University Hospital Wishaw
Acute Pain Service

NHS Lanarkshire

High Dose Buprenorphine

A guideline for the peri-operative care of opioid dependent patients maintained on buprenorphine, including Buvidal, Espranor, Subutex and Suboxone

Key Words: Suboxone, Subutex, Opioid Dependence, Acute Pain, Buprenorphine

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Introduction and Need for Guideline

Buprenorphine is used as maintenance therapy in opioid dependence, for individuals in whom methadone is unsuitable (1) or where buprenorphine is a good treatment option. An estimated 1.36% of the population (5084) in Lanarkshire in 2006 were problem drug users. A local audit in July 2021 revealed that Lanarkshire has approximately 2,650 people on substitute prescriptions, either buprenorphine (Buvidal, Espranor, Suboxone and Subutex) or methadone [(2)] In 2021 across NHSL approximately 25-30% of patients on substitute therapy were prescribed oral buprenorphine. Patients maintained on buprenorphine present for elective or emergency surgical conditions requiring acute pain control. As well as the patients having some dose related opioid tolerance oral buprenorphine formulations can act as a partial opioid agonist which can block or diminish the effect of therapeutic doses of strong opioids used for the peri-operative treatment of acute pain. Opioid dependent patients maintained on buprenorphine presenting for emergency or elective surgery therefore present a challenge to anaesthetists and other care professionals in managing their acute pain in the peri-operative period. This guideline suggests some strategies to assist clinicians in managing these patients through the peri-operative period.

Lower doses of buprenorphine are administered by transdermal patches for chronic pain, Butrans (transdermal buprenorphine) need not be discontinued prior to elective surgery regardless of dose, though clinicians may wish to do so at their discretion, in which case the information in this guideline may be helpful. These patients will have a degree of dose related opioid tolerance so may also require higher doses of opioids if needed for episodes of acute pain. To assist it is useful to be mindful of approximately equivalent opioid doses. Resources available include BNF, Scottish Palliative Care Guidelines or online calculators. e.g. Pain Management Opioid Dose Converter (paindata.org).

Pharmacology

Buprenorphine is a derivative of the morphine alkaloid, thebaine, and is a partial opioid agonist at the mu opioid receptors in the nervous system. It is also a kappa opioid receptor antagonist. It has low intrinsic agonist activity, only partially activating mu opioid receptors, thus producing a milder, less euphoric and less sedating effect than full opioid agonists such as heroin, morphine and methadone. (3) Nevertheless, its activity is usually sufficient to diminish cravings for heroin, and prevent or alleviate opioid withdrawal in dependent heroin users.

Preparation

Buprenorphine is available as:

i. a sublingual preparation containing a dose of 2mg or 8mg per tablet (Subutex or generic), Maximum dose 32mg daily

ii. an oro-dispersible wafer containing a dose of 2mg or 8mg per wafer (Espranor), Maximum dose 18mg daily

iii. a combined formulation (sub lingual or mucosal adherent film) with naloxone (a full opioid antagonist) (Suboxone) maximum dose 24mg daily (buprenorphine) and

iv. a prefilled subcutaneous long acting injection (either 7 day or 28-day duration in various strengths 8mg to 128mg) (Buvidal)

PHARMACOKINETICS

Buprenorphine is highly lipophillic enabling sublingual administration. Sublingual buprenorphine tablets have approximately 30-35% bioavailability. Orally there is very extensive first pass metabolism, with bioavailability as little as 3-6% making it relatively safe in case of accidental oral overdose as would be seen in children. Peak plasma concentrations are achieved 1-2 hours after sublingual administration. Distribution half life is 2 - 5 hours. Its lipophillicity and high protein binding give it a very high volume of distribution greater than 200 litres. It is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and N-de-alkylation. The metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the faeces and urine.

Elimination half life 24 – 37 hours varies with dose administered.

