20 - Buprenorphine

Buprenorphine

506 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 4 Methadone overdose In the event of methadone overdose, naloxone should be administered as described in the section on opioid overdose earlier in this chapter. Methadone and risk of torsades de pointes/QT interval prolongation Methadone, either alone or combined with other QT-prolonging agents, may increase the likelihood of QT interval prolongation, which is associated with torsades de pointes and can be fatal.26,42–44 Recommended ECG monitoring There is insufficient evidence to support the effectiveness of QT screening in preventing cardiac death in people prescribed methadone.45 However, in the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) recommends that patients with the following risk factors for QT interval prolongation receive regular electrocardiogram (ECG) monitoring while receiving methadone: ■ ■heart disease ■ ■liver disease ■ ■dose of >100mg per day ■ ■electrolyte abnormalities ■ ■concomitant CYP3A4 inhibitor treatment ■ ■concomitant medication that prolongs QT (e.g. certain antipsychotics and anti depressants, erythromycin). Other factors that may also increase risk of QT prolongation are: ■ ■cocaine use46 ■ ■synthetic cannabinoid receptor agonist (SCRA) use47 ■ ■eating disorder or malnutrition48 ■ ■human immunodeficiency virus (HIV) positive status.48 Individuals with the risk factors listed above should have a baseline ECG and subsequent ECG monitoring. This is especially the case in in-patient settings where ECGs are easily obtained. However, where patients refuse to attend for an ECG, the risk of stopping methadone should be weighed against the risk of continuing without QT data. There is no evidence base guiding frequency following initiation. Annual checks in the absence of cardiac symptomatology would be a reasonable minimum frequency. It is also important to check the actions of any medications being prescribed with methadone for CYP3A4 inhibitory activity, to inform the risk–benefit analysis when commencing methadone. Actions following a finding of prolonged QT interval are summarised in Table 4.13. Buprenorphine Buprenorphine is a synthetic partial opioid agonist with low intrinsic activity and high affinity at mu opioid receptors. This means that it produces less euphoria even at receptor-saturating doses and simultaneously blocks the action of other opioids. It is an effective treatment for heroin and prescribed opioid addiction although no more effective

Addictions and substance misuse CHAPTER 4 than methadone.49 It is associated with lower likelihood of retention in treatment than methadone25 and clinical experience with buprenorphine suggests it can be difficult to initiate using conventional methods because of the need for sufficient withdrawal symptoms to start, but not so much withdrawal that it prevents attendance at the treatment centre. This has been addressed by novel micro- and macro-induction methods (see later). It has also been found to be effective in reducing prescription opioid use and improving treatment adherence in prescription opioid-dependent patients. Sublingual buprenorphine

Buprenorphine is absorbed via the sublingual route, and this has long been the most used route of administration.50,51 Each tablet takes approximately 5–10 minutes to disintegrate, dissolve and be absorbed. It is effective in treating opioid dependence because of the following: ■ ■It alleviates/prevents opioid withdrawal and craving. ■ ■It reduces the effects of additional opioid use because of its high receptor affinity – what patients refer to as a 'blocking' effect.52,53 ■ ■It is long-acting, allowing daily (or less frequent) dosing. The duration of action is related to the buprenorphine dose administered: low doses (e.g. 2mg) exert effects for up to 12 hours; higher doses (e.g. 16–32mg) exert effects for as long as 48–72 hours, allowing thrice weekly dosing.54 Different brands of oral buprenorphine and bioavailability Espranor is a brand of buprenorphine that is increasingly used in UK community addictions services. Espranor is placed on the tongue, not under it. The pharmacokinetics of Table 4.13 Recommended ECG monitoring for people taking methadone. Borderline prolonged QTc Action Prolonged QTc Action Very prolonged QTc Action Females ≥470ms Repeat ECG Electrolytes Try to modify QT risk factors, e.g. cocaine use, SCRA use, methadone dose, psychotropic medications Regular ECG until normal ≥500ms Repeat ECG Electrolytes Try to modify QT risk factors Seek cardiology and addictions advice Reduce methadone dose If long QTc despite reduction, switch to buprenorphine Regular ECGs until normal ≥550ms Urgent cardiology and addictions advice Repeat ECG Electrolytes Try to modify QT risk factors Reduce methadone and re-evaluate within the week; switch to buprenorphine in in-patient setting Males ≥440ms SCRA, synthetic cannabinoid receptor agonist.

