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Recommendations for buprenorphine and methadone therapy in opioid use disorder: a European consensus

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Abstract

Introduction: Management of patients with opioid use disorder (OUD) commonly includes opioid agonist therapy (OAT) as a part of an integrated treatment plan. These interventions are associated with proven benefits to the individual and society.

Areas covered: The use of methadone and buprenorphine within an integrated treatment plan in the management of patients with OUD: this work provides consensus recommendation on pharmacotherapy in OUD to assist clinicians with practical decision making in this field.

Expert opinion: Pharmacotherapy is recommended as part of an integrated OUD treatment approach with psychosocial interventions, with the goal of reducing risks of illicit opioid use, overdose mortality, infection with HIV or HCV, improving health, psychological and social outcomes. Access to OAT should be prioritised in the treatment of OUD. Treatment choices in OUD pharmacotherapy should be based on the needs of the individual and characteristics of medications. Recommendations for choices of OAT are based on clinical efficacy, safety, patient preference, side effects, pharmacological interactions, quality of life, dose titration potential and outcomes (control craving, ongoing opioids consumption or other drugs, and potentially psychiatric comorbidities). Special groups, pregnant women, prisoners, patients with mental health problems have specific needs which must be addressed with expert input.

Keywords: Buprenorphine, methadone, opioid agonist therapy, opioid use disorder
**Article highlights box**

- Opioid use disorder (OUD) is characterised by repeated use of opioids with harmful consequences that may require long-term treatment. Opioid agonist therapy (OAT) is an important part of care with proven benefits to patients and society.
- Access to quality OAT for OUD should be prioritized. Patients should receive an individualised treatment approach with choices and ongoing management, including dose titration, based on their specific needs and progress.
- Buprenorphine treatment is recommended as an important option based on safety profile (low overdose risk).
- Buprenorphine/Naloxone is recommended in settings with increased risk of misuse/diversion.
- Methadone is an option with extensive clinical experience in patients who may continue to use other opioids, for those with pain and/or benefiting from sedative effects; there is an important risk of overdose with methadone therapy.
- Groups including pregnant women, prisoners and patients with mental health problems require special consideration, which must be addressed with expert input.
1 Introduction

Opioid use disorder (OUD) is characterised by repeated use of opioids with harmful consequences [1] and craving, defined as a strong desire or need for the substance that is overwhelming, a predictor of relapse and a target for treatment [2–5].

OUD is a complex and relapsing condition that may require long-term treatment and care including access to medication for its management. The integrated treatment model for OUD, including opioid agonist medication, is associated with important social and clinical benefits, reduces overdose deaths and crime, increases quality of life [6,7] and enables patients to contribute to society [2,8–12]. Evidence-based, good quality treatment helps achieve recovery outcomes [13].

An integrated treatment combines psychosocial support with pharmacological therapy [14], to incentivise recovery and support harm reduction, relapse prevention. Pharmacological therapy for OUD involves treatment with an appropriate choice of opioid agonist, administered at a dose, tailored to the individual, such that both withdrawal and intoxication are avoided [14]. Therapy is often planned to continue in the long-term providing opportunities to address health and social problems with psychosocial interventions. Psychosocial support is an important element of the integrated program [15–17], and refers to a wide range of social and psychological interventions which may include counselling, education, cognitive behavioural therapy, contingency management, interpersonal/ family therapies and peer support approaches for providing social networks and structured activities [18]. However, impact on outcomes of specific interventions is controversial and needs to apply stepped-care strategies and further investigations [15,19].

Psychiatric comorbidities associated with OUD are common [20,21]. An integrated treatment system, involving an interdisciplinary team, has shown enhanced effectiveness and improved functional outcomes compared to a parallel system [22–24].
The work refers to opioid agonist therapy (OAT) for OUD - established for many decades [25,26]. Methadone was the first medication approved in this indication and is most likely the best investigated drug [27]. In Europe, buprenorphine, indicated for the treatment of opioid dependence, was first registered in France in 1995 and has since been registered in many European countries [28,29], through national individual registration (for example – UK) [30]. A fixed dose combination product, buprenorphine/ naloxone is available in Europe under a central European Medicines Agency (EMA) registration [31].

In Europe, availability and access to OUD treatment varies in clinical practices among different countries [32,33]. In Europe, access to OAT in the community is increasing in many countries [34–36] while access in prison is often still limited [37]. This work aimed to build a consensus recommendation on best practice for methadone and buprenorphine pharmacotherapy in OUD care, as these are the most widely available and used treatments in Europe. Other available options for pharmacological treatment such as intravenous diamorphine (medical heroin), oral L-methadone and slow-release oral morphine are indicated in some countries for OUD care but are not included in this work. Review of the evidence for psychosocial interventions in conjunction with OAT is important but is not included in this work.

2 Methods

A recommendation for best practice in OUD care with buprenorphine or methadone was developed based on a consensus. Initially, a set of topics to work on was defined. To provide evidence for the recommendation, recent guidelines on the management of OUD published between 2014-2017 were collected. Experts, with more than 10 years’ clinical practice experience in OUD care, selected a subset of the most important guidelines for further analysis, based on experience [9,10,14,18,38–45] (Appendix 1). The development of recommendations follows a 2-step approach: Firstly, guidelines were reviewed for key guidance for practice.
Secondly, additional insights were included based on clinical practice experience of experts in areas where evidence-based information was not available. A consensus of the most important advice was developed.

3 Recommendations for pharmacotherapy in OUD

Recommendations for important steps in the management of OUD with opioid agonists based on the review of guidelines are summarised in Table 1 with recommendations for groups with special needs in Table 2. Recommendations for choices of opioid agonists methadone and buprenorphine, based on evidence review, are summarised in Table 3.

3.1 Methadone

Methadone is a long-acting synthetic opioid indicated for the treatment of OUD in combination with psychosocial interventions [38,42]. It addresses symptoms and signs of opioid withdrawal, reduces craving and may mitigate euphoria and other desired effects of opioids such as heroin [9]. Methadone is a full mu opioid receptor agonist which is rapidly absorbed following oral administration; effects start in 15-45 min, with a maximum plasma concentration 2.5-4h after administration. Methadone may accumulate and cause sedation and respiratory depression [9]. Concomitant ingestion with alcohol and sedatives (benzodiazepines and Z drugs) results in a potentially lethal increased toxicity [9]. Respiratory depression, with may be fatal, may occur on treatment initiation [14]. Tolerance to methadone develops at different rates in different people, affected by factors such as the number of days of exposure to opioids, higher opioid dosages, genetic background (fast and slow metabolizers), use of other prescribed drugs such as inhibitors or inducers of methadone metabolism [46–48].