In the case of Suboxone, the naloxone in the formulation is not absorbed by the sublingual route it can be discounted from consideration, it only being present to prevent the tablets being illicitly taken intravenously or intranasally as the naloxone would then precipitate acute withdrawal in an opioid dependant individual. Otherwise these two forms of high dose buprenorphine can be considered together as the naloxone present in Suboxone is not systemically active by the sublingual or oral route. Any reference to buprenorphine in the document can reasonably be extrapolated to include Suboxone.

PHARMACODYNAMICS

Onset of effects 30 - 60 minutes, though in practice it can be seen to attenuate opioids withdrawal symptoms in as little as 10 to 15 minutes.

Peak clinical effects 1 - 4 hours

Duration of effects 8 - 12 hours at low dose (e.g. < 4 mg)

24 - 72 hours at high dose (e.g. >16 mg)

The prolonged duration of effect at high doses enables alternate-day, and even 3 days a week dispensing regimes.

Buprenorphine has a very high affinity for opioid receptors though with relatively low intrinsic agonist activity. Its activity is usually sufficient to prevent or alleviate withdrawal from illicit heroin use; though as it has a greater affinity for opioid receptors than full agonists, such as morphine, diamorphine (heroin) or fentanyl, it can act as a partial antagonist when these drugs are taken illicitly or to treat concurrent acute pain episodes. It has some analgesic effect though this is perhaps short lived. On initial induction of buprenorphine it can precipitate acute withdrawal as it displaces more potent but lower affinity opioids from receptors. This unique pharmacology can prevent illicit opioid abuse whilst on buprenorphine maintenance in the community but peri-operatively high doses of buprenorphine can prevent prescribed full agonist opioids at conventional doses from alleviating acute pain.

Withdrawal syndrome from Buprenorphine

Opioid withdrawal syndrome is milder with the cessation of buprenorphine treatment, than with heroin, morphine or methadone. Typically, the withdrawal syndrome following the abrupt cessation of long-term buprenorphine treatment emerges within 3 to 5 days of the last dose, and mild withdrawal features continue for up to several weeks. Typical symptoms and signs of opioid withdrawal include yawning, sweating, anxiety, rhinorrhea, tachycardia, hypertension, diarrhoea, nausea, vomiting, abdominal pain and cramps.

Side effects

Typical of opioids: constipation, nausea, drowsiness, sleep disturbance, sweating, headaches, except respiratory depression less marked.

Drug Interactions

The principal drug interactions of Buprenorphine relate to its opioid activity.

- Buprenorphine exerts additive sedative effects when used in conjunction with other sedating medications. These include other opioids, benzodiazepines, alcohol, tricyclic antidepressants, sedating anti-histamines, and major tranquillisers. A number of deaths have been reported involving the combination of Buprenorphine with abuse of high doses of benzodiazepines and other sedatives.
- Opioid antagonists (naloxone and naltrexone). Buprenorphine has higher affinity for mu opioid receptors than the opioid antagonists. In the event of overdose of Buprenorphine, very high doses of naloxone are required to reverse its effects (10-35 mg have been reported).
- Hepatic enzyme inducers and inhibitors. Buprenorphine is metabolized by the hepatic microsomal enzyme system (CYP 3A4). Concurrent use of medications which inhibit CYP 3A4 (e.g. protease inhibitors, some drugs in the class of azole antimycotics such as ketoconazole, calcium channel antagonists such as nifedipine, and macrolide antibiotics) may lead to increased plasma concentrations of Buprenorphine however current evidence indicates minimal clinical impact on Buprenorphine dosing requirements.

Pain Management Issues

Generally, the peri-operative management of patients with a history of opioid abuse can be challenging. Patients taking any opioid regularly may have marked tolerance to opioids and may have opioid induced hyperalgesia. It may be difficult to separate genuine opioid analgesic requirement from drug seeking behaviour. Hyperalgesia may be less marked with buprenorphine than methadone. Patients may be anxious that they will be stigmatised and denied adequate analgesia with opioids due to their history. They should be reassured that their reported pain will be taken seriously and acted upon. Conversely patients with previous opioid addiction may be phobic of opioids even when administered for acute pain lest they relapse.

