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Pharmacological strategies for detoxification

Alison M. Diaper, Fergus D. Law & Jan K. Melichar

Psychopharmacology Unit, University of Bristol, Bristol, UK

Correspondence
Dr Alison Diaper, Psychopharmacology Unit, Academic Unit of Psychiatry, Oakfield House, Oakfield Grove, Bristol, BS8 2BN, UK.
Tel.: +011 7331 0149
Fax: +011 7331 4026
E-mail. alison.diaper@bristol.ac.uk

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Detoxification refers to the safe discontinuation from a substance of dependence and is distinct from relapse prevention. Detoxification usually takes between a few days and a few weeks to complete, depending on the substance being misused, the severity of dependence and the support available to the user. Psychosocial therapies alongside pharmacological treatments are essential to improve outcome. The dependencies considered in this overview are detoxification from opioids (with methadone, buprenorphine, α_2-adrenoceptor agonists and adjunct medications), alcohol (with benzodiazepines, anti-glutamatergics and γ-aminobutyric acid (GABA)-ergic drugs), stimulants and cannabis (with no clear recommended pharmacological treatments), benzodiazepines (with dose tapering) and nicotine (with nicotine replacement therapy, antidepressants and partial agonists). Evidence is limited by a lack of controlled trials robust enough for review bodies, and more research is required into optimal treatment doses and regimes, alone and in combination.

Introduction

Dependence on illicit, legal and prescription drugs continues to have great health and societal costs, and the alleviation of dependence remains the most desirable outcome. Detoxification is the safe and effective discontinuation of a substance of dependence or misuse, whether an illicit substance or a prescribed drug therapy. The goals of detoxification treatments are to minimize any withdrawal effects and alleviate any side effects, with the primary aim of successfully completing the withdrawal procedure and therefore providing the opportunity for sustained abstinence. The ultimate outcome may or may not be abstinence, as for example heroin dependence often has a chronic relapsing course over decades [1]. Abstinence may not be achievable or even be desirable to the user and many who complete detoxification do so only to reduce their dependence and associated costs [2]. In these cases, a first step to detoxification would be to achieve controlled or non-dependent drug use and reduce related harms, such as improving health, relationships, employment and housing, and reducing criminal activity and risky behaviour (such as sharing needles). Detoxification is best conceptualized not as an end in itself, but as a transitional state between dependence and abstinence or at least reduced harms. Recovery from substance misuse and dependence is, however, much more than simply undergoing detoxification and achieving abstinence as shown in Figure 1. Detoxification and cessation of drug or alcohol use may form one part of a person's recovery journey. The line between detoxification and abstinence/relapse prevention can sometimes be difficult to draw, especially with substances such as alcohol where there may be no clear separation between the withdrawal period and the relapse prevention period.

The choice of which strategy to use for detoxification can depend on many factors, involving clinical judgement, the user's personal preference and circumstances, lifestyle and expectations, degree of dependence and concomitant health problems. Clinicians may need to tailor pharmacological treatments, for example, in relation to risk of overdose if detoxification treatment can be diverted for injection, or if there are any risks to children living with the user if the treatment can be taken home. For effective treatment plans, users should be involved in their

