-occurring other mental health disorder increases the complexity of treatment, and heightens the risks associated with each condition[21, 23]. Treating only one disorder in this situation can increase relapse for

both disorders. ODT is the recommended treatment for opioid dependence, and targeted care for psychiatric symptoms improves the patient's overall treatment outcomes[21, 92].

Clinicians should assess and manage co-occurring other mental health disorders[93]. Where a diagnostic assessment is unclear, particularly where psychotic features are present, psychiatric opinion should be considered. People with significant co-occurring disorders are likely to be best managed in settings with the capacity to manage multimorbidity.

See the Queensland Health Guideline *Co-occurring substance use disorders and other mental health disorders: policy position statement for Mental Health Alcohol and Other Drugs Services 2021* for further detail and guidance.

4.8 Intoxication

Patients presenting as intoxicated at the time of medication administration should be assessed to identify any safety concerns. There is little clinical indication to withhold a LAI due to a patient presenting intoxicated, in contrast to intoxicated presentations for SL BPN or methadone where peak medication effects are likely to occur while the patient is still intoxicated. Patients should however be assessed as having capacity to provide informed consent to their usual medication dose, and to understand warnings regarding risks of sedation and overdose from polysubstance use.

If the patient is very intoxicated and unable to understand or follow instructions, medication administration should be deferred and rescheduled.

4.9 Correctional settings

LAI BPN has many benefits as a treatment option in the correctional setting. In Queensland LAI BPN is the recommended medication as part of ODT delivered across correctional centres by Hospital and Health Services in partnership with Queensland Corrective Services under an agreed model of service. Diversion of SL BPN is a particular risk and is associated with interpersonal violence as well as injecting related injuries and diseases. The formulations intended for SC injection have less capacity for diversion.

Administration of SL BPN is time intensive to minimise risk of diversion, requiring considerable correctional officer and health staff resource. Monthly administration of LAI BPN allows increased time for other health interventions and increases the capacity of correctional ODT programs.

The period immediately following release from custody is a higher risk period, with 3-8 times risk of overdose death. It is often challenging for patients to attend appointments for ODT medication on the first day after release due to geographic, housing, social and financial reasons. A LAI preparation may provide greater stability over this period with less urgency for immediate attendance, assisting both the patient and community treatment providers.

People receiving ODT in Queensland correctional centres are commonly released into the community via courts without notice for health service providers. The longer duration of action of LAI BPN allows greater flexibility to arrange community treatment options, and effectively transfer care. Patients on LAI BPN leaving custody should be provided education about the persistent clinical effects of LAI BPN.

As LAI BPN may take several doses to reach steady state, transfer of care both on entry into custody and on release will require specific documentation of medication and doses given over a period of several months.

Provision of THN to people on release from custody and considered at risk of opioid overdose is part of routine care for ODT patients and others not engaged in ODT in the correctional centre.

4.10 Hospital admission

4.10.1 For patients receiving ODT

Many patients receiving ODT have brief hospital admissions which may interrupt ODT. This is less of a concern with LAI BPN treatment, but coordination between hospital staff and LAI BPN treatment providers is required.

BPN or methadone treatment should not be discontinued in hospital unless for specific clinical reasons. Discontinuation of ODT can result in significant opioid withdrawal, complicate analgesia and treatment of other disorders and contribute to non-prescribed drug use or behavioural disturbances. ODT should not be withheld, or withdrawal attempted, without the specific consent of the patient[12, 94].

On admitting the patient, the hospital treating team should:

- Identify the QOTP prescriber and pharmacy for the patient. If the patient is unable to provide this information, this information is to be found in QScript. QOTP dispensing records in QScript provide only an *indication* of the amount of medicine the patient has been (or will be) dispensed – see Appendix 1.2 for further information.
- Contact the patient's prescriber/clinic to confirm current ODT medication and dose, medication orders, and obtain relevant clinical information
- Contact the community pharmacist to verify the date and time of last dose, details of any medication given for self-administration, and to ensure dispensing ceases while the patient is in hospital.
- Administer ODT medication according to their usual treatment regimen or modify consistent with the current clinical situation[12].

If contact cannot be made with the patient's QOTP prescriber or community pharmacist, a medical addiction specialist should be consulted.

4.10.2 Self-administered medication while in hospital

If a patient possesses ODT medication intended for self-administration when admitted to hospital, they should be asked to provide the medication to the ward staff to ensure clarity and certainty of dose and to ensure that storage of the medication is compliant with relevant legislation (see Appendix 1.1). The ODT medication can then be dispensed from the hospital pharmacy. If a patient declines to provide their ODT medication to ward staff, the rationale for this should be understood by staff and documented in the clinical record. Such situations should be appropriately assessed and managed within the clinical setting, with monitoring for intoxication or withdrawal. The patient should not be administered hospital stock opioids for those dates.

If a patient is admitted unexpectedly to hospital and does not have already supplied ODT medication, the treating team should consult the prescriber/clinic and be guided by their advice. A medical addiction specialist should be consulted if needed.

4.10.3 Treatment of an opioid-dependent patient not receiving ODT

Opioid dependent patients who are not receiving ODT may experience withdrawal during a hospital admission, which in turn can complicate analgesia and other medical or mental health conditions[95, 96]. Patients may leave hospital against advice due to withdrawal[96] or may use substances that can complicate assessment and treatment[96]. Adequate treatment of opioid dependence is likely to enhance engagement, assist in treatment of the primary disorder leading to hospitalisation and simplify patient management[12].

The treating team should complete a substance use screening prior to initiating any treatment, discuss options with the patient, and obtain informed consent prior to embarking upon a particular treatment. Local AOD services should be able to assist with assessment and care planning[12].

Initiating and continuing ODT should be recommended[12, 97]. If a patient chooses to initiate ODT with a plan to continue on discharge from hospital[96, 98], prior to commencing, a community prescriber should be organised to continue care after hospital discharge[12].

If ODT is not appropriate or possible or a patient chooses not to initiate ODT, there are alternative short-term treatments for opioid withdrawal, which may or may not occur depending on necessary analgesia[99]:

- Induction on SL BPN[98] with a planned rapid titrated reduction prior to discharge to the community. Patients may experience withdrawal during the reduction, so consideration should be given to how this will be managed.
- Symptomatic treatment with medication. Where the patient does not consent, symptomatic withdrawal medications can be used (refer to the Queensland Alcohol and Other Drug Withdrawal Guidelines).

Local AOD service providers can assist with inquiries regarding initiation and stabilisation of ODT. If local AOD providers or medical addiction specialist are not accessible locally, ADCAS can provide advice and support – see Appendix 17. Relapse to opioid or other substance use on return to the community is very likely without ODT and where possible the patient should be engaged in planning for such relapse, including provision of THN.

4.10.4 Coordination of care

The key principle is coordinated communication between prescribers and pharmacists, both in the community or in hospital or other settings (such as correctional centres), to avoid any disruptions in continuity of ODT. Appropriate documentation should support effective communication at transfers of care[100].

Hospital staff responsibilities:
The treating team prescribes inpatient ODT medication. Transfer of care should be coordinated to ensure safe and effective ODT and continuity at time of discharge, usually involving treating medical practitioners and clinical pharmacists. Usual transfer of care documentation should be provided. The focus should be on continuing ODT without interruption appropriate to the clinical situation[100].

Community prescriber responsibilities:
When a prescriber (or delegate) is informed about a patient's admission or discharge, they should ensure effective communication with the community pharmacy to ensure appropriate ODT availability.

Community pharmacist responsibilities:
The community pharmacist should ensure effective communication regarding the patient's ODT and should advise the prescriber/clinic as soon as possible regarding such contact from hospital staff[100].

4.11 Acute pain management

When managing acute pain in patients receiving ODT medication, it is important not to assume that the maintenance dose of opioid agonist treatment will effectively manage the pain.

Strategies for management of acute pain can be broadly divided into the following categories:

- non-pharmacological
- manage cause/precipitant of pain (e.g., immobilise fractured limb)
- simple analgesics (e.g., paracetamol, ibuprofen)
- opioid analgesics
- adjuvants (e.g., antidepressants, gabapentinoids)
- nerve blocks (e.g., local or regional blocks, epidural).

Generally, acute pain management strategies should start with the first category and work downwards. It is also important to identify if specific treatments are contraindicated (e.g., opioids should be avoided for headache[101]).

The Australian Faculty of Pain Medicine provides current evidence-based Acute Pain guidelines to assist practitioners.

Exploration of patient fears and explanation about their condition, and the likely progress and outcome, are important. ODT medications are potent analgesics, but have shorter analgesic inter-dosing intervals (i.e., the analgesic effects of methadone and BPN each lasts 8–12 hours). Consider splitting the ODT medication dose, increasing ODT medication dose, or adding an opioid analgesic to the ODT medication.

In all situations, communication about analgesic plans and projected duration of pain and medications between hospital treating teams, community ODT prescribers, and GPs if not the ODT prescriber, is critical. For elective procedures consider pre-anaesthetic assessment which should include consideration of post procedure pain management. For patients on BPN who have planned surgical procedures expected to have moderate to severe pain for more extended periods, a plan should be developed in advance between relevant practitioners including anaesthetist, surgeon and ODT prescriber. Input from a pain management or medical addiction specialist should be sought as needed.

4.11.1 Methadone and acute pain

In general, the current methadone dose should be continued. If acceptable to the patient, it can be divided into 2 or 3 doses across the day, which may improve analgesic effects. Where patients cannot tolerate oral intake, methadone can be administered parenterally. The suggested oral to IV conversion ratio is 2:1 initially, with dose escalation up to 1:1 required by some patients. When converting from IV to oral route a ratio of 1:1 is advised, with titration up to 1:2 where indicated[102, 103]. For methadone pharmacokinetics refer to appendix 13.

Patients on methadone requiring additional opioid analgesic typically require larger doses than opioid naïve people. Despite this, the initial dose of analgesia should be the usual recommended starting dose, with titration to the level needed to achieve effective analgesia. The route of administration should be the same as normal for their particular medical condition[104, 105]. Patient-controlled analgesia is an acceptable

mode of opioid delivery acutely. If analgesia is not achieved, consult practitioners with acute pain management expertise and/or a medical addiction specialist as needed.

Effective analgesia may sometimes be achieved with a short-term increase in the methadone dose. This is recommended for patients with acute pain that would normally be treated with oral opioid analgesics.

4.11.2 Buprenorphine and acute pain

In general, the current BPN dose should be maintained. The strong affinity of BPN for mu opioid receptors and its partial agonist properties reduce the response of patients on BPN to opioid agonists. Patients on BPN with severe or acute pain will therefore require higher doses of opioid analgesia than individuals not on BPN[30, 105].

The optimal management of patients on BPN maintenance in the peri-operative period is not settled, with limited evidence.

In patients receiving LAI, the prescriber may consider switching the patient to SL BPN and splitting the dose with the addition of another full agonist opioid. For patients receiving SL BPN, it is now recommended to continue the usual BPN dose, split into several doses, usually twice daily, with the addition of full agonist opioid[106]. Where additional opioid analgesia is required, the dose of opioid (e.g., morphine) should be titrated according to clinical response.

However, studies are examining pre-operative assessment and ceasing BPN prior to surgery to allow effective use of other opioids for post-operative analgesia[107]. The opioid dose should be closely monitored if BPN is reduced or stopped, since high opioid doses (such as morphine) may be required while BPN is exerting 'blockade' effects but, as BPN levels reduce (with a corresponding reduction in the 'blocking' effects of BPN), there may be over-sedation – or even overdose – from the high morphine doses. If BPN treatment stops completely (e.g., due to the hospital pharmacy not having the drug, doctor uncertainty or inexperience, or patient non-cooperation), the dose of morphine needs to be closely monitored daily for at least 4–5 days after the last sub-lingual BPN dose. Analgesic dose will likely need to be reduced over time to avoid overdose.

4.12 Emergency Department/GP Surgery out of hours

Patients receiving ODT with co-existing health problems

Patients receiving ODT may seek treatment from service providers other than their ODT prescriber, for health problems. The patient should be provided with appropriate care, with communication between their GP, and the ODT prescriber if not their GP.

Patients seeking replacement ODT medication

Patients receiving ODT may present to hospital EDs or medical practices with reports of missed, lost, broken, vomited or stolen ODT medications, reports of withdrawal and requesting replacement or additional ODT medications.

Lost, broken, missed, vomited or stolen medication cannot be replaced other than in exceptional circumstances.

This approach protects the safety of patients who may be seeking medication for the purpose of intoxication, encourages treatment adherence and supports an expectation that medication intended for self-administration is appropriately safeguarded. Given the long half-life of ODT medications, it is unlikely

that missing one dose will cause significant physical discomfort, particularly in a patient who is stable on their ODT dose.

In such situations, service providers should:

- contact the patient's prescriber/clinic if possible
- provide appropriate medication if the person's account can be corroborated
- provide opioid withdrawal symptom management medication as indicated if the prescriber cannot be contacted (Refer to the Queensland Alcohol and Other Drug Withdrawal Guidelines)
- advise the patient to contact their prescriber as soon as possible.

4.13 Consumption by a child

Ingestion by a child of ODT medication stored at home for self-administration can be particularly dangerous and potentially life-threatening, even with small amounts. BPN, while safer in adults, can still pose a significant risk to children[12].

When presented with suspected opioid ingestion by a child:

- Assess the level of consciousness and monitor this continuously until the child is in the care of Queensland Ambulance Service (QAS) /medical staff.
- Refer the child to a hospital ED without delay, providing available information about the amount of medication consumed, and the time since ingestion.
- Administer oxygen if available.
- Consider NX administration if the child is showing signs of respiratory depression (document any treatment given), QAS will still be required in community settings following NX administration
- Notify the prescriber of the incident.
- Cease providing medication for self-administration immediately and engage patient in other options for ODT medication access.
- A mandatory child safety notification should be made. A 'Report of suspected child in need of protection form' should be submitted, and the Child Safety Regional Intake Service for the relevant area telephoned to confirm receipt of the Report.
- In hospital, the treating medical officer should discuss concerns for the child and next steps with relevant staff, including Social Worker and/or Child Protection Liaison Officer, prior to discharge.
- QPS may be involved in exceptional circumstances[12].

4.14 Travel

Requests for provision of alternative arrangements for ODT (including self-administering medication) for travel should be considered carefully by the patient and prescriber. LAI BPN must only be handled by a healthcare provider after delivery to a clinic/administration site. It must not be supplied to patients.

Within Queensland

In consultation with their prescriber, patients may be able to arrange to collect ODT medication from an

alternative pharmacy. A letter of introduction which clearly documents arrangements by the prescriber or delegate should be provided to the patient's regular pharmacy and the temporary pharmacy.

Interstate

ODT requirements vary nationally. The prescriber should contact the relevant regulatory body to determine local regulations and processes. For patients receiving LAI BPN, there are no requirements beyond identifying ODT service providers and pharmacies that have access to Buvidal® and/or Sublocade®. Contact details for service providers in each State and Territory are in Section 18.

International

As LAI BPN cannot be given to patients, overseas travel will require careful planning if travel extends beyond four to six weeks. For a patient stable on monthly preparations, LAI BPN should be administered prior to departure and the patient supplied with SL BPN for use after five weeks for Buvidal® Monthly or six weeks for Sublocade®.

Alternatively, the Sublocade® prescribing information for US prescribers details that patients who are stable on 100 mg monthly may be given a single 300 mg dose to cover a two-month period with regular 100 mg dose to continue thereafter. This example of overseas practice could be adopted for appropriate circumstances however patients should be counselled that they may experience sedation or other BPN-related effects as their plasma levels of BPN will be higher following this dose.

Patients should contact the embassy or consulate of the transit and destination countries to ensure it is legal to arrive with, transit through, travel with and administer ODT medication. While each embassy/consulate is the definitive source, basic details about the possibility of travel to different countries can be found at INDRO e.V. Useful information can also be obtained at the Therapeutic Goods Administration website. Travel to some destinations while on ODT may not always be possible.

Arrangements with the prescriber should be made as early as possible and usually at least one month prior to travel. Some destinations may require that the prescriber provide a letter confirming the patient is legally prescribed the medication for personal use in Australia. The patient should keep this letter secure with their medication during travel. It may be a requirement for the letter to be translated into the language of the destination country. If the overseas authorities require a letter from the Australian Government, this can be obtained from the Therapeutic Goods Administration[6].

See also Pharmacist Appendix 5.3.1 and 5.3.2.

Sample letter for travel can be found in Appendix 16.

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Appendices

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1. Regulatory context

1.1 Legislation

The *Medicines and Poisons Act 2019* (MPA) and the supporting regulations form the legislative framework for medicines, poisons, pesticides, fumigants and prohibited substances (collectively known as regulated substances) in Queensland.

The *Medicines and Poisons (Medicines) Regulation 2021* (MPMR) is the legal instrument underpinning the prescribing of scheduled medicines, including methadone, BPN and other S8 and S4 medicines in Queensland. Enquiries about the MPMR and its application can be directed to HARU at HARU@health.qld.gov.au.

Useful factsheets and supporting documents related to the MPA can be found here: Fact sheets and supporting documents | Queensland Health .

Health practitioners in Queensland must prescribe, dispense or give treatment doses of monitored medicines (S8 and some S4 medicines), in accordance with the MPMR, which includes requirements to check QScript, Queensland's real-time prescription monitoring system, and comply with the Queensland Health Departmental Standard: Monitored Medicines.

Guidance on how a prescriber can comply with the departmental standard can be found in the Monitored Medicines Standard Companion Document.

Reporting requirements for monitored medicines (e.g., for lost or stolen medication or suspected diversion) and reporting forms can be found here Reporting medicines matters to the chief executive | Queensland Health.

1.2 QScript

QScript is Queensland's real-time prescription monitoring system. QScript is enabled by the MPA and managed by Queensland Health.

All relevant health practitioners are required to check QScript for patient records before:

- prescribing a monitored medicine for a person
- dispensing a monitored medicine for a person
- giving a treatment dose of a monitored medicine for a person.

All health practitioners dispensing monitored medicines (other than those practising in public sector hospitals) are required to upload records of all dispensed monitored medicines to QScript via a Prescription Exchange Service. Further information about QScript can be found here: Real-time prescription monitoring of monitored medicines.

Education is available at the QScript learning portal.

Note: QOTP dispensing records in QScript provide only an *indication* of the amount of medicine the patient has been (or will be) dispensed. The dispensing pharmacists should always be contacted in order to verify the date and details of last dose.

1.3 Prescribing and dispensing monitored medicines

Before prescribing or dispensing or giving a treatment dose of a monitored medicine, a relevant practitioner is required to check QScript and also comply with the Monitored Medicines Standard.

All prescriptions must include the date of birth of the person being prescribed the monitored medicine.

- If a prescriber holds a prescribing approval for prescribing an approved opioid (an ODT medication), the number of the prescribing approval must be included on the prescription.
- Prescriptions for approved opioids must comply with any prescription conditions specified in the prescriber's prescribing approval.
- There are requirements for prescriptions generally and for prescriptions for S8 medicines that must be met.

See this factsheet about lawful prescriptions.

Further information about the Monitored Medicines Standard can be found on the Supporting Documents web page, under 'Monitored Medicines'.

If a patient is on the QOTP and another prescriber is seeking to treat them with other monitored medicines, then that other prescriber must have a documented **joint prescribing plan** with the current QOTP prescriber. This is a requirement under the MPMR and a requirement for compliance with the *Monitored Medicines Standard*.

1.4 Approval to prescribe ODT medications

In Queensland, any prescriber who wants to treat opioid dependence using ODT medications (approved opioids) must hold a prescribing approval.

There are various types of QOTP prescriber with differences in type of medication that may be prescribed and required levels of supervision. Prescriber types and training requirements are detailed in the Queensland Opioid Treatment Program Prescriber Types factsheet.

For more information on making an application, contact HARU on QOTP@health.qld.gov.au and review the information on the department's website.

For further advice on QOTP procedures for prescribers refer to Appendix 4.

To cover urgent or planned leave a prescriber may have another health practitioner in their practice apply for a temporary prescribing approval to cover the period of absence. Under this temporary approval the dose and other arrangements should remain the same. If an urgent change is required to the person's treatment plan, then ADCAS should be consulted – see Appendix 17.

1.5 Support available for QOTP prescribers

QOTP prescribers can seek additional advice for ODT treatment decisions by consulting with a medical addiction specialist in their region or local AOD service, or by calling ADCAS – see Appendix 17.

2. Considerations for initial assessments

A comprehensive biopsychosocial assessment is important to determine the patient's needs and the most effective and appropriate evidence-based treatment.