Unfortunately, there is no good data on which to base the management of patients on buprenorphine maintenance programs requiring acute pain relief. However due to the particular pharmacology of buprenorphine in attenuating full opioid agonist effects, if shorter-acting opioid agonists will be required, a decision needs be made whether or not to continue buprenorphine: this is a complex decision which should be taken with the patient and involving their usual addiction services prescriber taking into account the nature and urgency of their surgery and other circumstances (social, co morbidity).

Suggestions for management vary from continuing the buprenorphine as usual, reducing to a lower dose (less than or equal to 12mg per day) before planned surgery or withholding the buprenorphine and substituting an alternative full agonist opioid (e.g. methadone), [4,5,6,7] Preoperative conversion to another opioid may be problematic: in case of methadone given that they were commenced on buprenorphine as an alternative and its perceived stigma or in case of conversion to sustained release oral morphine (MST) may be difficult to titrate and supervise in the community. The decision to reduce or stop buprenorphine with or without substitution on a planned basis prior to elective surgery should be a multidisciplinary decision taking account of the patient's views but with final decision with the implementing clinicians on the addiction services team who would oversee any change to opioid replacement therapy. Close liaison with all treating clinicians and substance misuse services, including the substance misuse team within the hospital, should occur if buprenorphine has been ceased and it should be recommenced before the patient is discharged from hospital; see below for suggested method.

However, in practice, in many cases, there appears to be little problem if the buprenorphine is continued and acute pain managed with the combination of a short-acting full opioid agonist as well as other multimodal analgesic strategies. As with methadone, dividing the daily doses on a temporary basis may take advantage of the short lived analgesic properties of oral buprenorphine (which tend to be better than the analgesic effects of methadone).

Comparison with peri-operative strategies for patients maintained on methadone or other high dose oral full agonist opioid.

Usually methadone maintenance, or other high dose oral full agonist opioid, therapy is continued, with the usual daily dose being taken on the morning of surgery whenever possible as a background with additional multimodal analgesia with full opioid agonists prn at appropriate doses orally or by PCA if necessary depending upon the nature of the surgery. Where the enteral route is interrupted for more than 24 hours (e.g. by elective abdominal surgery) the usual dose is given on the morning prior to theatre with a morphine PCA with or without background infusion being used until recommencement of enteral methadone is possible. In contrast buprenorphine with its sublingual, oral dispersible or depot routes of administration means non-availability of the oral route need not interrupt therapy however the functional antagonism due to buprenorphine's lesser partial agonist activity but high mu receptor affinity may prevent full mu agonists from providing adequate analgesia necessitating high doses and/or adjuvants such as ketamine which confer analgesia via different receptor pathways. Withdrawal of high dose buprenorphine during a period of high dose mu agonist administration may lead to delayed opioid toxicity as the buprenorphine is eliminated, vacating the mu receptors. Due to this risk a higher oral prn dose of oral morphine or a higher bolus dose on a PCA pump may be preferable to a high dose Modified release tablet or a high rate background infusion with conventional PCA bolus.

General pain management considerations in these patients are to utilise multimodal analgesia with regional blocks, paracetamol and NSAIDs where possible and consider adjuvants such as ketamine infusions, perioperative clonidine, lidocaine or Magnesium. During critical illness, where organ dysfunction may enhance opioid effects or affect elimination, opioid dose adjustment may be necessary to avoid accumulation. This requires vigilance and patient monitoring in particular when background infusions of opioid are in use.

Peri-operative Pain Management Strategies for patients stabilised on Suboxone

All patients taking buprenorphine attending for elective surgery should be identified at surgical outpatient or anaesthetic preadmission clinic and an individualised plan made involving the patient, surgical team, attending anaesthetist and substance misuse services whenever possible well in advance of the day of surgery.