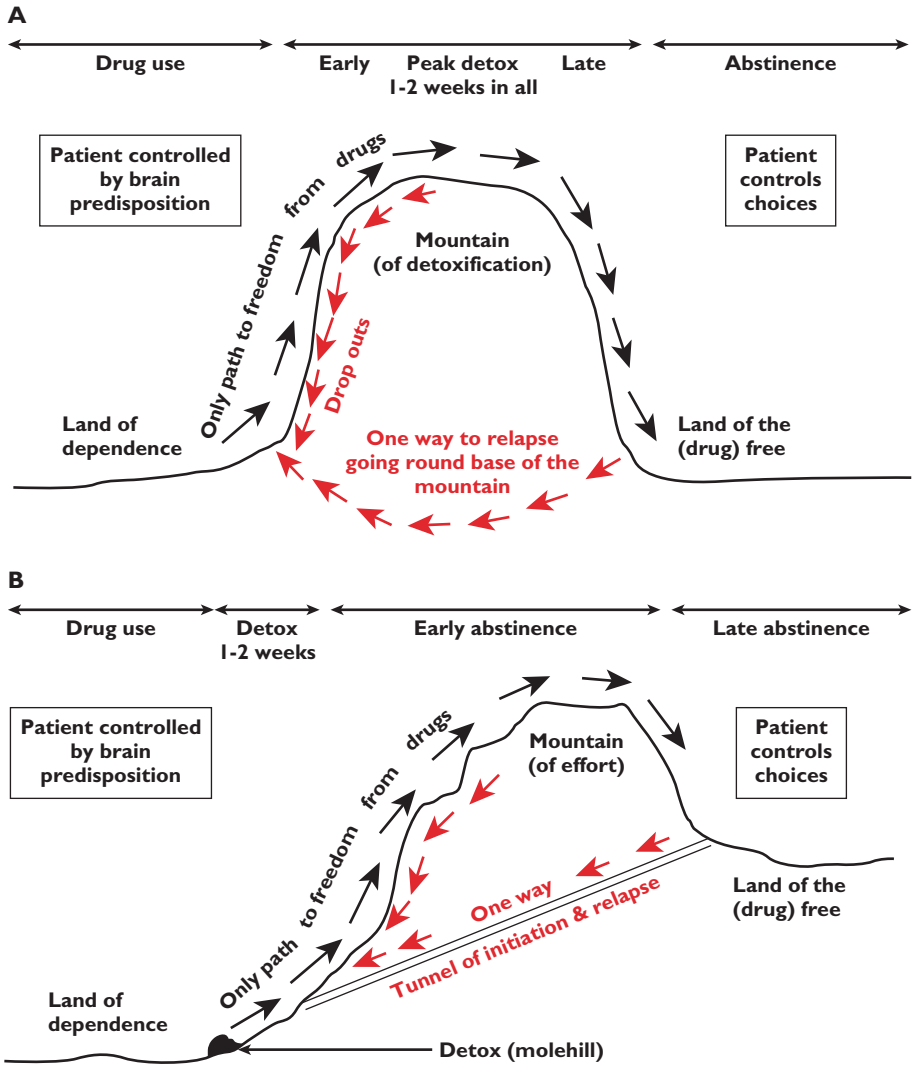

Figure 1

Perception is an issue. Patients, their families and staff frequently have a belief that detoxification is the key issue, whereas in fact this is a small part of the much longer road to abstinence. The figure is in two parts, subheading for each: (A) The fantasy: How patients (and staff) perceive progress in addiction treatment. (B) The reality: The road to abstinence

treatment choices and, with the user's permission, also the family or carers.

All guidelines including those of the National Institute for Clinical Excellence (NICE) [3] recommend pharmacological strategies for detoxification are deployed alongside psychosocial therapies for best outcome. Keyworkers are particularly important in this process, in coordinating the care plan and building a therapeutic alliance [3]. Department of Health (DH) Drug Misuse and Dependence guidelines [4] recommend detoxification should be offered to all users in an appropriate setting if they are ready and committed to abstinence, with thorough preparation (rationale for detoxification, expectations, risks and side effects) and robust post-detoxification support to prevent relapse. First attempts at detoxification rarely work and relapse can often occur very soon after completing detoxification programmes [5]. This can be dangerous as the user may have lost tolerance and may overdose on relapse [6]. NICE [3] recommend that detoxification is completed within a community-based programme, but inpatient observation may be needed if community programmes have been of limited benefit in the past, if medical care is needed due to health problems, if the user has complex polydrug dependency, or if their social situation may lead to failure. Detoxification can usually be completed more quickly in an inpatient setting, but the speed of detoxification depends on the severity of the dependence and the stability of the user

[3]. The nomenclature used in this review conforms with the Guide to Receptors and Channels [7].

Detoxification from opioids

The majority of users report using opioid drugs (primarily heroin) and those who are deemed dependent are usually transferred on to substitute opioid prescribing such as methadone or buprenorphine to provide stabilization on a controllable drug, dose and regimen [8]. Some users are stabilized on diamorphine (heroin) by injectable or intranasal delivery. Other opioids are also sometimes used, especially modified release forms of morphine, dihydrocodeine and tramadol. It is recommended that detoxification is initiated using the same drug used for maintenance [3].

Detoxification is defined as a process that is completed in up to a 28 day period as an inpatient, or up to 12 weeks in the community. Some clinicians report reducing doses over a period of months or years though this is not considered detoxification *per se*. Calsyn *et al*. [9] have found little success in this method, but it can be a useful step towards a formal detoxification procedure as it gives users some confidence that they can manage on lower doses of their maintenance drug. Users who are unsuccessful at their detoxification attempt can be inducted again onto maintenance therapy.