Methadone treatment involves induction of high levels of opioid tolerance such that street opioids become less reinforcing [49]. Increase in tolerance needs to be slow to minimize the risk of toxicity, and patients need to be closely monitored for toxicity,
especially in the first two weeks [14,46]. Tolerance may be decreased in short periods of time, as little as 3 days. This needs to be considered in the case of missed doses, to avoid overdose (evaluation including patient reassessment and dose adaptation). Cross-tolerance between other opioids and methadone can be unpredictable. During induction or dose changes, driving ability may be affected due to sedative effects and cognitive alterations [50]. The risk is lower in the maintenance period, except if the patient is not stable, or is using alcohol or other sedative drugs on top.

Methadone is administered orally either as a liquid or as a tablet, commonly in the supervised setting [42]. Methadone use should be monitored to manage potential unwanted responses and toxicity, and to prevent misuse and diversion [9,38,42]; unsupervised dosing should be considered after the patient’s clinical response and behaviour indicates this is safe and appropriate. The extended pharmacokinetics and individual response to methadone make the process of induction and achievement of stability highly variable: it may take 2-4 weeks with observation [43]. Methadone treatment is often managed, according to local treatment regulations, in drug treatment centre specialist settings, at least until patients are stable and risks of over sedation, toxicity, and even fatal overdose can be considered low.

Receiving an optimal dose of substitute opioid medication is critical to outcomes [13,51,52], including a reduction in opioid use [12,51] and risk behaviours [12,52,53], and increased likelihood to achieve abstinence [49]. Starting dose of methadone should not exceed 30 mg daily and may be lower than this, in some patients [9]. Increments of doses should be stepwise, based on a “go low, go slow” plan with 5-10 mg dose changes [9,18,42] over periods of 5 or more days [9,10,42]. Craving is a central driving force for ongoing drug use and relapse [54–56] and adequate OAT dose that decreases craving is determinant. Optimum dosing minimises withdrawal and craving, allowing the patient to refocus on livings and goals. Individualised
titration according to the initial evaluation and successive re-evaluation is key [57]. Craving is a multidimensional symptom which is not only related to titration of OAT but also conditioning, stress and negative affect. Therefore further psychosocial approaches may be required [58]. Based on clinical experience, dose increments are determined by various clinical parameters including successively symptoms of withdrawal, craving, and also potentially improvement in psychiatric comorbidity and other addictive behaviours [54–56]. It is not recommended to alter the dose without an assessment after each dose change because methadone plasma levels may require up to 5 days to reach a steady state [9]. The typical optimal dose is 60-120mg daily [10] but many factors (e.g. drug interactions, liver/renal failure or pharmacogenomics variability) may affect methadone clearance. The optimal dose varies [13] and has to be adapted to clinical assessment, and if necessary, to blood levels. Doses of 60 mg/day or greater have been shown to be more effective than lower doses in increasing patient retention, reducing illicit opioid use, and reducing risk behaviour [9,10,38,51,59]; dose titration usually takes more than 2 weeks during which patients may remain vulnerable, using both methadone and heroin to prevent/control withdrawals. Dividing doses may be beneficial for groups such as pregnant women, patients with rapid metabolism or patients with need for concurrent pain management [10,18].

Cigarette smoking is highly prevalent in methadone-treated patients, and this may be related to various pharmacodynamic [60] and pharmacokinetic [61,62] interactions. Therefore individually adaptation of methadone dosage in people with heavy cigarette use is important.

Patients on methadone should be advised to avoid alcohol and sedating drugs, including over-the-counter products [10]. For patients who are currently using other opioids, benzodiazepines, amphetamines or alcohol in large doses, the treating physician should consider increased supervision of consumption for agonist
treatment, for example, giving doses at clinics, not at pharmacy. Patients should be observed 3-4 hours after the first dose for signs of toxicity or withdrawal. Agonist treatment should be withheld or reduced if the patients show signs of intoxication. It is recommended to review the disadvantages versus the benefits of OAT treatment, and to weight the risks of combining OAT with other drug use against the benefits in reducing harms, improving health and improving social functioning. If the disadvantages predominate, and the patient appears unwilling or unable to change, it may be necessary to arrange the patient’s gradual withdrawal from the opioid treatment program. Depending on the individual case and risk profile, prescribers may limit or avoid prescribing any sedating drugs including benzodiazepines, non-benzodiazepine hypnotics, some anti-psychotics, some antidepressants, and sedating antihistamines [10], and pay special attention to presence of such drugs in urine samples [43].

Changing from methadone to buprenorphine may be an appropriate clinical strategy if intolerable side effects, unexpected contra-indications or difficulty in maintaining treatment goals are identified during treatment [7,38].

Methadone stored in the family home presents special risk that must be considered. It may be associated with overdose risk, with potential serious consequences in domestic settings which include children [18]. Storage packaging that is adequate to prevent children tampering is recommended.

Methadone can affect cardiac conductivity, which could potentially lead to prolonged QTc interval that is associated with risk of sudden cardiac death [14]. Based on the clinical experience of the expert group, for patients with severe QTc elongation (>500 ms) or with clinical signs of QTc prolongation due to high methadone dosage, decreasing the dose should be considered (after elimination or minimisation of other risk factors for QTc prolongation such as medications, cocaine, alcohol, etc). If lowering the dose is clinically inappropriate, and transfer to buprenorphine is not
feasible or adapted, transferring patients to slow-release oral morphine is an option [63–66].

3.2 Buprenorphine
Buprenorphine is a semi-synthetic opioid, recommended for the treatment of OUD as part of an integrated program with psychosocial interventions; buprenorphine addresses craving for opioids and is not associated with causing euphoria or other dangerous side effects of opioids when correctly used [67,68].