1. Day case procedures under local anaesthesia or sedation e.g. colonoscopy
   - ✦ continue buprenorphine at usual interval & dosage
   - ✦ Midazolam and/or Pethidine as protocol for the procedure with routine monitoring
   - ✦ Nurse operators/endoscopists should notify supervising clinician of patient in case requires more sedation than possible within their protocol. Additional sedation can be given at that clinician's discretion. (Literature cautions against possible buprenorphine interaction with benzodiazapines though only based on outcome of mixed overdoses in the community with large doses of benzodiazepines).
   - ✦ Recovery and discharge as per usual protocols
2. Day surgery/Minor operations with anticipated mild/moderate post op pain.
   - ✦ continue buprenorphine at usual interval & dosage
   - ✦ Multimodal: paracetamol +/- NSAID premedication/intraoperatively and continued post op regularly as take home analgesia
   - ✦ local/regional technique +/- GA to extend analgesia
   - ✦ peri-operative generous iv loading with full opioid agonist with further in recovery if required (morphine or fentanyl)
   - ✦ Consider adjuvants e.g. NMDA agonist: ketamine intra-operative loading dose and rescue bolus in recovery. Alpha 2 agonist: Clonidine. Other adjuvants could be considered as pre-medicants or peri-operatively e.g. gabapentin, pregabalin lidocaine infusion.
   - ✦ avoid mixed antagonist/agonist opioids e.g. tramadol
   - ✦ If pain is anticipated to be moderate for a few days' post operatively consider liaising with addiction services in advance for temporary increase of daily buprenorphine dose by up to 25% and/or total dose divided and taken in three or four doses daily to take advantage of relatively short analgesic effect of buprenorphine. Optimising the analgesic effect by increasing the dose to the maximum 32mg may be considered. (if on Suboxone, increasing the dose off label to 32mg could be considered in the interests of simplicity, continuity and maintaining the patient's confidence).
   - ✦ Acknowledge that patients may require unscheduled admission for analgesia failure. The list anaesthetist should plan for this contingency by handing over to on call staff once the patient leaves recovery and list is finished.
   - ✦ In case of analgesia failure requiring admission, then rescue with loading high dose full opioid agonists (morphine or fentanyl) then proceed to either high dose full agonist prn opioid or commence PCA with large bolus with longer or conventional 5 minute lockout PCA with / without background and/or ketamine infusion: at present if opioid background or ketamine infusion require HDU or Level 1 care.
   - ✦ Ensure discussion with patient to ensure aware that will be weaned off other strong opioids before discharge.
   - ✦ Care should be overseen by a consultant anaesthetist particularly if post-operative adjuvants or background infusions of opioids are being considered.
   - ✦ Inform pain team and on call anaesthetic team of patient and location.
   - ✦ Ensure at least daily review by acute pain team or in their absence (leave periods or out with office hours) the on call anaesthetist/intensivist.

3. Elective major surgery with anticipated moderate to severe post op pain.

   Choice needs to made in advance whether to:

   Either Continue buprenorphine throughout peri-operative period

   Or Reduce oral buprenorphine dose to 12mg per day 3 days prior to admission to allow a reasonable percentage of opioid receptors to be available to potent full agonists perioperatively [9]

   Or Stop buprenorphine and substitute other full opioid agonist preoperatively. Need to be aware if patient is prescribed Long Acting Injectable Buprenorphine as this cannot be stopped within 3 days and there is a very gradual taper of buprenorphine as the matrix releases dose. For full detox from a LAIB to happen this can take over 90 days

   - The list Consultant Anaesthetist or preadmission clinic anaesthetist should be consulted on this decision. As the latter strategy requires advanced planning and multidisciplinary working the Consultant Anaesthetist who will be anaesthetising the patient for the operative procedure should be contacted from the booking surgical clinic by the surgical team and take responsibility for planning and coordinating. If a Consultant Anaesthetist is not allocated to the list the preadmission clinic Consultant Anaesthetist should be contacted.

