University Hospitals of Leicester NHS
NHS Trust

Guidelines for the Management of Adult Patients with an Opioid Dependence

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Trust Lead :	Peeyoosh Pankhania
Board Director Lead:	Andrew Furlong, Medical Director
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Contents

1. Introduction

1.1 This document sets out the University Hospitals of Leicester (UHL) NHS Trust's Guideline for patients who are admitted with opioid dependence. This includes patients on treatment plans agreed with local practitioners, specialist providers and patients who are not on agreed treatment plans.

1.2 **Drug addiction statistics**

Drug misuse related hospital admissions (England**)**

In 2016/17 there were:

- 7,545 hospital admissions with a primary diagnosis of drug-related mental health and behavioural disorders.
- 14,053 hospital admissions with a primary diagnosis of poisoning by illicit drugs.

Deaths related to drug misuse (England and Wales)

In 2016 there were 2,593 registered deaths related to drug misuse. The highest level since comparable records began in 1993.

Drug use among adults (England and Wales)

In 2016/17, around 1 in 12 (8.4%) adults aged 16 to 59 had taken an illicit drug in the last year.

Information from NHS England (2018) Statistics on drugs misuse. England. (1)

1.3 Drug users have the same entitlement as other patients to the services provided by the National Health Service and it is the responsibility of all NHS staff to provide care for both general health needs and drug-related problems of the same high standard as that provided to non-drug users, whether or not the patient is ready to cease using drugs (2).

1.4 Patients may present to the hospital for a range of conditions either directly as a result of their opioid dependence or indirectly following acute or chronic illness. It is essential that they be treated in a professional way.

1.5 Many drug users will require pharmacological interventions to prevent drug withdrawal. The presence of withdrawal symptoms will often hinder clinical work, as most drug users will be more concerned with impending withdrawal symptoms than any other condition they may face.

1.6 The Substance Misuse Liaison Team (Turning Point), if available, should be the first point of call for all situations where a drug user is admitted to a ward.

2. Scope

2.1 This guideline applies to:

Staff group(s)

- The Named Consultant in charge of the patients overall care
- The Registered Nurses/Nurse Associates
- The hospital pharmacy team
- The Substance Misuse Liaison Team (Turning Point)

Clinical area(s)

- All clinical areas across UHL where a patient with opioid dependence is admitted to.

Patients group(s)

- Adult patients (above the age of 18 years) within all adult clinical areas across UHL, with the **exception** of patients under the care of obstetrics service (maternity services) at UHL.
- All patients either under the care of obstetrics, or breastfeeding, should be referred to:
  Angela Geraghty – Specialist Midwife, Substance Misuse.
  angela.m.geraghty@xuhl-tr.nhs.uk
  Tel: 07966 558286
- Patients under the age of 18 are not encompassed within the scope of this policy.

2.2 Roles and responsibilities in managing opioid dependence.

2.2.1 Management of opioid dependence requires a multidisciplinary approach and expert management.

2.2.2 The responsibility of the overall management of the patients sits with the consultant medical or surgical team in charge of the overall care.

2.2.3 The medical or surgical team holds the responsibility for:

- Confirming the patients past medical history
- Liaising with the regular prescriber and key worker if known
- Contacting the regular community pharmacy (if known) to confirm dose and quantity of the last dispensing.
- Confirming the patient medication history with regards to substance(s) misused, quantity of use, duration of use, method of administration, date and time of last consumption/administration.
- Initiating assessment for new presentation of dependence in liaison with substance misuse team.
- This all needs to be documented in the patient clinical notes.

2.2.4 The Registered Nurses/Nurse Associates will

- Assist in the monitoring of the patient.
- Administer the medication **only when the dose has been independently confirmed** and documented in the patients main clinical notes with:
  - The regular community prescriber (Turning Point, General Practitioner or HM Prison Services) and/or
  - Regular community pharmacy and/or
  - Presentation of the patient own medication with the patient's name, medication name, dose etc. clearly documented and not tampered with (this must be within 14 days from the date of dispensing).

2.2.5 The pharmacy team will ensure that necessary medications are supplied in accordance to an appropriate prescription (electronic or paper) only when:

a) The dose has been confirmed and documented as part of the medicine reconciliation process for patients on Opiate Substitution Therapy (OST) or

b) Checked against the substitute prescribing schedule in appendix 2 and an appropriate Clinical Opiate Withdrawal Scale (COWS) score of 13 or above documented in appendix 3.

3. Definitions

3.1 **Addiction** – substance addiction is defined as a chronic relapsing disorder characterized by:

1) Compulsion to seek and take the substance,

2) Loss of control in limiting substance intake and

3) The emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the substance is prevented

3.2 **Withdrawa**l – the physiological or acquired discomfort experienced upon the abrupt termination of the substance

3.3 **Tolerance** – tolerance is seen as a need to engage in substance use at a relatively greater level in order to achieve the same desired effects

3.4 **Craving** - the intense urge to engage in a specific act.

Definitions from Addiction by Nutt 2013 (3)

4. Admission and Opiate Substitution therapy (OST)

4.1 Admission

4.1.1 Every patient who is known to have a drug addiction problem should be referred to Turning Point, the substance misuse service for Leicestershire and Rutland. This includes in hours and out of hours. Turning Point run the Substance Misuse Liaison Team within UHL, and this team should be the first point of referral. They can be contacted on these numbers: 0116 258 7285, 07734694857, or 07535658329. The team can be emailed at TurningPointReferral@uhl-tr.nhs.uk or referred to on ICE under Service Provider "Substance Misuse".

4.1.2 Where possible the Substance Misuse Liaison Team will offer appropriate advice on treatment of the patient's drug problem and provide support to the patient and the medical/surgical team.

4.1.3 Patients may also be under the care of local prison services who can be contacted for advice as needed.

4.1.4 If a patient is not under a specialist service **and** a patient presents out of hours when the Substance Misuse Liaison Team or Turning Point itself is closed then the admitting doctor will have to assess the patient's drug addiction problem.

4.1.5 A retrospective contact with the Substance Misuse Liaison Team or Turning Point itself should be made at the earliest possible opportunity.

4.1.6 Good liaison with the specialist team will help establish suitable continuation of care for the drug problem after the patient has discharged.

4.1.7 Contact details for local service providers are included in appendix 4.

4.2 Opiate Substitution Therapy

4.2.1 The principle behind Opiate Substitution Therapy (OST) is to reduce the harm that drug use inflicts on drug users.

4.2.2 Within this are the aspects of reducing the amount of illicit drugs the drug user must use to keep opiate withdrawals at bay, to reduce the frequency of injecting and all of the inherent risks associated with that and to enable patients to break the drug using life cycle many chronic users fall into.

4.2.3 The theory is to change the illicit drug for a pharmaceutically pure opiate.

> **Note:** opiate substitution is essentially replacing one opiate with another that has fewer risks, but none the less still carries some of the significant risks associated with the opiate drug group.

