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Evidence Check

Management of withdrawal from alcohol and other drugs

An **Evidence Check** rapid review brokered by the Sax Institute for the NSW Ministry of Health. September 2019.

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This report was prepared by:
Nicholas Lintzeris, Sandra Sunjic, Apo Demirkol, Mira Branezac, Nadine Ezard, Krista Siefried, Liam Acheson, Florence Bascombe, Chris Tremonti, and Paul Haber.

September 2019

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An Evidence Check **rapid review brokered by the Sax Institute for the NSW Ministry of Health. September 2019.**

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Background

This review on management of withdrawal from alcohol and other drugs was commissioned by the NSW Ministry of Health to summarise the evidence available in the research literature since the last state Clinical Guidelines were published in 2008. The most recent evidence will be used to inform the revised Clinical Guidelines that are currently under review by NSW Health.

The project team consisted of: Prof Nicholas Lintzeris (lead), Dr Sandra Sunjic (project manager), medical librarian Mira Brazenac, Addiction Medicine specialists Associate Professor Apo Demirkol, Associate Professor Nadine Ezard, Professor Paul Haber, Dr Chris Tremonti, and researchers Dr Krista Siefried, Liam Acheson, and Florence Bascombe.

Review questions

This review addresses the following questions identified by the Ministry of Health:

Question 1: What have been shown to be the most effective practices for treatment of withdrawal from alcohol and other drugs?

This includes a rapid review of the evidence regarding psychosocial, physical and pharmacological interventions in the management of withdrawal from each of the following substances:

- Alcohol
- Benzodiazepines
- Amphetamines and methamphetamine
- Cocaine
- Methylenedioxy methamphetamine (MDMA)
- Opioids
- Cannabis
- Pregabalin/gabapentin
- Gamma hydroxybutyrate (GHB), and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD)
- High dose transfers from methadone to buprenorphine.

Question 2: What withdrawal management strategies are the most effective in improving treatment outcomes for the special population groups?

These were identified (by NSW Ministry of Health) as: elderly; Aboriginal; and lesbian, gay bisexual, transgender, intersex (LGBTI) people; people in custody; and medically unwell populations e.g. liver failure, delirium etc.

Question 3: What are the differential effects of withdrawal management approaches by setting?

Settings for withdrawal were identified as inpatient hospital settings, residential, and ambulatory (e.g. community and home-based settings).

Summary of methods

A search of the peer-reviewed literature was conducted for each drug, to identify relevant literature published from January 2008. This included a search of databases through the NSW Ministry of Health Clinical Information Access Portal (CIAP); Medline, Embase, Psychinfo, Cochrane and Pubmed, along with Google Scholar. Additional searches were conducted for settings, and special populations.

Relevant systematic reviews, randomised controlled trials (RCTs) (involving humans) and other papers were identified and reviewed for inclusion in the review for each drug. Where there were few, or there was no published literature on withdrawal (or detoxification) management of a drug, a further search utilising other key words (e.g. dependence), was undertaken to identify any related literature.

For each drug, a 'key' systematic review was identified (where available) as the main basis for the review of the evidence, and a further search was then conducted to identify any RCTs conducted since the 'key' systematic review. Only papers written in English were included. For some drugs, where there were no results from the literature search for systematic reviews or RCTs, a search was conducted for any case series reports or case studies.

For each chapter, the project team identified the literatre reviews available, and where more than one review was available, identified the most relevant review for the aims of the project; examined and summarised the findings and conclusions in the preferred review, compared those conclusions with findings of other relevant reviews, and considered whether more recent studies (published since the reviews) impacted upon the general conclusions.

Each chapter provides an overview of the identified literature, a narrative summary of the evidence findings, and a summary table of the evidence rating, evidence grade and recommendations for each intervention within that chapter. The level of evidence (evidence rating) was categorised according to the classification scheme outlined by Shekelle et al.[1] (see Appendix 1), or GRADE for systematic reviews (Cochrane rating scale). The quality of evidence utilises the the NHMRC Recommendation for grading i.e. A=excellent, B=good, C=satisfactory, D=poor, and D: good practice point (see Appendix 2).[2] These summaries are also compiled as a stand-alone quick reference guide.

Summary of key findings

Withdrawal management is an important component of an alcohol and other drug (AoD) treatment system. Withdrawal services represent an entry point for many people into AoD treatment, and provide an opportunity to engage patients and carers. Withdrawal services should be seen as part of a continuum of care, integrated into a broader care plan that addresses the individual's substance use, health and social issues.

The evidence regarding optimal withdrawal management—while patchy in many areas—is sufficiently robust in most cases to allow the development of evidence-based clinical guidelines.

1. Withdrawal services need to be seen as a short-term intervention in a longer continuum of care provided by a range of health and welfare services. Stand-alone withdrawal interventions have limited long-term impact upon substance use or health outcomes. It is not a stand-alone procedure to be undertaken in isolation of other services; but should occur against the context of the patient's other health conditions and in liaison with community treatment providers, consistent with the principles of integrated health care.
2. Effective withdrawal services involve: timely access to treatment, a comprehensive clinical assessment, and a treatment care plan that addresses the patient's substance use, health, psycho-social conditions and clinical risk factors (e.g. child protection, violence, homelessness, overdose); regular monitoring throughout the withdrawal period, and effective transfer of care procedures.
3. Withdrawal services should be seen as a 'package of care', integrating psychosocial, physical and pharmacological interventions.

- A range of psychosocial approaches – including motivational enhancement, cognitive behavioural approaches for coping with cravings and withdrawal symptoms, case management and care planning, and assertive approaches to post-withdrawal engagement, should be considered as standard care in withdrawal management.
- The role of physical interventions (e.g. exercise, relaxation) is still emerging – yet there is increasing evidence that exercise can assist with important symptoms during withdrawal (e.g. sleep, anxiety, reduced cravings). Whilst there is insufficient evidence to recommend widespread use of approaches such as yoga or acupuncture, these may be of benefit to some patients.
- The evidence remains unclear regarding the role of peer engagement during withdrawal (e.g. 12-step facilitation) and psychoeducation for patients and carers.

4. Regarding withdrawal management for specific drug classes:
    - Alcohol withdrawal is still underpinned by ensuring appropriate and safe withdrawal settings, the use of Benzodiazepines (BZDs) as the mainstay of medication, and ensuring appropriate monitoring and psychosocial services.
    - Opioid withdrawal is preferentially managed using opioid medications such as buprenorphine, often in an outpatient setting. The introduction of longer acting forms of BPN (e.g. depot products) should also be integrated into withdrawal management settings to enhance post-withdrawal treatment engagement.
    - The evidence regarding cannabis withdrawal is undergoing transformation. Historically, there were no evidence-based medication options, yet there is increasing evidence to support the use of cannabinoid-agonist medications (e.g. nabiximols), and this is an emerging area of research and clinical practice.
    - The evidence regarding management of withdrawal from amphetamine type stimulants (including methamphetamine) remains poor. The high prevalence of significant physical, psychiatric and social problems in patients with methamphetamine dependence will often mean that the settings and withdrawal interventions are shaped by these co-morbidities.
    - There has been the emergence of a new range of drugs for which there is little evidence and for which clinical experience is still developing. In particular, 'withdrawal' from drugs such as GHB, pregabalin, and ketamine, can pose new challenges for withdrawal services.
5. There is limited evidence from controlled trials regarding delivery of withdrawal interventions for certain populations (Aboriginal, LGBTI, and CALD people, and people in custody), although there is some evidence that tailored services can better engage these populations in treatment. There is also a need for better evidence regarding the management of withdrawal in older populations, which represents a growing demographic challenge for services. Further research is required.
6. Treatment settings. Clinical pathways must ensure that patients have access to the range of ambulatory, residential and hospital withdrawal settings, determined by clinical factors (e.g. severity of withdrawal, other substance use, health and social conditions), patient preference and resource availability. This is particularly important for patients from different cultural backgrounds, including Aboriginal people, where admission to a residential unit or hospital may impact culturally by not allowing the individual to remain close to family and country. In other contexts, some patients may need to be removed from their family environment or social networks in order to undertake withdrawal treatment. The important factor is that patients (and carers) have options and pathways – rather than single models of operation or care.

The challenge for many withdrawal services and for treatment planners is to ensure that effective services are available, patient-centred, evidence-based and efficient. Historically, NSW withdrawal services have emphasised residential or hospital-based approaches. While these are an essential component in the mix of withdrawal services, the over-reliance upon residential/inpatient withdrawal settings—sometimes with no available community withdrawal options—is neither effective, patient-centred nor resource-efficient. An integrated system that matches services to patient needs and enables 'step-up' and 'step down' approaches should make services more accessible and better meet patient needs.

The summary tables below, present the evidence and recommendations for the management of withdrawal for each substance (other than those substances where evidence was not available e.g. gabapentin/pregabalin). This includes recommendations in relation to: settings; pharmacological management; psychosocial interventions; physical therapies; and special populations related to that substance. In addition to these tables, there are also summary tables of evidence and recommendations for all drug classes, related specifically to particular interventions e.g. psychosocial interventions (see below).

For classification schemes for categorisation/grading of evidence see Appendices 1 and 2

Table A. Summary of evidence and recommendations for withdrawal settings

Withdrawal setting	Recommendation	Level of evidence	Quality of evidence
Inpatient (hospital) setting	Inpatient (hospital) withdrawal is indicated for those with a history of severe withdrawal (e.g. withdrawal seizures, psychosis, delirium, cardiovascular complications); withdrawing from multiple substances concurrently; medical (e.g. severe cardiovascular, respiratory or hepatic disease, diabetes, systemic infections); or psychiatric comorbidity (e.g. suicidal ideation, psychosis, severe depression or anxiety). It is mostly relevant to withdrawal that involves cessation of alcohol or other drugs that can be associated with severe withdrawal complications This is dealt with in further detail within the text for each substance.	Ib (alcohol, opioids) Extrapolated for other drugs	Grade B: Good (for alcohol, opioids) Grade D: GPP (Good Practice Point - for other drugs)
Residential withdrawal	Residential withdrawal is indicated for those patients with unsuitable home environments (e.g. homeless, other substance use in the home) or social supports; those who are unable to access outpatient or home-based withdrawal services; or who have had repeated failure at ambulatory withdrawal, and where severe withdrawal complications requiring inpatient hospital admission are not expected.		
Ambulatory withdrawal (home based and/ or outpatient)	Ambulatory withdrawal is feasible, effective, safe and cost-effective, and often has good patient and carer acceptance. It is the recommended withdrawal setting for most attempts at withdrawal, unless there are specific clinical reasons for more intensive residential or inpatient withdrawal settings. Withdrawal programs that involve gradual tapering off medications (e.g. opioids, benzodiazepines) should usually be conducted in an ambulatory setting.		

Table B. Evidence summary and recommendations regarding psychosocial interventions across all drug classes

Intervention	Recommendation	Level of evidence	Quality of evidence
Psychosocial interventions (as adjunct to medication)			
Motivational enhancement counselling	Motivational enhancement approaches (group or individual) appear to be effective in enhancing the uptake and engagement with subsequent post-withdrawal treatment for substance use disorder.	Ib	Grade C: Satisfactory
Peer engagement during withdrawal	The role of peer engagement during withdrawal episode (e.g. 12-step meetings) upon subsequent engagement in post-withdrawal treatment (or 12 step programs) remains unclear, with few controlled studies and inconsistent findings.	Ib	Grade D: Poor
Patient or consumer information	Few controlled studies were identified in withdrawal, however extrapolating from evidence for opioid withdrawal and from evidence regarding general consumer health literature, provision of structured information to patients may be associated with lower withdrawal severity and greater treatment retention.	4 for opioids. Extrapolated for other drugs	Grade D: GPP (Good Practice Point)
Linkages to post-withdrawal treatment services	Structured and assertive linkages to post-withdrawal treatment are associated with greater engagement with post-withdrawal treatment.	Ib	Grade C: Satisfactory

Table C. Evidence summary and recommendations regarding physical interventions across all drug classes

Intervention	Recommendation	Level of evidence	Quality of evidence
Acupuncture			
Auricular or traditional Chinese medicine acupuncture during withdrawal episode.	Most controlled studies have examined alcohol or opioid withdrawal, and usually as an adjunct to routine care. Meta-analyses indicate there is evidence of a reduction in withdrawal symptoms, cravings and anxiety symptoms, although no differences in completion rates. When individual drug types are examined (e.g. alcohol, opioids, stimulants) there are no benefits of acupuncture on withdrawal symptoms or cravings. The reviewers caution that there are inconsistent findings between studies, poor quality studies and evidence of publication bias, and suggest caution in interpreting evidence.	GRADE Low or Very Low for alcohol and opioids. Extrapolated for other drugs	Grade D: Poor
Exercise			
Aerobic exercise for opioid or cannabis withdrawal.	Aerobic exercise programs are associated with reductions in withdrawal symptoms, and specific symptoms of sleep disturbances, anxiety and depression, and should be encouraged in cannabis and opioid withdrawal attempts.	1b for cannabis and opioids. Extrapolated for other drugs	Grade: D Poor
Exercise for alcohol and stimulant disorders	Controlled studies were not identified examining aerobic exercise programs for alcohol or stimulant disorders, and further research is required, particularly given safety concerns in these populations.	Extrapolated for alcohol; Ib for stimulants	Grade D: Poor
Mind-Body exercise (e.g. yoga)	No controlled studies were identified examining yoga for substance withdrawal (excluding tobacco). Further research recommended.	Nil	Grade: Nil evidence.
Massage therapy			
Massage therapy during withdrawal	Limited evidence suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal.	1b for alcohol Extrapolated for other drugs	Grade D: Poor

Table D. Summary of evidence and recommendations for management of alcohol withdrawal

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient, residential and ambulatory withdrawal setting	*Inpatient admission* is indicated for patient safety reasons in the context of severe alcohol withdrawal (seizures or delirium tremens), comorbid severe substance use, medical or psychiatric conditions. *Residential withdrawal* settings may be appropriate for those with unsuitable home environments and supports to attempt ambulatory withdrawal, or for those with repeated failure at ambulatory attempts. *Ambulatory withdrawal* is a feasible approach for the management of alcohol withdrawal, is safe, effective and considerably less expensive when provided within a structured model of care. Ambulatory withdrawal can provide more timely access than residential or inpatient withdrawal, and often has good patient and carer acceptability. It is generally recommended unless there are clinical indications for a residential or inpatient withdrawal setting, such as a history of severe withdrawal.	Ib	Grade D: Poor
Psychosocial interventions (as adjunct to medication)			
Motivational enhancement counselling	Motivational enhancement approaches (group or individual) appear to be effective in enhancing the uptake and engagement with subsequent post-withdrawal treatment for substance use disorder.	Ib	Grade C: Satisfactory
Peer engagement during withdrawal	The role of peer engagement during withdrawal episode (e.g. 12-step meetings) upon subsequent engagement in post-withdrawal treatment (or 12 step programs) remains unclear, with few controlled studies and inconsistent findings.	Ib	Grade D: Poor
Patient or consumer information	No studies identified in alcohol withdrawal, however extrapolating from evidence from opioid withdrawal and from evidence regarding general consumer health literature, provision of structured information to patients may be associated with lower withdrawal severity and greater treatment retention.	IV	Grade D: GPP (Good Practice Point)
Linkages to post-withdrawal treatment services	Structured and assertive linkages to post-withdrawal treatment are associated with greater engagement with post-withdrawal treatment.	Ib	Grade C: Satisfactory
Physical interventions (as adjunct to medications)			
Massage therapy during withdrawal	Limited evidence (2 RCTs with small numbers) suggests massage therapy may be effective in reducing withdrawal symptoms and anxiety during withdrawal, as an adjunct to other interventions.	Ib	Grade D: Poor

Intervention	Recommendation	Level of evidence	Quality of evidence
Auricular or traditional Chinese medicine acupuncture during withdrawal episode.	Most controlled studies have examined alcohol or opioid withdrawal, and usually as an adjunct to routine care. Meta-analyses indicate there is evidence of a reduction in withdrawal symptoms, cravings and anxiety symptoms, although no differences in completion rates. When individual drug types are examined (e.g. alcohol, opioids, stimulants) there are no benefits of acupuncture on withdrawal symptoms or cravings. The reviewers caution that there are inconsistent findings between studies, poor quality studies and evidence of publication bias, and suggest caution in interpreting evidence.	GRADE Low or Very Low	Grade D: Poor
Exercise for alcohol	Controlled studies were not identified examining aerobic or mind- body (e.g. yoga) exercise programs for alcohol, and further research is required given safety concerns in these populations	No studies identified	Grade: No studies identified
Medications			
Benzodiazepines	Benzodiazepines show benefit against placebo with statistical significance for alcohol withdrawal seizures in systematic review. When compared to other drugs for prevention of alcohol withdrawal seizures, there is a trend towards benzodiazepines, however this did not reach statistical significance. No benzodiazepine has been shown to be superior to another, although benzodiazepines with good oral bioavailability and rapid onset of action (e.g. diazepam) are preferred, especially in preventing alcohol withdrawal seizures. Benzodiazepines do not appear to prevent alcohol withdrawal delirium.	Ia	Grade B: Good
Symptom-triggered versus fixed-dose benzodiazepines	Symptom-triggered use reduces total benzodiazepine dose and duration of treatment. However, there are no studies looking at safety outcomes. Symptom-triggered regimens are not validated for use in patients with severe medical or psychiatric comorbidity. Choice of regimens tends to relate to patient and programmatic factors (e.g. workforce training, treatment settings).	Ia	Grade D: GPP (Good Practice Point)
Loading-dose regimen versus symptom-triggered or fixed-dose benzodiazepine regimens	Loading-dose regimens are recommended for managing patients with a history of alcohol withdrawal seizures.	3	Grade D: GPP (Good Practice Point)
Benzodiazepines in the management of critically ill patients (e.g. ICU settings)	Benzodiazepines remain the standard of treatment in intensive care. Patients need to be recognised and treated early. There is increasing investigation into the use of alpha agonists and phenobarbital as adjunctive therapy, but at this stage neither can be recommended as monotherapy.	Ib	Grade C: Satisfactory

Intervention	Recommendation	Level of evidence	Quality of evidence
GHB	GHB may be better than placebo for alcohol withdrawal but does not appear to be better than benzodiazepines. There is no role at this stage in the treatment of alcohol withdrawal.	Ia	Grade: D Poor
Propofol	Propofol has a number of safety concerns, including higher rates of cardiovascular events and mechanical ventilation. It does not appear to offer benefits over benzodiazepines or alpha agonists. Furthermore, the timing, dose and duration of treatment remain unclear.	Ib	Grade D: Poor
Anticonvulsants	Anticonvulsants are well tolerated, a possible alternative to benzodiazepines in systematic review, however, meta-analysis reveals insufficient data to recommend anticonvulsants for the treatment of alcohol withdrawal syndrome (AWS).	Ia GRADE: Moderate	Grade C: Satisfactory
Alpha agonists	Alpha agonists only appear to have been evaluated in intensive care. Alpha agonists can help with the sympathetic symptoms of alcohol withdrawal and may help to lower the amount of benzodiazepine required, but at this stage can only be considered an adjunct to benzodiazepine treatment.	Ib	Grade C: Satisfactory
Combination carbamazepine/tiapride	One low quality systematic review showed evidence that this combination is effective. However, it lacked data around seizures and adverse events.	Ia	Grade D: Poor
Barbituates	Phenobarbital has been shown to have a role as an adjunct to benzodiazepines, especially in severe alcohol withdrawal. It may help to reduce duration of ICU admissions and prevent ICU admission. However, there is insufficient evidence to recommend it as monotherapy.	Ib	Grade C: Satisfactory
Baclofen	There is no evidence that baclofen is either safe or efficacious for alcohol withdrawal syndrome.	Ia	Grade D: Poor
Alcohol	There have been no new studies since 2010. Studies indicate alcohol dosing can be effective for preventing withdrawal complications (e.g. delirium), but not in treatment of alcohol withdrawal.	Ib	Grade D: Poor
Antipsychotic medications	The only systematic review since 2010 was of poor quality; this review cannot put forward any of its recommendations.	Ib	Grade D: Poor
Gabapentin	The only study since 2010 was of poor quality; this review cannot put forward any of its recommendations.	Ib	Grade D: Poor

Table E. Summary of evidence and recommendations for management of opioid withdrawal

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient admission	Unless inpatient admission is indicated for patient safety reasons (e.g. severe dehydration, comorbid medical, psychiatric or social conditions), there is no clear advantage in an inpatient (or residential) withdrawal setting over an ambulatory setting regarding completion of withdrawal, engagement in post-withdrawal treatment or post-withdrawal substance use, and as such, inpatient withdrawal is not routinely recommended.	Ib	Grade C: Satisfactory
Psychosocial interventions			
Psychosocial interventions (counselling, contingency management) in conjunction with pharmacotherapies	Adjunctive psychosocial interventions in addition to medication (e.g. buprenorphine or methadone tapering) are effective in terms of completion of treatment, use of opiates, participants abstinent at follow-up and clinical attendance in treatment. It is not possible at this time to identify optimal approaches to psychosocial interventions.	GRADE: Moderate to High	Grade C: Satisfactory
Patient information	Provision of structured information to patients is associated with lower withdrawal severity and greater treatment retention.	1b	Grade D: Poor
Linkages to post-withdrawal treatment services	Structured and assertive linkages to post-withdrawal treatment associated with greater engagement with post-withdrawal treatment.	1b	Grade D: Poor
Medications			
Tapered doses of opioid agonists Buprenorphine or methadone Tramadol	Effective for managing opiate withdrawal, with higher rates of treatment completion, and reduced withdrawal severity than symptomatic medications. Evidence does not specify optimal treatment duration or dose of agonists. Evidence does not indicate clear advantage of either methadone or buprenorphine. May be effective in reducing opioid withdrawal symptoms, however further research required.	GRADE: Low to Moderate Ib	Grade B: Good Grade D: Poor
Alpha-adrenergic agonists (high-dose clonidine)	Clonidine at doses ≥0.6mg/day is effective in reducing withdrawal symptoms, however its safety profile (hypotension, sedation) limits its utility outside of inpatient hospital settings, and it is recommended where opioid agonists cannot be used.	GRADE: Moderate	Grade B: Good

'Rapid detoxification' using opioid antagonists (naloxone or naltrexone)	Can be used to precipitate the onset (and severity) of opiate withdrawal in conjunction with other medications (e.g. alpha-adrenergic agonists, sedatives), usually in an inpatient setting. Safety concerns regarding severe adverse events (delirium, severe confusion).	GRADE: Low	Grade C: Satisfactory
Olanzapine	Single doses of olanzapine (IM) may have a role in the emergency management of opiate withdrawal (e.g. in Emergency Departments) where an opioid agonist cannot be given.	Ib	Grade D: Poor
Other medications: pregabalin, gabapentin, venlafaxine, diazepam.	Evidence is still emerging for the use in the management of opioid withdrawal and cannot be recommended at this time.	Variable according to medication	Grade D: Poor
Physical Interventions			
Auricular or traditional Chinese medicine acupuncture during withdrawal episode.	Most controlled studies have examined alcohol or opioid withdrawal, and usually as an adjunct to routine care. Meta-analyses indicate there is evidence of a reduction in withdrawal symptoms, cravings and anxiety symptoms, although no differences in completion rates. When individual drug types are examined (e.g. alcohol, opioids, stimulants) there are no benefits of acupuncture on withdrawal symptoms or cravings. The reviewers caution that there are inconsistent findings between studies, poor quality studies and evidence of publication bias, and suggest caution in interpreting evidence.	GRADE: Low or Very Low	Grade D: Poor
Exercise for opioid withdrawal	Exercise programs (e.g. jogging, walking) are associated with reductions in withdrawal symptoms, and specific symptoms of anxiety and depression, and should be encouraged in opioid withdrawal.	Ib	Grade D: Poor
Massage therapy during withdrawal	No evidence identified in opioid withdrawal. Limited evidence (extrapolated from alcohol withdrawal RCTs) suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal.	Ib	Grade D: Poor

Table F. Summary of evidence and recommendations for management of cannabis withdrawal