   - The patient's addiction service should be consulted.
   - If buprenorphine is to be stopped in advance and substituted this should be done by the patient's original prescribing addiction service. Buprenorphine needs to be stopped a minimum of 72 hours preoperatively to allow dissociation from opioid receptor sites and elimination Substitution treatment with a full opioid agonist (methadone or oral morphine) usually starts 24 hours after last dose of buprenorphine. Rough guide to **starting doses**:
   - Buprenorphine<4mg daily – 20mg/daily methadone or 10mgs MST bd, Buprenorphine>4mg daily – 40mgs/daily methadone or 20mgs MST bd) (8)
   - The full agonist opioid substitute: Methadone or its iv morphine equivalent should be continued as background throughout the peri-operative period.
   - If buprenorphine is not discontinued then post op management should be as above: continuing buprenorphine along with a high dose full agonist opioid as prn and/or background, utilising continuous regional anaesthesia e.g. epidural infusion with at least 4ug/ml fentanyl or peripheral catheter infusion technique and adjuvants which act via different receptor pathways such as iv ketamine intra and post operatively.
   - Care should be overseen by a consultant anaesthetist particularly if post-operative adjuvants are being considered.
   - Inform pain team and on call anaesthetic team of patient and location.
   - Ensure at least daily review by acute pain team or in their absence (leave periods or out with office hours) the on call anaesthetist, Page 003.

4. Emergency surgical admissions with severe acute pain (e.g. acute abdomen, trauma)
   - Initial therapy should include multimodal analgesia and local/regional anaesthesia where possible (e.g. Femoral nerve block for fractured shaft of femur) though the mainstay of treatment will be with loading and prn high dose morphine or fentanyl with adjuncts.
   - The Acute Pain team and/or on call anaesthetic team should be contacted early for advice and to ensure daily review.
   - If despite a generous loading with iv full agonist opioid, then commencement of PCA and Ketamine infusion, pain is still poorly controlled and is anticipated to last more than

     72 hours then Suboxone should be discontinued. The patient should be monitored with PCA level and frequency observations at a maximum 2hourly interval for signs of opioid toxicity which may manifest as Buprenorphine is eliminated unmasking opioid receptors to high dose circulating full agonist. For this reason opioid infusions should be used cautiously and reviewed frequently; a large bolus on PCA may be safer.
   - Any surgical procedures should utilise local or regional anaesthesia if possible +/- general anaesthesia.
   - The patient's addiction services prescriber should be contacted to inform of admission and obtain advice.
   - Once pain is controlled adjuvant therapy can be weaned and conversion to oral full agonist opioids can be undertaken once oral route is available. Ongoing analgesic requirements should be considered but maintenance Suboxone should ideally be recommenced prior to discharge.

Recommencement of buprenorphine

If buprenorphine is recommenced whilst the patient is still on high doses of full opioid agonist, then acute withdrawal with severe acute pain may be precipitated. Recommencement of buprenorphine will be done under the guidance of the substance misuse team once patient has stable analgesic requirement with well controlled pain and opioid requirements are less than or equal to approximately 80mg oral morphine equivalent per day. .

Criteria for recommencement of Suboxone:

- Stable analgesic requirement with well controlled pain
- Atypical adjuvants such as Ketamine have been weaned and stopped
- Opioid requirements less than or equal to approximately 80mg oral morphine equivalent per day.

Suggested regime:

Restart usual buprenorphine dose and titrate dose (assessment of withdrawal symptoms must be undertaken before reintroducing buprenorphine to minimise the risk of precipitate withdrawal) and continue simple analgesia (paracetamol) and/or NSAID if required but stop other opioids.

In case of precipitation of opioid withdrawal reassure and treat symptomatically:

- antiemetics (e.g. prochlorperazine: buccastem 5mg buccal tds)
- antidiahorreals (e.g. loperamide 2mg to max 16mg daily orally)
- anxiety/hypertension/sweating suggest Clonidine 25-50microgram orally up to tds
- consider further 2mg tablets of buprenorphine.