Assessing a patient for opioid dependence aims to:

- establish an effective therapeutic relationship with the patient
- clarify diagnoses and confirm diagnosis of opioid dependence
- determine treatment goals with the patient (with harm-reduction principles in mind)
- determine the most practicable evidence-based treatment
- enable the patient to make an informed decision about treatment
- develop an initial treatment plan[108].

Initial assessment consists of history-taking, risk assessment, examination, investigation, and review of relevant collateral information[12]. It should cover the range of medical and mental health conditions that frequently co-occur with opioid dependence[6, 7].

Relevant details for taking health-related history including physical and mental health and AOD use are outlined in this section. Assessment should result in an integrated diagnostic formulation and must be conducted by a prescriber when the proposed treatment includes pharmacotherapy.

Substance use history

- history of treatment for opioid dependence[7] including participation in QOTP and a patient's monitored medicines medication history is accessible on QScript (access is restricted to eligible health practitioners; www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/real-time-reporting)
- age when first used substances, including opioids, and relevant circumstances
- age when first dependent on substances, including opioids
- longest substance and opioid-free period: how was it achieved?
- number of significant substance and opioid-free periods: how were they achieved?
- all current substance use, including alcohol, tobacco, cannabis, over-the-counter medications, psychostimulants, inhalants, prescribed medications and caffeine
- confirmation of, and duration of, dependence on opioids, including therapeutic opioids
- cues for substance use
- history of substance related problems (e.g., substance-induced psychosis, withdrawal seizures)
- perceived advantages versus disadvantages of substance use in contrast to non-substance use
- time of last use of opioids and other substances
- routes of administration (including safe injecting practices)

Current QOTP registration status and recent treatment history can be obtained from QScript.

Risks and risk behaviours

- current pregnancy and contraception
- use of sterile injecting equipment (e.g., needles and syringes, water for injection)
- sharing of injecting equipment
- substance using situations and settings
- history of overdose and severity
- other complications of injecting drug use
- previous and current risk of self-harm and/or suicide
- history of violent behaviour[109] or of being a victim of violence or abuse including domestic and family violence
- historical or current risk of other vulnerabilities (e.g., financial abuse, sexual victimisation, impaired decision making)
- history of treatment non-adherence.

Other health related history

- childhood illnesses
- allergies, adverse reactions
- pain conditions, diagnosis, treatment, therapeutic opioid dependence
- obstetric and gynaecological conditions
- surgery and injury, including traumatic
- medical history including infectious diseases especially viral hepatitis, HIV, other sexually transmitted infections and tuberculosis[4]
- dental health: opioids reduce saliva flow (xerostomia) contributing to dental decay[110] and periodontal disease
- other mental disorders including anxiety, trauma and stress related disorders, mood disorders, schizophrenia spectrum and other psychotic disorders, attention-deficit hyperactivity disorder (ADHD), personality disorders, and suicide and/or self-harm related behaviours.

Family history

- family medical, risky or problematic substance use and mental health history
- childhood history, past and current relationships with family of origin
- marriage/de-facto relationships, children and quality of relationships
- child protection and domestic and family violence issues (history and current)

Social history

- work history (including home duties), educational level attained, qualifications
- legal problems, previous incarceration, drug court, current charges
- interests and activities, hobbies
- relationships, extent and quality of friendships within and outside the context of drug use

- cultural status and history, religious/spiritual beliefs, migration and/or refugee status
- sexual relationships: sexual preference(s), sexual practices and sexual health
- accommodation: living alone, with family, with friends, type (e.g., house, flat, caravan, etc.), rental or mortgage
- current income source, finances, debt, gambling

Examinations

- mental state examination
- general physical examination with emphasis on systems that may have been affected by substance use e.g., cardiovascular, gastrointestinal and neurological systems[7]
- presence of needle track marks and signs of infection at injecting sites
- signs of opioid (or other drug) intoxication or withdrawal

Investigations

Relevant investigations may include:

- full blood count
- biochemical screen (electrolytes, hepatic and renal function, C-reactive protein)
- screening for BBVs
- sexual health screen
- pregnancy test
- other as indicated by history or examination – e.g., electrocardiogram, chest x-ray
- urine drug screens (UDS). A UDS collected on the first visit may be valuable to confirm drug use history.
- breathalyser blood alcohol level (BAL)

Specific investigations are not compulsory for initiation of ODT; rather, they should be offered in the context of comprehensive care.

Pregnancy and lactation

Please see Section 4 for more detailed recommendations about treatment for patients who are pregnant. For women of child-bearing age, the following should be explored:

- plans for pregnancy and contraception,
- discussion about the effect of treatment on pregnancy and birth
- if pregnant, plans regarding pregnancy including post-partum period and breastfeeding[111, 112].

Pregnancy testing should always be considered in women of child-bearing age to aid in treatment planning and medication choices. Section 4.1 provides more detail on managing opioid-dependent patients who are pregnant or breastfeeding.

3. Considerations for treatment planning and review

An initial treatment plan should prioritise identified needs, and document treatment goals and processes[108, 113], including:

- medication planned and rationale
- psychotherapeutic interventions/counselling plan
- other identified issues and their targeted interventions[7].

Alternative treatment strategies should be in the treatment plan, such as:

- withdrawal management
- information about rehabilitation programs
- information about peer-based support organisations (e.g., QPAMS – see Appendix 17)

Addiction treatment planning should aim to optimise patient engagement and minimise burden, and be:

- an iterative process in collaboration with the patient, reflecting their circumstances and case complexity
- shared across service providers to address multiple domains
- documented so as to be meaningful to the patient, their carer and other service providers[6].

A key consideration in minimising ODT-linked burden is the degree of supervision requirements. Administering medication under supervision reduces risk of overdose[6] and diversion of medications by allowing:

- monitoring of current state of intoxication or withdrawal and general health
- monitoring of adherence to treatment, and
- an externally imposed structure and routine.

However, the restrictions inherent in supervised medication regimens make many activities more difficult, including those important for community re-integration and recovery such as work, study or care of others. Reducing the intensity of supervision and extending the period between treatment decision points can reduce cravings and other cues to opioid use. Recovery is promoted by supporting engagement with non-substance linked activities and encouraging patient autonomy and self-management[12], consistent with principles of chronic disease management[12, 114]. Simple treatment regimens are encouraged in medical care as much as possible to enhance engagement with and adherence to treatment, including

"*treatments that obviate the need for ongoing adherence, such as implantable treatments with minimal adverse effects …*"[115]

Long-acting injections and implantable devices have been used as adherence-promoting strategies in medicine over extended periods. Their availability for treating opioid dependence has potential to enable more widespread access to effective safe treatment.

3.1 Prevention-oriented risk management strategies

To minimise potential harms, risk-management strategies include:

- Providing NX to patient and relevant others (e.g., carers, family) which can be provided free of charge through the THN program see the About the Take Home Naloxone program resource.
- Use of safer opioid preparations:
  - BPN LAI is generally the safest and least restrictive mode of administration.
  - BPN administered sublingually is generally safer than methadone administered orally.
  - BPN/NX poses a reduced injecting risk compared to BPN or other opioids with associated reduced risk of diversion.
- Clear, regular and timely communication:
  - With the patient and relevant others (e.g., carers, family members) regarding responsible storage and use of medication, including NX.
  - Regarding the roles and responsibilities of the prescriber, delegate, pharmacist and patient, including in relation to safety concerns.
- Regular clinical reviews:
  - If patients regularly miss scheduled appointments, reasons should be explored (may include problems with transport, childcare, work).
- Addressing use of medications other than as prescribed:
  - Clinicians have a responsibility to address medication not taken as prescribed, such as missed medication, using additional medication to that prescribed, 'lost' or 'misplaced' medications, diversion to others and unauthorised routes (e.g., injecting) or intoxicated presentations.
  - Injection of BPN obtained from BPN tablets or BPN/NX should lead to consideration of alternative safer modes of administration, particularly BPN LAI.
  - Patients at higher risk of diversion or misuse should be monitored more closely, including via supervised administration of medication.
- Aberrant ODT-related behaviours or incidents require a review of the patient's treatment conditions.
- Clear documentation of the indications, risks and strategies to mitigate identified risks[12].

Table 12 Roles and responsibilities for ODT

QOTP prescriber responsibilities	Patient responsibilities	Pharmacist responsibilities
Planning and documenting instructions and communicating with pharmacies Regularly reviewing administration and supervision requirements, involving regular assessment and documentation of the indications, risks and risk mitigation strategies Communicating requirements to patients, enabling understanding of decision-making processes regarding supervision	Using medication as prescribed and according to instructions Safe storage of medication, particularly ensuring out of reach of children Notifying prescriber of any issues or concerns regarding medication (including lost or misplaced medication, consumption by others, or use of the medication not as prescribed) Seeking emergency medical assistance if medication is	Ensuring supervised medication is administered and dispensed as per prescription, unless there are safety concerns (e.g., intoxication, routinely missing medication) Keeping accurate records regarding dispensed medications Regularly communicating with the QOTP prescriber regarding factors that impact upon ODT safety, including intoxication, missed medication, attempts at not

QOTP prescriber responsibilities	Patient responsibilities	Pharmacist responsibilities
Regularly communicating with the patient regarding safe use and storage of opioids	consumed by others, particularly children or adults with low opioid tolerance, due to the risk of overdose and death	consuming supervised medication, or evidence of diversion to others Regularly communicating with the patient regarding safe use and storage of opioids

3.2 Infectious diseases

It is important to obtain a history of infectious disease transmission risk behaviours, specifically HIV and viral hepatitis, including unsafe injecting practices, sexual relationships and at-risk sexual behaviours. Universal infection control precautions should be in place regardless of the HIV or hepatitis status of individual patients.

All patients should receive education regarding HIV and viral hepatitis at the initial assessment, particularly as some patients may not return for treatment. Brief interventions can have significant individual and public health benefits. For patients who commence on ODT, more detailed information can be provided once the patient has stabilised on medication.

Education for patients should include the following components:

- information about safer injection practices (including where to obtain sterile injecting equipment)
- access to and use of NX
- access to services for health, alcohol and drug issues
- information regarding safer sexual practices
- prevention, testing and treatment of other sexually transmitted infections
- pregnancy advice for women
- assertion and negotiation skills
- promotion of BBV testing.

Some educational resources are available on Adis and QuIHN websites.

3.2.1 Hepatitis C virus (HCV)

The introduction of direct-acting antiviral (DAA) therapies has seen treatment adherence rates of 92% among people who inject drugs in a community-based setting[116]. Once daily frequency, minimal side-effect profile, reduced treatment time and high efficacy has generated optimism about improved treatment outcomes, with cure rates over 95%[117]. All patients should be strongly encouraged to undertake HCV antibody testing, and if positive HCV RNA testing to confirm ongoing infection. When indicated, commence treatment. While an integrated approach in ODT settings has been shown to improve patient engagement in HCV treatment, treatment can still be challenging[118-120].

The DAA's are co-listed on the PBS as both s100 and s85 drugs. They can be prescribed by GPs and nurse practitioners either in consultation with a specialist doctor or independently[121]. There is no evidence of drug interactions between DAA and ODT medication[122]. See University of Liverpool HEP Drug Interactions for further details.

For patients who are HCV negative (or hepatitis C reactive and have not yet commenced treatment), education and counselling should focus on minimising risk of further transmission and maintaining optimal health. Information should include advice on reducing hazardous use of all drugs (particularly alcohol, cannabis and tobacco). The risks associated with sharing injecting equipment (including tourniquets, spoons and water) as well as razors, toothbrushes etc. should be explained.

Hepatitis C reactive individuals should have their HBV status checked (HBsAg, sAb and cAb), since co-infection may cause their illness to be more aggressive and may be a risk factor in DAA treatment for HCV.

3.2.2 Hepatitis B (HBV)

Hepatitis B vaccination should be offered to all non-immune ODT patients and to sero-negative partners and close family contacts of patients who are hepatitis B sero-positive and potentially infectious[123]. Chronic HBV carriers (HBsAg or eAg positive) should be referred to a liver clinic or gastroenterologist for assessment.

Hepatitis B vaccination is free for at-risk groups and should be available in all ODT service settings. The identified at-risk group includes people who inject drugs, patients with chronic liver disease and/or HCV, and Aboriginal and Torres Strait Islander people who do not have immunity[123]. Local Public Health Units can be contacted regarding supply of hepatitis B vaccines.

3.2.3 Human immunodeficiency virus (HIV)

Patients who are HIV-positive should be managed in collaboration with specialist services and community-based support services. Assessment and management of possible drug interactions between ODT and other medications is necessary.

3.3 Intoxication

Safety is a key consideration when patients attend for medication while intoxicated[12]. Regular intoxication should lead to prescriber review, with a focus on reducing the potential for harm and engaging the patient in effective treatment. Patients who use other substances may fear consequences for their ODT, so it is important to consider further treatment plans collaboratively using a motivational approach.

Intoxication can result from an ODT medication dose that is too high, or other substance use. Benzodiazepines in combination with ODT should be avoided. If such a combination is necessary, it should be closely monitored and wherever possible, a plan developed for reduction and cessation. Non-opioid drug use does not in general respond to increased ODT dose.

The clinician administering ODT medication should always assess the patient first. If intoxicated, the risks associated with overdose must be evaluated. If significantly intoxicated, the clinician should withhold the medication or consult with the prescriber to reduce the dose to a very low level to ensure safety. Alternatively, the patient could be asked to return when no longer intoxicated for re-assessment. Unsupervised medication doses should not be given to an intoxicated patient. It is important to explain the rationale to the patient, so they understand the change in treatment plan.

See also Section 4.8

3.4 Polysubstance use

Polysubstance use can lead to poorer outcomes and harms so it is important to address problematic polysubstance use to support safe and effective ODT. The therapeutic relationship should encourage open disclosure, and consideration of how support networks can be used to inform and encourage such disclosure. This may include proactive collaboration with the patient to identify family members or close friends whom the patient consents to providing information to the QOTP provider about recurrent use or relapse.

Problematic substance use should be systematically addressed in clinical reviews. Pathology testing, including by UDS and breathalyser BAL monitoring can also identify undisclosed substance use. Continued higher risk drug use may be associated with:

- frequent presentations when intoxicated
- evidence of regular substance use on examination (e.g., recent injecting sites)
- overdoses or other high-risk substance using behaviours
- deteriorating medical, mental or social wellbeing related to substance use[12]
- changes in behaviour/clinical presentation.

Where higher risk substance use causes safety concerns and increased review requirements which are difficult to coordinate in primary care or some specialist private practice settings[12], patients may be more appropriately treated by a specialist multidisciplinary AOD service.

The patient should be educated about the risks of overdose due to combination of opioids and other medications, particularly sedatives including benzodiazepines, Z-drugs (i.e., zolpidem and zopiclone) and gabapentinoids. If possible, an agreed management plan including for withdrawal as needed, should be established.

If the patient's safety is not at risk from ongoing substance use in combination with their ODT, it will generally be in the patient's interest to persist with ODT. If the risks of combining ODT with other substance use outweigh the benefits, as a last resort a gradual withdrawal off ODT medication may be considered[12]. Advice from a medical addiction specialist should be considered in such situations.

3.5 Alcohol use disorder

About 33% of patients receiving ODT meet criteria for an alcohol use disorder[124, 125]. This cohort have an increased risk of overdose, impaired memory and cognitive performance, and altered pharmacokinetics (e.g., liver disease). These concerns may be more relevant to methadone than BPN, due to greater risk of sedation and overdose in combination, and hepatic metabolism of methadone[12].

Specific strategies should be considered in alcohol dependent patients receiving ODT, including:

- treatment interventions for alcohol dependence (withdrawal, counselling and anti-craving treatment)
- investigations such as liver function tests and BAL testing. A patient with a BAL greater than 0.05% should not receive medication
- review of case acuity - increased frequency of clinical reviews
- increased supervision of medication

- increased monitoring by pharmacy staff (including withholding medication and advising prescriber when patient is intoxicated)
- ODT medication dose increases alone are ineffective in addressing alcohol use, and may increase risks of over-sedation
- where safety concerns persist in alcohol dependent patients on methadone, transfer to BPN/NX or BPN LAI[12].

3.6 Benzodiazepine use

Safety concerns arise in patients receiving ODT concurrently using benzodiazepines, particularly in higher medication doses, due to the increased risk of overdose, impaired memory and cognition. These concerns apply more with methadone than BPN, due to lower risk of sedation and overdose in combination with BPN[12].

The management of benzodiazepine use disorders in patients receiving ODT is complex. While approximately 30–60% of QOTP patients have used benzodiazepines in the preceding year, only a minority (estimated at 10–20%) have a benzodiazepine use disorder. These individuals may experience complications from their benzodiazepine use such as increased anxiety, sleep disorders, intoxicated presentations, seizures, delirium and overdoses[12, 126].

A clinical assessment should include consideration of:

- pattern of benzodiazepine use (frequency, amount, source, when benzodiazepines are used, extent of dependence)
- adverse events or harms linked to benzodiazepine use (overdoses, withdrawal seizures, higher risk behaviours when intoxicated, memory or cognitive impairments)
- concurrent medical and mental health conditions (including anxiety and depression, neurological conditions, sleep disorders)
- a UDS
- review of ODT conditions (e.g. adequacy of ODT prescription and adherence, missed appointments, intoxicated presentations, medication supervision) and history (e.g. other health service providers, QScript).

If a patient is on the QOTP and another prescriber is seeking to treat them with other monitored medicines, such as benzodiazepines, then that other prescriber must have a documented **joint prescribing plan** with the current QOTP prescriber (or alcohol and drug treatment service). This is a requirement under the MPMR and a requirement for compliance with the Monitored Medicines Standard.

3.6.1 Benzodiazepine high dose/binge use

High-dose and/or binge patterns of benzodiazepine use are associated with significant harms (e.g., overdoses). There is a limited role for prescribing benzodiazepines for ODT patients with benzodiazepine misuse. Patient education should target potential ‘immediate’ effects of benzodiazepine intoxication (e.g., impairment of memory, cognition and judgement, and how this can in turn lead to higher risk behaviours and harms such as needle sharing, unsafe sex, deliberate self-harm, violence, crime and driving offences), as well as longer-term disturbances in sleep and mood.

Risk management strategies for persistent harmful benzodiazepine use should include:

- consider 'case acuity' - regular reviews, supervised medication administration
- consider reduction of higher ODT medication doses to minimise overdose risk in patient with frequent intoxicated presentations, and if currently prescribed methadone, transfer to BPN/NX or BPN LAI[12].

3.6.2 Benzodiazepine dependence

Prescribers should recognise their role in managing benzodiazepine dependence, and exercise caution in prescribing benzodiazepines because of the increased risk of adverse events, including consideration of staging supply to limit amount supplied at a point in time. However, for benzodiazepine dependent patients, it is important not to cease benzodiazepines abruptly due to the risk of withdrawal seizures. It is important to educate patients about this risk.

3.6.3 Benzodiazepine withdrawal regimen

The concerns regarding graduated withdrawal include relapse to illicit or opportunistic benzodiazepine use. The following strategies can assist with mitigating risk while managing this situation:

Table 13 Strategies for managing benzodiazepine dependence in patients receiving ODT[12]

Strategy	Action
Coordinate treatment providers	Prescriber to review S4 prescribing in QScript and make a clinical decision on available information
Address comorbidities	Including mood and sleep problems using evidence-based psychosocial and pharmacological approaches Treatment of benzodiazepine withdrawal is more than a prescription
Stabilise on a long-acting benzodiazepine	Diazepam is generally used for this purpose Dose conversions between benzodiazepines are unreliable. It is important to differentiate the amount of benzodiazepines reported for intoxication from that required to avert severe withdrawal Doses of more than 40 mg diazepam daily are rarely required to avert severe withdrawal Hospital admission may be considered to stabilise patients reporting very high or erratic benzodiazepine use
Attempt gradual reductions	An 8–16-week reduction regimen can be initially negotiated (up to 5 mg diazepam equivalent dose reduction every 1–2 weeks), some patients require periods of stabilisation along the way Reduction regimens may extend to more than 6 months, although this requires a review of treatment conditions and ancillary interventions Long-term prescribing should include regular assessment of functional outcomes, such as cognition, memory, anxiety, mood and sleep
Limit access to benzodiazepine medications	Supervise benzodiazepine medications Medications are the patient's responsibility once dispensed, and 'lost' tablets are not replaced

Strategy	Action
Identify and address aberrant drug behaviours in the treatment plan	Clear understanding between patient and all clinicians that persistent, severe aberrant drug behaviours may result in discontinuation of the treatment plan and cessation of benzodiazepine prescribing Aberrant drug behaviours include use of additional benzodiazepines, intoxicated presentations, missed ODT medication doses, persistent use of other drugs that may precipitate benzodiazepine use (e.g., stimulants) or increased safety concerns (e.g., alcohol or other opioids) A written care plan signed by the patient and clinician may be helpful
Undertake regular patient monitoring	Including clinical reviews, communication with pharmacy staff, and UDS, ideally with laboratory techniques (e.g., gas chromatography mass spectrometry (GC/MS) or equivalent) to differentiate benzodiazepine type Prescription monitoring where available
Use contingency management principles regarding treatment conditions	Supervision of ODT medication and frequency of dispensing benzodiazepines may be linked to benzodiazepine treatment plan adherence Transfer patient to LAI BPN
Document treatment decisions	There is minimal evidence supporting long-term benzodiazepine prescribing in this population, and given the high risk of adverse events, clinicians must be able to defend their decisions and prescribing practices in the event of severe harms

3.6.4 Benzodiazepine maintenance treatment

Concerns regarding maintenance benzodiazepine treatment include persistent additional benzodiazepine use (and related intoxication harms), use not as prescribed such as injecting, diversion to others, and increased risk of mortality[127, 128].

