Evidence-based consensus guidelines for the pharmacological management of substance dependence: Recommendations from the British Association for Psychopharmacology

Journal of Psychopharmacology
1–46

DOI: 10.1177/02698811251399593
journals.sagepub.com/home/jop

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Abstract

The British Association for Psychopharmacology guidelines for the management of substance dependence focus primarily on the pharmacological aspects of treatment. A group of international experts from a wide range of disciplines reviewed the current evidence in their field, considered the strength of the evidence and discussed the clinical implications at a consensus meeting. The guidelines focus on the pharmacological management of dependence on alcohol, benzodiazepines, 'z-drugs', γ-hydroxybutyrate (GHB), gabapentinoids, opioids, nicotine, cannabis and synthetic cannabinoids, cocaine, amphetamine and methamphetamine, dissociative drugs and their analogues. They are based on the available evidence and make recommendations to aid clinical decision making, as well as highlighting the gaps in the current evidence-base.

Plain Language Summary

This guidance aims to help healthcare professionals make decisions about prescribing medication to treat addictions to nicotine, alcohol, heroin and other drugs (also known as substance dependence). Shared decision-making and safe prescribing are key principles of this guidance. Effective treatment for substance dependence typically combines medication with psychosocial intervention e.g. cognitive behavioural therapy, motivational interviewing and other activities such as group work and recovery communities. Treatment is often divided into stages with different goals, such as reducing the harms caused by the substance, stabilising or reducing substance use to support further treatment, withdrawal from the substance under

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clinical supervision, preventing relapse back into substance use, and then recovery, an ongoing process which varies for each person. Treatment should be adjusted to the needs of each person, which may change, for example at different points in their lives, and when people have physical and mental health conditions at the same time as substance dependence.

This guidance recommends that for people with: **Alcohol dependence** a supervised reducing regime of benzodiazepines is the first-line treatment for withdrawal symptoms, alongside thiamine to prevent brain damage. There are several medications with good evidence to help prevent relapse back to heavy drinking or maintain abstinence. **Benzodiazepine dependence** is best managed through gradual dose reduction, with careful monitoring. **Opioid dependence** is most effectively managed with substitution therapies like methadone or buprenorphine rather than immediate withdrawal. Long-acting injectable buprenorphine is a newer option. Take Home Naloxone should be provided to people who use opioids as well as their friends and family alongside training to reverse overdose, and naltrexone may help prevent relapse following discontinuation of substitution treatment. **Nicotine dependence** is most harmful when tobacco is smoked, and has the strongest evidence base for treatment, including nicotine replacement therapy, varenicline, cytisine, and e-cigarettes. In **Cannabis dependence** the evidence is mixed. Reducing THC content and avoiding tobacco co-use can reduce harm. **Stimulant and dissociative drug dependence** currently lack approved medications, and more research is needed. Overall, the guidance emphasizes safe prescribing, shared decision-making, and integrating pharmacological treatment with psychosocial care to improve outcomes for people with substance dependence.

Keywords

substance use disorder, substance dependence, treatment, evidence-based guidelines, international, pharmacotherapy, medically assisted withdrawal, detoxification, substitution therapy, relapse prevention, harm reduction, tapering

Introduction

Many individuals use one or more psychotropic substances, usually in a recreational capacity, with limited negative consequences. However, across the world, substance use can also cause significant harm at the individual, family and societal level. At the individual level, direct harm may be caused acutely, for example, intoxication, overdose, psychotic symptoms, withdrawal syndromes, whereas more chronic, heavy use is associated with a range of long-term conditions, including cardiovascular, respiratory and liver disease, depression, psychosis and cancers to name but a few (Degenhardt et al., 2018; Rumgay et al., 2021; Shield et al., 2025). Indirect harms may also be caused by neglect of any co-occurring physical and mental health conditions, as well as from the wider impacts of health inequalities frequently experienced (Amaro et al., 2021; NIDA, 2020). An individual's substance use may also result in physical, psychological and social harm to immediate significant others, as well as wider society (Manthey et al., 2021; Mardani et al., 2023; Nutt et al., 2010).

Substance Use Disorders (SUD) are highly stigmatised conditions (Earnshaw, 2020; Fraser et al., 2020; Thornicroft et al., 2022). Despite the overwhelming evidence of increased morbidity and preventable mortality associated with them, the level and quality of treatment provided, as well as the amount of funding that is committed to developing and implanting effective treatments, is not on a par with other conditions of similar severity (WHO, 2024). As people with comorbid conditions are often excluded from randomised controlled trials (RCTs), this further limits the research evidence base for effective personalised management (Buffel du Vaure et al., 2016).

The aim of this guidance is to synthesise the available research evidence, together with other national and international guidance, to reach a consensus and offer a pragmatic summary of recommendations and uncertainties around the pharmacological management of substance dependence. We hope to aid clinicians in their decision-making to improve outcomes for a highly complex and often vulnerable group.

Scope and purpose

Diagnostic terminology. The previous British Association for Psychopharmacology (BAP) guidelines for the pharmacological management of 'substance misuse, addiction and comorbidity' were first published in 2004 and revised in 2012 (Lingford-Hughes, Welch, Peters and DJ Nutt, 2012). Since then, much has changed: psychotropic substances have evolved, increasing in availability and potency; some therapeutic developments have emerged; and updates to both the DSM (American Psychiatric Association, 2013) and ICD (WHO, 2019) diagnostic classifications have resulted in a significant divergence between the two systems in how disorders of substance use are conceptualised (Hasin et al., 2013; Saunders, 2017). DSM-5 has moved to a broader concept of 'substance use disorder' (SUD), whereas ICD-11 has retained the concept of a distinct category for 'substance dependence' as separate from 'harmful use', see Table 1. These changes have an impact on how evidence is synthesised (as most papers use data based on the previous DSM-IV and ICD-10 classifications) and extrapolated to different patient groups. Most pharmacological treatment trials have been undertaken in people who were diagnosed as 'dependent' on a substance. 'Dependence' also has relevance to the development of tolerance and withdrawal from prescribed medications (e.g. opioids, benzodiazepines, gabapentinoids) that need managing in clinical practice. Therefore, for clarity, we use ICD-11 terminology and keep the focus on pharmacological management of people with dependence on substances either prescribed or otherwise acquired.

Target readership. The content of this guideline is relevant for all clinicians who are involved in the holistic management of people with substance dependence, with a focus on pharmacological aspects. Although they are the primary target, this guideline is not just for prescribing clinicians, but we hope will be useful to other health and social care professionals, including specialist therapy team members, to understand the role, recommendations and uncertainties that remain in the pharmacological management of substance dependence, to support people in shared decision making, and understand how pharmacotherapy may integrate with wider aspects of care. We hope that it will also be of benefit to people seeking care and those who support them, to facilitate the shared decision-making process.

Pharmacological treatment is an important part of the wider management of substance dependence, but to be effective needs to be underpinned by a clear psychosocial understanding of the individual's needs (see below). This guideline specifically

Table 1. DSM-5 categorisation of Substance Use Disorder and ICD-10 Substance Dependence.

DSM-5 Definition of Substance Use Disorder (American Psychiatric Association, 2013)	ICD-11 Definition of Substance Dependence (WHO, 2019)
Diagnosis requires ⩾2 of 11 criteria within 12 months	⩾2 of 3 central features over 12 months or continuous use for ⩾3 months
1. Substance taken in larger amounts or longer than intended 2. Persistent desire or unsuccessful efforts to cut down/control use 3. Great deal of time spent obtaining, using, or recovering 4. Craving or strong desire to use 5. Failure to fulfil major role obligations 6. Continued use despite social/interpersonal problems 7. Important activities given up/reduced 8. Recurrent use in physically hazardous situations 9. Continued use despite physical/psychological problems 10. Tolerance 11. Withdrawal *Severity*: • *Mild: 2–3 criteria* • *Moderate: 4–5 criteria* • *Severe: 6+ criteria*	1. Impaired control: including onset, level, circumstances, or termination of use; often (but not necessarily) with craving 2. Substance use takes precedence over other interests, responsibilities, or health 3. Physiological features (indicative of neuroadaptation) manifested by tolerance, withdrawal, or use to prevent withdrawal

focuses on pharmacological management; the international evidence base and, where this is limited, a clinical consensus of the benefit and risk of specific pharmacological treatments for different substance dependencies. Prescribing of any medication needs to be underpinned by competence in assessment and diagnosis. There is a professional responsibility to manage the relative risks and benefits of treatment, which will vary depending on the prescriber, the clinical demographics of the individual, the level and complexity of their needs, as well as the treatment setting.

In offering this guidance, competence in the identification, assessment and wider management of substance dependence is assumed, as is knowledge of the health setting and jurisdiction in which clinical management is undertaken. Although international in scope, the availability and licensing of specific medications change over time in different settings, and the relative cost/benefit of specific medications will be dependent on the availability and conformation of specialist services, monitoring, as well as reimbursement for different patient groups, which is beyond the scope of this guideline.

Psychosocial underpinning of treatment of substance dependence. The complex aetiology of substance dependence, and the challenges involved in engaging with, and then sustaining, behaviour change are significant. A psychosocial framework is therefore essential to effectively assess, engage and retain people in treatment. This framework includes a range of processes, which together develop therapeutic alliance, encourage shared decision-making, monitor and review progress against identified needs and wishes (DoH, 2017; Haber et al., 2021; SAMHSA, 2024; DHSC, 2025). There is established evidence that mutual aid approaches (e.g. Alcoholics Anonymous), clinically delivered 12-Step Facilitation (TSF), and Self-Management and Recovery Training (SMART) are effective in achieving abstinence-related outcomes (Kelly et al., 2020). Behavioural treatments with a good evidence base for effectiveness include contingency management, cognitive behavioural therapies, motivational interviewing, and acceptance- and mindfulness-based interventions, although the evidence for efficacy of specific psychosocial interventions varies according to substance and between clinical populations (Dellazizzo et al., 2023; Minozzi et al., 2025). While pharmacotherapies are the focus of this guideline, it is important to keep in mind that best practices in addiction treatment should include combined behavioural treatments with pharmacotherapies (DoH, 2017; Ray et al., 2020; SAMHSA, 2024).

Wider Context. In addition to specific evidence-based psychosocial and pharmacological interventions for substance dependence, there are other important elements of treatment provision. These include but are not limited to: structure and resources for the assessment, planning and delivery of treatment; pathways across health and social care, voluntary sector and recovery organisations, housing, employment and criminal justice systems; workforce competence across these sectors to recognise and correctly direct people to the appropriate help; public health and prevention measures to reduce stigma. All of these are essential aspects in improving the access, experience and outcomes for people with substance dependence. Many of these are covered in excellent, detailed national guidance (Alvanzo et al., 2020; ASAM, 2020; DoH, 2017; Haber et al., 2021; DHSC, 2025) as their implementation varies significantly across healthcare systems, and readers are encouraged to ensure they are aware of this wider context.

Out of scope. As the aim of this guidance is to offer a pragmatic summary of recommendations and uncertainties around the pharmacological management of substance dependence, within the wider context discussed above, we will not cover management (including harm reduction) of non-dependent use of substances where early engagement and low barrier access are essential, and pharmacological management has a limited role to play. Also out of scope are other non-pharmacological treatments, screening and assessment of substance dependence across clinical settings, and the treatment of behavioural addictions.

Goals of treatment and terminology

As part of the assessment and shared decision-making process, it is important to determine the specific goal of treatment and how it will be monitored and reviewed (Reus et al., 2018) (IV).

Table 2. Terminology used in these guidelines.[a]

Term	Use in these guidelines
Intoxication/Toxicity	Acute clinical syndrome related to the pharmacological effect of the substance. It is not merely the presence of the substance (e.g. in the case of alcohol, a positive breathalyser reading) but also the clinical signs of the effects of a drug on the central nervous system (CNS) (e.g. dysarthria, disinhibition, ataxia).
Withdrawal Syndromes	Clinical syndrome related to withdrawal from the substance, which may be acute or more prolonged/ protracted (e.g. for some benzodiazepines and long-acting opioids). The risks related to withdrawal vary according to substance used.
Craving	Craving is a complex concept that can mean positive anticipation of reward, stress-related desire for relief, bodily responses to environmental cues, or a combination of these. People may say they don't crave substances, but on further enquiry report that they think about using/drinking, so asking about thoughts/urges/ bodily responses is important in eliciting this phenomenon. Unlike for DSM-5,craving is not required to make a diagnosis of substance dependence in ICD-11.
Harm Reduction (HR)	Interventions to reduce the risk associated with substance use, even in the presence of ongoing use. Also referred to as harm minimisation. The focus in this guideline is on HR as part of substance dependence; we do not cover wider public health aspects of harm reduction.
Substitute Prescribing	Using a medication with a similar pharmacology to the problem substance but with a better safety profile or at least more predictable contents than an illicitly obtained supply.
Opioid Substitution Therapy (OST)	Pharmacological treatment for opioid dependence using medications that also stimulate the mu opioid receptor, most commonly buprenorphine and methadone. May be used as part of stabilisation, harm reduction and withdrawal. Also referred to as opioid agonist treatment (OAT), methadone assisted treatment (MAT), opioid dependence treatment (ODT), etc., variably in the wider literature.
Stabilisation	Process to support sustained behaviour change, that is, reduction/cessation of substance use, with improvement in mental and physical health, and reduction risk-taking behaviours. Typically involves optimising substitute medication, for example, OST.
Medically Assisted Withdrawal	Prescribing of medication to reduce the symptoms of withdrawal from a substance, prevent complications, and as an interim step before engaging with further treatment and rehabilitation. Medically assisted withdrawal (detoxification) should rarely be a stand-alone intervention except in medical or psychiatric emergencies or in specialist addictions services with sufficient psychosocial care and assertive onward referral to promote recovery. It usually includes substitute prescribing and adjunctive medication to assist with symptom control and management of related symptoms (e.g. insomnia) and initiation of relapse prevention medication.
Tapering	Usually gradual reduction of a prescribed substitute medication.
Relapse Prevention (RP)	Interventions to prevent return to the previous level of substance use or promote abstinence following medically assisted withdrawal or tapering from substitution treatment.
Recovery	An ongoing process, rather than a state. It evolves over time and includes reduction and/or cessation of substance use as well as changes in self-care, outlook, functioning and relationships. It varies between individuals.

[a]The use of these terms varies across time, and in different health systems. For the avoidance of ambiguity, we define how we are using them in this guideline.

Pharmacotherapy may be an essential part of managing one or more of the phases of treatment, including a period of stabilisation, harm reduction (including reduction of substance use), acute withdrawal, substitution to longer acting/less harmful alternatives, tapering of drug doses and/or relapse prevention. It is essential that both the prescriber and individual are aware of, and agree, the goal of treatment, what it hopes to achieve, and in what time frame. There is significant variability in how different phases of treatment are referred to in the literature, with changes over time, and so Table 2 summarises the main terms and clarifies how we have used them in this guideline.

Methodology

The method used for this guideline was similar to previous BAP guidelines. To facilitate the contribution of an international group of experts, two online consensus meetings were convened in February 2025, with a remit to review the literature and produce up-to-date, evidence-based recommendations covering the pharmacological management of substance dependence, including key uncertainties where evidence was conflicting, of poor quality or lacking. All contributors have extensive clinical and/ or research experience in their field of the treatment of people with substance dependence. Group members spanned the UK, USA, Italy, India and Australia, with expertise across a range of jurisdictions, enabling a focus specifically on the pharmacological evidence base, rather than the wider management required as part of the treatment of substance dependence across highly diverse health settings.

No meeting costs were incurred, and all authors gave their time and expertise throughout the process without renumeration. Following the consensus meetings, co-authors drafted sections of the guideline in their area of expertise. These sections were edited by the core writing group (JS, NK, SK) into a first draft, which was then re-circulated to section experts for further clarification on level of evidence, and agreement on recommendations as necessary. A final draft of the full guideline was then circulated

Table 3. Categories for strength of evidence and recommendations.

Categories of evidence for causal relationships and treatment
Ia: Evidence from meta-analysis of RCTs
Ib: Evidence from at least one RCT
IIa: Evidence from at least one controlled study without randomisation
IIb: Evidence from at least one other type of quasi-experimental study
III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Categories of evidence for non-causal relationships
I: Evidence from large representative population samples
IIa: Evidence from small, well-designed, but not necessarily representative samples
IIb: Evidence from pharmacovigilance studies
III: Evidence from non-representative surveys, case reports
IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Strength of recommendations
A: Directly based on category I evidence
B: Directly based on category II evidence or extrapolated recommendation from category I evidence
C: Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D: Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence
S: Derived from a consensus view in the absence of systematic evidence

RCT: randomised controlled trial.

to all authors for review and agreement of the recommendations, particularly where these were derived from a consensus view in the absence of clear systematic evidence.

Identification of relevant evidence, strength of recommendations

Our methodology was not intended to be for a systematic review of all possible data from primary sources but aimed to synthesise data from recently published primary sources, systematic reviews and national guidelines to reach consensus on key recommendations. We have searched for new evidence on the pharmacological management of dependence on alcohol, benzodiazepines, z drugs, gabapentinoids, gamma-hydroxybutyrate (GHB), opioids, nicotine, cannabis, stimulants (cocaine, amphetamine and methamphetamine) and dissociative drugs and their analogues.

To assess the strength of included evidence and recommendations, we have retained the classification system (Shekelle et al., 1999), used in most BAP guidelines (Table 3), as well as the classification for non-causal relationships (Rogers et al., 2023). Where specific published national or other major guidelines have recommended non-licenced ('off-label') medications for substance dependence (based on clinical consensus), this is highlighted. Given the comorbidity with other physical and mental health conditions of most people with substance dependence who present for treatment, it has been necessary to extrapolate from the available evidence, leading to weaker levels of recommendation (B, C or D) based upon category I or II evidence statements. Also, given that for some recommendations the quality of the RCT is less than robust, this has led us to give a lower strength of recommendation (A/B). Where recommendations have a firm international clinical consensus (practical or ethical), despite a lack of systematic evidence, we have indicated 'S' (standard of care). The recommendations are there to give clinicians options to consider, rather than being seen as prescriptive.

Pharmacological management of substance dependence

Before discussing the evidence and recommendations for the management of specific drugs of dependence, we cover some general principles that pertain across the substances used.

Principles of managing comorbidity (physical and mental) and polysubstance use. As already stated, substance dependence is a highly comorbid condition, not only with dependence (or use) of more than one substance but also with other physical and mental health conditions. Most clinical trials of pharmacotherapy exclude people with significant (or all) comorbid conditions, and therefore, the clinician needs to extrapolate the available evidence to the specific clinical circumstances and individual (Haynes et al., 2002). In the face of limited robust evidence, with increasing morbidity and mortality from substance dependence, national consensus guidelines have evolved which have tried to bridge this gap (Crabb et al., 2020; DoH, 2017; Haber et al., 2021; Royal College of Psychiatrists, 2025), and these remain the best guide for the management of complex individuals within national healthcare systems. There are also BAP guidelines on the management of bipolar affective disorder and schizophrenia, which include sections on comorbid substance use (Drake et al., 2019; Goodwin et al., 2016). However, despite the paucity of high-quality evidence for the pharmacological management of people with substance dependence and one or

more comorbid conditions, there are a few principles to assist the clinician in providing individualised care.

1. Comorbidity should be considered the norm, rather than the exception when managing people with substance dependence (Level D).
2. While stabilisation of the person's substance use may improve a comorbid disorder, integrated monitoring of both/all conditions and timely intervention is essential to improve outcomes (Level D).
3. During medically assisted withdrawal and early recovery, clinicians need to actively monitor for, and manage, emergent symptoms of conditions that may have been masked by substance use (Level D)

Where there is specific evidence for a main comorbidity, these will be highlighted in each section.

Principles of pharmacological management in special populations

Adolescents. Most RCTs for pharmacological interventions in people with substance dependence include working-age adults rather than adolescents or older adults, which also need to be considered when extrapolating the evidence to specific individuals. This guideline focuses on people ⩾18 years, but where evidence also pertains to people <18 years, this is specifically stated.

Adolescence (age 10–19 years) is the peak time for initiation of substance use, usually with tobacco and alcohol, followed by illicit substances (Degenhardt et al., 2016), and there is a complex interplay between risk factors, and trajectory from sporadic and opportunistic use towards substance dependence, which may take several years to develop (Degenhardt et al., 2016). Consequently, the focus of treatment in young people includes early identification across settings, psychosocial interventions, family and community support, and addressing comorbid mental health problems (DoH, 2017; Fadus et al., 2019; Welsh et al., 2025; DHSC, 2025). However, for those who become severely dependent at a young age (often with significant co-morbidity), it is unclear whether adolescents might respond differently to pharmacotherapies when compared to adults. A review of pharmacotherapies (including people <25 years of age) (Squeglia et al., 2019) (Ia) demonstrated that the evidence for smoking cessation was most robust (see nicotine section below), but otherwise most studies were small, of short duration, often in non-dependent samples, with limited outcome measures. Given the lack of robust data, extrapolation from research in adult populations may be required (Level D).