508 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 4 buprenorphine show quite wide inter-individual variation and this variability is accommodated by titrating people against their personal therapeutic response. Table 4.14 shows the conversion from buprenorphine or other brands of buprenorphine to Espranor, based on clinical experience. Given the uncertainty regarding dose equivalence, it is prudent not to switch between brands without good cause. Conventional buprenorphine induction The same principles apply as for methadone initiation. Proof of recent use is more difficult for buprenorphine because it is not included in standard multiple urine drug testing kits. It is commonly identified using a separate urine drug screen kit, which is not usually available outside addiction services. Therefore, collateral information from the addiction service or the dispensing pharmacy is essential if continuing buprenorphine in a non-specialist setting. Of particular interest with buprenorphine is the phenomenon of precipitated withdrawal. Precipitated withdrawal occurs because buprenorphine is a partial agonist with a high receptor affinity. If it enters the brain when a full agonist (e.g. methadone or heroin) is still present it competes for binding at the opioid receptors and replaces the full agonist. Some receptors previously fully stimulated become partly stimulated. The patient experiences this change as opioid withdrawal. However, if the patient is already in withdrawal, they will experience the addition of a partial agonist as relief of that withdrawal. Patient education is an important factor in reducing the problems during induction. To summarise, buprenorphine is a partial agonist with higher affinity for opioid receptors than pure agonists. If given to someone with high occupancy of opioid receptors by full agonists, the net effect will be a reduction in agonist activity and withdrawal symptoms may result. If receptor occupancy by pure agonists is so low that withdrawal symptoms are already evident, then giving buprenorphine will have the effect of increasing overall opioid receptor stimulation and withdrawal symptoms will abate. When a full agonist is given to someone maintained on buprenorphine, the net effect is usually nothing: buprenorphine cannot be dislodged by lower affinity agonists. This is the 'blocking effect' of buprenorphine. Adding a full agonist to buprenorphine does not Table 4.14 Conversion from buprenorphine to Espranor. Buprenorphine

sublingual Espranor orodispersible 8mg 6mg 10mg 8mg 12mg 10mg 14/16mg 12mg 18mg 14mg 20/22mg 16mg

> 26mg 18mg

Addictions and substance misuse CHAPTER 4 (and indeed could not) precipitate withdrawal. This may seem obvious, but the belief that agonists can provoke withdrawal is apparently widely held. The initial dose recommendations are as follows:8 ■ ■Patient in withdrawal and no risk factors: 8mg buprenorphine. ■ ■Patient not experiencing withdrawal and no risk factors: 4mg buprenorphine. ■ ■Patient has concomitant risk factors (e.g. medical condition, polydrug use, low or uncertain severity of dependence, psychiatric medications): 2–4mg buprenorphine. No more than 8mg buprenorphine should be given on the first day in a non-specialist setting. In some cases, 8mg may be sufficient, but this may need to be increased to 12–16mg the following day if there is no evidence of intoxication. The doses can be given in divided doses so that they can be reviewed promptly in the event of any intoxication, although in practice this is difficult in the absence of on--site dispensing. For maintenance, the 'Orange Book'8 recommends a dose between 12 and 24mg a day. If patients are on other respiratory depressants such as benzodiazepines, the patient should be monitored for intoxication and respiratory depression. Low-dose induction for buprenorphine initiation In North America, the fentanyl epidemic has led to the development of innovations to facilitate initiation of buprenorphine. These include a low-dose induction technique that involves a slower titration of buprenorphine in a patient who is still actively using full opioid agonists and is not in withdrawal.55 The protocols are similar to those discussed later in the section on methadone to buprenorphine transfer. Prolonged-release buprenorphine injection A prolonged-release subcutaneous buprenorphine injection (trade name Buvidal in the UK and EU, Sublocade and others in the USA and Australia) is licensed in the UK in weekly and monthly injectable form (Table 4.15). In Australia, the proportion of patients prescribed buprenorphine in depot form has grown from around 4% in 2019 to around 50% in 202251 and expansion of the use of buprenorphine long--acting injections is part of the 10-year drug strategy in England.50 Table 4.15 Conventional sublingual buprenorphine daily treatment doses and recommended corresponding doses of weekly and monthly Buvidal. Dose of daily sublingual buprenorphine Dose of weekly Buvidal Dose of monthly Buvidal 2–6mg 8mg 8–10mg 16mg 64mg 12–16mg 24mg 96mg 18–24mg 32mg 128mg