If low-dose maintenance of benzodiazepine medication is being considered, the patient should be referred to a medical addiction specialist or psychiatrist. A management plan should include periodic reviews by the medical addiction specialist or psychiatrist, regular collection of their benzodiazepine medication (e.g., with their ODT medication dose), and other risk mitigation strategies such as UDS.

QScript: Although the patient's permission is not required by law, it is good practice for patients to be made aware that their history of obtaining benzodiazepines will be monitored through QScript.

3.7 Use of psychostimulants

The major concerns about psychostimulant use in patients receiving ODT are risk-taking behaviours such as ongoing injecting drug use. The most common problems seen with psychostimulant use are symptoms of other mental disorders, such as anxiety, agitation, depression, misperception, delusions, paranoia, magical thinking, hallucinations and psychosis[12].

Related physical health problems include loss of weight and insomnia, while people who regularly or intensively use psychostimulants may be vulnerable to BBV infection or sexual health risks and the complications of intravenous injection. Other health problems may include cardiac arrhythmias or ischemia and stroke[12]. Psychostimulant use with methadone may lead to hazardous, prolonged QTc intervals[129].

Some patients who use psychostimulants also use CNS depressants (e.g., cannabis, benzodiazepines, alcohol) to reduce anxiety or insomnia. Screening for problematic use of these substances in this population should be considered.

3.8 Polypharmacy

While opioids alone can cause overdose and death through respiratory depression, even in those who have developed opioid tolerance, the risk of respiratory depression is increased when opioids are combined with other depressants. These include benzodiazepines and Z drugs, gabapentinoids, antipsychotics such as quetiapine, and of course alcohol. Thus, extreme caution should be exercised in co-prescribing CNS depressants with methadone or BPN. While NX is effective in reversing opioid overdose it may be less successful in mixed overdose. While flumazenil is a specific reversal agent for benzodiazepine overdose there are no specific agents to reverse gabapentinoids, antipsychotics or alcohol.

3.9 Cannabis use (including medicinal cannabis)

Cannabis use is common among people with opioid dependence, with many people using cannabis regularly.[65, 130]. Although most people do not identify significant associated harms, it can be associated with significant medical (e.g., respiratory problems), psychiatric (e.g., anxiety, psychosis, paranoia, memory impairment) or social (e.g., financial, legal) consequences. When cannabis is mixed with tobacco there is the additional risk of tobacco-related harm and a need to assist with nicotine dependence[12].

If a patient is on the QOTP and another prescriber is seeking to treat them with other monitored medicines, such as S8 medicinal cannabis, then that other prescriber must have a documented **joint prescribing plan** with the current QOTP prescriber. This is a requirement under the MPMR and a requirement for compliance with the *Monitored Medicines Standard*.

Cessation of cannabis amongst people with cannabis dependence can be associated with a clinically significant withdrawal syndrome in about half of people who use opioids daily, typically presenting as sleep disturbance, cravings, agitation and low mood. However, symptoms are usually of short duration (1–2 weeks). There are currently no medications specifically for cannabis withdrawal[131]. There is modest evidence that psychotherapeutic approaches of cognitive behavioural therapy (CBT) and motivational enhancement therapy (MET) may help some patients reduce or cease cannabis use[131].

3.10 Nicotine

Tobacco use is very common among people with opioid dependence, with associated long-term health risks[124, 132]. Tobacco cessation can enhance reductions in other substances in the short-term and long term. People with opioid dependence respond to similar approaches to quitting as the general population; however, they may need more intensive treatment. Pharmacotherapy can double the chances of successful quitting. These can be prescribed for ODT patients for 3-6 months through the PBS. Information about quitting smoking can be found on the QLD Health website, and there is a Smoking Cessation Clinical Pathway for patients accessing public health services.

3.11 Selective withdrawal management

Patients receiving ODT with poly- substance dependence– in particular benzodiazepines, alcohol or psychostimulants – may require assistance to withdraw from those drugs while continuing opioid treatment[99]. The service provider should support and encourage the patient by offering selective withdrawal treatment, and in this context should:

- review the patient frequently
- monitor closely for evidence of intoxication with sedative drugs in combination with ODT
- provide only small quantities of withdrawal medication at a time.

Consultation with a medical addiction specialist should be undertaken in more complicated cases, or if the prescriber is unfamiliar with the appropriate withdrawal treatment.

3.12 Dental health

A few simple countermeasures may help to manage the dental health of ODT patients:

- examine the mouth and gums regularly, and develop a management plan for any problems identified
- recommend sugar-free gum to stimulate saliva production. Note that many sugar-free products may have low pH which may facilitate loss of tooth structure
- provide information about diet and oral hygiene when appropriate
- recommend regular dental visits, considering community dental clinics for concession card holders.

3.13 Missed medication

The prescriber, pharmacist and patient should plan for management of missed medication, appropriate to the medication regimen and mode of delivery. An individualised plan should include expectations for shared communication. The pharmacist should notify the prescriber or delegate when a patient fails to attend as expected for supervised medication, and when the patient has restarted medication at pharmacy after missing medication. Repeated non-adherence can be associated with reduced tolerance, withdrawal and/or use of other substances, which impact on treatment safety and effectiveness[6]. The response to non-adherence varies with medication and treatment regimen and mode of delivery, duration, and the patient's clinical presentation on prescriber review or pharmacy attendance. When clinically significant non-adherence occurs, a prescriber review of the current medication regimen should consider the circumstances of non-adherence, any recent substance use, and other relevant medical or social issues.

3.13.1 Reported lost/stolen medication

If a patient reports lost, stolen or damaged medications, a specific plan for treatment should be developed which manages individual risks e.g., withdrawal symptoms, pregnancy. When a replacement is indicated, the patient should be reviewed by the prescriber or delegate and any supplementary medication titrated accordingly. Replacement medication is usually not the full dose. Careful assessment and monitoring are required to ensure that the patient is not overdosed, and to inform decision making about further ODT regimens and pathways. The patient should report lost or stolen medication to QPS[30]

and prescribers are required to report suspected lost or stolen medications under the MPMR. Further information and relevant forms for reporting can be found at reporting medicine matters.

3.13.2 Safe storage

Patients are responsible for their medications including care and their proper consumption. They should be informed that medication will generally not be replaced if lost or stolen, that they should be stored securely, in a place not easily accessible to others, and particularly, out of reach of children[12]. A locked receptacle like a small cash box is recommended to minimise the risk of accidental consumption. Medication should not be stored in a refrigerator.

3.14 Suspension of ODT

Regular prescriber or delegate reviews are necessary for safety and quality of care. Non-attendance at scheduled appointments, particularly if recurrent, may in exceptional circumstances require reconsideration of prescribing including suspension or cessation. Liaison between the prescriber or delegate and the pharmacist and, if possible, the patient is key to this process. Prescribers and pharmacists should clearly document attempts to engage the patient. If suspension is planned, the pharmacist may be instructed by the prescriber to withhold medication on a particular date, with documented attempts to inform the patient of this in a timely way.

3.15 Urine drug screens

Urine drug screens can be used to:

- identify the type of substances used in recent days, with some drugs detectable for up to six weeks
- enhance the validity of patients' self-reported use of substances
- identify substances not reported by the patient that may assist diagnosis and management (e.g., identifying amphetamine or cannabis use in a patient developing features of psychosis), and
- assist in treatment planning.

Clear explanation of rationale and planned contingencies is important since a request for a UDS can be perceived by patients as not accepting their self-report or a possible threat to continuation of ODT[6] or to non-health related aspects of their lives. A UDS should only be ordered for clinical reasons, which should not be confused with the different purposes for which they can be used such as sports surveillance or the justice, correctional and child safety systems.

Directly observed urine samples are intrusive and impact negatively on therapeutic engagement. Mechanisms such as management of toilet facilities, checking sample temperature and testing for non-human sources or dilution are generally sufficient to ensure the sample is genuine[12].

A UDS is useful at treatment initiation; however, delayed results should not delay treatment initiation unless a positive result for opioids is considered necessary for diagnosis. Further UDS should be performed based on clinical indications. An intermittent schedule of random testing is likely to ensure more useful information than frequent screening[12].

A UDS may provide false positive or negative results. Where appropriate, prescribers and delegates should review the screening tests used by their pathology service, the drugs or drug classes tested for,

and the cut-offs applied to assist interpretation of screening tests. It may be appropriate to discuss individual UDS results and possible additional further testing.

Benchtop (dipstick) testing systems can be useful; however, limitations include cost, and the range and amount of substances able to be detected.

The Medicare Benefits Schedule limits the number of drug screens funded to 36 per year. Prescribers should endorse the UDS pathology request to note that the patient is undertaking a drug rehabilitation program. The level of reimbursement does not cover confirmatory testing by specialised techniques such as gas chromatography mass spectrometry. See:

- Item 66626 describes the Medicare Benefits Schedule
- MBS Online Note PN.0.33 at 25(b) describes the annual limit

3.16 Authorised agent

An agent may need to be authorised to collect medication for a patient in extreme circumstances, where pharmacy attendance is not possible and other options for ODT are not available. Authorisation should be for a brief, specified period only. Such a plan requires:

- confirmation of reasons for inability to attend, such as a medical condition and associated impairment, with the patient's treating medical practitioner
- clarification of current medications prescribed to patient
- assessment of continued safe ODT subject to current medical condition and treatment.

The prescriber should advise the pharmacist of the patient details, the name of the nominated agent (e.g., specific family member), and the period they are authorised to collect the medication. The authorised agent is to provide photo identification when they attend pharmacy to collect the medication.

3.17 Declared emergencies

Where a State Emergency declaration is in place or imminent (e.g., cyclone, flood), supervision requirements should be varied to account for the expected duration of the emergency. The prescriber must approve these variations after consideration of risks and the nature of the emergency.

4. QOTP procedures

4.1 Admission and discharge procedures

Submission of QOTP Admission and Discharge forms is a legal requirement under the provisions of the MPMR. Admission and discharge forms are available from HARU QOTP@health.qld.gov.au.

The Queensland Opioid Treatment Program – Admission Form is to be completed for all new patients, re-admissions and transfers from another prescriber or another practice or service. The date of the first medication administration must be documented on the admission form, noting it may be after the date of the initial assessment. The QOTP Admission Form is to be forwarded to HARU (email: QOTP@health.qld.gov.au) by the end of the business day after the first medication administration. A copy of the form is to be kept in the patient's health record. On completion of treatment or transfer to another prescriber, the prescriber must ensure notice is given. Notice is given by completion of a Queensland Opioid Treatment Program – Discharge Form. The discharge form should be forwarded to HARU (email: QOTP@health.qld.gov.au) as soon as practicable, but within three business days after the treatment stops. If a patient does not return for further treatment, there is no set time within which a patient must be deregistered. Common practice is typically two weeks for those on methadone and SL BPN and 4-6 months for those on LAI BPN.

4.2 Transfer of care

ODT is often long term and may involve transfers of care between prescribers[7, 12]. Transfers may be intrastate, interstate or international, and temporary or permanent[12]. The transferring prescriber should contact the patient's regular pharmacy advising the date for cancellation of any prescriptions. Transfers of care should be organised well in advance of the intended date, with standard risk assessments[13]. Interstate contact details are available in Appendix 18.

Within Queensland, a patient can be registered with only one QOTP prescriber at a time. Generally, the transferring prescriber initiates contact with QOTP service providers and once a new prescriber has agreed to accept the patient, transfer arrangements can commence. Communication between the transferring and receiving prescribers and pharmacies is essential[12]. Written documentation containing the following details should be received by the new prescriber, prior to the arrival of the patient:

- identifying information
- BPN or methadone dose and mode, including last dose if LAI BPN
- contact details of previous service provider
- exact dates of transfer
- details of any medication provided for self-administration
- relevant clinical details (e.g., clinical progress, relevant health history including medications)[6].

The transferring prescriber completes and forwards the QOTP Discharge Form as above. The receiving prescriber completes and forwards a QOTP Admission Form as above.

Particular attention is required when communicating with other health care providers regarding transfer of care for patients treated with LAI BPN. Many health care providers may be unfamiliar with LAI BPN formulations, including their prolonged duration of action and the differences between Buvidal® and

Sublocade® as LAI BPN formulations. When transferring care or providing clinical handover to other health care providers, ensure the following is communicated:

- Details of service providers prescribing and administering LAI BPN injections and previous injection sites (in order to avoid injecting into same site)
- Dose and date of recent LAI BPNs ensuring details of last dose administered are included
- The formulation of LAI BPN that was administered: Buvidal® Weekly, Buvidal® Monthly or Sublocade® and the dose (in mg)
- Scheduled next dose of LAI BPN (formulation, date, dose strength and route of administration),
- Any adverse events, risks or concerns regarding LAI BPN treatment that is relevant to other health care providers

LAI BPN medication may not be commonly administered during a brief inpatient hospital admission or, when given, may be erroneously omitted from hospital discharge summaries and medication reconciliation procedures. Treatment providers should endeavour to ensure that LAI BPN treatment is accurately documented in transfer of care documentation and related clinical handover activities.

4.3 Script transfer to pharmacies

In relation to transfer of QOTP prescriptions from prescribers to pharmacies, paper prescriptions may not be given by prescribers directly to patients. This requirement has been historically linked to concerns about risk of alterations of prescriptions.

A change to these administrative requirements is under active consideration so that paper prescriptions for opioid dependence treatment would be treated in the same way as other medications, including other opioids.

4.4 Shared care

Shared care is a model of service delivery where stable patients in a QOTP clinic are referred to a GP for ODT support[7]. Shared care arrangements are established voluntarily by the relevant AOD service and shared care prescriber on a case-by-case basis and require Departmental approval. They can only be established if the Department of Health has issued a prescribing approval to the shared care prescriber (see section 67 of the MPA) authorising the arrangements.

Shared care is consistent with stepped care models and can reduce perceptions of stigma and enhance patient autonomy. Further benefits may include:

- the GP (and other doctors in the practice) have links with specialist AOD services
- less specialist contact, allowing specialist care to be directed to new/complex patients.

For appropriate cases with a GP the QOTP clinic will coordinate the application for a shared care prescribing approval. The QOTP clinic retains overall management of QOTP for the patient, with the responsibilities of each party documented in an agreement. The GP should review the patient regularly, provide prescriptions to pharmacy, and contact the QOTP clinic to discuss any changes in ODT medication or patient stability. Annual review with the QOTP clinic is routine, in addition to minimum three-monthly patient reviews with the GP. If the GP or patient has concerns, care can be transferred back to a Queensland Health public AOD service or a private medical addiction specialist.

Some Hospital and Health Services have a Shared Care Policy with formalised agreement and consent forms for each party. The shared care model may also be appropriate for patients transitioning to other services, such as aged care or palliative care.

5. Information for pharmacists

5.1 Regulatory requirements

Pharmacy involvement in QOTP is central to provision of ODT.

5.1.1 To become a QOTP dispensing pharmacy

Pharmacists do not require an approval from Queensland Health to become a QOTP dispensing pharmacy. The management and use of all scheduled medicines, including dispensing of medication under the QOTP, must comply with the relevant provisions of the *Medicines and Poisons Act 2019* and associated regulations and standards.

In addition to the requirements under the MPA and associated regulations and standards, pharmacy business ownership in Queensland is regulated under the *Pharmacy Business Ownership Act 2001* (the PBO Act). All community pharmacies in Queensland must ensure compliance with the requirements of the PBO Act.

Medications for use under the QOTP are Commonwealth Government subsidised and, as of 1 July 2023, became part of the Section 100 Highly Specialised Drugs (HSD) program community access arrangements. Prescribing and dispensing arrangements will be the same as for other Pharmaceutical Benefits Scheme (PBS) eligible medicines.

5.1.2 Role of the pharmacist

The pharmacist's role will vary but may include:

- checking the prescription
- ensuring patient identification
- explaining any side-effects of medication when appropriate
- assessing the patient for intoxication and contacting the QOTP service provider if necessary
- supervising administration of oral and SL medications
- administering LAI BPN
- dispensing medication for self-administration
- communicating as needed with the QOTP service provider, including in relation to clinical concerns
- reporting incidents to the QOTP service provider
- ensuring that medications are stored and recorded in compliance with MPMR and MPA[30, 133].

5.1.3 QOTP prescriptions

Opioid dependence treatment medication prescriptions must be either hand-written or electronic on a standard PBS approved prescription form.

See writing lawful prescriptions factsheet.

A QOTP prescription can be sent to the pharmacist as a fax or digital image. The prescriber must then send the original paper prescription to the pharmacist no later than the end of the next business day

after the digital image or fax was sent.

The pharmacist may not make any changes, additions or deletions to prescriber's instructions except to add additional information to the prescription to clarify the prescriber's direction in accordance with section 117 of the MPMR.

Under the MPMR the pharmacist is required to record each QOTP transaction.

The prescriber may modify treatment by new prescription.

Prescriptions for QOTP patients are **not transferable between pharmacies**. If a patient asks for their prescription to be sent to another pharmacy, always direct the patient back to their QOTP service provider to arrange a new prescription.

Section 96 of the Medicines and Poisons Regulation states requirements for additional content of written prescription for approved opioid, including for administration name, place and other instructions.

See: https://www.legislation.qld.gov.au/view/html/inforce/current/sl-2021-0140#sec.96

QOTP prescriptions must not be given to patients.

5.1.4 Temporary interstate transfers

Queensland Health approval is not required for temporary interstate transfers to Queensland provided the prescriber is authorised to prescribe for the person in their home state. An interstate-approved opioid treatment prescriber can provide a hand-written or computer-generated prescription on standard PBS prescription stationery or an electronic prescription for a patient who is travelling to Queensland for short-term visits or pending transfer to a Queensland treatment provider. A prescription must comply with Sections 86-90 of the MPMR to be lawful for dispensing in Queensland.

5.1.5 Schedule 8 medicines storage and record-keeping

Note that health practitioners dispensing S8 medicines (other than those practicing in public sector hospitals) must make these dispensing records in dispensing software connected to a Prescription Exchange Service to ensure these records are uploaded into QScript in real-time.

Schedule 8 medications must be stored in compliance with the MPMR in order to prevent unauthorised access. Further information about how to ensure compliance with the Regulation is detailed in the Queensland Health Departmental Standard: secure storage of S8 medicines.

See: Storage and record-keeping requirements for S8 medicines factsheet.

5.1.6 Confidentiality

The pharmacist's duty of care to the patient may, at times, necessitate balancing the privacy and confidentiality of the patient's health information with the need to share information in order to ensure the patients' ongoing safety. The following should be considered in balancing these potentially competing ethical and legal obligations:

- Australian Health Practitioner Regulation Agency Shared Code of Conduct
- Pharmaceutical Society of Australia's Code of Ethics

- National Privacy Principles

5.2 Administration of QOTP medication

See administration sections for BPN (section 2.4) and Methadone (section 3.4) for specific administration guidelines.

5.2.1 The treatment environment

Clinical assessment and administration of medication should occur in settings with appropriate privacy and security of medications and staff. The layout should enable the pharmacist to effectively supervise administration of medications, ideally separate from the dispensary.

5.2.2 Medication administration

A check prior to administration of medication must include:

- correct patient
- signs of intoxication
- a current prescription with clear medication orders
- correct day (including not already received self-administered medication for that day) and recent medication administration (e.g. missed doses)
- correct QOTP medication, correct dose and correct route of administration.