Older Adults. As most high-income countries have a growing and ageing population (WHO, 2020), the number of older adults requiring treatment for substance dependence is also increasing (Butt et al., 2020; Kuerbis et al., 2014). Two distinct cohorts have been described: 'early onset users' and 'late onset users' (DoH, 2017).

The 'early onset' group may have had many years of opioid substitution treatment, or had decades of alcohol and tobacco dependence, with the consequences of that to be considered. These include physical, psychiatric and social complications, as well as polypharmacy with the associated risks (e.g. falls and cognitive impairment), risk of drug-drug interactions, and other consequences of ageing (e.g. multiple long-term conditions, isolation) (DoH, 2017). In addition, it is important to note that these complications of 'older age' may well be present at a relatively young age (Bachi et al., 2017). Given the increased premature mortality and high levels of morbidity in people with longstanding substance dependence, some may have the same risks as 'frail elderly' but at a much younger age, requiring adaptation of doses and monitoring as part of pharmacological management (level D).

The 'late onset users' are more commonly dependent on alcohol, cannabis and prescription drugs (Han et al., 2017; Hu et al., 2024). As of 2024, cannabis was legal in 24 states in the USA for 'recreational use' and in 38 states for 'medical use'. The trend for older adults increased use of 'legal' drugs (Han et al., 2017) will require further research and clinical expertise, to guide the use and safety of pharmacological treatments for substance dependence in this group. Given the lack of robust data, extrapolation from research in 'younger' adult populations will usually be required (Level D).

Perinatal considerations. Prior to any treatment initiation involving people of childbearing potential, especially for substitution therapy or relapse prevention medications, which may be taken for many months, it is important to discuss potential perinatal considerations (Level D).

During pregnancy, decisions about the use of pharmacological treatment to optimise outcomes remain an ongoing challenge, which require consideration of the risks of unmanaged substance use, the impact of any underlying mental disorder and the risks posed (to mother and fetus) by the prescribed drug (DoH, 2017; McAllister-Williams et al., 2017; Guille, 2025). As a general principle, exposure to substances in the first trimester affects foetal organogenesis, while use in the second and third primarily impacts growth and functional abnormalities in the newborn (Day and George, 2005). Shared decision-making with the pregnant person and wider multidisciplinary team is an essential part of management to understand the risks and benefits of any proposed management plan (Guille, 2025).

Sex and Gender differences. Historically, women have been under-represented in pharmacological treatment trials, limiting our understanding of the sex differences in effectiveness and tolerability of specific treatments (Agabio et al., 2016). Biological differences such as hormonal fluctuations, body composition, and pharmacokinetics are likely to influence medication response, yet these factors are often overlooked. Psychiatric comorbidities, more prevalent among women with SUD, as well as gendered social determinants, for example, carer responsibilities and stigma, complicate treatment engagement and outcomes (Greenfield et al., 2010).

A narrative review exploring these considerations found that where there were adequate data to explore sex differences (e.g. nicotine replacement therapy), clinically different responses between men and women have been found (McKee and McRae-Clark, 2022) (Ib). There is less evidence for other pharmacological treatments; naltrexone may be more effective in men for alcohol dependence (Canidate et al., 2017) (Ib), in opioid use disorder, methadone and buprenorphine are effective for both sexes, but women often exhibit lower retention rates, partly due

to higher psychiatric comorbidity (McKee and McRae-Clark, 2022) (Ib).

Addressing these uncertainties requires not only intentional trial design but also gender responsive clinical strategies, including awareness of potential differences in side effect profile and effective doses (McKee and McRae-Clark, 2022; Zakiniaeiz and Potenza, 2018).

Structure of the guideline. We have structured each section to give an overview of the substance under consideration, prior to a summary of the available evidence. Only key recommendations are highlighted at the end of each section, and so, as part of the evidence review, the level of any recommendation associated with it is also highlighted. For each drug considered, the evidence is presented for the goals of treatment for which it is available, for example, medically assisted withdrawal, stabilisation, substitution, relapse prevention, etc. (see Table 2), and a summary of key uncertainties and future work ends each section.

Alcohol

Alcohol dependence and alcohol withdrawal syndrome

The pathophysiology of Alcohol Withdrawal Syndrome (AWS) involves dysregulation of CNS receptor function. Alcohol, like benzodiazepines and barbiturates, is a CNS depressant (Schuckit, 2014). Acutely, alcohol potentiates the inhibitory action of γ-aminobutyric acid (GABA), stimulating GABA-$_B$ receptors and increasing chloride movement through these receptors (MacKillop et al., 2022). Acute alcohol also inhibits the excitatory action of glutamate, reducing calcium-ion movement through N-methyl-D-aspartate (NMDA) receptors. Chronic or heavy alcohol consumption induces the development of tolerance to these effects through a downregulation of CNS inhibitory GABA-$_A$ receptors and upregulation of NMDA receptors (MacKillop et al., 2022).

Hence, cessation of alcohol intake results in a global CNS hyperexcitability due to the NMDA-mediated hyperactivity of glutamatergic neurotransmission, together with the reduced activity of GABAergic neurotransmission. This underlies the manifestations of AWS and associated neuropsychiatric syndromes, including seizures, delirium, alcohol-related brain damage, and hallucinosis. This pathophysiology also underpins the pharmacological management of AWS, the aim of which is the control of symptoms and prevention of complications in severe cases, for example, seizures, delirium tremens, and Wernicke Korsakoff Syndrome (WKS).

Complications of AWS. Seizures most commonly occur as part of severe AWS, 6-48 hours after the last alcohol use (Pace, 2025). Usually, they are single or a brief flurry of generalised tonic-clonic seizures with a short postictal period, while status epilepticus is rare.

Delirium tremens (DT) is estimated to affect up to 5% of people hospitalised for AWS (Pace, 2025; Schuckit, 2014; Wood et al., 2018). DT is characterised by rapid onset, fluctuating disturbances of attention and cognition, agitation, tachycardia, hypertension, fever and diaphoresis sometimes with hallucinations (Pace, 2025; Schuckit, 2014). It usually begins approximately 2–3 days after the last alcohol use and lasts up to around a week (Pace, 2025; Schuckit, 2014). Up to 4% of people with DT die (Schuckit, 2014). Death usually results from hyperthermia, cardiac arrhythmias, complications of seizures and/or concomitant medical disorders (Schuckit, 2014).

Pharmacological management of AWS. Validated scales should be used to identify people at risk for severe or complicated AWS as well as for active responsive monitoring of symptoms (Alvanzo et al., 2020; Kast et al., 2025) (Level D). Decisions about the appropriate healthcare setting for management will be based on the severity of AWS, risk of complications, and local service provision. However, people at high risk of complications, guided by validated tools and risk stratification criteria (Alvanzo et al., 2020) should be monitored in an inpatient setting (Haber et al., 2021; Schuckit, 2014) (Level D), considering the mortality risk associated with severe AWS (Sansone et al., 2024) (III).

There is substantial heterogeneity of patient groups included in reviews of clinical trials for AWS (Bahji et al., 2022; Fluyau et al., 2023), and the likelihood of complications (e.g. seizures and DTs), is increased in those with greatest severity. Therefore, the confidence with which the findings for specific drugs in preventing those complications may be extrapolated across patient groups and settings is low (Holleck et al., 2019; Koh et al., 2021; C Lee et al., 2024), and it may be more accurate to consider the prevention of seizures and DTs as a primary outcome in the treatment of severe AWS rather than as a separate treatment target (Level D).

Benzodiazepines. Benzodiazepines are the gold standard medications because of their efficacy in both reducing the severity of symptoms and preventing seizures and DTs (Alvanzo et al., 2020; Amato et al., 2010, 2011; Bahji et al., 2022; Kast et al., 2025) (Ia). Diazepam, chlordiazepoxide, oxazepam and lorazepam are most commonly used (Bahji et al., 2022; Soyka et al., 2017) (Ia). As all benzodiazepines are effective, the choice is guided by a number of factors, including availability, clinical considerations related to the specific drug (e.g. half-life; potential for non-prescribed use), and the individual (e.g. age, liver disease) (Alvanzo et al., 2020; Mayo-Smith et al., 2004). Benzodiazepines with a longer half-life and active metabolites (e.g. diazepam, chlordiazepoxide) are the preferred agents due to their longer duration of action (Alvanzo et al., 2020; Kast et al., 2025; Mayo-Smith, 1997) (Ib). However, compared to shorter half-life benzodiazepines, their use increases the risk of oversedation and respiratory depression in people with impaired liver function or the elderly for whom shorter half-life benzodiazepines (e.g. lorazepam, oxazepam), which are directly conjugated, are preferred (Alvanzo et al., 2020; Kast et al., 2025; Mayo-Smith, 1997). Benzodiazepines should be discontinued following AWS treatment because of the risk of misuse/dependence (Reus et al., 2018) (Level D).

Doses of benzodiazepines required for AWS treatment vary substantially between people, and their response represents the best guide (Shaw, 1995). Usually, people with more severe alcohol dependence require higher doses (Kast et al., 2025; Shaw, 1995) often much higher than the doses used in other conditions (Alvanzo et al., 2020). Although a consensus definition of AWS resistant to benzodiazepines is lacking, the suggested threshold corresponds to requiring over 40 mg diazepam equivalents per hour (Kast et al., 2025). Dosing regimens comprise fixed-dose, symptom-triggered regimens, and front-loading regimens (Alvanzo et al., 2020; Kast et al., 2025).

In the fixed-dose schedule, benzodiazepines are administered according to a predetermined tapered-dosing schedule over a specified number of days (e.g. 5–10 days), with a suggested dose reduction of at least 25% daily (Kast et al., 2025; Shaw, 1995). This protocol is effective (Bahji et al., 2022) (Ia; Level A), easy to institute and is often chosen in routine practice but risks under- and over-treatment, and therefore requires regular monitoring and review in the first 48-72 hours with dose adjustments based on clinical response (Alvanzo et al., 2020; Kast et al., 202) (IV; Level D).

In the symptom-triggered regimen, people are monitored using a scale for the severity of AWS (e.g. Clinical Institute Withdrawal Assessment for Alcohol – Revised (CIWA-Ar scale)) (Sullivan et al., 1989) and receive benzodiazepines only when needed (Lejoyeux et al., 1998). People with mild AWS (e.g. CIWA-Ar score < 10) may receive supportive care alone, while those with moderate or severe AWS (i.e. CIWA-Ar scores 10–18 or $\geqslant 19$, respectively) should receive benzodiazepines until the CIWA-Ar score is <10 (Alvanzo et al., 2020; Lejoyeux et al., 1998). This approach is most feasible and effective where sufficient monitoring is available or in less severe cases of AWS (Bahji et al., 2022; Holleck et al., 2019) (Ia; Level A).

In the front-loading regimen, loading doses of long-acting benzodiazepines are given (every 1 to 2 hours until symptoms disappear, or the person becomes sedated (Lejoyeux et al., 1998; Shaw, 1995). This is recommended primarily for people at risk of severe AWS closely monitored in inpatient settings (Alvanzo et al., 2020) (Level D).

Fixed-dose schedule benzodiazepines are recommended for routine use, particularly in general medical settings, as they are both effective in reducing signs and symptoms of AWS and the risk of seizures and DT; however, given the significant interpersonal variability in response, this may need to be combined with additional symptom triggered medication for at least the first 48-72 hours (Alvanzo et al., 2020; Bahji et al., 2022; Holleck et al., 2019; Kast et al., 2025) (Level A).

Other agents. Although the quality of evidence is mixed, and often low (Bahji et al., 2022), there have been several studies demonstrating the efficacy of some anticonvulsants in managing AWS (Bahji et al., 2022; Ghosh et al., 2021; Hammond et al., 2015; Mattle et al., 2022; Rojo-Mira et al., 2022). Carbamazepine is approved in Germany for AWS treatment (Kast et al., 2025) and recommended as an adjunctive or alternative to benzodiazepines (Hammond et al., 2015; Kast et al., 2025; NICE, 2010) (IIb,Ib,IV). It may be useful in cases where benzodiazepines are contraindicated (e.g. concurrent respiratory failure) or in (rare) cases of allergy to benzodiazepines (Level B). There is some evidence that gabapentin use is increasing in emergency department (ED) settings (Gottlieb et al., 2025) (IIa), and it may have an adjunctive role in the management of alcohol withdrawal (Ghosh et al., 2021) (Ib), but insufficient evidence for monotherapy (Bahji et al., 2022; Mattle et al., 2022) (Ia, IIa; Level A).

Phenobarbital (a barbiturate) may have a role in the specialist management of AWS in hospital settings, as an adjunct to benzodiazepines, or as monotherapy for people with contraindications for benzodiazepines (Alvanzo et al., 2020; Borgundvaag et al., 2024; Haber et al., 2021; Kast et al., 2025; IV: Level D). Its use is increasing in Intensive Care Units (ICU) and ED settings (Gottlieb et al., 2025), but there remains limited evidence for its effectiveness (Gottlieb et al., 2025; Koh et al., 2021; Lee et al., 2024) (Ia; Level A). Clomethiazole (a short-acting hypnotic with anticonvulsant effects) has good evidence of effectiveness and may be considered for closely monitored inpatient settings after consideration of its safety (Bahji et al., 2022; Fluyau et al., 2023) (Ia; Level A).

Dexmedetomidine (an α2-adrenergic agonist) has similarly been recommended as an adjunct to benzodiazepines for people with AWS in general medical/ICU settings (Alvanzo et al., 2020; Bahji et al., 2022; Wood et al., 2018)(IV). However, although it suppresses hyper-autonomic symptoms without respiratory depression, its mechanism of action does not address the GABA insensitivity and NMDA hyperactivation that is thought to be the cause of AWS, and recent systematic reviews have not found it to be more effective than standard therapy (Fiore et al., 2024; Polintan et al., 2023)(Ia; Level A).

Dopamine antagonists should not be given as monotherapy (Alvanzo et al., 2020) as they do not address the underlying pathophysiology of AWS and increase the mortality risk (Mayo-Smith et al., 2004). However, in cases of benzodiazepine-refractory delirium tremens, addition of a dopamine antagonist, for example, haloperidol or olanzapine, can be useful (Alvanzo et al., 2020; Haber et al., 2021)(IV; Level D) provided they are used in addition to, i.e. not instead of, adequate doses of benzodiazepines (Alvanzo et al., 2020), and sufficient monitoring of side effects, for example, extrapyramidal side effects, oversedation, etc., is undertaken.

There is insufficient evidence to recommend GHB (Bahji et al., 2022)(Ia) as adjunct or monotherapy for the management of AWS. Sodium oxybate (the sodium salt of GHB) has mixed evidence for effectiveness in the maintenance of abstinence (Cheng et al., 2020; Guiraud et al., 2023). It is licenced for use in Italy and Austria, but the European Medicines Agency is undertaking a review of its risk-to-benefit profile (EMA, 2025).

Ethanol (orally or i.v.) is not recommended for the treatment of AWS as there is no robust evidence of superiority to benzodiazepines (Gipson et al., 2016; Mayo-Smith, 1997; Quelch et al., 2025; Weinberg et al., 2008) (III,Ia,III,Ib), and evidence that its administration increases the risk of adverse events and dropouts (Bahji et al., 2022; Mayo-Smith, 1997) (Ia) as well as some concerns from a medical ethics perspective.

Thiamine and AWS. Despite thiamine being recommended for everyone with AWS to prevent Wernicke's encephalopathy, it has been estimated that it is only given to less than 5% of people presenting with AWS (Peck et al., 2021). There is general consensus that those at very low risk of WKS maybe prescribed oral thiamine (100–300 mg/day for 3–5 days; Level D) but those with risk factors for developing WKS (signs of malnutrition or poor diet, peripheral neuropathy, memory disturbance, decompensated liver disease, high metabolic state) should always be offered higher doses of parenteral thiamine (300–1500 mg/day for 3–5 days; Level A), followed by a longer course of oral medication (Dingwall et al., 2022; Kast et al., 2025)(Ib,Ia). Two recent RCTs (Dingwall et al., 2022)(Ib) did not find differences in cognitive outcomes related to WKS between patients in the lower and higher parenteral thiamine dose range (Dingwall et al., 2022), although the interpretation of these results requires caution. Wernicke encephalopathy and Korsakoff syndrome (see section below) are medical emergencies and should immediately be treated with parenteral thiamine (Level D).

Electrolyte imbalances in AWS. People with AWS, particularly if older, malnourished and/or with other physical or mental disorders, often suffer electrolyte imbalances such as hyponatraemia, hypokalaemia, hypophosphataemia, hypomagnesaemia and hypocalcaemia, which should be monitored and potential imbalances managed (Bianda et al., 2025).

Magnesium is required for the conversion of thiamine to its active form, thiamine pyrophosphate, in the liver. There is currently insufficient evidence to recommend the prophylactic use of magnesium for people in alcohol withdrawal (Airagnes et al., 2023; Alvanzo et al., 2020; Sarai et al., 2013; Wilson and Vulcano, 1984) (Ib,IV,Ia,Ib), although it is recommended for those with hypomagnesaemia, cardia arrhythmias or a previous history of alcohol withdrawal seizures (Alvanzo et al., 2020) (IV). A recent RCT found that people with AWS who received magnesium, alone or added to thiamine, reduced the duration of AWS compared to those who received thiamine alone (Maguire et al., 2022).

Summary. Benzodiazepines and thiamine remain the mainstay of treatment. Alternatives or adjuncts to benzodiazepines may be required in medically unwell patients or potentially suitable for milder AWS in ambulatory care.

Comorbidities and special populations

Comorbidities. AWS ranges from mild to severe, and may be complicated by seizures, hallucinations and DT (Bojdani et al., 2019; Pace, 2025). Complicated AWS is more likely among people with more severe alcohol dependence (AD), systolic blood pressure greater than 140 mmHg, prior DT or seizures, older ages, concomitant medical problems (e.g. cirrhosis, malnutrition, respiratory, cardiac, or gastrointestinal disease) and/or people who develop symptoms while still positive for blood alcohol level (Schuckit, 2014; Wood et al., 2018). People who experience repeated episodes of AWS are more likely to have worse long-term outcomes, develop more severe AWS and may develop complicated withdrawal without manifesting symptoms of mild AWS (Kast et al., 2025; Wood et al., 2018). According to this 'sensitisation' or 'kindling' effect', repeated episodes of AWS progressively increase AWS severity because of increased neuronal excitability, although this remains a poorly understood phenomenon (Alvanzo et al., 2020; Becker, 1999; Kast et al., 2025; Ooms et al., 2021).

Finally, because of the combined neurotoxic effects of alcohol and malnutrition, people with AD often present multiple deficiencies, electrolyte abnormalities, and are at risk of developing thiamine deficiency and/or hypomagnesaemia that may contribute to worsening AWS (Kast et al., 2025; Thomson et al., 2002).

Alcohol-induced psychotic disorder (previously 'alcoholic hallucinosis') is characterised by the appearance of auditory, visual, and/or tactile hallucinations (Jordaan and Emsley, 2014). It is frequently triggered by AWS, but the diagnosis should not be made until clear consciousness is restored, and it can be differentiated from DTs. There is some evidence of benefit with antipsychotics, but no clear evidence as to which may be most effective (Masood et al., 2018; Skryabin et al., 2023) (Ib; III)(Level C).

Special Populations. During pregnancy, hospitalisation is recommended for the treatment of AWS (Thibaut et al., 2019) (Level S). Benzodiazepines should be used with caution, at the lowest doses and for the shortest duration (Thibaut et al., 2019). Among the different benzodiazepines, oxazepam may be the preferred one for pregnant women because of its intermediate half-life without active metabolites (Thibaut et al., 2019) (Level S). Clinicians will need to weigh up the relative risks, being aware that risks of high alcohol intake and/or withdrawal complications during pregnancy are likely to be significantly greater than any potential risks of genotoxicity from chlordiazepoxide (Mylan, 2022).

Alcohol-related brain damage. Alcohol-related brain damage (ARBD) is an umbrella term for several brain disorders, including: WKS, originally divided into Wernicke Encephalopathy (WE), Korsakoff psychosis (KP), Marchiafava–Bignami disease, Osmotic Demyelination Syndrome (ODS) and others (Eva et al., 2023; Wolfe et al., 2023). WE caused by thiamine (vitamin B1) deficiency, and the neurotoxic effects of alcohol, can be diagnosed by the Caine classification requiring two of four features of dietary deficiency, eye signs (ranging from subtle nystagmus to complete ophthalmoplegia), cerebellar dysfunction and altered mental state (Eva et al., 2023; Wolfe et al., 2023), and increasingly presents as an acute on chronic picture as part of WKS. If left untreated, ~80% of cases of WE progress to KP (MacKillop et al., 2022). The latter is an irreversible brain disease, characterised by anterograde amnesia and confabulation (Eva et al., 2023; Wolfe et al., 2023).