4.3 Methadone

4.3.1 The first line treatment for OST is methadone.

4.3.2 Methadone has the following benefits:

- Long acting enabling once daily dosage (daily doses can be split into two doses if necessary, good practice in the in-patient hospital setting); its half-life is 13 to 50 hours with chronic administration.
- Orally active, so drug users do not have to inject drugs.
- A full opiate agonist and will have the same pharmacological profile as heroin (diamorphine), i.e. it will treat the opiate withdrawal syndrome.
- The best evidence base of all therapies available.

4.3.3 Methadone does have some risks and should not be regarded as a completely safe alternative. These risks include:

- Toxic in overdose – like heroin – causing respiratory depression and death.
- Long duration of action means that the effect of the overdose will last a lot longer. Naloxone, the opiate antagonist used to treat overdose has a short duration of action hence it needs to be given as a continuous infusion when used in methadone overdose, unlike in the heroin overdose situation.
- Cumulative pharmacokinetics. Methadone partitions into the fat tissue and only when this is saturated do you see a steady blood concentration of methadone, this process can take up to five days. In practice this means that if doses are escalated too quickly then it is possible to overdose. For example if a patient were given 40mg on day one then 80 mg on day two and 120 mg on day three, then the blood level of methadone on day three would be higher in reality than the level expected from that days dose. Therefore the patient would be at risk of overdose.

4.3.4 In light of these risks it is vital that methadone is prescribed responsibly and safely.

4.4 Buprenorphine

4.4.1 The other drug commonly used for opiate substitution is Buprenorphine (Subutex).

4.4.2 A combination of Buprenorphine and Naloxone (Suboxone) is also used in some patients in the community but is not held as stock at UHL.

4.4.3 Temgesic is not licensed for use in opiate substitution therapy, unlike Subutex and has different strengths of buprenorphine compared to Subutex.

5. Assessment of Opioid Dependence

Initial assessment is vital upon admission to determine current opiate use and dependency.

Advice

OST is only indicated in patients who are dependent on opiates. People using cocaine, crack cocaine, cannabis, alcohol, amphetamines or any other non-opiate drug of abuse **on its own** should **not** be given OST.

Methadone/Buprenorphine would be indicated if the patient was using a mixture of drugs **including** an opiate **and** were dependent on the opiate.

5.1 Taking an Illicit Drug History

As part of the admission assessment determine the following:

- What the patient is 'using'.
- How they are using the opiate, e.g. by injection, smoking, inhaling or another route. If they are injecting where are they injecting, the formulation of the injected product (liquid/powder) and if they are using a filter
- The amount of opiate they use and how often they use it.
- When they started using the drug and how long they have used the drug.
- The patient's experience of withdrawal symptoms, the patient should be able to describe what they go through when withdrawing from opiates.
- Also enquire about other substances used; it may be necessary to prescribe medication to deal with other substance misuse issues such as alcohol, benzodiazepines and gabapentinoids. Again these other substances must be used in a dependent manner in order to warrant a pharmacological intervention.
- Patients may use the street names drugs of abuse. An up to date list of these drugs of abuse can be found at www.talktofrank.com in the section "The A-Z of drugs". The full list has not been included in this document as the list is vast and new names join the list frequently.

5.2 Physical Examination

Examine the state of any injection sites bearing in mind some may be in private areas of the body.

Look for evidence of drug use such as needle marks, track marks (thrombosed veins). If they are injecting examine injection sites. If they are currently injecting these will appear red and sore and they should be able to describe exactly where they last injected.

5.3 Blood Borne Virus Screening

- All patients should be asked about their blood borne virus (BBV) status (Hepatitis B & C and HIV)
- Patients should be asked when they were last tested and the result of the test.

- Patients should be encouraged to be tested for BBV, especially if they haven't been tested in the last four months and social activities or patient circumstances preclude increase risk.
- Patients who are known to be positive or found to be positive as an inpatient should be referred to the infectious disease team.

5.4 Signs of Opiate Withdrawal

Look for signs of opiate withdrawal (Table 1), however it may be necessary to initiate methadone before the patient starts withdrawal symptoms.

A dependent patient should be able to describe past experiences of withdrawal from opiates.

Early Signs	Restlessness, anxiety, agitation, discomfort, drug seeking behaviour / craving
Intermediate Signs	Yawning, sweats*, runny nose, runny eyes, hot / cold flushes, dilated pupils*, irritability, loss of appetite
Late Signs	Restlessness in legs whilst in bed, insomnia, abdominal cramps, low grade fever, nausea and vomiting, increased pulse rate, diarrhoea*, trembling, pale clammy skin with goose bumps (piloerection)*, deep aching pain in bones / muscles, raised blood pressure*.

Table 1 Signs of Opiate Withdrawal (* = Objective signs)

- The withdrawal syndrome associated with heroin can start to appear 6 to 8 hours after the last use.
- By 12 to 15 hours post dose the drug user will be feeling uncomfortable.
- By 18 to 24 hours they will be very unwell with restlessness, difficulties sleeping sweating, runny nose and runny eyes.
- 24 to 72 hours post dose the symptoms reach their peak with aches and pain in the bones, muscles and joints, stomach cramps, vomiting and diarrhoea.
- Thereafter symptoms gradually fade away but it may be 7 to 10 days before the drug user begins to feel well.

The withdrawal syndrome following cessation of **methadone** dosing has the same features except it takes longer. Symptoms would begin 1 to 2 days post dose and peak after 4 to 6 days. Symptoms can persist for 10 to 14 days and it may be several days before the drug user starts to feel well again.

The withdrawal syndrome associated with **buprenorphine** is qualitatively less intense than those associated with methadone and heroin. Symptoms may not appear for 1 to 2 days post dose.

There is a psychological aspect to the withdrawal syndrome, which includes symptoms like craving and responding to cues. This aspect can last for unpredictable periods of time ranging from days to years.

Note: the opiate withdrawal syndrome is very unpleasant but not life threatening. If it is not managed adequately its presence will greatly hamper any other interventions aimed at the patient and may cause the patient to self-discharge against medical advice.

However inappropriate use of medications such as methadone, benzodiazepines and dihydrocodeine is potentially more dangerous.

The Clinical Opiate Withdrawal Scale (COWS) is a validated scoring system that enables clinicians to objectively grade the severity of the main withdrawal symptoms that patients are experiencing (see appendix 3).

5.5 Signs of Opiate intoxication

Look for signs of opiate intoxication (see below). Do not administer doses of methadone/buprenorphine against signs of intoxication

Signs and symptoms include

- Difficulty keeping the eyes open
- Head falling to one side
- Drowsiness
- Reduced breathing rate / shallow breathing
- Constricted pupils (this symptom is always present in regular opiate users and only goes during withdrawal)

5.6 Signs of Opiate overdose

In cases of overdose the following may be seen

- Nausea and vomiting
- Constricted pupils (pin point pupils),
- Unconsciousness (drowsiness)
- Respiratory depression (<8 breaths per minute),
- Cold to touch/blue lips as a result of reduced heart rate, reduced systolic blood pressure and reduced body temperature.

If the dose is large enough and the patient is left untreated this could lead to respiratory arrest and death. Urgent contact with the Oncall Resuscitation team must be made via the hospital switchboard via 2222 and using the NEWS escalation procedure for suspected acute overdose during any stage of the patients hospital stay.