510 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 4 Buprenorphine depot injection offers the same benefits as sublingual buprenorphine. It has a sustained release, and some patients find it reduces the noticeable peaks and troughs experienced on sublingual buprenorphine. Contraindications to prolonged- release buprenorphine injection are: ■ ■Hypersensitivity or allergy to active substance or excipients. ■ ■Severe hepatic impairment. ■ ■Alcohol dependence and delirium tremens. Adverse effects relate in the main to the delivery of the medication, with injection site reactions (pain, a lump) being the most common. Long-acting buprenorphine may be more effective than sublingual buprenorphine. While early randomised controlled trials (RCTs) tested non-inferiority to sublingual buprenorphine, a recent trial testing superiority of Sublocade found superior retention, higher odds of early remission from opioid use disorder, reduced or absent craving and better clinician- and patient-reported outcomes for depot buprenorphine.56 Sustained abstinence rates following buprenorphine depot medication were

around 70% at 18 months. The longer the period on buprenorphine depot, the greater the proportion of patients who sustained abstinence.57 Transferring from methadone to buprenorphine This should usually be done under the supervision of a specialist prescriber. Patients transferring from methadone are at risk of experiencing precipitated withdrawal symptoms that may continue at some level for 1–2 weeks. Available evidence, albeit of low quality, suggests that conventional methods, which involve stopping methadone either at the stable dose or following a fixed or flexible taper of methadone, are successful in the majority of cases.58 Failure is associated with a methadone dose of

> 60mg per day. Recently, different techniques have been tried to facilitate transfer without the need for precipitating withdrawal. These include: ■ ■Bridging techniques, using opioids such as oxycodone or non-opioids such as ketamine.59 ■ ■Low-dose induction of buprenorphine, where buprenorphine is slowly titrated to a therapeutic dose while methadone remains at 100% of starting dose, with methadone tapered subsequently.60 Conventional transfer: transferring from methadone dose <40 mg to buprenorphine Methadone should be ceased abruptly, and the first dose of buprenorphine given at least 24 hours after the last methadone dose. The following conversion rates at the start of treatment are recommended but higher buprenorphine doses may be subsequently needed depending on clinical presentation (Table 4.16).

Addictions and substance misuse CHAPTER 4 Transferring from methadone 40–60mg to buprenorphine Either immediately stop methadone and transfer directly to buprenorphine, or taper to 30mg methadone following a fixed or patient-led plan (evidence does not favour one over the other58). The first buprenorphine dose is usually delayed until the patient displays clear signs of withdrawal, generally 48–96 hours after the last dose of methadone. An initial dose of 2–4mg should be given. The patient should then be reviewed 2–3 hours later. If withdrawal has been precipitated or worsened, further symptomatic medication can be prescribed. If there has been no precipitation or worsening of withdrawal, an additional 2–4mg of buprenorphine can be given on the same day. The patient should be reviewed the following day at which point the dose should be increased to between 8 and 12mg. Alternatively, a technique of continuing to increase the buprenorphine on day 1 until withdrawal symptoms subside has also been reported as successful in a case report, but this relies on high levels of trust in the therapeutic relationship.61 Transferring from methadone doses >60mg to buprenorphine Such transfers should not be attempted in an out-patient setting except in exceptional circumstances by an experienced practitioner. Usually, patients would be partially detoxified from methadone and transferred to buprenorphine when the methadone was at or below 30mg daily. However, if transfer from higher dose methadone to buprenorphine is required, a referral to a dedicated addictions in-patient unit should be considered where possible. Transfer from low-dose methadone to buprenorphine Case series of low-dose induction using varying protocols has been reported (Table 4.17). Most are in-patient based, although there is some evidence that it can also be done in the community with remote monitoring.62 Protocols using transdermal buprenorphine patches initially or alongside sublingual buprenorphine have also been published.63 The schedules for reducing methadone following establishment of therapeutic doses of buprenorphine also vary widely, some suggesting a dead

stop from 100% original dose and some a rapid reduction (e.g. reduce to 50%, then stop). Few studies report withdrawal phenomena in detail or how these relate to the pharmacokinetics of the two opioids. Table 4.16 Transferring from methadone to oral buprenorphine. Last methadone dose Day 1: initial buprenorphine dose Day 2: buprenorphine dose 20–40mg 4mg 6–8mg 10–20mg 4mg 4–8mg 1–10mg 2mg 2–4mg