Marchiafava–Bignami disease and ODS are characterised by damage to neural myelination (Danyalian and Heller, 2023; Wolfe et al., 2023). Symptoms of Marchiafava–Bignami disease may comprise personality change, encephalopathy, gaze disorders and, occasionally, seizures. Other features can be cognitive decline, gait problems, incontinence, hemiparesis, aphasia and apraxia (Wolfe et al., 2023). The classic presentation of ODS is confusion, dysarthria, dysphagia and tetraparesis, but with MRI imaging detecting milder cases, there is some evidence that it can also mimic Wernicke's encephalopathy (i.e. ataxia, oculomotor abnormalities) and should be considered in the differential if there is an inadequate response to thiamine treatment. The neuropathological lesion is pontine demyelination, which may be precipitated by over-rapid correction of hyponatraemia during AWS (Danyalian and Heller, 2023; Singh et al., 2014; Wolfe et al., 2023).

Recommendations

- Benzodiazepines (often at high doses) are recommended as first-line treatment of AWS for the management of symptoms and prevention of complications (Level A).
- Thiamine is recommended for all people with AWS; orally for those in ambulatory settings at low risk of WKS (Level D), but parenterally (i.m./ i.v.) for those with at-risk factors for developing WKS (Level A).
- Ethanol (oral or i.v.) should not be prescribed for AWS where access to evidence-based pharmacotherapy is available (Level A).

Key uncertainties and future work

- There is a need for clearer stratification of the severity of AWS in the synthesis of data from clinical studies of AWS.

- Further clinical studies are needed to clarify the efficacy and safety, routes of administration, and doses of other agents as adjuncts and/or monotherapy in AWS.
- Further studies are required to ascertain the optimal treatment route, dose and duration of thiamine administration, and which people are at greatest risk of WKS.
- Further work is required to understand the implications of disordered electrolytes (e.g. magnesium, sodium, phosphate and calcium) during AWS and their effective management.

Pharmacotherapy for reduction, relapse prevention and maintenance of abstinence in alcohol dependence

The substantial morbidity and mortality associated with AD is largely due to the high level of alcohol consumed and consequent medical and psychiatric disorders (Rehm and Shield, 2019; Witkiewitz et al., 2019). The prevention of these in alcohol-dependent people is primarily by the reduction in total alcohol consumption (Rehm and Roerecke, 2013; Witkiewitz et al., 2025), preventing relapse and maintenance of abstinence.

Reduction in alcohol consumption and transition to abstinence.

For many, there are benefits in initiating relapse prevention medication during alcohol withdrawal treatment; to reduce the symptoms of AWS, as part of a benzodiazepine 'sparing' protocol, and/or assist with the transition to abstinence and relapse prevention. Most of the medications that have regulatory approval for maintenance of abstinence and/or relapse prevention in AD are based on studies conducted in people who had recently undergone medically assisted alcohol withdrawal, or who had become abstinent without medical assistance (Maisel et al., 2012).

Therefore while there is insufficient evidence to recommend topiramate (Fluyau et al., 2023; Hammond et al., 2015) (Ia; IIb), acamprosate, or gabapentin (Ghosh et al., 2021; Mattle et al., 2022) (IIa; Ia), and uncertainty to recommend baclofen (Crunelle et al., 2023; Gulati et al., 2019; Liu and Wang, 2019; Vourc'H et al., 2021) (Ib; IIb; Ia; Ib) as monotherapy for AWS, the evidence above also suggests that initiation during alcohol withdrawal as an adjunct medication may reduce symptoms of AWS (Ghosh et al., 2021; Gual and Lehert, 2001) (IIa; Ib).

While abstinence remains the primary goal for many treatment episodes, there is a growing recognition that non-abstinent outcomes may also be of benefit, and the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) now endorse non-abstinent outcomes as additional accepted outcomes in pivotal RCTs (Henssler et al., 2021; Witkiewitz et al., 2019, 2025). There are health benefits associated with reducing alcohol consumption commensurate with a two-category reduction of WHO drinking levels (Shmulewitz et al., 2021; Witkiewitz et al., 2025) (I; Level A) and goal setting with the individual is an important part of treatment (Reus et al., 2018) (Level D).

Medications for relapse prevention and alcohol reduction

Acamprosate. Whilst not fully understood, acamprosate's mechanism of action involves modulating hyperactive glutamatergic states, possibly acting as an NMDA receptor antagonist (Kalk and Lingford-Hughes, 2014). Acamprosate is moderately effective in increasing abstinence after medically assisted withdrawal (number needed to treat (NNT) = 9–11) for return to any drinking (McPheeters et al., 2023; Rösner et al., 2010) (Ia), and given its mechanism of action may offer some neuroprotection during alcohol withdrawal (Quelch et al., 2024) (III). The evidence is based on early initiation after alcohol withdrawal, but in those who intend abstinence, it can be initiated during (or before) alcohol withdrawal, in conjunction with benzodiazepines (Lingford-Hughes, Welch, Peters and DJ Nutt, 2012; Reus et al., 2018) (Level D). Acamprosate was not found to benefit return to heavy drinking (McPheeters et al., 2023) (Ia). Acamprosate is contraindicated in severe renal impairment, and dose adjustment is required in those with mild or moderate renal impairment. Acamprosate is not metabolised via the liver, and there is no change in pharmacokinetics in Child-Pugh A and B cirrhosis (Kalk and Lingford-Hughes, 2014). In people who experience difficulties with medication adherence, taking acamprosate may be challenging due to its t.i.d. regimen (Koeter et al., 2010) (I).

Naltrexone. The opioid receptor antagonist naltrexone is available both as an oral daily formulation and as a monthly extended-release injectable formulation. Naltrexone reduces alcohol craving and is most effective in reducing heavy drinking. Naltrexone's efficacy has been repeatedly confirmed (Elmosalamy et al., 2025; Kranzler et al., 2009; McPheeters et al., 2023); with a number needed to treat (NNT) of 11 (for return to heavy drinking) (I) and 18 (return to any drinking). Injectable naltrexone was associated with a greater reduction in the percentage of drinking days and of heavy drinking days (Elmosalamy et al., 2025; McPheeters et al., 2023) (I) and may have particular use in those whose adherence to medication is poor. The main contraindication for naltrexone is current opioid use (including prescribed opioid analgesia); in these cases, naltrexone should be started after at least a week of being opioid-free to avoid precipitation of severe opioid withdrawal (Sinclair et al., 2016). Special consideration should be given to anyone who has received long-acting buprenorphine in the last 12 months, in whom naltrexone may precipitate opioid withdrawal and is best avoided (Level S). The concerns that naltrexone may be hepatotoxic have been challenged, and as with acamprosate, naltrexone may be used in patients with alcohol-associated liver disease (Thompson et al., 2024) (Level A). However, caution should be used in those with Child-Pugh B and C cirrhosis or acute alcoholic hepatitis due to the risk of accumulation of naltrexone's active metabolites (Leggio and Mellinger, 2023) (Level C).

Disulfiram. Disulfiram acts via irreversible inhibition of aldehyde dehydrogenase and consequent acetaldehyde accumulation during the metabolism of alcohol, leading to several unpleasant symptoms, for example, tachycardia, headache, flushing, nausea, and vomiting, when alcohol is consumed. Therefore, disulfiram acts as a deterrent aimed at preventing a return to drinking in people who are already abstinent (Kranzler and Hartwell, 2023) (IIb). As such, the efficacy of disulfiram may vary largely as a function of an individual's motivation to take the medication and/or 'witnessed' administration (Allen and Litten, 1992; Kranzler and Hartwell, 2023; Skinner et al., 2014) (Level A). Most RCTs of disulfiram are many decades old (Fuller et al., 1984) and often excluded from meta-analyses, given their small sample sizes and/or study designs. Nonetheless, while concerns

exist around disulfiram – such as its use under some form of 'supervision' – it remains a useful medication to treat AD (Lingford-Hughes et al., 2012). It is widely available and cheap, preferred by some, and may play a clinically important role for those who are highly motivated to maintain total alcohol abstinence (Haber et al., 2021; Kranzler and Hartwell, 2023).

Nalmefene. Nalmefene is a mu- and delta-opioid receptor antagonist and a partial agonist of the kappa-opioid receptor. Nalmefene is effective in reducing heavy drinking days (Mann et al., 2016) (Ib) and is approved in the European Region as a targeted 'as needed' (rather than daily dosing) medication for reduction in drinking from dependent levels (Sinclair et al., 2014), an approach also investigated for naltrexone (Kranzler et al., 2009; Santos et al., 2022). Overall, given the pharmacological similarities between naltrexone and nalmefene, it is conceivable that nalmefene might have an efficacy similar to naltrexone, although side-by-side comparative trials are lacking. As for naltrexone, the main contraindication for nalmefene is current opioid (including analgesic) use.

Underutilisation of medications approved for the treatment of AD. Despite the evidence of safety and effectiveness of medications to maintain abstinence or reduce consumption (Agabio et al., 2024; Amato et al., 2011) (Ia), they are rarely used (Han et al., 2021). Worldwide. it has been estimated that only one in six people receives any kind of medical treatment for their AD, with the lowest rates in low and lower-middle-income countries (Mekonen et al., 2021).

Medications used off-label. The anticonvulsants topiramate and gabapentin have both been endorsed by the American Psychiatric Association for off-label use as potential second-line treatments (Reus et al., 2018) (Level B) for moderate to severe AUD.

Topiramate has shown moderate strength evidence for significant reductions in the percentage of drinking days, percentage of heavy drinking days, and drinks per drinking day (Cheng et al., 2020; Hammond et al., 2015; Kranzler and Hartwell, 2023; McPheeters et al., 2023) (Ia,IIb). The narrow therapeutic index of topiramate needs to be considered, given its potentially significant side-effects, especially in terms of cognition and memory, highlighting the need for careful attention to the target dose, slow titration, and monitoring for side effects (Witkiewitz et al., 2019).

The evidence for the effectiveness of gabapentin and the second-generation agent pregabalin is less robust. For gabapentin, reducing the percentage of heavy drinking days was the only significant positive outcome out of six measured (Kranzler et al., 2019) (Ia); nonetheless gabapentin may be effective in certain groups, for example, those with alcohol-related insomnia and negative affect (Mason et al., 2014) (Ib) and with a history of AWS (Anton et al., 2020) (Ib). There is less data for pregabalin, but given its effectiveness in people with generalised anxiety disorder (GAD) (Baldwin et al., 2015) (Level A) may be of benefit in those with comorbid anxiety (Guglielmo et al., 2012) (Level D). However, the risks of non-prescribed use for both need to be considered before prescribing (DoH, 2017) (Level D).

The GABA-$_B$ receptor agonist baclofen, long used for spasticity, has a developing, but mixed evidence base for managing AD (De Beaurepaire et al., 2019). Clinical trials and meta-analyses have yielded conflicting results (Agabio et al., 2023; Bschor et al., 2018; Cheng et al., 2020) (Ia), but baclofen is increasingly used off-label, and has been formally approved in France. As baclofen undergoes minimal liver metabolism, it has been conditionally recommended by clinical consensus as a potential off-label treatment for AD in people with alcohol-related liver disease (Agabio, Sinclair, et al., 2018; Crabb et al., 2020; Jophlin et al., 2024) (IV; Level D). Optimal doses and potential sedative synergistic effects with alcohol are variable. Baclofen should be started at a low dose (5 mg t.i.d.) and slowly titrated upwards (e.g. 5–10 mg/day, every 3 days) to minimise possible side-effects, including sedation and overdose, and slowly discontinued to avoid withdrawal symptoms (Agabio, Sinclair, et al., 2018) (Level D). There are significant safety concerns relating to coadministration with alcohol and other CNS depressants, as well as in overdose (Reynoard et al., 2020; Rolland et al., 2018), causing severe respiratory and CNS depression. Current evidence favours the use of baclofen as a second-line relapse prevention agent with doses tailored against its effectiveness in reducing craving, with careful monitoring of side effects, for example, sedation, confusion, and affective instability (Agabio et al., 2023; de Beaurepaire and Jaury, 2024; Haber et al., 2021) (Ia; Ib; Ib; Level B).

Combining relapse prevention medications. Given the different mechanisms of action of the currently available relapse prevention (RP) medications, as in other long-term conditions, combination pharmacotherapy may benefit those who do not respond to monotherapy (Lee and Leggio, 2014). However, there is a paucity of studies in this area, although combinations of naltrexone with disulfiram (Petrakis et al., 2006)(Ib), varenicline (Ray et al., 2021) (Ib), gabapentin (Anton et al., 2011) (Ib), prazosin (Simpson et al., 2024) (Ib), or memantine (Krishnan-Sarin et al., 2019) (IIb) are safe and may be beneficial. Conversely, no additional benefits were found by the combinations of acamprosate and naltrexone (Anton et al., 2006; Mann et al., 2013) (Ib).

Comorbidities. There is good evidence for improved outcomes with active management of AD when comorbid with another physical or mental health condition (Agabio, Trogu, et al., 2018; Pettinati et al., 2010; Volkow and Blanco, 2023) (Ia; Ib;Ia) and the choice of pharmacological agents will be dependent on the risk/benefit across conditions.

Specifically, in patients with alcohol-related liver disease (ARLD), the severity of liver disease and associated treatments for it will guide the appropriate RP medication, with acamprosate and baclofen with less hepatic metabolism and therefore potentially safest (Alvarado-Tapias et al., 2025; Crabb et al., 2020; Jophlin et al., 2024; Lee and Leggio, 2015) (Level D). In people who have co-morbid nicotine dependence, varenicline has a growing evidence base (Falk et al., 2015; Haber et al., 2021; Ray et al., 2021) (IV, Ib, Ib; Level B). In those with psychiatric comorbidity, baclofen should be used with caution in patients with affective disorders due to the concerns regarding overdose (Sinclair et al., 2016); in patients with bipolar disorder, naltrexone (given its effectiveness for preventing relapse back to heavy drinking rather than maintaining abstinence) has been recommended as first line treatment (Goodwin et al., 2016) (Level D).

Other agents. Additional pharmacotherapies with promise for AD, but outside the scope of these guidelines, include, but are not limited to ondansetron, prazosin/doxazosin, ibudilast, apre-

milast, ketamine, GLP-1 receptor agonists and spironolactone (Heilig et al., 2024; Witkiewitz et al., 2019).

Recommendations

- After medically assisted alcohol withdrawal, pharmacotherapy should be offered as part of relapse prevention (Level A).
- Acamprosate and naltrexone are first-line treatments for maintaining abstinence and preventing relapse to heavy drinking, respectively (Level A).
- Acamprosate should be preferred for those who have already achieved abstinence (e.g. after hospitalisation or alcohol-specific inpatient treatment), as its most consistent results and beneficial effects are on maintaining abstinence (Level A).
- Naltrexone and possibly nalmefene should be preferred for people experiencing high levels of craving, those who have frequent lapses, or are still actively drinking and wishing to reduce their drinking (Level A).
- Disulfiram still holds a place in clinical practice, especially for people who are highly motivated to maintain total abstinence and who have appropriate family/social support (Level A/B).
- Baclofen should be considered for relapse prevention in patients with ARLD and for those for whom other licensed medications are contraindicated or have proven ineffective (Level A).

Key uncertainties and future work

- What are the risks and benefits of combining medications with different mechanisms of action in relapse prevention pharmacotherapy?
- Understanding the efficacy and risk profile of other novel treatments, including varenicline, ondansetron, prazosin/doxazosin, ibudilast, apremilast, GLP-1 receptor agonists and spironolactone.

Sedatives

Benzodiazepines

Benzodiazepines enhance the effects of the major inhibitory neurotransmitter γ-aminobutyric acid (GABA), acting as a 'positive allosteric modulator' at $GABA_A$ receptors, resulting in anticonvulsant, anxiolytic, hypnotic and myorelaxant effects. Benzodiazepines differ in chemical structure and pharmacokinetic properties (potency, time to effect, duration of effect, frequency of dosing) but share a common mechanism of action and a range of similar clinical effects. The neural basis of the dependence-forming properties of benzodiazepines is not fully understood, and neither are the mechanisms underlying withdrawal; however the emergence of a wide range of physical and psychological symptoms has been described following abrupt stopping or rapid reduction following long-term or high-dose use (Baldwin, 2022).

The pharmacological management of benzodiazepine dependence and withdrawal can be divided into two main groups: therapeutic dose users, and high dose and/or non-prescribed users who may be using benzodiazepines alongside other illicit drugs. Therapeutic dose users include those who have been prescribed benzodiazepines for an extended period, generally for anxiety or insomnia, and have become dependent on the hypnotic-sedative effects. High dose/non-prescribed users may source diverted pharmaceutical benzodiazepines or obtain unlicensed, unregulated forms, which are often combined with other substances, sometimes termed 'street benzos'.

The evidence-based and practice guidelines for management of therapeutic dose dependence is more extensive than for high dose non-prescribed dependent use (Brunner et al., 2025). The management principles for each group also vary. In the therapeutic use group, safe withdrawal with minimal side effects is key, as well as awareness of the potential re-emergence of any underlying conditions, and the increased mortality from all causes in people who discontinue benzodiazepine use after stable long-term use (Maust et al., 2018). While these concerns relate to high-dose, non-prescribed users as well, in addition a strong harm reduction component will also be necessary to reduce the risk of overdose (Brunner et al., 2025; Scottish Government, 2024).

Management of benzodiazepine dependence in 'therapeutic dose' users

Pharmacological management of withdrawal. There is very little high-quality research evidence to guide the management of withdrawal from benzodiazepines; however, there is substantial international clinical consensus for gradual reducing doses (tapering) over abrupt withdrawal (Brandt et al., 2024; Brunner et al., 2025; Gould et al., 2014; Taylor et al., 2025) (IV, IV, Ia,IV). There is also a lack of evidence to support long-term or maintenance prescribing in therapeutic users (beyond the treatment of any underlying condition). However, the additional risks of long-term use, especially in older adults, including impaired cognitive function, falls and accidents (Brunner et al., 2025; Gould et al., 2014; Taylor et al., 2025), are sufficient to encourage regular review of the risks and benefits of deprescribing benzodiazepines through gradual withdrawal.

Early or mild dependence may be managed with minimal interventions (e.g. targeted, written advice and a planned taper) (Ng et al., 2018; Reeve et al., 2017)(Ib). Established dependence is best managed by a collaborative approach, involving the discussion of the risks and consequences of continuing, stopping or withdrawing from a benzodiazepine; which may need revisiting over time (Brandt et al., 2024; Brunner et al., 2025; Darker et al., 2015; Ng et al., 2018; NICE, 2024)(Ib).

Medication consolidation and gradual dose reduction. A flexible and individualised approach to withdrawal through a gradual dose reduction is advised to minimise withdrawal symptoms (Baldwin, 2022; Brunner et al., 2025; Soyka, 2017)(IV). Shorter acting benzodiazepines may be associated with more rapid onset of withdrawal symptoms. Therefore, conversion to a longer acting drug such as diazepam or clonazepam is an option. There is no comparative evidence that one benzodiazepine is superior to another for tapering, but monotherapy is advised over polypharmacy (Baldwin, 2022). The choice of drug should be informed by individual preference, tablet size (if there is any difficulty swallowing) and the ability to enable small reductions through a range of available doses. Many benzodiazepines are metabolised in the cytochrome P450 hepatic system, therefore in

people with hepatic impairment lorazepam or oxazepam should be considered (Level S).

Recommendations on the pace of reduction vary widely (Soyka, 2017); 1–2 mg diazepam every 2–4 weeks (NICE, 2024); 5%–10% every 2–4 weeks and not exceeding 25% every 2 weeks (Brunner et al., 2025) depending on starting dose and the ability of people to tolerate any emerging symptoms (Baldwin, 2022; Soyka, 2017). The majority (60%–80%) of people on a deprescribing intervention were able to stop benzodiazepine use (Pottie et al., 2018)(IV), however, in some people the goal for dose reduction may be to reach a dose where risks of benzodiazepine use no longer outweigh the benefits (Brunner et al., 2025)(IV).