5.7 Body Fluid Analysis

As directed by the Drug Misuse and Dependence: UK Guidelines on Clinical Management (2), Illicit prescribed drugs and medication can be detected in a variety of biological samples using different testing methods. Drug testing can be used for:

- Initial assessment and confirmation of drug use (although testing does not confirm dependence or tolerance and should be used alongside other methods of assessment)
- Confirming treatment compliance – that a patient is taking prescribed medication
- Monitoring illicit drug use, including as a drug-specific treatment goal (for example, as part of a psychosocial intervention).

All patients who have a history of or a new presentation of dependence to illicit substances should be tested using:

- Urine toxicology screening through pathology.

5.7.1 Urine toxicology laboratory test results from pathology.

All new patients who are not on a methadone/buprenorphine programme must have a formal urine toxicology test processed by the pathology department at UHL using a standard universal container.

A full pathology test can detect illicit substances

A positive result to any appropriate opioid in the formal pathology test can be used to instigate therapy

Where a patient has been admitted for a prolonged period of time, pathology urine tests should be undertaken weekly to determine continued illicit use, which may inform treatment choice.

5.7.2 Points to note regarding urine tests:

- The current turnaround time for urine tests within UHL is 3 to 5 working days and can detect the following substances as detailed in table 2. **The result from this test can be reviewed by Turning Point, even if the patient has been discharged.**

Drug / drug metabolite		
4-MEC	Fentanyl	Morphine
6-MAM	Gabapentin	Nitrazepam
Amitriptyline	Lorazepam	Norbuprenorphine
Amphetamine	MDA	Nordiazepam
Benzoylecgonine	MDEA	Oxazepam
Buprenorphine	MDMA	Oxycodone
Clonazepam	Mephedrone	Pregabalin
Cocaethylene	Methadone	Quetiapine
Cocaine	Methamphetamine	Temazepam
Codeine	Methylecgonine	THCCOO-glucuronide
Diazepam	Midazolam	Venlafaxine
Dihydrocodeine	Mirtazapine	Zopiclone
EDDP		

Table 2: Drug and Drug metabolites tested by UHL pathology services

- Dilute samples of urine can give false negative results. Lab tests will usually give the amount of creatinine in the sample and this will be a guide of how dilute the sample is.

- If the patient drinks a large volume of liquid before they do the test this will produce low concentration urine.

- The best sample is the first sample of urine passed in the morning.

- Some people give contaminated or substituted samples. A sample just produced by the patient should be at body temperature and have a normal colour. If it unusually cold or has an odd colour it may have been tampered with.

- Many tests have a cut-off point. This is the concentration below which the test will disregard any of the metabolite it is testing for and show a negative result.

- A positive result for an opiate urine test will mean that opiates have been taken recently. Bear in mind simple opiate tests such as the dipsticks and enzyme immuno-assay type tests cannot differentiate between different opiates. If the patient takes codeine, dihydrocodeine, morphine

or diamorphine (heroin) these tests will register positive. Some of these opiates are found in over the counter preparations like Co-Codamol, Paramol, Nurofen Plus and Kaolin and Morphine mixture. Multiple brands and manufacturers of medication are available in the pharmaceutical market, if further assistance is required to ascertain the contents of a medication please contact a member of the UHL pharmacy team or the medicine information department via the hospital switchboard.

- Opiate tests generally look for the presence of morphine and its metabolites. These can be detected in the urine for up to 48 hours after the last dose.

- A positive result on a methadone urine test will mean that the patient has used methadone recently. Note methadone taken regularly in a maintenance program could be detected in the urine up to 9 days after the last dose.

- Urinalysis cannot give an indication of how much drug was taken.

- A negative result merely means the test did not detect any opiate or methadone metabolites. It would be interpreted that the patient has not used opiates or methadone recently.

- However there are plausible reasons why false negatives may occur: The patient may be pregnant. During pregnancy hormones are released which speed up the metabolism of methadone. The urine may be dilute – see earlier.

  In light of these facts urinalysis must be viewed in conjunction with the rest of the assessment in particular the onset of withdrawal symptoms and cannot be relied upon in isolation.

  Table 3 gives a guide to how long drugs of abuse can be detected in the urine once the user has stopped using the drug.

Substance Drug or its metabolite(s)	**Duration of detectability**
Amphetamines / amfetamines, including methylamphetamine and MDMA	2 days
Benzodiazepines: Ultra-short-acting (half-life 2h) (e.g.midazolam) Short-acting (half-life 2–6h) (e.g. triazolam) Intermediate-acting (half-life 6–24h) (e.g. temazepam, chlordiazepoxide) Long-acting (half-life 24h) (e.g. diazepam, nitrazepam)	 12 hours 24 hours 2–5 days 7 days or more
Buprenorphine and metabolites	8 days
Cocaine metabolite	2–3 days
Methadone (maintenance dosing)	7–9 days (approximate)
Codeine, dihydrocodeine, morphine, propoxyphene (heroin is detected in urine as the metabolite morphine)	48 hours
Cannabinoids: • Single use • Moderate use (three times a week) • Heavy use (daily) • Chronic heavy use (more than three times a day)	 3–4 days 5–6 days 20 days Up to 45 days

Table 3: Time frame for detection of drugs of abuse in urine samples. (4)

5.8 Alcohol withdrawal

Treatment for patients who are found to be misusing and/or undergoing withdrawal with alcohol must be treated following the UHL guideline for alcohol withdrawal B30/2014. Caution should be taken with the use of benzodiazepine in this patient group due to the additive effect of CNS depression and respiratory depression

5.9 Other Drugs of Abuse

In general if a patient is found to be misusing other non-opiate substances the first point of reference for ward staff should be the Substance Misuse Liaison Team (Turning Point).

Other drugs commonly encountered include crack cocaine, alcohol, cannabis, benzodiazepines, amphetamines, gabapentinoids (gabapentin or pregabalin) and synthetic cannabinoid receptor agonists.

Opioid Substitution Therapy is **not indicated** in the treatment of addiction to any of these substances.

6 Confirmation and prescribing of OST

6.1 Confirmation of prescribed medication (OST) used prior to admission

Many patients will be under the care of a prescriber for the treatment of their addiction in the community.

This will usually be the community drug team (Turning Point) in association with the patient's GP.

In general if the patient is an injector or uses several different types of drug or has a psychiatric diagnosis as well then it is likely that if they have a community prescriber and also a community pharmacy.

It is vital that the community prescriber and the community pharmacist are informed of their patient's admission to hospital for a number of reasons:

- The community prescriber (or the Substance Misuse Liaison Team if the community prescriber is Turning Point) can confirm the dose of methadone or buprenorphine prescribed in the community without the need for a full assessment being done. The substance misuse liaison team at the LRI can access patients records at Turning Point
- The prescriber will know not to give further prescriptions until the patient has been discharged.
- The community pharmacy should also be contacted, who can confirm the last administered/dispensed dose and help establish if there is a Three-day gap in therapy. This will be more pertinent if the community prescriber is not available
- The community pharmacist will cancel any current prescriptions they have until the patient has been discharged and this has been confirmed by the prescriber.
- If the community based clinicians are not contacted patients may go and still collect prescriptions, in effect get a double dosage, which presents a risk of overdose.
- The ward will be able to establish when the item was last dispensed or consumed if on supervised therapy. If more than three days has passed and the patient has not used any opiates in that time then restarting methadone at the same dose may not be safe, due to reduced tolerance. The decision depends on what the patient wants, how they present and the hospital prescriber's clinical judgement.