5.2.3 Administering LAI BPN

Section 9 of the MPMR authorises pharmacists to administer LAI BPN. Pharmacists who wish to administer LAI BPN must meet requirements to be a pharmacist immuniser which include but are not limited to:

- current first aid certificate
- current cardiopulmonary resuscitation certificate
- completion of anaphylaxis management training
- completion of accredited training program for pharmacist administration of immunisations.

These requirements are outlined in the Queensland Extended Practice Authority for Pharmacists under the MPA. Further information can also be found in the Pharmaceutical Society of Australia Practice Guidelines for pharmacists providing immunisation services and Guidelines for pharmacists administering medicines by injection.

LAI BPN may be administered when prescribed by an authorised QOTP prescriber on a current prescription. The prescription must specify whether the LAI BPN is to be administered by the pharmacist or whether it is to be returned to the QOTP prescriber.

The LAI BPN must not be provided directly to the patient.

Pharmacists and QOTP providers should engage in clear and timely communication, particularly in

relation to any missed administrations or any concerns for the patients' health, safety and wellbeing.

See Section 2.4.1 for further information regarding administration of LAI BPN.

5.2.4 Variations in prescribed regimens

Prescriptions may outline variable dose regimens, including a supervised SL BPN that is more than the daily prescribed amount. For example, double dose regimens in which a patient receives twice their prescribed daily dose on day 1 and their next dose on day 3, and triple dose regimens in which a patient receives triple their prescribed daily dose on day 1 and their next dose on day 4.

The pharmacokinetics of BPN allow a patient to remain stable on such a regimen without experiencing intoxication or withdrawal. It may not suit all patients as some will experience increased cravings or features of withdrawal on the days between medication administration. This may result in a return to daily administration after review with the prescriber.

5.2.5 Prescriptions above recommended levels

Prescriptions may occasionally state a daily dose that is above the recommended level of 32 mg / day SL BPN. To reduce risk of medication error, prescribers should make a notation on the prescription verifying this order. If uncertain, the pharmacist should clarify the dose with the QOTP service provider.

5.2.6 Split doses

The prescription should specify the regimen. Usually, this involves administration of a supervised half dose with the remainder half dose for that day given for self-administration. Occasionally, it may involve supervised medication administration twice per day.

5.2.7 Suspension of ODT

Regular prescriber or delegate reviews are necessary for safety and quality of care. Non-attendance at scheduled appointments, particularly if recurrent, may in exceptional circumstances require reconsideration of prescribing including suspension or cessation. Liaison between the prescriber or delegate and the pharmacist and, if possible, the patient is key to this process. Prescribers and pharmacists should clearly document attempts to engage the patient. If suspension is planned, the pharmacist may be instructed by the prescriber to withhold medication on a particular date, with documented attempts to inform the patient of this in a timely way.

5.2.8 Administration at an alternative pharmacy

As prescriptions for QOTP patients are not transferrable between pharmacies, where a patient needs to receive medication at an alternative pharmacy temporarily (e.g. due to work/travel arrangements) the patient is to contact the QOTP service provider to coordinate this.

If an incident necessitates a change of treatment location, the pharmacist should notify the QOTP service provider.

5.3 Medication intended for self-administration

Self-administered medication may only be provided to the patient for whom they are prescribed and can

only be dispensed in accordance with prescriber instructions on a valid prescription. If a QOTP service provider authorises self-administered medication verbally to the pharmacist, the prescriber must dispatch written confirmation of the verbal instruction within 24 hours clearly indicating that it is confirmation of the direction given.

Self-administered medication must be given directly to the patient on the day(s) before the scheduled day(s) of absence from the pharmacy [29]. Medication intended for self-administration must not be provided to a third party on behalf of any patient without written approval by the QOTP service provider.

Advice should be given about the dangers of misuse, the hazards of using BPN and methadone in combination with other drugs, and the toxic potential if taken by a child or a person not tolerant to opioids.

Pharmacists should advise patients about secure storage of medication out of reach of children. The refrigerator is not an appropriate place (condensation may affect stability of the medication, and the medication may be accessible to others). Patients are solely responsible for the care and proper consumption of each medication once they have taken possession of it. Patients should be reminded to remove the labels and rinse single use take-away methadone containers after use and before disposal[30].

5.3.1 Dilution of methadone intended for short-term self-administration

Diluting methadone (Methadone or Biodone) intended for self-administration lowers the concentration of methadone in a given volume. This reduces the chance of an entire dose being accidentally swallowed by an opioid naïve person (e.g. a child), discourages injection, and reduces the value of diverted methadone.

Each self-administered dose of methadone (Methadone or Biodone) must be made up to 200 mL with purified water unless the prescriber has provided written approval on the contrary[31].

Patients may be given up to seven consecutive days of methadone (Methadone or Biodone) diluted to 200 mL. This is in consideration of the stability of the diluted product. For patients approved for longer periods of self-administration see section 5.3.2.

5.3.2 Extended period of self-administration of methadone for travel

Patients approved for self-administration over an extended period for travel will require the QOTP prescriber to provide a prescription to the pharmacist for methadone tablets to cover the approved travel period.

See also Section 4.14 for further information regarding travel.

5.3.3 Floating supervision requirements

‘Floating supervision’ directions enable flexibility with supervised administration. Prescriber directions for number and frequency of required supervised doses should be clearly stated on the prescription. The pharmacist and patient can then determine on a weekly basis which days best suit administration while meeting these directions.

Due to these changes, accurate records are of particular importance for safety and clear communications.

5.3.4 Unsupervised medication administration

Unsupervised medication administration may be authorised for patients on BPN/NX, BPN (mono) and methadone assessed as lower risk rating regarding self-administration of medication. See Section 1.2.3 Table 3.

The prescriber should provide clear unsupervised administration instructions on the prescription.

5.3.5 Changes to self-administered treatment regimen

Section 117 of the MPMR states that a dispenser may amend a prescription before dispensing the medicine by adding additional information to the prescription to clarify the prescriber's direction, and lays out requirements for this, including obtaining consent to the amendment from the person obtaining the medicine and agreement from the prescriber, and related record-keeping.

The following changes cannot be made by the pharmacist and require a new prescription from the QOTP service provider:

- change to the day of medication collection (when specified by the prescription)
- change to the number of doses of self-administered medication provided
- provision of additional or replacement medication
- change the way in which medication is supplied (e.g. providing two consecutive self-administered medication doses when two non-consecutive self-administered medication doses have been authorised)
- change the dilution volume of the medication from a final volume of 200 mL.

5.3.6 Authorised Agent

An agent may rarely be authorised to collect self-administered medication on behalf of a patient e.g. when a patient is severely ill, and a family member has been approved to collect their QOTP medication. The QOTP service provider is to advise the pharmacist of the patient details, the name of the nominated agent, and the period of authorisation of collection. Supply requires production of photo identification by the nominated agent.

5.3.7 Labelling and containers

Self-administered medication must be dispensed in accordance with the following instructions.

Methadone

Methadone for self-administration must be supplied in a clean 200 mL amber bottle (glass or plastic) and fitted with a child resistant closure. Each dose must be diluted to 200 mL with purified water. Reusing of bottles is not acceptable due to contamination risks.

Methadone intended for self-administration is packaged as one daily dose per bottle. Patients prescribed split doses of methadone must have a separate bottle for each dose. Each bottle must be labelled with:

- medication name, strength and quantity of the drug
- patient's name
- adequate directions, including the date when the medication is to be taken

- date when medication was supplied
- medication expiry date (7 days from date medication was prepared).
- name, address and telephone number of the pharmacy
- dispenser's initials
- 'keep out of reach of children' warning in red font on a white background affixed to bottle
- ancillary Label #1 [29, 133].

Sample label:

Methadone Liquid 5 mg/mL (60 mg / 12 mL, diluted)

60mg for Tuesday 15.02.23

Mr John Citizen 14.02.23

Expiry date: 21.02.23 IC

KEEP OUT OF REACH OF CHILDREN

SMITHTOWN PHARMACY 22 Browns Rd SMITHTOWN 4123

PH: 1234 5678

Ancillary label #1:

'This medication may cause drowsiness and may increase the effects of alcohol. If affected, do not drive a motor vehicle or operate machinery'.

Buprenorphine

Buprenorphine mono and BPN/NX for self-administration must be supplied in the original blister packs or sealed pouches. The daily dosage does not need to be individually packaged and labelled. Each strength of BPN or BPN/NX can be dispensed in its own envelope or box and labelled to reflect the daily dose prescribed. Each envelope or box must be labelled with:

- medication name, strength and quantity of the drug
- patient's name
- adequate directions, including the date when the medication is to be taken
- date when medication was supplied
- medication expiry date
- name, address and telephone number of the pharmacy
- dispenser's initials
- 'keep out of reach of children' warning in red font on a white background affixed to envelope or box
- ancillary Label #1[29, 133].

Example: A patient on a daily dose of BPN/NX (Suboxone) film 18mg who receives 28 doses at a time may receive 2 boxes or envelopes of films labelled as follows:

Buprenorphine / naloxone (Suboxone) Film 2 mg / 0.5 mg (qty 28 films)

Take ONE film daily from 01/02/2023 to 28/02/2023, inclusive. (To be taken in conjunction with buprenorphine / naloxone (Suboxone) 8mg/2 mg films to make up a total daily dose of 18mg.)

Mr John Citizen 31.01.23

Expiry date: 30.06.23 IC

KEEP OUT OF REACH OF CHILDREN

SMITHTOWN PHARMACY 22 Browns Rd SMITHTOWN 4123

PH: 1234 5678

Buprenorphine / naloxone (Suboxone) Film 8 mg / 2 mg (qty 56 films)

Take TWO films daily from 01/02/2023 to 28/02/2023, inclusive. (To be taken in conjunction with buprenorphine / naloxone (Suboxone) 2mg/0.5mg films to make up a total daily dose of 18mg)

Mr John Citizen 31.01.23

Expiry date: 30.06.23 IC

KEEP OUT OF REACH OF CHILDREN

SMITHTOWN PHARMACY 22 Browns Rd SMITHTOWN 4123

PH: 1234 5678

Attach Ancillary label #1 to each box:

'This medication may cause drowsiness and may increase the effects of alcohol. If affected, do not drive a motor vehicle or operate machinery.'

It is advisable to count out the medication in front of the patient at the time of supply so that parties are satisfied that the correct number of tablets or films have been supplied for the given period.

5.4 Missed medication administration

When a patient does not attend pharmacy to collect their medication, missed medication is calculated based on the equivalent number of daily doses not administered or supplied. A daily dose that has not been administered is one missed dose, while a double dose that has not been administered is two missed doses. With self-administered medication, each daily dose that has not been supplied to the patient is also counted as a single missed dose.

Some patients may respond to missed medication by accessing other substances [134]. Assessment of intoxication is particularly important when the patient next attends, and any patients who are intoxicated are to have their medication withheld and the QOTP service provider notified [29]. In determining their responsibility for administered medication to patients who have missed medication administration, pharmacists are to refer to Table 14.

Further information about missed doses of BPN can be found in Section 2.5.1 and missed doses of methadone in Section 3.5.1.

Table 14 Pharmacist Actions following missed doses

Equivalent of daily doses missed	Response
1 or 2 days of medication missed	If no evidence of intoxication administer as usual. Inform QOTP service provider that patient has resumed medication.
3 or more days of medication missed	Do not dispense medication. Patient must be reviewed by the QOTP service provider, who may reduce medication dose due to reduced tolerance [30]. The pharmacist must not recommence medication without approval from the prescriber.

5.5 Hospitalised patients

If clinically appropriate, ODT should continue on hospital inpatient admission. Hospital staff should contact the ODT prescriber and dispensing pharmacy to inform both that the patient is in hospital. To ensure safe continuation of treatment, the dispensing pharmacy should provide the hospital treating team with information about the patient's history and current treatment regimen; particularly any self-administered medication supplied (which may not have been consumed yet).

A copy of the relevant prescription can be provided to hospital staff. The pharmacist must record that the patient is an inpatient and therefore being provided with medication continuously elsewhere and ensure that the QOTP service provider is advised at the earliest opportunity.

Upon discharge, hospital staff must contact the prescriber or delegate directly. The QOTP service provider can then verify the patient's last dose at hospital, and coordinate return to pharmacy for medication administration. If communication does not occur, the pharmacist must obtain confirmation of discharge, and the date the patient was last administered medication at hospital before resuming community treatment [30]. The community pharmacist must also inform the QOTP service provider of patient's hospital discharge.

See also section 4.10

5.6 Specific situations

5.6.1 Intoxicated patients presenting for medication administration

Patient safety is the key consideration in responding to those who present for methadone or BPN administration when intoxicated with opioids, alcohol, benzodiazepines or other drugs. **Patients who**

appear intoxicated must not be administered their usual prescription of BPN or methadone or any medication intended for self-administration at that time. The pharmacist is to contact the QOTP service provider for instructions [12, 13]. If the prescriber or delegate are unavailable and the pharmacist has safety concerns, the medication must still be withheld, and the patient advised to contact their prescriber or delegate in relation to further steps including any likely withdrawal management. The pharmacist is also to notify the QOTP service provider at the earliest opportunity. Refer to the Monitored Medicines Standard for further information.

The pharmacist is not obliged to supply medication to patients who present, in their opinion, as intoxicated. Their professional obligation should be the health of the patient.

5.6.2 Other medications

A combination of opioid and sedating medication may be potentially hazardous. If a patient presents with a prescription for a sedating medication written by someone other than their QOTP prescriber, the pharmacist must contact the other prescriber to discuss their safety concerns. The QOTP service provider must also be contacted [30]. If a patient is on the QOTP and another prescriber is seeking to treat them with other monitored medicines, then that other prescriber must have a documented **joint prescribing plan** with the current QOTP prescriber. This is a requirement under the *Medicines and Poisons (Medicines) Regulation 2021* and a requirement for compliance with the *Monitored Medicines Standard*.

Patients may need Pharmacy Only or Pharmacist Only products at certain times. Pharmacists should exercise the usual care in these circumstances. If there is any suspicion of inappropriate or hazardous use of medication, the QOTP service provider must be notified.

5.6.3 Lost, stolen or broken medication intended for self-administration

Lost or stolen medication must not be replaced by the pharmacist and must be reported by the patient to both the QOTP service provider and QPS[30]. Similarly, broken or damaged medication must not be replaced without advice from the QOTP service provider.

Reporting lost or stolen medication

Pharmacists are required to report suspected lost or stolen medications under the Medicines and Poisons (Medicines) Regulation 2021. Further information and relevant forms for reporting can be found at reporting medicine matters.

5.6.4 Diversion

Diversion refers to methadone or BPN being used other than as intended or prescribed.

Diversion of supervised and self-administered methadone and SL BPN does occur. While most patients do not divert their medication, the potential for some patients to attempt to divert their medication, for a range of reasons, always remains a risk and is treated very seriously [30, 135].

Identifying diversion

To minimise the risks of diversion, patients should be provided with clear guidance on how and why medication is given, and how they should present during the observed consumption of the dose to avoid

unnecessary suspicion of diversion. Behaviours that may give rise to suspicion of diversion include:

- removing medication from mouth
- receptacles in the mouth (e.g. plastic caps, glad wrap, cotton wool)
- not co-operating with requested supervision or observations e.g. refusing to demonstrate BPN dissolving in the mouth, not wanting to speak or have mouth checked, not wanting to stay for the supervision period or inappropriately moving around the area
- causing distractions, e.g. attending for treatment with others then attempting to pass the medication on (e.g. kissing immediately after receiving medication)
- covering their face e.g. with hand or sleeve or other objects
- suspicious activity with cups, drink bottles and various kinds of containers
- spitting, coughing, sneezing
- out of character behaviour, nervousness, being 'overly-nice', watching the pharmacist closely
- suspicious interaction with other patients or acquaintances after medication administration
- reports of stockpiling medication intended for self-administration [17, 30].

Suspected diversion

Where the pharmacist suspects the patient of diverting or attempting to divert their medication, the pharmacist should discuss their concerns with the patient. This may clarify any misunderstandings regarding the administration requirements. If required, a formal first warning should be given by the pharmacist to the patient, outlining their concerns as well as consequences of further diversion attempts. The QOTP service provider must be notified.

Management of diversion

In all situations, discussion should occur with the patient regarding their behaviour, and the QOTP service provider must be notified. The pharmacy may also ask the treating clinician to place the patient at another pharmacy.

Confirmed incidents of diversion or attempted diversion

Where diversion has occurred, the QOTP service provider is to be notified. The prescriber should review the patient's situation and advise the pharmacist of any treatment changes, which may include:

- changes to supervision requirements
- change of QOTP pharmacotherapy with consideration to the particular clinical situation of the patient (e.g. pregnancy) [136].
- discontinuation of QOTP.

The pharmacy may also ask the QOTP service provider to refer the patient elsewhere.

5.6.5 Temporary closure of pharmacy due to emergency

In the event of declared emergencies or unexpected severe weather events, the prescriber or delegate should advise the pharmacist regarding authorisation for contingency self-administered medication.

5.7 Medication errors

All pharmacists, including locums and part-time staff, should be familiar with QOTP requirements. All prescriptions, patient identification records and other information must be readily accessible.

The following procedures should be adopted to reduce the possibility of medication administration errors:

- use a day book, diary or computerised administration system, to record and communicate important information to other pharmacists. This book should be inspected by staff daily
- check the date range on the current prescription to ensure validity. Indicate the end date of current prescription on the patient's record
- do not confuse millilitres (mL) with milligrams (mg) of methadone as this may result in a five-fold overdose or underdose
- if the dose is written in millilitres check the dose with the QOTP service provider
- if more than one patient has the same surname, attach an alert note to the patient's record card
- check that telephone contact details for patients are kept up-to-date monthly [30].

5.7.1 Excess dose/overdose

Inducing vomiting may be dangerous and is contraindicated, particularly if the patient has respiratory depression, an obstructed airway, is drowsy, or has other signs and symptoms of CNS depression. If there is concern about the amount of methadone or BPN consumed, it is best to be cautious and have the patient present to an ED without delay.

A patient who receives a methadone or BPN dose in excess of that prescribed is at risk of overdose, depending on the size of the overdose as a proportion of the usual dose and the duration of the current dose. Other individual factors of significance include impaired liver or kidney function and other recent drug consumption. Patients should be informed of the risks, in addition to symptoms of opioid toxicity such as nausea, dizziness, sedation or 'nodding off', unsteady gait, slurred speech, snoring, slow pulse, shallow breathing, frothing at the mouth, and coma [13, 15].

In the event of an excess dose the pharmacist should:

- advise the patient of any medication error
- advise the QOTP service provider of any medication error

Further management should vary depending on whether the patient and the prescriber can be contacted. The Queensland Poisons Information Centre may also be called on 13 11 26.

If the patient and the prescriber (or delegate) can be contacted, the prescriber (or delegate) should advise the pharmacist on what action is needed to ensure patient safety. Responses should be based on the clinical scenario and may include the patient being advised to attend an ED for monitoring, in which case the clinical situation should be handed over to ED staff by the prescriber or delegate or the pharmacist.

If the patient has left pharmacy and cannot be contacted, the prescriber (or delegate) should inform the pharmacist if there is a need to contact QPS for a welfare check.

If the prescriber (or delegate) is not available, the pharmacist should contact relevant emergency services. In the event the patient cannot be contacted by telephone, the pharmacist should contact QPS

to conduct a welfare check. If contact is made with the patient, QAS is to be called to take the patient to ED for medical monitoring. The prescriber (or delegate) is to be notified about the medication error at the earliest opportunity.

The pharmacist is to withhold further medication until notified by the QOTP service provider, to allow the patient to be reviewed and possible dose adjustments made.

5.7.2 Documentation

All medication administration errors should be documented in the patient record, including persons notified and actions taken.

Under the MPMR there are certain obligations to report medication events. For further information please see the general report to the chief executive.

5.8 Treatment of opioid withdrawal

Patients can experience opioid withdrawal symptoms when they are stabilising on ODT, reducing their dose or have missed medication administration. To assist with managing withdrawal symptoms pharmacists can provide treatments such as paracetamol, ibuprofen, loperamide, hyoscine butylbromide, oral rehydration therapy, vitamin and mineral supplements as required. Sedating anti-histamines - especially doxylamine and diphenhydramine - may be misused and should not be used without approval by the QOTP service provider. Other advice such as sleep hygiene, smoking cessation and guidelines on low-risk alcohol intake, may also be provided by the pharmacist.

5.9 Naloxone

Pharmacists are authorised to dispense NX (solution for injection or nasal spray) as an S3 medicine to treat opioid overdose. Furthermore, NX may be supplied for free if the pharmacy is a participant of the National THN program. For more information, including how to apply to be a participating pharmacy see Take Home Naloxone program.