Because of an extensive first-pass metabolism, buprenorphine is sublingually administrated and reaches peak concentration in 1-4 hours, with onset of action after 30-45 minutes and effects observed for 8-12 hours at low doses (2mg), 48-72 hours at higher doses (16 or 32mg) [38]. Buprenorphine is a partial mu opioid receptor agonist with a high affinity; it is associated with a limited maximal or “ceiling effect” which limits severity of respiratory and central nervous system depression. In adults, overdoses of buprenorphine alone are not normally fatal. Buprenorphine at appropriate dose has a long effect duration: the signs and symptoms of abstinence syndrome in adults are less common on withdrawal compared to those treated on methadone; it is associated with limited euphoria and other drug-seeking effects when other opioids are used “on top” of buprenorphine doses [14,69].

Competition at the mu opioid receptor due to the high affinity of buprenorphine may lead to potential precipitated opioid withdrawal if treatment initiation and dosing are not managed appropriately [38,42]. This can be avoided by asking the patient to cease taking other opioids prior to starting buprenorphine therapy, and waiting for withdrawal symptoms.

Buprenorphine is also available as a fixed dose combination product with the opioid antagonist naloxone [69]. When administrated orally or sublingually, naloxone is not associated with clinically relevant effects as the bioavailability is low. However, when
naloxone is taken via intravenous route or snorted by people dependent on opioids, it produces marked antagonistic effects that reduce the reinforcing properties of misused buprenorphine and can even lead to opioid withdrawal symptoms (as does buprenorphine alone). This reduces attractiveness for misuse and diversion [14,69], however the product may be associated with inappropriate routes of administration such as inhalation and injection in some cases [70]. Buprenorphine is administered as a sublingual tablet and is often recommended for outpatient-type management without the need for extensive monitoring, but is also used in the setting with monitoring, depending on patient needs. Induction or treatment initiation with buprenorphine is normally relatively simple and is usually safer, faster and easier compared with methadone, providing care is taken to manage risk of precipitated withdrawal [14,18,38]; patients may reach maintenance doses more quickly with buprenorphine [14,18,38,43]. To avoid precipitated withdrawal, it is recommended that the first doses of buprenorphine be delayed until patients are experiencing withdrawal symptoms [18,38,42] when starting therapy. Buprenorphine may have lower risk of misuse compared to full opioid agonists related to, for example, reduced sensations of euphoria [14,68]. It is however recommended, as with all agonist therapy, that physicians should be aware of the risk and consider actions, including more frequent office visits for relevant testing and counselling, or the option of buprenorphine/naloxone therapy [42].

Buprenorphine starting dose is from 2-4mg up to 8mg per day, depending on clinical response [38,43]. Dose should be increased by 2-4mg each time in most cases based on individual response [13], this may be higher in cases of severe dependence. When the initial dose is well-tolerated, dose can be increased with relative ease [14,18,43]. Doses of buprenorphine at the end of the first week of treatment to achieve stabilisation typically range from 8 to 24 mg/day [43] with the proportion of patients who relapse decreasing as the initial dose is increased. Clinical studies and a meta-analysis of outcomes data indicates that doses greater than 16
mg are associated with a greater reduction in on-top use of illicit drugs compared to doses lower than 16 mg [11,71–73]. Once a stable daily dose is established, it may be appropriate in some cases to alter frequency of dosing to alternate day dosing or 3 times weekly [9,38].

Buprenorphine at the adequate dose tailored to patient needs is effective in reducing illicit opioid use, improving retention in treatment and reducing engagement in risk behaviours [74–78]. Buprenorphine exhibits comparable efficacy to methadone as substitute maintenance medication when used in appropriate doses [79]. In terms of outcomes, compared to methadone, buprenorphine retains fewer people when doses are flexibly delivered and at low fixed doses [72]; if fixed medium or high doses are used, buprenorphine and methadone retention rates are no different [12,79–81]. Retention is relevant for opioid maintenance treatment but observed rates are different with treatment settings. Rates of illicit “on top” opioid use during therapy do not significantly differ between methadone and buprenorphine [12,79], although some studies report treatment with buprenorphine to be associated with lower continued use of illicit opioids [72,80]. Rates of mortality in people on buprenorphine treatment may be lower than those with methadone [12], but data is inconclusive. Buprenorphine/ naloxone was shown to improve social life status, education level and rate of illicit opioid use when compared to methadone [81,82].

3.3 Special populations

3.3.1 Treatment of patients with co-existing psychiatric comorbidities

Dual diagnosis of psychiatric comorbidity with OUD is common. A systematic review reported a pooled prevalence of 43% for the co-occurrent psychiatric diagnoses (Axis-1 psychiatric diagnoses and symptoms with focus on depression and anxiety) among non-medical prescription opioid users [21]. Among patients enrolled in OAT programs, psychiatric comorbidities are detected in 67% of people (anxiety 53%, mood disorders 48%, sleep disorders 41%, substance-related disorder 36%) [20].
Opioid use in schizophrenia is less common than other substance use [83]. There are growing evidence that endogenous opioid system is involved in various addictions and psychiatric disorders, and both addictions and psychiatric disorders may aggravate each other [84–87]. Diagnosing comorbidity and the relationship between comorbid conditions is important to select appropriate treatment but disentangling comorbidities can be difficult. As psychiatric disorders may affect the outcome of the OUD treatment, treatment of co-existing psychiatric disorders is important and, whenever possible, treatment of patients with OUD and other mental disorders should be provided by individuals or teams with expertise in the management of dual diagnoses.

Depressive and anxiety symptoms are common at the time of admission. Because OAT are associated with substantial improvements in these symptoms, specific psychosocial interventions and medications should be considered in the absence of improvement [38,88]. In situations where a pre-existing psychiatric disorder is well documented, a specific treatment should be cautiously associated after OAT is initiated.

An assessment of mental health status should be undertaken in patients with OUD. There may be a specific risk of suicide for some with dual diagnosis – this must be addressed urgently. OUD and co-existent psychiatric disorders must both be treated as there is an increased risk of relapse and failed stabilisation rate in both disorders if only one condition is treated. As integrated and comprehensive approaches, assessment and treatment for either disorder should begin as early as possible, without the imposition of arbitrary waiting periods of abstinence and without a requirement for psychiatric stabilization. Upon stabilisation of OAT, status of psychiatric disorder and management plan should be reassessed.