6.2 Prescribing OST in hospital

The two licensed medications for opiate substitution therapy available are methadone and buprenorphine.

Methadone has the larger research evidence base but buprenorphine has a better safety profile.

There are studies evaluating the use of buprenorphine in substance misuse and it is well recognised as an effective treatment.

However methadone is still considered the first line treatment because buprenorphine initiation is more complex than methadone initiation.

6.2.1 Methadone prescribing

6.2.1.1 Confirmed methadone prescription

If the patient is prescribed methadone in the community and the dose has been confirmed with the community prescriber or community pharmacist and there has been no break in methadone dosing then the community dose can be prescribed, if it is clinically appropriate to do so. NB the patient's medical condition may prevent this.

A break of more than 3 days will require reduced dosages and reinitiating therapy. This will be advised by Turning Point. In the event that Turning Point hasn't been used as a source or contact to confirm the dose and they are not available, this patient group will need to be re titrated using the schedule described in the unconfirmed methadone prescription (section 6.2.1.2)

UK guidance on the clinical management of drug misuse and dependence recommends that the patient's total daily dose should be split in half and given as a twice-daily dose, even if they had it as a single daily dose in the community. (1)

For example a patient on 50mg of methadone, it should be prescribed 25mg twice daily. This enables doses to be withheld or delayed if the patient leaves the ward and returns intoxicated. Methadone OST can mask symptoms and compound symptoms of other conditions e.g. sepsis, conditions where consciousness can be altered, respiratory disorders, hinder effective monitoring of acute pain control and interact with a variety of medications (see appendix 5)

Patients should be reassured that acute withdrawal from methadone should not occur due to the long half-life of methadone (24 to 48 hours)

There are a number of methadone formulations available. The only one patients will be prescribed within UHL is methadone oral mixture 1mg/1ml and prescribed as milligrams. The concentrated version, injections and tablets are not to be prescribed for OST, even if these were prescribed pre-admission. The evidence suggests that the indications for tablets and injectable methadone are limited.

6.2.1.2 Unconfirmed methadone prescription

Prescribing of OST in this group of patients should only occur when

1. Confirmation of a patient's regular prescription cannot be ascertained.

Or

2. Contact with the Substance Misuse Liaison Team (Turning Point) cannot be established (e.g. weekends and bank holidays).

Or

3. The patient has been admitted to the ward having missed three continuous days of therapy, if confirmed with the patient's community pharmacist.

Or

4. The patient is not on a plan, Turning Point is unavailable, the patient is actively using an opioid and the patient needs to start therapy

It is important to explain as clearly as possible to the patient the titration process, the need for continued monitoring and the reasons for it. This explanation should be repeated as often as is necessary to help allay the patients concerns regarding treatment for their drug use.

The full treatment plan can be found in appendix 2

The underlying theme of questioning during the dose assessment is whether the prescribed dose of methadone is preventing withdrawals symptoms for at least 24 hours. Doses of methadone should be titrated against this measure.

Use the COWS to get a better idea of the severity of withdrawal symptoms. Try to correlate the dose and the time it was taken with the time it took for withdrawal symptoms appear.

An adequate dose of methadone will “hold” (i.e. prevent withdrawal symptoms) for at least 24 hours. This is the aim of methadone prescribing. Doses should always be titrated against signs of withdrawal and how long the patient is comfortable on the current daily dose.

Never titrate doses against signs of opiate intoxication; this puts the patient at risk of methadone overdose. Doses should only be titrated against withdrawal symptoms

The MHRA has advised that doses of methadone above 100mg could be associated with cardiovascular irregularities causing an increase in QT intervals. Current advice is that all Patients with the following risk factors for QT-interval prolongation should be carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval; patients requiring more than 100 mg daily should also be monitored. Appendix 5 has a list of medications know to increase QT intervals.

Methadone is cumulative so doses cannot be escalated rapidly. Hold doses for a couple of days to allow the methadone to distribute throughout the body.

Patients on doses above 100mg should be discussed with the clinician at Turning Point. Patients on all other doses do not need to be reviewed by the clinicians at Turning point. Contact numbers can be found in appendix 4.

Contact a specialist in substance misuse, or the Substance Misuse Liaison Team to review all opiate dependent patients at the earliest opportunity.

6.2.2 Buprenorphine prescribing

6.2.2.1 Confirmed buprenorphine prescription

Once the dose has been confirmed by the community prescriber it can be prescribed as in the community.

It should be prescribed as a single daily dose.

Buprenorphine is a partial agonist with a high affinity for the opiate receptors in the brain, higher than morphine and diamorphine (heroin). Hence it may antagonize opiate pain relief administered during the patient’s stay in hospital. This could impact on any surgical procedures that are required.

If large doses of buprenorphine are needed, it may be possible to split the daily dose into a twice daily regimen to allow adequate pain control. The decision to do this must be discussed with Turning Point and documented in the patient’s notes.

6.2.1.2 Unconfirmed buprenorphine prescription

Buprenorphine will **not** be initiated whilst patients are in hospital. Initiation of buprenorphine is not easy and requires the patient to be in withdrawal and is best left to specialists in addiction. If the assessment confirms the patient to have opiate dependence then they should be started on methadone as above. Patients who cannot have methadone should have supportive treatment until contact with Turning Point has been made.

6.2.3 Overdose Guidance

6.2.3.1 Opioid Overdose

The treatment for opiate overdose is the antagonist Naloxone.

A NHS England Patient Safety Alert in November 2014 (6) highlighted risks associated with inappropriate naloxone use:

Naloxone must be given with great caution to patients who have received longer- term opioid/opiate treatment for pain control or who are physically dependent on opioids/opiates. Use of naloxone in patients where it is not indicated, or in larger than recommended doses, can cause a rapid reversal of the physiological effects for pain control, leading to intense pain and distress, and an increase in sympathetic nervous stimulation and cytokine release precipitating an acute withdrawal syndrome. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest may result from inappropriate doses of naloxone being used for these types of patients

Naloxone is a short acting drug with a half-life of approximately 4 hours.

The short half-life means that repeated injections are needed following opiate overdose for example heroin.

The recommended dose range to reverse acute opioid/opiate overdose in adults within a hospital can be undertaken with the following

- An injection of naloxone of 400 micrograms stat
- Followed by 800 micrograms up to 2 doses at 1 minute intervals if no response to the preceding dose
- Then increased to 2mg for 1 dose if still no response
- 4mg dose may be required in seriously poisoned patients
- Aim for reversal of respiratory depression, not full reversal of consciousness.
- Then review diagnosis; further doses may be required if respiratory function deteriorates

Naloxone is given by the intravenous route. If that route is not accessible then it can be given via the subcutaneous or intramuscular route but the clinical effect is delayed (7, 8).