When supplying NX in ampoule form, check if the patient needs the additional equipment to administer the injection in an emergency (e.g. needle). The patient should be directed to information about how to use NX, and management of an overdose:

- Insight - Toolkits - Take Home Naloxone
- Overdose - QuIHN

5.10 Pharmacy opening hours

When a pharmacy is not open to administer medication for a designated period (e.g. public holiday), it is important to minimise any interruptions to the patient's treatment. Pharmacists should inform QOTP service providers of closures with sufficient notice for alternative arrangements to be made for patients.

5.11 Patient complaints mechanism

Patients who do not agree with a decision made by their pharmacists or prescribers may make a complaint using the mechanism appropriate to their service provider [13, 30]. Patients can also contact QPAMS for advocacy and support – see Appendix 17.

See Appendix 20 for Quick Reference Guide - Pharmacists

6. Clinical Opioid Withdrawal Scale (COWS)[137]

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was engaged in jogging just prior to assessment, the increase pulse rate would not add to the score.

Resting pulse rate: _____ beats/minute

Measured after patient is sitting or lying for one minute

0 pulse rate 80 or below
1 pulse rate 81-100
2 pulse rate 101-120
4 pulse rate greater than 120

GI Upset: *over last ½ hour*

0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhoea
5 multiple episodes of diarrhoea or vomiting

Sweating: *over past ½ hour not accounted for by room temperature or patient activity.*

0 no report of chills or flushing
1 subjective report of chills or flushing
2 flushed or observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face

Tremor: *observation of outstretched hands*

0 No tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching

Restlessness: *Observation during assessment*

0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 unable to sit still for more than a few seconds

Yawning: *Observation during assessment*

0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment
4 yawning several times / minute

Pupil size:

0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
2 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Anxiety or Irritability:

0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable or anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Bone or Joint aches: *if patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*

0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

Gooseflesh skin:

0 skin is smooth
3 piloerection of skin can be felt or hairs standing up on arms
5 prominent piloerection

Runny nose or tearing: *not accounted for by cold symptoms or allergies*

0 not present
1 nasal stuffiness or unusually moist eyes
2 nose running or tearing
4 nose constantly running or tears streaming down cheeks

Total Score

The total score is the sum of all 11 items

5-12 = mild
13-24 = moderate
25-36 = moderately severe
>36 = severe withdrawal

7. Subjective Opioid Withdrawal Scale (SOWS)

The Subjective Opioid Withdrawal Scale (SOWS)[138] is a self-report measure that provides patients with an opportunity to assess the severity of their withdrawal symptoms. This can assist patients in taking an active role in the management of withdrawal symptoms, reducing anxiety about being appropriately medicated.

Please score each of the 16 items below according to how you feel now (circle one number per symptom). Add the total score which will range from 0-64. A higher score reflects more severe withdrawal.

Date: _____ Time: _____

	Symptom	Not at all	A little	Moderately	Quite a bit	Extremely
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goose bumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

8. Objective Opioid Withdrawal Scale (OOWS)[138]

Observe the patient during a 5-minute period. Then indicate a score for each of the opioid withdrawal signs listed below (items 1-13). Add the scores for each to obtain the total score.

Date: _____ Time: _____

	Sign	Measures		Score
1	Yawning	0 = no yawning	1 = yawning	
2	Rhinorrhoea	0 <3 sniffs	1 = 3 or more sniffs	
3	Piloerection (observe arm)	0 = absent	1 = present	
4	Perspiration	0 = absent	1 = present	
5	Lacrimation	0 = absent	1 = present	
6	Tremor (hands)	0 = absent	1 = present	
7	Mydriasis	0 = absent	1 ≥3 mm	
8	Hot and cold flushes	0 = absent	1 = shivering/huddling for warmth	
9	Restlessness	0 = absent	1 = frequent shifts of position	
10	Vomiting	0 = absent	1 = present	
11	Muscle twitches	0 = absent	1 = present	
12	Abdominal cramps	0 = absent	1 = holding stomach	
13	Anxiety	0 = absent	1 = mild to severe	
Total score:				

9. Acute intoxication symptoms and signs

Class of drug	Intoxication	Overdose
Opioids (e.g., heroin, morphine)	Miosis Itching Sedation/somnolence Lowered blood pressure Slowed pulse Hypoventilation	Unconscious Respiratory depression Pinpoint pupils Hypotension Bradycardia Pulmonary oedema
Stimulants (e.g., cocaine, amphetamines)	Hyperactivity Restlessness Agitation Anxiety/nervousness Mydriasis Elevated blood pressure Increased pulse Raised temperature Sweating Tremor	Panic Acute paranoid psychosis Seizures Cardiac arrhythmias Myocardial ischemia (rarely infarct) Hypertensive crisis Cerebrovascular accidents Hyperpyrexia Dehydration
Benzodiazepines (e.g., diazepam, oxazepam, flunitrazepam)	Disinhibition Sedation Drooling Incoordination Slurred speech Lowered blood pressure Dizziness	Stupor/coma Ataxia Confusion Respiratory depression
Cannabis	Relaxation Decreased concentration Decreased psychomotor performance Impaired balance Conjunctival injection	Paranoid psychosis Confusion Agitation Anxiety/panic Hallucinations
Alcohol	Relaxation Disinhibition Impaired coordination Impaired judgement Decreased concentration Slurred speech Ataxia Vomiting	Disorientation/confusion Respiratory depression Loss of consciousness Loss of bladder control

10. Substance withdrawal states[12]

Drug Class	Onset	Duration	Symptoms of withdrawal
Opioids	8–12 hours	Peaks 2–4 days, ceases 7–10 days	Anxiety, muscle tension, muscle and bone ache, muscle cramps, sleep disturbance, sweating, hot and cold flushes, piloerection, yawning, lacrimation, rhinorrhoea, abdominal cramps, nausea, vomiting, diarrhoea, palpitations, elevated blood pressure and pulse, dilated pupils
Stimulants	8–36 hours	Several days, occasionally 2–3 weeks	Lethargy, depression, irritability, hyperphagia, anhedonia, dysphoria, desire for sleep increased
Benzodiazepines	1–10 days (depending on half-life)	3–6 weeks (may be longer)	Anxiety, insomnia, muscle aching and twitching, perceptual changes, feelings of unreality, depersonalisation, seizures
Cannabis	Usually days	Weeks	Irritability, anxiety, insomnia, anorexia, sweating, muscle spasms, headaches
Alcohol	As BAL falls, depends on rate of fall and hours after last drink	5–7 days	Anxiety, agitation, sweating, tremor, nausea, vomiting, abdominal cramps, diarrhoea, anorexia, craving, insomnia, elevated blood pressure and pulse, temperature, headache, seizures, confusion, perceptual distortions, disorientation, hallucinations, hyperpyrexia

11. Product information

For product information, refer to the Therapeutic Goods Administration eBusiness Services - Product and Consumer Medicine Information:

- Methadone product information
- Biodone Forte® product information
- Suboxone® product information
- Subutex® product information
- Naltrexone product information
- Naloxone product information
- Buvidal® Weekly product information AUS
- Buvidal® Monthly product information AUS
- Sublocade® product information AUS
- Sublocade® prescribing information US

12. Pharmacokinetic properties of buprenorphine

12.1 Onset and duration of action

Buprenorphine is a long-acting drug with a terminal elimination half-life of 24–37 hours. Peak plasma concentrations are achieved 1-4 hours after sublingual administration. Typically, effects will continue to be experienced for up to 12 hours at low doses (2 mg), but up to 48–72 hours at higher doses (16 or 32 mg)[6]. The prolonged duration of effect at high doses enables double (alternate-day administration), and even triple (third-day administration) dispensing regimens[139].

12.2 Metabolism

Buprenorphine is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and N-dealkylation, mediated by the CYP450 3A4 isoenzyme. The metabolites are excreted in the biliary system, with enterohepatic cycling of BPN and its metabolites. Most of the drug is excreted in the faeces and, to a lesser extent, in the urine[6].

BPN undergoes extensive first pass metabolism in the small intestine and the liver when taken orally, so oral use is not appropriate. The bioavailability of SL BPN reflects the time the drug is in contact with the oral mucosa and is approximately 30-40%.

The metabolism of BPN is unaffected by the formulation. Variation in plasma terminal half-life and duration of effect relates to differences in the rate of release of BPN from the three different formulations. Subcutaneous administration of LAI BPN results in significantly lower plasma concentrations of norbuprenorphine metabolite compared to SL BPN, avoiding the first-pass metabolism invariably seen with some swallowing of SL medication.

On similar doses of BPN, females have higher blood concentrations and active metabolites than males, likely due to different body composition, and unlikely to be a major concern[140].

12.3 Withdrawal

The partial agonist properties of BPN and its slow dissociation from opioid receptors result in a withdrawal syndrome that is milder than that from full agonists. Typically, the withdrawal syndrome following the abrupt cessation of long-term BPN treatment emerges within three to five days of the last medication dose, and mild withdrawal features continue for several weeks[139].

12.4 Long-acting injectable BPN

The key pharmacokinetic properties of Buvidal® and Sublocade® are detailed in the Product Information (see previous Section 11) and summarised in this section for comparison between the two products.

Repeated use of the LAI BPN formulations results in accumulation over time, and steady state equilibrium is achieved after approximately three to six weekly/monthly doses. The average (Cavg), peak (Cmax) and trough (Cmin) BPN plasma concentrations seen at steady state (after four doses) of the various LAI and SL BPN formulations are shown in Figure 3, allowing a framework for comparing effects across different formulations. While dose-proportional increases are seen within each category (SL,

weekly and monthly) of BPN products, there is nevertheless considerable variation in BPN plasma levels between individuals, and these should be interpreted as guides only.

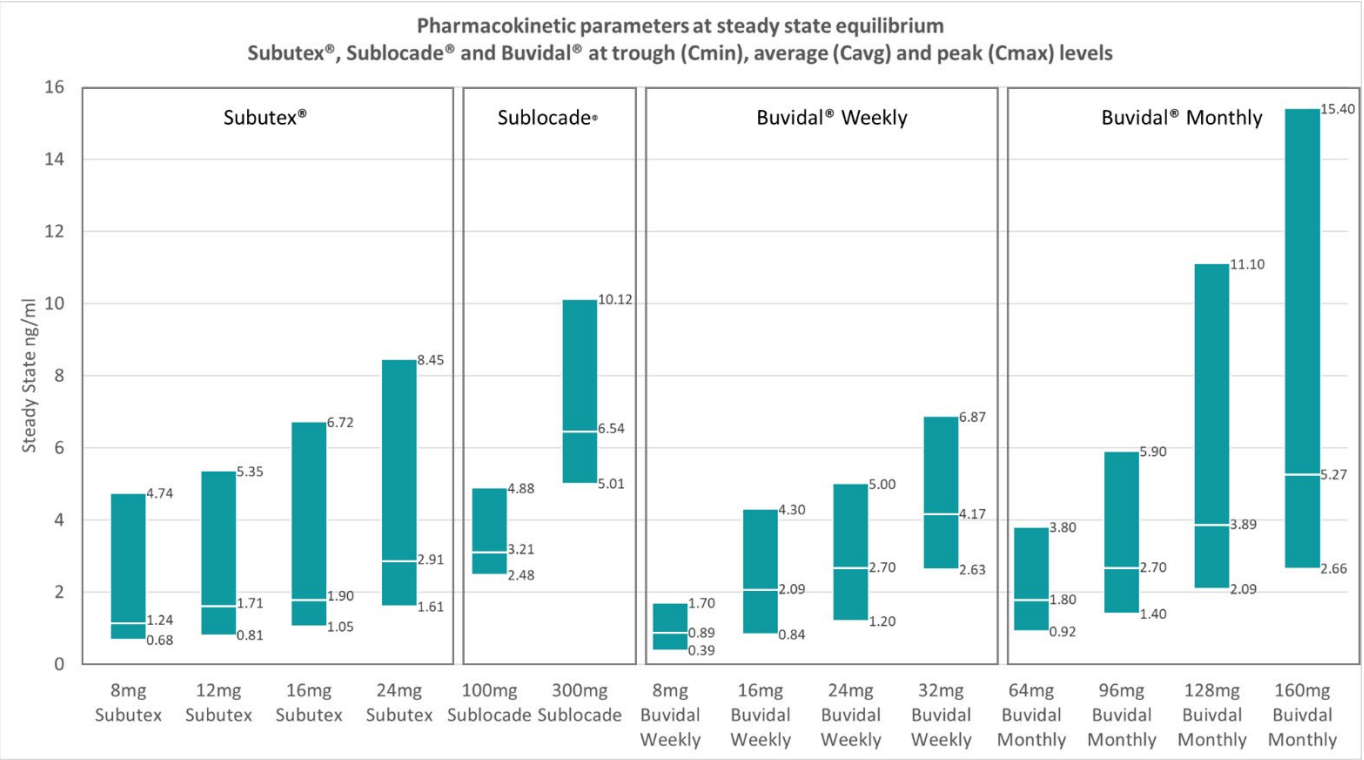


Figure 3 Pharmacokinetic parameters – steady state

Suppression of signs and symptoms of withdrawal may require ≥ 50% mu opioid receptor occupancy (μORO), often associated with BPN plasma concentrations ≥ 1 ng/mL; whereas opioid blockade (defined as the inhibition of the positive subjective effects (i.e., drug liking) of exogenous opioids) appears to require higher proportion (e.g. ≥ 70-80%) μORO, which is commonly associated with higher BPN plasma concentrations (e.g. ≥ 2-3 ng/mL[141, 142]). These plasma levels are generally achieved by all LAI BPN formulations. While laboratory receptor-binding studies are of interest in understanding this treatment approach, they do not translate into clinical practice readily, and there is no clinical role for monitoring BPN plasma levels as part of patient care. At this time, routine measures of BPN plasma levels are not available nor can opioid receptor occupancy be assessed in clinical practice: few laboratories have the capacity to accurately quantify BPN and norbuprenorphine levels, tests are not reimbursed by Medicare, requiring the patient or clinician to pay for the tests, and findings are very difficult to interpret. Rather clinicians should focus upon individual patient responses to treatment, with reviews of patient experience of withdrawal, cravings and continued substance use. Furthermore, continued heroin or other opioid use may be a result of inadequate BPN dose – but may also be related to social or other health issues.

However, it should be emphasised that plasma BPN levels only partially account for the clinical effects experienced by patients – such as prevention of opioid withdrawal and cravings, and blockade effects. A range of other factors impact upon the clinical effects of BPN and must be considered when titrating BPN doses to achieve desired clinical outcomes – including patient expectation, concomitant health

conditions, use of opioids and other substances, DDIs, adverse events and genetic variation in BPN metabolism. While expected plasma concentrations routinely achieved with formulations can serve as a guide to the choice of BPN doses and formulation, titration with regular patient monitoring is required.

12.4.2 Absorption and onset of effects

After sub-cutaneous injection, BPN peak concentrations are observed approximately 6-10 hours after the Buvidal® monthly injection, and approximately 24 hours after the Buvidal® weekly and Sublocade® injections. After the initial BPN peak, the plasma BPN concentrations decrease slowly to a plateau.

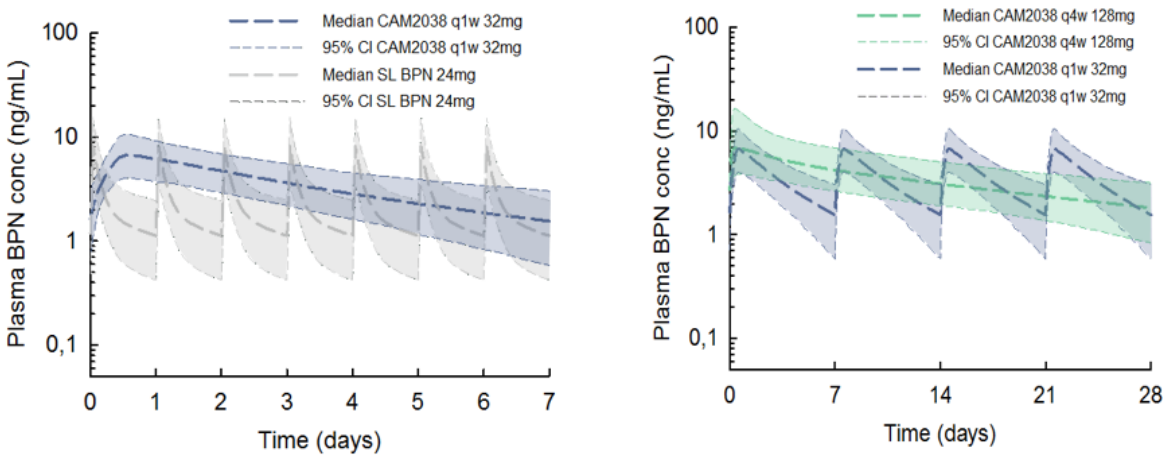


Figure 4 **Buvidal® Weekly and Buvidal® Monthly versus daily SL BPN**

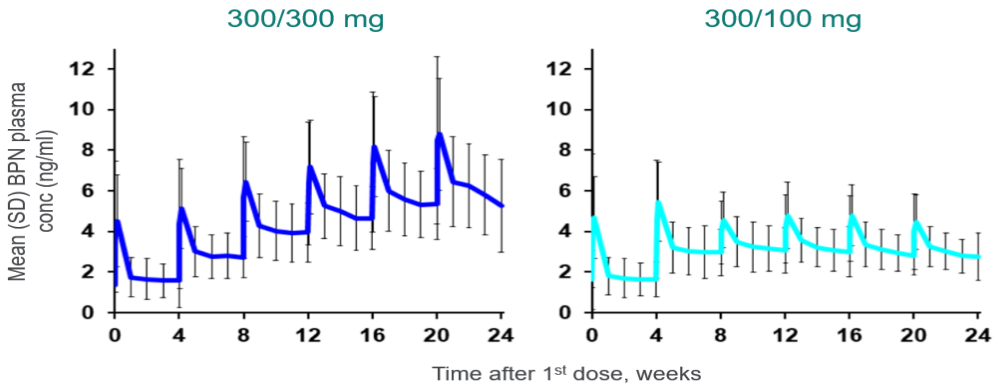


Figure 5 **Sublocade® PK profile**

12.4.3 Elimination and duration of effects

The slow release of BPN from the LAI formulations results in extended duration of action of these products. The terminal plasma half-life of single doses of the LAI formulations are:

- Buvidal® Weekly: 3 to 5 days
- Buvidal® Monthly: 19 to 25 days
- Sublocade®: 43 to 60 days

With repeated administration, BPN plasma levels accumulate until steady-state equilibrium is achieved typically after five half-lives of administered medication and needs to be considered when adjusting medication during the first few weeks or months of treatment. For Buvidal® this typically means after the fourth dose (one month for Buvidal® Weekly, 4 months for Buvidal® Monthly). For Sublocade® this means after the 6th month of the 300/300 regimen, however steady state is achieved after two loading doses of 300 mg and the patient is changed to 100mg. The clinical effects of discontinuing LAI BPN will depend upon the formulation administered (weekly or monthly), the dose of BPN administered (longer duration with higher doses), and the duration of treatment (whether steady state has been achieved following multiple doses).

Model simulations and clinical experience indicate that steady‑state BPN plasma concentrations decrease slowly over time following the last injection and remain at therapeutic levels for extended periods – potentially up to 12 weeks (Buvidal® Monthly, Sublocade® 100mg) or up to 20 weeks (Sublocade® 300mg). The prolonged duration of effects of LAI formulations may impact upon the (delayed) emergence of withdrawal symptoms, experience of adverse events, DDIs, and transitioning onto other opioid medications (e.g., SL BPN, methadone). It may also result in delayed loss of tolerance to opioids and be protective against overdose following relapse to heroin or other opioid use.

12.4.4 Withdrawal, cravings, opioid blockade and safety

Clinical trials indicate that both Buvidal® and Sublocade® are well-tolerated and effective in reducing opioid withdrawal and opioid cravings, with a number of clinical trials summarized in Table 15. 'Opioid blockade', inhibition of the positive physiological and subjective effects (i.e. drug liking) of exogenous opioids, is achieved by BPN due to its greater affinity for mu opioid receptors than many other opioids such as morphine, heroin, methadone, oxycodone. The blockade of subjective opioid effects has been demonstrated with laboratory hydromorphone challenge studies with Buvidal® Weekly and Sublocade® products.