'Microdosing' typically refers to ultra-slow tapering over extended periods towards the end of a standard taper when the dose is minimal. This approach is often led by the individual with the use of small parts, even shavings, of a tablet rather than stop completely. There is little robust evidence to support it, however, there is clearly a strong psychological component which could be managed through psychological support (Horowitz and Taylor, 2024)(IV)

Other key aspects of pharmacological management

- Accompanying psychological interventions improve effectiveness, including techniques based on targeted psychoeducation, motivational interviewing and shared decision-making to support withdrawal and maintain abstinence (Baldwin, 2022; Brunner et al., 2025; Darker et al., 2015; Gould et al., 2014) (IV,IV,Ia,Ia).
- Concomitant pharmacological treatment of underlying conditions (including depression, anxiety disorders and other substance use) is recommended (Brunner et al., 2025)(IV).
- Assessment and management of insomnia should take a multimodal approach including sleep hygiene, CBT-i and potentially melatonin (Morera-Fumero et al., 2020; Soyka et al., 2023)(I,IV).
- There is insufficient evidence to support the use of alternative medications (e.g. antidepressants (including buspirone), anticonvulsants (especially sodium valproate), β-blockers, gabapentinoids, flumazenil, anaesthetics) for benzodiazepine withdrawal (Baandrup et al., 2018; Brunner et al., 2025; NICE, 2024)(Ia IV,IV; Level A).

Special populations. *Older adults*: In older adults, the ongoing risks of continuing regular benzodiazepines are significant, and therefore a successful planned withdrawal from them is more important, especially with increasing comorbidities and polypharmacy (Baandrup et al., 2018; Brunner et al., 2025; Pottie et al., 2018)(Ia, IV,IV; Level A).

Pregnancy: All recommendations for the management of benzodiazepine dependence in pregnancy are based on clinical consensus. An individualised approach to benzodiazepine management in pregnancy considering the needs of the woman and fetus needs to be taken. Neonatal withdrawal and 'floppy infant syndrome' (FIS) can occur with third-trimester BZ exposure (Brunner et al., 2025)(IV). Tapering should be gradual, with close monitoring for withdrawal symptoms and psychiatric destabilisation. If tapering leads to significant anxiety or other symptoms, continuation of BZ may be justified. Lorazepam is generally preferred during pregnancy and lactation due to the lack of active metabolites, and the low relative infant dose in breastfed infants. Breastfeeding is not contraindicated with benzodiazepine use and may mitigate neonatal abstinence syndrome symptoms (Brunner et al., 2025)(Level S).

Z-drugs. The 'Z-drugs' zopiclone, eszopiclone, zaleplon and zolpidem are approved for the treatment of insomnia only and the most common non-prescribed use is to induce sleep (McHugh et al., 2023). Z-drugs differentially bind to benzodiazepine 1 receptor subtypes on the GABA-$_A$ receptor complex to enhance GABAergic neuronal inhibition and cause the desired pharmacological effects (Gunja, 2013). Tolerance, withdrawal, dependence and deaths related to toxicity have been reported, particularly in polysubstance-use populations (Aquizerate et al., 2024; Schifano et al., 2019; Tralla et al., 2024). Case report data suggest benzodiazepines, gabapentinoids, trazodone, and quetiapine may have utility in treating withdrawal symptoms during medically assisted withdrawal (Leal et al., 2024; Mariani and Levin, 2007; Pottie et al., 2018; Xie et al., 2024).

Recommendations

- Where dependence is established, gradual dose reduction of a prescribed benzodiazepine is recommended (A).
- There is insufficient evidence to support the use of alternative medications for benzodiazepine withdrawal (A).
- Additional psychological therapies increase the effectiveness of gradual dose reduction with stronger evidence for CBT (A).
- Melatonin can be a useful adjunctive medication for the management of insomnia (A)

Key uncertainties and future work

- What is the evidence for the effectiveness of ultra-slow tapering over extended periods?
- The impact of cognitive function on ability to engage with a benzodiazepine tapering regime.

Management of high-dose benzodiazepines/ co-use of benzodiazepines with illicit drugs

Use of illicit or 'street' benzodiazepines has increased dramatically in the last decade and is considered to be a key factor in the sharp increase in drug-related deaths globally (EMCDDA, 2018; McAuley et al., 2025; Rock et al., 2025).

Almost all drug deaths, and non-fatal overdoses, involving benzodiazepines are poly-substance deaths, including people on opioid substitution therapy (OST) (Matheson et al., 2024; McAuley et al., 2025; Rock et al., 2025). Analysis of medications purchased as benzodiazepines show they may contain the stated benzodiazepine, another benzodiazepine, some of which are not licensed medications (e.g. bromazolam), or a different substance (e.g. high potency synthetic opioids) (Wedinos, 2024). This creates complexity for clinicians as the person themselves may not accurately know what they are taking.

High dose non-prescription benzodiazepine use may include patterns of binge use or 'mega-dosing' of very large quantities. High dose use is often part of a complex picture of polysubstance use, including with opioids, and is distinct from dependence on lower dose prescribed benzodiazepines (Darker et al., 2015).

Management of withdrawal. There is a very limited evidence base to guide pharmacological management (Berry et al., 2023; Best Practice Advocacy Centre New Zealand, 2021; Brunner et al., 2025; DoH, 2017). A comprehensive assessment is essential, including doses, route of administration, patterns of use and how they vary with motivations (Berry et al., 2023; Family et al., 2025). Understanding motivations can help clinicians in planning management, including harm reduction support (Vojt et al., 2025). If co-morbidities, e.g. anxiety or insomnia, can be addressed with an alternative treatment strategy, this should be tried (Vogel et al., 2013).

A meta-analysis of prescribed benzodiazepines taper plus CBT was shown to be more effective at 4 weeks (relative risk (RR) 1.40, 95% CI 1.05–1.86) and 3 months post-treatment (RR 1.51, 95% CI 1.15–1.98), but these were not sustained at 6 months (Darker et al., 2015)(Ia). Tapering regimens were typically reductions of 25% every 1–2 weeks.

People taking benzodiazepines at high doses (e.g. >20 mg diazepam/day) or for a long period of time (e.g. >10 years) are likely to require a long withdrawal period and more intensive psychological support (Best Practice Advocacy Centre New Zealand, 2021)(IV). The rate of reduction may need to be slower (e.g 5% drop every 2–8 weeks, with rest periods when needed) than that used for 'therapeutic dose' use (Best Practice Advocacy Centre New Zealand, 2021) (IV).

Stabilisation. There are significant challenges and limited evidence on how to balance the risks and benefits in prescribing for people using illicit benzodiazepines as part of a stabilisation phase. Longstanding clinical consensus is that only very rarely should doses of more than 30 mg diazepam equivalent per day be prescribed, and where this is initially above 30 mg, to aim to reduce to 30 mg or below, at a faster rate than lower doses would be tapered (DoH, 2017; Scottish Drug Deaths Taskforce, 2024) (IV). If very high dosing is required, this should occur in specialist settings (DoH, 2017)(IV).

Maintenance/ harm reduction in people on OST and polysubstance use. There is little evidence to suggest that long-term substitute prescribing of benzodiazepines reduces the harm associated with benzodiazepine misuse (DoH, 2017). Benzodiazepines prescription in people on OST is associated with a significant increased risk of all-cause mortality (Best et al., 2024; Hestevik et al., 2024; Matheson et al., 2024). However, co-prescription of benzodiazepines with OST has also been associated with either longer retention in treatment or no impact (Matheson et al., 2024). Longer retention in treatment is associated with reduced mortality in people prescribed OST and was found to be protective during the rise of synthetic opioid use (Pearce et al., 2020).

Those at greatest risk of harm from illicit benzodiazepine use may benefit from being prescribed benzodiazepines as part of a harm reduction approach to establish stability (Park et al., 2021), however, there is no high-quality evidence to guide clinicians in prescribing benzodiazepine substitution therapy to high-dose benzodiazepine users ± opioids.

OST should be optimised and the impact on additional opioid use assessed before addressing benzodiazepine dependence (DoH, 2017). The balance of risk of prescribing versus not prescribing for the individual should be considered and documented (Scottish Drug Deaths Taskforce, 2024). The goal of prescribing should be agreed. If no prior detox has been attempted or previous detoxes have resulted in abstinence sustained for a reasonable period, a tapered regimen should be considered first (DoH, 2017).

As the first step in harm reduction prescribing, practice guidelines advise conversion to an appropriate dose of diazepam to assist with once daily dosing. A starting dose 10–20 mg diazepam is advised, titrating up to stabilise the dose prior to detox (DoH, 2017; Scottish Drug Deaths Taskforce, 2024). Regular monitoring and review of the treatment plan is essential (Park et al., 2021). Taper rates may need to slow and or reduction % be smaller at lower ends of the taper dose (DoH, 2017).

Recommendations

- For people who co-use opioids, OST should be optimised (see opioid dependence section for therapeutic range of methadone and buprenorphine) before considering benzodiazepine substitution therapy (D).
- Where extremely high risks exist, for example, very high dose use, chaotic polysubstance and alcohol use, a period of inpatient stabilisation should be considered (S).

Key uncertainties and future work

- What are the risks and benefits of prescribing maintenance therapy with benzodiazepines in non-prescribed and high dose users with and without OST
- What are the most effective interventions to support people using benzodiazepines at very high doses to reduce to a stable lower dose?

GHB (γ-hydroxybutyrate) and GBL (γ-butyrolactone)

GBL is a colourless liquid. It is a pro-drug, rapidly converted to GHB, which is an agonist at GABA-$_B$ and GHB receptors. Both GBL and GHB can be purchased for use. GHB has a very short half-life (30-60 min), is sedative and has a very narrow therapeutic window (Busardò and Jones, 2015). Treatment of toxicity is supportive, as there is no antidote. Signs of dependence can be using it to go to sleep or stay asleep and cycling between GBL/GHB use, and use of other sedatives, e.g. alcohol or benzodiazepines, to manage withdrawal symptoms. Withdrawal is similar to that from other sedative drugs, that is, craving, anxiety, sweating, shaking, feeling hot and cold, with the exception that there is no association between withdrawal severity and autonomic features (Wolf et al., 2021). Severe cases may rapidly develop hallucinations and delirium (Borelli et al., 2025; Sivilotti et al., 2001), rarely requiring ITU admission (Siefried et al., 2022). However, one case series indicated that out-patient MAW is feasible in a specialist setting with rapid access to inpatient treatment if required (Bell and Collins, 2011) (III).

The evidence base is small, and there are no randomised controlled trials. Clinical consensus indicates that very high doses of benzodiazepines are necessary to manage withdrawal (Level S). Case series indicate that baclofen is an effective adjunct to benzodiazepine treatment due to its action at GABA-$_B$ receptors (Bell and Collins, 2011) (III). Prompt administration of baclofen and initial diazepam loading were associated with reduced discharge against medical advice in a

retrospective chart review (Siefried et al., 2022) (III). There is also limited observational data of standard care in two different countries, suggesting that tapering using GHB may be safer and better tolerated than modest doses benzodiazepines alone (Beurmanjer et al., 2020) (III). Severe benzodiazepine-refractory cases of GHB withdrawal have been described in general hospital settings, and there are case reports of effective management in ITU settings with phen- or pentobarbital (Borelli et al., 2025; Sivilotti et al., 2001) (III). Evidence from a large multi-centre observational study ($N = 229$ in six centres) demonstrated successful completion of GHB/GBL withdrawal in 85% of cases by titration on and then tapering off prescribed GHB over the course of 12 days (Dijkstra et al., 2017) (II).The same study also found relapse rates of 69% in 3 months following medically assisted withdrawal (Dijkstra et al., 2017). Currently, there is no evidence base for relapse prevention treatment for GBL/GHB dependence.

Key uncertainties and future work

- What is the most effective strategy for management of GHB withdrawal in terms of agent, combination of agents and dose?
- What medication is effective for relapse prevention in GBL/GHB dependence?

Gabapentinoids

Gabapentin and pregabalin were originally developed as antiseizure agents and further approved as first-line treatments for neuropathic pain (BNF, 2025; Chincholkar, 2020) and pregabalin for the management of GAD (Baldwin and Ajel, 2007). Despite their structural similarity to GABA, they do not act on them but through inhibitory properties on neuronal voltage-gated calcium channel currents, reducing central sensitisation (Baldwin and Masdrakis, 2022). Concomitant use of gabapentinoids and opioids may induce respiratory depression and opioid-related overdose (Cavalcante et al., 2017; Myhre et al., 2016; Piovezan et al., 2017; Rahman et al., 2021).

Discontinuation symptoms of gabapentinoids vary depending of severity of use, and case reports include insomnia, anxiety, flu-like symptoms, pains and seizures (Parsons, 2018) (III).

Summary of evidence. Despite the increasing recognition of its harms (Baldwin and Masdrakis, 2022), there is limited evidence on the management of gabapentinoid withdrawal from high-dose dependent use (Aindow et al., 2021; Anderson et al., 2023). People on supratherapeutic doses of gabapentinoids should have a reduction plan discussed that allows for an illicit reduction in the community (Parsons, 2018) (IV).

There is no robust evidence on the effectiveness of any withdrawal strategies or interventions to aid withdrawal from a gabapentinoids in this group (NICE, 2022; RCPsych & BAP, 2025), although 3 RCTs described pregabalin tapering regimens in patients with GAD, for therapeutic (150–600 mg/day) doses of pregabalin (Feltner et al., 2003; Kasper et al., 2014; Pande et al., 2003) (Ib). Based on this evidence, tapering is suggested as an appropriate intervention for people using gabapentinoids at supra-therapeutic prescribed use (Aindow et al., 2021; Horowitz and Taylor, 2024; Parsons, 2018) (IV), with suggested maximum reduction rates for the gabapentinoids are 50 mg–100 mg/week for pregabalin and 300 mg every 4 days for gabapentin (Public Health England, 2014) (IV).

Given the delayed and cumulative effect of gabapentinoids, hyperbolic tapering may facilitate dose reductions (Holford, 2018). One case report of a patient who experienced severe withdrawal symptoms when reducing from 1200 to 900 mg/day, tolerated a gradual tapering (20–30 mg/month at 300 mg/day, 5 mg/month at 100 mg/day) over the course of 18 months (Deng et al., 2021) (III). While hyperbolic tapering can be of clinical benefit, it may not be compatible with commercially available formulations. Compounded medication and liquid formulations of both gabapentin and pregabalin are available, but these require training on usage and dilution (Horowitz and Taylor, 2024).

The role of benzodiazepines in managing withdrawal symptoms is unclear, and concurrent use may increase susceptibility to harm (Parsons, 2018), although some clinical protocols use a combination of diazepam and carbamazepine and reduce about 25-50 mg/day over a period of 2–3 weeks (Level S). As most research has been conducted in individuals using opioids further risk stratification, along with ongoing monitoring of withdrawal symptoms, is advised (Bonnet and Scherbaum, 2017) (Level C), together with how these may influence the management of withdrawal symptoms (Aindow et al., 2021).

Special populations. *Older age*: Deprescribing of gabapentinoids in older adults is recommended as part of wider clinical guidance on polypharmacy (regular use of $\geqslant 5$ medications) interventions in therapeutic users (All Wales Medicines Strategy Group, 2023; RCPsych & BAP, 2025) (IV).

Perinatal period: Foetal exposure to gabapentinoids has been reported to have effects on birth outcomes, postnatal neurodevelopment and increase risks of congenital malformations (Carrasco et al., 2015; Dudukina et al., 2023) (III).

Recommendations, key uncertainties and future work

Recommendations

- Abrupt cessation is not encouraged, and the rate of withdrawal should be tolerable and acceptable for the individual (S)

Uncertainties and future research

- What constitutes the optimal length of tapering, and which factors shape its determination?

Opioids

Opioid dependence is associated with significant physical, psychological and social harms. It adds substantially to the burden of morbidity and mortality through increased risk of soft tissue infections, COPD, overdose, transmission of blood-borne viruses (e.g. HIV and hepatitis C) and mental health comorbidities. Prior to 2012, most research involved people dependent on heroin. The emergence of highly potent synthetic opioids (e.g. fentanyl, nitazenes) has contributed to sharp rises in opioid-related deaths and encouraged the evolution of pharmacological management for people with opioid dependence. Synthetic opioids appear to require more aggressive management both in terms of dose and speed of initiation of OST, and understanding continues to evolve.

Increasing attention has also been given to those who develop dependence to prescription opioids. Those using pharmaceutical opioids may differ from those who use illicit opioids in several ways which may alter approaches to pharmacological management. They are more likely to be employed, less likely to inject drugs and have a different spectrum of physical and mental health comorbidities, notably chronic pain (Brands et al., 2004; Fischer et al., 2008; Moore et al., 2007). The impact of these differences on management remains poorly understood: a Cochrane review of 8 RCTs ($N = 709$) found low-quality evidence supporting the use of OST in pharmaceutical opioid dependence (Nielsen et al., 2022) (Ia), but better outcomes were found overall for people dependent on pharmaceutical compared with those using illicit opioids (Banta-Green et al., 2009; Nielsen et al., 2013, 2015)(II; II; Ib).

As the range of opioids on which people become dependent continues to evolve, it is important that clinical guidelines reflect this diversity, including the type of opioid used (illicit/prescription), comorbid physical and mental health conditions, severity of dependence, and preferences. Thus, effective pharmacological management of opioid dependence requires a flexible, person-centred approach. The core pharmacological strategies to support recovery include maintenance OST, medications for medically assisted withdrawal from OST after a period of maintenance prescribing, interventions for relapse prevention (notably naltrexone) and overdose management (notably naloxone). Maintenance therapy with methadone or buprenorphine remains the mainstay of treatment, with the use of long-acting injectable formulations of buprenorphine (LAIB) offering new options for care delivery.

Summary of key evidence

Harm reduction, including overdose. There are a number of harm reduction interventions in opioid dependence which are beyond the scope of these guidelines: for example, provision of clean needles and other injecting supplies; training in safe injecting; testing strips for high potency opioids; blood-borne virus testing and vaccination; and safe injecting rooms (DoH, 2017). Stabilisation using OST can be considered a form of harm reduction and is discussed in section 'Maintenance treatment for opioid dependence'.

Opioid toxicity occurs in the company of family or friends in around 80% of cases (Strang et al., 1999), and there is an available antidote: naloxone. Given that people who use opioids and their friends and family are keen to intervene when toxicity occurs, take-home naloxone kits with accompanying training have been developed as a key pharmacological strategy for harm reduction and a way of reducing drug-related death. There is a large observational body of evidence across different contexts and countries demonstrating that take-home naloxone is used to reverse toxicity, and is associated with a reduction in drug-related deaths where implemented (Giglio et al., 2015; McDonald and Strang, 2016; Walley et al., 2013) (I). Take-home naloxone is available as a preloaded syringe and nasal spray. There is a suggestion that people suffering toxicity from high-potency synthetic opioids may need higher initial and/or cumulative doses of naloxone for reversal (Amaducci et al., 2023; Moe et al., 2020) (III,1b).

Maintenance treatment for opioid dependence. Maintenance treatment implies long-term prescribing of a relatively constant dose of OST. It has been shown to be superior to detoxification as an immediate strategy in attaining the goal of reduced non-prescribed use of opioids, and in retaining people in treatment (Mattick et al., 2009) (Ia). Methadone or buprenorphine have the most robust evidence base (Mattick et al., 2009, 2014) (Ia). Other agents with a smaller and/or lower quality evidence base include diamorphine/heroin, hydromorphone, injectable methadone, slow-release oral morphine (SROM), buprenorphine implant, dihydrocodeine and opium tincture. The goals of treatment are not merely to reduce mortality and withdrawal severity but rather to reduce non-prescribed opioid use in the longer term and facilitate engagement in psychosocial aspects of drug treatment for holistic care to improve quality of life and function. For maintenance treatment, high-quality evidence is predominantly derived from clinical populations using heroin, and from studies with supervised dosing of oral medication. OST is effective for harm reduction, with evidence that for those in OST programmes, overall mortality risk, and suicide risk are reduced by more than half (Fraser et al., 2024; Santo et al., 2021) (Ia) as well as reduced participation in high-risk behaviours such as injecting drug use (Gossop et al., 2002) (I) compared with those out of OST.

Methadone. Methadone is a full agonist at the mu opioid receptor. Oral methadone maintenance treatment (MMT), using liquid methadone, is supported for the treatment of heroin dependence by the strongest level of evidence (Mattick et al., 2022) (Ia). Demonstrating its efficacy in reducing illicit opioid use, improving treatment retention, lowering the risk of overdose and mortality, and improving physical and mental health (Mattick et al., 2022) (Ia). There is emerging evidence base supporting MMT for opioid dependence, which includes high-potency opioids, showing equivalent success in retention and remission with MMT for those who used non-prescribed fentanyl at baseline and those who did not (Stone et al., 2020) (III).