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient, residential and ambulatory withdrawal setting	No controlled studies were identified comparing withdrawal settings for cannabis withdrawal. Recommendations extrapolated from evidence for alcohol and opioid withdrawal. Inpatient admission is indicated for patient safety reasons in the context of severe comorbid medical or psychiatric conditions. Residential withdrawal settings may be appropriate for those with unsuitable home environments and supports to attempt ambulatory withdrawal, or those with repeated failure at ambulatory withdrawal attempts. Ambulatory withdrawal a feasible approach for management of cannabis withdrawal and generally recommended.	Extrapolated evidence: Ia (alcohol); Ib (opioids). Evidence for cannabis: III	Grade D: Poor
Psychosocial interventions			
Psychosocial interventions (structured counselling, case management, provision of information)	No controlled trials examining psychosocial interventions (e.g. counselling, case management, provision of information) in the management of cannabis withdrawal were identified. Evidence extrapolated from evidence for alcohol and opioids. Psychosocial interventions (structured withdrawal counselling, case management) should be incorporated into the management of cannabis withdrawal.	Extrapolated evidence	Grade D: GPP (Good Practice Point)
Patient information	Provision of structured information to patients is associated with lower withdrawal severity and greater treatment retention.	Ib	Grade D: Poor
Linkages to post-withdrawal treatment services	Structured and assertive linkages to post-withdrawal treatment associated with greater engagement with post-withdrawal treatment.	Ib	Grade D: Poor
Medications			
Cannabinoid agonist medications (nabiximols, dronabinol, nabilone)	Studies in human laboratory and clinical populations consistently suggest that cannabinoid agonists (at CB1 receptors) such as THC (e.g. in nabiximols) and synthetic THC analogues (dronabinol, nabilone) effectively reduce cannabis withdrawal symptoms, and are well tolerated in cannabis users. Evidence does not specify optimal treatment duration or dose of agonists, and further research is required to establish optimal medication regimens.	Ib	Grade C: Satisfactory

Intervention	Recommendation	Level of evidence	Quality of evidence
Hypnotic medications (zolpidem, benzodiazepines)	Hypnotic GABA-A medications zolpidem and benzodiazepines (specifically nitrazepam) improve sleep during withdrawal in clinical populations undergoing cannabis withdrawal (Ib), although there are caveats regarding the risks of dependence and rebound symptoms with long term sedative use, and the potential for non-medical use must be considered.	Ib	Grade C: Satisfactory
Mirtazepine	A laboratory study suggests mirtazepine may assist with increasing appetite and sleep symptoms, but no impact on global withdrawal, mood or anxiety.	IIb	Grade D: Poor
Other medications	There is limited or no evidence to support the current use of medications including: noradrenergic (e.g. venlafaxine) and serotonergic (esclitalopram, buspirone, flouxetine) antidepressants, baclofen, lithium, gabapentin, topiramate, N-acetlcysteine, quetiapine, cannabidiol.	Variable according to medication	Grade D: Poor
Physical Interventions			
Aerobic exercise for cannabis withdrawal	Aerobic exercise programs are associated with reductions in withdrawal symptoms, and specific symptoms of sleep disturbances, anxiety and depression, and should be encouraged in cannabis withdrawal.	Ib	Grade D: Poor
Mind-body exercise (e.g. yoga)	No controlled studies were identified examining yoga for substance withdrawal (excluding tobacco). Further research recommended.	Nil	Grade: No studies identified
Massage therapy during withdrawal	Limited evidence suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal.	Ib	Grade D: Poor

Table G. Summary of evidence and recommendations for management of benzodiazepine withdrawal

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Setting	All reviews indicate that benzodiazepine withdrawal can be safely managed in the community setting. An inpatient admission may be indicated to stabilise a patient with a history of erratic high-dose benzodiazepine use prior to a gradual taper in the community, or for managing withdrawal from other substances, significant co-morbidities, or other vulnerabilities. However rapid dose reductions in a brief inpatient admission (e.g. less than two weeks) is usually not recommended for a patient using moderate or high doses of benzodiazepines, due to the risk of severe withdrawal symptoms (e.g. seizures, panic) emerging after discharge.	Ib	Grade C: Satisfactory
Psychosocial interventions			
Psychosocial interventions (e.g. CBT), in conjunction with pharmacotherapies	Both cognitive behavioural therapy (CBT) (Moderate GRADE evidence) and relaxation training (Low GRADE) are effective in reducing benzodiazepine use during withdrawal and in the immediate (three month) post withdrawal period, as adjuncts to benzodiazepine taper.	GRADE: Moderate (CBT), Low (relaxation)	Grade C: Satisfactory
Prescribing interventions and patient information	There is emerging evidence to suggest that a tailored general practitioner's letter (for low dose patients (e.g. using <10mg ODE), a standardised interview, or provision of written information/instructions from the prescriber to patients could be effective in patients with low dose long-term benzodiazepine use. No evidence to suggest it is effective with patients using high doses/illicit use of benzodiazepines.	Ib	Grade D: Poor
Physical interventions			
Massage therapy during withdrawal	Limited evidence extrapolated from alcohol withdrawal literature suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal. Evidence supports relaxation training (see psychosocial interventions above).	Extrapolated from Alcohol (Ib)	Grade D: Poor
Medications			
Tapered doses of benzodiazepines	Gradual taper more favourable than abrupt cessation or rapid taper. Rate 10–25% wk/fortnight, duration 8–24 wks. Individually adjusted withdrawal rate; consider; benzodiazepine type, dosage, psychosocial/environmental factors, comorbities. Expert panel - British Association for Psychopharmacology Guidelines suggest initial taper of the benzodiazepine the patient has been on, prior to transfer to a longer-acting benzodiazepine, for patients on "therapeutic" doses.	GRADE: Moderate to High	Grade B: Good

Intervention	Recommendation	Level of evidence	Quality of evidence
	A benzodiazepine dose of 30mg /day (oral diazepam equivalent) is usually adequate as a starting dose for dose reductions for patients with a pattern of erratic high dose benzodiazepine use.		
'Rapid' dose reduction (less than two weeks)	It has been suggested that inpatient rapid taper over one week may be as safe and effective as gradual outpatient taper. Two poor quality studies – findings have not been replicated. The main concern with rapid dose reductions is the emergence of severe withdrawal symptoms after cessation of medication, especially for patient stake moderate or high dose benzodiazepines (e.g. ODE 10mg / day).	IIa	Grade D: Poor
Other medications to manage benzodiazepine withdrawal: Pregabalin Captodiame Paroxetine Tricyclic antidepressants	Potential for selective serotonin re-uptake inhibitors (SSRIs) e.g. paroxetine and carbamazepine in treatment of benzodiazepine withdrawal. However, all studies are of very low quality, therefore, not clinically recommended. Flumenazil – serious adverse effects resulting in the study being prematurely terminated.	GRADE: Low	Grade D: Poor
Maintenance benzodiazepines	May be effective for patients dependent on high doses/ illicit benzodiazepine use, those with repeated failure at attempted withdrawal. However, there is insufficient evidence from controlled studies to support 'maintenance' treatment for the management of benzodiazepine dependence. Lack of evidence to support efficacy.	IIb	Grade D: Poor
Pharmacological management of anxiety post-withdrawal: Carbamezapine Pregabalin Captodiame Paroxetine Flumazenil	Emerging evidence for pharmacological management of anxiety, post-benzodiazepine withdrawal. Carbamezapine is one of the most promising drugs, but due to low- to very low-quality of evidence, cannot be clinically recommended at this time. The use of the benzodiazepine antagonist flumazenil ('rapid detox') has not been demonstrated to be safe in published studies and is not recommended for use.	Ib	Grade D: Poor

Table H. Summary of evidence and recommendations for management of amphetamine withdrawal

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient admission	Unless inpatient admission is indicated for patient safety reasons (e.g. cardiac complications or psychosis, comorbid medical, psychiatric or social conditions), there is no clear advantage in an inpatient (or residential) withdrawal setting over an ambulatory setting regarding completion of withdrawal, engagement in post-withdrawal treatment or post-withdrawal substance use, and as such, inpatient withdrawal is not routinely recommended.	Extrapolated from other substances, and from profile of withdrawal syndrome	Grade D: Poor
Psychosocial interventions			
Psychosocial interventions (counselling, contingency management) in conjunction with pharmacotherapies	While psychosocial therapies have been associated with better outcomes in people with stimulant use disorder there is little evidence to suggest that these interventions may be effective in the withdrawal setting.	III	Grade D: Poor
Physical interventions			
Exercise for stimulant use disorders	Controlled studies were not identified examining aerobic exercise programs for stimulant use disorders, and further research is required, particularly given safety concerns (cardiovascular effects) in these populations.	Extrapolated from literature for other substances	Grade D: Poor
Mind-body exercise (e.g. yoga)	No controlled studies were identified examining yoga for substance withdrawal (excluding tobacco). Further research recommended.	Nil	Grade: No controlled studies identified
Massage therapy during withdrawal	Limited evidence suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal.	Ib Extrapolated from alcohol	Grade D: Poor

Intervention	Recommendation	Level of evidence	Quality of evidence
		withdrawal literature	
Medications			
Antidepressants			
Mirtazapine	Contradictory evidence for the efficacy of mirtazapine. May reduce hyperarousal and anxiety, reduce craving and lessen symptom severity during withdrawal. May have no effect on any of the above outcomes. May reduce sexual risk-taking among men who have sex with men. Evidence is highly contradictory, and a recommendation cannot be made.	Ia	Grade D: Poor
Amineptine	May not reduce withdrawal symptoms or craving as compared to placebo.		
Imipramine	May improve retention in treatment.		
Sertraline	Has demonstrated adverse effects on retention in treatment and abstinence compared with placebo		
Bupropion	Evidence suggests bupropion may or may not improve abstinence rates.		
Antipsychotics			
Olanzapine	May be effective in managing MA induced psychosis. May lead to more weight gain compared with haloperidol.	IIa	Grade C: Satisfactory
Haloperidol	May be effective in managing MA induced psychosis. Associated with a higher rate of acute extrapyramidal motor effects and lower treatment retention compared with olanzapine.		
Quetiapine	As effective as haloperidol in the management of MA induced psychosis.		
Risperidone	Generally well accepted medication. May be more effective at managing MA induced psychosis than aripiprazole.		
Aripiprazole	May reduce retention in treatment of patients with MA induced psychosis. Caution regarding length of treatment is required.		
Benzodiazepines			

Intervention	Recommendation	Level of evidence	Quality of evidence
Diazepam Midazolam Lorazepam	There have been no studies that assess benzodiazepines in the context of MA withdrawal; however, the underlying mechanism of action and medication effects are well understood and can therefore be used to manage symptoms associated with MA withdrawal. Caution regarding length of treatment is required.	IV for withdrawal, Ia for symptomatic management	Grade C: Satisfactory (outside of withdrawal context, but symptomatic management)
Psychostimulants			
Dexamphetamine	May reduce craving but not use. Insufficient RCT evidence.	IIa	Grade D: Poor
Modafinil	May or may not be effective at reducing withdrawal symptoms and craving. May improve memory.		
Opioid agonists			
Methadone	May reduce craving, however less effective than buprenorphine when length of treatment is greater than 10 days. Unknown if more effective than placebo.	IIa	Grade D: Poor
Buprenorphine	May reduce craving, more effective than methadone when length of treatment is greater than 10 days. Unknown if more effective than placebo.		
Riluzole	May reduce craving during MA withdrawal.	IIb	Grade D: Poor
Pexcerfont	May reduce craving during MA withdrawal.		
Amantadine	May reduce fatigue in post-acute withdrawal only.		

Table I. Summary of evidence and recommendations for management of withdrawal from gamma hydroxybutyrate (GHB) and its precursors gammabutyrolactone (GBL) and 1,4-butanediol (1,4-BD)

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient admission	Hospital admission required for severe withdrawal, including delirium. ICU may be required. Planned withdrawal from GHB is possible in an outpatient setting in less severe dependence.	IIb Extrapolated from other substances and profile of withdrawal features	Grade D: Poor
Psychosocial interventions			
Psychosocial interventions (counselling, contingency management) in conjunction with pharmacotherapies	No review or case report has investigated or described psychosocial interventions during GHB withdrawal.	N/A	Grade D: Poor
Physical interventions			
Massage therapy during withdrawal	Limited evidence suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal.	Ib Extrapolated from alcohol withdrawal literature	Grade D: Poor
Medications			
Benzodiazepines	Benzodiazepines are frequently employed to manage symptoms following GHB cessation, typically with titration and tapering of very high doses. They should not be used if a history of psychosis or resistance is known/apparent. All data in this context (GHB withdrawal) derived entirely from case reports.	IV	Grade D: Poor
Diazepam	Evidence of successful withdrawal from GHB with high dose diazepam.		
Lorazepam	Evidence of successful withdrawal from GHB with high dose lorazepam.		

Intervention	Recommendation	Level of evidence	Quality of evidence
Barbiturates	May be effective as adjunct therapy to benzodiazepines given intravenously in severe cases in inpatient settings. May also be considered as primary treatment option however there is no evidence to support this. All data in this context (GHB withdrawal) derived entirely from case reports.	IV	Grade D: Poor
Baclofen	May be effective as an oral adjunct therapy to benzodiazepines, particularly to help manage seizures and tremors.	IIb	Grade D: Poor
Gamma hydroxybutyrate	Titration and tapering of pharmaceutical GHB (usually as sodium oxybate) may assist in successful GHB detoxification. Particularly effective where high-dose benzodiazepines have failed (one explorative pilot study [n=23]; one observational cohort study [n=274]; case reports).	III	Grade D: Poor
Dexmedetomidine	Dexmedetomidine infusion has shown success during abrupt GHB cessation when benzodiazepines proved ineffective in intensive care settings (review of case series).	IIb	Grade D: Poor

Table J. Summary of evidence and recommendations for management of methadone to buprenorphine transfer

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Treatment setting	Transfers from low- to moderate-dose methadone can usually occur in outpatient specialist settings. Transfers from high methadone doses (>50mg) may require a brief inpatient admission for transfer procedures.	III	Grade D: Poor
Psychosocial intervention	No controlled studies but recommended in Australian MATOD and NSW OTP Clinical Guidelines. Patient and carer information and education is an important aspect of treatment planning.	IV	Grade D: GPP (Good Practice Point)
Monitoring	Regularly monitor through transfer process using a structured opiate withdrawal scale (e.g. COWS, SOWS) Review patient regularly throughout transfer process (including daily for first several days of buprenorphine dosing until dose stable).	IV	Grade D: GPP (Good Practice Point)
Medication	Few controlled trials, most evidence from case series. Discontinue methadone dose and initiate buprenorphine (low dose with incremental dose increases every 1–2 hours until comfortable), with aim of achieving daily buprenorphine dose (usually 16–32mg) within 1–3 days.	III	Grade D: Poor

For classification schemes for categorisation/grading of evidence see Appendices 1 and 2.

Abbreviations

The following abbreviations are used in this report

1,4BD	1,4-butanediol
AE	adverse events
AoD	alcohol and other drugs
AWS	Alcohol withdrawal syndrome
BPN	buprenorphine
BZD	benzodiazepine
CBD	cannabidiol
CBT	cognitive behavioural therapy
CNS	central nervous system
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol
COWS	Clinical Opiate Withdrawal Scale
CRA	Community reinforcement approach
CUD	cannabis use disorder
DT	delerium tremens
DZP	diazepam
ER	extended release
GHB	gamma-hydroxybutyrate
GBL	gammabutyrolactone
ICU	Intensive care unit
LGBTI	Lesbian, gay, bisexual, transgender, intersex
OUD	opioid use disorder
MA	methamphetamine
MDMA	methylenedioxy methamphetamine
NTX	naltrexone
PHB	phenobarbital
RCT	randoised controlled trial
SOWS	Subjective Opiate Withdrawal Scale
SSRI	selective serotonin reuptake inhibitor
SUD	substance use disorder
TCM	traditional Chinese medicine
THC	tetrahydrocannabinol

Glossary

This list has been adapted from NSW Drug & Alcohol Withdrawal Clinical Practice Guidelines, 2008.
Note: quotation marks denote that the expression is slang or jargon.

Ambulatory detoxification
Managed withdrawal from a drug undertaken with the patient visiting the medical practitioner from home or travelling to and from a day care facility.

Amphetamines
Synthetic central nervous system stimulants.

Antidepressant
One of a group of psychoactive drugs prescribed for the treatment of depressive disorders. Also used for other conditions such as panic disorder.

Benzodiazepine (BZD)
One of the sedative-hypnotic groups of drugs. Introduced as safer alternatives to barbiturates, they have a general depressant effect that increases with the dose, from sedation to hypnosis to stupor. BZDs have significant potential for dependence. These are also referred to as minor tranquillisers.

Brief intervention
A treatment strategy in which a short-structured therapy is offered (between five minutes and two hours) and typically on a single occasion. Aimed at helping a person to reduce or stop substance use.

Buprenorphine (BPN)
A partial opioid agonist drug used in the treatment of opioid withdrawal and as a maintenance treatment for opioid dependence.

Cannabis
The generic name given to the psychoactive substances found in the marijuana plant Cannabis sativa. The main active constituent is delta 9- tetrahydrocannabinol (THC).

Cocaine
A central nervous system stimulant derived from the coca plant, used non-medically to produce euphoria or wakefulness. Often sold as white translucent, crystalline flakes or powder.

Continuing care
In the context of withdrawal managment, continuing care means managing the transition to life after withdrawal, when patients are likely to have continuing issues arising from their drug dependence. Includes referral to counselling, maintenance treatment, self-help groups and family services.

Craving
A very strong desire for a substance, or for the intoxicating effects of that substance.

Delirium tremens (DT)
An acute confusional state occurring during withdrawal from alcohol, characterised by rapid pulse, clouding of consciousness, dehydration, delirium, elevated body temperature, sweating, extreme fear, hypertension, tachycardia, tremor and hallucinations

Dependence
The physiological adaptation that occurs when medications acting on the central nervous system are ingested with rebound when the medication is abruptly discontinued.

Depressant
Any substance that suppresses, inhibits or decreases some aspects of CNS activity. The main classes of CNS depressants are sedatives/hypnotics, opioids and neuroleptics.

Detoxification

Now outmoded term for managed withdrawal from a drug of dependence, the process by which a person is withdrawn from a psychoactive substance on which they are dependent.

'Ecstasy' (MDMA, 3,4-methylenedioxy-N-methylamphetamine)

A synthetic drug with stimulant effects on the central nervous system.

Comorbidity

In the context of withdrawal management, refers to a person who has coexisting substance use, with mental and/or other physical health problems.

Forest plot or 'blobbogram'

A graphical display of estimated results from a number of scientific studies addressing the same question, along with overall results.

GHB (gamma-hydroxybutyrate)

A central nervous system depressant, sometimes used illegally, usually in liquid form. Its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD) are also used.

Hallucinogen

A substance that alters perception, typically by inducing illusions or even hallucinations. Hallucinogens can include naturally occurring compounds (eg, magic mushrooms) and synthetic chemicals. They are usually taken orally.

Hashish

A concentrated form of cannabis.

Heroin

Heroin is the most common illicit opioid drug of dependence. It is usually intravenously injected, but it can also be smoked.

'Ice'

A potent crystalline form of methamphetamine. It is usually inhaled or injected.

Illicit drug

A substance obtained and used illegally for its psychoactive or physical effect.

Intoxication

The condition resulting from use of a psychoactive substance that produces behavioural and/or physical changes.

Ketamine

A dissociative general anaesthetic used legally for human and veterinary use and traded illegally as a recreational drug.

Maintenance therapy

A form of treatment of substance dependence by prescribing a substitute drug (e.g, methadone for the treatment of heroin dependence).

Marijuana

See cannabis.

Meta-analysis

A statistical analysis that combines the results of multiple studies on the same subject, in order to determine overall trends.

Methadone

A long acting synthetic opioid drug used in maintenance therapy for those who are dependent on opioids (prescribed in oral doses).

Methamphetamine

The most commonly used illicit stimulant, available in powder, base or crystalline ('ice') form.

Naloxone

An opioid receptor blocker that reverses the features of opioid intoxication. It is sometimes prescribed for the treatment of opioid overdose.

Naltrexone (NTX)

A specific opioid antagonist similar to naloxone, but more potent and long-acting.

Neuroadaptation

Physical dependence on a psychoactive substance. This means that a person has developed tolerance to the substance. If the drug is withdrawn, the person is likely to experience withdrawal symptoms.

Neuroleptic

One of a class of drugs used for treating acute and chronic psychoses. Also known as major tranquillisers and antipsychotics.

Opiate

One of a group of substances derived from the opium poppy with the ability to induce analgesia, euphoria and, in higher doses, stupor, coma, and respiratory depression.

This term excludes synthetic opioids.

Opioids

The generic term applied to alkaloids from the opium poppy, their synthetic analogues, and similar compounds synthesised within the body.

Overdose

The use of any drugs in such an amount that acute adverse physical or mental effects are produced. A dose that exceeds the individual's tolerance. Overdose may produce transient or lasting effects, or death.

Patient

In withdrawal management – refers to the individual seeking and/or obtaining treatment/assistance.

Pharmacotherapy

Drug treatment: in the context of withdrawal management, drug treatment for the symptoms and signs of withdrawal from a drug of dependence.

Polydrug use

Where a person uses more than one drug, often at the same time or following one another, and usually with the intention of enhancing, potentiating, or counteracting the effects of another substance.

Psychoactive substance

A substance that, when ingested, affects mental processes.

Psychostimulants

A class of drug with stimulatory effects on the central nervous system. The psychostimulants most commonly used illicitly in Australia today are amphetamines, ecstasy and cocaine.

Psychotropic

In the most general sense, a term with the same meaning as "psychoactive" (ie, affecting the mind or mental processes).

Rehabilitation

The process by which a person recovers from a substance use disorder to achieve an optimal state of health, psychological functioning, and well-being.

Relapse

A return to substance use after a period of abstinence.

Sedative/hypnotic

Any of a group of central nervous system depressants that can relieve anxiety and induce calmness and sleep.

Selective withdrawal

Managed withdrawal of one drug of dependence from a person with multiple drug dependencies.

Stimulant

Any agent that activates, enhances, or increases neural activity of the central nervous system. Stimulants include the amphetamines, cocaine, caffeine and nicotine.

Substance use disorders

Defined by the Diagnostic & Statistical Manual of Mental Disorders 5th ed (DSM-5) according to the following criteria: A problematic pattern of substance use, leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring at any time in the same 12–month period:

- *Tolerance,* as defined by either of the following: a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect; b) a markedly diminished effect with continued use of the same amount of the substance
- *Withdrawal,* as manifested by either of the following: a) the characteristic withdrawal syndrome for the substance; b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
- The substance is often taken in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful efforts to cut down or control substance use
- A great deal of time is spent in activities necessary to obtain the substance (e.g. visiting multiple doctors), use the substance (e.g. chain smoking), or recover from its effects
- Craving or a strong desire or urge to use the substance
- Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance use
- Important social, occupational, or recreational activities are given up or reduced because of substance use
- Recurrent substance use in situations in which it is physically hazardous
- Substance use is continued, despite knowledge of having a persistent or recurrent physical or physiological problem that is likely to have been caused or exacerbated by the substance.

THC

Tetrahydrocannabinol, the main active constituent in cannabis.

Therapeutic community

A structured environment in which people with drug use problems live in order to achieve rehabilitation. Such communities are often specifically designed for people with moderate or severe substance use disorders.

Tolerance

A decrease in response to a drug dose that occurs with continued use. Increased doses of the drug are required to achieve the effect originally produced by lower doses.

Wernicke's encephalopathy

An acute, life threatening, neurological syndrome consisting of confusion, apathy, dullness, a dreamy delirium, palsies of the ocular muscles and of gaze, nystagmus and disturbances in equilibrium, and ataxia. Its most common cause is thiamine deficiency associated with long-term excessive use of alcohol. If not treated immediately with thiamine, the patient is likely to progress to an amnestic syndrome. In some cases fatality can occur.

Withdrawal syndrome

A series of symptoms that develop within hours to a few days following cessation or reduction in use of a drug, by an individual with a substance use disorder.