Table 15 LAI BPN studies

Study Reference	Product	Setting	Author
NCT02672111 HS-14-499 (Braeburn)	**Buvidal®**	**Community AUS**	**Frost et al 2019**
Aims: To assess long-term safety of subcutaneous buprenorphine depot (CAM2038) weekly and monthly regimens in adult outpatients with opioid use disorder. **Methods:** This phase 3, open-label, multicentre, 48-week study (ClinicalTrials.gov NCT02672111) was conducted at 26 sites (US, UK, Hungary, Denmark, Sweden, Germany, and Australia). Participants were administered CAM2038 weekly (8, 16, 24, or 32mg) or CAM2038 monthly (64, 96, 128, or 160mg) with flexible treatment schedules and individualised titration up or down utilising the multiple CAM2038 weekly and monthly dose options. Safety variables, urine toxicology samples, and self-reported illicit opioid use were collected at each visit. 162/227 (71.4%) participants were administered a patient satisfaction survey. **Results:** Between December 14, 2015, and April 12, 2017, 228 opioid-dependent participants enrolled, and 227 participants received CAM2038 (37 initiated directly onto CAM2038 and 190 converted from sublingual buprenorphine). 167/227 (73.6%) participants completed the treatment period. 143/227 (63.0%) participants			

reported at least 1 treatment emergent adverse event (TEAE), and 60/227 (26.4%) reported a drug-related TEAE. 46/227 (20.3%) participants reported injection site reactions, with most (45/46 [97.8%]) reported as mild to moderate. 128/227 (56.4%) of the TEAEs were mild or moderate in severity. Five participants (2.2%) discontinued study drug due to a TEAE, of which 2 cases (0.9%) were injection site related. No serious adverse events were attributed to study drug. At end of study, the percentage of the composite outcome comprising illicit opioid-negative urine samples and self-reports was 63.0% (17/37) in new-to-treatment participants and 82.8% (111/190) for participants converted from sublingual buprenorphine. Participants reported high levels of satisfaction with CAM2038.

Conclusions: CAM2038 was well-tolerated and demonstrated a systemic safety profile consistent with the known profile of sublingual buprenorphine. Weekly and monthly CAM2038 was associated with high retention rates and low levels of continued illicit opioid use throughout the study[27].

Study Reference	Product	Setting	Author
NCT02611752	**Buvidal®**	**US**	**Walsh et al 2017**

Importance Buprenorphine is an efficacious, widely used treatment for opioid use disorder (OUD). Daily oral transmucosal formulations can be associated with misuse, diversion, and nonadherence; these limitations may be obviated by a sustained release formulation.

Objective To evaluate the ability of a novel, weekly, subcutaneous buprenorphine depot formulation, CAM2038, to block euphorigenic opioid effects and suppress opioid withdrawal in non–treatment-seeking individuals with OUD.

Design, Setting and Participants This multisite, double-blind, randomized with in-patient study was conducted at 3 controlled inpatient research facilities. It involved 47 adults with DSM-V moderate-to-severe OUD. The study was conducted from October 12, 2015 (first patient enrolled), to April 21, 2016 (last patient visit).

Interventions A total of five 3-day test sessions evaluated the response to hydromorphone (0, 6, and 18mg intramuscular in random order; 1 dose/session/day). After the first 3-day session (ie, qualification phase), participants were randomized to either CAM2038 weekly at 24mg (n = 22) or 32mg (n = 25); the assigned CAM2038 dose was given twice, 1 week apart (day 0 and 7). Four sets of sessions were conducted after randomization (days 1-3, 4-6, 8-10, and 11-13). Weekly CAM2038 doses were initiated directly from adults maintained on oral morphine.

Main Outcomes and Measures The primary end point was maximum rating on the visual analog scale for drug liking. Secondary end points included other visual analog scale (eg, high and desire to use), opioid withdrawal scales, and physiological and pharmacokinetic outcomes.

Results A total of 46 of 47 randomized participants (mean [SD] age, 35.5 [9] years; 76% male [n = 35]) completed the study. Both weekly CAM2038 doses produced immediate and sustained blockade of hydromorphone effects (liking maximum effect, CAM2038, 24mg: effect size, 0.813; P < .001, and CAM2038, 32mg: effect size, 0.753; P < .001) and suppression of withdrawal (Clinical Opiate Withdrawal Scale, CAM2038, 24mg: effect size, 0.617; P < .001, and CAM2038, 32mg: effect size, 0.751; P < .001). CAM2038 produces a rapid initial rise of buprenorphine in plasma with maximum concentration around 24 hours, with an apparent half-life of 4 to 5 days and approximately 50% accumulation of trough concentration from first to second dose (trough concentration = 0.822 and 1.23 ng/mL for weeks 1 and 2, respectively, with 24mg; trough concentration = 0.993 and 1.47 ng/mL for weeks 1 and 2, respectively, with 32mg).

Conclusions and Relevance CAM2038 weekly, 24 and 32mg, was safely tolerated and produced immediate and sustained opioid blockade and withdrawal suppression without any evidence of precipitating withdrawal upon depot initiation. The results support the use of this depot formulation for treatment initiation and stabilization of patients with OUD, with the further benefit of obviating the risk for misuse and diversion of daily buprenorphine while retaining its therapeutic benefits.[143]

Study Reference	Product	Setting	Author
	Buvidal®	**US**	**Liu et al 2018**

CAM2038, FluidCrystal injection depot, is an extended release formulation of buprenorphine given subcutaneously every 1 week (Q1W) or every 4 weeks (Q4W). The purpose of this research was to predict the magnitude of drug-drug interaction (DDI) after coadministration of a strong CYP3A4 inducer or inhibitor using physiologically based pharmacokinetic (PBPK) modelling.

A PBPK model was developed for CAM2038 based on the previously published buprenorphine PBPK model after intravenous and sublingual administration and the PK profiles after subcutaneous administration of CAM2038 from 2 phase I clinical trials. The strong CYP3A4 inhibitor ketoconazole was predicted to increase the buprenorphine exposure by 35% for the Q1W formulation and 34% for Q4Wformulation, respectively. Also, the strong CYP3A4 inducer rifampin was predicted to decrease the buprenorphine exposure by 26% for both the Q1W and Q4W formulations.

The results provided insight into the potential DDI effect for CAM2038 and suggested a lack of clinically meaningful DDI when CAM2038 is coadministered with CYP3A4 inhibitor or inducer. Therefore, no dose adjustment is required when CAM2038 is coadministered with CYP3A4 perpetrators.[144]

Study Reference	Product	Setting	Author
NCT02357901	**Sublocade®**	**Community US**	**Haight et al 2019**

Background: RBP-6000, referred to as BUP-XR (extended-release buprenorphine), is a subcutaneously injected, monthly buprenorphine treatment for opioid use disorder. BUP-XR provides sustained buprenorphine plasma concentrations to block drug-liking of abused opioids over the entire monthly dosing period, while controlling withdrawal and craving symptoms. Administration of BUP-XR in a health-care setting also mitigates abuse, misuse, diversion, and unintentional exposure. We aimed to investigate the efficacy of different BUP-XR dosing regimens in participants with opioid use disorder.

Methods: This randomised, double-blind, placebo-controlled, phase 3 trial was done at 36 treatment centres in the USA. Treatment-seeking adults aged 18–65 years who had moderate or severe opioid use disorder (as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders) entered an open-label run-in phase of up to 2 weeks' treatment with buprenorphine-naloxone sublingual film. Eligible participants were then randomly assigned (4:4:1:1) with an interactive voice/web-response system to receive BUP-XR 300 mg/300 mg (six injections of 300 mg), BUP-XR 300 mg/100 mg (two injections of 300 mg plus four injections of 100 mg), or volume-matched placebo every 28 days, and received weekly individual drug counselling. No supplemental buprenorphine was allowed. The primary efficacy endpoint was participants' percentage abstinence from opioid use, defined as the percentage of each participant's negative urine samples and self-reports of illicit opioid use from week 5 to week 24, analysed in the full analysis set. Safety was assessed in all participants who received at least one dose of BUP-XR or placebo. This study is registered with ClinicalTrials.gov, number NCT02357901.

Findings: From Jan 28, 2015, to Nov 12, 2015, 1187 potential participants were screened, 665 entered run-in, and 504 received BUP-XR 300 mg/300 mg (n=201), BUP-XR 300 mg/100 mg (n=203), or placebo (n=100). Mean participants' percentage abstinence was 41·3% (SD 39·7) for BUP-XR 300 mg/300 mg and 42·7% (38·5) for 300 mg/100 mg, compared with 5·0% (17·0) for placebo (p<0·0001 for both BUP-XR regimens). No compensatory non-opioid drug use was observed during BUP-XR treatment. The most common adverse events were headache (17 [8%] participants in the BUP-XR 300 mg/300 mg group vs 19 [9%] participants in the BUP-XR 300 mg/100 mg group vs six [6%] participants in the placebo group), constipation (16 [8%] vs 19 [9%] vs 0), nausea (16 [8%] vs 18 [9%] vs five [5%]), and injection-site pruritis (19 [9%] vs 13 [6%] vs four [4%]). The BUP-XR safety profile was consistent with other buprenorphine products for treatment of opioid use disorder, except for injection-site reactions, which were reported in more than 5% of all participants who received BUP-XR, but were mostly mild and not treatment-limiting.

Interpretation: Participants' percentage abstinence was significantly higher in both BUP-XR groups than in the placebo group. Treatment with BUP-XR was also well tolerated. The availability of this monthly formulation, delivered by health-care providers, represents an advance in treatment for opioid use disorder that enhances the benefits of buprenorphine by delivering sustained, optimal exposure, while reducing risks of current buprenorphine products.[145]

Study Reference	Product	Setting	Author
NCT02044094	**Sublocade®**	**Community US**	**Indivior 2002**

Background: Buprenorphine's two key effects of reducing craving and attenuating the response to opioid drugs contribute to reduce the self-administration of opioids. In the development of Buprenorphine as a monthly, sustained-release formulation (Sublocade®) achieving plasma levels to demonstrate attenuation of opioid effects is an important dose confirmation step.

Objective: The objective of this study was to demonstrate that Sublocade® blocks the subjective effects and reinforcing efficacy of the μ-opioid receptor agonist hydromorphone (intramuscularly administered) in subjects with moderate or severe opioid use disorder.

Methods: Subjects were first inducted and dose stabilized on sublingual buprenorphine/naloxone (8–24 mg daily; dose expressed as the buprenorphine component), then received two subcutaneous injections of RBP-6000 (300 mg) on Day 1 and Day 29. Hydromorphone (HM) challenges (6 mg, 18 mg or placebo administered in randomized order) occurred on 3 consecutive days of each study week before and after receiving RBP-6000. Subjects reported their responses to each challenge on various 100-mm Visual Analogue Scales (VAS). Subjects also completed a choice task to assess the reinforcing efficacy of each hydromorphone dose relative to money. The noninferiority (NI) margin, the largest difference allowed for the 6 or 18 mg HM VAS to exceed the placebo VAS (the maximum VAS recorded following IM injection of 0 mg HM) before being considered significant, was set at 20. Based on comparison to the historical response to opioid agonists in unblocked subjects, a difference of less than 20 points (on a unipolar scale) between the mean maximum response to hydromorphone and the mean maximum placebo response for the same challenge was considered to indicate near-complete blockade.

Results: All 12 weeks of the treatment period demonstrated blockade for both 6 mg and 18 mg following Sublocade® injections. However, wide variation can be seen in isolated measurements from individual subjects, shown in the figure below. Complete blockade continued throughout the 8 weeks of observation that followed the 2nd Sublocade® injection. For comparison, stabilization doses of SL buprenorphine in Week 0 failed to provide full blockade to 18 mg of HM.

Conclusion: This study demonstrated that RBP-6000 at a 300 mg dose provides durable and potent blockade of the subjective effects and reinforcing efficacy of hydromorphone in subjects with moderate or severe opioid use disorder.

Summary based on US prescribing information

Study Reference	Product	Setting	Author
NCT02651584	**Buvidal®**	**Community US**	**Lofwall et al 2018**

Objective To determine whether treatment involving novel weekly and monthly subcutaneous (SC) buprenorphine depot formulations is non-inferior to a daily sublingual (SL) combination of buprenorphine hydrochloride and naloxone hydrochloride in the treatment of opioid use disorder.

Design, Setting and Participants This outpatient, double-blind, double-dummy randomized clinical trial was conducted at 35 sites in the United States from December 29, 2015, through October 19, 2016. Participants were treatment-seeking adults with moderate-to-severe opioid use disorder.

Interventions Randomization to daily SL placebo and weekly (first 12 weeks; phase 1) and monthly (last 12 weeks; phase 2) SC buprenorphine (SC-BPN group) or to daily SL buprenorphine with naloxone (24 weeks) with matched weekly and monthly SC placebo injections (SL-BPN/NX group).

Main Outcomes and Measures Primary end points tested for non-inferiority were response rate (10% margin) and the mean proportion of opioid-negative urine samples for 24 weeks (11% margin). Responder status was defined as having no evidence of illicit opioid use for at least 8 of 10 pre-specified points during weeks 9 to 24, with 2 of these at week 12 and during month 6 (weeks 21-24). The mean proportion of samples with no evidence of illicit opioid use (weeks 4-24) evaluated by a cumulative distribution function (CDF) was an a priori secondary outcome with planned superiority testing if the response rate demonstrated non-inferiority.

Results A total of 428 participants (263 men [61.4%] and 165 women [38.6%]; mean [SD] age, 38.4 [11.0] years) were randomized to the SL-BPN/NX group (n = 215) or the SC-BPN group (n = 213). The response rates were 31 of 215 (14.4%) for the SL-BPN/NX group and 37 of 213 (17.4%) for the SC-BPN group, a 3.0%difference (95%CI, −4.0%to 9.9%; P < .001). The proportion of opioid-negative urine samples was 1099 of 3870 (28.4%) for the SL-BPN/NX group and 1347 of 3834 (35.1%) for the SC-BPN group, a 6.7%difference (95%CI, −0.1%to 13.6%; P < .001). The CDF for the SC-BPN group (26.7%) was statistically superior to the CDF for the SL-BPN/NX group (0; P = .004). Injection site adverse events (none severe) occurred in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group.

Conclusions and Relevance Compared with SL buprenorphine, depot buprenorphine did not result in an inferior likelihood of being a responder or having urine test results negative for opioids and produced superior results on the CDF of no illicit opioid use. These data suggest that depot buprenorphine is efficacious and may have advantages.[146]

Study Reference	Product	Setting	Author
ISRCTN24987553 **HS-13-438**	**Buvidal®**	**Community**	**Albayaty et al 2017**

Introduction CAM2038 q1w (once weekly) and q4w (once monthly) are investigational buprenorphine subcutaneous (SC) formulations based on FluidCrystal® injection depot technology. These two drug products are being developed for opioid dependence treatment, with a target for once-weekly and once-monthly SC dosing. The rationale for developing two products with different dosing frequencies is that treatment strategies/routines, and hence different treatment preferences, can vary between patients, different stages of opioid maintenance treatment, and countries. This study evaluated the pharmacokinetics and safety of buprenorphine and norbuprenorphine following administration of CAM2038 q1w or q4w versus active controls.

Methods Healthy volunteers were randomized to five treatment groups. All received a single intravenous dose of buprenorphine 600 µg, followed post-washout by a single dose of CAM2038 q4w 96mg, a single dose of CAM2038 q4w 192mg, or sublingual buprenorphine 8, 16, or 24mg daily for 7 days, followed post-washout by a single dose of CAM2038 q4w 64 or 128mg or four repeated weekly doses of CAM2038 q1w 16mg. All subjects received daily naltrexone.

Results Eighty-seven subjects were randomized. Median buprenorphine tmax after CAM2038 q4w was 4–10 h (24 h for CAM2038 q1w); mean terminal half-life was 19–25 days (5 days for CAM2038 q1w). CAM2038 q4w showed dose-proportional buprenorphine release, with similar exposure to repeat-dose CAM2038 q1w at comparable monthly dose level. Both CAM2038 formulations showed complete absolute bioavailability of buprenorphine and 5.7- to 7.7-fold greater buprenorphine bioavailability versus sublingual buprenorphine. CAM2038 q1w and q4w were well tolerated; subjects' acceptance was higher for CAM2038 than for sublingual buprenorphine 1 h post-dose.

Conclusions The pharmacokinetic profiles of CAM2038 q1w and q4w versus sublingual buprenorphine support expected treatment efficacy with once-weekly and once-monthly dosing, respectively. CAM2038 formulations were safe and showed good local tolerability.[147]

Study Reference	Product	Setting	Author
NCT03604861	**Sublocade®**	**Community**	**Ling et al 2020**

Objectives: While evidence has mounted regarding the short-term effectiveness of pharmacotherapy for opioid use disorder (OUD), little is known about longer-term psychosocial, economic, and health outcomes. This study reports 12-month outcomes for an observational study enrolling participants who had previously taken part in a long-acting buprenorphine subcutaneous injection (BUP-XR) trial for moderate to severe OUD.

Methods: The RECOVER (Remission from Chronic Opioid Use: Studying Environmental and Socioeconomic Factors on Recovery) study enrolled participants from 35 US community-based sites. Self-reported sustained opioid abstinence over 12 months and self-reported past-week abstinence at 3-, 6-, 9-, and 12-month visits were assessed. Multiple regression models assessed the association of BUP-XR duration with abstinence, controlling

for potential confounders. Withdrawal, pain, health-related quality of life, depression, and employment at RECOVER baseline and 12-month visits were also compared to values collected before treatment in the BUP-XR trial.

Results: Of 533 RECOVER participants, 425 completed the 12- month visit (average age 42 years; 66% male); 50.8% self-reported sustained 12-month and 68.0% past-week opioid abstinence. In multiple regressions, participants receiving 12-month versus 2-month BUP-XR treatment duration had significantly higher likelihood of sustained opioid abstinence (75.3% vs 24.1%; P = 0.001), with similar results for past-week self-reported abstinence over time. During RECOVER, participants had fewer withdrawal symptoms, lower pain, positive health-related quality of life, minimal depression, and higher employment versus pre-trial visit.

Conclusions: RECOVER participants reported positive outcomes over the 12-month observational period, including high opioid abstinence and stable or improved humanistic outcomes. These findings provide insights into the long-term impact of pharmacotherapy in OUD recovery.[148]

Study Reference	Product	Setting	Author
	Sublocade®	**Community**	**Jones et al 2021**

Background: BUP-XR (RBP-6000)is an extended-release subcutaneous buprenorphine formulation for the treatment of opioid use disorder. BUP-XR was designed to provide sustained buprenorphine exposure throughout the monthly dosing interval, at concentrations sufficient to control all aspects of the disease (withdrawal, craving, and blockade of opioid subjective effects).

Objectives: To characterize the population pharmacokinetics of BUP-XR based on phase II and phase III data and to evaluate whether target therapeutic concentrations were reached with the dosing regimens evaluated in the phase III program.

Methods: The population pharmacokinetic analysis included 570 subjects with opioid use disorder who received up to 12 monthly BUP-XR injections following induction with sublingual buprenorphine.

Results: In phase III studies, target therapeutic concentrations of buprenorphine were achieved from the first injection and maintained over the entire treatment duration. Buprenorphine plasma concentration–time profiles were well described by a two-compartment model, with first-order absorption for sublingual buprenorphine and a dual absorption submodel for BUP-XR. A covariate analysis evaluated the effects of subjects' demographic characteristics, laboratory data, and genetic status regarding buprenorphine-metabolizing enzymes. Only two covariates, body mass index and body weight, were retained in the final model. Overall, their effects were not of sufficient magnitude to justify a dose adjustment. Finally, pharmacokinetic simulations showed that buprenorphine plasma concentrations decreased slowly after discontinuation of treatment and that a 2-week occasional delay in dosing would not impact efficacy, which translated into labelling claims.

Discussion: In conclusion, the present analysis led to the development of a robust population pharmacokinetic model and confirms the ability of BUP-XR to deliver and maintain therapeutic plasma concentrations over the entire treatment duration.[149]

Study Reference	Product	Setting	Author
NCT03809143	**Sublocade®**	**Community**	**Farrell**

Background: Opioid agonist treatment (OAT) is an effective intervention for opioid dependence. Extended-release buprenorphine injections (BUP-XR) may have additional potential benefits over sublingual buprenorphine. This single-arm trial evaluated outcomes among people receiving 48 weeks of BUP-XR in diverse community healthcare settings in Australia, permitting examination of outcomes when BUP-XR is delivered in standard practice.

Methods: Participants were recruited from a network of specialist public drug treatment services, primary care and some private practices in three states. Following a minimum 7 days on 8-32 mg of sublingual buprenorphine (±naloxone), participants received monthly subcutaneous BUP-XR injections administered by a healthcare practitioner and completed monthly research interviews. The primary endpoint was retention in treatment at 48 weeks.