OUD should be treated in patients with psychiatric co-morbidities, including consideration for pharmacotherapy. Opioid agonist medications have psychoactive
properties with therapeutic efficacy on psychiatric symptoms (i.e. anxiolytic, antidepressant and antipsychotic effects). Titration of dose, often increased doses, is important as it may improve OUD and concomitant psychiatric disorder. Treatment choice is influenced by potential interactions of concomitant medications with opioid agonist therapy. Based on clinical experience of the expert group, methadone, due to sedative effects, may be most appropriate for patients with concomitant severe anxiety and psychotic symptoms although hypotensive, sedative effects, prolongation of QTc, may be potentiated with some drugs such as antipsychotics and some antidepressants. Buprenorphine, due to its kappa antagonist activity, may have some advantages over methadone in treating OUD in people with depression [38,89–92] although this needs to be further investigated.

Sleep disorders such as insomnia are common in patients with OUD, and may contribute to anxiety and depression symptoms and subsequent use of opioids or other drugs. OUD patients with sleep problems should be considered when planning OAT therapy: patients on methadone or buprenorphine may be at increased risk of nocturnal respiratory disorders such as central sleep apnoea leading to excessive daytime sleepiness, cognitive and psychological degradation. This respiratory risk is further increased with concurrent use of benzodiazepines. The use of benzodiazepines is common worldwide, and is associated with risk of overdose in association with opioid use [93]. It is important to ask about sleep problems and plan medication choices and dose titration based on this information [93].

3.3.2 Treatment of patients with polydrug & alcohol use problems

Both the initiation of OAT in patients with OUD using other psychoactive drugs or alcohol, and ongoing management of OAT in patients continuing to use other drugs or alcohol, present important challenges.

Patients with OUD and other substance use disorders should be offered initiation of OAT treatment. This should be offered in the context of managing other substance
use disorders. Patients using hypnotic, sedative or anxiolytic drugs or those regularly consuming alcohol are a challenging group to manage safely [94–97] – integrated care with individualised dose titration is central to success as comorbid substance use may reflect an inadequate OAT dosage [95–98]. Outcomes may be less successful as treatment with OAT is undermined by continuing substance use.

One-third of methadone maintenance participants may have problematic alcohol use, which is associated with negative clinical outcomes [94]. Chronic alcohol use increases metabolism of methadone [94], and opioid users who are chronically intoxicated with alcohol are difficult to manage [95]. Despite a controversial literature [95], OAT can dose-dependently reduces alcohol craving and intake in people with heroin and alcohol dependence [98].

Cocaine may lower methadone and buprenorphine plasma concentration [99–101], which may negatively impact treatment outcomes if dose is not titrated according to individual need. Buprenorphine alone or associated with naloxone and naltrexone at appropriate dose (16 mg/d) may reduce cocaine use in subjects with cocaine and opioid dependence [102,103].

The co-abuse of benzodiazepines and opioids is substantial and has negative consequences for general health, overdose lethality, and treatment outcome. As other drugs, benzodiazepines can be used for different motives (e.g. to increase sedative effect of opioid, to compensate other drugs (opioid or alcohol or cannabis decrease), anxiety symptoms, insomnia…). Physicians should address this important and underappreciated problem with more cautious prescribing practices, and increased vigilance for abusive patterns of use [96,97].

In summary, for patients currently using OAT and engaged in use of other drugs, optimizing OAT dosing may be a lever for reducing the use of other drugs. In these groups, careful dose titration of OAT can be successful in helping reduce the use of
other substances. With careful changes in dose and monitoring it is possible to improve outcomes.

3.3.3 Treatment of patients with co-existing health problems, including pain

The management of OUD should include treatment of common co-existing health problems. Management of other health problems can improve the chances of adherence to OUD treatment regimen.

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection are important co-existing health problems which must be managed. Treatment of HCV, for example, is associated with psychological and wellbeing improvements that may promote success in addressing OUD. Other important health problems should be considered. A review of concomitant medication should be completed to assess for potential clinically relevant drug-drug interactions; OAT dose adaptation may be required as a result of other drugs prescribed. It is essential to treat or refer patients for specific medical conditions such as chronic hepatitis C treatment and HIV.

Buprenorphine is a preferred treatment choice in some patients with coexisting medical problems due to a lower chance of clinically relevant drug-drug interactions (including CYP3A4 alterations) and lower likelihood of QTc prolongation [38,104]. For patients with advanced liver disease, it is necessary to monitor dosing of both buprenorphine and methadone as reductions may be required.

The management of pain in patients with OUD is a complex area; it is beyond the scope of this work to provide a detailed analysis. General points in management are described for the two main groups:

1. Patients receiving OAT that develop pain. According to the type of pain (acute, chronic, nociceptive, neuropathic) and its severity, different strategies can be proposed, such as prescribing, in a stepwise approach these options: non opioid analgesics in mild to moderate pain, increasing and fractionating
the OAT in moderate to severe pain, and if not enough either associating strong opioid analgesics (patient under methadone) or switching to strong opioids (patient under buprenorphine to avoid competition although some associations are possible).

2. Patients that develop OUD while treated with licit opioids, especially patients with chronic non cancer pain. There is currently no consensus on how to treat opioid analgesic-dependent patients, but a pragmatic and realistic strategy adapted to each patient and including regular monitoring can be proposed. When pain is no longer present, or when opioid-induced hyperalgesia is suspected, a progressive tapering should be the first-line therapy. However, since psychiatric disorders are common in patients with chronic non cancer pain, even progressive opioid tapering can be difficult and may destabilise patients, leading to addiction transfer, relapse and overdose without or with suicidal intent. Long acting OAT (i.e. buprenorphine +/- naloxone or methadone), therefore, represents an alternative strategy allowing the treatment of comorbidities, followed by progressive medication tapering. In patients with pain, a structured and more adapted analgesic treatment (e.g. long acting opioid analgesics) can be sufficient for behavioural resolution. If not, OAT should be considered; the choice between buprenorphine and methadone will depend on several determinants (type of pain and severity, associated medications, social environment, psychiatric disorders, etc.) [38,105–107]

3.3.4 Physiological situations: pregnant women and older people

Pregnant women’s acute opioid withdrawal and/or untreated OUD present important risk to the unborn child in pregnancy. It is recommended that a plan to start or continue OAT pharmacotherapy in conjunction with psychosocial treatment is developed with expectant mothers who have OUD. Management of withdrawal and
detoxification, aiming for abstinence is not recommended in pregnancy due to the risk of miscarriage or preterm labour.