Methadone

Methadone is a full μ opioid receptor agonist usually taken as an oral liquid. Opioid treatment may also be injectable if the users have failed optimized oral treatment. Most users will be stabilized on methadone as it is the recommended treatment by NICE [8], with the advantage that it is cheaper than buprenorphine with marginally better quality-adjusted life years, doses can be easily supervised and retention on treatment can be better than buprenorphine [10]. However it carries more risk of diversion if taken home, and may have cardiotoxic effects of a prolonged QT interval at doses higher than 100 mg [11]. Induction onto methadone from heroin should start at a low dose (usually 30–40 mg), and more can be given after 1–2 h if withdrawal symptoms are still present. Caution should be exercised as methadone's long-half life can result in cumulative effects and overdose, even if the dose initially appeared to be tolerated [12]. Detoxification from methadone can be a lengthy process and doses can be reduced to zero in approximately 12 weeks, by reducing the dose by 2–5 mg every 1–2 weeks. Senay *et al*. [13] reported less craving and withdrawal discomfort with slower tapering. However, users report a preference towards a faster reduction initially. A faster detoxification using adjunct therapies such as lofexidine can be beneficial, as a slower detoxification can result in an increased relapse rate [14]. However, some authors recommend electrocardiogram monitoring with this co-administration due to the increased risk of QT_c interval prolongation [15]. Faster detoxification can also be achieved by converting to buprenorphine once methadone doses reach 20–40 mg in the last 2 weeks [16].

Buprenorphine

Buprenorphine is a partial μ opioid receptor agonist and therefore has less risk of respiratory depression than methadone. It is also a partial κ opioid agonist, meaning it also has less risk of dysphoria than methadone. Buprenorphine is available as sublingual tablets, transdermal patches and injectable ampoules. Induction from heroin starts when withdrawal symptoms emerge, initially with 2–4 mg sublingually, with a second dose a couple of hours later if needed. Buprenorphine is less sedating than methadone, and may be more suitable for less dependent users, those with less chaotic lives or those with codeine dependence. It also has limited respiratory depression and no cardiotoxic effects [17, 18]. A Cochrane review has concluded that buprenorphine is equivalent to methadone in reducing symptom severity [19]. However it has an advantage in detoxification in that it can be reduced more quickly than methadone. It can be reduced by 2–4 mg every 2 weeks or so in the community, with the final dose being up to 8 mg prior to stopping (due to its much longer half-life). Also, due to a longer half-life than methadone, buprenorphine can be prescribed for dosing on alternate days or three times a week [20]. Gowing *et al*. [19] concluded that buprenorphine was more successful than methadone and α_2-adrenoceptor agonists for treatment completion, although other studies have found no difference [21].

A sublingual tablet called Suboxone, approved in the European Union in 2006, is a combination of buprenorphine and naloxone in a ratio of 4 : 1 (e.g. 8 mg : 2 mg). When taken sublingually, the naloxone has low bioavailability and so has no opioid antagonistic effects. However, should the tablet be crushed and injected or snorted, bioavailability becomes high and the drug takes effect, leading to withdrawal symptoms which can, for some, discourage misuse [22].

Other opioids for detoxification

Slow release oral morphine (SROM) is not recommended as a detoxification treatment as studies into this strategy are limited [3]. However, Madlung-Kratzer *et al*. [23] have shown it has a similar effectiveness to methadone in a double-blind parallel group study of tapering over 16 days, a conclusion also supported by a recent systematic review [24]. It may be suitable for users who do not want or cannot tolerate methadone or buprenorphine.

Levo-α-acetylmethadol (LAAM) is a synthetic opioid similar in structure to methadone, and can be used for detoxification in a similar way to methadone with similar results [25]. However it also has cardiotoxic effects like methadone, and particularly a prolonged QT interval [26]

and is little used. Like SROM, it was used as a second line treatment for users who failed to respond to methadone or buprenorphine. Like buprenorphine, its half-life is long enough to enable dosing two or three times a week, rather than daily [27].

Tramadol is an analgesic with an intensity of one-tenth the strength of morphine [28], and a more favourable side effect profile compared with methadone. It has partial affinity for the μ opioid receptor, and is also a serotonin and noradrenaline re-uptake inhibitor. A dose of 600 mg day^{-1} was found to be as effective for limiting opioid withdrawal symptoms as methadone 60 mg day^{-1} [29], and few clinical differences were noted between the use of tramadol and buprenorphine in a recent retrospective matched cohort controlled study [30].

α_2-Adrenoceptor agonists

Opioids inhibit noradrenaline release, and detoxification from opioids can cause noradrenaline rebound. α_2-adrenoceptor agonists, such as lofexidine, can be used as an adjunct therapy to help limit this noradrenergic detoxification 'storm'. Clinical judgement and close monitoring is required to enable the peak effects of an α_2-adrenoceptor agonist to coincide with peak withdrawal effects. α_2-adrenoceptor agonists can be used alongside methadone and buprenorphine, but can be used alone for detoxification if maintenance therapy is not wanted, if a user has requested detoxification in a short time frame or if the user has a mild or uncertain dependence. The results are similar to using tapered methadone for detoxification, although in this group detoxifying with an α_2-adrenoceptor agonist alone is not as effective as detoxifying with buprenorphine [19]. However, a meta-analysis by Meader [21] found completion rates were similar to buprenorphine. Ockert *et al*. [31], in a study of 223 users detoxifying from heroin, found α_2-adrenoceptor agonists, with adjunct tramadol and a stimulant, produced better rates of retention in treatment than detoxification with opioids.