Longer cumulative MMT duration was associated with lower mortality and better outcomes (Huang et al., 2023). When different doses of methadone are compared, doses of 60 mg/day or more are associated with better retention in treatment (Bao et al., 2009) (Ia); doses <60 mg/day are associated with two- to three-fold risk of treatment dropout (Faggiano et al., 2003; Hser et al., 2013). Reduction in non-prescribed opioid use is also associated with higher doses (Strain et al., 1999) (Ib), although some observational evidence showed 38% achieving abstinence at doses <60 mg/day (Trafton et al., 2006) (III). Flexible dosing is also associated with retention in treatment (Bao et al., 2009) (Ia). There is also evidence to suggest that dose and blood levels correlate only modestly at higher doses, reflecting wide PK variability and clinical responsiveness (Chalabianloo et al., 2024) emphasising the importance of using clinical response to determine the appropriate dose.

The benefits of higher doses need to be weighed against dose-related toxicity (Gao et al., 2021) (III), dose-related side effects, particularly QT prolongation, and the risks associated with concurrent use of other sedating medications, such as benzodiazepines (Abrahamsson et al., 2017; Bharat et al., 2024; Hestevik et al., 2024; Leece et al., 2015; Lyndon et al., 2017; Macleod et al., 2019) (III). There is also evidence that methadone-related mortality increases steeply with age, from as young as 35 years old (Pierce et al., 2018) (III). Subsequent work has suggested that the relationship between opioid-related mortality and age may be

due to an accumulation of comorbidity, particularly cardiovascular and respiratory comorbidity (Larney et al., 2023)(I). Given the high interindividual pharmacokinetic variation of methadone (Chalabianloo et al., 2024) and its accumulation with repeated dosing, the first weeks of treatment are associated with excess mortality (Santo et al., 2021). Until recently, starting doses between 10 mg and 40 mg/day were recommended, and expert consensus advocated dose increases spaced by more than 2 days and limiting total dose increase to 30 mg/day in the first week (DoH, 2017; SAMHSA, 2024) (IV). However, with the advent of fentanyl, higher starting doses of up to 70 mg on the first day, and more rapid titration protocols are being explored (Buresh et al., 2022; Klaire et al., 2023) (IV). There is some data to suggest that for dependence on higher potency opioids, this approach, in a general hospital setting, is associated with very low rates of sedation or need for naloxone or ITU support (Klaire et al., 2023; Taylor et al., 2022) (III). A single out-patient retrospective study described rapid titration with daily increments up to 60 mg on day three and a high first day dose (up to 50 mg) with promising treatment retention at 1 month (Taylor et al., 2022) (III).

MMT initiation and initial stabilisation are typically supervised (DHSC, 2024) to ensure full dosing and avoid diversion, which is associated with drug-related death in the non-treatment-seeking population. Dispensing arrangements may influence retention in treatment, but evidence for their effect is conflicting (Saulle et al., 2017) (Ib). Injectable (see below) and tablet formulations are also available but not widely used. Tablet formulations are not recommended due to the risks of diversion and harms from injection of crushed tablets (DoH, 2017) (IV).

Transmucosal buprenorphine. Unlike methadone, buprenorphine is a high-affinity partial mu-opioid receptor agonist and kappa antagonist. Its respiratory depressant effect typically plateaus in people with normal respiratory function, but other clinical effects may continue to be felt. This influences its safety profile, initiation considerations, and subjective effects. Transmucosal buprenorphine (BUP) is available in several formulations, including transmucosal tablets (with or without naloxone), and buccal lyophilizate wafers, which have faster absorption and higher bioavailability. Most of the evidence is derived from trials involving transmucosal preparations (often buprenorphine-naloxone combination) in populations using illicit heroin,

Buprenorphine-naloxone combination was developed to address concerns about diversion, as naloxone has poor oral bioavailability (7-9%) but reasonable intranasal bioavailability (~40%), so it would block the effects of injected or inhaled buprenorphine (Chiang and Hawks, 2003; Saari et al., 2024). However, 'real-world' evidence of its effectiveness in this regard is mixed (Blazes and Morrow 2020).

Transmucosal buprenorphine maintenance treatment (BMT) is effective in retaining people in treatment in any dose above 2 mg/day relative to placebo (Mattick et al., 2014) (Ia). Doses in meta-analyses have been considered in the following categories: low dose (2–6 mg/day); medium dose (7–15 mg/day) and high dose (⩾16 mg/day). High doses (⩾16 mg/day) are effective for reducing illicit opioid use (measured by urinalysis), more effective in retaining people in treatment, and are associated with a longer time to ED attendance or hospital admission relative to lower doses (Axeen et al., 2024; Degenhardt et al., 2023; Fareed et al., 2012; Mattick et al., 2014) (Ia). At doses of ⩽8 mg/day, doses of 4–8 mg/day increase retention relative to 1-3 mg/day (Kennedy et al., 2022) (Ia). There is observational evidence that 32 mg/day is superior to 24 mg/day in treatment retention and reduction in non-prescribed opioid use (D'Agata Mount et al., 2024) (IIb). If treatment dose is considered as a continuous variable, the relationship between dose, retention and abstinence from non-prescribed opioids still holds (Bergen et al., 2022; Hser et al., 2013) (Ib).

Very high doses, that is, ⩾24 mg/day may be necessary to treat dependence on high potency synthetic opioids (Mariani et al., 2021; Weimer et al., 2023) (IV). Pharmacodynamic studies suggest that plasma levels in excess of 2 ng/ml, that is, those reached at doses of 24–32 mg/day, would be necessary to protect against fentanyl-induced respiratory depression (Moss et al., 2022; Olofsen et al., 2022).

Treatment initiation with buprenorphine has historically been cautious, involving waiting until the person is in objective withdrawal and then incremental dose escalation, to avoid the risk of precipitated opioid withdrawal. Precipitated opioid withdrawal occurs when buprenorphine, which has a high affinity for the opioid receptor, displaces a full agonist, without providing a sufficient level of opioid receptor activation. This is uncomfortable for people, and the evidence is currently limited as to the best way to treat it, although there are case reports suggesting that additional doses of buprenorphine may reverse this (Oakley et al., 2021; Quattlebaum et al., 2022; Spadaro et al., 2023) (III).

Dose escalation is more rapid than with methadone – daily increments in dose until a therapeutic dose is achieved is standard. Evidence is emerging (but confined to case-studies; level IV) for different initiation approaches including; high dose induction, for example, up to 12 mg are achieved on the first day (Herring et al., 2021) (III); induction without waiting for withdrawal symptoms, and low-dose induction, where buprenorphine is dosed regularly from a very low level, that is, <1 mg/day and increased every day until a therapeutic dose is achieved (Moe et al., 2021) (III).

Methadone vs transmucosal buprenorphine. MMT is superior to BMT in retaining people in treatment, irrespective of dose (Degenhardt et al., 2023) (Ia). While early evidence suggested that this was concentrated at the initiation of treatment, for example, Hser 2014 1b, there is evidence of disparity up to 24 months (Degenhart et al, 2023) (Ia).

There is some evidence that non-prescribed opioid use was lower in those receiving BMT in RCTs that measured this outcome by urinalysis (three studies, $N = 841$), but no differences when using other measures. There is some evidence that non-prescribed use of cocaine (Ib), craving (Ib), anxiety (Ib) and might be lower among people prescribed BMT than MMT (Degenhardt et al., 2023). Two RCTs have found lower prevalence of alcohol use in people prescribed MMT (Degenhardt et al., 2023) (Ib), and one large longitudinal study found that opioid-related hospitalisations decreased more in people prescribed MMT (Shah et al., 2018)(1). Evidence consistent across RCTs and longitudinal studies demonstrates that QT prolongation is more common in those prescribed MMT than BMT (Anchersen et al., 2009; Athanasos et al., 2008; Fanoe et al., 2007; Fareed et al., 2013; Isbister et al., 2017; Wedam et al., 2007) (I; Ia). However, non-prescribed drug use, for example, cocaine (Mayet et al., 2011) and co-prescribed medication may also be contributing factors and should be reviewed (Level S).

Evidence suggests that transmucosal buprenorphine has a lower overdose mortality risk in the first month of treatment (but not thereafter) compared with methadone (Santo et al., 2021). However, this needs to be weighed against the evidence for improved retention rates during the first month for people prescribed methadone, which also has a protective effect in terms of harm reduction. The superiority of MMT in retaining people in treatment is a major consideration since mortality increases significantly in the period immediately after treatment cessation (Santo et al., 2021; Sordo et al., 2017).

There is observational evidence that the risk of all-cause mortality and opioid related death is lower in older adults prescribed buprenorphine than it is in those prescribed methadone (Hickman et al., 2018) (I). BMT is associated with a lower risk of opioid-related death in the presence of cardiovascular and respiratory comorbidity (Larney et al., 2023) (Ib). Buprenorphine-related mortality does not appear to be increased when dispensing requirements are relaxed, in contrast to mortality related to MMT (Aldabergenov et al., 2022) (II).

There is limited evidence comparing MMT and BMT for people dependent on prescribed opioids (Nielsen et al., 2022) (Ia). Outcomes appear similar to those with heroin dependence, although the evidence on retention and opioid use was considered low certainty/quality as opposed to high/moderate quality for those reported in Mattick (2014) (Ia) and Degenhardt (2023) (Ia). Overall, better retention was found for MMT versus BMT, and BMT was superior to non-opioid treatments for both retention and reductions in opioid use (Nielsen et al., 2022).

Long-acting injectable buprenorphine. LAIBs are currently available in different forms and dosing (weekly or monthly) schedules and be more effective than placebo in terms of retention in treatment and abstinence from opioids (Degenhardt et al., 2023) (Ia). One RCT demonstrated better retention rates and reduced heroin use compared to lower doses of transmucosal buprenorphine (median dose <16 mg/day) or methadone (<60 mg/day) (Marsden et al., 2023) (Ib). A recent secondary analysis suggests that higher LAIB doses may be more effective in injecting populations (Greenwald et al., 2023). Patient satisfaction with LAIBs is superior relative to BMT (Lintzeris et al., 2024) (Ib). Retention in treatment, as assessed by longitudinal research, appears to be higher for LAIB than BMT and MMT, although this is based on a few longitudinal studies (Degenhardt et al., 2023) (II).

There is also evidence accruing for a range of secondary outcomes including reductions in other substance use (Farrell et al., 2024) (II), depressive symptoms (Farrell et al., 2024; Ling et al., 2020b) (II), improved quality of life (Farrell et al., 2024; Ling et al., 2020a) (II), reduced acute healthcare use (Ling et al., 2020a; Yarborough et al., 2024) (II) reduced re-incarceration (Mlilo et al., 2025)(II) and likelihood of being employed (Farrell et al., 2024) (II).

Buprenorphine implant. A buprenorphine implant consists of 4–5 rods containing buprenorphine, which are surgically inserted into the subdermis of the upper arm and provide the equivalent of an 8 mg daily dose for 6 months, at which point they need to be removed, again via minor surgery, and a fresh set can be re-inserted in the other arm. The implant was shown to be efficacious in three UK RCTs (Ib), showing reduced cumulative illicit opioid use compared with placebo implant at 16 weeks (Ling et al., 2010), and at 24 weeks (Rosenthal et al., 2013) and was subsequently shown to be non-inferior to transmucosal BUP for opioid use at 24 weeks (Rosenthal et al., 2016) (Ib), with continued safety data at 1 year. People's experiences of the implant were positive (III), though there were some concerns that the dose may be insufficient to ensure stabilisation for many, with complications arising from insertion/removal of the implant and high rates of adverse events at implant sites (Scurti et al., 2023).

Injectable opioid agonists. Three injectable opioid agonists are available as treatment. The bulk of the evidence relates to diamorphine (see below) that is, heroin-assisted treatment (HAT). Hydromorphone is advocated as an alternative where HAT is not available (CRISM, 2019) (IV).

Diamorphine/diacetylmorphine/HAT. There is good evidence to support the use of HAT (Ferri et al., 2011; Strang et al., 2015) (Cochrane) (Ia). In those who were treatment refractory, HAT was superior to oral methadone with greater reductions in heroin use (Ia), premature treatment discontinuation (Ib), criminal activity (Ib), incarceration (Ib), as well as improving overall health and social functioning (Ib). While HAT programmes have been associated with improved overall health and reduced risky behaviours, direct evidence of reduced mortality rates remains inconclusive. Despite the high intensity of treatment and the clinical oversight required, HAT was found to be cost effective (Dijkgraaf et al., 2005; Ferri et al., 2011; Nosyk et al., 2012).

Doses used were typically 150–250 mg diamorphine per injection under direct medical supervision. All trials included individuals with severe, chronic heroin dependence and a previous failure to respond to oral methadone, with the exception of Haasen et al. (2007) in which participants had no history of being prescribed oral methadone, but also demonstrated relative superiority of HAT with higher retention rates, greater improvement in physical and/or mental health and greater decrease in non-prescribed drug use, in this high-risk injecting group (Haasen et al., 2007) (Ib).

Hydromorphone: Injectable hydromorphone is a potent semi-synthetic opioid agonist used as injectable maintenance therapy in those with severe, refractory opioid dependence. Similar to HAT, it is administered under medical supervision, typically 2–3 times daily in a clinical setting. Hydromorphone is non-inferior in the per protocol analysis relative to injectable diacetylmorphine with respect to retention, reduced non-prescribed opioid use and criminal activity (Oviedo-Joekes et al., 2010, 2016) (Ib).

Injectable methadone: A single RCT (RIOTT) demonstrated superiority of injectable methadone for retention in treatment as compared with oral MMT and a significant reduction in illicit opioid use over time (Strang et al., 2010) (Ib). However, there was no benefit of injectable methadone over injectable diamorphine for non-prescribed opioid use, and the latter was superior for retention and reduction in opioid use.

Other forms of maintenance treatment

Slow-release oral morphine (SROM). SROM is a slow-release formulation of morphine, a full mu-opioid receptor agonist, that is taken orally, typically 1–2×/day (polymer-coated capsule; 200–1200 mg). The SROMOS study, a longitudinal observational cohort study of one year (Lehmann et al., 2021)

(Ib), showed reduced heroin use, reduced injecting, a lower number of drinking days, and improved mental and physical health following the switch from conventional OST. Smaller studies also suggested that SROM may result in less QT prolongation, higher treatment satisfaction (Hämmig et al., 2014) (Ib) and comparable efficacy to methadone (Bond et al., 2012; Mitchell et al., 2004; Winklbaur et al., 2008) (Ib). The potential for diversion of SROM is a recognised concern, but the extent of the problem appears to vary depending on clinical setting, for example, supervised vs unsupervised consumption practices (Beer et al., 2010; Peyriere et al., 2013, 2016).

Dihydrocodeine (DHC). DHC, a full mu opioid receptor agonist, licensed for mild/ moderate pain, has limited evidence of efficacy for maintenance treatment. A Cochrane review showed it was no more effective than MMT or BMT for reducing illicit opioid use, retention in treatment or other health outcomes (Carney et al., 2020) (Ia) . Its tablet formulation is difficult to supervise, is short-acting (frequent dosing required) and easily diverted. However, it does have utility in certain situations, for example, police custody or prison admissions, for short-term symptomatic relief in the absence of methadone (Sheard et al., 2009). Caution is required due to an increase in DHC-related deaths (Rock et al., 2022). More data are required for it to be considered as a potential alternative treatment for opioid dependence.

Opium tincture (OT). One systematic review of nine studies (observational or case series) of OST maintenance for, predominantly, opium dependence supports OT-assisted treatment in Iran. Studies were of poor quality but suggest that OT-assisted treatment may have some comparable outcomes with MMT for people with opium dependence in particular (Noroozi et al., 2021) (IIa, III).

Recommendations for maintenance treatment

- People with opioid dependence and their significant others should be provided with take-home naloxone and training in reversal of opioid toxicity using naloxone (A).
- OST to enable stabilisation, retention in treatment, and reduce risk of death is the recommended initial approach to opioid dependence, rather than immediate detoxification (A).
- MMT, BMT and LAIB are all effective maintenance treatments. Opioid-dependent people should be offered a choice of medication, guided by availability and safety considerations (A).
- MMT is effective in reducing heroin use, for harm reduction, and for retaining people in treatment (A).
- MMT should be optimised at doses which enable the person to remain engaged in treatment and cease use of non-prescribed opioids, typically $>$ 60 mg/day (A). Doses should be adjusted to suit individual needs with consideration for tolerance to opioids, management of withdrawal symptoms, safety, especially where there are co-occurring physical health conditions, and individual preference (A).
- BMT (transmucosal) is effective in reducing heroin and prescription opioid use (A). BMT should be optimised to doses which enable the person to remain in treatment and cease use of non-prescribed opioids, typically $\geqslant$16 mg/day (A).
- LAIB maintenance treatment is an alternative first line treatment option for people who prefer buprenorphine and for whom a long-acting injectable may be more effective or preferred over daily transmucosal dosing (A).
- Supervised injectable diamorphine maintenance treatment should be considered for those who have failed to respond to optimised MMT or BMT (A).

Key uncertainties and future work

- What is the optimal form, initiation regime and optimised dose of OST for people who are dependent on high-potency opioids?
- What is the optimal method to switch people from methadone to buprenorphine, including LAIB?
- What are the most effective treatment strategies for managing buprenorphine-related precipitated withdrawal once it has occurred?
- What are the additional pharmacological strategies for using non-opioid medications to facilitate improved outcomes on OST in different phases of treatment?
- What are the impacts of different comorbidities and ageing on risk/benefit profile of different treatments?

Medically assisted opioid withdrawal

Medically assisted withdrawal from opioids in the context of addiction treatment is ordinarily undertaken as a taper of prescribed OST after a period of maintenance treatment, with the person fully committed to the process (DoH, 2017).The severity and duration of opioid withdrawal syndrome depends on the opioid half-life, duration of use, and person-specific factors. Withdrawal is generally accepted to be easier from longer than shorter-acting opioids (NICE, 2022) (IV), and people withdrawing from high-potency synthetic opioids (e.g. fentanyl, nitazenes) may require modified pharmacological strategies compared to standard treatments, due to the unique pharmacokinetics and potency of these substances (Bird et al., 2023; Weber et al., 2024) (IV).

Abrupt discontinuation of short-acting or high-potency opioids (e.g. heroin, fentanyl, nitazenes, hydrocodone, oxycodone) results in intense withdrawal symptoms that typically begin within 12 hours of the last dose, peak between 36 and 72 hours, and subside over 4–7 days. Withdrawal from longer-acting opioids (methadone, buprenorphine) tends to produce similar but milder symptoms that persist for longer. Methadone withdrawal can last 2 weeks or longer, and withdrawal from buprenorphine is of similar duration but less severe. LAIB withdrawal effects vary according to formulation, weekly preparations typically emerging and peaking within 1–3 weeks and monthly between 6 and 24 weeks or longer.

It is important to pay particular attention to later stages of the withdrawal process, including pharmacological management of any emergent symptoms; agitation, anxiety, gastrointestinal disturbance, sleep disruption (Kosten and Baxter, 2019). These may require holding the dose before slowly trying to reduce it again. Care is needed to ensure that use of medications to manage pain and anxiety do not substitute one dependence for another (PHE, 2021) (IV), or increase the risk of respiratory depression and elevated mortality rates (Abrahamsson et al., 2017; Bharat et al., 2024; Gomes et al., 2017; Hestevik et al., 2024; Leece et al., 2015).

Evidence regarding medically assisted withdrawal from prescription opioids is scarce (Langejan et al., 2022; NICE, 2022) (IV), so extrapolation from the wider opioid dependence literature may be helpful.

Medically assisted opioid withdrawal strategies

Gradual tapering. Tapering refers to the gradual reduction in opioid dose to zero, typically referring to the tapering of OST. Good practice guidelines advise a process of shared decision-making with the person to agree on duration, usually lasting about 28 days as an inpatient or up to 12 weeks as an outpatient (DoH, 2017; Lintzeris et al., 2024).

Methadone: Methadone tapering has good evidence of effectiveness and retention rates in studies lasting 9 days to 41 months (Amato et al., 2013; Degenhardt et al., 2023) (Ia), Methadone dose reduction should be gradual with a suggested rate of 2–5 mg/d every 1–2 weeks, depending on dose and emergent symptoms (DoH, 2017) (IV). While there is little evidence of superiority of a linear vs exponential dose reduction, it is clinically accepted that tapering of methadone becomes more challenging in the latter stages, often requiring a slower taper, or switching to BUP (or LAIBS) once doses of <30 mg/day are achieved (DoH, 2017) (IV).

Buprenorphine: Buprenorphine has a similar capacity to methadone to ameliorate opioid withdrawal symptoms (Gowing et al., 2017) (Ia) and can typically be reduced more quickly and easily than methadone (IV). Tapering of transmucosal BUP can be achieved by gradual dose reduction, for example, ~2 mg every ~2 weeks, with final reductions of ~400 μg (DoH, 2017) (IV). It is more effective than α2-adrenoceptor agonists alone for managing opioid withdrawal in terms of severity, duration of treatment, and likelihood of completion over short durations (Gowing et al., 2017) (Ia). There is also evidence of effect in those with a history of prescription opioid dependence (Sigmon et al., 2013) (Ib), and some evidence to support transfer to naltrexone for relapse prevention at the end of tapering, if required (Bisaga et al., 2018; Sigmon et al., 2013) (Ib).