The above are guidelines only rather than protocols to reflect the paucity of high level evidence and acknowledge that management plans will require being adapted to individual patients and their circumstances.

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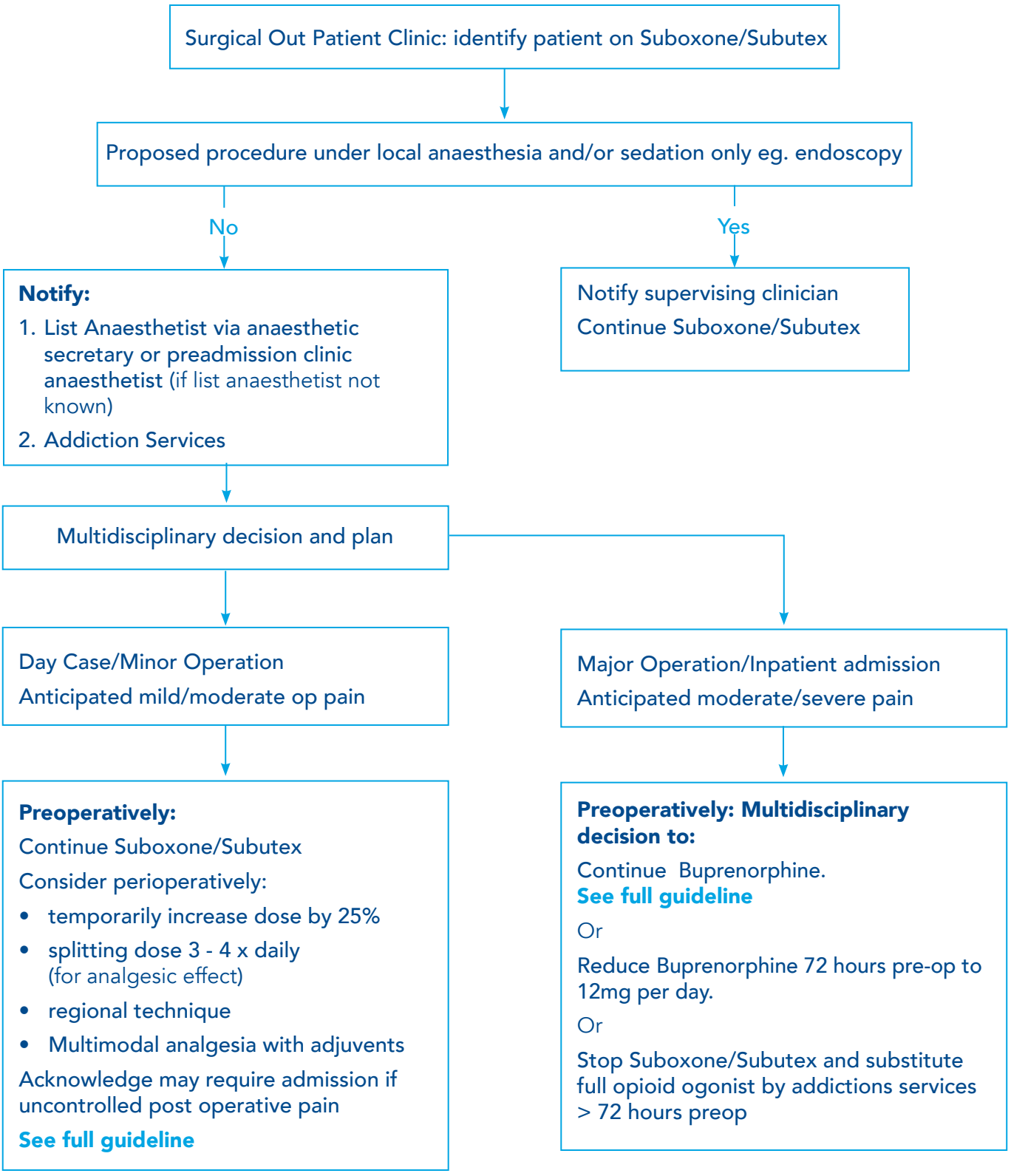
Appendix 1: Pain and Addiction Terminology