Lofexidine is a non-opioid α_2-adrenoceptor agonist effective for reducing withdrawal symptoms [32], and taking part of the daily dose at bedtime can be effective for withdrawal-related insomnia. It is effective for users where dependence is uncertain, for younger people or for those who have a shorter drug history. It can be used for the first 7–10 days of detoxification with a starting dose of 800μg day^{-1} (usually four divided doses, due to a short half-life), rising to 2.4 mg day^{-1}, and then reduced again to zero. In itself it has several side effects such as a dry mouth and mild drowsiness, which can lead to sedation when used with alcohol or other central nervous system depressants. There have been occasional reports of clinically significant hypotension and bradycardia [33] and opioid withdrawal type symptoms on dose reduction which can be limited by tapering doses, but daily monitoring is recommended to assess withdrawal symptoms and to measure the pulse and blood pressure.

Clonidine is also an α_2-adrenoceptor agonist which has been used since the late 1970s to assist opioid withdrawal and can reduce many of the symptoms [34]. However, symptoms such as anxiety, restlessness, insomnia, muscular aching and craving may not respond, and it can cause sedation and insomnia [35]. It is not routinely recommended for use by NICE [3] due to its effects of hypotension and bradycardia, which are much more pronounced than lofexidine. Due to these problems, it is rarely recommended for use in outpatient settings.

Other adjunct treatments

Many withdrawal symptoms can occur during detoxification from opioids and concomitant medications in the form of analgesics and hypnotics are often needed. Some medications can interact with detoxification treatments and prescriptions should be carefully considered. For example, fluoxetine can slow down methadone metabolism and elimination, whilst phenobarbital can speed it up. If a dose of a sedative is too high, there could be a risk of death through respiratory depression. Doses of adjunct medication should be the minimum dose that is clinically effective. Aches and pains can be counteracted with paracetamol, aspirin and topical rubefacients. Other adjunct therapies may include muscle relaxants, antiemetics, antidiarrhoeals and anxiolytics for agitation, anxiety, and insomnia. For example, oral diazepam 5–10 mg up to three times daily or as needed, or a Z drug such as zopiclone 7.5 mg–15 mg at bedtime can be given for insomnia if the user has been dependent on benzodiazepines. Venlafaxine, given at 300 mg day^{-1} over 5 days of heroin detoxification and gabapentin, given at 1600 mg day^{-1} over 3 weeks of methadone-assisted detoxification, were found to reduce withdrawal symptoms [36, 37]. Buspirone may be a useful detoxification treatment by itself, as Buydens-Branchey *et al*. [38] found 30 mg and 45 mg daily was as effective for managing withdrawal symptoms as tapered methadone.

Naltrexone/naloxone and rapid, ultra-rapid and accelerated detoxification

Naltrexone is a μ opioid receptor antagonist which is non-addictive and has no euphoric effects. It competitively displaces and blocks opioid agonists, such as heroin and methadone, rendering them ineffective [39]. Naltrexone is an oral tablet, and both implant and depot are available but these are not yet licensed in the UK. Dosing with naltrexone starts at 25 mg on the first day of treatment, rising to 50 mg day^{-1} thereafter, or doses can be given three times a week if preferable to the user. Treatment is recommended for 3 months, but can continue as long as needed. NICE guidelines [8] recommend that naltrexone is only used for patients who are supervised, highly motivated to stay in an abstinence programme, and who are

fully informed of side effects (such as dysphoria, depression and insomnia) which may be due to the opioid withdrawal or to naltrexone itself. It is these side effects which lead to poor compliance and retention rates, as users will either stop taking the naltrexone or relapse. Many studies have emphasized the importance of an adjunct psychosocial therapy for this reason. It reduces but does not prevent all craving [40], and there is a risk of fatal overdose if larger doses of heroin are taken in an attempt to counteract the naltrexone blockade. Naltrexone has, at high doses, been shown to derange liver enzymes so it was recommended that liver function was monitored [4]. However, current NICE guidance does not recommend routine hepatic monitoring but suggests monitoring be considered in older and obese people or as a motivational aid.