LAIBs and subdermal implants: Preliminary observational data from case series found minimal withdrawal symptoms (Epland et al., 2024; Hayes et al., 2025; Ritvo et al., 2021; Rodriguez and Suzuki, 2023) (III), which peaked around 6 weeks after discontinuation of a monthly LAIB (Hayes et al., 2025) (III). In two case series, this successful medically assisted withdrawal to abstinence with LAIB occurred following intolerable withdrawal symptoms during previously attempted transmucosal BUP taper (Epland et al., 2024; Ritvo et al., 2021)(III). Observational data following medically assisted withdrawal using LAIB found sustained abstinence from illicit opioids without return to OST in 47% of patients at 18 months (Boyett et al., 2023) (III). A case series suggests that the long-acting buprenorphine 6-monthly implant is associated with few withdrawal symptoms 7 months after insertion in people wishing to discontinue use (Pierlorenzi et al., 2024) (III). Recent practice guidance suggests initiation with low-dose transmucosal BUP at approximately the time of the next scheduled LAIB injection may assist with mitigating withdrawal symptoms (Lintzeris et al., 2024) (S).

Other Opioids: Opium tincture showed comparable outcomes to methadone in gradual tapering regimens, though most data came from observational studies (Amato et al., 2013; Noroozi et al., 2021). Two RCTs (n = 150) comparing DHC with buprenorphine for withdrawal (≤20 days), found low-quality evidence of equivalent efficacy for abstinence at 6 months (Carney et al., 2020).

Non-opioid α2-adrenergic agonists (α2 agonists): There is evidence for the effectiveness of α2 agonists, notably lofexidine and clonidine, as mono-therapy relative to placebo or as an equally effective alternative to a rapid methadone taper (Gowing et al., 2016; Urits et al., 2020) (Ia). However, expert consensus is that monotherapy with α2 agonists should be undertaken only for those dependent on lower potency opioids (DoH, 2017) (Level S).

Ultra-rapid withdrawal using sedation with an anaesthetic agent is not recommended. A Cochrane review of 9 studies (8 RCTs with n = 1109 patients; Gowing et al., 2010) (Ia) showed that heavy sedation with propofol, midazolam or isoflurane conferred no additional benefits on the severity of withdrawal or increased naltrexone initiation. Adverse events are potentially life-threatening, and the intervention entails high cost and use of scarce intensive care resources, without superior benefit.

Medically assisted withdrawal from prescription opioids. Transmucosal BUP has long been used in clinical practice for chronic pain management despite limited evidence (Lazaridou et al., 2020; Rosen et al., 2014)and recent UK national guidance (NICE, 2021). For those dependent on prescription or over-the-counter opioids, there is little evidence to guide medication choice. Clinical practice includes use of BUP (NICE, 2021) or the use of the original prescribed drug in reduced doses (DoH, 2017) (IV). Extrapolating the evidence from managing patients prescribed opioids for pain, to withdrawal from OST or illicit opioids (or vice versa) may not be straightforward, though one review suggests that buprenorphine transfer strategies are effective for comorbid opioid dependence and pain (Spreen et al., 2022) (III). Those presenting for medically assisted withdrawal from iatrogenic opioid dependence may have different treatment goals and are often seen by different services from those with a history of non-prescribed opioid use.

Symptomatic Management of Withdrawal Symptoms. Adjunctive medications can be used to manage emergent withdrawal symptoms either during gradual tapering, more rapid withdrawal, abrupt discontinuation (and sometimes also during initiation). For detailed reviews, see Diaper et al. (2014); Sarkar and Mattoo (2012); Toce et al. (2018).

The best evidence is for α2 agonists (lofexidine, clonidine). There is no evidence for the superiority of clonidine over lofexidine in managing withdrawal symptoms (Gowing et al., 2016) (1a), although the hypotensive effects of clonidine are dose-limiting and require monitoring, such that lofexidine is the preferred option where available (ASAM, 2020) (IV). However, lofexidine has not been available in the UK since it was discontinued by the manufacturer in March 2018.

A range of adjunctive medications and psychosocial interventions is likely to be required for relief of opioid withdrawal symptoms. There is limited evidence base for these, but clinical consensus for targeting agitation, anxiety, gastrointestinal disturbance, muscle pains, sleep disruption and dehydration, which are well covered in other guidance (ASAM, 2020; DoH, 2017).

Baclofen has demonstrated some potential for reducing withdrawal symptoms in small studies (Ahmadi-Abhari et al., 2001;

Akhondzadeh et al., 2000; Assadi et al., 2003) (Ib), (Krystal et al., 1992) (II). Buspirone, a D_2 antagonist/5-HT_{1a} agonist, was shown to be equivalent to MTD in controlling opiate withdrawal symptoms in one small RCT (Buydens-Branchey et al., 2005) (Ib) and to improve sleep and opioid withdrawal during BUP taper in another (Bergeria et al., 2022) (Ib). A single RCT of quetiapine demonstrated reduced craving, anxiety, and insomnia (Pinkofsky et al., 2005) (Ib), an RCT of an orexin antagonist improved sleep and reduced opioid withdrawal during BUP taper (Huhn et al., 2022) and an open-label case series of ibogaine (Mash et al., 2018), which reportedly diminished opioid withdrawal symptoms and cravings. Negative trials included those of venlafaxine (Lin et al., 2008) (Ib), and gabapentin (Kheirabadi et al., 2008; Salehi et al., 2011) (Ib).

Switching between opioid substitution therapy. The option to switch medications should be available to support individual choice or changing clinical need. Buprenorphine is generally considered easier to withdraw from than methadone, due to its partial mu-agonist activity and less severe withdrawal profile (Breen et al., 2003a; Law et al., 1997; Meader, 2010) (IV; Ia; Ib). There is no high-quality systematic evidence on how to best achieve this, but several recent reviews of different methods (Ghosh et al., 2019; Lintzeris et al., 2022; Moe et al., 2021; Soyka, 2021).

The most recent (Lintzeris et al., 2022) (Ib) systematic review with narrative findings included 18 studies (2 RCTs, 17 observational; 8 outpatient, 7 inpatient) of $n = 382$ people receiving 30–100 mg methadone daily (mean 52 mg) with varied transfer protocols. Low incidence of precipitated withdrawal was reported, with some evidence that switching at lower doses of methadone was associated with a higher rate of successful transfer. However, it was not possible to directly compare different approaches, and shared decision-making should guide the best option. Approaches with some evidence and reasonable clinical consensus include:

Traditional induction. This involves tapering methadone to ⩽40 mg/day, stopping for 24–36 hours for emergence of moderate withdrawal (COWS ⩾8–12) before titration on to BUP, starting at low-dose (e.g. 2–4 mg) over 1–2 day (Breen et al., 2003; Bruneau et al., 2018; Gowing et al., 2014; NICE, 2019; SAMHSA, 2021) (Ib; IV). However, it carries a risk of precipitated withdrawal if induction is poorly timed and can entail weeks of discomfort while methadone is tapered to 30–40 mg. Supervised settings (e.g. inpatient) may improve outcomes when using this method.

Low-dose induction. Previously referred to as the Bernese method or microinduction, this involves gradual induction of BUP overlapping with full agonist use. Due to the higher affinity and longer receptor binding time, buprenorphine will accumulate at the receptor; thus, over time, an increasing amount of a full mu-agonist will be replaced by buprenorphine at the opioid receptor. Typically BUP is started at sub-therapeutic doses (e.g. 0.2–0.4 mg bd) while the individual continues full agonist use, slowly increasing the dose over 5–10 days to the therapeutic range, and only then rapidly discontinuing the full agonist (Hämmig et al., 2016) The most recent systematic narrative review of 19 case studies/series, with 26 protocols described highlighted the need for more robust studies (Moe et al., 2021) (III).

High-dose transfer: Transfer from higher doses of methadone to BUP is possible, usually following methadone taper and cessation, with adjunctive medication for symptomatic relief. It is typically undertaken in inpatient settings, where supportive treatment and need for adjunctive medication can be monitored (Foran et al., 2022; Glasper et al., 2005; Levin et al., 1997; Oretti, 2015) (III).

Bridging Interventions: Methods include the use of SROM to facilitate transition between moderate/high doses of methadone and buprenorphine, for example, (Costa et al., 2023; Foran et al., 2022), or transdermal patches (Baumgartner et al., 2022; Hess et al., 2011) and fentanyl patches (Azar et al., 2018). Some methods are reported to be suited for outpatient settings, for example, buprenorphine patch, also used in pain literature (Kornfeld and Reetz, 2015).

Switching from methadone to LAIB: This may be achieved directly from methadone at doses ⩽30 mg after the emergence of withdrawal symptoms, although there is little empirical evidence other than a case series of low-dose induction (Tay Wee Teck et al., 2021) (III). Alternatively, indirect transfers can occur via transmucosal preparations using the methods above, see (Lintzeris et al., 2024) (III).

Relapse prevention in opioid dependence

Once stabilised on OST and having discontinued illicit opioid use, continued OST could be considered relapse prevention treatment in that it prevents relapse to illicit opioid use. However, the focus of this section is on naltrexone, which is initiated following a taper from OST or in countries where OST is not available as a treatment option.

Naltrexone: Oral naltrexone is an opioid antagonist with evidence of limited effectiveness to help maintain abstinence following medically assisted withdrawal from opioids (Minozzi et al., 2011; NICE, 2007) (Ia).

No significant difference for primary outcomes was found when compared to placebo or psychotherapy alone. Retention and abstinence improved with oral naltrexone when people had some form of enforced adherence. Oral naltrexone is supported by Canadian clinical practice guidelines once abstinence is achieved (Bruneau et al., 2018) (IV).

Naltrexone implants and injectable sustained release naltrexone: Long-acting injectable naltrexone is available as a monthly injection, and naltrexone implant lasts for 6 months. Evidence suggests that both are effective in increasing retention in treatment relative to placebo, whereas oral naltrexone was not, although none were associated with a significant increase in opioid abstinence (Zangiabadian et al., 2022) (Ia). A randomised controlled trial ($n = 60$) comparing forms of naltrexone directly showed improved retention in treatment in those on long-acting injectable naltrexone (57.1%) over 24 weeks compared with oral naltrexone (28.1%) (Sullivan et al., 2018) (Ib). The American Society of Addiction Medicine supported the use of long-acting injectable naltrexone, but not oral naltrexone except under limited circumstances – and in these cases recommended thrice weekly dosing to aid concordance (ASAM, 2020) (IV).

Initiation of long-acting injectable naltrexone involves medically assisted withdrawal from opioids and initial challenge with a shorter-acting antagonist (oral naltrexone or naloxone), which can be a substantial barrier to initiation (Bisaga et al., 2018; Lee

et al., 2018) (Ib). A randomised controlled trial comparing a 'rapid' (5–7 day procedure) with 'standard' (12–14 day procedure) in a large well-designed study (60%–70% people with fentanyl dependence) concluded long-acting injectable naltrexone initiated 'rapidly' in an inpatient setting was non-inferior to the standard procedure, and took half the time (Shulman et al., 2024) (Ib).

Other than naltrexone, one small trial of baclofen (60 mg/day) in abstinent people with opioid dependence showed promise in promoting abstinence, reducing withdrawal and depressive symptoms (Assadi et al., 2003) (Ib). Nalmefene hydrochloride (an opioid antagonist derivative of naltrexone) is now available as an intranasal spray, and its longer pharmacodynamics make it a potentially superior alternative to naloxone in the reversal of high potency synthetic opioids; however, evidence is currently lacking as a relapse prevention medication (Green et al., 2024).

As with all pharmacological treatment of opioid dependence, there are concerns regarding the loss of tolerance to opioids during treatment, and the impact on overdose risk (Darke et al., 2019) (III). However, in a large open-label study in the USA of people randomised to extended-release naltrexone or 'usual care' after 78 weeks, there were no overdose events in the naltrexone group and seven in the usual care (Lee et al., 2016) (Ib).

Comorbidities and special populations.

Comorbidities: The efficacy of OST in improving mental health outcomes is well established (Moazen-Zadeh et al., 2021) (Ia) and should be the first step in managing comorbidity. Co-use of cannabinoids are associated with higher buprenorphine levels via liver enzyme inhibition, which may impact on doses required (Vierke et al., 2021)(III). For individuals focused on abstinence, long-acting injectable naltrexone could be considered, although evidence remains limited (Latif et al., 2018) (IIa).

In many people, depression remits within a month of initiating OST, so unless symptoms are severe watchful waiting is recommended, and antidepressants initiated if depressive symptoms worsen or persist (Pani et al., 2022) (Ia). Evidence suggests stabilisation on BMT improved depressive symptoms, in people with comorbid depression with no added benefit of adding escitalopram compared to placebo (Stein et al., 2010) (Ib), and that in those already established on MMT, depressive symptoms were improved by addition of a TCA but not SSRIs (Hassan et al., 2017; Torrens et al., 2005)(Ia), although these included older studies and the safety risks of combining TCA and methadone are no longer advised (Level S).

The management of schizophrenia and bipolar disorder in individuals with opioid dependence follows general psychiatric guidelines (Drake et al., 2019; Goodwin et al., 2016; Swartz et al., 2008). A recent large representative Swedish cohort study suggests that antipsychotic treatment significantly reduces the risk of psychiatric hospitalisation in people with schizophrenia and comorbid substance use disorder, and that clozapine, antipsychotic polytherapy and any long-acting injectable antipsychotics are most effective at reducing this risk (Lähteenvuo et al., 2022; Mortazavi et al., 2025) (I).

Trazodone (100 mg at bedtime) has demonstrated efficacy in treating insomnia among individuals receiving buprenorphine maintenance therapy (Goyal et al., 2023) (Ib).

Pregnancy: Opioid substitution treatment is important in pregnancy to prevent opioid withdrawal, which increases the risk of spontaneous miscarriage and stillbirth, and to enable the mother to engage with antenatal and other healthcare (Jones et al., 2008). Both MMT and BMT are efficacious in reducing opioid use, retention in treatment, reduced foetal death, decreased premature delivery (Minozzi et al., 2020) (Ia; Level A). There is good evidence that buprenorphine is safe in pregnancy (Ordean and Tubman-Broeren, 2023; Zedler et al., 2016)(III, Ia). There is some suggestion that BMT is associated with lower rates of Neonatal Abstinence Syndrome (NAS) than MMT. There is significant selection bias in the observational literature (Brogly et al., 2014) (IIa). There is low-quality evidence that BMT is associated with higher birth weight than MMT (Fischer et al., 2006; Jones et al., 2005). However, switching from MMT to BMT in pregnancy is not recommended because of the risk of withdrawal (DoH, 2017) (IV; Level D).

There are alterations in methadone pharmacokinetics in the third trimester: increased clearance, reduced half-life (from 24 hours to 8 hours) and enzyme induction (Shiu and Ensom, 2012) (IIb). Peaks and troughs may be associated with poor outcome – this may explain the wide variability in NAS observed at birth (McCarthy et al., 2015) (III). It is likely beneficial to split methadone doses in order to minimise foetal exposure to peaks and troughs (Level S).

The data regarding LAIBs in pregnancy is limited to case reports of people receiving weekly doses, with no adverse maternal or foetal/infant outcomes (Hubbell et al., 2024) (III). The results of the MOMS trial of weekly buvidal are awaited (Ramage et al., 2025; Winhusen et al., 2020) (III). New South Wales guidance recommends switching to transmucosal BUP unless there is a compelling reason not to (Lintzeris et al., 2024) (IV).

Medically assisted withdrawal has high risks relative to maintenance treatment; if an individual prefers to undertake MAW following thorough provision of information, this should be avoided in the first trimester, preferred in the second trimester, and undertaken with great caution in the third trimester (DoH, 2017) (Level S).

Recommendations for opioid withdrawal and relapse prevention

- Methadone and buprenorphine are effective in reducing the symptoms of opioid withdrawal (A) and tapering the dose of these for medically assisted withdrawal should be considered (A).
- Adjunctive medication may be helpful to support emergent withdrawal symptoms during tapering, including $\alpha 2$ adrenergic agonists (B).
- Switching to buprenorphine (transmucosal or injectable) can be considered for those suitable for MAW who are receiving methadone and struggling to taper to abstinence (D).
- All people with opioid dependence and co-occurring mental health disorders should be prescribed and continued on appropriate OST (A).
- People wishing to be abstinent from opioids should be offered naltrexone as a relapse prevention as opposed to MAW alone (S).
- Ultra-rapid detoxification is not recommended (A).

Key uncertainties and future work

- How do LAIBs compare with MMT and BMT with respect to relapse risk in the immediate period of early abstinence?
- What is the most effective strategy to switch from methadone to buprenorphine?
- What is the optimal low-dose induction strategy?
- Is there a role for other agents (e.g. baclofen and nalmefene) to support relapse prevention from opioid dependence either as adjunctives to OST or as monotherapy?

Nicotine

Nicotine is delivered through a variety of products classified into combustible tobacco, non-combustible tobacco, heated tobacco products and non-tobacco nicotine products that differ markedly in their dependence potential and health risks (RCP, 2024). Nicotine binds to nicotinic acetylcholine receptors (nAChRs) in the brain, particularly in areas involved in reward, mood, and cognition. Combustible tobacco delivers nicotine rapidly via pulmonary absorption, reaching the brain within seconds, which contributes significantly to its high dependence potential (Benowitz, 2010). Due to nicotine's short half-life (~2 hours), users dose frequently, leading to sustained exposure. While nicotine maintains dependence, most harms from smoking arise from the combustion of tobacco. Cigarette smoke contains thousands of toxicants, including carbon monoxide, volatile organic compounds, nitrosamines and polycyclic aromatic hydrocarbons, that contribute to cardiovascular and respiratory disease, and cancers. Non-combustible tobacco products (e.g. chewing tobacco, moist snuff, snus) are absorbed more slowly via the oral mucosa, and total systemic nicotine exposure can equal or exceed that of cigarettes. These products carry dependence risk and increase the risk of health harms, including oral cancer and cardiovascular disease, although snus, primarily used in Scandinavia, has a lower risk profile than smoked tobacco (Berrendero et al., 2010; SCENIHR, 2008). Heated tobacco products (HTPs) heat tobacco to create an aerosol without combustion. Manufacturers claim lower toxicant exposure, but current evidence is insufficient to confirm a significant harm reduction benefit (Tattan-Birch et al., 2022). Non-tobacco nicotine products include nicotine replacement therapy (NRT), oral nicotine pouches, and e-cigarettes (also known as vaping devices/vapes). NRT delivers nicotine slowly and at lower peak levels, with minimal risk, even with long-term use (NICE, 2025) (Ia). E-cigarettes and oral nicotine pouches deliver nicotine more efficiently than NRT, and depending on dose and duration of use, comparable levels to tobacco cigarettes (Mallock-Ohnesorg et al., 2024; McNeill et al., 2022).

The primary goal of treatment is permanent smoking cessation. An abstinent period of 6 months or longer is considered a marker of success (West et al., 2005). Misconceptions about nicotine's harm remain a barrier to treatment uptake (McNeill et al., 2022). Clinicians play a key role in correcting these beliefs.

Summary of key evidence

Withdrawal and maintenance. Withdrawal symptoms include irritability, low mood, and insomnia, which typically peak after 24–48 hours and subside over about 4 weeks, though the urge to smoke may persist for several months and even years for some people (Benowitz, 2010; Hughes, 2010). All cessation aids can support withdrawal management. Behavioural support from a trained advisor alongside pharmacotherapy improves quit success (NICE, 2025) (Ia).

Nicotine Replacement Therapy. All NRT products are effective when used correctly. A Cochrane review of 68 studies with 43,327 participants found high-certainty evidence that combination NRT (patch + fast-acting form) is more effective than single-form NRT (RR 1.27) (Theodoulou et al., 2023) (Ia). Higher-dose patches (e.g. 21 mg) may improve outcomes over lower doses. Preloading NRT before a quit date is associated with a 25% increase in success. Highly dependent smokers typically start with 21–25 mg patches for up to 12 weeks, stepping down gradually. Oral/nasal NRT should be used hourly. Correct technique (e.g. 'chew, rest, chew' for gum) and avoiding acidic drinks improve absorption. Side effects are usually mild and localised (e.g. skin irritation, mouth/throat discomfort). Nicotine overdose is rare but may cause nausea, headache, and vomiting (Mayer, 2014). Continued nicotine product use can help maintain abstinence, prevent relapse and is safe to use long-term (NICE, 2025) (Ia).