Joint approaches for comprehensive care by the obstetrics team, paediatricians and addiction medicine specialists, should be followed. Treatment may allow identification of other health and social needs and provide interventions to improve pregnancy outcomes. Breastfeeding should be encouraged in mothers treated with buprenorphine or methadone. It is recommended that women who become pregnant while undergoing treatment with opioid agonists are encouraged to continue treatment of current OAT choice with appropriate dose titration (increased doses may be needed) throughout pregnancy.

Buprenorphine treatment has advantages over methadone for outcomes of foetal wellbeing (third trimester evaluation of foetal heart rate/movements before and after dosing), neonatal abstinence syndrome and neonatal neurobehavioral functioning [108].

Pregnant women currently treated on buprenorphine are advised to continue this treatment in pregnancy. It is not advised to transfer pregnant women to treatment with buprenorphine if they became pregnant to methadone; buprenorphine should be considered as an initial choice for pregnant women dependent on opioids who are naive to OAT in many situations. Care must be taken with the initiation of buprenorphine treatment as this may be associated with precipitated withdrawal, which should be avoided by careful management. Naloxone in pregnancy: buprenorphine/ naloxone should only be used during pregnancy when benefit outweighs the potential risk to the foetus. There is extensive historical experience with methadone in pregnancy. Doses of methadone may need to be increased during pregnancy to compensate for normal physiological changes as the gestational age increases, requiring increased doses typically of 15% greater, led by clinical assessments [38]. It is often necessary to split methadone doses to reduce blood
concentration fluctuations as the pregnancy advances. Doses may need to be adjusted after giving birth as some of these changes reverse [109]. Women who are stable on methadone treatment for OUD who fall pregnant should not be switched to buprenorphine therapy.

For the treatment of older patients, detection and diagnosis of addiction in the elderly can be difficult, since physical and psychiatric disorders common in older patients may be similar in presentation to substance use disorders. Older people with OUD may have increased drug-related and non-drug-related health needs (e.g. cardiovascular disease, liver disease, cancer). The increased risk of drug-drug interactions should be considered when prescribing medication for OAT. Drug metabolism may be altered and careful dose titration is often needed with reduced doses of OAT. Methadone should be used with caution in the elderly, who are at greater risk of opioid-related falls and other adverse events than younger patients.

3.3.5 Treatment of prisoners

Prisoners are at risk of both limited access to, and lower quality of, OUD care including suboptimal OAT treatment: this may include inadequate duration of treatment or dose.

Prisoners should be offered treatment options and managed in a similar way to any other patients with OUD. OAT choices are often determined by risk of misuse and diversion. Observed administration of methadone or buprenorphine/naloxone are recommended choices. Access to needle equipment provision programs is commonly limited in many prisons; access to harm reduction and OAT is key to treatment of OUD in the prison setting.

OAT should be available immediately on arrival in prison and assessments made in the initial healthcare check; where history of exposure or tolerance is unclear, lower doses of OAT with close monitoring is recommended. Prisoners stable on OAT in
prison may require a higher dose upon release to maintain stability. Advice and support with continued OAT treatment in the community setting are central to successful long-term treatment.

4 Conclusion

Pharmacotherapy is recommended as part of an integrated OUD treatment approach with psychosocial interventions, with the goals of reducing risks of illicit opioid use, overdose mortality, infection with HIV or HCV, improving health, psychological and social outcomes.

The treatment of patients with opioid use disorder (OUD) should include the appropriate choice of opioid agonists as a part of the integrated treatment plan when indicated and agreed by patient and healthcare professional and aligned with treatment goals and specific needs. Other harm reduction resources such as needle equipment programs should also be easily available. This work provides a consensus recommendation on pharmacotherapy in OUD to assist clinicians with practical decisions.

5 Expert Opinion

Opioid agonists, methadone and buprenorphine, are an important part of the overall approach to OUD treatment: there is no product choice that is effective for all individuals. The characteristics of these opioid agonists are different and their benefits should be matched to the needs of the individual. Patients and physicians should reach an agreement on the goals patients aim to achieve from the recommended treatment program, and how goals may evolve over time with progress [9]. The broad goal of treating OUD is to improve the physical health and wellbeing [13,18,38], to limit social and economic harm to the individual and community [38]. Short term goals are to manage withdrawal-related physical symptoms, then the psychological component, craving [110], and potentially psychiatric comorbidity, for example anxiety disorder. Complete abstinence from any
illicit opioid may be an important goal [13,38,40]: the complexities of OUD mean that this is not always a stated goal or is not achieved [38]. Some patients are able to reach abstinence with significant support [68,111], through a gradual taper of medication over a few months [38]. Patients should be informed on the process, involved in decision making, and given time to adjust to necessary physiological, behavioural and social changes [38]; not achieving abstinence should not limit access to therapy in OUD. Extended treatment may benefit some people to achieve improved social functions without necessarily ceasing illicit drug use [18,38].

Therapy with buprenorphine or methadone is pragmatic [18], and superior to detoxification or withdrawal management for outcomes of retention in treatment, sustained abstinence, reduced risk of morbidity and mortality [39,112]. Detoxification as treatment alone is not recommended; there may be specific scenarios where it is required. Methadone and buprenorphine therapies are cost-effective. Achieving good quality treatment with medications and psychosocial therapy is important; quality is determined by factors including the appropriate dose and duration of therapy and psychological or social input. Appropriate dose of medication is one able to eliminate individual sensitivity to the effects of opioids. It is important for decision-makers to maintain investment in quality medication and associated integrated components of care. Access to appropriate quality treatment including methadone or buprenorphine in OUD should be prioritized. A broad initial assessment or patient inventory should be made. Patients should receive an individualised treatment approach with choices and ongoing management including medication dose titration based on individual needs and evolving challenges and outcomes.

OAT delivery is highly variable across Europe; greater treatment benefits could be achieved with greater flexibility, less pressure to reduce dose, and optimisation of treatment structures [33,113]. Take-home medication strategies are attractive to treatment services due to lower costs, and place less restrictions on patients [114].
Effectiveness of take home dosing was comparable to that with supervised daily dosing in terms of retention in treatment, adverse events, abstinence and diversion of medication [114].

Recommendations for methadone or buprenorphine therapy are based on clinical efficacy, safety, patient preference, side effects, pharmacological interactions, quality of life, dose titration potential and outcomes (control of craving, ongoing opioids consumption or other drugs, potentially, psychiatric comorbidities).