Z –drug

GABA-A receptor agonists. Non-benzodiazepines, but with similar actions e.g. Zolpidem. They cause sedation and result in physical and psychological dependence following high dose or long-term use.

Background

Purpose of the rapid review

The scope and purpose of the review was identified by the NSW Ministry of Heath Alcohol and Other Drugs Program in consultation with the Sax Institute. The purpose of this review on management of withdrawal from alcohol and other drugs is to summarise the evidence available in the research literature since the last NSW Ministry of Health Clinical Guidelines were published in 2008. The review findings will inform the revised Clinical Guidelines that are currently under review by the NSW Ministry of Health, which commissioned this review.

This review includes withdrawal management in relation to the following substances:

- Alcohol
- Amphetamines and methamphetamine
- Methylenedioxy methamphetamine (MDMA)
- Cannabis
- Gamma hydroxybutyrate (GHB) and precursors: gamma-butyrolactone (GBL), and 1,4-butanediol (1,4BD)
- Benzodiazepines (BZDs)
- Cocaine
- Opioids
- Pregabalin/gabapentin
- High-dose transfers of opioid agonists.

Particular attention was given to:

a) The evidence for interventions (including pharmacological, psychosocial and physical therapies) in the management of withdrawal from each drug class, and where evidence was not available for particular interventions for a specific drug class (e.g. stimulants, cannabis), the ability to extrapolate from evidence for other substances with a more robust evidence base (e.g. alcohol, opioids).
b) The evidence regarding settings identified as inpatient hospital settings, residential, and ambulatory e.g. community and home-based settings.
c) The evidence for special populations identified for this review include the elderly, Aboriginal, and Lesbian Gay Bisexual Transgender Intersex (LGBTI) people, people in custody, and medically unwell populations e.g. liver failure, delirium etc.

Withdrawal syndromes

The American Psychiatric Association's Diagnostic and Statictical Manual v.5 (DSM-5)[3] classifies a Substance Use Disorder as mild, moderate or severe, depending on how many of the 11 diagnositc criteria are met, one of which is withdrawal. Withdrawal criteria in DSM-5 consist of two items:

1. Criteria A and B from the specified characteristic withdrawal syndrome for the substance.
2. The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

Criteria A and B differ slightly across substances. Criterion A specifies that the person has to have ceased (or reduced) heavy and prolonged use of the substance. Criterion B specifies that a certain number of symptoms, from a list provided, developed within several hours to a few days after the cessation (or reduction) of the substance. Deviations from this general pattern occur for sedative, hypnotic, or anxiolytics and stimulants, where in the Criterion A specifies only prolonged use (not heavy), and cannabis, which specifies that the Criterion B symptoms develop within approximately one week of ceasing or reducing use.

Some of the drugs included in this rapid literature review do not have an identified withdrawal syndrome according to the DSM-5 or ICD-10 classification systems. They include; MDMA, pregabalin/gabapentin, and GHB. Nevertheless, there is increasing clinical experience and case reports whereby individuals experience a

range of symptoms after stopping use of these substances, and this review includes the evidence regarding the management of these clinical sitiuations. Common signs and symptoms and management approaches described in the literature (usually from case studies) are reported in these chapters.

Methods

Peer-reviewed literature

A search of the peer-reviewed literature was conducted for each drug to identify relevant literature published after January 2008. This included a search of databases through the NSW Ministry of Health Clinical Information Access Portal (CIAP); Medline, Embase, Psychinfo, Cochrane and Pubmed, along with Google Scholar. These were searched for relevant literature, using the search term "withdrawal" and the name of the drug. Additional searches were conducted for settings, and special population related terms.

Both database-specific subject terms and other keywords were utilised e.g. drug name, withdrawal management, substance withdrawal syndrome etc.

Relevant systematic reviews, randomised controlled trials (RCTs) (involving humans) and other papers were identified and reviewed for inclusion in the chapter for each drug. Where there was limited or no published literature on withdrawal management of a drug, a further search utilising other key words e.g. 'dependence', was undertaken to identify any related literature.

For each drug, a 'key' systematic review was identified, and a further search was then conducted as a rapid combined databases search across MEDLINE, EMBASE and PSYCHINFO with a separate Cochrane search, to identify any RCTs conducted since the 'key' systematic review. The same broad keywords (e.g. drug name, withdrawal etc.) were used except with the addition of terms such as "*randomized*" or "*randomised*" (to ensure variants of this spelling were identified). The date limits set were 2008–2019/2020 (depending on what the database allowed), and language restriction was applied for only papers written in English.

For some drugs, where there were no results from the literature search for systematic reviews or RCTs, a search was conducted for any case series reports or case studies to identify any relevant information. It was not unexpected that there would be no literature in relation to withdrawal management for some drugs, given that they e.g. GHB and gabapentin, do not have a recognised withdrawal syndrome according to the International Classification of Diseases v. 10 (ICD-10), or the Diagnostic and Statistical Manual v.5.0 (DSM-5).

Where no literature was identified within the date limits set (2008–2019/2020), or where a systematic review did not clearly articulate the findings of an original study; relevant studies published before 2008, or original studies were reviewed, and in some cases were also included in the report.

Selecting reviews for evidence grading

The systematic reviews on each subject area were selected on the quality of the review and search strategy utilised, its relevance to the subject or intervention type, and recency. For some interventions several reviews were identified. Each chapter describes and summarises the reviews identified in tables, and where more than one review was identified, these reviews were rated according to their relevance for our rapid review as follows:

Green indicates the systematic review that has been used to directly base the evidence review for that particular subject or intervention type. It generally signifies the review is most relevant to the subject, has been well conducted and of high quality, and considered the 'gold standard' review(s) for that subject.

Yellow is the grade given to reviews of 'medium' quality or relevance to the subject. In general, the scope of studies and conclusions from an orange category review are considered against the 'Green' review where relevant, and any discrepancies addressed.

Red indicates reviews that are of low quality (e.g. no systematic search strategy) or are not particularly relevant to the subject or intervention being reviewed. In general, they are not utilised in this review to contribute to the conclusions on the withdrawal management of the drug.

One of the key principles in selecting systematic reviews and studies for this report was the focus upon interventions for withdrawal management, rather than withdrawal measures during longer-term treatment. Specifically, addiction research in this area has either looked at withdrawal interventions (examining withdrawal outcomes such as severity of withdrawal symptoms, cravings, completion of withdrawal, adverse events, uptake of post-withdrawal treatment), or 'post-withdrawal' longer-term studies looking at broader outcomes such as substance use and general health (sometimes referred to 'relapse prevention'). The latter also often collect withdrawal -related measures as secondary outcomes (such as cravings or withdrawal symptoms). Common examples of the latter category of studies include 12-week study (RCT) of a counselling intervention (e.g. CBT) or a medication (e.g. methadone). This latter group of studies are generally not included in this review, and the focus remains on studies examining withdrawal interventions.

Included studies

There was a large discrepancy in relation to the level of evidence for management of withdrawal of each drug. Opioids and alcohol have a large amount of literature available, and cannabis, benzodiazepines (BZDs) and amphetamines have a moderate availability of peer-reviewed literature, while, GHB, MDMA and cocaine, have little to no literature (pertaining to systematic reviews or RCTs) available in relation to withdrawal management. The quality of evidence also varied significantly according to the drug. Each drug chapter includes a summary table of the studies included.

Grey literature

A desktop search was conducted for relevant grey literature (research produced outside of traditional academic publishing, eg reports, white papers, working documents) for pregabalin/gabapentin, and MDMA, which had little peer -reviewed literature in relation to management of withdrawal. Relevant clinical guidelines from four states were identified, but only one (South Australia) was accompanied by an evidence report.[4] Evidence-linked Australian clinical guidelines relating to alcohol[5] and opioids[6] were also referenced where appropriate. A similar search was conducted for 'special' population groups, which identified some reports, guidelines and university graduate theses.

Evidence rating and grading of recommendations

Evidence rating and grading of recommendations for management of withdrawal are as follows:

The level of evidence was categorised according to the classification scheme outlined by Shekelle et al. (see Appendix 1), or GRADE for systematic reviews (Cochrane rating scale).

The quality of evidence and recommendations were graded according to the National Health and Medical Research Council (NHMRC) Recommendation grades: [2]

A=Excellent
B=Good
C=Satisfactory
D=Poor and D: Good Practice Point (GPP) (see Appendix 2)

Chapter 1. Overview of interventions for withdrawal management

This chapter provides an overview of approaches to withdrawal management that are shared across different drug classes, to avoid repetition in subsequent chapters. Specifically, an overview of:

- Treatment settings for withdrawal
- Psychosocial interventions, including counselling, patient information, self-help facilitation and linkages to subsequent treatment
- Physical therapy interventions, including exercise, acupuncture and massage therapy
- Symptomatic medications used for specific symptoms that commonly occur in different types of drug withdrawal
- Special populations, including elderly, people in custody, Aboriginal, and LGBTQI communities.

Treatment settings

Withdrawal can be broadly undertaken in a number of clinical settings. These include:

- Inpatient hospital (e.g. specialist withdrawal unit, general ward, mental health ward or short stay unit),
- Residential withdrawal unit (usually a specialist withdrawal unit not in a hospital, and without significant nursing or medical support)
- Ambulatory setting, that includes outpatient setting (where the patient attends a specialist or primary care health facility), or home-based withdrawal (where the AoD withdrawal service reviews the patient at home) or a hybrid of the two approaches
- Correctional facility (prison, remand or police cells).

This rapid review aims to review the evidence regarding the suitability of different withdrawal settings for each substance examined. Given the limited capacity for clinical trials in correctional settings, this review will not consider the evidence for withdrawal management in correctional settings to make treatment recommendations.

It should be noted that the evidence for different withdrawal settings is impacted upon by a number of patient safety, clinical and logistic factors, and that many of the treatment decisions regarding setting are not a matter of evidence of efficacy derived from controlled trials. For example, evidence from RCTs of carefully selected study participants does not directly inform decisions regarding treatment setting for patients with significant medical (e.g. pneumonia) or psychiatric comorbidity (e.g. suicidal or psychosis) that require a hospital admission; or for homeless patients where ambulatory withdrawal is not an option.

A general framework for decision-making regarding withdrawal settings is extrapolated from the work of the 2009 Australian Alcohol Treatment Guidelines, Management of alcohol withdrawal[5] , summarised below and in Table 1.1.

- Inpatient (hospital) withdrawal is indicated for those with a history of severe withdrawal (for example withdrawal seizures, psychosis, delirium, cardiovascular complications (e.g. severe hypertension, arrhythmias); withdrawing from multiple substances concurrently; medical (e.g. severe cardiovascular,

respiratory or hepatic disease, diabetes, systemic infections) or psychiatric comorbidity (e.g. suicidal ideation, psychosis, severe depression or anxiety). 'Non-elective' withdrawal may also occur in patients admitted to hospital for other indications or procedures.

- Residential withdrawal is indicated for those with unsuitable home environments (e.g. homeless, other substance use in the home) or lack of social supports, are unable to access outpatient or home-based withdrawal services, or with repeated failure at ambulatory withdrawal.
- Ambulatory withdrawal (either 'home based' and/or outpatient) is feasible, effective, safe and cost-effective, and often has good patient and carer acceptance. It is the recommended withdrawal setting, unless there are specific clinical reasons for more intensive residential or inpatient withdrawal settings. Ambulatory withdrawal involves a combination of structured approaches to assessment, monitorinig, psychosocial support and use of medication. 'Home-based' withdrawal involves services delivered at the patient's home setting, 'Outpatient' involves the client attending health services, with many ambulatory withdrawal services involving a combination of both activities delivered in home and health service settings.

Table 1.1 Considerations for selection of withdrawal setting

	Ambulatory	Residential	Inpatient (hospital)
Likelihood of severe withdrawal complications	N/A	N/A	History of severe withdrawal, (e.g. withdrawal seizures, delirium, cardiovascular complications or psychosis).
Medical or psychiatric comorbidity	Minor comorbidity	Minor comorbidity	Significant comorbidity
Other substance use	No heavy drug use	Heavy or unstable use other drugs	Heavy or unstable use other drugs
Social environment	Supportive home environment (not homeless, no substance use in home). Regular monitoring by reliable support people. Good access to outpatient service.	Unsupportive home environment or social supports. Poor access to outpatient services.	Unsupportive home environment or social supports. Poor access to outpatient services.
Previous withdrawal attempts		Repeated failure at ambulatory withdrawal	Repeated failure at ambulatory withdrawal

*For further details see text.

Within each chapter, the review examines the evidence for different settings for different substances. For many substances, there is limited evidence to inform clinical guidelines, however in this report we have attempted to extrapolate from evidence for other drugs, and from our understanding of the nature of different withdrawal syndromes in order to make recommendations regarding withdrawal settings. For some of the 'newer' substances which may be associated with severe symptoms or complications following cessation of regular and heavy use (e.g. GHB, baclofen, pregabalin, gabapentin), we recommend that patients be closely supervised by medical and nursing staff in inpatient hospital settings as a precautionary measure, until there is a more robust evidence base and understanding of these conditions.

The emphasis upon ambulatory withdrawal may be a significant departure from clinical practice for many drug and alcohol services in NSW. A number of review authors highlight the importance and potential benefits of ambulatory withdrawal in increasing treatment options and access to withdrawal treatment for patients and carers (avoiding waiting lists for residential or inpatient services), enhancing engagement with ongoing post-withdrawal services, and reducing the costs of withdrawal service provision.

Table 1.2 Summary of evidence and recommendations for withdrawal settings

Intervention	Recommendation	Level of evidence	Quality of evidence
Inpatient (hospital) setting	Inpatient (hospital) withdrawal is indicated for those with a history of severe withdrawal (for example withdrawal seizures, psychosis, delirium, cardiovascular complications); withdrawing from multiple substances concurrently; medical (e.g. severe cardiovascular, respiratory or hepatic disease, diabetes, systemic infections) or psychiatric comorbidity (e.g. suicidal ideation, psychosis, severe depression or anxiety). It is mostly relevant to withdrawal that involves cessation of alcohol, stimulants, or drugs that can be associated with severe withdrawal complications such as pregabalin, gabapentin, GHB. There may be a role for inpatient admission for patients stabilising on BZDs or transferring from high-dose methadone to buprenorphine.	Ib (alcohol, opioids) Extrapolated for other drugs.	Grade B: Good (for alcohol, opioids) Grade D: GPP for other drugs.
Residential withdrawal	Residential withdrawal is indicated for those patients with unsuitable home environments (e.g. homeless, other substance use in the home) or who lack of social supports, are unable to access outpatient or home-based withdrawal services, or have had repeated failure at ambulatory withdrawal.		
Ambulatory withdrawal (either home based and/or outpatient)	Ambulatory withdrawal is feasible, effective, safe and cost-effective, and often has good patient and carer acceptance. It is the recommended withdrawal setting for most attempts at withdrawal, unless there are specific clinical reasons for more intensive residential or inpatient withdrawal settings. Withdrawal programs that involve gradual tapering off medications (e.g. opioids, BZDs) should usually be conducted in an ambulatory setting.		

For classification schemes for categorisation/grading of evidence see Appendices 1 and 2.

Psychosocial interventions

Our search identified few controlled studies examining psychosocial (e.g. counselling, patient information, self-help supports) during withdrawal interventions across different drug classes. Studies for these interventions tended to be mostly available for alcohol or opioids. However, as many of the clinical principles of withdrawal management are shared across different drug classes, we have extrapolated findings for these interventions from one or two drug classes to other drugs where we considered the findings to be relevant. For example, in all the literature only one RCT (for opioid withdrawal) was identified that examined withdrawal outcomes associated with the structured provision of information (psychoeducation) to patients regarding withdrawal. Nevertheless, we considered the findings of this study to be relevant to other drug classes, and to be consistent with broader evidence regarding consumer health literacy, thus it could be considered a 'good practice point'. As such, the recommendation is extrapolated across all drug classes.

Where an evidence base has been identified regarding psychosocial interventions for a particular drug class (e.g. opioids, alcohol, BZDs), it is reviewed and summarised in that chapter. However, to avoid repetition across every chapter, the sections on psychological therapies are summarised below.

Summary of evidence regarding counselling interventions

Systematic reviews were identified examining psychosocial interventions for alcohol (predominately motivational enhancement approaches) and opioids (predominately motivational enhancement, contingency management), and these are reviewed in detail in the relevant chapters. In all studies, psychosocial interventions are considered as adjunct treatments in addition to routine care (usually involving medications). The main focus of studies of psychosocial withdrawal interventions has been the outcomes of withdrawal completion rates and engagement with post-withdrawal services. The evidence from both alcohol and opioid literature indicates that psychosocial interventions—particularly those using motivational enhancement approaches (in group or individual delivery—are effective in enhancing withdrawal completion and post-withdrawal treatment engagement.

Summary of evidence regarding patient information

While only one controlled study reported on the role of psychoeducation or patient information regarding withdrawal (in opioid users)[7], the finding that patient information improved patient outcomes is consistent with the broader evidence regarding consumer or patient information upon health outcomes, and we have extrapolated this finding across all drug classes.

Summary of evidence regarding self-help and peer engagement

The evidence for the role of self-help or peer engagement (e.g. 12-step meetings) during withdrawal is largely limited to alcohol withdrawal, for which there are inconsistent findings between studies. As such, it is not possible to make recommendations from the evidence as to whether this approach should be routinely incorporated into withdrawal management.

Summary of evidence regarding linkages to post-withdrawal treatment services

Evidence from alcohol and opioid treatment literature suggests that structured and assertive linkages (e.g. visits, follow-up appointments) between withdrawal and post-withdrawal treatment are associated with greater engagement with ongoing treatment. These findings can be extrapolated across other drug classes.

Table 1.3 Reviews of psychosocial interventions for withdrawal management

Review authors, title, reference	Date studies reviewed	Type of review/ study	Abstracts / summary	Evidence Grade
Timko C, Below M, Schultz NR, Brief D, Cucciare MA. Patient and Program Factors that Bridge the Detoxification-Treatment Gap: A Structured Evidence Review. Journal of Substance Abuse Treatment. 2015, 52, P 31-39 DOI: https://doi.org/10.101[6]/j.jsat.2014.11.009.	April 2014 Narrative review	Limited database systematic review	Although completion of detoxification (detox) and a successful transition from detox to substance use disorder (SUD) treatment and/or mutual-help groups are associated with better SUD outcomes, many patients do not complete detox or do not receive SUD care following detox. The purpose of this structured evidence review, summarisng data extraction on a yield of 26 articles, is to identify patient, program, and system factors associated with the outcomes of completion of alcohol detox and successful transitions from alcohol detox to SUD treatment and mutual-help group participation. The review found wide variability among studies in the rates at which patients complete a detox episode (45-95%) and enter SUD treatment or mutual-help groups after detox (14-92%). Within program factors, behavioral practices that contribute to both detox completion and transitioning to SUD care after detox entail involving the patient's family and utilising motivational-based approaches. Such practices should be targeted at younger patients, who are less likely to complete detox. Although more studies using a RCT design are needed, the evidence suggests that barriers to detox completion and transition to SUD care can be overcome to improve patient outcomes.	
Amato L; Minozzi S; Davoli M; Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for *opioid detoxification*. Cochrane Database of Systematic Reviews. (9)CD005031, 2011 Sep 07.	June 2011	Systematic review. Meta-analysis. 11 RCTs, 1592 participants	RCTs and controlled clinical trials that focus on any psychosocial associated with any pharmacological intervention aimed at opioid detoxification. People less than 18 years of age and pregnant women were excluded.	

Table 1.4 Evidence summary and recommendations regarding psychosocial interventions across all drug classes

Intervention	Recommendation	Level of evidence	Quality of evidence
Psychosocial interventions (as adjunct to medication)			
Motivational enhancement counselling	Motivational enhancement approaches (group or individual) appear to be effective in enhancing the uptake and engagement with subsequent post-withdrawal treatment for SUD.	Ib	Grade C: Satisfactory
Peer engagement during withdrawal	The role of peer engagement during withdrawal episode (e.g. 12-step meetings) upon subsequent engagement in post-withdrawal treatment (or 12 step programs) remains unclear, with few controlled studies and inconsistent findings.	Ib	Grade D: Poor
Patient or consumer information	Few controlled studies identified in withdrawal, however extrapolating from evidence for opioid withdrawal and from evidence regarding general consumer health literature, provision of structured information to patients may be associated with lower withdrawal severity and greater treatment retention.	IV	Grade D: GPP (Good Practice Point)
Linkages to post-withdrawal treatment services	Structured and assertive linkages to post-withdrawal treatment associated with greater engagement with post-withdrawal treatment.	Ib	Grade C: Satisfactory

For classification schemes for categorisation/grading of evidence see Appendix 1 and 2

Physical therapies

Our search identified few controlled studies examining physical interventions (e.g. exercise, acupuncture, massage) during withdrawal interventions across different drug classes. Studies for these interventions tended to be mostly available for alcohol or opioids. However, as many of the clinical principles of withdrawal management are shared across different drug classes, we have extrapolated findings for these interventions from one or two drug classes to other drugs where we considered the findings relevant. For example, evidence for massage therapy being effective in reducing anxiety from alcohol studies can most likely be extrapolated to other drug classes. In other circumstances, we argue that findings should not be extrapolated for safety reasons until further research has been conducted, for example, findings from exercise programs for opioid and cannabis withdrawal may not be able to be extrapolated to apply to patients undergoing alcohol or methamphetamine withdrawal for safety reasons.

Where an evidence base has been identified regarding a physical therapy intervention for a particular drug class, it is reviewed and summarised in that chapter. However, to avoid repetition across every chapter, the sections on physical therapies are summarised in this section.

Summary of evidence regarding acupuncture.

Liu et al.[8] identified 11 RCTs of acupuncture for alcohol withdrawal, while Grant et al[9] identified 26 RCTs with 1175 participants reporting data on withdrawal or craving symptoms, across different drug classes (most examined alcohol and opioids, but studies also of stimulants). Both reviews identified the quality of the evidence as 'low or very low' (Grant used GRADE classification system), and with likely publication biases, highlighting caution in interpretation of the findings.

Liu et al identified no difference between acupuncture and controls (usually sham acupuncture) regarding alcohol withdrawal completion rates, or total alcohol withdrawal symptoms, although some studies point to reduced craving during withdrawal, and general improvements in anxiety related measures. Grant et al pooled all studies and a meta-analysis suggests a moderate effect size for reduced withdrawal symptoms or cravings immediately post-acupuncture, however with considerable heterogeneity and findings between studies, and rated the evidence as Low GRADE. The benefits arise predominately in studies of traditional Chinese medicine (TCM) acupuncture rather than auricular acupuncture, although the authors caution about possible publication bias and a very low quality of evidence regarding RCTs of TCM acupuncture. Findings for individual drug classes (alcohol, opioids, stimulants) showed no significant benefits on withdrawal symptoms or cravings.

In summary, the available evidence regarding acupuncture indicates that across the different withdrawal substances, the RCTs indicate no consistent benefits of acupuncture on withdrawal severity or withdrawal completion rates. The evidence suggests there may be some benefits on post-withdrawal anxiety, however this was not a consistent finding across studies. The evidence is of low quality and better studies are required. At this stage, acupuncture is not recommended for routine implementation.

Summary of evidence regarding exercise

The systematic review by Wang identified five RCTs – four in heroin users and one in tobacco. Since then, two further RCTs in cannabis[10] and alcohol[11] dependent users have been identified relevant to this review. The meta-analysis by Wang[12] indicates a significant reduction in global withdrawal symptoms – although considerable heterogeneity between studies; and also significant improvements in symptoms of anxiety and depression (consistent with the broader literature and evidence for exercise upon mental health outcomes). These findings are consistent with the findings for cannabis users[13], although further research is required in alcohol and stimulant use disorders. Most studies have examined aerobic exercise programs, and there is

less evidence regarding mind-body exercise programs such as yoga for substances other than tobacco, and further research is recommended in this area.

Given the potential cardiac complications seen in alcohol withdrawal (arrhythmias, hypertension, cardiomyopathy) and stimulant users (arrhythmias, hypertension), further research is required regarding the safety of exercise in patients undergoing withdrawal from alcohol or psychostimulants.