Findings: Participants (n = 100) were 28% women, mean age 44 years with a long history of OAT (median 5.8 years); heroin was the most common opioid of concern (58%). Treatment retention at 24 and 48 weeks was 86% and 75%, respectively. Participants with past-month injecting drug use (OR 0.23; 95%CI: 0.09-0.61) or heroin use (OR 0.23; 95%CI: 0.08-0.65) at baseline had lower odds of being retained in treatment to 48 weeks. Reductions in multiple forms of extra-medical drug use were observed. Improvements in quality of life, participation in employment, and treatment satisfaction measures were also observed.

Interpretation: This real-world implementation study of BUP-XR demonstrated high retention and treatment satisfaction. This study provides important additional data on the uptake and experience of clients, with relevance for policy makers, health service planners, administrators, and practitioners.[150]

13. Pharmacokinetic properties of methadone

13.1 Onset and duration of effects

Methadone is well absorbed after oral administration, with a mean bioavailability of around 75%. It can be detected in the blood 15-45 minutes after oral administration, with peak plasma concentration at 2.5-4 hours[6]. Estimates of the elimination half-life of methadone vary across a range of 20 to 36 hours[6, 151], with a mean value of around 22 hours. Methadone reaches a steady state concentration after approximately five half-lives, or 3–10 days. Once stable, variations in blood levels are relatively small. For some, fluctuations in methadone levels may lead to withdrawal symptoms in the latter part of the interval between doses. If dose increases or administering split doses within the day do not prevent this, other agonist replacement treatment approaches such as BPN should be considered[15].

13.2 Metabolism

Methadone is primarily metabolised in the liver via the CYP450 CYP3A4 and CYP2B6 isoenzymes, as well as CYP1A2, CYP2C8, CYP2C19, CYP2D6 and CYP2C9 systems[152]. 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 small amounts in breast milk[6].

13.3 Withdrawal

Onset of methadone withdrawal typically occurs 36 to 48 hours after last dose, with peak symptoms at 5-7 days. A staged reduction of methadone will reduce the severity of withdrawal symptoms[30].

14. Clinically significant drug interactions

14.1 BPN and Methadone

This list includes prescription medications that are known to, or may potentially result in, clinically significant interactions when used in combination with methadone or BPN[6, 12]. The list is not exhaustive: if in doubt, seek specialist advice. The list draws on information from www.opioiddruginteractions.com; site inactive 8 March 2022.

In the tables, ++ indicates a strong clinical interaction, + indicates an interaction of less significance and ? indicates the potential for interaction with limited supporting evidence. All interactions should be avoided if possible, or patients should be monitored, and drug regimens adjusted if necessary.

14.1.1 Increased sedative effects

The medications in this group may increase the risk of overdose through additive CNS depression, or increased plasma levels of methadone or BPN resulting from deceased metabolism or decreased urinary clearance.

Table 16 Drug-Drug Interactions causing increased sedation[6]

Clinical significance for:		Medication
Methadone	Buprenorphine	
++	++	Amitriptyline
	++	Atazanavir
++	++	Benzodiazepines (alprazolam, diazepam)
?		Ciprofloxacin
++		Citalopram/escitalopram
?		Erythromycin
++	?	Fluconazole
+	?	Fluoxetine
++	+	Fluvoxamine
+	?	Indinavir
?	?	Ketoconazole
+		Moclobemide
?		Omeprazole
?	?	Ritonavir (avoid using in combination with atazanavir)
?		Sertraline
+		Urine alkalisers (e.g., sodium bicarbonate)
++	+	Zopiclone

14.1.2 Withdrawal symptoms or adverse effects

The medications in this group may cause decreased plasma levels and withdrawal symptoms due to increased metabolism of methadone or BPN, or may cause adverse effects through other mechanisms[12].

Table 17 Drug-Drug Interactions causing withdrawal symptoms or adverse effects[6]

Clinical significance for:		Medication
Methadone	Buprenorphine	
++		Carbamazepine
+	?	Cimetidine
+		Disulfiram (if used in conjunction with methadone syrup containing alcohol)
+	?	Hypericum perforatum (St John's Wort)
+		Moclobemide
+		Nevirapine
	?	Nifedipine
++	?	Phenytoin
++	?	Rifampicin
++	++	Rifabutin
+	+	Urine acidifiers (e.g., ascorbic acid)

14.1.3 Prolongation of QTc interval

These medications may be contraindicated for use with methadone either due to their independent capacity to cause prolongation of the QTc interval[12] or due to inhibition of methadone metabolism. Other factors may also influence the QTc interval: increasing age, female gender, hypocalcaemia, hypokalaemia and hypomagnesaemia[153].

Table 18 Methadone Drug Interactions causing QTc prolongation[153]

Medication Class	Medication
Antidepressants	Citalopram/escitalopram
	Moclobemide
	Tricyclic antidepressants
	Lithium
Antihistamines	Loratadine
	Diphenhydramine
Antimicrobials	Ciprofloxacin, moxifloxacin
	Erythromycin, clarithromycin
	Fluconazole, voriconazole

Medication Class	Medication
	Pentamidine
Antipsychotics	Amisulpride
	Chlorpromazine
	Haloperidol
	Ziprasidone
Cardiac Drugs	Sotalol
	Disopyramide
Other drugs	Domperidone
	Cisapride
	Ondansetron, dolasetron
	Chloroquine

When assessing risk of QTc prolongation a QT nomogram, as shown in Figure 6, may be used. A QT-heart rate pair above the line is associated with increased risk and below the line with lower risk.

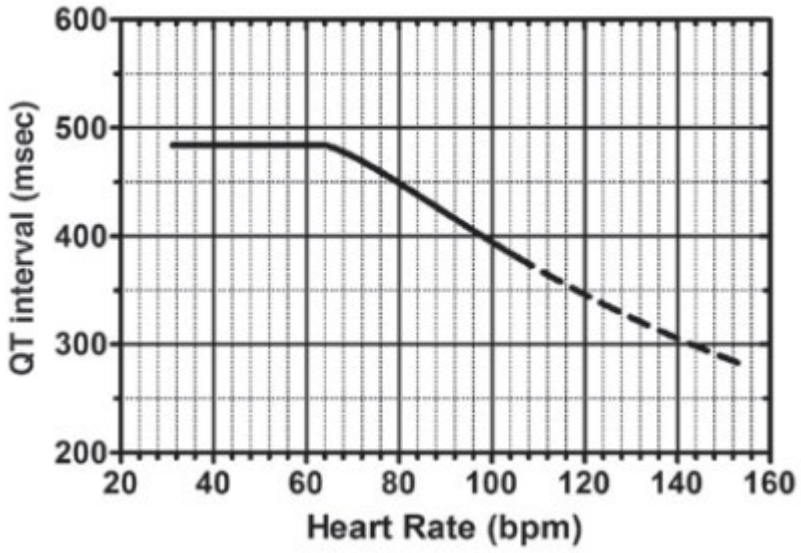


Figure 6 QT nomogram[153]

14.1.4 Effects on other medications

Methadone and BPN may also impact adversely on the other medications that may be used in combination.

Table 19 Effects on other medications[6]

Clinical significance for:		Medication
Methadone	Buprenorphine	
++		Atazanavir (methadone may decrease serum levels)
++		Desipramine (metabolism decreased leading to increased plasma levels of desipramine)
++		Nifedipine (methadone may inhibit metabolism)
++		Zidovudine (metabolism is decreased leading to increased plasma levels of zidovudine. Symptoms of zidovudine toxicity can be misinterpreted as opioid withdrawal)

14.2 LAI BPN

Table 20 Drug-drug interactions of potential clinical relevance with LAI BPN[12]

Drug Class	Drug(s) within Class	Clinical effect and suggested management
Benzodiazepines and Other CNS Depressants	Alcohol, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, antipsychotics, and other opioids	• Increases the risk of respiratory depression, profound sedation, coma, and death • Use of these substances should be avoided or minimised during treatment with BPN formulations. Patients should be advised of the potential for sedation and increased risk of overdose from concomitant use of sedatives while participating in LAI BPN treatment.
CYP3A4 inhibitors:	Macrolide antibiotics azole-antifungal agents protease inhibitors (e.g. erythromycin, ketoconazole, ritonavir, nelfinavir, indinavir, itraconazole)	• An interaction study of BPN with ketoconazole resulted in increased Cmax (approximately 50%) and area under the curve (approximately 70%) of BPN and, to a lesser extent, of the metabolite, norbuprenorphine • Patients receiving BPN should be closely monitored for signs and symptoms of BPN toxicity and may require reduction if combined with potent CYP3A4 inhibitors. The dose of either BPN or the CYP3A4 inhibitor may need to be adjusted accordingly. In practice, medication rarely needs to be adjusted. • Monitor for BPN withdrawal if the concomitant medication is discontinued after the patient is stable on LAI BPN.

Drug Class	Drug(s) within Class	Clinical effect and suggested management
CYP3A4 Inducers	Rifampicin Carbamazepine Phenytoin Phenobarbital	• Concomitant use of CYP3A4 inducers with BPN may decrease BPN plasma concentrations, potentially resulting in sub-optimal treatment of opioid dependence. It is recommended that patients receiving BPN should be closely monitored if inducers are co-administered. The dose of either BPN or the CYP3A4 inducer may need to be adjusted accordingly. In practice, medication rarely needs to be adjusted. • Monitor for signs and symptoms of BPN toxicity or overdose, if the CYP3A4 inducer is discontinued after the patient is stable on LAI BPN.
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz Nevirapine	• Significant pharmacokinetic interactions between NNRTIs and SL BPN have been shown, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects. • Monitor for increase or decrease in therapeutic effects of NNRTIs.
Antiretrovirals: Protease inhibitors (PIs)	Atazanavir Ritonavir	• Treatment with atazanavir or atazanavir/ritonavir may result in elevated levels of BPN • If atazanavir +/- ritonavir is initiated once the patient is stable on LAI BPN, monitor for signs and symptoms of over-medication with BPN. If necessary, reduce LAI BPN dose from 300 to 100mg, or discontinue LAI BPN and treat with SL BPN to enable rapid medication adjustments.
Drugs that affect the serotonin neurotransmitter system	SSRIs Serotonin and norepinephrine reuptake inhibitors (SNRIs) Trazodone, Tramadol Linezolid and intravenous methylene blue Tricyclic antidepressants (TCAs)	• May result in serotonin toxicity in high doses (e.g. overdose) or when multiple serotonergic drugs are combined. Monitor for signs and symptoms of serotonin toxicity, particularly during treatment initiation, and during dose adjustment of the serotonergic drug.
Monoamine Oxidase Inhibitors (MAOIs)	e.g. Phenelzine, tranylcypromine	• MAOI interactions with opioids may manifest as serotonin toxicity or opioid toxicity (e.g., respiratory depression, coma). • It is recommended that patients receiving BPN and MAOI should be closely monitored. • Exacerbation of the opioid effects based on experience with morphine

Drug Class	Drug(s) within Class	Clinical effect and suggested management
Diuretics		• May reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. • Intervention: Monitor patients for signs of diminished diuresis and/or effects on blood pressure, oedema or cardiac failure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs		• May increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. • Monitor for signs of urinary retention or reduced gastric motility.
Opioid antagonists	Naltrexone NX	• Opioid antagonists should generally not be used outside of emergency situations in patients in opioid agonist treatment, including LAI BPN. • NX may be administered in response to an opioid overdose, multiple injections or an infusion of NX may be required. • For opioid-dependent patients currently receiving BPN treatment, naltrexone may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently receiving naltrexone treatment, the intended therapeutic effects of BPN administration may be blocked by naltrexone.
Opioid analgesics	Opioids	• BPN may reduce the effects of opioid analgesics through receptor blockade. Patients requiring analgesia should include non-opioid approaches (e.g. non-steroidal anti-inflammatories, ketamine). Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration, requiring close monitoring of opioid effects • Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving BPN. The potential for overdose also exists with a full agonist, especially when attempting to overcome BPN partial agonist effects, or when BPN plasma levels are declining. • Titrate opioid analgesics according to clinical response. • Call ADCAS on 1800 290 928 for advice on complex cases.

Drug Class	Drug(s) within Class	Clinical effect and suggested management
Gabapentinoids and other GABA agonists	Gabapentin, pregabalin, baclofen	• This combination may result in death due to respiratory depression. Therefore, dosages must be closely monitored, and this combination must be avoided in cases where there is a risk of misuse. Patients should be cautioned to use gabapentinoids concurrently with this product only as directed by their physician.
Alcohol	Alcoholic drinks or medications containing alcohol	• Alcoholic drinks or medications containing alcohol as alcohol increases the sedative effect of BPN

15. Letter of introduction to pharmacy (sample)

25.01.2023

Dr John Prescriber
Local GP Practice
123 Prescriber Crescent
BRISBANE Q 4000
Ph: 07 3333 3333
Fax: 07 4444 4444

Local Day & Night Chemist
111 Apothecary Way
BRISBANE Q 4500

Dear Sir/Madam

Re: **PATIENT EXAMPLE - D.O.B. 01.01.1961**

Thank you for accepting this patient at your pharmacy for treatment under the Queensland Opioid Treatment Program. The first dose is scheduled for 1st February 2022. The patient's details are below:

Name:	Patient Example
Address:	111 Patient Street
	BRISBANE Q 4001
Phone:	07 38921111
Date of birth:	01.01.1961
Sex:	Female
Height:	172cm
Weight:	80kg
Medical conditions:	
Current medications:	

Should you have any queries or concerns, please do not hesitate to contact me on the above number. Thank you for your assistance.

Yours faithfully,

Dr John Prescriber

Local GP Practice

16. International travel letter (sample)

25.08.2023

Dr John Prescriber
Local GP Practice
123 Prescriber Crescent
BRISBANE Q 4000
Ph: 07 3333 3333
Fax: 07 4444 4444

Dear Sir/ Madam

Ms XYZ - 01.01.1961
15 Brisbane Street
Brisbane QLD 4000
AUSTRALIA

XYZ is a patient of the Local GP Practice in Brisbane. She is receiving long term treatment for opioid dependence with methadone. Her current treatment regimen is seventy mg (70 mg) each day. She is travelling overseas on holiday with her husband, departing Australia on 14 October 2022, and returning on 31 October 2022.

When she leaves the country, she will carry 16 days of medication with her, i.e. a total of **1,120** mg of methadone supplied in 10 mg tablets, i.e. **112** tablets of methadone (Physeptone tablets). This will provide her with daily doses of 70 mg or 7 tablets from 15 October to 30 October.

This patient is being treated in accordance with State and Federal legislation.

Please feel free to contact me if further information is needed.

Yours sincerely

J PRESCRIBER
Local GP Practice

17. Contact numbers for Queensland

Alcohol and Drug Clinical Advisory Service (ADCAS)

Phone: 1800 290 928
Available: 8.00am-11.00pm 7 days a week
For health professionals only

Adis 24/7 Alcohol and Drug Support

Phone: 07 3837 5989
Free call: 1800 177 833
Available: 24/7 State-wide
Contact for details of AOD Clinics

Athena Clinic

(Alcohol and Drug Ante-natal care)
Athena Clinic Coordinator
Maternity Outpatients
Royal Brisbane and Women's Hospital
Butterfield Street, Herston Qld 4029
Phone: 07 3647 3957

Athena Clinic available each Monday
If Athena unavailable, contact:
Nurse Unit Manager, Maternity Outpatients RBWH
Phone: 07 3647 3962 (Business hours)

CHAMP Clinic

(Alcohol and Drug Ante-natal care)
CHAMP Coordinator
Mater Mother's Hospital
Raymond Terrace, South Brisbane, Qld 4101
Phone: 07 3163 2417
Email: champ@mater.org.au

Healthcare Approvals and Regulation Unit (HARU)

GPO Box 48
Brisbane QLD 4001
Fax: 07 3708 5431
Email: QOTP@health.qld.gov.au
Operating hours: 9am-5pm, M-F

Hepatitis B Vaccination

Queensland Health Immunisation Program
PO Box 2368, Fortitude Valley BC Qld 4006
Phone: 3328 9888
Fax: 3328 9720
Email: immunisation@health.qld.gov.au
(for provision of vaccines)
Vaccines are funded for specific groups including:
- ATSI people
- People with chronic liver disease and/or Hepatitis C
- Persons who inject drugs
Contact your local Public Health Unit for Information

Hospital Alcohol and Drug Service (HADS)

(Hospital inpatient withdrawal management service)
Royal Brisbane and Women's Hospital (RBWH)
Herston Qld 4029
Phone: 07 3646 8704 (available 24/7)
Fax: 07 3646 7772

Office of the Health Ombudsman (OHO)

PO Box 13281 George Street, Brisbane Qld 4003
Phone: 133 646
Email: complaints@oho.qld.gov.au
Web: www.oho.qld.gov.au

Queensland Pharmacotherapy Advice and Mediation Service (QPAMS)

Located at: Queensland Injectors Health Network (QuIHN)
1 Hamilton Place, Bowen Hills Qld 4006
PO Box 2470 Fortitude Valley BC Qld 4006
Phone: 07 3620 8111
Free call: 1800 175 889
Fax: 07 3854 10701070
Web: www.quihn.org
Available for telephone advice/advocacy State-wide
Web: www.quivaa.org.au

18. Interstate contact list

New South Wales

Pharmaceutical Services
New South Wales Ministry of Health
1 Reserve Road, ST LEONARDS NSW 2065
Locked Mail Bag 2030 ST LEONARDS NSW 1590
Phone: 02 9424 5921
Fax: 02 9424 5885
Email: MOH-OTP@health.nsw.gov.au

Victoria

Medicines and Poisons Regulation
Department of Health
GPO Box 4057
Melbourne VIC 3001
Fax: 1300 360 830
Email: dpcs@health.vic.gov.au
Web: https://www.health.vic.gov.au/drugs-and-poisons/pharmacotherapy-opioid-replacement-therapy

South Australia

Drugs of Dependence Unit
South Australia Department of Health
PO Box 6, Rundle Mall,
Adelaide SA 5000
Phone: 1300 652 584
Fax: 1300 658 447
Email: HealthDrugsofDependenceUnit@sa.gov.au

Australian Capital Territory

Opioid Treatment Service
Alcohol and Other Drugs Program
Building 7
The Canberra Hospital
Palmer Street, GARRAN ACT 2605
Phone: 02 5124 9977
Fax: 02 6205 0951

Western Australia

Health Department of Western Australia
PO Box 8172
Perth BC WA 6849
Phone: 08 9222 6812
Fax: 08 9222 2463

Northern Territory

Chief Poisons Officer
Poisons Branch, NT Health
PO Box 40596
Casuarina NT 0811
Phone: 08 8922 7341
Fax: 08 8922 7200
Email: poisonscontrol@nt.gov.au

Tasmania

Alcohol and Drug Service South
Tasmanian Health Service
GPO Box 125
Hobart, TAS 7000
Phone: 03 6166 0736
Fax: 03 6173 0810
Email: ads.southintake@ths.tas.gov.au

Therapeutic Goods Administration

PO Box 100
Woden ACT 2606
Phone: 1800 020 653 or 02 6289 4124
Fax: 02 6203 1605
Email: info@tga.gov.au

19. Quick Reference Guide – Prescribers

Day 1

- Take a detailed history, over more than one appointment if required.
- Make a diagnosis of opioid dependence.
- Choose an appropriate evidence-based treatment
  - For withdrawal management: BPN (see Queensland Alcohol and Other Drug Withdrawal Guidelines)
  - For maintenance: BPN or methadone.
- Obtain informed consent, providing information regarding the effects and side effects of BPN and methadone.
- Check QScript to confirm that the patient is not concurrently registered with another QOTP provider and to review their monitored medicines medication history.
- Advise the patient about the processes for their first administration of BPN or methadone. It is recommended they commence either on BPN/NX or LAI BPN.
- The approach for SL BPN stabilisation varies with method. If commencing using:
  - moderated withdrawal method - '*start low and go quickly*'.
  - low-dose or very-low-dose method - '*start low and go slow*'.
- The approach for methadone stabilisation is '*start low and go slow*'.
- Administer medication for the first time or inform an approved pharmacy of the initial dose.
- BPN or BPN/NX or LAI BPN:
  - *Moderated withdrawal*: Once clear objective signs of withdrawal are present, commence BPN 4 - 8mg.
  - *Low-dose or very-low-dose*: Gradually increase BPN dose from 0.4 mg / day to 4 mg / day over 7 days while maintaining current opioid use, then cease short-acting opioid use; gradually increase BPN to 12 mg/day over the next 7 days before stopping use of all other opioids.
  - *LAI BPN:* variable initial dose depending on current opioid and dose.
- Methadone 5–20 mg / 1–4 mL.
- Review 2 - 4 hours after initial dose (optional). For methadone patients, if objective withdrawal persists, up to 5 mg / 1 mL methadone (to a total ≤ 30 mg / 6 mL) may be ordered. For BPN patients using moderated withdrawal method, if objective withdrawal persists without evidence of precipitated withdrawal, then a further 2–6 mg (to a total of 8 mg) may be ordered.
- QOTP Admission Form to be sent to HARU (QOTP@health.qld.gov.au) on the first day of treatment but no later than the end of the next business day after the treatments starts.