In August 2021 a further Patent safety alert (NatPSA/2021/007/PHE) was issued warning about the adulteration of heroin with potent synthetic opioids such as isotonitazene. It's potency and toxicity are uncertain but perhaps similar to or more than fentanyl, approximately 100x morphine. There is good evidence that naloxone works in these cases but delivering it rapidly and completely is even more critical, as progression to respiratory arrest, and recurrence of respiratory arrest, are more likely.

Intravenous infusions of naloxone are useful when repeated doses are likely to be required.

> Start with an hourly infusion equal to 60% of the doses required to adequately reverse respiratory depression.
>
> For example, if 800 micrograms was required (either as single dose or two 400microgram doses) then start the infusion at 500micrograms per hour. The infusion will require titrating to the desired clinical effect.
>
> For adults
> 10mg (25 x 400microgram in 1ml ampoules) made up to a final volume of 50ml with glucose 5% will produce a 200microgram/ml solution to be administered via an IV pump.
>
> Ref : Toxbase

The half-life of methadone is significantly longer and effects of an overdose can last as long as 72 hours. Hence these patients will need to be observed for at least 72 hours.

In treating methadone overdose it will be necessary to administer a continuous intravenous infusion.

Bear in mind once Naloxone starts to take effect the patient will be in severe withdrawal symptoms and may try to leave the ward prematurely.

Naloxone cannot displace buprenorphine from opiate receptors as buprenorphine has a higher affinity. Hence Naloxone will at best only partly reverse the effects of buprenorphine. However buprenorphine overdose is rare if taken alone, if another opiate is used it will act as an antagonist or block the effect of the second opiate. If it is taken with another depressant like alcohol or benzodiazepine the safety profile is compromised. General supportive measures would be taken.

All ward staff should know what procedure to follow if there is a drug overdose on the ward and where to obtain the required antidotes.

Following discharge, an opioid-dependent patient may have a lower dependence/tolerance threshold than on admission, and is therefore at an increased risk of overdose. Naloxone is a potentially life-saving medicine when used in settings associated with opiate misuse and overdose. Systematic reviews conclude that pre-provision of naloxone to heroin users can be helpful in reversing heroin overdoses (2). Under current legislation the Substance Misuse Liaison Team can supply naloxone without a prescription, which can be taken home by the patient, family or friends for use in an emergency situation. The naloxone supplied will be in prefilled syringes only.

6.2.3.2 Overdose with other drugs of abuse

Treatment of these overdoses should be aimed at the presenting symptoms and may include management of unconsciousness and management of acute psychosis. There may not be any specific antidotes for overdoses caused by the other drugs of abuse.

Information for specific overdoses and/or poisons can be obtained through:

- The National Poisons Information Service and
- Toxbase. Access to Toxbase is restricted and access can be made through contact via the A&E department if required

Benzodiazepines. The antidote for benzodiazepine overdose is flumazenil but this should only be used on expert advice (an anaesthetist), as its use is hazardous.

6.2.4 Detoxification

The decision to detoxify a patient from opiates should be a patient led decision. The patient will require support from Turning Point and have counseling on the risks, benefits and types of programmes available, how to go about getting into this type of treatment and aftercare packages available. The key issue relating to detoxification is:

There is a risk to the patient should they relapse, many opiate overdoses and deaths arise in cases where a patient has relapsed and uses pre-detoxification doses of opiates to which they no longer have tolerance.

Patients do better in treatment than out of treatment. There is a greater risk of drug related morbidity and mortality in drug users out of treatment. If patients have been detoxed they will be out of treatment and without adequate follow up and aftercare there is a strong likelihood of relapse due to the psychological aspects of dependence (such as craving) that will not have been addressed.

Evidence suggests that pharmacological detoxification with additional psychosocial therapy is more effective than pharmacological detoxification alone in terms of treatment completion; compliance and results at follow up. The decision to detoxify from opiates should not be taken by the clinician unilaterally.

7 OST in specific patient groups

7.1 Acute pain control

Acute pain management of OST patients can be difficult due to patient experiences and tolerance to analgesia seen in common practice.

Where possible regular paracetamol and non-steroidal anti-inflammatory medications such as ibuprofen /naproxen should be prescribed according to the patients allergy status, interactions, licensed recommendations and taking into account current/past medication histories.

The WHO standard of keeping to one opioid for chronic and acute pain isn't achievable in the setting of OST. Titrating acute pain with the opioid used for OST can complicate long term therapy.

The use of OST with methadone or buprenorphine doesn't necessitate the avoidance of short acting opioids, epidurals and/or patient controlled analgesia (PCA) in the post-operative phase.

Patients should be offered the most appropriate analgesia according to their acute medical condition, with the addition of non-opioid analgesics such as nerve infiltration, nerve block etc. according to the anaesthetist post-surgery.

Patients can still be given their regular methadone/buprenorphine, however usage of epidural and PCAs may be higher by the patient and the necessity to monitor for opioid intoxication should be taken into account by medical and nursing staff.

If a patient is on a large dose of buprenorphine, it may be possible to split the daily dose into a twice daily regimen to allow adequate pain control. The decision to do this must be discussed with Turning Point and documented in the patient's notes. Reestablishment of a once daily regimen would be reinitiated back in the community.

Cyclizine should not be prescribed due to its potential for increasing euphoria states and must not be given on discharge. Where possible metoclopramide or prochlorperazine should

be prescribed for the relief of nausea and vomiting. Ondansetron may be prescribed as an alternative for patients known to be allergic to other antiemetics.

Tramadol should not be prescribed due to its potential for addiction, its side effect profile and interactions with medication such as antidepressants and antipsychotics which are commonly prescribed patients undergoing OST.

Avoid gabapentin and pregabalin as there is potential for abuse with these medications. Only prescribe for licensed indications where clinically appropriate

7.2 OST during palliative therapy

Patients on OST with pain resulting from terminal illness should be co-managed by palliative care services within UHL (i.e LOROS) with advice from specialists in addiction (e.g. Turning point). Multidisciplinary assessment and care management is essential, patients should be discussed and therapies individualised.

Patients receiving OST will need to continue their prescription but it is advisable to split the daily dose of methadone or buprenorphine and administer doses 8-12 hourly in addition to the analgesic regimen, which will commonly involve immediate-acting opioids but can include a combination of slow-release and immediate-acting drugs.

The prescribed dose or type of opioid in OST or its route of administration may need to be changed as, for example, when renal function deteriorates or the oral route of administration is no longer an option.

Methadone can be used as a CSCI, however it is known to cause localised inflammatory responses and may need to be co-administered with a small dose of dexamethasone. The CSCI methadone dose should be 50% of usual oral dose. Also with converting oral to the subcutaneous route, there would possibly need to be a delay from the last oral dose to starting the CSCI (approx. 8 to 12 hours). This might be alleviated by splitting the patient's usual oral dose in to two, thus preventing adverse drug reactions and overdoses.