All patients should undertake a medical assessment prior to embarking upon exercise programs during withdrawal.

Summary of evidence regarding massage therapy

Two controlled studies were identified, but there were no systematic reviews of the subject. The studies examined the effects of massage in patients undergoing alcohol withdrawal[14] or a mixed population undergoing withdrawal from alcohol, cocaine or opioids.[15] Both studies found that massage was more effective than control ('rest' or 'relaxation') in reducing withdrawal symptoms – most notably anxiety symptoms. While the evidence is limited, the positive findings, low safety risk and intervention costs, and potential attractiveness of the massage therapy for some individuals, massage therapy is recommended as adjunctive therapy in withdrawal management, recognising the need for further research.

Table 1.5 Systematic reviews of physical therapies in withdrawal management (acupuncture, exercise and massage)

Review authors, title, reference	Date studies reviewed	Type of review	Abstract	Evidence Grade
Acupuncture				
Liu X, Qin Z, Zhu X, Yao Q, Liu Z. Systematic review of acupuncture for the treatment of alcohol withdrawal syndrome. Journal of the British Medical Acupuncture Society, 2018;36:275–283.	August 2016	Systematic Meta-analysis	*Background*: Acupuncture has been used as a potential therapy for alcohol withdrawal syndrome (AWS), but evidence for its effects on this condition is limited. *Objective* To assess the effects and safety of acupuncture for AWS. *Data sources:* Central Register of Controlled Trials (CENTRAL), PubMed, Embase, the Cochrane Library, PsycINFO, Chinese Biomedicine Literature (CBM), China National Knowledge Infrastructure (CNKI) and Wan-Fang Database were searched from their inception to August 2016. Study eligibility criteria Randomised Controlled Trials (RCTs) of drug plus acupuncture or acupuncture alone for the treatment of AWS were included. *Data collection and analysis* Continuous data were expressed as mean difference (MD) with 95% confidence intervals (95% CI). Dichotomous data were expressed as risk ratio (RR) with 95% CI. *Results* Eleven RCTs with 875 participants were included. In the acute phase, two trials reported no difference between drug plus acupuncture and drug plus sham acupuncture in the reduction of craving for alcohol; however, two positive trials reported that drug plus acupuncture was superior to drug alone in the alleviation of psychological symptoms. In the protracted phase, one trial reported acupuncture was superior to sham acupuncture in reducing the craving for alcohol, one trial reported no difference between acupuncture and drug (disulfiram), and one trial reported acupuncture was superior to sham acupuncture for the alleviation of psychological symptoms. Adverse effects were tolerable and not severe. *Conclusion* There was no significant difference between acupuncture (plus drug) and sham acupuncture (plus drug) with respect to the primary outcome measure of craving for alcohol among participants with AWS, and no difference in completion rates (pooled results). There was limited evidence from individual trials that acupuncture may reduce alcohol craving in the protracted phase and help alleviate psychological symptoms; however, given concerns about the quantity and quality of included studies, further large-scale and well-conducted RCTs are needed. Protocol reg: PROSPERO CRD42016039862.	
Grant S, Kandrack R, Motala A, Shanman R, Booth M, Miles J, et al. Acupuncture for	Nov 2014	Systematic	*Background*: This systematic review aimeds to estimate the effects of acupuncture for adults with substance use disorders (SUDs).	

Review authors, title, reference	Date studies reviewed	Type of review	Abstract	Evidence Grade
substance use disorders: A systematic review and meta-analysis. Drug and Alcohol Dependence. 2016: 163;1–15.		Meta-analysis	*Methods*: We searched 7 electronic databases and bibliographies of previous studies to identify eligible randomised trials. Two independent reviewers screened citations, extracted data, and assessed risks of bias. We performed random effects meta-analyses. We assessed quality of evidence using the GRADE approach. *Results*: We included 41 studies with 5,227 participants. No significant differences were observed between acupuncture and comparators (passive controls, sham acupuncture, treatment as usual, and active interventions) at post-intervention for relapse (SMD −0.12; 95%CI −0.46 to 0.22; 10 RCTs), frequency of substance use (SMD −0.27; −2.67 to 2.13; 2 RCTs), quantity of substance use (SMD 0.01; −0.40 to 0.43; 3 RCTs), and treatment dropout (OR 0.82; 0.63 to 1.09; 22 RCTs). We identified a significant difference in favor of acupuncture versus comparators for withdrawal/craving at post-intervention (SMD −0.57, −0.93 to −0.20; 20 RCTs), but we identified evidence of publication bias. We also identified a significant difference in favor of acupuncture versus comparators for anxiety at post-intervention (SMD −0.74, −1.15 to −0.33; 6 RCTs). Results for withdrawal/craving and anxiety symptoms were not significant at longer follow-up. Safety data (12 RCTs) suggests little risk of serious adverse events, though participants may experience slight bleeding or pain at needle insertion sites. *Conclusions*: Available evidence suggests no consistent differences between acupuncture and comparators for substance use. Results in favor of acupuncture for withdrawal/craving and anxiety symptoms are limited by low quality bodies of evidence.	
Wu SL; Leung AW; Yew DT. Acupuncture for Detoxification in treatment of Opioid Addiction. East Asian Archives of Psychiatry. 2016;26(2):70–-6.	2015	Meta-analysis	Clinical trials of acupuncture for the management of different withdrawal symptoms were reviewed. The potential of acupuncture to allay opioid-associated depression and anxiety, and its possible use as an adjuvant treatment were evident. A lack of effect was indicated for opioid craving. Most studies were hampered by inadequate reporting details and heterogeneity, thus future well-designed studies are needed to confirm the efficacy of acupuncture in opioid addiction treatment. Findings consistent with Grant and Liu reviews listed above.	
D'Alberto A. Auricular Acupuncture in the tTreatment of Cocaine/Crack Abuse: A Review of the Efficacy, the Use of the National Acupuncture Detoxification	2004	Systematic Meta - Analysis	Six randomised controlled trials (RCTs) met the inclusion criteria and were included in this review. All studies scored over 60 points indicating a relatively adequate methodology quality. The mean was 75 SD (6.80). A linear regression analysis did not yield a statistically significant association (n=6, p=0.11). Conclusions: This review could not confirm that	

Review authors, title, reference	Date studies reviewed	Type of review	Abstract	Evidence Grade
Association Protocol, and the Selection of Sham Points. Journal of Alternative and Complementary Medicine. 2004; 10(6); 985–1000			acupuncture was an effective treatment for cocaine abuse. The NADA protocol of five treatment points still offers the acupuncturist the best possible combination of acupuncture points based upon Traditional Chinese Medicine. Throughout all the clinical trials reviewed, no side-effects of acupuncture were noted. Review relevant to cocaine withdrawal only, and hence less relevant than Grant and Liu reviews listed above.	
Baker TE, Chang G. The use of auricular acupuncture in opioid use disorder: A systematic literature review. American Journal on Addictions. 2016;25(8):592-602.	May 2015	Systematic Review	Incorporation of the NADA protocol into existing evidence-based treatment approaches may facilitate recovery and, through its impact on treatment retention and completion, indirectly impact morbidity, and mortality in individuals with Opioid Use Disorder (OUD). Given limitations of current review, conclusions are tentative and directions for future research discussed.	
Exercise Interventions (includes yoga)				
Wang D; Wang Y; Wang Y; Li R; Zhou C. Impact of physical exercise on substance use disorders: a meta-analysis. PLoS ONE. 9(10):e110728, 2014.	2013	Systematic, meta-analysis	We conducted a meta-analysis on withdrawal symptoms in drug abusers after physical exercise intervention. 4 RCTs were included that examined heroin withdrawal (Liu 2002, 2013; Huang 2000a, 2000b), and one examined nicotine withdrawal (Ussher 2003). The Q test (Q(4)=151.4, p,0.001) and I2 test (I2=97.4%) showed heterogeneity in the included studies. We chose the random effects model in meta-analysis and the result indicates that exercise can significantly ease withdrawal symptoms in subjects with SUD (SMD=21.24 (95% CI: 22.46, 20.02), z=22.00, p,0.05) (Figure 3). The sub-group analysis finds that different types of physical exercise affect withdrawal symptoms of Substance Use Disorder (SUD differently. Exercise also effective in reducing anxiety and depression symptoms; enhancing longer term abstinence rates.	
Zschucke E, Heinz A, Strohle A. Review rticle: Exercise and physical activity in the therapy of substance use sisorders. The Scientific World Journal. 2012, Article ID 901741, 19 pages doi:10.1100/2012/901741	2011	N/A	Very useful journal as separates into tobacco/alcohol and illicit drugs – thereby overcoming problems of Wang et al that combine tobacco cessation into meta-analyses. Fewer studies with alcohol and other drugs make conclusions more cautious than when including tobacco. Also, few studies in withdrawal settings. General findings of reduced psychological symptoms, and cravings with exercise in post-withdrawal exercise interventions. Similar generalisations in withdrawal also, however studies few and poor quality.	
Lintzeris N, Allsop D, Bhardwaj A, Rooney K, Haber P, Bruno R et al. Findings of an	2018	N/A	Not a review but individual RCT completed after systematic review and relevance.	

Review authors, title, reference	Date studies reviewed	Type of review	Abstract	Evidence Grade
inpatient RCT of aerobic exercise for the management of cannabis withdrawal syndrome. Paper presented at Australasian Professional Society on Alcohol and other Drugs, National Conference, Melbourne 2018.			*Introduction*: Increasing evidence exists for the benefits of regular exercise on mood, wellbeing and general health. Aerobic exercise relieves withdrawal symptoms from tobacco and other drugs, but has yet to be tested in cannabis users. To address this, an RCT was developed to examine whether aerobic exercise can ameliorate the symptoms of cannabis withdrawal in a cannabis-dependent population undergoing inpatient detoxification and improve treatment outcomes for cannabis dependence. *Method*: A single blind, parallel two-group RCT compared a structured daily aerobic exercise intervention to a control stretching intervention during a seven-day inpatient hospital admission, with follow-up at 28-days post-discharge. Participants in the intervention group underwent 35 minutes of aerobic exercise daily, at 60% of their VO_2 Max. Control group engaged in a structured non-aerobic stretching routine for 35 minutes. The primary outcome measure is the severity of cannabis withdrawal symptoms assessed daily using the Cannabis Withdrawal Scale and Marijuana Cravings Questionnaire, across the week. Mechanisms by which exercise may affect cannabis withdrawal were assessed by analyzing endogenous cannabinoids, plasma and urine cannabinoid levels. *Results*: Forty-six cannabis dependent users, used $\overline{x}$ 1.62 (1.07SD) grams/day over a $\overline{x}$ of 19 years completed the 7-day inpatient detox. Mean age of participants was 35.49 (11.82SD) years, with BMI 23.93 (4.11SD). Twenty-five were randomised to daily aerobic exercise. Overall, patients who underwent the intervention arm (exercise) reported lower cannabis withdrawal symptoms over the 7-days compared to the control group $F_{1,53.20}=3.74$, $P<0.05$, reporting significant improvements in irritability [$F_{1,56.13}=6.16$, $P<0.05$], anxiety [$F_{1,51.58}=4.32$, $P<0.05$], sleep difficulty [$F_{1,53.24}=6.60$, $P<0.01$] and appetite [$F_{1,52.85}=4.00$, $P<0.05$]. There were no differences in the two groups regarding cannabis use at one-month follow-up following withdrawal. *Conclusion*: The findings have important implications for the treatment of cannabis and other drug withdrawals as an effective, inexpensive and accessible treatment approach.	
Bichler C, Niedermeier M, Fruhauf A et.al. Acute effects of exercise on affective responses, cravings and heart rate variability in inpatients with alcohol use disorder-A randomized cross-over trial.	2017		Not a review but individual RCT published since review and of relevance. N=16 within subject cross-over design comparing single session Nordic walking (NW), Yoga (YG) and passive control. Results demonstrated that an acute exercise bout improved affective responses in inpatients with alcohol use disorder and indicated preferences towards NW	

Review authors, title, reference	Date studies reviewed	Type of review	Abstract	Evidence Grade
Mental Health and Physical Activity. 2017;13.:68–76.			compared to YG regarding affective valence during exercise. However, there were no differences after the interventions.	
Massage interventions				
Reader M; Young R; Connor JP. Massage therapy improves the management of alcohol withdrawal syndrome. Journal of Alternative & Complementary Medicine. 2005;11(2):311–3,	N/A	Single RCT	The study was a randomised controlled trial comparing massage therapy to a 'rest' (control) condition in patients undergoing alcohol detoxification. SETTINGS/LOCATION: Hospital-based alcohol and drug detoxification clinic. SUBJECTS: Fifty (50) patients with alcohol dependence (41 males, 9 females). INTERVENTIONS: The massage intervention involved a seated back, shoulder, head, and neck massage. OUTCOME MEASURES: Alcohol Withdrawal Scale, respiration, pulse rate, and subjective patient evaluation. RESULTS: Those receiving massage generally showed reductions in pulse rate on 3 of the 4 days of treatment compared to the control group. Massage was also more effective in reducing Alcohol Withdrawal Scale scores in the early stages of the detoxification process. Respiration in the massage group was reduced toward the end of the detoxification admission. CONCLUSIONS: Massage shows promise as an adjunct to traditional medical detoxification for alcohol.	

Review authors, title, reference	Date studies reviewed	Type of review	Abstract	Evidence Grade
Black S, Jacques K, Webber A, Spurr K, Carey E, Hebb A, Gilbert R. Chair massage for treating anxiety in patients withdrawing from psychoactive drugs. Journal of Alternative and Complementary Medicine. 2010 Sep;16(9):979–87. doi: 10.1089/acm.2009.0645.		Single RCT	The aim of this study was to investigate the effectiveness of chair massage for reducing anxiety in persons participating in an inpatient withdrawal management program for psychoactive drugs. DESIGN: The design was a randomised, controlled clinical trial conducted from June 2008 to January 2009. SUBJECTS: Eighty-two (82) adult patients received inpatient treatment for psychoactive drug withdrawal (alcohol, cocaine, and opiates). SETTING: This study was conducted at the Withdrawal Management Services at the Capital District Health Authority, Halifax, Nova Scotia. INTERVENTIONS: Subjects were randomly assigned to receive chair massage (n = 40) or a relaxation control condition (n = 42). Treatments were offered for 3 consecutive days. Standard counselling and pharmacologic management were also offered concurrently to patients in all conditions. MEASUREMENTS: The primary outcome measure was anxiety assessed using the Spielberger State-Trait Anxiety Inventory (STAI). State and trait anxiety scores were determined immediately prior to and following each treatment intervention. RESULTS: Analysis of STAI scores showed a significant reduction in state and trait anxiety for both interventions ($p < 0.001$). The magnitude in the reduction in state ($p = 0.001$) and trait ($p = 0.045$) anxiety was significantly greater in the chair massage group where the effect on state anxiety was sustained, at least in part, for 24 hours. CONCLUSIONS: Within the clinical context of this study, chair massage was more effective than relaxation control in reducing anxiety. Further investigation of chair massage as a potential nonpharmacologic adjunct in the management of withdrawal related anxiety is warranted.	

Table 1.6 Evidence summary and recommendations regarding physical interventions across all drug classes

Intervention	Recommendation	Level of evidence	Quality of evidence
Acupuncture			
Auricular or traditional Chinese medicine acupuncture during withdrawal episode	Most controlled studies have examined alcohol or opioid withdrawal, and usually as an adjunct to routine care. Meta-analyses indicate there is evidence of a reduction in withdrawal symptoms, cravings and anxiety symptoms, although no differences in completion rates. When individual drug types are examined (e.g. alcohol, opioids, stimulants) there are no benefits of acupuncture on withdrawal symptoms or cravings. The reviewers caution that there are inconsistent findings between studies, poor quality studies and evidence of publication bias, and suggest caution in interpreting evidence.	GRADE Low or Very Low	Grade D: Poor
Exercise			
Aerobic exercise for opioid or cannabis withdrawal	Aerobic exercise programs are associated with reductions in withdrawal symptoms, and specific symptoms of sleep disturbances, anxiety and depression, and should be encouraged in cannabis withdrawal.	Ib	Grade D: Poor
Exercise for alcohol and stimulant disorders	Controlled studies were not identified examining aerobic exercise programs for alcohol or stimulant disorders, and further research is required, particularly given safety concerns in these populations	Extrapolated for alcohol	Grade D: Poor
Mind-body exercise (e.g. yoga)	No controlled studies were identified examining yoga for substance withdrawal (excluding tobacco). Further research recommended.	Nil	Grade: No controlled studies
Massage Therapy			
Massage therapy during withdrawal	Limited evidence suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal.	Ib	Grade D: Poor

For classification schemes for categorisation/grading of evidence see Appendices 1 and 2.

Symptomatic medications

All withdrawal syndromes are associated with a range of symptoms such as anxiety, irritability, and sleep disturbances, while different symptoms can be associated with specific withdrawal syndromes particular to a drug class, such as nausea, vomiting or diarrhoea in alcohol or opioid withdrawal. These symptoms can be distressing for patients and can be associated with poor withdrawal outcomes such as failure to complete withdrawal.

It should be noted that the evidence regarding medications in the management for withdrawal syndromes tend to target global withdrawal syndromes – usually measured using withdrawal scales that measure a number of withdrawal symptoms specific to that syndrome. For example, the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) and Clinical Opiate Withdrawal Scale (COWS) each measure a number of signs and symptoms in alcohol and opioid withdrawal respectively. In this regard, the evidence presented in later chapters for each drug usually targets global withdrawal syndromes. However, there are many medications that are well established as being effective for a specific symptom, for which it is not necessary to source additional evidence to support use during withdrawal. For example, a patient complaining of nausea may be administered metoclopramide to help their nausea symptoms. This occurs without the need for an evidence base from studies in withdrawal settings as to whether metoclopramide is effective for nausea. In this way, many clinical recommendations regarding withdrawal management do not require separate evidence reviews. This is an important distinction in understanding the 'evidence' for particular interventions that may be used in the management of particular symptoms during withdrawal.

Common withdrawal symptoms (and their commonly used symptomatic medications) across different drug classes, for which a separate evidence base regarding use in withdrawal context is unnecessary, include:

- NSAIDs or paracetamol for headaches, joint pain, generalised aches
- Metoclopramide, prochlorperazine, ondansetron for nausea
- BZDs, z-drugs, low-dose quetiapine for sleep problems.

These medications may have their own concerns for particular patients that need to be considered. For example, a patient with a history of peptic ulcer should avoid NSAIDs, whereas a patient with a history of sedative misuse may require particular caution in their use of BZDs for assistance with sleep.

Special populations

The special populations in this review of the evidence include: the elderly, Aboriginal; and lesbian, gay, bisexual, transgender, intersex (LGBTI) people; people in custody; and medically unwell populations e.g. liver failure, delirium etc.

Apart from individual differences, each of the special population groups have their own needs (e.g. medically unwell people require close monitoring, Aboriginal people may wish to remain close to family and country, etc), which can impact on aspects of withdrawal management, including; appropriate setting, pharmacotherapies used, and post-withdrawal support and continued care.

Respect and cultural sensitivity provide the basis for service provision to all people with alcohol and other drug problems, while an appreciation, understanding and knowledge of issues for specific population groups assists in achieving positive interactions, engagement in treatment, and successful outcomes.

Three of the special populations identified for this review, were: Aboriginal; LGBTI people; and people in custody. There is a paucity of literature in relation to each of these populations, and no systematic reviews.

Similarly, there are a small number of studies/systematic reviews on the medically unwell. In terms of the elderly, a systematic review and a meta-analysis of RCTs on BZDs was identified.

Aboriginal

Setting

There are a number of studies that look at Indigenous people in Canada and withdrawal outcomes. These studies found significant differences between Indigenous and non-Indigenous people in relation to reasons for treatment dropout, which tended to be social factors e.g. homelessness among Indigenous peoples, while substance-specific factors were more common for non-Indigenous people.[16] Within the Canadian Indigenous population, women were more likely to have a range of psychological and medical needs in addition to their substance use.[17]

There are few studies in relation to Aboriginal people in Australia and withdrawal management from alcohol and other drugs. Those that are available are of low quality and are generally descriptive surveys.

Consultations with health services providing outpatient alcohol withdrawal management for Aboriginal communities, and a study which explored a model for outpatient detox for Aboriginal communities, concluded that the outpatient setting is feasible and safe for a select group of alcohol dependent patients.[18, 19] It is acknowledged that among Aboriginal people with alcohol addiction, drinking is often sporadic, and therefore, risk of withdrawal symptoms is lower than in those who drink alcohol more regularly. However, for those requiring detoxification, an outpatient setting may not be an option for some people, as their environment is not safe and they are not free from the drinking behaviour of others. [20]

Psychosocial interventions

No studies looked at psychosocial interventions during withdrawal for Aboriginal people. A survey of Aboriginal people in a rural setting to determine their perceptions of two CBT interventions to reduce alcohol-related harm, found that the Community Reinforcement Approach (CRA) was most acceptable for delivery to individuals after alcohol withdrawal had been completed, and achieved positive results at three month follow-up, with reduced substance use and decreased psychological distress.[21]

A qualitative study of drug and alcohol rehabilitation for Aboriginal men found that cultural activities such as learning about culture/heritage/land and spending time on country, played an important role in restoring social and emotional wellbeing.[22] It has also been noted that traditional healing e.g. bush medicine, is still very much a part of Aboriginal culture[23], and should be incorporated into treatment where possible.

Similarly, the concept of family is very important in Aboriginal culture, and remaining close to family and country is important. Separation can have a negative effect on treatment.[24, 25] Therefore, the option of having a family member with the patient during treatment is important. It is, however, also important to bear in mind that some Aboriginal people seeking treatment may prefer to be away from family influences, particularly where there is ongoing alcohol or other drug use among family members.[24]

Practical and supportive aspects of counselling/case management were identified as important for Aboriginal people. Engagement, rapport, trust, and flexibility, are also important, to reduce the risk of a window of opportunity being missed, and the patient disengaging.[18]

People in custody

Aboriginal people in custody

A study of drug and alcohol use and treatment of Aboriginal people in prison in Australia was based on a survey of prison staff and a review of the literature. A high proportion of the Australian prison population is Indigenous, and substance use is five times greater among prisoners compared with the general population. It was concluded that prison provided an opportunity for treatment and rehabilitation, particularly for the Indigenous population, who were more likely to use health services in prison than in the community.[26]

A separate study of cannabis withdrawal among Indigenous people in prison in Australia found that the majority of current cannabis users experienced withdrawal symptoms, indicating that this is common, but there was no standard treatment for managing cannabis withdrawal in prison.[27]

Opioid withdrawal in custody

In addition to the studies on withdrawal management in the custodial setting involving Indigenous populations (discussed above), there are a number of other studies in relation to pharmacological management of opioid withdrawal in prisons populations Clonidine was found to reduce withdrawal related symptoms[28], and buprenorphine was reported by study participants to be superior to methadone in reducing craving, improving sleep patterns, and producing higher levels of motivation to set goals.[29] A randomised double blind controlled trial found no significant difference in relation to severity of withdrawal symptoms between those receiving lofexidine and those receiving methadone for withdrawal management, thus providing support for the use of a non-opioid medication, which is preferred by some correctional systems.[30]

Another study identified that when patients do not receive treatment for opioid withdrawal in prison, the experience is negative; they resort to 'unhealthy' behaviours to relieve symptoms and are less receptive to seeking methadone treatment upon release from custody.[31] Methadone and buprenorphine were found to be equally effective in achieving abstinence at eight days post-withdrawal in prison.

Other than reference to availability of treatment services in prisons, preference in some locations for non-opioid withdrawal treatment options, and pre- or post-release engagement in treatment, there was little in these studies that was specific to the custodial population, as opposed to those undergoing withdrawal from opioids in another setting.