Ultra-rapid, rapid and accelerated detoxification are not recommended by NICE [3] due to the substantial risks involved, and they may be no more effective than more traditional techniques [41, 42]. Ultra-rapid detoxification is performed over a 24 h period with up to 50 mg of the opioid antagonist, naltrexone, per day, under general anaesthetic or heavy sedation, where the airways need supporting. It requires dedicated medical and nursing care and complex adjunct medications because of a risk of serious side effects and death [43], and indeed these have been reported [42, 44]. Rapid detoxification is performed over 1–5 days with moderate sedation. It is safer than ultra-rapid detoxification and although not recommended, NICE guidelines [3] state it may be considered for users who have specifically asked for it, understand the risks and are able to manage any adjunct medications. Completion rates of rapid detoxification using naltrexone and clonidine are reported to be 75–81%, compared with 40–65% when using methadone or clonidine alone [45, 46]. Another technique is to switch from heroin to buprenorphine for 1 day, followed by a clear day before starting naltrexone/clonidine [34]. The α_2-adrenoceptor agonist, dexmedetomidine, has also been successfully used to decrease withdrawal symptoms [47]. Again, rapid detoxification is a burden for medical and nursing staff as users must be able to maintain response to verbal stimulation to maintain their airway and require regular monitoring. Accelerated detoxification is achieved by giving limited doses of naltrexone or naloxone after the start of the normal detoxification process in order to speed up the process. This has a risk of increasing the severity of withdrawal symptoms and the need for adjunct medications. All three of these detoxification techniques would be performed with a view to maintaining naltrexone dosing after detoxification to prevent relapse.

Detoxification from alcohol

Withdrawal from alcohol may not require pharmacological intervention, if the severity of dependence and withdrawal symptoms do not require it. However, thiamine supplements may be necessary to avoid the Wernicke–Korsakoff syndrome [48]. Those with alcohol dependency tend to have a reduced level of thiamine in their diet and ethanol can disrupt thiamine storage and use [49, 50]. In addition to the treatments outlined below, it can be argued that other drugs have a role in detoxification, such as naltrexone, nalmefene, acamprosate, baclofen and disulfiram, although these are more suited to relapse prevention. Another treatment with a potential role in alcohol detoxification is the psychotropic analgesic nitrous oxide (PAN), which has been identified by a Cochrane review for mild to moderate alcohol withdrawal [51]. This may have a rapid therapeutic effect with minimal sedation.

Benzodiazepines

All guidelines, including NICE [52] and two Cochrane reviews [53, 54], support the use of benzodiazepines, such as chlordiazepoxide, in detoxification from alcohol and it is a well established treatment, reducing withdrawal severity and risk of seizures and delirium tremens [55]. Diazepam, in particular, may be useful for reducing *de novo* seizures and other useful benzodiazepines include oxazepam and lorazepam. However, benzodiazepines may not be suitable for long term abstinence treatment due to risks when combined with alcohol. The British Association for Psychopharmacology guidelines [55] warn that the use of selective serotonin re-uptake inhibitors (SSRIs) are not recommended unless the user is also depressed and should be avoided or used with caution in type 2 alcoholics (early onset, positive family history, impulsive/antisocial personality traits) as they may worsen outcomes. In a recent review, Muzyk *et al*. [56] concluded that clonidine and dexmedetomidine may be useful as an adjunct therapy to benzodiazepines.

Anticonvulsants/antiglutamatergics

Reducing glutamate overactivity in withdrawal is important for reducing toxicity. Antiglutamatergic drugs are as effective as benzodiazepines for detoxification. However evidence for efficacy of anticonvulsants is limited and they may have more of a role in alleviating certain symptoms [53]. Chlormethiazole is a γ-aminobutyric acid (GABA)-ergic drug for inpatient use, rather than use in the community because of the risk of death due to respiratory depression when combined with alcohol. Another useful drug with GABA-ergic properties is pregabalin, which binds to the α_2-δ subunit of voltage-gated calcium channels, and inhibits neurotransmitter release. It can be given in doses of 150–450 mg daily, has similar reported outcomes to using naltrexone and has been reported as superior to placebo in many studies [57]. Other potentially effective drugs include gabapentin, tiagabine, vigabatrin, memantine (an NMDA antagonist), lamotrigine (a glutamate release inhibitor), oxcarbazepine, leviracetam, valproic acid [58], flumazinil and valproate [59].

Carbamazepine primarily blocks voltage sensitive sodium channels, meaning that fewer of these channels are available to open, and therefore reduces excitability. It has been shown to be as effective as benzodiazepines for improving sleep and reducing cravings and psychological distress, although there are concerns over its tolerability and lack of protective effects against seizures [60]. Topiramate (an AMPA/kainite inhibitor) can be given in doses up to 300 mg daily and reduces the percentage of heavy drinking days and improves health [61]. It has been shown to be more effective than naltrexone [62] but less so than disulfiram [63]. It can have side effects such as paraesthesia, taste problems, anorexia and difficulty concentrating. These can be minimized by slow titration up to the full therapeutic dose.