Varenicline and cytisine. Both are partial agonists at nicotinic acetylcholine receptors and are indicated for adults motivated to quit. They are contraindicated in pregnancy and breastfeeding. A Cochrane review of 75 trials (n = 45,049) found high-certainty evidence that varenicline is more effective than placebo (RR 2.32), bupropion (RR 1.36), and single-product NRT (RR 1.25), and likely similar to combination NRT (Livingstone-Banks et al., 2023) (Ia). Cytisine showed moderate-certainty evidence of greater effectiveness than placebo (RR 1.30) and NRT (RR 1.43).

Varenicline dosing (12 weeks): Days 1–3: 0.5 mg daily; Days 4–7: 0.5 mg twice daily; Day 8 onward 1 mg twice daily. A quit date should be set 1–2 weeks after starting. A flexible quit date (days 8–35) is also an option (Rennard et al., 2012). A second 12-week course may be considered to maintain abstinence (Tonstad et al., 2006).

Cytisine dosing (25 days): Days 1–3: 1.5 mg every 2 hours (max 6/day); Days 4–12: every 2.5 hours (max 5/day); Days 13–16: every 3 hours (max 4/day); Days 17–20: every 5 hours (max 3/day); Days 21–25: 1–2 tablets/day.

Some evidence suggests extending cytisine to 12 weeks may improve efficacy, potentially making it comparable to varenicline (Walker et al., 2021). Both medications can cause gastrointestinal symptoms and sleep disturbances. Nausea and abnormal dreams are reported less often with cytisine (Courtney et al., 2021).

Bupropion. Bupropion is a non-nicotine medication originally developed as an antidepressant. A Cochrane review of 44 trials (n = 13,979) found high-certainty evidence that bupropion increases quit rates compared to placebo (RR 1.64). It is likely similarly effective to single-form NRT but less effective than varenicline or combination NRT (Hajizadeh et al., 2023) (Ia). Dosing: (7–12 weeks): Days 1–3: 150 mg once daily; Day 4 onwards 150 mg twice daily. The quit date should be set 1–2 weeks after starting. Bupropion should be used with caution in people with a history of or high risk of seizures, eating disorders and bipolar disorder.

Side effects include insomnia and dry mouth. There is no evidence of increased neuropsychiatric events (Hajizadeh et al., 2023).

Harm reduction. E-cigarettes/vaping devices are devices that heat a liquid to produce an inhalable aerosol to deliver nicotine without tobacco combustion and are widely used in quit attempts. A Cochrane review of 90 studies (of which 27 were RCTs, n = 13,663) found high-certainty evidence that nicotine e-cigarettes improve quit rates versus NRT (RR 1.63) or non-nicotine e-cigarettes (RR 1.94) (Lindson et al., 2023) (Ia). Transitioning from smoking tobacco to vaping nicotine involves selecting a suitable nicotine strength, flavour, and propylene glycol/vegetable glycerine ratio to manage cravings and support cessation. Nicotine exposure is higher with stronger e-liquids, nicotine salts (vs freebase), tank or modular devices, and experienced rather than novice users due to more efficient puffing (McNeill et al., 2022). Flavour variety can help initiate switching, and non-tobacco flavours are associated with higher quit success (McNeill et al., 2022). In the UK, EU, and some other countries, e-liquids are capped at 20 mg/mL nicotine. While there are no formal switching guidelines, people who smoke <10 cigarettes/day may use 3–12 mg/mL; those who smoke 10–20/day, 12–18 mg/mL; people who smoke >20/day may benefit from higher frequency vaping or combining with a nicotine patch (Level S).

Side effects such as throat irritation, cough and nausea are common but usually mild and short-lived (Lindson et al., 2025). Based on multiple reviews, public health bodies agree that regulated e-cigarettes are significantly less harmful than smoking and effective for quitting in dependent smokers, with minimal risk to bystanders (COT, 2020; McNeill et al., 2022; RCP, 2024). Any smoking is harmful, so people who smoke and vape concurrently should be encouraged to stop smoking entirely (McNeill et al., 2022; NICE, 2025) (Ia). Those who have never smoked should avoid starting either. If someone chooses to start using nicotine, e-cigarettes are less harmful than smoking. Long-term effects remain uncertain, but biomarker studies suggest far lower risk than cigarettes (COT, 2020; McNeill et al., 2022; RCP, 2024).

A component network meta-analysis of 332 RCTs (n = 157,179) compared the effectiveness of pharmacotherapies and e-cigarettes. Nicotine e-cigarettes, varenicline and cytisine were associated with the greatest chances of quitting tobacco smoking at 6 months or longer, with no clear evidence of a difference in effectiveness between the three (Lindson et al., 2023) (Ia). The point estimate was slightly lower for combined NRT, but credibility intervals overlapped. In practice, this means that combination NRT is an effective option, especially when e-cigarettes or varenicline are not suitable or available.

Observational data from England (2006–2024; n = 25,094) showed that e-cigarettes (used by 40.2% of participants in 2024) were most strongly associated with quit success (OR 1.95), followed by varenicline (OR 1.80) and HTPs (OR 2.37) (Jackson et al., 2025) (I). However, findings for HTPs were less certain due to low usage (0.7% in 2024). Prescription NRT (used by 4.5% in 2024) was also effective (OR 1.33), while over-the-counter NRT (used by 17.3% in 2024) and nicotine pouches (used by 3.1% in 2024) were not associated with improved quit rates. Given their high uptake, e-cigarettes are likely supporting more people to quit smoking tobacco than other methods (Jackson et al., 2025) (I).

Smokeless tobacco cessation. There is less research to guide prescribing practice for people who use smokeless tobacco. A Cochrane review identified 43 studies (n = 23,346) (Livingstone-Banks et al., 2025). Studies of pharmacological interventions found varenicline increases quit rates by about 35% compared to placebo, based on moderate-certainty evidence. There is low-certainty evidence that NRT increases quit rates by around 18% compared to placebo or no medication. Evidence for bupropion is limited and does not show a consistent benefit over placebo.

E-cigarette cessation. People who use e-cigarettes to stop smoking may risk returning to tobacco if they stop vaping. People's history and severity of tobacco dependence, as well as their risk of relapse, should be assessed, and they should only be advised to stop vaping if they feel confident they will not relapse back to smoking (NICE, 2025) (Ia). Interventions for vaping cessation are beginning to emerge. A Cochrane review of nine RCTs found behavioural interventions designed to help people stop nicotine vaping may help more youth and young adults to successfully stop than no/minimal support, and low-certainty evidence that varenicline may also help people quit vaping (Butler et al., 2025). Findings on the effectiveness of combination NRT, cytisine, and nicotine/vaping behaviour reduction were inconclusive. More research is underway.

Drug Interactions. Smoking induces hepatic CYP IA2 enzymes due to exposure to polycyclic aromatic hydrocarbons in tobacco smoke (not nicotine). This is especially relevant for: clozapine, olanzapine, haloperidol, fluvoxamine, and duloxetine (Taylor et al., 2025). Monitor people closely during quit attempts or enforced temporary abstinence. Consider dose reductions for affected medications, guided by therapeutic drug monitoring and clinical response. NRT, e-cigarettes, and other non-combustible products do not induce CYPIA2.

Comorbidities and special populations. *Comorbidities*: Varenicline is also effective in populations with cardiovascular disease, COPD, and HIV. There is growing use of e-cigarettes among people with mental health and substance use disorders. Although more research is needed, current evidence suggests they are effective and acceptable in these groups (Lindson et al., 2025). A Cochrane review reported no significant increase in neuropsychiatric adverse events (e.g. anxiety, depression, aggression, psychosis, suicidal behaviour) of varenicline compared to placebo or nicotine patches, regardless of psychiatric history (Livingstone-Banks et al., 2023) (Ia). Varenicline has no known pharmacokinetic interactions with psychotropic medications.

Smoking is more common in people who use alcohol and other substances and is related to poor outcomes. For example, co-use of smoked tobacco and cannabis is linked to greater health risks than using either substance alone. Co-use is associated with higher levels of dependence, increased toxicant exposure, and poorer cessation outcomes for both tobacco and cannabis (Nguyen et al., 2024). Tobacco dependence among people with mental illness or a substance use disorder does not appear to exacerbate mental health symptoms, or negatively affect abstinence from alcohol and other drugs and there is evidence that stopping smoking is associated with improved mental health and substance use outcomes (Apollonio et al., 2016; Kock et al., 2023; Prochaska et al., 2004; Taylor et al., 2021) (Ia; I)

Children and adolescents: NRT can be used from age 12 to manage withdrawal and support quitting in young people. When compared to adults, NRT has not been shown to be as effective, and behavioural support appears to play a larger role (Beis et al., 2025) (Ia).

Pregnancy: NRT is the only licensed pharmacotherapy for use in pregnancy. While behavioural support is preferred, NRT may be offered if behavioural support alone is not sufficient. Intermittent forms (e.g. gum, lozenges) are preferred to minimise nicotine exposure, though patches may be used if needed. A Cochrane review found that NRT may increase smoking cessation rates in late pregnancy. However, this evidence is of low certainty (Claire et al., 2020) (Ia). An RCT of 1140 pregnant smokers randomised to receive either e-cigarettes or nicotine patches found that e-cigarettes may be more effective with similar safety profiles (Hajek et al., 2022) (Ib).

Recommendations

- E-cigarettes, combination NRT, varenicline, or cytisine should be offered as first-line treatments for nicotine dependence in adults. (A) These options are more effective than single-form NRT or bupropion (A).
- Behavioural support should be offered alongside pharmacotherapy. However, pharmacological treatment should still be offered if behavioural support is declined (A).
- Varenicline should not be withheld due to outdated safety concerns. Evidence confirms no increased neuropsychiatric risk, including in people with mental illness. (A).

Key uncertainties and future work

- Cytisine is under-researched in priority groups (e.g. people with mental illness or substance use disorders); studies should evaluate its safety and efficacy in these populations.
- The optimal use of high-dose or combination nicotine products for people with severe dependence requires further investigation.
- More research is needed on the implementation and long-term use of effective treatments in routine clinical practice, including settings where smoking prevalence is high.
- Research is needed on the best ways to manage nicotine withdrawal in settings where people must temporarily abstain from smoking but do not intend to quit, such as hospitals.
- The role of nicotine pouches and HTP in smoking cessation is unclear; independent RCTs are needed to assess their effectiveness and safety.
- There are no established clinical guidelines for treating tobacco-cannabis co-use; dedicated interventions should be developed and evaluated.

Cannabis and synthetic cannabinoids

Cannabis

The psychoactive effects of cannabis are mediated by delta-9-tetrahydrocannabinol (THC), a partial agonist at the cannabinoid type 1 (CB_1) and type 2 (CB_2) receptors (Felder et al., 1992; Howlett et al., 2002; Shahbazi et al., 2020). In adults, comorbid disorders account for the majority of cannabis-related disability (Weye et al., 2021); however, in non-clinical populations, cannabis use is associated with psychotic-like experiences and schizotypal personality, as well as earlier onset and development of psychosis (Groening et al., 2024) (Ia). Cannabis dependence is associated with dependence on other substances, interpersonal difficulties, cardiovascular and respiratory disease, cyclical vomiting syndromes, road traffic accidents, cognitive impairment, and reduced motivation (COT, 2020; McNeill et al., 2022; RCP, 2024). Reduction (and abstinence) in regular cannabis use is associated with improved cognitive and functional outcomes (Krzyzanowski and Purdon, 2020; McClure et al., 2024). In controlled abstinence studies, up to half of treatment-seeking cannabis users report severe withdrawal symptoms (Budney et al., 1999). Symptoms of cannabis withdrawal include nightmares, strange dreams and insomnia, irritability, anxiety, low mood, restlessness and reduced appetite (Allsop et al., 2011). Withdrawal symptoms typically begin 1–3 days after cessation, peak between days 2–6, and last for 4–14 days (Budney et al., 2003). Cannabis withdrawal syndrome has been identified as a possible trigger for psychosis onset and has been linked with clinical deterioration in psychiatric inpatients (Chesney et al., 2025; Malik et al., 2025)(III).

Summary of key evidence

Managing acute cannabis withdrawal. Clinical guidelines suggest the use of benzodiazepines, *z*-drugs and promethazine for insomnia, benzodiazepines for restlessness, anxiety and irritability, paracetamol and NSAIDS for pain, for example, headaches, promethazine and metoclopramide for nausea, hyoscine for stomach pain, benzodiazepines for tremor, and antipsychotics for psychotic symptoms (Connor et al., 2022; NSW Ministry of Health, 2022) (IV; Level D). Studies have shown some benefit for zolpidem (Herrmann et al., 2016; Vandrey et al., 2011) (IIb), mirtazapine (Haney et al., 2010) (IIb) and quetiapine (Cooper et al., 2013) (IIb) for sleep disturbance (Level C), limited impact of baclofen for craving during active cannabis use but no impact on relapse (Haney et al., 2010) (IIb), and no effect for quetiapine on withdrawal and relapse (Cooper et al., 2013) (IIb). A small trial of the α2a-adrenergic agonist guanfacine had promising effects on sleep and irritability (Haney et al., 2019) (IIb).

Several small studies provided preliminary evidence that cannabinoid receptor partial agonists such as THC/dronabinol and nabilone can reduce withdrawal symptoms in people who regularly use cannabis (Budney et al., 2007; Haney et al., 2004, 2008, 2013; Herrmann et al., 2016; Vandrey et al., 2013) (Ib/IIa), however, these were primarily human laboratory studies undertaken in non-treatment-seeking populations. An updated Cochrane review (Spiga et al., 2025) which included only treatment seeking populations found that abstinence at the end of treatment was no more likely with THC preparations (RR1.04, 95% CI 0.71 to 1.52; 4 studies 290 participants; moderate-certainty evidence), and may be no more likely with cannabidiol (RR 2.23, 95% CI 0.54 to 9.32; 1 study, 68 participants; low-certainty evidence).

Nicotine withdrawal symptoms are associated with greater cannabis withdrawal severity (Yeap et al., 2023) in people with co-dependence. Preliminary trial evidence suggests that nicotine replacement therapy may increase abstinence from tobacco and

consequently cannabis in individuals who use tobacco with cannabis, in particular as part of a psychosocial intervention (Ramage et al., 2025) (Ib-III). In people who use cannabis but not tobacco, nicotine should not be provided as it increases nausea (Gilbert et al., 2020) (Ib; Level A). An experimental study of varenicline in people with tobacco and cannabis dependence (Herrmann et al., 2019) (IIa)found that the varenicline group was more likely (46% vs 24%) than the placebo group to achieve cotinine-verified tobacco abstinence.

Cannabis maintenance treatment. Four RCTs have investigated cannabinoid receptor partial agonists as cannabis-substitution therapy (Levin et al., 2011, 2016; Lintzeris et al., 2019; Trigo et al., 2018) (Ib), with mixed results on withdrawal, retention and abstinence. These studies were included in the updated Cochrane review (Spiga et al., 2025) (Ia), which concluded that given the limited evidence of efficacy, pharmacotherapies should still be considered experimental.

Alternative pharmacological approaches to reducing use, promoting abstinence and reducing relapse. Clinical trials of N-acetylcysteine, buspirone, gabapentin, and a fatty acid amide hydrolase have not consistently demonstrated benefits over placebo (D'Souza et al., 2019; Gray et al., 2012, 2025; Mason, 2017; Mason et al., 2012; McRae-Clark et al., 2009) (Ib), (Spiga et al., 2025) (Ia).

A pilot RCT of varenicline (for 6 weeks compared to placebo) in 72 people with a cannabis dependence found numerically greater rates of self-reported abstinence at week 6 with varenicline compared to placebo (McRae-Clark et al., 2021)(Ib) with results from a larger RCT forthcoming (McRae-Clark, 2024). An RCT of cannabidiol (versus placebo) on top of a psychosocial intervention in 82 people with dependence found benefits of daily cannabidiol compared to placebo in reducing cannabis use (Freeman, Hindocha, et al., 2020) (Ib). A larger trial is underway (Bhardwaj et al., 2024).

Harm reduction. The average potency of cannabis (i.e. its concentration of THC) has increased considerably in recent years (Freeman, Craft, et al., 2020). Higher potency cannabis is associated with an increased risk of psychosis and cannabis use disorder compared to lower potency use (Petrilli et al., 2022); therefore, use of lower potency cannabis can be recommended for minimising harm, as well as using cannabis less frequently, and less cannabis overall (IV; Level D). There is interest in the use of cannabis products containing higher levels of cannabidiol (CBD) to reduce harms, but laboratory studies have consistently failed to support this (Englund et al., 2017; Lawn et al., 2023; Morgan et al., 2018) (IIa). For those with tobacco and cannabis co-dependence who are unable or unwilling to reduce their cannabis use, a reduction or cessation of tobacco co-use should be encouraged, such as using a cannabis only dry-herb vaporiser (Walsh et al., 2020), which may also improve respiratory health (IV; Level S). Care should be taken to minimise the risk of increased THC exposure when changing the method of use.

Special populations

Adolescents. Most RCTs for cannabis dependence have included adults rather than adolescents, and it is unclear whether adolescents might respond differently to pharmacotherapies when compared to adults. RCTs in other age groups (e.g. older adults) are lacking.

Main psychiatric comorbidities. There is insufficient evidence to support the use of specific pharmacotherapies for the treatment of cannabis dependence in comorbid psychiatric populations. However, there is an evolving evidence base regarding clinically significant drug interactions and CYP450 enzyme inhibition by cannabinoids of which the prescriber should be aware (Lopera et al., 2022; Nachnani et al., 2024; Nasrin et al., 2021) RCTs of antidepressant medications for individuals with depression and co-morbid cannabis dependence have shown no benefit for mood symptoms or cannabis use outcomes (Cornelius et al., 2010; Levin et al., 2013) (Ib). There are no clear differences in the efficacy of antipsychotics for people with schizophrenia and co-morbid cannabis dependence (Wilson and Bhattacharyya, 2016) (Ib). However, ongoing cannabis use should not exclude people with schizophrenia from receiving clozapine (Rafizadeh et al., 2023) (IIa; Level C). A Swedish nationwide cohort study on first episode psychosis and cannabis dependence found that clozapine and long-acting injectables of risperidone, aripiprazole and paliperidone were associated with the lowest risk of relapse, and clozapine was associated with a very large reduction in risk of hospitalisation (Denissoff et al., 2024) (I).

Recommendations

- There is evidence to support the use of cannabinoid receptor partial agonists to palliate withdrawal symptoms in people admitted to hospital for other reasons; however, there is insufficient evidence to support the use of such compounds to change the course of a cannabis dependence (A).
- Where cannabis is co-used with tobacco, reduction or cessation of tobacco use should be encouraged, with preliminary evidence for varenicline (B).

Key uncertainties and future work

- What is the optimal dose, dosing frequency, treatment duration and person characteristics (e.g. thresholds for severity of symptoms) for the use of cannabinoid receptor partial agonists for managing cannabis withdrawal syndrome?
- In people who are reducing their cannabis use, what are the most effective adjunctive medications to manage specific psychological and somatic symptoms of cannabis withdrawal, such as insomnia?
- Which approaches are most helpful for those who co-use cannabis with tobacco?
- Are there effective relapse prevention pharmacological interventions for cannabis dependence

Synthetic cannabinoids

Many different synthetic cannabinoids have been identified, and street drug preparations (often referred to as 'Spice') may include one or more of these. Typically, synthetic cannabinoids are added to plant material for smoking, infused on paper (Craft et al., 2023) or dissolved in liquid vaping products (Cozier et al., 2024). Synthetic cannabinoids partially mimic the effects of THC but typically act as full high-affinity agonists at CB_1 and CB_2

receptors (Cordeiro et al., 2018; Heal et al., 2024). This increased potency is associated with more severe clinical effects, including dependence, agitation, psychosis, seizures, reduced conscious levels, bradycardia, tachycardia, hypertension and rhabdomyolysis (Prete et al., 2025; Tait et al., 2016).

Summary of evidence. Synthetic cannabinoids produce a more severe withdrawal syndrome than cannabis (Craft et al., 2022) and may require inpatient detoxification (Macfarlane and Christie, 2015) (III). Evidence from retrospective healthcare records and case reports supports the use of benzodiazepines to manage withdrawal symptoms, as well as antipsychotics for the management of acute psychosis and agitation (Cooper, 2016; Sharma and Weinstein, 2025) (III; Level C). Prescribers should be aware that synthetic cannabinoids are associated with cardiac arrhythmia (Ozturk et al., 2019). There is no evidence-based pharmacotherapy for maintenance or relapse prevention for synthetic cannabinoids.

Key uncertainties and future work

- What is the optimal pharmacotherapy, dose and dosing frequency for the use of benzodiazepines and antipsychotics for managing synthetic cannabinoid intoxication and withdrawal?
- Is there a role for drugs that target the CB_1 receptor in the treatment of synthetic cannabinoid intoxication and withdrawal?