Buprenorphine treatment is recommended as an important option based on safety profile which includes a low risk of overdose. Buprenorphine/ Naloxone is recommended in settings with increased risk of misuse or diversion. Methadone is an option with extensive clinical experience in patients who may continue to use other opioids, for those with pain or benefiting from sedative effects; there is an important risk of overdose with methadone therapy. Groups including pregnant women, prisoners and patients with co-existing, other mental health problems have specific needs which must be addressed with expert input.

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Declaration of Interest

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provided consultancy to Martindale, Indivior & Mundipharma. C Leonardi is consultant for Indivior, Molteni, Gilead, Merck-MSD, Mundipharma. I Maremmani served as consultant for Indivior, Molteni, Gilead, Merck-MSD, Mundipharma, D&A Pharma, Lundbeck, Angelini, and CT Sanremo. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have received an honorarium from Expert Opinion on Pharmacotherapy for their review work. A reviewer on this manuscript has disclosed that they have received research funding from Reckittbenckiser, and have received consultancy fees from Martindale Pharma and Indivior. They have also received honorarium for presentations they have performed on behalf of Indivior. A second peer reviewer has disclosed that they have received untied education grants from both Indivior and Mundipharma for post-surveillance research projects. All other peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

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References

   • This work defines OUD and provides diagnostic criteria which have been widely adopted in clinical practices


   • This work shows that OAT treatment is critical as leaving treatment is associated with with higher mortality rate among others


   • This work provides important recommendations to elements of pharmacotherapy for OUD

   • This work provides important recommendations to elements of pharmacotherapy for OUD


therapy (and drug treatment and recovery systems) be optimised to maximise recovery outcomes for service users? 2015.

- **This work provides a core overview of the decisions related to outcomes in treating OUD**


- **This work provides comprehensive guidance for OUD treatment**


- **This work provides important recommendations to elements of pharmacotherapy for OUD**


- The European comparison showed that motives for starting OAT vary distinctly between countries in Europe, and called for a joined European Quality Care Approach. Greater flexibility and less pressure to reduce treatment dose, greater treatment structure might facilitate treatment retention


- This work provides important recommendations to elements of pharmacotherapy for OUD


- This work provides comprehensive review of previously published guidelines before 2014 on OUD treatment including OAT


44. WHO. Guidelines for the identification and management of substance use and substance use disorders in pregnancy [Internet]. 2014. Available from: www.who.int/substance_abuse


50. Meesmann U, Boets S, Alvarez FJ, Gier H de;, Knoche A, Schumacher M, et al. Main DRUID results to be communicated to different target groups Main DRUID results to be communicated to different target groups. 2011;


62. Talka R, Salminen O, Tuominen RK. Methadone is a non-competitive antagonist at the a4b2 and a3* nicotinic acetylcholine receptors and an agonist at the a7 nicotinic acetylcholine receptor. Basic Clin Pharmacol Toxicol. 2015;116(4):321–8.


78. Heikman PK, Muhonen LH, Ojanperä IA. Polydrug abuse among opioid maintenance treatment patients is related to inadequate dose of maintenance treatment medicine. BMC Psychiatry [Internet]. 2017;17(1):245. Available
This work emphasizes the importance for individualised OAT medication dosing adjustment


Table 1 Recommendations for important steps in pharmacotherapy in OUD

<table>
<thead>
<tr>
<th>Step in treatment</th>
<th>Guidelines Assessment for Relevant Evidence</th>
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<tbody>
<tr>
<td><strong>When to start treatment</strong></td>
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<tr>
<td>A diagnosis of OUD should be made and agreed with the patient prior to starting treatment</td>
<td>[9,10,14,18,38–43,45] [44]</td>
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<tr>
<td>A broad initial assessment or patient inventory should be made. This should include assessment of consumption of opioids, other drugs, alcohol, other addictive behaviours related to substance use disorders or otherwise, assessment of health including sleep, anxiety and other mental health problems, social and family life, criminal involvement</td>
<td>[9,10,14,18,38–45]</td>
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<tr>
<td>A treatment plan including choice of medication should be made with the patient, considering preferences and goals</td>
<td>[9,10,14,18,38–45]</td>
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<tr>
<td><strong>Goals of treatment</strong></td>
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<tr>
<td>Short-term goals of treatment include avoiding the risk of overdose and death and to cease or reduce dangerous illicit opioid use, to eliminate exposure from unsafe injecting to HIV, HCV transmission</td>
<td>[9,10,14,18,38–45]</td>
</tr>
<tr>
<td>The wider goals of treatment include: improving physical and mental health, wellbeing and limiting social or economic harm associated with illicit drug use, such as criminal activity, to the individual and community</td>
<td>[9,10,14,18,38–43,45] [44]</td>
</tr>
<tr>
<td>Abstinence from illicit opioids may be a goal of therapy: complexities of OUD mean that this is not always achieved or a necessary goal for all. This is not a reason to limit access to care</td>
<td>[9,10,14,18,38,43,45] [39–42,44]</td>
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<tr>
<td><strong>Treatment choice</strong></td>
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<tr>
<td>Opioid agonists, methadone and buprenorphine, when administered at appropriate doses, with psychosocial therapy are effective at achieving positive outcomes in the treatment of individuals with OUD</td>
<td>[9,10,14,18,38–45]</td>
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<tr>
<td>OAT choices should be agreed by the healthcare professionals and patients based on each individual’s clinical profile and advantages and disadvantages of methadone, buprenorphine</td>
<td>[9,10,14,18,38–43,45] [44]</td>
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</table>
Important factors in making OAT treatment choice and recommendations are side effects, pharmacological interactions, patient profile such as goals, ongoing consumption of opioids or other drugs, psychiatric comorbidities and patient preferences.

Buprenorphine treatment is a recommended choice of opioid agonist therapy based on its favourable safety profile (low risk of overdose or respiratory depression, in general or polydrug use situations), relatively easy induction, potential to transfer to other options if needed and the ability to treat in the community setting. Buprenorphine/ Naloxone is recommended in settings with increased risk of misuse or diversion.

Methadone is an important choice for treatment in patients who may continue to use other opioids; it is associated with important safety risks including that of overdose and misuse and diversion – treatment initiation is commonly more complicated than for buprenorphine, and completed under observation until clinical experience is accrued.

Detoxification is not recommended. Treatment approaches including OAT are superior.

**How to start treatment**

Methadone starting dose should not exceed 30 mg, adjusted to an individual’s tolerance; care must be taken to manage the risk of overdose; initial treatment with methadone should be supervised, with a progressive and cautious titration during the induction phase.