Day 2

- Review patient prior to second administration of medication.

- **For BPN with moderated withdrawal:** decrease the dose only if there is evidence of significant sedation in the previous 24 hours. Maintain the dose if the patient is comfortable at review. Increase the dose by 4-8 mg if the patient shows evident withdrawal. Maximum dose on day 2 = 16 mg.
- **For methadone:** decrease the dose if there are no signs of withdrawal 24 hours after initial dose. Size of reduction should vary depending on initial starting dose. Maintain the dose if the patient was initially comfortable and not sedated but develops withdrawal prior to review. Increase the dose by 5 mg / 1 mL if the patient shows marked withdrawal and reports no suppression of withdrawal during the previous 24 hours. Maximum dose on day 2 ≤35 mg.

Days 3 & 4

- Review daily prior to medication administration.
- As above, maximum dose ≤40 mg methadone; ≤24 mg BPN.
- Daily review is essential due to medication accumulation effects as the long half-lives result in increased effects even without increase in oral dose. (The effect is not unlike that seen in warfarin treatment).

Day 5 and ongoing

- If the above medication doses do not control withdrawal symptoms by day 5, consult with a medical addiction specialist. Review weekly for 4-6 weeks and then fortnightly for a further 6-8 weeks.

Optimal dose

Increases in methadone to achieve the target dose should not exceed 5 - 10mg / 1 - 2mL at a time, with a maximum of 20 mg / 4 mL per week. The dose should not exceed 40 mg / 8 mL in the first week of induction. Physical assessment to exclude sedation should occur both before and after the increase.

- Target doses for effective maintenance are 60-100 mg / 12-20 mL methadone and 8 – 24 mg BPN.
- BPN patients should be expected to achieve 8mg or more during initial stabilisation.
- Methadone patients must be commenced on low initial doses, and only increased gradually.

Medication for self-administration

- BPN patients should be offered conversion to LAI BPN once stabilised; if SL BPN is preferred, patients should be offered double dose regimens.
- ODT medication for self-administration should only be provided based on risk assessment rating and implementation of risk mitigation strategies.

Cessation of QOTP

- On completion of treatment or transfer to another prescriber, the QOTP discharge form should be forwarded to HARU (QOTP@health.qld.gov.au) as soon as practicable, but within three business days of treatment ending.

20. Quick Reference Guide – Pharmacists

The pharmacist has a professional responsibility to ensure all staff (including locum pharmacists) are appropriately trained and informed regarding QOTP requirements.

When should medication not be given?

- Stop dose
- Missed 3 or more consecutive days of treatment (calculated as 3 daily dose equivalents)
- Safety concerns regarding sedation/intoxication
- Patient requests replacement of lost or stolen medication
- Patient requests replacement of vomited medication
- Post pharmacy overdose error and prescriber/clinic has not advised to resume administration of medication
- Prescription does not comply with legal requirements
- Prescription expired, incomplete or unclear
- No prescription
- Third party requests medication (and is not an “authorised agent” for patient)
- Patient not scripted to have medication dispensed that day
- Unable to verify identity of new patient (when patient has no photo ID)
- Post hospital discharge and unable to confirm date of last medication administration in hospital
- Request for additional medication intended for self-administration by the patient.

When should the pharmacist contact the prescriber/clinic?

- Missed medication administration (and restart after missed administration)
- Intoxication
- Vomited medication
- Diversion or suspected diversion
- Lost or stolen medication intended for self-administration reported
- Inappropriate behaviour
- Suspicion of inappropriate use of other substances including over-the-counter and prescription medicines
- Patient prescribed S4 or S8 medication of concern from different prescriber
- Attending for medication administration on days for which self-administered medication was provided
- Patient advises of variation to prescription
- Third party attends to collect medication (and not an “authorised agent” for patient)
- Request for additional self-administered medication

- Prescription - expired
- Prescription - incomplete, unclear or ambiguous order
- Unusual dose on prescription
- Administration of incorrect dose
- Significant and concerning changes in patient's behaviour or general health
- Patient discharged from hospital
- Pharmacy closures
- Patient presents with a prescription for medication that has a significant interaction with QOTP medication.

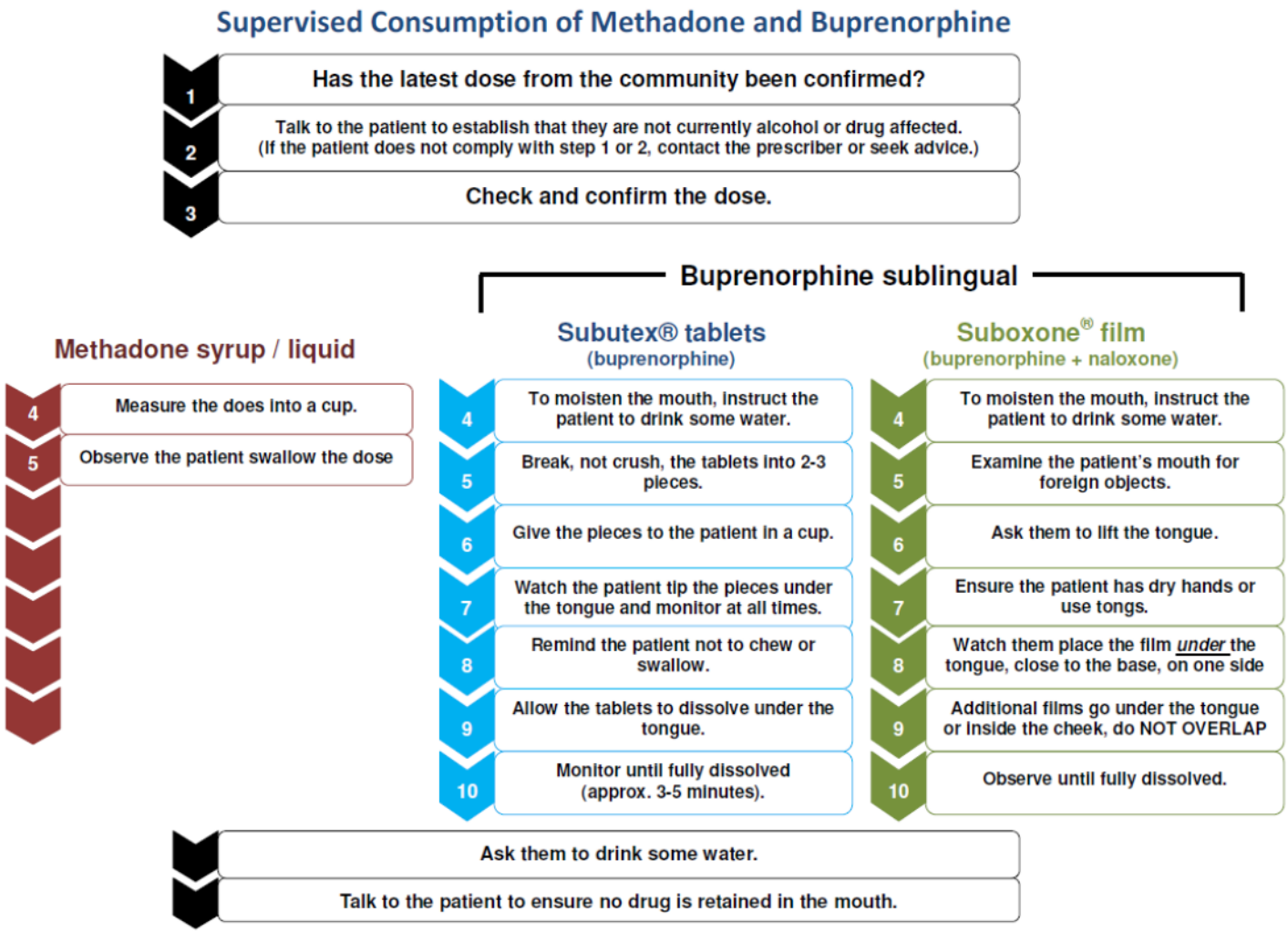
When can the pharmacist initiate resumption of dose?

- Patient has missed 1 or 2 doses (daily dose equivalents), and
- Patient has no evidence of intoxication when attends to restart dosing.

Management of issues when prescriber unavailable:

- Attempt to call prescriber – leave message identifying self, phone number, patient name and issue.
- Follow prescription (in situations where conflict between written order and patient report).
- Refer patient to GP or ED for any medical issues (e.g. concerns with substance withdrawals).
- QAS to be called for any medical emergencies (e.g. seizure, severe intoxication).
- QPS to be called to conduct a Welfare Check, when incorrect excess dose administered, and patient cannot be contacted.
- Contact ADCAS for support and advice (1800 290 928)

21. Quick Reference Guide – Administration of Opioid Dependence Medication in Hospital



22. Websites

The following are the web addresses for links provided within the body of this document. This is not intended to be an exhaustive list of resources or services.

Queensland Health – Queensland Opioid Treatment Program
Queensland Opioid Treatment Program www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/monitored-medicines/queensland-opioid-treatment-program QOTP prescriber types factsheet www.health.qld.gov.au/__data/assets/pdf_file/0018/1211544/fs-qotp-prescriber-types.pdf QOTP prescribing approvals www.health.qld.gov.au/system-governance/licences/medicines-poisons/medicines/prescribing-approvals

Queensland Health – Regulation and monitoring of monitored medicines
Medicines, poisons and pest management regulatory framework www.health.qld.gov.au/system-governance/licences/medicines-poisons/medicines-poisons-act Queensland Health Departmental Standard: Monitored medicines www.health.qld.gov.au/__data/assets/pdf_file/0029/1108937/ds-monitored-medicines.pdf Monitored Medicines Standard Companion Document www.health.qld.gov.au/__data/assets/pdf_file/0014/1111721/monitored-med-stand-companion.pdf. Monitored Medicines Standard supporting documents www.health.qld.gov.au/system-governance/licences/medicines-poisons/medicines-poisons-act/supporting-documents Reporting requirements and forms for monitored medicines www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/reporting-medicines-matters#s226 Writing lawful prescriptions factsheet www.health.qld.gov.au/__data/assets/pdf_file/0011/1115003/writing-lawful-prescriptions.pdf QScript www.qscript.health.qld.gov.au Information about real-time prescription monitoring of monitored medicines www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/real-time-reporting QScript learning portal https://insight.qld.edu.au/toolkits/qscript-learning/detail Storage and record-keeping requirements for S8 medicines www.health.qld.gov.au/__data/assets/pdf_file/0024/1159071/storage-record-keeping-s8-medicines.pdf

Queensland Health – AOD policy and guidelines
Co-occurring substance use disorders and other mental health disorders: policy position statement for Mental Health Alcohol and Other Drugs Services 2021 www.health.qld.gov.au/__data/assets/pdf_file/0023/1118246/qh-gdl-964.pdf Queensland Alcohol and Other Drug Withdrawal Guidelines qheps.health.qld.gov.au/__data/assets/pdf_file/0027/1519506/24904_p1.pdf

Alcohol and Other Drugs Therapeutic Intervention Overview
insight.qld.edu.au/shop/poster-3-alcohol-and-other-drugs-therapeutic-intervention-overviewhttps://qheps.health.qld.gov.au/__data/assets/pdf_file/0028/594325/3_aod20therapies20a3.pdf
Queensland Clinical Guidelines: Perinatal substance use: neonatal
www.health.qld.gov.au/__data/assets/pdf_file/0018/140814/g-psuneo.pdf
Smoking cessation
www.qld.gov.au/health/staying-healthy/atods/smoking
Smoking cessation clinical pathway
www.health.qld.gov.au/__data/assets/pdf_file/0031/435469/smoking-pathway.pdf

Queensland Health – other

Better Care Together
www.health.qld.gov.au/system-governance/strategic-direction/plans/better-care-together
Chief Psychiatrist Policy – Treatment and Care of Patients
www.health.qld.gov.au/__data/assets/pdf_file/0019/465202/cpp-treatment-care-patients.pdf
Comprehensive Care: Partnerships in Care and Communication
qheps.health.qld.gov.au/mentalhealth/mha/clinicaldocs
Queensland Health Aboriginal and Torres Strait Islander Cultural Capability Framework 2010 – 2033
www.health.qld.gov.au/__data/assets/pdf_file/0014/156200/cultural_capability.pdf
Queensland Health Aboriginal and Torres Strait Islander Mental Health Strategy 2016 – 2021
www.health.qld.gov.au/__data/assets/pdf_file/0030/460893/qhatsi-mental-health-strategy.pdf
Queensland Health Guidelines - Information Sharing - Between mental health staff, consumers, family, carers, nominated support persons and others
www.health.qld.gov.au/__data/assets/pdf_file/0026/444635/info_sharing.pdf
Working with parents: guidance for mental health alcohol and other drugs services
www.health.qld.gov.au/__data/assets/pdf_file/0016/1104613/qh-gdl-963.pdf

Legislation

Legislation, standards and extended practice authorities
www.health.qld.gov.au/system-governance/licences/medicines-poisons/medicines-poisons-act/legislation-standards
Medicines and Poisons Act
https://www.legislation.qld.gov.au/view/whole/html/inforce/current/act-2019-026
Medicines and Poisons Act fact sheets and supporting documents
www.health.qld.gov.au/system-governance/licences/medicines-poisons/medicines-poisons-act/supporting-documents
Medicines and Poisons (Medicines) Regulation 2021
www.legislation.qld.gov.au/view/html/inforce/current/sl-2021-0140
Pharmacy Business Ownership Act 2001
www.legislation.qld.gov.au/view/pdf/2012-07-01/act-2001-012

General information

Understanding pharmaceutical opioids
www.adis.health.qld.gov.au/drug-profile/pharmaceutical-opioids

Opioids – Alcohol and Drug Foundation
www.adf.org.au/drug-facts/opioids
HEP Drug Interactions
www.help-druginteractions.org/checker
Montreal Cognitive Assessment
https://mocacognition.com

Take Home Naloxone

The National Take Home Naloxone program
www.health.gov.au/initiatives-and-programs/take-home-naloxone-program/about-the-take-home-naloxone-program
Program Rules – Take Home Naloxone
www.ppaonline.com.au/wp-content/uploads/2022/06/Take-Home-Naloxone-Program-Rules.pdf.
Registered service providers for Take Home Naloxone
www.ppaonline.com.au/wp-content/uploads/2022/08/Registered-sites-for-Take-Home-Naloxone.pdf
Insight Take Home Naloxone toolkit
insight.qld.edu.au/toolkits/take-home-naloxone/detail
The Penington Institute Naloxone Training
www.penington.org.au/workforce-development/naloxone-training
Overdose - QuIHN
www.quihn.org/living-with-drugs/overdose

Pharmacists

Australian Health Practitioner Regulation Agency Shared Code of Conduct www.ahpra.gov.au/Resources/Code-of-conduct/Shared-Code-of-conduct.aspx
Pharmaceutical Society of Australia's Code of Ethics
www.psa.org.au/practice-support-industry/ethics/
Extended practice authority
https://www.health.qld.gov.au/__data/assets/pdf_file/0027/1108944/epa-pharmacists.pdf.
Practice Guidelines for pharmacists providing immunisation services
https://my.psa.org.au/servlet/fileField?entityId=ka10o0000009JkqAAE&field=PDF_File_Member_Content__Body__s
Guidelines for pharmacists administering medicines by injection
https://my.psa.org.au/s/article/Guidelines-for-pharmacists-administering-medicines-by-injection
Pharmaceutical Benefits Scheme (PBS) | Highly Specialised Drugs Program
https://www.pbs.gov.au/info/browse/section-100/s100-highly-specialised-drugs
Pharmaceutical Benefits Scheme (PBS) | Opiate Dependence Treatment Program
https://www.pbs.gov.au/info/browse/section100-md#Dosing-sites-participating-in-state-and-territory-ODT-programs

Services and Non-Government Organisations

Adis
https://adis.health.qld.gov.au/

QNADA
www.qnada.org.au
Queensland Centre for Perinatal and Infant Mental Health
https://qheps.health.qld.gov.au/qcpimh/perinatal-referrals
QuIHN
www.quihn.org

Travel

INDRO e.V. provides advice on restrictions and regulations in various countries
www.indro-online.de/en/home
Therapeutic Goods Administration Leaving Australia fact sheet
www.tga.gov.au/leaving-australia

MIMS online prescribing information

Buvidal® Weekly
www.mimsonline.com.au/Search/ShowPDF.aspx?xmlDoc=14792.xml&XSLKey=PIxsl_pdf&PathKey=FullPIxmlPath
Buvidal® Monthly
www.mimsonline.com.au/Search/ShowPDF.aspx?xmlDoc=14788.xml&XSLKey=PIxsl_pdf&PathKey=FullPIxmlPath
Sublocade®
www.mimsonline.com.au/Search/ShowPDF.aspx?xmlDoc=14970.xml&XSLKey=PIxsl_pdf&PathKey=FullPIxmlPath
Suboxone®
www.mimsonline.com.au/Search/ShowPDF.aspx?xmlDoc=08826.xml&XSLKey=PIxsl_pdf&PathKey=FullPIxmlPath
Subutex
www.mimsonline.com.au/Search/ShowPDF.aspx?xmlDoc=05505.xml&XSLKey=PIxsl_pdf&PathKey=FullPIxmlPath
Methadone syrup
www.mimsonline.com.au/Search/ShowPDF.aspx?xmlDoc=02796.xml&XSLKey=PIxsl_pdf&PathKey=FullPIxmlPath
Biodone Forte®
www.mimsonline.com.au/Search/ShowPDF.aspx?xmlDoc=05216.xml&XSLKey=PIxsl_pdf&PathKey=FullPIxmlPath

TGA product information

Methadone Product Information:
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2009-PI-00948-3&d=2016061416114622483
Biodone Forte® Product Information:
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2009-PI-00726-3&d=2016061416114622483&d=2016080916114622483
Suboxone® Product Information:
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-01894-3

Subutex Product Information:
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-02289-1
Naltrexone Product Information:
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01168-1
Naloxone Product Information:
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2022-PI-02055-1
Buvidal® Weekly product information AUS
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-02610-1
Buvidal® Monthly product information AUS
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-02611-1
Sublocade® product information AUS
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01756-1
Sublocade® prescribing information US
https://www.sublocade.com/Content/pdf/prescribing-information.pdf

Queensland policy documents

Queensland Mental Health Commission: Changing attitudes, changing lives
www.qmhc.qld.gov.au/sites/default/files/downloads/changing_attitudes_changing_lives_options_to_reduce_stigma_and_discrimination_for_people_experiencing_problematic_alcohol_and_other_drug_use.pdf
Queensland Multicultural Policy: Our story, our future
https://cabinet.qld.gov.au/documents/2016/Dec/MPlan/Attachments/Policy.pdf
Shifting minds: Queensland Mental Health, Alcohol and Other Drugs Strategic Plan 2018 – 2023
www.qmhc.qld.gov.au/2018-2023-strategic-plan

National policy documents and reports

Alcohol, tobacco and other drugs in Australia report
www.aihw.gov.au/reports/alcohol/alcohol-tobacco-other-drugs-australia/contents/about
Equally Well – Improving the physical health and wellbeing of people living with mental illness in Australia, National Mental Health Commission www.mentalhealthcommission.gov.au/lived-experience/contributing-lives,-thriving-communities/equally-well
National Drug Strategy Household Survey 2019
www.aihw.gov.au/reports/illicit-use-of-drugs/national-drug-strategy-household-survey-2019/contents/summary
National Privacy Principles
www.oic.qld.gov.au/about/privacy/the-privacy-principles/national-privacy-principles
National Safety and Quality Health Service Standards www.safetyandquality.gov.au/standards/nsqhs-standards
National Standards for Mental Health Services 2010, Australian Government Department of Health
www.health.gov.au/sites/default/files/documents/2021/04/national-standards-for-mental-health-services-2010-and-implementation-guidelines-national-standards-for-mental-health-services-2010.pdf
Penington Institute Australia's annual overdose report
www.penington.org.au/overdose/overdose-projects-campaigns/australias-annual-overdose-report/

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