When using opioids for palliative care, fast acting preparations such as buccal fentanyl should be avoided and this also applies to those dependent on opioids, unless agreed recommended by the palliative team.

If there are any concerns in these circumstances contact the palliative care team via switchboard or Turning point.

8. Discharge

The inpatient team must try to co-ordinate the continuing treatment of the patient's opiate addiction. A community prescriber will continue treatment but only if a referral has been made and enough notice has been given to carry out this task.

Final dosage, date and time of administration of OST (methadone or buprenorphine) should be noted in the ICE discharge letter.

In all cases, please liaise fully with the Substance Misuse Liaison Team (Turning Point). At discharge, Turning Point (if they are the community prescriber) will require paper evidence of the patient's final dose and time of administration. This is so continuation script can be generated (by Turning Point) starting the first day post-discharge. A scan of the patient's drug chart, screenshot of relevant page of ePMA, or the discharge letter if the information is there, will suffice. These should be forwarded to the Substance Misuse Liaison Team either by email to TurningPointReferral@uhl-tr.nhs.uk or the Substance Misuse Liaison Recovery Worker with whom you have been liaising directly. The evidence can also be sent by fax to x17299.

If this is not done then there is a risk that there will not be a community prescription available for the patient on discharge which may result in further drug related harm and probable re-admission to the ward with similar complications.

Patients must not be given take away methadone on discharge because of the risk of diversion into the illicit drug market.

If methadone take away doses are prescribed the pharmacy department must not dispense them.

For patients going on overnight leave doses of methadone can be administered before they depart. Once they return the dose can go back to a split regimen.

Patients should not be discharged with codeine, dihydrocodeine, combination analgesics containing opiates such as co-codamol or co-dydramol, benzodiazepines, zopiclone or zolpidem unless indicated and following discussion with the clinicians based at Turning Point. This decision should not be undertaken by the liaison team. If advised by the clinician in substance misuse no more than 3/7 of these agents can be supplied. Dose of these items should not exceed that recommended.

9.0 Education and training

A comprehensive training package will be provided by the Substance Misuse Liaison Team on the medical and other wards within UHL where patients with opioid dependence are frequently admitted.

Training is available for other areas upon request, e.g. substance-specific training, poly-drug use, alcohol misuse, etc. To request training contact the Substance Misuse Liaison Team on x17285, 07734694857 or 07535658329 or email: TurningPointReferral@uhl-tr.nhs.uk

10 Monitoring and Audit Criteria

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Incidents related to inappropriate use of methadone	Datix incidents	Medication safety pharmacist	Monthly	Medicines Optimisation Committee

11. Key Words

Methadone, Buprenorphine, Opioid addiction, Opioid dependence, addiction, psychoactive substances, OST

12. Further information / References

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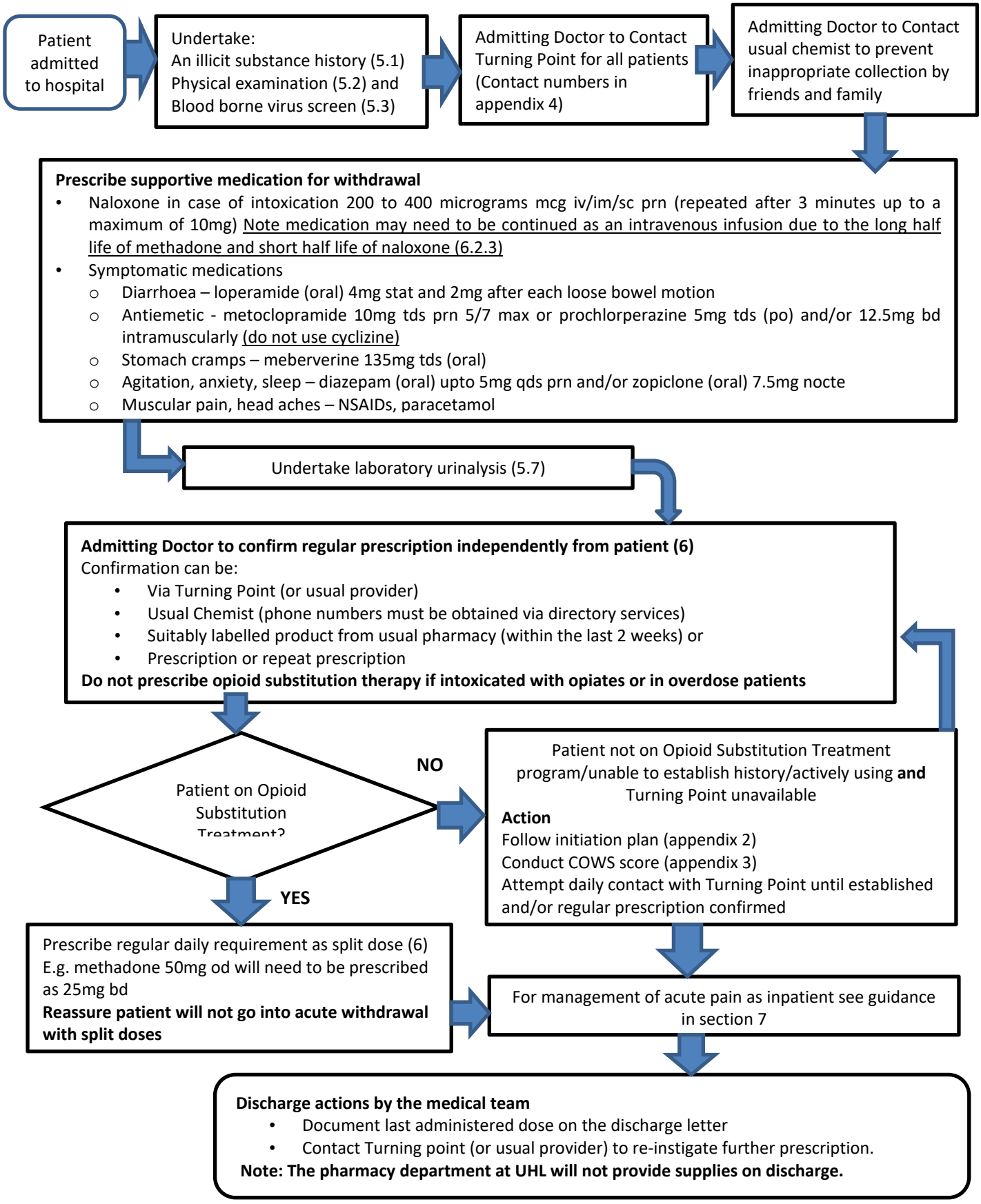
13. Acknowledgements.