Buprenorphine treatment should commence when signs of opioid withdrawal are seen to avoid precipitated withdrawal; initial treatment often requires supervision but may not, depending on the patient profile. Buprenorphine starting dose is 2–4mg and up to 8mg; treatment starts are relatively simpler with buprenorphine compared to methadone, with a rapid titration during the induction phase.

**How to maintain & complete treatment**

Methadone dose in maintenance treatment is commonly 60-120mg a day; doses above 60mg are likely more effective considering...
<p>| <strong>retention, illicit opioid use, risk behaviours</strong> | [9,10,18,38,42,43,45] | [14,39,40,44] |
| Adjustment of methadone must be approached with care; doses of methadone may be adjusted by increments of 5-10mg with periods of 5 days between each dose adjustment | [9,10,18,38,42,43,45] | [14,39,40,44] |
| Buprenorphine dose in maintenance treatment is commonly of 12-24mg. Meta-analyses indicate that doses greater than 16mg are associated with potentially improved outcomes including improved retention in therapy, reduced illicit opioid use or risk behaviours | [9,14,18,38-40,42,43,45] | [10,44] |
| Treatment completion is possible when a patient has achieved a stable medical, psychiatric and social status. Treatment should be reduced gradually in alignment with patient preference. Success is predicted by how treatment completion is attempted and absence of unstable or problematic use of alcohol or other drugs | [9,10,14,18,38] | [39–45] |</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Guidelines Assessment for Relevant Evidence</th>
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<tr>
<td><strong>Treatment of patients with co-existing psychiatric comorbidities</strong></td>
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<tr>
<td>Integrated care for OUD and mental health problems is recommended when possible; treatment for OUD including OAT should be offered</td>
<td>[9,14,18,38,40,43,45] [10,39,41,42,44]</td>
</tr>
<tr>
<td>Decision on OAT choices should be based on potential interactions of concomitant medications</td>
<td>[14, 18, 38, 40, 42,43] [9,10,39,41,44,45]</td>
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<tr>
<td><strong>Treatment of patients with co-existing health problems</strong></td>
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<tr>
<td>An integrated approach to care for co-existing medical disorders is recommended including education on risk behaviours, cardiovascular, testing and treatment for infectious diseases (e.g. HIV and HCV) and vaccination status assessment</td>
<td>[9,14,18,38,40,43,45] [10,39,41,42,44]</td>
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<tr>
<td>OAT choices should be made and titrated considering interactions of concomitant medications and health status, including potential worsening of liver function</td>
<td>[9,10,14,18,38,43] [39–42,44,45]</td>
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<tr>
<td><strong>Management of pregnant women</strong></td>
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<tr>
<td>Maintenance or initiation of OAT during pregnancy and breastfeeding is recommended</td>
<td>[9,10,14,18,38,40,42-45] [39,41]</td>
</tr>
<tr>
<td>Careful assessment of risk factors in pregnancy should be performed and a multidisciplinary approach should be taken to OUD care, with support from other appropriate services into the postnatal period</td>
<td>[9,10,14,18,38,40,42-45] [39,41]</td>
</tr>
<tr>
<td>Methadone and buprenorphine are recommended choices for OAT in pregnancy. There is substantial experience with methadone in pregnancy; evidence shows buprenorphine treatment is associated with some improved foetal outcomes</td>
<td>[9,10,14,18,38,40,42-44] [39,41,45]</td>
</tr>
<tr>
<td>OAT dose titration should be planned; increased OAT dosing, including split dosing, may be required.</td>
<td>[9,10,18,38,40,42-45] [14,39,41]</td>
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<td><strong>Treatment of older patients</strong></td>
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<tr>
<td>Co-morbidities, existing long-term drug use and side effects should be reviewed and monitored. Coordinated care is recommended</td>
<td>[14,18,38,40,41,43,45]</td>
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<tr>
<td>Dose titration is recommended to account for potential altered metabolism in elderly.</td>
<td>[14,38,40,43]</td>
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| **Patients using opioids to manage pain** |  |
| --- | --- | --- |
| For pain management it is recommended to first identify therapeutic goals and assess conditions for opioid use. Medication choice and treatment goals should be approached comprehensively, with caution, planned clearly. | [10,14,18,38,39,42,43,45] | [9,40,41,44] |
| Pain management plan should be developed in consultation with patient, pain and addiction specialists. Opioid medications should be rationalised within the context of the broader pain management plan | [10,14,18,38,39,42,43,45] | [9,40,41,44] |
| Both methadone and buprenorphine may be considered. Dose should be carefully adjusted based on assessment of tolerance; patients on OAT may require larger doses of analgesia. Suboptimal doses should be avoided. Dose titration is needed for methadone and buprenorphine | [14,18,38,39,42,43,45] | [9,10,39–41,44] |
| For mild acute pain, non-opioid analgesics are recommended; increasing dose of methadone or buprenorphine may be appropriate. For severe pain the possibility of additional opioids such as morphine should be considered. | [14,18,38,42,45] | [9,10,39–41,43,44] |
| For chronic pain, specialists should be consulted for recommendations: a trial of opioid analgesics may be effective; if ineffective higher dose OAT may be an option with methadone, buprenorphine or if misuse or diversion is a risk buprenorphine/ naloxone | [10,14,18,38,43,45] | [9,39–42,44] |
| Some patients with chronic pain may benefit from dosing 2-3 times daily during maintenance therapy | [14,18,43] | [9,10,38–42,44,45] |

| **Treatment of patients with polydrug & alcohol use problems** |  |
| --- | --- | --- |
| Treatment for OUD with OAT is recommended for patients with | [9,14,18,38,40,41] | [10,39,42–45] |
concomitant polydrug and alcohol use disorders. Interventions should be offered to reduce or cease alcohol and polydrug use.

Drug interactions should be carefully assessed, especially the use of sedative drugs in combination with OAT.

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<td>[9,14,18,38,40,43]</td>
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**Treatment in the criminal justice setting, prisoners**

OAT should be offered regardless of custody duration and should not be limited for example with suboptimal doses of OAT nor altered or discontinued for disciplinary reasons.

Treatment should be coordinated between prison healthcare and community health services based on an integrated treatment approach similar to that outside of prison. OAT choices should be made with prisoners and prison healthcare using information from community healthcare records when possible.