LGBTI populations

There were no studies specifically in relation to LGBTI populations and withdrawal management. One study was identified that investigated outcomes for LGBTI clients receiving counselling for methamphetamine use from a LGBTI-specific treatment service. It found positive outcomes in terms of: reduced psychological distress; improvement in quality of life; reduced methamphetamine use; and improved psycho-social functioning. The authors suggested that these outcomes demonstrated the effectiveness of a LGBTI-specific treatment service.[32]

Elderly populations

Many patients with a long-term history of substance use disorder have features of 'premature ageing with regards to health and cognitive status, so that whereas in general health settings age 65 is considered the threshold for an older patient population, for AoD treatment populations, a threshold of 50 years of age is sometimes considered as an older population. Studies of 'elderly' patients in AoD settings have varied from including those aged 50-70 years or over.

Little attention has been paid to issues of withdrawal management in older populations outside of alcohol and benzodiazepines (BZDs). Despite there being an awareness of some of the health problems seen in older patients with substance use disorders, few controlled studies have been conducted. The following summary examines the evidence on alcohol and BZD withdrawal issues.

Alcohol withdrawal in the elderly

The incidence of medical complications (myocardial ischaemia, arrhythmias, pneumonia, orthostatic hypotension) and neurological complications (hallucinations, delirium tremens, dizziness, convulsions) during alcohol withdrawal syndrome (AWS), in the elderly alcohol-dependent population, is higher than in younger populations.[33]

No systematic reviews or RCTs evaluating the efficacy of medications for the treatment of AWS in elderly patients were identified. One quasi-experimental study[34] compared symptom-triggered versus fixed-dose BZD regimens in 63 alcohol-dependent patients over the age of 70 undertaking withdrawal in an inpatient hospital setting. The symptom-triggered regimen was reported to reduce the total BZD dose and duration of treatment in this patient group.

Concerns regarding impaired metabolism of long-acting BZDs such as diazepam has led many authors to recommend the use of shorter-acting BZDs (e.g. lorazepam, or oxazepam) for alcohol withdrawal management, in order to avoid the risks of over-sedation, and to use doses of one-third to half of doses used in younger adults.[33, 35]

Elderly patients are particularly susceptible to alcohol-related complications, including Wernicke-Korsakoff syndrome, which may present with features of ophthalmoplegia (nystagmus, ocular paralysis), ataxia, and confusion, progressing to amnesia and confabulation. Thus, in addition to BZDs, the treatment of AWS should include the administration of thiamine and assessment and management of electrolyte abnormalities.

Benzodiazepine withdrawal in the elderly

In the context of high levels of 'low-dose' BZD use in elderly patients in the community (estimated at 10% in many studies), there has been considerable interest in examining interventions to assist elderly patients using low-dose BZDs. Two systematic reviews of interventions for reducing low-dose BZD use in elderly patients were identified.[36, 37] The authors identified a number of strategies that have been recommended regarding the management of elderly patients using low-dose BZDs, including:

- 'Prescribing interventions' such as medication reviews, consultations with patients, providing educational outreach programs to prescribers, conducting audits and providing feedback on prescribing patterns, implementing electronic prescribing alerts and providing patient support groups
- Withdrawal interventions – generally involving gradual taper over weeks to months
- Psychotherapy – including CBT or relaxation training.

The Gould et al. review identified 10 withdrawal RCTs (approximately 1300 participants) and eight prescribing RCTs. The main outcome examined was use of BZDs at post-intervention (generally 1–3 months after the intervention). The meta-analysis found a significantly higher odds of not using BZDs for supervised withdrawal with psychotherapy (OR=5.06, 95% CI 2.68–9.57, P<0.00001) and withdrawal with prescribing interventions (OR=1.43, 95% CI 1.02–2.02, P=0.04) in comparison with treatment as usual, education placebo, withdrawal alone, or psychotherapy alone. Significantly higher odds of not using BZDs were also found for multifaceted prescribing interventions (OR=1.37, 95% CI 1.10–1.72, P=0.006) in comparison with control interventions (treatment as usual and prescribing placebo). The authors concluded that elderly patients using low-dose BZDs could be successfully withdrawn using a gradual taper together with either

psychotherapy (e.g. CBT, relaxation training) and/or prescribing interventions such as medication reviews, patient education and medication audits.

The Reeve review (2017) systematically examined studies evaluating the success of interventions used to reduce BZDs and Z-drug use in patients aged 65 or over. Seven studies of BZDs and Z-drug withdrawal were identified up until 2015. As reported in the Gould et al. review, studies examined different approaches – including gradual BZD taper with counselling, patient education and tapering, or use of other medications (e.g. melatonin), with variable rates of BZD discontinuation ranging from 27-80%. Four of the five studies that examined clinical outcomes identified no increase in withdrawal symptoms or sleep problems in those discontinuing BZDs, which highlights the diagnostic uncertainty as to what proportion of these (low-dose) patients were dependent on BZDs. Furthermore, the sustainability and indeed benefits of these approaches are unclear in this patient population. Nevertheless, the findings of these two reviews indicates that a number of withdrawal and prescribing interventions can be effective in reducing BZD use in elderly patients with a history of low-dose, long -term BZD use.

Chapter 2. Alcohol

Description of the withdrawal syndrome

Alcohol withdrawal, as defined by the DSM-V, is diagnosed by the following:[3]

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged

B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use described in criterion A:

   1. Autonomic hyperactivity
   2. Increased hand tremor
   3. Insomnia
   4. Nausea or vomiting
   5. Transient visual, tactile, or auditory hallucinations or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Generalised tonic-clonic seizures

C. The signs or symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Onset and duration of alcohol withdrawal

Alcohol withdrawal is likely to occur six to 24 hours after the last drink. The blood alcohol level does not have to reach zero for a dependent drinker to go into alcohol withdrawal.[5] In some individuals, the withdrawal syndrome is short–lived and inconsequential, with the acute phase resolving well within five days with minimal or no medical intervention. However, in others it increases in severity over the first 48 to 72 hours of abstinence. Alcohol withdrawal seizures typically occur within the first six to 48 hours after the last drink (and before the onset of other withdrawal symptoms), whilst complications such as delirium tremens can occur 48 to 96 hours post–drinking. Some symptoms of alcohol withdrawal – such as sleep disturbances and anxiety may persist for weeks after cessation of alcohol use and can be difficult to differentiate from comorbid conditions.

Predictors of severity of alcohol withdrawal

The severity of alcohol withdrawal varies across patients and consumption rates, previous history of withdrawal symptoms and known coexisting medical or psychiatric illnesses. It has been suggested (although the evidence for these assertions are unclear) that alcohol withdrawal is likely to occur following the cessation of alcohol use in dependent daily drinkers who drink eight standard drinks (80 grams alcohol) or more for an adult male[5] and less for adult females, frail people or adolescents. This serves as a good practice point, particularly for inexperienced clinicians.

Two systematic reviews (see Table 2.1 for details) examined the potential predictors of which patients would develop severe alcohol withdrawal, focusing on alcohol withdrawal seizures or delirium.[38, 39] Both reviews were meta-analyses, and both noted heterogeneity of the diagnostic criteria of alcohol withdrawal. The major difference was that Goodson et al. utilised odds ratio or mean difference, while Wood et al. looked at

likelihood ratio. Goodson et al. performed a funnel plot, which noted publication bias. The review explored multiple outcomes, reviewing associations of severe alcohol withdrawal and laboratory tests such as hypokalaemia, but was unable to show solid causation or association. Wood et al. reviewed assessment tools to see if they could predict patients who would have severe withdrawal; they concluded that they could not. Both studies showed that the major predictor of severe alcohol withdrawal (e.g. withdrawal seizures) was a past history of severe alcohol withdrawal, with no other patient predictors were consistent across studies. This has important clinical implications in assessment and treatment planning, with assessment of past withdrawal experiences a key issue.

Selection of reviews and studies

Table 2.1 is a summary of the systematic reviews and meta-analyses for alcohol withdrawal since 2008 included in this review. These look at a variety of topics, including pharmacological interventions, special patient populations, in particular intensive care patients, and inpatient versus outpatient management.

Amato and colleagues provided the most extensive review of pharmacological management of alcohol withdrawal.[40] Their paper summarised five other Cochrane reviews, which were meta-analyses of five different pharmacological interventions:

- Benzodiazepines (BZDs) – (Amato, Minozzi & Vecchi, 2010)[41]
- Nitrous oxide - (Gillman, Lichtigfeld, & Young, 2007)[42]
- Gamma-hydroxybutyrate - (Leone, Vigna-Taglianti, Avanzi, Brambilla, & Faggiano, 2010)[43]
- Baclofen - (Liu & Lu-Ning, 2017)[44]
- Anti-convulsants - (Minozzi, Amato, Vecchi, & Davoli, 2010).[45]

The main concern with this review is that it only looks at Cochrane reviews and ignores other meta-analyses. That said, there were few other meta-analyses that covered alcohol withdrawal, as most reviews were narrative reviews. Furthermore, the individual Cochrane reviews themselves covered the majority of the literature on each particular pharmacological agent. On top of this, where there was more than one review on a topic, the Cochrane review appeared to do a superior job. For example, Chhatlani et al. performed a systematic review on the role of anticonvulsants in alcohol withdrawal.[46] However, the majority of the studies they included (16 in total) were covered in the Cochrane review on anticonvulsants by Minozzi et al., with the exception of studies since 2010.[45] The Chhatlani review also lacked meta-analysis. Despite being more recent, we would not recommend the Chhatlani review over the Cochrane review.

For some interventions, no Cochrane review was identified, however other systematic reviews were available. This included reviews that looked at treatment setting[47], acupuncture[8], and psychosocial interventions.[48] While these reviews were not of the quality of a Cochrane review and did not attempt meta-analyses, they remain the best reviews available and were used for evidence generation.

Table 2.1 Summary of reviews on pharmacological interventions in the management of alcohol withdrawal

Review authors, title, reference	Date studies reviewed	Type of review	Commentary on review	Evidence grade
Amato L, Minozzi S, Vecchi S DM. Benzodiazepines for Alcohol Withdrawal Syndrome. Cochrane Database of Systematic Reviews. 2010;(3).	2010	Cochrane meta-analysis N=64	BZDs showed a protective benefit against alcohol withdrawal symptoms, in particular seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with other drugs. Nevertheless, no definite conclusions about the effectiveness and safety of BZDs was possible, because of the heterogeneity of the trials both in interventions and the assessment of outcomes.	
Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome. Cochrane Database of Systematic Reviews. 2010;(6).	2010	Cochrane review of five reviews combined N=5	Among the treatments considered, BZDs showed a protective benefit against seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with antipsychotics. Nevertheless, no definite conclusions about the effectiveness and safety of BZDs were possible, because of the heterogeneity of the trials both in interventions and in the assessment of outcomes. Data on potential harms are sparse and fragmented. Results do not provide sufficient evidence in favour of anticonvulsants for the treatment of AWS, but anticonvulsants seem to have limited side effects. There is also not enough evidence of effectiveness and safety of baclofen, because only one study considered this treatment and that of GHB, for which no strong differences were observed in the comparisons with placebo, BZDs and anticonvulsants.	
Liu J, Ln W. Baclofen for alcohol withdrawal. Cochrane Review. 2017;(8). Summary of findings for the main comparison.	2017	Meta analysis N=3	No conclusions can be drawn about the efficacy and safety of baclofen for the management of alcohol withdrawal due to insufficient and very low-quality evidence.	
Minozzi S, Amato L, Vecchi S, Davoli M. Anticonvulsants for alcohol withdrawal. Cochrane Database of Systematic Reviews. England; 2010 Mar;(3):CD005064.	2010	Meta analysis N=56	Results of this review do not provide sufficient evidence in favour of anticonvulsants for the treatment of AWS. There are some suggestions that carbamazepine may actually be more effective in treating some aspects of alcohol withdrawal when compared to BZDs, the current first-line regimen for AWS. Anticonvulsants seem to have limited side effects, although adverse effects are not rigorously reported in the analysed trials.	
Holleck JL, Merchant N, Gunderson CG. Symptom-triggered therapy for alcohol withdrawal syndrome: a systematic review	2019	N=6 (1 outpatient,	Moderate strength evidence suggests that symptom-triggered therapy improved duration of therapy and total BZD dose in specialised detoxification settings in low-risk patients but the applicability of this evidence in general hospital settings is low. There	

and meta-analysis of randomized controlled trials. Journal of General Internal Medicine. 2019;34(6);1018–24.		5 inpatient)	was insufficient evidence for any conclusions about symptom-triggered therapy for the major outcomes of mortality, seizure, and delirium in any setting.	
Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. Cochrane Database of Systematic Reviews. England; 2010 Feb;(2):CD006266.	2010	Meta analysis N=13	There is insufficient randomised evidence to be confident of a difference between GHB and placebo, or to determine reliably if GHB is more or less effective than other drugs for the treatment of alcohol withdrawl or the prevention of relapses. The small amount of randomised evidence available suggests that GHB 50mg may be more effective than placebo in the treatment of AWS, and in preventing relapses and craving in previously detoxified alcoholics during the first three months of follow-up. This review does not provide evidence in favour or against GHB compared to BZDs and clomethiazole for treatment of AWS; but, again based on a small amount of randomised evidence, GHB appears better than naltrexone (NTX) and disulfiram in maintaining abstinence and preventing craving in the medium term (3-12months). The review does not provide evidence of a difference in side effects between GHB and BZDs, NTX or disulfiram. These findings should be considered alongside concerns that have been raised about GHB regarding the risk of developing addiction, and the misuse or abuse of the drug, suggesting GHB use only under strict medical surveillance.	
Awissi DK, Lebrun G, Coursin DB, Riker RR, Skrobik Y. Alcohol withdrawal and delirium tremens in the critically ill: A systematic review and commentary. Journal of Intensive Care Medicine. 2013;39(1):16–30.	2013	Review, no meta analysis ICU focus N=34 Poor	• Could not identify specific risk factors in ICU patients • Five studies that used a modified AWS for ICU patients • No study documented a link between frequency of assessments and outcomes • Sedation agitation score (SAS) • Four studies on **prevention** Ethanol infusions – single arm (2) – 1 retrospective, 1 prospective – both fail Ethanol infusion v Benzos – ethanol – more agitation Ethanol v flunitrazepam-clonidine, chlormethiazole-haloperidol, flunitrazepam-haloperidol – no difference; bolus better than continuous • 10 studies on treatment • 3 studies on protocol driven treatment o Infusion v symptom driven (36 patients): Less BZD use (P<0.014); Lower complication rates; Similar hospital and ICU length of stay. o One study tested their new hospital protocol – more BZD, but less need to ventilate	

			○ One study found less ICU stays with an alcohol withdrawal protocol post op • BZD guidelines are associated with reduced ICU stay • Clonidine suggested as efficacious in reducing adrenergic symptoms of alcohol withdrawal	
Chhatlani A, Farheen SA, Manikkara G, Setty MJ, Deoreo E, Tampi R. Anticonvulsants as monotherapy or adjuncts to treat alcohol withdrawal: A systematic review. Annals of Clinical Psychiatry. 2018;30(4):312–25.	2018	Review without meta analysis Note that majority of studies included in Cochrane review (Minozzi 2010) N=16 Poor	*Gabapentin* • Bonnet – 400mg gabapentin no better than placebo in amount of clomethiazole required • Bonnet (2) – 'vigor scores' in patients withdrawing • Myrick – No difference in gabapentin v placebo for alcohol craving, sedation • Malcom – gabapentin good for reducing insomnia in withdrawal v lorazepam • Myrick (2) – gabapentin v lorazepam – gabapentin similar for AWS; better for maintaining abstinence • Stock – reduced craving and less sedation v chlordiazepoxide *Carbamazepine* • Bjorkqvist – Carbmazepine better than placebo for AWS • Ritola – Carbamazepine as effective as chlordiazepoxide for AWS • Agricola – Carbmazepine v tiapride similar for DT – both could be considered as alternative • Malcolm – Cabrmazpeine v lorazepam – equal for AWS, carbamazepine better to reduce post treatment drinking • Malcolm (2) – mild to mod. AWS – Carbamazepine v Lorazepam – Carbmazepine better for sleep *Valproate* • Valproate v control (? Placebo used as control) – use of chlordiazepoxide lower in valproate • Hillbom – valproate v cabrnazepine v placebo – adverse events outweigh benefit in using as prophylaxis *Lamotrigine* • Djokic – lamotrigine is efficacious in treatment of DT, but not decrease mortality	
Cooper E, Vernon J. The effectiveness of pharmacological approaches in the treatment of alcohol withdrawal syndrome (AWS): A literature review. Journal of Psychiatric and Mental Health Nursing. 2013;20(7):601–12.	2013	Review of literature N=63	Several studies that have shown pharmacological alternatives that could compare or act as adjunct with BZDs but need for further quality research No statistical difference between BZDs Lorazepam and alprazolam preferable in compromised liver function – but based on one study	

		Poor	Phenobarbital – poor safety profile; unsafe when used with alcohol (no community use); quality of evidence variable *Nitrous Oxide* • Gilman 2004 – NO + diazepam v diazepam + night sedation – reduction of sedative use 80%; reduction of symptoms 50% • Cochrane review by Gilman, Psychotropic Analgesic Nitrous oxide (PAN) as effective as BZDs Other findings covered by Cochrane No study has provided adequate evidence to suggest definite advantage of using alternative to BZDs. They stated that there is optimism for using nitrous oxide: however, the reviewer urges caution.	

Goodson CM, Clark BJ, Douglas IS. Predictors of severe alcohol withdrawal syndrome: A systematic review and meta-analysis. Alcoholism, Clinical and Experimental Research. 2014;38(10):2664–77.	2014	Meta-analysis
		
		N=15
			Similar study to Wood, (see below) only using Odds Ratio (OR) or mean difference (MD). 15 studies; asymmetric funnels – publication bias. Moderate heterogeneity for severe AWS diagnosis
			Predictors:
			• Previous DT as predictor for DT – OR 2.58 (6 studies), I2 59; did not cross 1
			• Previous seizure as predictor for seizure – OR 2.80 (2 studies); I2 44, did not cross 1
			• Previous seizures and DT – OR 1.78, no association
			• Lab tests. Platelets and K lower in patients with DT (2 studies)
			  o K - 0.2 mEq
			  o Pl – 60Pl lower
			  o ALT higher in SAWS – 21 pt higher (1 study only)
			  o GGT higher in seizure – 202 pt higher (2 studies)
			Age, cirrhosis, pancreatic disease NOT a factor. Previous patients who had AWS – fewer admissions for DT	

Hammond DA, Rowe JM, Wong A, Wiley TL, Lee KC, Kane-Gill SL. Patient outcomes associated with phenobarbital use with or without benzodiazepines for alcohol withdrawal syndrome: A systematic review. Hospital Pharmacy. 2017;52(9):607–16.	2017	Review, not meta analysis N=9	Preamble stated that the review was "*looking at patients who get discharged from ED who may need medication with a longer half-life*", then proceeded to look at moderate-severe AWS Looked at the studies individually *With BZDs* • Phenobarbital (PHB) v placebo – less lorazepam, less ICU • PHB once diazepam hit 120mg – less ICU	

			• Postguideline group – PHB effective (but may have been guideline) • Overall: some benefit, but may be due to having a guideline *Monotherapy* • Versus 2mg lorazepam – similar CIWA reduction • In DT v diazepam IV • Used v valproate; no difference in Modified Selective Severity Assessment (MSSA) but twice the rescue medications Conclusions • Potential role as adjunct in patients non-responsive to BZDs alone • Not enough evidence to recommend a general, non-individualised regimen • Poor safety profile makes it inferior to benzos	
Latifi S, Messer T. The efficacy of tiapride and carbamazepine combination therapy in reducing alcohol withdrawal symptoms: A systematic review and meta-analysis. Pharmacopsychiatry. 2019;52(5):209–16;	2018	Meta analysis N=5	*Tiapride (TIA) and carbamazepine (CBZ)* • 5 studies – 3 had no control; also 3 with same author *Tiapride* • Good tolerance, though risk of Neuroleptic Malignant Syndrome (NMS); little risk of abuse; unsatisfactory results in DTs as monotherapy, so needs an adjunct • Heterogeneity - I2 of 91.7% (should be <75%) • 800 patients; 700 in studies without comparator • "*TIA and CBZ could effectively reduce the AWS assessed by CIWA*" (p<0.0001, z value 4.07)	
Mo Y, Thomas MC, Karras GE. Barbiturates for the treatment of alcohol withdrawal syndrome: A systematic review of clinical trials. Journal of Critical Care Medicine. 2016;32:101–7. Available from: http://dx.doi.org/10.1016/j.jcrc.2015.11.022	2016	Review, not meta analysis N=7	Seven studies. BZDs v BZDs + Phenobarbital (PHB). No forest plots Study notes: *Rosenson* • Lorazepam (LZP) v Lorazepam + PB • Reduced ICU admission rate and less LZP use *Hendy/Kaim* • Favourable outcomes, but no superiority *Kramp* • Barbituates superior to diazepam (DZP) in grade 3 DTs; similar for ½ *Michaelson* • Retrospective study done after systemic change of AWS treatment • 9% of patients treated with DZP failed to respond to large doses – DTs successfully treated with PB *Duby*	

			• Protocolised management of AWS • PB added when BZDs escalated to 120mg – lower rates of ventilator days, requirement for mechanical ventilation, BZD use, continuous sedation and shorter hospital stays • Study raised issue that outcomes may be just due to the protocol itself. • Baseline characteristics very different (older in the preintervention group) *Gold* • More PHB and DZP use in pre-guidelines group Overall • Little high-quality evidence • Barbituates + BZDs – may have a role in severe • PHB may be used in refractory AWS • PHB well tolerated – risks are respiratory depression, over sedation and hypotension	
Ungur LA, Neuner B, John S, Wernecke K, Spies C. Prevention and therapy of alcohol withdrawal on intensive care units: Systematic review of controlled trials. Alcoholism, Clinical and Experimental Research. 2013;37(4):675–86.	2013	Review of papers, no meta analysis N=14 ICU focus	• BZDs (PO and IV), ethanol, clonidine, clomethiazol and haloperidol – all reportedly effective; Clomethaizol had higher rates of tracheobronchitis due to bronchial hypersecretion • Ethanol for prophylaxis in ICU patients – two studies that suggest some benefit • GHB – one study showed that GHB better than flunitrazepam for vegetative symptoms but weaker against psychotic symptoms • Do not use lomethiazol – higher pneumonia rate (One study) • Discussion: sufficient evidence that BZDs effective for alcohol withdrawal prevention; moderate evidence that ethanol is safe and effective prophylaxis • "*Thin evidence base*" Key conclusions • BZDs standard of care – symptom triggered better than continuous infusion • ETOH – effective for prevention, not for therapy • GHB – effective, but not first choice due to inability to prevent hallucinations, safety concerns, and legal concerns • Clonidine and haloperidol – adjuncts	
Wood E, Albarqouni L, Tkachuk S, Green CJ, Ahamad K, Nolan S, et al. Will this hospitalized patient develop severe alcohol withdrawal syndrome? The rational clinical	2018	Meta analysis N=14	Sensitivity, specificity and likelihood ratios (LRs) tables for each symptom/sign to predict SEVERE AWS Good stats for epidemiological purposes • 1% in 'general population' – epidemiological studies	

examination systematic review. JAMA. 2018;320(8):825–33.			• 23% in inpatient rehab (600 patents) • Hospitalised trauma patients – 0.4% (28000) • Hospitalised patients gen med surg ward – 0.67% (36000) • If Blood Alcohol Concentration (BAC) available + trauma – 10% (3729) Risk factors for severe withdrawal: • Previous DTs – 2.9 LR • 3 or more seizures – 2.8 LR • 1 or 2 seizures – 1.6 LR No symptoms were predictive. BAC>200mg/dL (0.2) – increased likelihood – 3.5 LR. Urea>9.28 mmol/L – 3.3 LR. Pl<150 – 2.2	
Masood B, Lepping P, Romanov D, Poole R. Treatment of alcohol-induced psychotic disorder (Alcoholic Hallucinosis)-A systematic review. Alcohol and Alcoholism. 2018;53(3):259–67.	2018	Review, not meta analysis N=15, plus 10 case reports	Inconclusive findings due to hetergenity, and high publication bias. Trials only looked at first generation antipsychotics (haloperidol, chlorpromazine, trifluoperazine, reserpine, thiotixene and levopromazine). Anticonvulsants in 3 trials – lamotrigine, valproate, phenobarbitone – high partial remission rates, but in trials only 10 days long without long term outcomes. GABA receptor drugs in two trials – piractam, cloazepate. Few trials of antipsychotic monotherapy Treatment: 3–546 days; some studies didn't state. Treatments idiosyncratic. Questionable statement by the authors: "*Our systematic review suggests that there is adequate evidence that some patients with AIPD [alcohol-induced psychotic disorder] show a favourable response to antipsychotic medication. There is nothing to indicate the superiority of any particular drug. Both fst and 2nd generation drugs appear to be effective. However, it seems highly unlikely that many patients show little or no response to antipsychotics and that persistence when they fail to produce remission cannot be justified. No evidence to guide duration – first principles suggest as brief as possible to avoid side effects*." The authors found no efficacy of the antipsychotics, but then dismissed the findings.	