Acamprosate

Acamprosate works by reducing the amount of glutamate in the brain (and therefore reduces the hyperglutamatergic state during withdrawal [64]). It acts as a functional glutamatergic NMDA antagonist, and may have neuroprotective qualities useful during and after detoxification [65]. For example, due to the overactivation of glutamate receptors, cessation of chronic ethanol treatment in rats can lead to seizures and hyperexcitability [66]. al Qatari *et al*. [67], using cultures of foetal rat brains, found acamprosate reduced glutamate-induced neurotoxicity in alcohol withdrawal, whilst Koob *et al*. [68] found acamprosate reduced excitatory postsynaptic field potentials in the hippocampus. In healthy volunteers, acamprosate improved delayed word recall and may facilitate long term potentiation [69], and may protect cognitive function during detoxification. It is well tolerated but may cause gastrointestinal disturbance [70] and is contraindicated in severe liver and renal impairment. There is evidence to suggest acamprosate should be started during or before detoxification, as starting after detoxification has been shown to increase the percentage of heavy drinking days and the amount drunk per day [71]. Starting acamprosate 8 days before detoxification and continuing for 15 days was associated with improvements in sleep [72]. After detoxification, acamprosate can be given for the following 6 months [52] to 1 year (SPC). However, not all users respond to acamprosate and Morley *et al*. [73] found no advantage over placebo in detoxification.

Baclofen

Baclofen is a $GABA_B$ agonist, used to control muscle spasms in detoxification because $GABA_B$ receptors are modulators of dopaminergic neuronal firing. It has been shown to suppress withdrawal symptoms and craving, with efficacy and safety in abstinence [74]. It is well tolerated and can be given to those with liver impairment (hence its use in liver centres) where a low dose is clinically sufficient, although higher doses (e.g. 20–30 mg three times a day) can be more effective than lower doses (10 mg three times a day). However, some studies have found no benefit over placebo [75] and a recent Cochrane review has questioned its use without further research [76].

γ-Hydroxybutyric acid (GHB)

GHB acts on GHB receptors and has the same mechanism of action and similar effects to baclofen. It has been shown to have efficacy in both alcohol withdrawal and relapse prevention [77]. Specifically, dosing at 50 mg reduces craving more effectively than placebo and disulfiram, but GHB has not been found to be superior to benzodiazepines [78]. GHB has as a licence in some European countries but, unlike baclofen, it is growing in popularity as an illicit recreational drug and concerns over abuse potential has limited its use in the UK [78]. Availability in a solid formulation (Alcover) may make this less of an issue.

Detoxification from stimulants and cannabis

There are still no recommended pharmacological methods for detoxifying from stimulants and cannabis despite extensive research. For example, over 60 medications have been examined for the treatment of cocaine dependence [79]. It is often the case that drugs researched for this purpose are found to be ineffective or studies have mixed results.

Propranolol for cocaine detoxification is only more effective than placebo if the users are adherent to the medication. Amantadine and other dopamine receptor agonists were found to be no more effective than placebo [80, 81]. GABA-ergic drugs may be a better route of investigation, as glutamate depletion is associated with repeated cocaine administration [82, 83]. For example, progesterone, tiagabine, topiramate and gabapentin were found to decrease cocaine use in users with low withdrawal severity [84]. Modafinil increases histamine release via the orexinergic system [85] and is a weak monoamine re-uptake inhibitor. Downstream, modafinil is a selective α_1-adrenceptor agonist, possibly limited to the beta subtype as the genetic ablation in rats of α_{1B}-adrenoreceptors attenuates its effects [86]. Modafinil may enhance glutamate and inhibit GABA, and has been found to be superior to placebo with respect to higher abstinence levels [87]. It is thought to act as an 'agonist substitution', inhibiting the dopamine transporter and, to a weaker extent, the noradrenaline transporter [88], increasing extracellular dopamine and noradrenaline [88–90]. Studies show modafinil may enhance electrotonic coupling, whereby the connections over gap junctions become more effective [91]. Coupling on a larger scale may also occur, as Schmaal *et al*. [92] found negative coupling of neural networks was enhanced by modafinil in

alcohol dependent participants, leading to greater cognitive control. A review by Sofuoglu & Kosten [93] suggests other noradrenergic drugs may also be useful in cocaine detoxification, such as lofexidine or disulfiram (which blocks noradrenaline synthesis and increases dopamine). For amphetamine detoxification, mirtazapine and amineptine were found to be ineffective [94]. However, a review by Ling *et al*. [95] concluded that bupropion and modafinil may be helpful as an adjunct to behavioural therapies.