Diversion or misuse of OAT in prisons may be a significant problem; OAT choice can help to address this problem. In prisons OAT choices including supervised dosing of methadone or use of buprenorphine/naloxone are recommended.

Regular review during initial treatment following incarceration should be planned to manage risk of emergent problems. These include risk of overdose or side effects related to treatment initiation, and other mental health problems such as acute psychosis, risk of suicide.

On release from prison, continuity of treatment should be ensured with care pathways to promote engagement with community drug treatment services and social support.

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<td>[10,14,38,40,42,45]</td>
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Table 3 Assessment of characteristics of opioid agonists in the treatment of OUD

Advantages of methadone in the treatment of OUD

Potent opioid agonist with extensive treatment experience [9,10,14,38–40,42–44]; for patients with high opioid tolerance, may be appropriate [10,14,38,39]

No precipitated withdrawal: may be appropriate in patients continuing to use other opioids including those that need opioid analgesics for pain [18,38,39]

For patients with concurrent mental health problems, sedative, antidepressant and antipsychotic effects may be beneficial [9,18,38,43]

Improved treatment retention in some patients, may benefit unstable patients or those more likely to cease therapy [14,38,39]

Disadvantages of methadone in the treatment of OUD

Safety profile: risk of fatal overdose and toxicity risks, sedation and respiratory depression which in severe cases may be fatal, risk of delayed toxicity occurring hours after exposure for the patient [9,10,14,18,38–40,42,43,45]. May be associated with overdose risk in domestic settings for other parties including families and young children, with serious consequences [14,18]

Drug interactions: patients on sedative hypnotics, including benzodiazepines, stimulants, cocaine, any other medications that interfere with methadone metabolism, and alcohol are at risk of methadone toxicity [9,10,14,18,38,39,42,43,45]. Liver & renal failure affect methadone clearance leading to requirement for variable doses [14,18,38]

Risks for cardiac patients, (QTc prolongation and fatal torsade de pointes arrhythmia) [14,18,39,42,43,45]: Need for ECGs in patients using doses above 100-120mg and patients with cardiac risk factors [9,10,14,38,40,42,43,45]

Initiation phase may be challenging [9,10,14,38,43,45] with unpredictable patient responses over time which may be associated with increased induction treatment drop out [14]. Overdose risk high during first 2 weeks of initiation [9,10,14,18,38,42,45] in the presence of sedatives and in patients with low opioid tolerance or altered pharmacokinetics

Unsupervised administration of methadone may be associated with problems of misuse and diversion [14,38,42]. Take home dosing is a risk for diversion [9,18,43]; fatal overdose noted in children after accidental ingestion at home [14,18]

Daily supervision may be required for legal and/ or clinical reasons [9,10,14,38,39,42,45]: this may limit autonomy and prevents patient undertaking work or participating in other daily activities of living. Cognitive impairment [38] and sedation, in not-well stabilized patients, may limit opportunities for work [43]

Important adverse events profile: central sleep apnoea, painful joints and bones, constipation, perspiration, endocrine effects such
as abnormal thyroid function, impact on sex hormones such as decreased libido, dry mouth, dysphoria, dyspepsia, opioid-induced oedema, pruritus, weight gain, tooth damage [9,18,38,43]

Hard to transition from methadone, and longer more challenging discontinuation compared to buprenorphine [18,38,42]

Advantages of buprenorphine in the treatment of OUD

Safety profile: low risk of fatal overdose [9,14,18,38–40,42,43,45], low risk of respiratory depression [9,14,18,38,39,42,43], lower cognitive impact (e.g. sedation) [9,14,18,38,39]

Few clinically relevant drug interactions [9,14,18,38–40]

Side effect profile [9,18,38–40]

Flexible treatment profile [14,18,38,39,43,45] (e.g. easy to switch to alternative therapies such as methadone, take-home or alternate dosing)

Misuse and diversion with buprenorphine/ naloxone combination product less attractive than with other OAT choices [9,10,14,18,38–40,42,43]

Initiation of treatment can be easy, taking care to avoid precipitated withdrawal; potential to reach optimal stable maintenance in days rather than weeks [14,18,38,39,42,43,45]

Limited monitoring and supervision on therapy (depending on country-specific legislation) [14,18,38,42]

Treatment-related problems in patients with concomitant medical problems uncommon [18•], need for dose adjustment in renal and liver impairment and in the elderly uncommon [38]

Withdrawal symptoms (which are often tolerable) [9,18,39,43]

Disadvantages of buprenorphine in the treatment of OUD

May be associated with precipitated withdrawal if dosed inappropriately [9,10,14,18,38,39,42,43,45]

May block opioid analgesics used for concurrent pain treatment [14,39]

May be associated with misuse including inappropriate routes of administration (snorted or injected) [14,43]

At low, insufficient doses there may be lower rates of retention in treatment [14,38,39]. Doses may be suboptimal for certain patients (e.g. patients seeking intense effects of opioids such as euphoria, relief or other desired effects, or in patients with high
opioid tolerance). May not provide sedation-type effects where desired [14,39].
<table>
<thead>
<tr>
<th>Title</th>
<th>Region</th>
<th>Year</th>
<th>Reference</th>
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<tbody>
<tr>
<td>National Guidelines for Medication-Assisted Treatment of Opioid Dependence</td>
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<td>[38]</td>
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<tr>
<td>Saskatchewan Methadone Guidelines and Standards for the Treatment of Opioid Addiction/Dependence</td>
<td>Canada</td>
<td>2015</td>
<td>[10]</td>
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<tr>
<td>Methadone and Buprenorphine: Clinical Practice Guideline for Opioid Use Disorder</td>
<td>Canada</td>
<td>2016</td>
<td>[9]</td>
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<tr>
<td>New Zealand Practice Guidelines for Opioid Substitution Treatment</td>
<td>New Zealand</td>
<td>2014</td>
<td>[18]</td>
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<tr>
<td>Policy of the Department for the Treatment of Substance Abuse Ministry of Health</td>
<td>Israel</td>
<td>2017</td>
<td>[40]</td>
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<tr>
<td>National Guidelines for care and support in cases of misuse and addiction. Support for governance and management</td>
<td>Sweden</td>
<td>2016</td>
<td>[41]</td>
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<td>American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of the Medications in the Treatment of Addiction Involving Opioid Use</td>
<td>USA</td>
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<td>[42]</td>
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