Table 2.2 Reviews and studies relating to treatment setting, psychosocial and physical interventions in the management of alcohol withdrawal

Review authors, title, reference	Date studies reviewed	Type of review/ study	Abstract or description
Treatment setting			
Nadkarni A, Endsley P, Bhatia U, Fuhr DC, Noorani A, Naik A, et al. Community detoxification for alcohol dependence: A systematic review. Drug and Alcohol Review. Australia; 2017 May;36(3):389–99.	2017	Narrative systematic review. N=20 studies of which only 4 RCTs	*Aim*: synthesise literature about management of alcohol detoxification in the community to examine its effectiveness, safety, acceptability and feasibility. *Excluded:* non-English language; specialist addictions centre (even if outpatient). Safety: Only 2 studies compared inpatient v home, no difference in safety outcomes; 5 studies with no adverse events Completion: Range 50-100%; completion rates better as outpatient (2 studies). Across studies there was heterogeneity of outcomes measure, precluding a quantatitive synthesis of the effectiveness data. Nonetheless – 3 studies showed community detox better than inpatient detox for duration of abstinence, and level of consumption; however, one study showed no difference in rates at 6 months. *Cost:* Inpatient detox 10-22x more expensive (Aus); 4x cost of homeless shelter (UK); inpatient detox 6x more expensive than outpatient (UK). *Post-withdrawal engagement*: 50-75% continue services when do home detox. Completing detox at home preferable – able to work, more attention, more counselling. Lessons: Clearly defined eligibility criteria, non-ambiguous medication protocols based on objective measurement of withdrawal symptoms, daily structured monitoring of the patient's progress and linkage with continuing psychosocial care. *Authors conclusions*: "*policy makers, especially those in low-resource settings, should focus on de-centralising services for detoxification from specialist services to a stepped care model where detoxification is managed in primary care in the first instance with referral of complex cases to specialist services*"
Psychosocial interventions			
Timko C, Below M, Schultz NR, Brief D, Cucciare MA. Patient and Program Factors that Bridge the Detoxification-Treatment Gap: A Structured Evidence Review. Journal of Substance Abuse Treatment. 2015, 52, P 31-39 Available from:https://doi.org/10.1016/j.jsat.2014.11.009	April 2014 Narrative review.	Limited database systematic review	Although completion of detoxification (detox) and a successful transition from detox to substance use disorder (SUD) treatment and/or mutual-help groups are associated with better SUD outcomes, many patients do not complete detox or do not receive SUD care following detox. The purpose of this structured evidence review, summarising data extraction on a yield of 26 articles, is to identify patient, program, and system factors associated with the outcomes of completion of alcohol detox and successful transitions from alcohol detox to SUD treatment and mutual-help group participation. The review found wide variability among studies in the rates at which patients complete a detox episode (45–95%) and enter SUD treatment or mutual-help groups after detox (14–92%). Within program factors,

Review authors, title, reference	Date studies reviewed	Type of review/ study	Abstract or description
			behavioral practices that contribute to both detox completion and transitioning to SUD care after detox entail involving the patient's family and utilising motivational-based approaches. Such practices should be targeted at younger patients, who are less likely to complete detox. Although more studies using a randomised controlled trial design are needed, the evidence suggests that barriers to detox completion and transition to SUD care can be overcome to improve patient outcomes.
Individual studies of psychosocial interventions published since Timko et al (2015) review			
Bachiller D; Grau-Lopez L; Barral C; Daigre C; Alberich C; Rodriguez-Cintas L; Valero S; Casas M; Roncero C. Motivational interviewing group at inpatient detoxification, its influence in maintaining abstinence and treatment retention after discharge. Adicciones. 27(2):109-18, 2015 (in Spanish).	2015	Prospective cohort study	The relapse rate after discharge from inpatient detoxification is high. The objective of this pilot study is to assess the sociodemographic, clinical and therapeutic factors associated with maintaining abstinence in patients who participated in a brief motivational interviewing group during admission for detoxification. A total of 46 patients, diagnosed substance dependent according to DSM -IV, and admitted to the Hospital Detoxification Unit, participated in a brief motivational interviewing group. Sociodemographic, clinical, motivation to change (University of Rhode Island Change Assessment, URICA) and satisfaction with the treatment group (Treatment Perceptions Questionnaire, CPT) data were collected. Abstinence and treatment retention two months after discharge were assessed by weekly telephone calls. A survival analysis was performed. Being male, having more cognitions of the maintenance stage of change at discharge, being satisfied with group therapy and therapist during hospitalization are associated with longer abstinence after discharge. The brief motivational interviewing group approach with patients admitted for detoxification is related to greater likelihood of maintaining abstinence and subsequent treatment retention.
Ostergaard M.; Jatzkowski L.; Seitz R.; Speidel S.; Weber T.; Lubke N.; Hocker W.; Odenwald M. Integrated treatment at the first stage: increasing motivation for alcohol patients with comorbid disorders during inpatient detoxification. Alcohol and Alcoholism. 2018;53(6): 719-27.	2018	Quasi-randomised study	Co-occurring mental disorders can complicate the detoxification treatment process and outcome. The aim of this study is to examine whether a brief psychoeducational group counselling session during detoxification treatment can increase the motivation for and utilisation of subsequent treatments. Short summary: Interventions increased utilisation of post-detoxification treatment (F2=6.15, P=0.02) and reduced alcohol-related readmissions (F2=7.46, P=0.01). Higher depression or trauma scores were associated with higher rates of utilisation of treatment. N=171; quasi-randomised study. Conclusion(s): An integrated intervention approach for dual diagnosis at the beginning of the treatment can increase motivation for continued AUD treatment. Especially affected dual diagnosis patients can benefit from this treatment.

Review authors, title, reference	Date studies reviewed	Type of review/ study	Abstract or description
Manning V; Staiger PK; Hall K; Garfield JB; Flaks G; Leung D; Hughes LK; Lum JA; Lubman DI; Verdejo-Garcia A. Cognitive bias modification training during inpatient alcohol detoxification reduces early relapse: A randomized controlled trial. Alcoholism, Clinical and Experimental Research. 2016;40(9):2011-9.	2016	RCT	RCT (n=83) of cognitive bias modification (CBM) (four sessions) vs control during inpatient alcohol withdrawal impact on drinking outcomes two weeks after withdrawal. Seventy-one (85%) participants were successfully followed up, of whom 61 completed all four training sessions. With an intention-to-treat approach, there was a trend for higher abstinence rates in the CBM group relative to controls (69% vs. 47%, p=0.07); Craving score, time to relapse, mean drinking days, and mean standard drinks per drinking day did not differ significantly between the groups.
Patient information: **No controlled studies of patient information in alcohol withdrawal were identified. See Chapter 1 for discussion.**			
Physical therapies			
Acupuncture			
Liu X, Qin Z, Zhu X, Yao Q, Liu Z. Systematic review of acupuncture for the treatment of alcohol withdrawal syndrome. Acupuncture in Medicine. 2018;36(5):275–83.	August 2016	Systematic. Meta-analysis of 11 RCTs with 875 participants	*Background*: Acupuncture has been used as a potential therapy for alcohol withdrawal syndrome (AWS), but evidence for its effects on this condition is limited. Objective To assess the effects and safety of acupuncture for AWS. Data sources Central Register of Controlled Trials (CENTRAL), PubMed, Embase, the Cochrane Library, PsycINFO, Chinese Biomedicine Literature (CBM), China National Knowledge Infrastructure (CNKI) and Wan-Fang Database were searched from their inception to August 2016. Study eligibility criteria Randomised controlled trials (RCTs) of drug plus acupuncture or acupuncture alone for the treatment of AWS were included. *Data collection and analysis*: Continuous data were expressed as mean difference (MD) with 95% confidence intervals (95% CI). Dichotomous data were expressed as risk ratio (RR) with 95% CI. *Results*: Eleven RCTs with 875 participants were included. In the acute phase, two trials reported no difference between drug plus acupuncture and drug plus sham acupuncture in the reduction of craving for alcohol; however, two positive trials reported that drug plus acupuncture was superior to drug alone in the alleviation of psychological symptoms. In the protracted phase, one trial reported acupuncture was superior to sham acupuncture in reducing the craving for alcohol, one trial reported no difference between acupuncture and drug (disulfiram), and one trial reported acupuncture was superior to sham acupuncture for the alleviation of psychological symptoms. Adverse effects were tolerable and not severe.

Review authors, title, reference	Date studies reviewed	Type of review/ study	Abstract or description
			Conclusion: There was no significant difference between acupuncture (plus drug) and sham acupuncture (plus drug) with respect to the primary outcome measure of craving for alcohol among participants with AWS, and no difference in completion rates (pooled results). There was limited evidence from individual trials that acupuncture may reduce alcohol craving in the protracted phase and help alleviate psychological symptoms; however, given concerns about the quantity and quality of included studies, further large-scale and well-conducted RCTs are needed.
Grant S, Kandrack R, Motala A, Shanman R, Booth M, Miles J, Sorbero M, Hempel S. Acupuncture for substance use disorders: A systematic review and meta-analysis. Journal of Drug and Alcohol Dependence. 2016; 163;1–15.	Nov 2014	Systematic Meta-analysis. Not limited to alcohol withdrawal 41 studies with 5227 participants	*Note: Not preferred review for alcohol as includes all SUD conditions.* *Background:* This systematic review aims to estimate the effects of acupuncture for adults with substance use disorders (SUDs). *Methods:* We searched 7 electronic databases and bibliographies of previous studies to identify eligible randomised trials. Two independent reviewers screened citations, extracted data, and assessed risks of bias. We performed random effects meta-analyses. We assessed quality of evidence using the GRADE approach. *Results:* We included 41 studies with 5227 participants. No significant differences were observed between acupuncture and comparators (passive controls, sham acupuncture, treatment as usual, and active interventions) at post-intervention for relapse (SMD−0.12; 95%CI −0.46 to 0.22; 10 RCTs), frequency of substance use (SMD −0.27; −2.67 to 2.13; 2 RCTs), quantity of substance use (SMD 0.01; −0.40 to 0.43; 3 RCTs), and treatment dropout (OR 0.82; 0.63 to 1.09; 22 RCTs). We identified a significant difference in favour of acupuncture versus comparators for withdrawal/craving at post-intervention (SMD −0.57, −0.93 to −0.20; 20 RCTs), but we identified evidence of publication bias. We also identified a significant difference in favour of acupuncture versus comparators for anxiety at post-intervention (SMD −0.74, −1.15 to −0.33; 6 RCTs). Results for withdrawal/craving and anxiety symptoms were not significant at longer follow-up. Safety data (12 RCTs) suggests little risk of serious adverse events, though participants may experience slight bleeding or pain at needle insertion sites. *Conclusions:* Available evidence suggests no consistent differences between acupuncture and comparators for substance use. Results in favour of acupuncture for withdrawal/craving and anxiety symptoms are limited by low quality bodies of evidence.
Massage therapy. No reviews identified. Individual RCTs identified			
Reader M; Young R; Connor JP. Massage therapy improves the management of		Single RCT	Randomised controlled trial comparing massage therapy to a 'rest' (control) condition in patients undergoing alcohol detoxification.

alcohol withdrawal syndrome. Journal of Alternative & Complementary Medicine. 2005;11(2):311-3.			SETTINGS/LOCATION: Hospital-based alcohol and drug detoxification clinic. SUBJECTS: Fifty (50) patients with alcohol dependence (41 males, 9 females). INTERVENTIONS: The massage intervention involved a seated back, shoulder, head, and neck massage. OUTCOME MEASURES: Alcohol Withdrawal Scale, respiration, pulse rate, and subjective patient evaluation. RESULTS: Those receiving massage generally showed reductions in pulse rate on 3 of the 4 days of treatment compared to the control group. Massage was also more effective in reducing Alcohol Withdrawal Scale scores in the early stages of the detoxification process. Respiration in the massage group was reduced toward the end of the detoxification admission. CONCLUSIONS: Massage shows promise as an adjunct to traditional medical detoxification for alcohol.
Black S, Jacques K, Webber A, Spurr K, Carey E, Hebb A, Gilbert R. Chair massage for treating anxiety in patients withdrawing from psychoactive drugs. Journal of Complementary Medicine. 2010 Sep;16(9):979-87. doi: 10.1089/acm.2009.0645.		Single RCT	The aim of this study was to investigate the effectiveness of chair massage for reducing anxiety in persons participating in an inpatient withdrawal management program for psychoactive drugs. DESIGN: The design was a randomised, controlled clinical trial conducted from June 2008 - January 2009. SUBJECTS: Eighty-two (82) adult patients received inpatient treatment for psychoactive drug withdrawal (alcohol, cocaine, and opiates). SETTING: This study was conducted at the Withdrawal Management Services at the Capital District Health Authority, Halifax, Nova Scotia. INTERVENTIONS: Subjects were randomly assigned to receive chair massage (n=40) or a relaxation control condition (n=42). Treatments were offered for 3 consecutive days. Standard counseling and pharmacologic management were also offered concurrently to patients in all conditions. MEASUREMENTS: The primary outcome measure was anxiety assessed using the Spielberger State-Trait Anxiety Inventory (STAI). State and trait anxiety scores were determined immediately prior to and following each treatment intervention. RESULTS: Analysis of STAI scores showed a significant reduction in state and trait anxiety for both interventions ($p < 0.001$). The magnitude in the reduction in state ($p=0.001$) and trait ($p=0.045$) anxiety was significantly greater in the chair massage group where the effect on state anxiety was sustained, at least in part, for 24 hours. CONCLUSIONS: Within the clinical context of this study, chair massage was more effective than relaxation control in reducing anxiety. Further investigation of chair massage as a potential non-pharmacologic adjunct in the management of withdrawal related anxiety is warranted.
Exercise: No controlled studies of exercise in alcohol withdrawal were identified. See Chapter 1 for discussion on exercise.			

Summary of the evidence

2.1 Treatment setting

One relevant systematic review[47] recently examined the role of community (specifically home and outpatient) withdrawal settings for alcohol withdrawal, using a systematic search strategy, with a narrative review of the evidence, examining the outcomes of patient safety, effectiveness (completion rates, drinking patterns), acceptability and cost. The review examined studies until 2016, and included 20 studies, including four RCTs (involving 347 subjects), three quasi-experimental (175 participants), two case series, three qualitative studies, six observational and two 'mixed methods' studies. Studies were included if a specific alcohol withdrawal intervention was delivered at home or in an outpatient setting.

The studies themselves included eligibility criteria relevant to delivering ambulatory withdrawal, including: availability of a safe home and carer; able to reach the clinic and follow medical instructions; no other substance use in the home. Medical ineligibility criteria included a history of severe alcohol withdrawal, withdrawal seizures or delirium tremens; severe medical (e.g. epilepsy, severe hepatic, cardiovascular or cerebrovascular disease, diabetes mellitus, hypertension) or psychiatric (e.g. psychosis, suicidality, severe cognitive impairment) comorbidity.

The community withdrawal interventions lasted three to 12 days, generally included medications (usually BZDs), some level of withdrawal monitoring using standardised scales and breathalyser readings, and psychosocial support of patients and carers from community-based withdrawal nurses, including telephone support.

There were a limited number of RCTs and quasi-experimental studies, and the authors did not attempt a meta-analysis of outcomes comparing community versus residential (or inpatient) settings. Nevertheless, the authors make the following conclusions:

- Community withdrawal is at least as effective (and better in some studies) as residential withdrawal on the outcomes of completion of the withdrawal episode, uptake of continuing care, and post-withdrawal drinking outcomes
- There were no significant safety concerns identified in conducting community withdrawal, although these studies all involved structured screening, assessment and treatment procedures
- Cost of services suggest a marked saving in community-based withdrawal services, with estimates that residential/hospital-based withdrawal services were between 10-23 times more expensive in an Australian setting[49], six times more expensive in a UK setting[50], and four or nine times more expensive in US studies.[51, 52] While these studies were conducted over a decade ago, there is little to suggest that the cost of residential, hospital or community withdrawal services would have changed significantly in that time
- A key issue regarding acceptability was timely support and access to services, with lengthy delays to the initial assessment appointment being associated with poorer patient and carer experience and engagement with services. Studies indicated that the majority of patients preferred a community rather than residential withdrawal setting.

In summary, *ambulatory withdrawal* (either home based and/or outpatient) is feasible, effective, safe and cost-effective, and often has good patient and carer acceptance. It is the recommended withdrawal setting, unless there are specific clinical reasons for residential or inpatient withdrawal settings. Ambulatory withdrawal should include clearly defined eligibility criteria, non-ambiguous medication protocols based on

daily structured monitoring of the patient's progress and withdrawal symptoms, and linkage with continuing psychosocial care.

Inpatient (hospital) withdrawal is indicated for those with a history of severe alcohol withdrawal (including severe symptoms, withdrawal seizures, psychosis, cardiovascular complications (e.g. severe hypertension, arrhythmias, or delirium), and for those with concomitant substance use (e.g. also withdrawing from other substances) medical (e.g. hepatic failure, severe cardiovascular, respiratory or cerebrovascular disease, diabetes, systemic infections) or psychiatric comorbidity (e.g. suicidal ideation, other causes of psychosis, severe depression or anxiety).

Residential withdrawal is indicated for those with unsuitable home environments (e.g. homeless, other substance use) or without social supports, those who are unable to access outpatient or home-based withdrawal services, or those who have had repeated failure at ambulatory withdrawal. These are highlighted in the table below.

Table 2.3 Considerations for selection of withdrawal setting for alcohol withdrawal

	Ambulatory	Residential	Inpatient (hospital)
Likelihood of severe withdrawal complications	N/A	N/A	History of severe alcohol withdrawal, including withdrawal seizures, delirium, cardiovascular disease or psychosis
Medical or psychiatric comorbidity	Minor comorbidity	Minor comorbidity	Significant comorbidity
Other substance use	No heavy drug use	Heavy or unstable use other drugs	Heavy or unstable use other drugs
Social environment	Supportive home environment (not homeless, no substance use in home). Regular monitoring by reliable support people. Good access to outpatient service	Unsupportive home environment or social supports Poor access to outpatient services	Unsupportive home environment or social supports Poor access to outpatient services
Previous withdrawal attempts		Repeated failure at ambulatory withdrawal	Repeated failure at ambulatory withdrawal

*For further details see text.

2.2 Psychosocial interventions

Summary of evidence regarding psychosocial interventions in alcohol withdrawal management

The main focus of studies examining psychosocial interventions has been the outcomes of withdrawal completion, and engagement in subsequent post-withdrawal treatment.

Seven RCTs were identified in the Timko[48] review examining the role of different psychosocial interventions in facilitating post-withdrawal treatment engagement. The findings suggest that motivational enhancement approaches during the withdrawal episode appear to be effective in enhancing withdrawal completion and

subsequent engagement in post-withdrawal treatment. There are inconsistent findings regarding the role of peer-based programs (e.g. 12-step programs) during the withdrawal episode and subsequent treatment engagement.

No controlled studies that examined the impact of psychosocial interventions upon completion of the withdrawal episode were identified in the Timko review. Several cohort studies reported in the review identified different programmatic factors as impacting upon completion rates – however these were not consistent between studies, and no conclusions can be made.

Furthermore, the role of consumer or patient information in alcohol withdrawal management has not been examined in controlled studies. Recommendations are extrapolated from studies in other withdrawal syndromes (e.g. opioid withdrawal – see Chapter 3).

2.3 Physical therapies

Summary of evidence regarding acupuncture

Liu et al. identified 11 RCTs of acupuncture for alcohol withdrawal, while Grant et al. identified 26 RCTs with 1175 participants reporting data on withdrawal or craving symptoms, across different drug classes (most examined alcohol and opioids, but studies also of stimulants). Both reviews identified the quality of the evidence as low or very low (Grant used GRADE classification system), and with likely publication biases, highlighting caution in interpretation of the findings.[8, 9]

Liu et al. identified no difference between acupuncture and controls (usually sham acupuncture) regarding alcohol withdrawal completion rates, or total alcohol withdrawal symptoms, although some studies point to reduced craving during withdrawal, and general improvements in anxiety related measures. Grant et al pooled all studies and a meta-analysis suggests a moderate effect size for reduced withdrawal symptoms or cravings immediately post-acupuncture, however with considerable heterogeneity and findings between studies, and rated the evidence as Low GRADE. The benefits arise predominately in studies of traditional Chinese medicine (TCM) acupuncture rather than auricular acupuncture, although the authors caution the possible publication bias and Very Low quality of evidence regarding RCTs of TCM acupuncture. Findings for individual drug classes (alcohol, opioids, stimulants) showed no significant benefits on withdrawal symptoms or cravings.

In summary, the available evidence regarding acupuncture indicates that across the different withdrawal substances, the RCTs indicate no consistent benefits of acupuncture on withdrawal severity or withdrawal completion rates. The evidence suggests there may be some benefits on post-withdrawal anxiety, however this was not a consistent finding across studies. The evidence is of low quality and better studies are required. At this stage, acupuncture is not recommended for routine implementation.

Summary of evidence regarding exercise

No controlled studies of exercise were identified for alcohol withdrawal management. Given the potential cardiac complications seen in alcohol withdrawal (arrhythmias, hypertension, cardiomyopathy), which may be compounded by electrolyte abnormalities (e.g. hypokalaemia) and mobility problems (e.g. ataxia, neuropathy, myopathy), further research is required regarding the safety of exercise in patients undergoing withdrawal from alcohol. All patients should undertake a medical assessment prior to embarking upon exercise programs during withdrawal.

Summary of evidence regarding massage therapy

Two controlled studies were identified, with no review of the subject. The studies examined the effects of massage in patients undergoing alcohol withdrawal or a mixed population undergoing withdrawal from

alcohol, cocaine or opioids. Both studies found that massage was more effective than control ('rest' or 'relaxation') in reducing withdrawal symptoms – most notably anxiety symptoms. While the evidence is limited, the positive findings, low safety risk and intervention costs, and potential attractiveness of the massage therapy for some clients, massage therapy is recommended as adjunctive therapy in withdrawal management, recognising the need for further research.

2.4 Medications

Medications with evidence of safety and efficacy for use in alcohol withdrawal

Benzodiazepines (BZDs) have by far the most robust evidence base. There have been attempts to compare different BZDs for superiority in seizures, delirium and adverse events, but none have been shown to be statistically, significantly better.[40, 53] Pharmacologically, BZDs with good oral bioavailability and rapid onset of action (e.g. diazepam) are preferred, although long-acting BZDs (e.g. diazepam) may be problematic for patents with poor metabolism and clearance (e.g. those with hepatic failure, the elderly).

Fixed-, symptom-triggered or loading-dose benzodiazepine regimens

Attempts have also been made to assess if symptom-triggered use is preferential to fixed-dosing across markers such as length of stay in hospital and risk of adverse events such as seizures. At this stage, neither has been shown to be superior to the other.[40, 54] Holleck's analysis showed that triggered regimens may result in less use of BZDs, but this is subject to selection bias, in that patients at lower risk of withdrawal are more likely to be on symptom triggered regimes. Nevertheless, in the context of patients with no history of severe alcohol withdrawal syndrome, symptom-triggered regimens appear to be associated with less duration and less total BZD dose over the withdrawal episode, while achieving comparable withdrawal treatment outcomes.