In detoxification for cannabis, anticonvulsants such as valproate semisodium [96] and antidepressants such as bupropion, fluoxetine, mirtazepine and nefazadone have shown little benefit [97–100]. Cravings are reduced, but irritability, anxiety and tiredness are increased. A major problem in cannabis withdrawal is difficulty sleeping, and a study by Vandrey *et al*. [101] has shown this may be alleviated with zolpidem. Research into rimonabant, a cannabinoid receptor antagonist, was terminated due to intolerable side effects [102]. Some promise for cannabis detoxification has been shown by oral tetrahydrocannabinol (THC or dronabinol) and lithium carbonate. A dose of 30–90 mg daily of THC, particularly when combined with lofexidine, has been shown to reduce withdrawal symptoms, sleep problems, anxiety, cravings and depressive symptoms [96, 103]. Dronabinol (δ-9-tetrahydrocannabinol) and lithium carbonate have been shown to be useful for alleviating withdrawal [104–106].

However, for illicit drugs including stimulants, cannabis and ecstasy (MDMA), psychosocial therapies such as keyworking and contingency management remain the recommended treatment [3]. There is still a role for the clinician in the monitoring and treating of any mental health issues, including psychosis, depression or risk of suicide. Withdrawal symptoms from GHB and its precursors (γ-butyrolactone, GBL and 1,4-butanediol, 1,4-CB) can include severe neuropsychiatric problems and autonomic instability, which may be life-threatening and require intensive care. Less severe but persisting side effects include insomnia, anxiety and depression. Bell & Collins [107] report pharmacological methods to treat this include the use of high dose benzodiazepines (for example, 40–120 mg of diazepam), possibly combined with baclofen or other sedatives like pentobarbital if there is no response to benzodiazepines. SSRIs should ideally be avoided in cocaine and amphetamine users due to possible serotonin syndrome, although they are commonly used.

Detoxification from benzodiazepines

Long term prescribing of high doses of benzodiazepines (over 30 mg of diazepam) can be harmful. Benzodiazepine dependence is usually treated in secondary care, but may present alongside other drug dependence. It is recommended that users of methadone and benzodiazepines should undergo detoxification from benzodiazepines first [4]. However there is evidence that opioid/benzodiazepine users may have less withdrawal effects if buprenorphine is used for detoxification [108]. Benzodiazepine dependence is not only via repeat prescription. They are also purchased and misused illicitly and there may be some value in 'maintenance' prescribing for high dose illicit users before withdrawal [109]. Prescriptions for benzodiazepines should be reduced slowly to the lowest dose to control the dependence. There is no evidence that week-on week-off (pulse) dosing is effective [55]. Dependency on high doses may require specialist treatment but can have a faster rate of reduction, such as reducing doses by half over 6 weeks, without a risk of convulsions [110]. Reduction of high dose use to a therapeutic dose level may be a useful therapeutic objective in some dependent users [55]. Z drugs, such as zolpidem, or melatonin may be helpful for any resulting insomnia [111]. The DH Drug Misuse and Dependence guidelines [4] recommend converting all benzodiazepines to an appropriate dose of diazepam, which has a long half-life, and then reducing the dose by an eighth every 2 weeks. Phenobarbital can also be used in this way [112]. Other strategies include switching to a non-benzodiazepine anxiolytic, or the prescription of adjunct medications such as antidepressants or anticonvulsants [109]. For example, pregabalin at higher doses of 225–900 mg have been found to be effective [113], and a recent Cochrane review identified carbamazepine as a possible adjunct to reduce withdrawal effects [114]. Flumazenil, the benzodiazepine antagonist, also shows promise when given by very slow infusion, and has the advantage that both high and low doses can be detoxified equally well, and patients feel well following the detoxification [115].

Detoxification from nicotine

Nicotine dependence is often overlooked in detoxification, despite most patients being smokers. Drug treatment services do not often offer smoking cessation advice, possibly due to thinking it unimportant, or perhaps because clinicians lack the expertise or have concerns that detoxification from smoking may interfere with other detoxification treatments. Smoking cessation is important for a number of reasons besides the health benefits. Cigarettes can act as a cue to consume other drugs by smoking, and cessation can help with drug treatment outcomes, such as coping with cravings and preventing relapse. The main nicotine detoxification treatments are considered below, but in addition, clonidine can be considered as a second-line treatment. Tiagabine, baclofen, gabapentin, varencline, mecamylamine (a non-selective NAch receptor antagonist) and topiramate have all been shown in studies

to have positive effects on cessation. However naltrexone has shown little promise [116].