- This policy has been adapted from the 2011, Guidelines for inpatient management of opiate addiction. East London NHS foundation Trust
- This policy has been written in liaison with the local Substance Misuse Team for Leicester, Leicestershire and Rutland – Turning Point

APPENDIX 1: PROCEDURE ON EMERGENCY ADMISSION FOR OPIATE DEPENDENT PATIENTS - MULTIDISCIPLINARY GUIDANCE (PAGE 1 OF 2)



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APPENDIX 1: PROCEDURE ON EMERGENCY ADMISSION FOR OPIATE DEPENDENT PATIENTS - MULTIDISCIPLINARY GUIDANCE (PAGE 2 OF 2)

Safety Notes

Do not give into pressure to prescribe
• Poly- drug and alcohol misusers may develop multiple withdrawal symptoms, which methadone may mask
• Care should be undertaken in head injury, liver disease and respiratory depression
• Care should be taken with medications know to
  o Induce and inhibit metabolism of medications
  o Medications which are known to enhance sedation and
  o Those known to cause QTc prolongation

See appendix 5 for further information

Objective signs of withdrawal		
• Yawning	• Coughing	• Sneezing
• Runny nose	• Lachrymation	• Raise blood pressure
• Raise pulse	• Dilated pupils	• Cool clammy skin
• Diarrhoea	• Nausea	• Fine muscle tremor
Do not use subjective signs of withdrawal to treat patient E.g. depression, drug craving, abdominal cramps, sleep disorders		
See COWS scores for further guidance (Appendix 3)		

APPENDIX 2: SUBSTITUTE PRESCRIBING – METHADONE INITIATION PLAN FOR PATIENT NOT ON OPIOID SUBSTITUTION THERAPY.

First 24 hours of admission

In the first 24 hours after admission OST therapy **should not be** administered/prescribed and the patient should be managed with symptomatic treatment options

Contact should be made with the Substance Misuse Liaison Team where possible.

Patients must have a urine test conducted.

Patients should be prescribed

- Naloxone incase of intoxication
- Symptomatic medications
  - Diarrhoea - loperamide 4mg stat and 2mg after each loose bowel motion
  - Antiemetic - metoclopramide 10mg tds prn 5/7 max or prochlorperazine 5mg tds (po) and/or 12.5mg bd intramuscularly
  - Stomach cramps – meberverine 135mg tds
  - Agitation, anxiety, sleep – diazepam upto 5mg qds prn, zopiclone 7.5mg nocte
  - Muscular pain, head aches – NSAIDs, paracetamol.

Patients should be monitored for objectives signs of withdrawal using the COWS (appendix 3) this should be repeated every 4 hours.

COWS score

Score 5 to 12 = mild withdrawal

Score 13 to 24 = Moderate withdrawal

Score 25 to 36 = severe withdrawal.

24 to 48 hours of admission

- In the 24 to 48 post admission period, contact with the Substance Misuse Liaison Team (Turning Point) should be established if possible.
- If confirmation of a regular prescription can be made e.g. via the community pharmacy/GP or the Substance Misuse Liaison Team/Turning Point, treatment should be followed as described in section 6.2.1.1.
- If the patient reports no symptoms for 24 hours OR feeling able to wait for longer than 24 hours between doses then they are on an adequate dose.
- Withdrawal from opioids should be continued to be monitored using the COWS every 4 hours.
- Methadone should not be given unless the objective signs of opiate withdrawal are present.
- The COWS score that is used to decide on whether to prescribe methadone must be conducted by the prescriber
  - COWS = 12 or less do not prescribe
  - COWS >13 prescribe 10mg 1mg/ml methadone stat dose.
- Prescribe 10mg of methadone oral mixture 1mg/1ml as a **stat** dose, if a patient has a COWS score of 13 or more.
- The patient should be monitored 1 to 2 hours post dose and the COWS repeated every 4 hours.
- If the patient is scoring 13 or more on the COWS, 8 hours after the initial stat dose or later a second 10mg stat dose of methadone 1mg/ml can be prescribed. The decision to administer the second dose should only be undertaken if the COWS score is 13 or more and the

COWS score at this scheduled time must be conducted by a doctor.

- It is important to clearly document the decision making process especially when the decision is taken to increase or withhold the dose if showing signs of intoxication.
- No more than 20mg of methadone should be administered in the first 24 hours.
- No more than 20mg of 1mg/ml methadone can be ordered for patients at this stage of therapy through pharmacy

48 to 72 hours of admission

- Between the 48 and 72 hours of admission, contact with Substance Misuse Liaison Team/Turning point should be established if possible.
- If confirmation of a regular prescription can be made e.g. via the community pharmacy or Substance Misuse Liaison Team/Turning Point, treatment should be followed as described in section 6.2.1.1.
- If the patient reports no symptoms for 24 hours OR feeling able to wait for longer than 24 hours between doses then they are on an adequate dose.
- If contact with Substance Misuse Liaison Team/Turning Point cannot be established, the total daily dose of methadone administered in the 24 to 48 hour period should be prescribed as a single dose. The patient should be monitored 1 to 2 hours post dose. Withdrawal from opioids should be continued to be monitored using the COWS every 4 hours.
- It is important to clearly document the decision making process especially when the decision is taken to increase or withhold the dose if showing signs of intoxication.
- Should the patient have a COWS score of 13 or more in the 48 to 72 hours post admission period, a further 10mg stat dose of methadone may be prescribed if required. This must not be less than 8 hours after the initial dose given during the day. The COWS score at this scheduled time must be conducted by a doctor.
- No more than 30mg of methadone should be administered within the third day of admission.
- No more than 30mg of 1mg/ml methadone can be ordered for patients at this stage of therapy through pharmacy

72 hours after admission

- If confirmation of a regular prescription can be made e.g. via the community pharmacy or Substance Misuse Liaison Team/Turning Point, treatment should be followed as described in section 6.2.1.1.
- If the patient reports no symptoms for 24 hours OR feeling able to wait for longer than 24 hours between doses then they are on an adequate dose.
- If contact with Substance Misuse Liaison Team/Turning Point cannot be established, the total daily dose of methadone administered in the 48 to 72 hour period should be prescribed as a single dose.
- Contact with Substance Misuse Liaison Team/Turning point should be established as, further dose increases **should not** occur without prior instruction by Turning point (or until the dose holds withdrawal symptoms at bay for 24 to 36 hours)
- No more than 30mg of 1mg/ml methadone can be ordered for patients at this stage of therapy through pharmacy

APPENDIX 3: CLINICAL OPIATE WITHDRAWAL SCALE (COWS) - LOG

CLINICAL OPIATE WITHDRAWAL SCALE Assessment form must be completed and signed before a dose can be administered				Addressograph
Ward		Site		

	Baseline	1	2	3	4	5	6	7	8	9	10
Date											
Time											
Resting pulse											
Sweating											
Restlessness											
Pupil size											
Bone or Joint aches											
Runny nose or tearing											
GI upset											
Tremor											
Yawning											
Anxiety or irritability											
Gooseflesh skin											
Total score											
Contact with Turning Point must be undertaken at the earliest opportunity											
Has contact with turning point made?	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Dose required? (COWS ≥ 13)	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Assessed by: Signature											
Print name											
Profession											

APPENDIX 3: CLINICAL OPIATE WITHDRAWAL SCALE (COWS) – GRADING

A Doctor should observe the patient during a 5 minute observation period then indicate a score for each of the opioid withdrawal signs listed below on the reverse of this chart. Add the scores for each item to obtain the total 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 diarrhea 5 Multiple episodes of diarrhea 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 assessmen*t 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 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	The COWS scale must be completed prior to each dose during the assessment period. Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe withdrawal. Scores of 13 and above are sufficient to warrant additional doses.