Table 1 from [3]

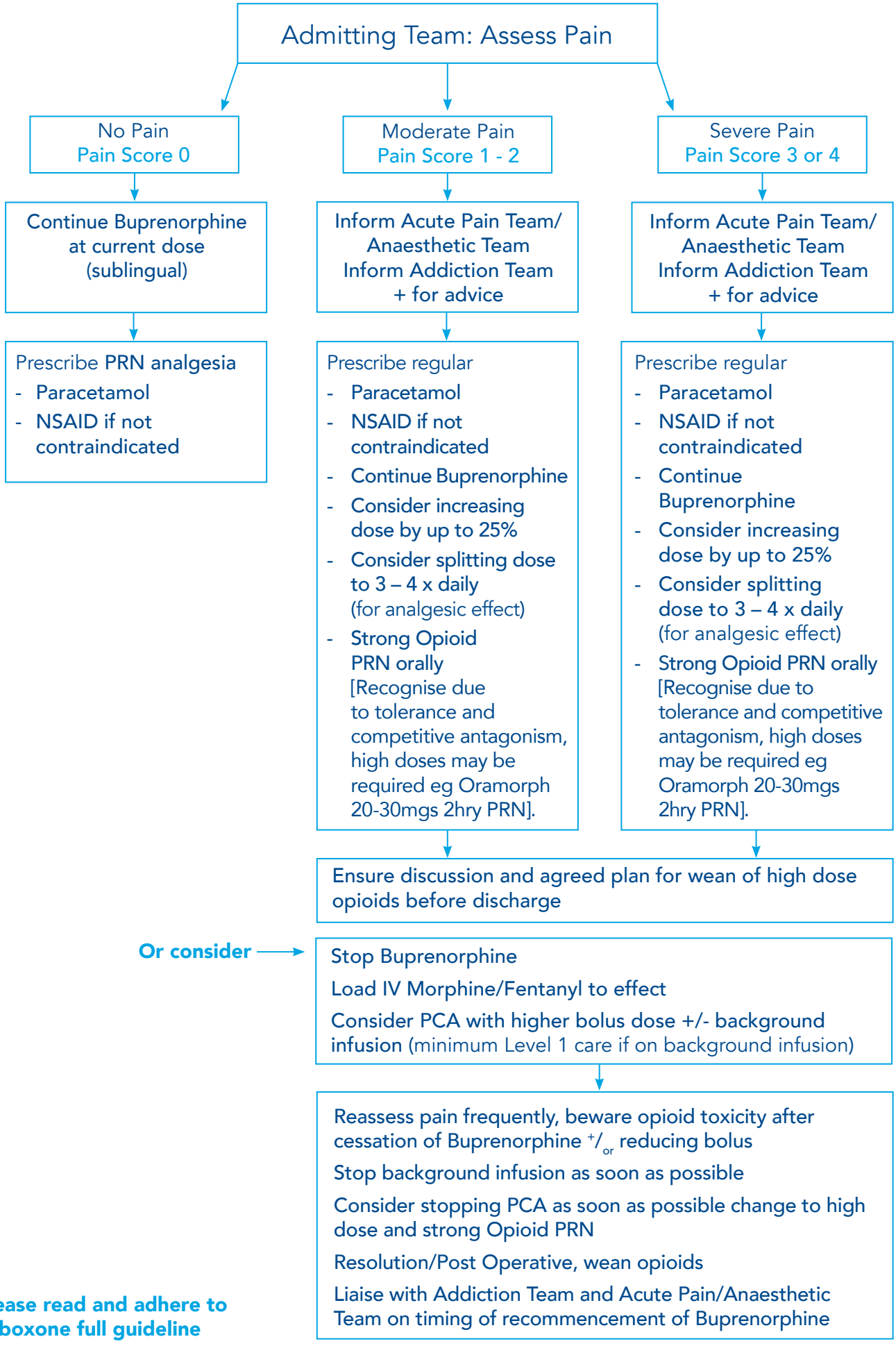
Term	Definition
Physical dependence	Normal physiologic adaptation defined as the development of withdrawal or abstinence syndrome with abrupt dose reduction or administration of an antagonist.
Tolerance	Normal neurobiological event characterized by the need to increase the dose over time to obtain the original effect.
Cross-tolerance	Normal neurobiological event of tolerance to effects of medication within the same class.
Substance (opioid) dependence (addiction)	Chronic neurobiological disorder defined as a pattern of maladaptive dependence (addiction) behaviours, including loss of control over use, craving and preoccupation with nontherapeutic use, and continued use despite harm resulting from use with or without physical dependence or tolerance.
Pseudoaddiction patients	Behavioural changes in patients that seem similar to those in patients with opioid dependence or addiction but are secondary to inadequate pain control.
Drug-seeking behaviours	Directed or concerted efforts on the part of the patient to obtain opioid medication or to ensure an adequate medication supply; may be an appropriate response to inadequately treated pain.
Therapeutic dependence	Patients with adequate pain relief may demonstrate drug-seeking behaviours because they fear not only the re-emergence of pain but perhaps also the emergence of withdrawal symptoms.
Pseudo-opioid resistance	Adequate pain relief continue to report persistent severe pain to prevent reduction in current opioid analgesic dose.
Opioid-induced hyperalgesia	A neuroplastic change in pain perception resulting in an increase in pain sensitivity to painful stimuli, thereby decreasing the analgesic effects of opioids.