Nicotine replacement therapy (NRT)

NRT binds to nicotine acetylcholinergic (NAch) receptors in the central nervous system in a dose dependent manner. This reduces the urge to smoke, withdrawal effects and any reward from cigarettes if the user should relapse. It also provides a less harmful and less reinforcing method of administration compared with smoking, and can improve cessation rates by 50–70% [117]. The regimen for detoxification treatment should start 2 weeks before the cessation attempt, as this has been shown to be more effective than starting treatment on the day of cessation itself. NRT should be continued for a minimum of 8 weeks, or for as long as necessary. There is some evidence that psychological support is also useful, as abstinence with NRT is higher on prescription than when it is purchased over the counter [55]. The slowest method of delivering NRT is via transdermal patches. These come in varying doses, where higher doses may be more beneficial for highly dependent smokers. Efficacy can be improved by using patches in conjunction with a faster delivery method [118]. Chewing gum, in doses of 2 mg and 4 mg, is an example of a faster delivery method, as are inhalers, oral sprays, sublingual tablets and lozenges. The fastest delivery method is by nasal spray, which can replace about half the blood nicotine levels of smoking within 5–10 min [119]. Even so, NRT does not provide nicotine as efficiently as smoking and does not mimic the behavioural rituals, which compromises its effectiveness for cessation [120]. If the user continues to smoke during NRT, they may experience side effects of nicotine toxicity, such as nausea, abdominal pain, diarrhoea, dizziness and palpitations, and mistake these for nicotine withdrawal [119].

Antidepressants

Nicotine withdrawal may produce depressive symptoms, possibly because nicotine itself may be an antidepressant [121]. Nortriptyline, SSRIs (fluoxetine, paroxetine, sertraline), MAOIs, venlafaxine and St John's Wort are second line treatments which may be helpful with mood problems after smoking cessation [55]. Some antidepressants may be useful because of their pathway of action, independent of their antidepressant properties. For example, bupropion is an atypical antidepressant with dopaminergic and adrenergic action, which also binds to NAch receptors. Bupropion improves cessation rate compared with placebo, and has been found to reduce craving and satisfaction with smoking [122]. It may be beneficial for users concerned about weight gain after smoking cessation [123]. Treatment is started 1 week before the cessation attempt, starting at 150 mg day^{-1} for 3–5 days, increasing to 150 mg twice daily, which continues for 7–12 weeks. Using concomitant NRT with bupropion can double the cessation rate and can be considered for users struggling to quit with NRT alone [124].

Nicotine receptor partial agonists

Nicotine receptor partial agonists counteract nicotine withdrawal symptoms (by acting as an agonist) and reduce smoking satisfaction (by acting as an antagonist), and may be useful for improving long term cessation. Varenicline is a selective partial agonist for the a4-b2-NAch receptor with a moderate affinity for the 5-hydroxytryptamine-3 receptor. Cahill *et al.* [125] showed varenicline improved long term cessation by 2–3 times compared with placebo or bupropion, and was still effective at lower doses which also reduced the side effects of the drug (such as nausea). The recommended dose is 1 mg twice daily for 12 weeks, which is reached by gradually increasing the dose from 0.5 mg once daily during the week before smoking cessation begins. Another 12 weeks of dosing can be used as relapse prevention. It is unclear if these treatments are superior to NRT and there have been unsubstantiated links between these drugs and depression with suicidal ideation [55]. More research is required.

Conclusion

Detoxification is not an end in itself, but a transitional state between dependence and abstinence or reduced use. It can provide an opportunity for abstinence as part of the recovery journey, but for some drugs may increase the risk of overdose and sustained relapse. It is a balance between the substance user's needs and preference, choice of medication, methods of administration, and the intensity of keyworking and psychosocial programmes. Evidence has shown that pharmacological treatment for substance misuse works [4], but that it needs to be combined with psychosocial treatment [3]. We should now ask how we can best tailor established treatments to suit the needs of individuals in difference circumstances [55]. Questions remain regarding comparisons between treatments, combinations of treatments and optimal treatment regimens [126]. Much attention has been given to approved treatments such as methadone tapering for opioid dependence and benzodiazepines for alcohol dependence, and more research is required into emerging treatment possibilities, such as oxytocin [127] and flumazenil [115]. Other treatments for misuse are less well researched, in part due to the regulatory hurdles involved in setting up studies of substances of misuse and controlled drugs. Current research into additional or alternative treatments is not robust enough for major review bodies, meaning recommendations are difficult to achieve. A persistent research effort will be required to gain an understanding of the substance of misuse itself through detoxification treat-

ments, to tailor treatments to specific users and circumstances, and also to tackle the problem of detoxification from polydrug misuse.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work. FDL and JKM have been reimbursed by Schering Plough, the manufacturer of buprenorphine, for attending several conferences. FDL has acted as a consultant, on focus groups, market research, and on an advisory board for Schering-Plough, and has been funded as a researcher on a study by Schering-Plough and Reckitt-Benckiser. FDL and JKM have received honoraria from Britannia Pharmaceuticals for speaking at symposia and JKM has received a small unconditional grant from them. FDL is on the UK national faculty of the Quality Patient Care Initiative, funded by Reckitt-Benckiser, and has received honoraria in this role. FDL has acted as a consultant and has been on a focus group for Britannia Pharmaceuticals. FDL has taught the staff of Schering-Plough and Dupont. AMD declares that she has no competing interests.

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