While controlled studies do not advise optimal approaches to questions of fixed- or symptom-triggered BZD regimens, a number of clinical and logistical issues will impact upon the choice of regimen for a particular patient or setting. For example, symptom-triggered regimens have not been validated (and indeed case reports indicate concerns) for use in patients with significant medical comorbidity (e.g. severe respiratory, cardiac or hepatic disease, infections) or psychiatric (e.g. anxiety, psychosis), and as such should not be used for such patients. Symptom-triggered regimens also require a trained and skilled workforce with regular monitoring (e.g. three or four times a day) – which may be feasible in some settings (e.g. a dedicated withdrawal unit with trained staff), but may be difficult to implement in a general hospital or psychiatric ward, or in an outpatient setting. These issues are described in detail in Chapter 4 of the Commonwealth Alcohol Treatment Guidelines.[5]

Similarly, RCTs have not examined the role of loading-dose regimens versus fixed- or symptom-triggered BZD regimens. Haber, et al. (2009) recommend the use of loading-dose regimens (e.g. 20mg oral diazepam 2 hourly x 3 doses) for patients with a history of alcohol withdrawal seizures – as seizures may occur as one of the early manifestations of alcohol withdrawal and before other withdrawal symptoms are detected on an alcohol withdrawal scale (e.g. CIWA-Ar). Similarly, doses used in fixed-dose regimens (e.g. 10mg oral diazepam 6-hourly on day 1) are too slow to achieve the plasma levels of BZDs required to reliably prevent seizures in high risk patients (those with a history of seizures). As such, loading-dose regimens are recommended for management of patients with a history of alcohol withdrawal seizures.

Medications for which there is limited or no evidence for use in alcohol withdrawal

No study has demonstrated choice of agent for patients with BZD intolerance. Ethanol infusion may have a role in prevention of severe alcohol withdrawal in patients with a history of severe alcohol withdrawal[55], or

in the prevention of delirium tremens[56], however it has no role in the management of patients experiencing alcohol withdrawal, and as such there appears to be little benefit in its routine use.

GHB is too unsafe to be considered for routine management of alcohol withdrawal[43], as are barbituates.[53, 57] Baclofen has insufficient evidence to be suggested as a treatment option.[44] Anticonvulsants do not have enough evidence to be considered treatment for AWS.[40, 46]

Table 2.4 Summary of evidence and recommendations for management of alcohol withdrawal

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient, residential and ambulatory withdrawal setting	*Inpatient admission* is indicated for patient safety reasons in the context of severe alcohol withdrawal (seizures or delirium tremens), comorbid severe substance use, medical or psychiatric conditions. *Residential withdrawal* settings may be appropriate for those with unsuitable home environments and supports to attempt ambulatory withdrawal, or for those with repeated failure at ambulatory withdrawal attempts. *Ambulatory withdrawal* is a feasible approach for the management of alcohol withdrawal, is safe, effective and considerably less expensive when provided within a structured model of care. Ambulatory withdrawal can provide more timely access than residential or inpatient withdrawal, and often has good patient and carer acceptability. It generally recommended unless there are clinical indications for a residential or inpatient withdrawal setting, such as a history of severe withdrawal.	Ib	Grade C: Satisfactory
Psychosocial interventions (as adjunct to medication)			
Motivational enhancement counselling	Motivational enhancement approaches (group or individual) appear to be effective in enhancing the uptake and engagement with subsequent post-withdrawal treatment for substance use disorder.	Ib	Grade C: Satisfactory
Peer engagement during withdrawal	The role of peer engagement during withdrawal episode (e.g. 12-step meetings) upon subsequent engagement in post-withdrawal treatment (or 12 step programs) remains unclear, with few controlled studies and inconsistent findings.	Ib	Grade D: Poor
Patient or consumer information	No studies identified in alcohol withdrawal, however extrapolating from evidence for opioid withdrawal and from evidence regarding general consumer health literature, provision of structured information to patients may be associated with lower withdrawal severity and greater treatment retention.	IV	Grade D: GPP (Good Practice Point)
Linkages to post-withdrawal treatment services	Structured and assertive linkages to post-withdrawal treatment associated with greater engagement with post-withdrawal treatment.	Ib	Grade C: Satisfactory

Physical interventions (as adjunct to medications)			
Massage therapy during withdrawal	Limited evidence (two RCTs with small numbers) suggests massage therapy may be effective in reducing withdrawal symptoms and anxiety during withdrawal, as an adjunct to other interventions.	Ib	Grade D: Poor
Auricular or traditional Chinese medicine acupuncture during withdrawal episode	Most controlled studies have examined alcohol or opioid withdrawal, and usually as an adjunct to routine care. Meta-analyses indicate there is evidence of a reduction in withdrawal symptoms, cravings and anxiety symptoms, although no differences in completion rates. When individual drug types are examined (e.g. alcohol, opioids, stimulants) there are no benefits of acupuncture on withdrawal symptoms or cravings. The reviewers caution that there are inconsistent findings between studies, poor quality studies and evidence of publication bias, and suggest caution in interpreting evidence.	GRADE Low or Very Low	Grade D: Poor
Exercise for alcohol	Controlled studies were not identified examining aerobic or mind-body (e.g. yoga) exercise programs for use in alcohol withdrawal, and further research is required given safety concerns in these populations.	No studies identified	Grade: No studies identified
Medications			
Benzodiazepines (BZDs)	BZDs show benefit against placebo with statistical significance for alcohol withdrawal seizures in systematic review; when compared to other drugs for prevention of alcohol withdrawal seizures, there is a trend towards BZDs, however this did not reach statistical significance. No BZD has been shown to be superior to another, although BZDs with good oral bioavailability and rapid onset of action (e.g. diazepam) are preferred, especially in preventing alcohol withdrawal seizures. BZDs do not appear to prevent alcohol withdrawal delirium.	Ia	Grade B: Good
Symptom-triggered versus fixed-dose BZD regimens	Symptom-triggered dose regimens reduce total BZD dose and duration of treatment. However, there are no studies looking at safety outcomes. Symptom-triggered dose regimens are not validated for use in patients with severe medical or psychiatric comorbidity. Choice of regimens tend to relate to patient and programmatic factors (e.g. workforce training, treatment settings).	Ia	Grade D: GPP (Good Practice Point)
Loading-dose regimen versus symptom -triggered or fixed-dose BZD regimens	Loading-dose regimens are recommended for managing patients with a history of alcohol withdrawal seizures.	III	Grade D: GPP (Good Practice Point)
BZDs in the management of critically ill patients (e.g. ICU settings)	BZDs remain the standard of treatment in intensive care. Patients need to be recognised and treated early. There is increasing investigation into the use of alpha agonists and phenobarbital as adjunctive therapy, but at this stage neither can be recommended as monotherapy.	Ib	Grade C: Satisfactory

GHB	GHB may be better than placebo for alcohol withdrawal but does not appear to be better than BZDs. No role at this stage in the treatment of alcohol withdrawal.	Ia	Grade D: Poor
Propofol	Propofol has a number of safety concerns, including higher rates of cardiovascular events and mechanical ventilation. It does not appear to offer benefits over BZDs or alpha agonists. Furthermore, the timing, dose and duration of treatment remain unclear.	Ib	Grade D: Poor
Anticonvulsants	Anticonvulsants are well tolerated, and a possible alternative to BZDs in systematic review; however, meta-analysis reveals insufficient data to recommend anticonvulsants for the treatment of AWS.	Ia GRADE: Moderate	Grade C: Satisfactory
Alpha agonists	Alpha agonists only appear to have been evaluated in intensive care. Alpha agonists can help with the sympathetic symptoms of alcohol withdrawal and may help to lower the amount of BZD required, but at this stage can only be considered an adjunct to BZD treatment.	Ib	Grade C: Satisfactory
Combination carbamazepine/tiapride	One low quality systematic review showed evidence that this combination is effective. However, it lacked data around seizures and adverse events.	Ia	Grade D: Poor
Barbituates	Phenobarbital has been shown to have a role as an adjunct to BZDs, especially in severe alcohol withdrawal. It may help to reduce duration of ICU admissions and prevent ICU admission. However, there is insufficient evidence to recommend it as monotherapy.	Ib	Grade C: Satisfactory
Baclofen	There is no evidence that baclofen is either safe or efficacious for alcohol withdrawal syndrome.	Ia	Grade D: Poor
Alcohol	There have been no new studies since 2010. Studies indicate alcohol dosing can be effective for preventing withdrawal complications (e.g. delirium), but not in treatment of alcohol withdrawal.	Ib	Grade D: Poor
Antipsychotics	The only systematic review since 2010 was of poor quality; we cannot put forward any of its recommendations.	Ib	Grade D: Poor
Gabapentin	The only study since 2010 was of poor quality; we cannot put forward any of its recommendations.	Ib	Grade D: Poor

For classification schemes for categorisation/grading of evidence see Appendices 1 and 2.

Chapter 3. Opioids

Description of the withdrawal syndrome

DSM-5 criteria for Opioid Withdrawal:

A. Presence of either of the following:
   1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e. several weeks or longer)
   2. Administration of an opioid antagonist after a period of use

B. Three (or more) of the following developing within minutes to several days after Criterion A:
   1. Dysphoric mood
   2. Nausea or vomiting
   3. Muscle aches
   4. Lacrimation or rhinorrhea
   5. Pupillary dilation, piloerection, or sweating
   6. Diarrhea
   7. Yawning
   8. Fever
   9. Insomnia

C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

In general, the withdrawal syndrome from ceasing short-acting opioids (e.g. heroin, morphine, codeine) commences within 24–48 hours of last use, peaks by 48–96 hours, and starts to subside over five to seven days, although many symptoms (low mood, sleep disturbances, cravings) persist for weeks or months. Withdrawal from long-acting opioids (e.g. methadone, buprenorphine) occurs over a longer time frame with later onset (1–3 days) and peak (2–10 days) period of symptoms, with resolution over weeks to months.

There is considerable variability in the severity, onset, peak and duration of opioid withdrawal between individuals, which can only be partially accounted for by 'substance use' factors such as duration of opioid use, quantity or frequency of use, or type of opioid used. Environmental (e.g. setting), psychological (e.g. anxiety, depression) and comorbid health conditions (e.g. pain, sleep disorders) can contribute to the experience of withdrawal.

Heroin withdrawal syndrome and the role of withdrawal management in the treatment of opioid use disorder

Withdrawal treatment underpins entry to alcohol and other drug treatment for many substance use disorders (SUDs) such as alcohol, cannabis and stimulant use disorders, and is often required prior to participation in outpatient or residential psychosocial treatments or commencing relapse prevention medications (e.g. naltrexone). As with other SUDs, stand-alone withdrawal treatment that is not linked to ongoing treatment (e.g. psychosocial and/or medication-assisted treatment) is usually associated with poor short-term and longer-term outcomes and should be discouraged as an elective procedure. Furthermore,

the evidence for the treatment of opioid use disorder highlights the advantages and central role of medication-assisted treatments using buprenorphine or methadone. Opioid agonist treatment is associated with superior treatment outcomes for most patients than either withdrawal-only, withdrawal + counselling, counselling-only[58], withdrawal + naltrexone-assisted treatment, or withdrawal + residential rehabilitation treatment approaches[59-61], and as such the role of a withdrawal treatment episode for a patient with opioid use disorder should be considered carefully.

Indeed withdrawal episodes for opioid dependence can be problematic due to the increased mortality rates following opiate withdrawal reported in a number of studies.[62, 63] This increased mortality is most likely linked to the increased risk of overdose following the resumption of opioid use in the context of reduced opioid tolerance that occurs as part of withdrawal. All patients entering withdrawal treatment for opioid dependence should be provided with a take-home-naloxone intervention as part of routine care, given the very high rates of relapse to opioids and increased mortality rates following opioid withdrawal.

Selection of reviews and studies

Systematic reviews

Table 3.1 describes the review articles identified from the search, summarising the type of review, dates of studies reviewed, and relevance to scope of this chapter.

Recent Cochrane reviews for the management of opioid withdrawal were identified for the use of buprenorphine, adrenergic agonists (lofexidine, clonidine), opioid antagonists and methadone. Many of these reviews 'overlap' in their comparisons (see Table 3.6). One review examined the role of psychosocial interventions (in addition to medication), and one review examined the role of treatment setting (inpatient versus outpatient).

Several reviews were not considered further – either because the studies examined withdrawal from opioids from which patients are unlikely to present for withdrawal treatment in Australia (e.g. opium) and no RCTs were identified (e.g. codeine), and both groups of authors of these reviews highlighted the poor-quality studies in these areas prevent meaningful conclusions. The role of antagonists under anaesthesia was not considered further due to the safety concerns with this approach.

Relevant papers published since the review(s)

A review for studies conducted since the Cochrane reviews indicated a number of RCTs had examined pharmacotherapies (see Table 3.2) and treatment setting (see Table 3.3) for opioid withdrawal.

Table 3.1 Summary of reviews of interventions for opioid withdrawal

Review authors, title, reference	Date studies reviewed	Type of review	Commentary on review
Gowing L; Ali R; White JM; Mbewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database of Systematic Reviews. 2:CD002025, 2017 02 21.	Dec 2016	Systematic review. Meta-analysis. 27 studies involving 3048 participants	Preferred review for buprenorphine (BPN) assisted opioid withdrawal. Comparison interventions involved reducing doses of methadone, alpha2-adrenergic agonists (clonidine or lofexidine), symptomatic medications or placebo, and different buprenorphine-based regimens.
Gowing L; Ali R; White JM. Opioid antagonists with minimal Cochrane Database of Systematic Reviews. 5:CD002021, 2017 05 29.	Dec 2016	Systematic review Qualitative review 10 studies (6 RCTs, 4 cohort studies) 955 participants	Preferred review for opioid antagonist-assisted opioid withdrawal. Comparison of opioid antagonist-adrenergic agonist combination versus a treatment regimen based primarily on an alpha2-adrenergic agonist (clonidine or lofexidine). Other comparisons (placebo, tapered doses of methadone, buprenorphine) made by included studies were too diverse for any meaningful analysis.
Gowing L; Farrell M; Ali R; White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews. (5)CD002024, 2016 May 03.	Nov 2015	Systematic review Meta-analysis. 26 RCTs involving 1728 participants	Comparing alpha2-adrenergic agonists (clonidine, lofexidine, guanfacine, tizanidine) with reducing doses of methadone, symptomatic medications or placebo, or comparing different alpha2-adrenergic agonists.
Amato L; Minozzi S; Davoli M; Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database of Systematic Reviews. (9)CD005031, 2011 Sep 07.	June 2011	Systematic review Meta-analysis 11 RCTs, 1592 participants	RCTs and controlled clinical trial that focused on any psychosocial intervention associated with any pharmacological intervention aimed at opioid detoxification. People less than 18 years of age and pregnant women were excluded.
Amato L; Davoli M; Minozzi S; Ferroni E; Ali R; Ferri M. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database of Systematic Reviews. (2)CD003409, 2013 Feb 28.	May 2012	Systematic review Meta-analysis 23 trials involving 2467	All RCTs focused on the use of tapered methadone versus all other pharmacological detoxification treatments or placebo for the treatment of opiate withdrawal.
Day E, Ison J, Strang J. Inpatient versus other settings for detoxification for opioid dependence. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD004580.	May 2008	Systematic review. Qualitative analysis	Only one RCT analysed in the review. One older study (Wilson et al 1975) and one more recent study (Day and Strang 2011) identified, and the three studies are described (narrative review).

Review authors, title, reference	Date studies reviewed	Type of review	Commentary on review
DOI: 10.1002/14651858.CD004580.pub2.			
Nielsen S; MacDonald T; Johnson JL. Identifying and treating codeine dependence: a systematic review. Medical Journal of Australia. 2018;208(10):451-461.	Nov 2016	Systematic review Qualitative review 10 studies on codeine dependence treatment, but no RCTs	Relating to codeine, not heroin dependence. No RCTs or controlled studies identified.
Gowing L; Ali R; White JM. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Cochrane Database of Systematic Reviews.(1)CD002022, 2010 Jan 20.	Aug 2009	Systematic review Quantitative review	Intervention no longer practised in NSW due to safety concerns. Old review. No recent studies.
Rahimi-Movaghar A; Gholami J; Amato L; Hoseinie L; Yousefi-Nooraie R; Amin-Esmaeili M. Pharmacological therapies for management of opium withdrawal. Cochrane Database of Systematic Reviews. 6:CD007522, 2018 06 21.	Sep 2017	Systematic review. 13 trials involving 1096 participants	Relating to opium withdrawal, not heroin. Low quality studies identified.
Nikoo M, Nikoo N, Anbardan SJ, Amiri A, Vogel M, Choi F, et al. Tincture of opium for treating opioid dependence: a systematic review of safety and efficacy. Addiction. 2017:112(3);15–429.	2016	Systematic review of opium tincture for treatment opioid dependence. 2 RCTs of withdrawal, remainder 'maintenance studies'	Opium tincture comparable to methadone taper in one RCT, and less effective than buprenorphine taper in another RCT in suppressing withdrawal symptoms. Not progressed as opium tincture not available in Australia.

Table 3.2 Additional RCTs examining pharmacological interventions for opioid withdrawal identified in systematic search

Paper authors, title, reference	Study description	Commentary on paper and main conclusions
Buprenorphine versus methadone		
Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: A randomised controlled trial of low dose short-term opiate-dependent individuals. Journal of Psychopharmacology. 2017;31(8);1046–1055.	N=80 parallel group RCT comparing tapered buprenorphine (BPN)/naloxone (from 4mg/1mg / day) versus tapered methadone (from 30mg / day) and lofexidine. Low dose opioid dependent users treated in outpatient setting.	During detoxification, withdrawal symptoms were significantly greater and the peak of withdrawal was earlier for the methadone/lofexidine group than the buprenorphine/naloxone group ($p<0.01$, 95% confidence interval 3.0, 8.3). Findings suggest advantages of less severe and shorter duration withdrawal using BPN taper than methadone. The likely role of lofexidine in the methadone arm ameliorating withdrawal severity further highlights the potential advantage of buprenorphine. Generally consistent with Cochrane review (Gowing et al. 2017) and strengthens evidence for use of buprenorphine over methadone.
Lofexidine		
Guo S, Manning V, Yang Y, Koh PK, Chan E, de Souza NN, et al. Lofexidine versus diazepam for the treatment of opioid withdrawal syndrome: A double-blind randomized clinical trial in Singapore. Journal of Substance Abuse Treatment. 2018;91:1–11.	Inpatient RCT of opioid-dependent patients (n=111) comparing 10-day course of lofexidine (n=56) to diazepam (n=55). Primary endpoint: Objective Opioid Withdrawal Scale (OOWS) score on days 3 & 4. Secondary outcomes: Short Opioid Withdrawal Scale (SOWS) score, retention rate and cravings.	No significant difference on primary outcome (Day 3, 4 OOWS). Lofexidine group significantly less severe SOWS, craving and higher retention than diazepam. Findings generally consistent with Cochrane review of alpha-adrenergic agonists (Gowing et al 2016).
Gorodetzky CW, Walsh SL, Martin PR, Saxon AJ, Gullo KL, Biswas K. (A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. Drug and Alcohol Dependence. 2017;176;79-88.	Inpatient eight-day, randomised, double-blind, placebo-controlled, parallel-group study in 264 patients dependent on short-acting opioids, comparing lofexidine (0.8mg QID) to placebo. Primary endpoint: subjective withdrawal Days 3+4 (Short Opiate Withdrawal Scale). Secondary outcomes: treatment completion, objective withdrawal (OOWS), total SOWS over five days.	Lofexidine significantly decreased mean Day 3 SOWS scores compared to placebo (6.32 versus 8.67, $p<0.05$). Fewer lofexidine patients were early terminators compared to placebo (59 versus 80, respectively). Secondary endpoints consistently favoured lofexidine. Findings consistent with Cochrane review of alpha-adrenergic agonists (Gowing et al. 2016).
Tramadol		
Dunn KE; Tompkins DA; Bigelow GE; Strain EC. Efficacy of tramadol extended-release for opioid	Inpatient RCT 103 participants with opioid use disorder (OUD). A 7-day taper using clonidine (n=36),	Study examined withdrawal symptoms whilst receiving medication, and then following post-medication phase.

Paper authors, title, reference	Study description	Commentary on paper and main conclusions
withdrawal: A randomized clinical trial. JAMA Psychiatry. 2017;74(9):885–93.	tramadol ER (n=36), or buprenorphine (n=31), and patients were crossed over to double-blind placebo during a post-taper (second phase) period. Rescue medications throughout both phases available.	BPN participants were significantly more likely to be retained at the end of the taper (90%) compared with clonidine participants (61%); tramadol ER intermediate (72%); P=.01). No significant difference in withdrawal symptoms in either phase or between groups. Significantly more rescue medications for tramadol ER and clonidine than BPN, suggesting higher withdrawal discomfort. The results of this trial suggest that tapering doses of tramadol ER is more effective than clonidine in reducing opioid withdrawal symptoms; and may be comparable to BPN. Small numbers limit conclusions.
Lofwall M.R.; Babalonis S.; Nuzzo P.A.; Siegel A.; Campbell C.; Walsh S.L. (Efficacy of extended-release tramadol for treatment of prescription opioid withdrawal: A two-phase randomized controlled trial. Drug and Alcohol Dependence. 2013;133(1):188–97.	Threegroup RCT (placebo, 200mg, 600mg) of Extended Release (ER) tramadol in two phase study: Phase 1: in alleviating opiate withdrawal (and reducing need for breakthrough medication); Phase 2: examining withdrawal off tramadol after seven days. Enrolment until n=12 per group completed.	Tramadol 200mg less withdrawal severity and rescue medications than placebo, but no different than 600mg. Greater rebound withdrawal (Short Opiate Withdrawal Scale) + rescue medications from discontinuing 600mg tramadol than placebo. Conclusion: ER tramadol 200 mg modestly attenuated opioid withdrawal. Mild opioid withdrawal occurred after cessation of treatment with 600mg tramadol. Small numbers and recruitment approach do not allow intention to treat analysis and limit conclusions.
Zarghami, M; Masoum, B; Shiran, MR. Tramadol versus methadone for treatment of opiate withdrawal: A double-blind, randomized, clinical trial. Journal of Addictive Diseases. 2012;31(2);112–7.	N=70 outpatient RCT comparing tapered doses of methadone (from 60mg/day) and tramadol (from 600mg/day).	No significant differences in withdrawal severity (OOWS), treatment completion or adverse events between groups.
GABAnergic medications		
Krupitskii EM, Ilyuk RD, Mikhailov AD, Kazankov KA, Rybakova KV, Skurat EP et al. A randomized controlled study of the efficacy of pregabalin in the treatment of opiate withdrawal syndrome. Neuroscience and Behavioral Physiology. 2017;47(9);1094–1101.	RCT of N=34 opioid dependent patients undergoing inpatient withdrawal compared up to 600mg pregabalin to up to 600mg clonidine. Outcomes of completion, withdrawal severity, related symptoms (anxiety, sleep, cravings).	Some benefits for pregabalin group in withdrawal completion (79% v 47%), anxiety and depression scores, however no significant differences in global opiate withdrawal symptoms. Small numbers prohibit conclusions.