512 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 4 Transferring from prescription opioids to buprenorphine Evidence is accruing in the treatment of prescribed opioid dependence with buprenorphine. Buprenorphine improves adherence to drug treatment and reduces prescription opioid misuse.68 In the UK, the 'Orange Book' recommends that small divided doses are given to establish the dose required for stabilisation.59 Less than daily dosing with buprenorphine Buprenorphine is licensed in most countries as a medication to be taken daily. International evidence and experience indicate that many clients can be comfortably maintained on one dose every 2–3 days.54,69 This has been considered pertinent for patients in buprenorphine treatment who are considered unsuitable for take-away medication because of the risk of diversion but it may well be replaced by long-acting formulations. The following conversion rate is recommended: ■ ■2-day buprenorphine dose = 2 x daily dose of buprenorphine (to a max. 32mg) ■ ■3-day buprenorphine dose = 3 x daily dose of buprenorphine (to a max. 32mg) In the event of patients being unable to stabilise comfortably on buprenorphine (often those transferring from methadone), the option of transferring to methadone Table 4.17 Example protocols for transition from low-dose methadone to buprenorphine. Daily dose (mg) Study Day 1 3 5 7 9 Terasaki et al. 201964 0.5 0.5 twice daily 1 twice daily 4 twice daily 8+4 Titrate Tay Wee Teck et al. 202162 0.4 0.4 0.8 1.2 1.6 1.6 4 8–12 Weimer et al. 202165 ≈0.5 once daily (buccal 0.225 twice daily) ≈0.5 twice daily (buccal 0.225 twice daily) ≈1 twice daily (buccal 0.45 twice daily) 2 twice daily 4 twice daily 4 three times a day 4–8 twice daily Bhatraju et al. 202266 0.5 once daily 0.5 twice daily 1 twice daily 2 twice daily 4 twice daily 8+4 8 twice daily Anderson et al. 202367 0.5 once daily 0.5 twice daily 1 twice daily 2 twice daily 3 twice daily 4 twice daily 6 twice daily 8 twice daily 12/8 12/8

Addictions and substance misuse CHAPTER 4 should be available. Methadone can be commenced 24 hours after the last buprenorphine dose. Doses should be titrated cautiously according to clinical response, being mindful of the residual 'blockade' effect of buprenorphine, which may last for several days, meaning that methadone toxicity can occur in a delayed manner. Cautions with buprenorphine Intoxication Buprenorphine should normally not be given to any patient showing signs of intoxication, especially due to alcohol or other depressant drugs (e.g. benzodiazepines, sedating antipsychotics, pregabalin). Buprenorphine in combination with other sedative drugs can result in respiratory depression, sedation and coma. Nonetheless, buprenorphine is usually preferred to methadone in these clinical situations. Liver function There is some evidence suggesting that high-dose buprenorphine can cause changes in liver function in individuals with a history of liver disease and can rarely cause hepatitis.70,71 Such patients should have LFTs measured before commencing with follow-up investigations conducted 6–12 weeks after commencing buprenorphine. More frequent testing should be considered in patients of particular concern (e.g. with severe liver disease). Elevated liver enzymes in the absence of clinically significant liver disease, however, does not necessarily contraindicate treatment with buprenorphine and if the patient refuses or it is practically difficult to obtain LFTs, the risk of withholding treatment should be weighed against the risk of prescribing without LFTs. Overdose with buprenorphine Buprenorphine (as a single drug in overdose) is generally regarded as safer

than methadone and heroin because in experimental studies it causes no respiratory depression at up to 8mg72 and is less likely to be associated with overdose death. However, in combination with other respiratory depressant drugs the effects may be harder to manage.73 Higher than standard doses of naloxone may be needed to reverse buprenorphine overdose, with the optimal dose being between 2 and 4mg and a possible diminishing effect beyond 5mg.6,74 As a consequence, ventilator support is often required in cases where buprenorphine is contributing to respiratory depression (e.g. in polydrug overdose). Buprenorphine with naloxone (Suboxone) Suboxone is a buprenorphine/naloxone combination preparation that may reduce the risk of diversion and injection. The different sublingual and parenteral absorption profiles of buprenorphine and naloxone are the key factor. If used sublingually, the naloxone component will have a negligible effect, but buprenorphine will be absorbed and act as usual. However, if Suboxone is injected, the naloxone will have a substantial antagonist effect and will attenuate the effects of the buprenorphine and is also likely to precipitate withdrawal in opioid-dependent individuals using full opioid agonists.

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