COWS scores can be undertaken to help establish withdrawal from Opiates and can be used in patient both ON or OFF a OST program.

COWS table has been adapted from Wesson (2003) The Clinical Opiate Withdrawal Scale (COWS)

APPENDIX 4: CONTACT NUMBERS AND OPENING TIME FOR LOCAL SERVICE PROVIDERS

For all inpatient referrals, the first point of contact should be the UHL Substance Misuse Liaison Team. Run by Turning Point, it is based at the Leicester Royal Infirmary.

The team can be emailed at TurningPointReferral@uhl-tr.nhs.uk or referred to on ICE under Service Provider "Substance Misuse".

The office hours are Monday-Friday 8-5pm. For referrals outside of these times, please leave a message which will be followed up.

Substance Misuse Liaison Team (Turning Point)
TIA/DVT Admin Office
Level 1, Balmoral
LRI
X17285, 07734694857, 07535658329

Drug and Alcohol Services in Leicester City and Leicestershire County and Rutland - Turning Point

Turning Point is the commissioned provider for Drug and Alcohol treatment in Leicester, Leicestershire and Rutland.

For all enquiries call 0330 303 6000.

Opening times	
Day	**Times**
Monday	09:00 to 17:00
Tuesday	09:00 to 17:00
Wednesday	09:00 to 20:00
Thursday	09:00 to 19:00
Friday	09:00 to 17:00
Saturday	09:00 to 17:00

Local Prison (Leicestershire)

HMP Glen Plava, Welford Road and Gatree. - Contact onsite medical team - Phone number available via hospital switchboard

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Community Pharmacies –

Obtain numbers via directory services through hospital switchboard

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Useful References

National Poisons Information Service - Phone number available from hospital switchboard or http://www.npis.org. Information available on Toxbase.

The street names of all drugs of abuse can be found at www.talktofrank.com in the section "The A-Z of drugs". Patients can ring Talk to Frank on 0800 776600

National helplines (patient self referral)

Narcotics Anonymous – Website: http://ukna.org. Telephone: 0300 999 1212

Alcoholics Anonymous - Website: http://www.alcoholics-anonymous.org.uk

Telephone: 0800 9177 650 Email: help@aamail.org

APPENDIX 5: IMPORTANT INTERACTIONS WITH METHADONE AND BUPRENORPHINE

Common interaction with methadone and buprenorphine are listed below. Further information regarding interactions can be obtained in the BNF, by contacting a member of the pharmacy team or by contacting the medicine information department.

Interaction type	Which medicines or other substances?	How?	Effect?
CNS depressants and opioids including buprenorphine	• other opioids • hypnotics, anxiolytics, sedatives • benzodiazepines • many tricyclic antidepressants and MAOIs • many antipsychotics • older antihistamines • clonidine • anaesthetics • barbiturates • alcohol **For methadone:** • lofexidine	increased CNS depression	additive effect – potentiation of respiratory depression, hypotension
Medicines which increase methadone or buprenorphine levels	• cimetidine • ciprofloxacin • antimicrobials including: macrolides: (erythromycin, clarithromycin, telithromycin), azoles: (ketoconazole, itraconazome, fluconazole, voriconazole) • antidepressants: fluvoxamine and possibly other SSRIs • some cardiovascular agents: amiodarone • some anti HIV agents **For buprenorphine:** • other CYP3A4 inhibitors e.g. gestodene, protease inhibitors indinavir, saquinavir, nelfinavir, ritananovir, boceprivir **For methadone:** • disulfiram • grapefruit juice • delavirdine • quinidine • verapamil • dihydroergotamine	Increased blood levels of methadone or buprenorphine by inhibition of the enzyme CYP3A4, CYP2D6 or reduced protein binding	dose of methadone or buprenorphine may need to be decreased to prevent toxicity or overdose AND may need to be increased when the enzyme inhibitor is stopped to prevent withdrawal symptoms (sedation, confusion, respiratory depression)
Medicines which decrease methadone or buprenorphine levels	• anticonvulsants e.g. barbiturates, carbamazepine, phenytoin, primidone, fosphenytoin • rifampicin • rifabutine • spironolactone	decreased blood levels of methadone or buprenorphine by induction of enzyme CYP3A4 or increased urinary excretion	dose of methadone or buprenorphine may need to be increased to prevent withdrawal symptoms AND decreased when the enzyme inducer is stopped to prevent overdose

	• St. John's Wort **For methadone:** smoking (CYT1A2) fucidic acid (not topical) Dexamethasone antiretrovirals: abacavir, amprenavir, lopinavir, efavirenz, nevirapine, nelfinavir, ritanovir, nevirapine, nelfinavir, ritanovir		
Buprenorphine and other opioid agonists	• methadone • diamorphine other full agonists e.g. fentanyl	buprenorphine is a partial agonist and displaces other opioids from receptor sites	can precipitate withdrawal symptoms - advise waiting until opioid is excreted (confirmed by presence of withdrawal symptoms) before taking buprenorphine
Opioid agonists or partial agonists with opioid antagonists	naltrexone (active orally) naloxone (active intra-nasally and parenterally)	naltrexone and naloxone are full antagonists and displace other opioids (including buprenorphine, pentazocine) from receptor sites	will precipitate withdrawal symptoms if taken when agonist or partial agonists have recently been taken
Methadone plus medicines affecting QTc interval	• antidepressants: tricyclics, SSRIs including sertindole, citalopram/escitalopram, fluoxetine • antipsychotic medicines including haloperidol • antimicrobials: pentamidine, macrolides (erythromycin, clarithromycin, azithromycin), quinolones (moxifloxacin, sparfloxacin), azoles (fluconazole, itraconazole, ketoconazole, voriconazole) • antiemetics: domperidone, droperidol, ondansetron • antiarrhythmic/cardiovascular drugs: digoxin, dronedarone, sotalol, quinidine, amiodarone, flecanide, procainamide, dofetilide disopyramide • some antimalarials • some cancer treatments • some HIV protease inhibitors e.g. atazanivir • cocaine and stimulants including atomoxetine, dexamfetamine, methylphenidate • terodiline • antihistamines including: terfenadine, astemizole, loratidine possibly lithium and lofexidine	prolongation of QTc interval can cause torsades de pointes	• life threatening ventricular arrhythmias use cautiously with methadone

Methadone plus medicines affecting cardiac conduction or which may affect electrolyte imbalance	• cytotoxics • rifampicin • atomoxetine • protease inhibitor crizotinib • antimalarials	precipitated ventricular arrhythmias	• risk of cardiac eventsavoid concomitant use
Medicines affecting urine pH	• vitamin C • ammonium chloride • sodium bicarbonate (antacids)	affect excretion of methadone: − increased excretion in acidic urine (ammonium chloride) − decreased excretion in alkaline urine (sodium bicarbonate)	• increased excretion may cause withdrawal decreased excretion may cause toxicity

Table 5: Common interaction with Methadone and Buprenorphine. From Drug misuse and dependence: UK guidelines on clinical management