Stimulant drugs

This section focuses on cocaine and amphetamines (methamphetamine and amphetamine) as the stimulant drugs most often associated with dependence. Both cocaine and amphetamines exert their psychostimulant effects through distinct but overlapping neuropharmacological mechanisms. Cocaine acts primarily as a monoamine reuptake inhibitor, binding with high affinity to the dopamine transporter (DAT), norepinephrine transporter (NET) and serotonin transporter (SERT) preventing the reuptake of these neurotransmitters into presynaptic neurons (Heikkila et al., 1975a, 1975b; Nielsen et al., 2024). Amphetamines additionally facilitate presynaptic monoamine (primarily dopamine and noradrenaline) release (Turton and Lingford-Hughes, 2024). The major harms associated with stimulants include significantly elevated mortality, increased incidence of HIV and hepatitis C infection, poor mental health (suicidality, psychosis, depression, risk of violence) and increased cardiovascular events (Farrell et al., 2019). Both cocaine and amphetamines are linked to binge patterns of use, which intensify the risk of acute cardiovascular events, seizures, and sudden death, particularly when polysubstance use is present (Roberts et al., 2025). High dosage intoxication can be associated with psychiatric complications, including anxiety, panic and paranoia, while withdrawal from stimulants can bring about a profound pseudo-depressive state which can be accompanied by an increased risk of suicidal ideation (McGregor et al., 2005; Schwartz et al., 2022). Chronic use of both cocaine and amphetamines may be associated with longer-term neurocognitive and neuropsychiatric disturbances that stem from lasting alterations in the regulation of dopaminergic, noradrenergic and serotonergic systems, neurotoxicity, and neuroinflammatory processes (McKetin et al., 2019; Paulus and Stewart, 2020). Polydrug use, common among people who use stimulants, further compounds the risks, increasing the likelihood of overdose and complicating treatment (Bobashev and Warren, 2022; Schepis et al., 2025). Stimulant use is increasingly being implicated in drug-related deaths (Ciccarone, 2021; Darke et al., 2023; ONS, 2024).

Summary of evidence

There are currently no approved pharmacotherapies for stimulant use (including for cocaine or for amphetamines), and the evidence supporting pharmacological treatment is weak. There is growing evidence that commonly used pharmacotherapy approaches (e.g. the use of prescription stimulants, the use of antidepressant medications) may have either minimal or no benefit. There are substantial knowledge gaps around the utility of novel approaches to manage stimulant use. There has been no substantial progress to further the very limited body of research on pharmacological treatments to manage the withdrawal syndrome from stimulant use. Most trials in this area are small and the evidence remains largely low or very low quality. Clinicians should be aware that the evidence may change with larger more robust trials.

Stimulant withdrawal. A systematic review of nine RCTs found insufficient evidence to support the use of mirtazapine (Ia), modafinil (Ib), or amantadine (Ib) for the treatment of methamphetamine withdrawal. Studies were small and of low quality (Acheson et al., 2023) (Ia). There are no systematic reviews or meta-analyses of pharmacological treatments for cocaine withdrawal. A review of 9 RCTs of cocaine dependence maintenance therapies did not find compelling evidence for reducing withdrawal symptoms (mirtazapine, bupropion, naltrexone, topiramate) (Li and Shoptaw, 2023) (Ib).

Cocaine dependence: preventing relapse, maintaining abstinence. *Prescription stimulants and dopamine agonists*: A meta-analysis of 26 RCTs (2,366 participants) of prescription psychostimulant drugs (bupropion, dexamphetamine, lisdexamfetamine, methylphenidate, mazindol, methamphetamine, mixed amphetamine salts and selegiline) found they did not reduce cocaine use, or improve retention in treatment, but may increase sustained cocaine abstinence (Castells et al., 2016) (Ia).

Anticonvulsants: Two meta-analyses in up to 20 RCTs have not found any effect of anticonvulsants on cocaine use outcomes, including cocaine use or negative urines, or craving or retention (Bentzley et al., 2021; Minozzi et al., 2015) (Ia).

Disulfiram: A meta-analysis of 13 RCTs found low quality of evidence that disulfiram may increase point abstinence (3 RCTs, $n = 142$; Ia) but had no effect on frequency or amount of use, continued abstinence or dropout (Traccis et al., 2024) (Ia).

Antidepressants: In a meta-analysis of 11 RCTs, antidepressants did not increase the likelihood of negative cocaine urines (Bentzley et al., 2021) (Ia). A large retrospective cohort study investigated the effectiveness of 13 antidepressants on cocaine use disorder remission using electronic health data in 161,544 individuals with cocaine use disorder and depression. Among these antidepressants, only bupropion use was associated with higher rates of remission from cocaine use disorder compared to propensity-score matched individuals prescribed other antidepressants, providing preliminary evidence of efficacy for this indication (Gao et al., 2023) (I).

Antipsychotics: In a meta-analysis of 12 RCTs (Álvarez et al., 2013) (Ia), antipsychotics did not significantly reduce cocaine use, or improve retention in treatment. Another meta-analysis of 9 RCTs also found that antipsychotics did not increase the likelihood of negative urines (Bentzley et al., 2021) (Ia).

Anticholinergics: A systematic review of 13 studies of four anticholinergics (varenicline, biperiden, galantamine, citicholine) did not find consistent evidence of benefit over placebo on cocaine use (Salloum et al., 2024) (Ia).

Amphetamine and methamphetamine dependence: preventing relapse, maintaining abstinence. *Prescription stimulants.* A meta-analysis of 10 trials (7 for methylphenidate and 3 for dexamphetamine) found that prescription stimulants reduced craving but did not decrease the use of amphetamines or improve retention in treatment (Sharafi et al., 2024) (Ia). Doses of methylphenidate ranged from 54 to 180 mg/day (extended-release formulations) and 60–110 mg of dexamphetamine. One RCT found high-dose long-acting amphetamine, lisdexamfetamine, produced a very small decrease in days of methamphetamine use (mean difference 2.2 days, 95% CI −0.5 to 5.0 days) at 13 weeks after treatment compared to placebo, but did not increase abstinence (Ezard et al., 2024) (Ib).

Modafinil: A meta-analysis of five RCTs found that modafinil did not significantly reduce amphetamine-type stimulant (ATS) use, craving for ATS, or improve retention in treatment (Elkrief et al., 2024) (Ia).

Naltrexone. A meta-analysis of five RCTs found low-quality evidence that naltrexone had no benefit over placebo for ATS use, study retention, and craving (Bastien et al., 2024) (Ia). However, one large RCT found that long-acting injectable naltrexone combined with extended-release bupropion significantly reduced methamphetamine use compared to placebo (Trivedi et al., 2021) (Ib).

Antidepressants. *Bupropion*: A meta-analysis of eight RCTs found that bupropion may produce a small reduction in ATS use and craving after 12 weeks of treatment (Bakouni et al., 2023) (Ia).

Mirtazapine: A meta-analysis (Naji et al., 2022) of two RCTs (Coffin et al., 2020; Colfax et al., 2011) (Ia), found that mirtazapine may result in a small reduction in methamphetamine use. The larger of the two trials found a significant reduction in depressive symptoms (Coffin et al., 2020) (Ib). Neither trial included people with clinical depression.

Other antidepressants: Individual trials of fluoxetine (Batki 2000 & 2001-unpublished, cited (Srisurapanont et al., 2001) (Ib), imipramine (Galloway et al., 1996) (Ib), desipramine (Tennant Jr. et al., 1986) (IIa), and sertraline (Shoptaw et al., 2006) (Ib) have not found reductions in the use of amphetamines. Fluoxetine may decrease craving in the short term, and imipramine may increase adherence to treatment in the medium term (Srisurapanont et al., 2021) (Ib). Sertraline may increase adverse events and reduce retention (Shoptaw et al., 2006) (Ib).

Cholinergic agents: Current limited evidence does not support the use of cholinergic agents to treat dependence on amphetamines. A single RCT of citicoline (2000 mg/day × 12 weeks) failed to detect any significant reduction in methamphetamine use in people with unipolar depression (Brown and Gabrielson, 2012) (Ib). A single trial of varenicline (1 mg/day for 9 weeks) failed to detect any changes in methamphetamine use (Briones et al., 2018) (Ib).

Buprenorphine: Three small-scale clinical trials conducted in Iran suggest buprenorphine may be associated with a reduction in craving for methamphetamine (Ahmadi and Razeghian Jahromi, 2017; Salehi et al., 2015) (Ib). One of these trials also reported a reduction in methamphetamine use (Salehi et al., 2015) (Ib).

Other agents: Single trials of other agents have not provided compelling evidence of benefit in reducing methamphetamine use. These include the glutaminergic agents, ifenprodil (Kotajima-Murakami et al., 2022) (Ib) and N-acetylcysteine (McKetin et al., 2021) (Ib), oxytocin (Stauffer et al., 2020) (Ib), the neuroprotective agent ibudilast (Heinzerling et al., 2020) (Ib), the antipsychotic aripiprazole (Coffin et al., 2013) (Ib), the anticonvulsant topiramate (Elkashef et al., 2012) (Ib), the corticotropin-releasing factor antagonist pexacerfont (Morabbi et al., 2018) (Ib), amlodipine 10 and 5 mg/day (Srisurapanont et al., 2001) (Ib), and the combination product PROMETA™ (a combination of flumazenil, gabapentin and hydroxyzine) (Ling et al., 2012) (Ib). A single Iranian trial of the glutaminergic agent riluzole reported reductions in methamphetamine use, but findings need replication in a broader sample (Farahzadi et al., 2019) (Ib).

Special populations

Methamphetamine-related psychosis: Antipsychotic agents can be used to treat symptoms of methamphetamine-associated psychosis. A meta-analysis of six trials of antipsychotics (Srisurapanont et al., 2021) (Ia) found low-quality evidence that olanzapine or quetiapine may be a preferred antipsychotic for methamphetamine-associated psychosis.

Co-occurring opioid dependence and amphetamine-type stimulant use: Two small-scale trials of the selective norepinephrine re-uptake inhibitor atomoxetine (40 mg/day) (Rabiey et al., 2019) (Ib) and 80 mg/day (Schottenfeld et al., 2018) (Ib) found preliminary evidence of reductions in methamphetamine use compared to placebo amongst people on opioid agonist therapy. Schottenfeld et al (2018) also found benefits on depression symptoms (Ib).

Co-occurring opioid dependence and cocaine use disorder: A meta-analysis of 55 studies (5139 participants) of people with co-occurring opioid and cocaine dependence found that buprenorphine or methadone was associated with a reduction in cocaine use (Bentzley et al., 2021) (Ia).

Co-occurring ADHD and amphetamine-type stimulant use: Two RCTs have trialled methylphenidate for methamphetamine use in adults diagnosed with ADHD. The first was a pilot study which failed to find any benefit of methylphenidate (72 mg/day) on either ADHD symptoms or amphetamine use (Konstenius et al., 2010) .The second was a larger trial that used a higher dose of methylphenidate (180 mg/day) over 24 weeks and found both improvements in ADHD symptoms and reductions in amphetamine use relative to placebo (Konstenius et al., 2014) (Ib).

Recommendations

Amphetamine

- Current evidence does not support the use of prescription stimulants for the treatment of dependence on amphetamine. This evidence remains low quality (A).

- There is preliminary evidence to support the use of depot naltrexone and extended-release buproprion in combination for treatment of dependence on methamphetamine (A/B).
- For adults with ADHD, prescription stimulants may both improve ADHD symptoms and reduce amphetamine use (A/B).
- There is preliminary evidence to support the use of the norepinephrine re-uptake inhibitor atomoxetine to reduce methamphetamine use among people receiving opioid agonist therapy (A/B).
- Antipsychotic agents can be used to treat symptoms of methamphetamine-associated psychosis (A/B).

Cocaine

- There is no conclusive evidence to support prescription stimulants, dopamine agonists, anticonvulsants or antipsychotics for the treatment of cocaine use disorder (A).
- Overall, there is no conclusive evidence to support antidepressants for cocaine use disorder (A). However, there is limited preliminary evidence for bupropion for some cocaine use outcomes, and clinicians should remain alert to a growing evidence base in this area (B).

Key uncertainties

- What is the best way to pharmacologically manage symptoms of stimulant withdrawal?
- Is there a potential role of novel pharmacological strategies that are yet to be evaluated (e.g. vaccines, GLP-1 receptor agonists, psychedelics, neurosteroids, glutamate agents) in managing stimulant use disorder?
- What are the likely risks and benefits of using prescription stimulants to manage ADHD amongst people with stimulant dependence in clinical practice?

Dissociative drugs

Dissociative drugs and their analogues, for example, ketamine, phencyclidine, dextromethorphan and methoxphenidine, are a class of psychedelic compounds which can cause individuals to feel separated or detached from their body or physical environment. Dissociatives have been widely used in human and veterinary medicine for over half a century, with substantial recent expansion in their therapeutic use. There is emerging evidence for the use of some dissociatives in treating certain mental and behavioural disorders (e.g. ketamine for severe treatment-resistant depression); however, despite recent expansions in research for therapeutic indications, there remains an extremely limited evidence base for the treatment of dependence on dissociative compounds. This is despite international reports of increasing rates of both non-medical use and dependence on these compounds (Roberts et al., 2024).

Summary of evidence

Managing dependence and withdrawal. A systematic review (Roberts et al., 2024) (III) summarising results of a case series (Chen et al., 2020) (III) and six case reports (Błachut et al., 2009; Critchlow, 2006; Lim, 2003; Pal et al., 2002; Roxas et al., 2021) (III) involving110 people with ketamine dependence, found improvements across a range of withdrawal symptoms with differing oral benzodiazepine regimens, as both monotherapy and as adjuncts, with doses typically ⩽20 mg/day diazepam equivalents.

Three RCTs (Giannini et al., 1986, 1993; Tennant Jr. et al., 1986)(Ib) and two controlled trials (Giannini and Loiselle, 1987; Tennant et al., 1981)(IIa) involving 86 people with phencyclidine dependence, did not report improvements across a range of withdrawal symptoms with either oral desipramine (50-200mg/day) or buspirone (90 mg/day).

One case report (Champeau et al., 2017) (III) of a single person with methoxphenidine dependence reported improvements in withdrawal symptoms with 20 mg/day of intravenous diazepam.

Dextromethorphan, is a semi-synthetic morphine derivative, widely available in many over-the-counter cough and cold preparations. Two case reports (Akerman et al., 2010; Desai et al., 2006) (III) each of a person with dextromethorphan dependence, found improvements in withdrawal symptoms with unspecified doses of oral chlordiazepoxide and clonidine.

Management of relapse prevention/craving. A systematic review (Roberts et al., 2024) (III) summarising results from case reports (Bhad et al., 2016; Garg et al., 2014; Huang et al., 2016; Pérez Gómez et al., 2015Avra et al., 2024; Lee et al., 2024) (III), of seven people with ketamine dependence, found improvements in craving and maintenance of abstinence with a range of medications including: oral naltrexone (50mg/day), lamotrigine (⩽100mg/day), gabapentin (⩽ 300mg/day) combined with topiramate (⩽100mg/day), and i.m. paliperidone (⩽150mg) combined with unspecified doses of oral bupropion.

Case reports (Ledwos et al., 2023; Miller, 2005; Ramaswamy, 2015) (III) of three people with dextromethorphan dependence, found improvements in craving and maintenance of abstinence with oral topiramate (⩽50 mg/day), oral naltrexone (⩽100 mg/day) alone and in combination with gabapentin (⩽900 mg/day).

Main psychiatric comorbidities. A single case report (Zuccoli et al., 2014) (III) of a person with ketamine-induced psychosis found improvement in psychotic symptoms with oral paliperidone (6 mg per day).

Case reports (Berlant, 1985; Dinwiddie et al., 1988; Rosen et al., 1984) (III) of six people with psychosis occurring in the context of phencyclidine dependence, published prior to the availability of second-generation antipsychotics, found improvements across a range of psychotic symptoms with differing oral first-generation antipsychotic regimens.

Case reports (Caracci et al., 1983) (III) of three people with depression occurring in the context of phencyclidine dependence, published prior to the availability of second-generation antidepressants, found improvements across a range of depressive symptoms with oral imipramine (⩽100mg/day).

Recommendations

- The available experimental evidence does not support the use of desipramine or buspirone in the management of phencyclidine withdrawal (B).

Key uncertainties and future work

- What is the best way to pharmacologically manage symptoms of withdrawal (e.g. using benzodiazepines), treat cravings and prevent relapse (e.g. with naltrexone, lamotrigine, paliperidone, bupropion, topiramate and/or gabapentin), in people dependent on dissociative compounds and their analogues?
- What is the most effective pharmacological strategy for the treatment of dissociative-related psychosis and depression?

Summary

Substance dependence remains a major contributor to global morbidity and mortality, with profound impacts on individuals, families, and society. Despite advances in understanding of its diverse neurobiological and psychosocial underpinnings, treatment provision continues to lag behind other chronic conditions of similar severity. These guidelines aim to bridge this gap while recognising the inherent complexities of comorbidity, polysubstance use, and diverse patient needs. Pharmacotherapy is a critical component of treatment, but it is most effective when integrated within a comprehensive psychosocial framework. Across substances, principles of care include shared decision-making, clear goal setting, and ongoing monitoring to balance benefits and risks.

Special populations – including adolescents, older adults, pregnant individuals, and those with complex comorbidities – need tailored approaches, often requiring the clinician to extrapolate from the available data. Future research should prioritise pragmatic trials in real-world settings, explore combination pharmacotherapies, and address gender-specific and age-related considerations.

Ultimately, these guidelines emphasise that substance dependence is a treatable condition. By implementing evidence-based recommendations and addressing identified uncertainties, we can improve access, engagement, and outcomes for people with substance dependence, reducing stigma and advancing parity with other chronic health conditions.

Acknowledgements

Many thanks to: members of the British Association for Psychopharmacology Expert by Experience Advisory Panel for their collective thoughtful consideration and amendments of an earlier draft of the lay summary. Professor Owen Bowden Jones for his contribution to the consensus meeting, Professor David Baldwin for his review and feedback on the final draft of this guideline

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Ethical considerations

There are no human participants in this article and informed consent is not required.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The following authors acknowledge funding sources for their research time: JMAS is supported by the National Institute for Health and Care Research (NIHR Southampton Biomedical Research Centre (NIHR203319); NJK by the National Institute for Health and Care Research (NIHR) Maudsley Biomedical Research Centre (BRC); SJK has received Wellcome Trust and NIHR research funding via the Mental Health Implementation Network, Manchester Academic Health Science Centre and Greater Manchester Applied Research Collaboration, and the Efficacy and Mechanism Evaluation programme; SA is supported by Australian National Health and Medical Research Council (NHMRC) Investigator Grant (GNT2008193); TPF is funded by a UKRI Future Leaders Fellowship (MR/Y017560/1); LL is a NIH federal employee and is supported by the NIH Intramural Research Program (NIDA/NIAAA). The contributions of the NIH authors were made as part of their official duties as NIH federal employees, follow agency policy requirements, and are considered Works of the United States Government. However, the findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services; ER is funded by an NIHR Advanced Fellowship (NIHR302215).

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: NJK collaborates with Camurus, maker of Buvidal, on an NIHR-funded study: BUILD2depot (NIHR206657). SJK Collaborates with Eli Lilly and Company related to substance use disorder interventions. AB Received consulting fees from Lilly and research support from Alkermes. LL receives an honorarium from the UK Medical Council on Alcohol as Editor-in-Chief for Alcohol and Alcoholism and he also receives royalties from Routledge as co-editor of a textbook. ALH has received Honoraria paid into her Institutional funds for speaking and Chairing engagements from Lundbeck, Lundbeck Institute UK, Janssen-Cilag, Pfizer, Servier; received research grants or support from Lundbeck, GSK, Indivior; unrestricted funds support from Alcarelle for a PhD; consulted by Silence, NET Device Corps, Sanofi-Aventis, Astra Zeneca, Indivior, Neurocentrx and also consulted by but received no monies from Britannia Pharmaceuticals, GLG, Opiant, Lightlake, Dobrin, Nodthera, Libero and Eli Lilly. She is Chair of Addiction Healthcare Goals, Office for Life Sciences. Prof Lingford-hughes is Associate editor of Addiction. LMP has provided consultancy services to Indivior Plc. DR is a trustee of Action on Smoking & Health. JS has received funding from Gilead Sciences, Inc. She is in receipt of workshop funding but not salary costs from Council for British Research in the Levant. She receives payment for teaching on substance use from the following: College of Mental Health Pharmacy, University of Bradford, Aston University, University of Bath. She is an honorary visiting adjunct professor at the University of Jordan, for which she receives no payment but is supported to attend an associated symposium.

The remaining authors declared no personal interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

Data sharing not applicable to the article as no datasets were generated or analysed during the current study.

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