Appendix 2: Elective Surgery



Use multimodal opioid sparing techniques or adjuvants (see full guideline) and nerve blocks.
It should be acknowledged that patients on Buprenorphine may require high doses of strong opioids due to tolerance and competitive antagonism (limited available opioid receptors).
Advice - Oral High dose Oramorph 2hrly PRN eg 20-40mgs OR IV Loading OR PCA.

Appendix 3: Emergency Surgical Admissions



Please read and adhere to Suboxone full guideline

Appendix 4: Useful Contact Details

Acute Pain Services:

Note: Nurse specialists during office hours though may not be available due to leave. Lead clinician availability is limited by other commitments. Out of hours and leave is covered by on call anaesthetic team in respective hospitals.

University Hospital Wishaw, Acute Pain Service. Monday - Friday 9am - 5pm

Nurse Specialists: Sharon Anderson, Linsey Steele (Dect 6224, Page 021),

Dr Colum Slorach, Consultant Anaesthetist (Page 133)

Dr Iain McKevitt (Page 679)

After hours or if unavailable, contact ICU resident (Page 003)

University Hospital Monklands, Acute Pain Service. Monday - Friday 9am - 5pm

Nurse Specialist - Ashleigh Connolly: DECT 404680

Dr Joanne Bell, Consultant Anaesthetist,

After hours or if unavailable, contact Duty Anaesthetist via switchboard.

University Hospital Hairmyres, Acute Pain Service. Monday - Friday 9am - 5pm

Specialist Nurse Practitioner Katie Ramage, Laura Cameron-01355 584589 or Dect phone 5731

Dr Vera Sokolova, Dr Mike McCusker, Dr John O'Donoghue- Consultant Anaesthetists,

After hours or if unavailable, contact Duty Anaesthetist via switchboard.

Addiction Services

Dr Stephen Conroy, Coathill House	Tel. 01236 707 157
Dr Edmund Stewart	Tel. 01698 753839
Duncan Hill, Specialist Pharmacist in Substance Misuse	Mob. 0792 0711131

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