Paper authors, title, reference	Study description	Commentary on paper and main conclusions
Kheirabadi GR, Salehi M, Bahrami M, Maracy MR (2018) Gabapentin, pregabalin, and placebo in reducing opioid withdrawal symptoms in ppioid-dependent Individuals: A randomized-controlled trial. Addictive Disorders and their Treatment. 2018;17(2);55–64.	Outpatient RCT with N=50. Iran. Three-group RCT of pregabalin, gabapentin and placebo as adjunct medication in buprenorphine assisted withdrawal.	Dosages of 450 mg/d of pregabalin and 1600 mg/d of gabapentin are not significantly superior to placebo in controlling opiate withdrawal symptoms.
Other medications		
Lin, Shih-Ku; Chen, Chia-Hui; Pan, Chun-Hung. Venlafaxine for acute heroin detoxification: A double-blind, randomized, control trial. Journal of Clinical Psychopharmacology. 2008;28;189–194.	N=34 heroin-dependent patients randomised to seven-day regimen of venlafaxine (300mg/day) or placebo. Rescue medications if required. Global impression from clinician (GCI-C) and patients; withdrawal severity (OOWS) outcomes.	Small numbers and analysis of protocol completers only (8/15 venlafaxine, 12/19 placebo) limits conclusions. No difference in global impressions from patients or clinicians. Less withdrawal severity in venlafaxine group. Cannot draw conclusions with these limitations.
Klein LR, Cole JB, Driver BE, Fagerstrom E, Martel ML. A randomized trial of intramuscular olanzapine vs oral clonidine for symptomatic treatment of opioid withdrawal in the emergency department. Academic Emergency Medicine. 2018;25; S145.	Randomised clinical trial comparing 10mg of IM olanzapine to 0.3mg of oral clonidine for the symptomatic treatment of acute opioid withdrawal. Adult ED patients presenting with opiate withdrawal necessitating medical treatment. Examined single doses of medication in alleviating COWS and need for rescue medications within 1 hour. N=63 (33 olanzapine, 30 clonidine).	Rescue for olanzapine in 9 (27%) and for clonidine in 19 (63%) (difference 36%, 95% 13-59%). Change in COWS score at one hour was 8.3 for olanzapine and 5.1 for clonidine (difference 3.2, 95% CI 0.3-6). Adverse events were uncommon. Conclusion: Treatment of opioid withdrawal symptoms with 10mg of IM olanzapine results in a lower incidence of rescue medication administration and improved symptoms than 0.3mg oral clonidine.

Summary of the evidence

3.1 Treatment setting

Only three studies [64-66] (see Table 3.3) were identified that directly compared inpatient to outpatient management of opiate withdrawal. The quality of the evidence is Very Low, with few subjects in all three studies (total n=168, of which 128 randomised), unclear reporting of outcomes in two studies [64, 65], and all three studies examined prolonged duration of inpatient treatment (10–21 days) or used withdrawal medication regimens (lofexidine, prolonged methadone taper) that are not routinely used in management of opiate withdrawal in the Australian treatment context. Furthermore, participants who were assessed as ineligible for outpatient withdrawal (e.g. due to comorbidities, unsuitable home environments) were excluded from these studies.

Despite these limitations, the evidence suggests there is no clear advantage in an inpatient (or residential) withdrawal setting over an ambulatory or outpatient setting regarding completion of opioid withdrawal, engagement in post-withdrawal treatment or post-withdrawal substance use, and as such, inpatient withdrawal is not routinely recommended. Indeed, for many patients, issues regarding difficulties in accessing inpatient treatment (e.g. waiting lists), stigma, cost and dislocation from community supports suggest that outpatient withdrawal services should be available as a treatment option.

However, there are a number of medical or social conditions that warrant inpatient (or residential) withdrawal setting for safety reasons.

Inpatient hospitalised withdrawal setting

Opiate withdrawal is not usually associated with severe withdrawal complications that warrant inpatient hospital admission. An exception may be severe dehydration and/or electrolyte disturbances requiring intravenous rehydration and correction of any electrolyte abnormalities (e.g. low potassium).

Inpatient admission may also be indicated for the management of withdrawal in the context of complex comorbidities. Opiate use or related complications of injecting drug use is potentially associated with a range of psychiatric (e.g. suicidal ideation, depression), and physical (e.g. infections, overdose) conditions that may warrant hospital admission, and during which the patient may undergo opiate withdrawal that requires management. A patient presenting for elective withdrawal treatment may require inpatient admission in the context of complex comorbidities (e.g. withdrawal from multiple drugs, psychiatric or medical problems) that require medical management and monitoring. It should be noted however, that withdrawal treatment may not be the optimal treatment approach under such conditions – and induction onto opioid agonist treatment may be preferred.

Residential withdrawal settings

Residential withdrawal settings may be appropriate for those with unsuitable home environments and/or community supports to attempt withdrawal, or for those with repeated failure at ambulatory withdrawal attempts. Residential withdrawal may also be delivered as the 'first phase' of a longer-term residential treatment program, with the aim of achieving greater uptake of residential rehabilitation.

Ambulatory withdrawal

Ambulatory withdrawal is a feasible approach for the management of opiate withdrawal. This is particularly the case given the preferred medication approach (a tapered withdrawal using an opioid agonist such as buprenorphine) generally involves a tapered reduction over 1–4 weeks, with withdrawal symptoms persisting for several days after last dose. Hence, unless the withdrawal episode is considered part of a

longer-term residential treatment program (e.g. residential rehabilitation) or in response to a hospital admission for other reasons (non-elective withdrawal), outpatient withdrawal is generally recommended.

Table 3.3 Studies examining treatment setting in management of opiate withdrawal

Paper authors, title, reference	Study description	Commentary on paper and main conclusions
Day E and Strang J. Outpatient versus inpatient opioid detoxification: A randomized controlled trial. Journal of Substance Abuse Treatment 2011;40(1);56–66.	N=68 opioid-dependent patients (most using heroin in addition to methadone treatment) randomly allocated to 21-day inpatient or outpatient withdrawal intervention using lofexidine, symptomatic medications, and daily supportive counselling. Primary outcome of opioid free at completion of the three-week withdrawal episode, with secondary outcomes of opioid use one and six months after withdrawal. Results indicate no significant difference in withdrawal completion by setting; inpatient (18/35, 51%), outpatients (12/33, 36%). 11 (16%) and 8 (12%) participants were opioid-free at the one- and six-month follow-ups respectively, with no between-group differences.	The study suggests few advantages from inpatient treatment. Although the inpatient arm had a higher opioid-free completion rate, this difference was not significant. There were no differences in relapse rates at 1 and 6 months follow-up after withdrawal. However, the study excluded patients most likely to require inpatient treatment due to complex comorbidity or unsuitable home environment, and hence may not reflect outcomes for such patient populations. The treatment interventions (three-week programs using lofexidine) is not comparable to Australian approaches to inpatient or outpatient opioid withdrawal management. The patient population was mainly using heroin in addition to methadone, and hence may explain the protracted nature of the treatment interventions.
Gossop M, Johns A, & Green L. Opiate withdrawal: Inpatient versus outpatient programmes and preferred versus random assignment to treatment. British Medical Journal; 1986;293;103–4.	N=60 participants assigned to one of four groups: randomised outpatient group, randomised inpatient group, preferred outpatient group, and preferred inpatient group. Participants asked if prepared to accept either inpatient or outpatient withdrawal, with those willing to accept either randomly assigned to one of the two randomised groups; whilst those with a strong preference for inpatient or outpatient withdrawal were assigned to their preference group. The inpatient program lasted for 21 days (n=31). The outpatient program lasted for 56 days and entailed weekly counselling (n=29). Both withdrawal schemes used reducing-doses of oral methadone. The principal aim was to achieve abstinence at the end of the withdrawal regimen. Results reported by setting (with self-selected and randomised data pooled). N=60 participants, with most (47, 78%) primarily dependent on illicit heroin, methadone (11, 18%), other opioids (2, 3%). Over half (31, 52%) were intravenous users, and most (39, 65%) also using non-opioid drugs. 45 (75%) men; mean age 26 yrs.	Higher completion rates (reached methadone dose of 0mg and no other substance use confirmed by urinalysis) in inpatient setting (25/31, 81%) than outpatient setting (5/29, 17%). Participants who expressed a clear preference for either inpatient or outpatient treatment (and so were not randomised, n=40) tended to do better than those who expressed no preference (and so were randomised, n=20), although this was not a significant difference at the 5% level. The outpatient sample was more likely to remain in contact with post-withdrawal treatment services (e.g. counselling, methadone treatment), (16/29, 55%), compared to inpatient sample (9/31, 29%).

Paper authors, title, reference	Study description	Commentary on paper and main conclusions
Wilson, B. K., Elms, R. R., & Thomson, C. P. Outpatient vs hospital methadone detoxification: An experimental comparison. The International Journal of the Addictions. 1975;10(1);13–21.	Randomly allocated 40 heroin-dependent patients to 10-day methadone taper (plus psychosocial intervention) in either inpatient adult psychiatric ward in a general hospital (n=10) or outpatient detoxification (n=30). Some patients refused treatment rather than accept hospitalisation, and hence imbalance in numbers reported. Mean age 22 years, but gender not reported. Costs of treatment also estimated.	Seven out of 10 (70%) in the inpatient detoxification group were opioid-free on discharge, compared with 11 out of 30 (37%) in the outpatient group, however report did not use 'intention to treat analysis' with 'inpatient treatment refusers' not included, distorting the outcomes. Of the post-withdrawal outcomes, all seven participants in the inpatient group that were followed up had relapsed within three months. 18 of the 20 (90%) outpatients that were followed up had relapsed to heroin use within three months. Costs for delivering outpatient withdrawal were estimated at $USD100 for a 10-day program, compared to $USD497 for the inpatient 10-day program.

Table 3.4 Considerations for selection of withdrawal setting for opioid withdrawal

	Ambulatory	Residential	Inpatient (hospital)
Likelihood of severe withdrawal complications	N/A	N/A	Severe dehydration, electrolyte imbalance, or confusion can uncommonly require inpatient admission
Medical or psychiatric co-morbidity	Minor co-morbidity	Minor co-morbidity	Significant comorbidity. Opiate withdrawal can exacerbate other conditions
Other substance use	No heavy drug use	Heavy or unstable use other drugs.	Heavy or unstable use other drugs
Social environment	Supportive home environment. Regular monitoring by reliable support people. Good access to outpatient service.	Unsupportive home environment or social supports. Poor access to outpatient services.	Unsupportive home environment or social supports. Poor access to outpatient services
Previous withdrawal attempts		Repeated failure at ambulatory withdrawal.	Repeated failure at ambulatory withdrawal

*For further details see text.

3.2 Psychosocial interventions

Psychosocial interventions

Counselling and other psychosocial interventions during withdrawal

The evidence for psychosocial interventions from the Cochrane review by[67] is summarised in Table 3.6. The review of adjunctive psychosocial interventions in addition to medication (buprenorphine or methadone tapers) indicate psychosocial interventions are effective in terms of completion of treatment, use of opiates, rates of abstinence at follow-up and clinical attendance in treatment. Moderate to High Grade quality of evidence.

While this evidence suggests that management of opiate withdrawal should incorporate psychosocial interventions in addition to the use of medication, it is not possible at this time to identify optimal approaches to psychosocial interventions. While some interventions examined in RCTs may be difficult to implement routinely in clinical practice (e.g. contingency management, community reinforcement approach, family therapy), structured counselling (e.g. using motivational enhancement approaches) and case management during withdrawal have been shown to be effective in clinical trials and should be able to be incorporated into routine withdrawal management.

Patient information

One RCT[7] examined the role of structured information provision in management of withdrawal from heroin. The study showed that opioid-dependent individuals who had been informed of the nature and severity of their likely withdrawal response experienced lower peak withdrawal scores, showed lower levels of residual withdrawal symptoms, and were more likely to complete the detoxification process. While only one study (low level evidence), this is consistent with the broader literature regarding consumer information and outcomes in healthcare.

Importance of linkages to post-withdrawal treatment services for people undertaking opioid withdrawal

Research across various SUDs demonstrates that patients who participate in treatment following opioid detoxification have better outcomes in terms of abstinence[68] and re-admission rates[69, 70]; than those who do not enter post-withdrawal treatment. In an observational prospective study[71], for inpatients who did not continue in post-withdrawal treatment, there were no significant differences between withdrawal non-completers and withdrawal completers on the majority of measures of drug use during follow-up, whereas post-withdrawal residential rehabilitation was associated with significantly better treatment outcomes than those without follow-up treatment.

Similarly Australian research found that structured aftercare following a four-week inpatient admission was associated with a fourfold increase in subsequent treatment attendance and one-third the rate of uncontrolled principal substance use at follow-up.[72]

However, studies suggest low rates of transition from inpatient withdrawal treatment to post-withdrawal treatment services. Familiarising the patient with the aftercare program has been found to enhance contact rates relative to standard referral procedures for both alcohol and drug problems[73], as has addressing practical barriers to treatment entry such as transport.[74] Chutuape et al. randomly assigned 196 patients admitted to an inpatient AoD treatment unit to one of two methods of increasing transition to outpatient aftercare and a standard referral control. More participants who received staff escort from detoxification to aftercare and a financial incentive (76%) completed intake procedures than those who received only the incentive (44%) or standard conditions (24%).[75] Further research is required to better understand how to

optimise post-withdrawal treatment engagement, particularly where opioid substitution treatment is not recommended.

3.3 Physical therapies

Exercise

An overview of exercise in withdrawal management is provided in Chapter 1. Four RCTs examined exercise for the management of heroin withdrawal (Li 2000, N=60 (Qi Long); Huang 2000, N=120 (jogging); Huang 2000, N=120 (brisk walking) Li 2013, N=33 (Tai Chi). Three of four studies demonstrated exercise was associated with reduced physical withdrawal symptoms during withdrawal, and with reduced anxiety or depression symptoms during withdrawal in the studies that measured these outcomes. While the quality of the studies was low, the evidence is sufficient to support recommendation that exercise be incorporated into opioid withdrawal interventions.

Acupuncture

An overview of the evidence for acupuncture in the management of withdrawal is provided in Chapter 1. The review of acupuncture for all withdrawal conduced by Grant and colleagues (2016) identified 11 RCTs primarily examining acupuncture for opioid withdrawal (in most cases heroin). A second review published in the same year[76] focused on clinical trials of acupuncture for opioid withdrawal. Both reviews identified similar concerns regarding the poor quality of the studies and publication bias. While Grant did not publish meta-analyses findings by study drug (e.g. opioids), the review did report that there were no significant differences regarding withdrawal severity or cravings for specific drug classes. Wu and colleagues in their narrative review likewise concluded no significant advantages for acupuncture regarding cravings nor global withdrawal, however did identify reduced anxiety or depression scores in some studies. The poor quality of the available evidence, and the limited evidence for effects on global opioid withdrawal or cravings suggests acupuncture is not recommended as part of routine opioid withdrawal management.

Table 3.5 Review of evidence for psychosocial interventions in management of opioid withdrawal

Intervention	Comparator	Studies	Commentary	Recommendation & evidence level
Psychosocial interventions during withdrawal management	Psychosocial interventions + medication versus medication only	11 studies, 1592 participants, included in the review	The studies considered five different psychosocial interventions and two pharmacological treatments (methadone and buprenorphine). Compared to any pharmacological treatment alone, the association of any psychosocial with any pharmacological was shown to significantly reduce dropouts RR 0.71 (95% CI 0.59 to 0.85), use of opiate during the treatment, RR 0.82 (95% CI 0.71 to 0.93), at follow up RR 0.66 (95% IC 0.53 to 0.82) and clinical absences during the treatment RR 0.48 (95%CI 0.38 to 0.59). The RCTs examined a range of psychosocial interventions, including behavioural treatments (Contingency Management, Community Reinforcement); various structured counselling approaches (psychotherapeutic counselling, intensive role induction with or without case management, counselling and education on high risk behaviour, Therapeutic Alliance intervention); and one study examined family therapy. The studies do not allow comparison of different approaches to psychosocial interventions, nor any data regarding optimal intensity or duration of intervention.	Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, use of opiate, participants abstinent at follow-up and clinical attendance. Moderate to High Grade quality of evidence. Management of opiate withdrawal should incorporate psychosocial interventions in addition to the use of medication. The evidence currently available does not support a particular psychosocial approach.

3.4 Medications

The following section summarises evidence regarding pharmacological management of opiate withdrawal based on reviews and studies identified in Tables 3.2 and 3.6.

Opioid agonist medication

Specifically-tapered doses of BPN or methadone are effective for managing opiate withdrawal – with higher rates of treatment completion, and reduced withdrawal severity than symptomatic medications. While evidence does not specify optimal treatment duration or dose of agonists, dosing regimens from three- to 60-day tapers have been shown to be effective.

The evidence from RCTs remains inconclusive comparing BPN to methadone, although some studies suggest that buprenorphine may be associated with an earlier onset, shorter duration and lower overall severity of withdrawal symptoms than methadone tapers.

Evidence is still emerging regarding the role of tramadol (low quality evidence), and while three recent studies suggest tramadol can reduce withdrawal severity compared to symptomatic medications (e.g. lofexidine, diazepam), and may be comparable to low dose BPN or methadone in reducing opiate withdrawal symptoms (low quality evidence), rebound withdrawal symptoms can occur after cessation of tramadol (as with other opioid medications), and its role compared to buprenorphine or methadone taper is unclear. Tramdol is not licensed for this indication (treatment of opiate dependence or withdrawal), and not routinely recommended at this time.

Alpha-adrenergic agonists

When used in the management of opioid withdrawal, alpha2-adrenergic agonists are typically administered orally, in three or four doses per day, to a maximum of around 1.2mg per day for clonidine (and around 2mg per day for lofexidine). Clonidine at doses ≥0.6mg/day have been shown to be effective compared to placebo in reducing withdrawal symptoms, however the drug's safety profile (hypotension) limits its utility outside of inpatient hospital settings, and it is recommended where opioid agonists cannot be used. Lofexidine has been shown to have a greater safety profile (but not better efficacy) than clonidine, however is expensive and not licensed in Australia.

Rapid detoxification using opioid antagonists

Naloxone or naltrexone can be used to precipitate the onset (and severity) of opiate withdrawal from heroin or other opioids, which is then managed with the use of other medications (e.g. alpha-adrenergic agonists, sedatives), often in an inpatient setting. The low-quality evidence from available studies does not allow comparison of this approach to conventional withdrawal management (e.g. using clonidine) with regards to withdrawal severity or completion rates, whilst concerns regarding severe adverse events (delirium, severe confusion in 6% and 8% of participants in two RCTs), suggest this is not recommended in the management of opioid withdrawal.

GABA-related medications

Evidence is still emerging for the use of pregabalin and gabapentin for the management of opioid withdrawal, and their use cannot be recommended at this time.

Other medications

Venlafaxine, diazepam do not have sufficient evidence to support their use for managing opiate withdrawal. Single doses of olanzapine (IM) may have a role in the emergency management of opiate withdrawal (e.g. in ED) where an opioid agonist cannot be given.

Medications which may have a role for specific symptom management

A range of medications can be used to assist in the management of specific symptoms in withdrawal, although controlled studies regarding their use in this context have not been conducted. Specifically, medications may be used for symptomatic management of:

- Nausea, vomiting
- Abdominal cramps
- Diarrhoea
- Arthralgia, back pain, muscle pain, tension headaches
- Sleep disturbance.

Fluid replacement

Dehydration can occur in opiate withdrawal (increased sweating, micturition, diarrhoea, vomiting) and fluids and electrolyte management may be required.

Take home naloxone

While not used for the management of opiate withdrawal, the high rates of relapse following withdrawal and evidence of increased mortality from related overdose suggests that take home naloxone interventions, with appropriate patient (and carer) education and supply of naloxone, should be routinely available as part of opiate withdrawal management.

Table 3.6 Summary of evidence for pharmacological management of opioid withdrawal

Medication	Comparator	Studies	Commentary	Recommendation & evidence level
Buprenorphine (BPN)	Methadone	Seven RCTs (Petitjean 2002; Seifert 2002; Bickel 1988; Umbricht 2003; Steinmann 2008; Wright 2011; Law 2017)	No significant differences in withdrawal severity, although lower withdrawal severity for BPN than methadone in some studies (Seifert 2002, Law 20017), whilst no differences in others (Petitjean 2002, Bickel1988, Umbricht 2003). No significant differences in completion rates for withdrawal between medications (Bickel 1988, Petitjean 2002, Seifert 2002, Steinmann 2008, Wright 2011). No significant differences in adverse events (AEs). There remains possibility that pattern of withdrawal symptoms may be different when using buprenorphine or methadone, with buprenorphine regimens experiencing greater withdrawal early, while withdrawal may occur later (after cessation medication) with methadone withdrawal regimens.	Data comparing BPN versus methadone in tapered doses for managing opioid withdrawal remains limited but are suggestive of BPN and methadone having similar capacity to ameliorate opioid withdrawal, without significant adverse events. The available data suggest there is no significant difference between BPN and methadone in terms of average treatment duration or rates of completion of withdrawal treatment. Low to moderate quality of evidence.
	Alpha-adrenergic agonists	14 studies in 750 people receiving buprenorphine and 615 receiving an alpha2-adrenergic agonist (103 with lofexidine)	Significantly less withdrawal severity in BPN treated groups compared to clonidine or lofexidine, both in terms of the peak average withdrawal score and the average daily withdrawal score over the withdrawal episode. Evidence of greater completion rates for BPN over clonidine in both inpatient (RR 1.74, 95% CI 1.1-2.9; N=539; studies=6) and outpatient (RR 1.45, 95% CI 1.1-1.9; N=725; studies=6) settings. The overall result (RR 1.59, 95% CI 1.2-2.1; N=1264; studies=12) translates to a number needed to treat for an additional beneficial outcome of 4 (95%CI 2.8-6.7). Quality of evidence for this outcome as moderate. No significant differences regarding AEs across studies.	BPN associated with significantly less withdrawal severity and greater completion rates than alpha-adrenergic agonists. Quality of evidence is low to moderate.
	BPN duration of withdrawal regimen	Seven studies involving 730 participants	Studies compared rapid (1–2 weeks duration) to slow (2–8 weeks) regimens. Findings indicate no clear evidence regarding rapid or slow buprenorphine dose taper and suggest the possibility that outcomes may depend on the context of withdrawal.	No recommendation re: optimal duration of treatment and will often be defined by conditions of treatment (e.g. inpatient, outpatient).
Alpha-adrenergic agonists	Placebo	Six RCTs compared an alpha2-adrenergic	Moderate-quality evidence that alpha2-adrenergic agonists were more effective than placebo in ameliorating withdrawal in terms of the likelihood of severe withdrawal (risk ratio (RR) 0.32, 95% confidence	Alpha-adrenergic agonists are more effective than placebo. Moderate quality evidence.

Medication	Comparator	Studies	Commentary	Recommendation & evidence level
		agonist with placebo	interval (CI) 0.18-0.57; 3 studies; 48 participants). Moderate-quality evidence that completion of treatment was significantly more likely with alpha2-adrenergic agonists compared with placebo (RR 1.95, 95% CI 1.34-2.84; 3 studies; 148 participants).	
	Methadone	12 RCTs with reducing doses of methadone	Peak withdrawal severity may be greater with alpha2-adrenergic agonists than with reducing doses of methadone, as measured by the likelihood of severe withdrawal (RR 1.18, 95% CI 0.81-1.73; 5 studies; 340 participants; low quality), and peak withdrawal score (SMD 0.22, 95% CI -0.02 to 0.46; two studies; 263 participants; moderate quality), but these differences were not significant and there is no significant difference in severity when considered over the entire duration of the withdrawal episode (SMD0.13, 95%CI -0.24-0.49; 3 studies; 119 participants; moderate quality). The signs and symptoms of withdrawal occurred and resolved earlier with alpha2-adrenergic agonists. The duration of treatment was significantly longer with reducing doses of methadone. (SMD -1.07, 95% CI -1.31 to -0.83; 3 studies; 310 participants; low quality). Hypotensive or other AEs were significantly more likely with alpha2-adrenergic agonists (RR 1.92, 95% CI 1.19-3.10; 6 studies; 464 participants; low quality). There was no significant difference in rates of completion of withdrawal treatment (RR 0.85, 95% CI 0.69-1.05; 9 studies; 659 participants; low quality).	Opioid withdrawal was similar with alpha2-adrenergic agonists and reducing doses of methadone, but the duration of treatment was longer and there were fewer adverse effects with methadone. Withdrawal signs and symptoms occurred earlier with alpha2-adrenergic agonists, within a few days of cessation of the opioid drugs. The chances of completing withdrawal treatment were similar. Clonidine is recommended where opioid agonist medication cannot be used for managing opioid withdrawal. Low to moderate quality evidence.
	Different alpha-adrenergic agonists (clonidine, lofexidine)	Three RCTs compared clonidine with lofexidine (Carnwath 1998; Kahn 1997; Lin 1997); two compared clonidine to	No significant difference in withdrawal severity or completion rates for clonidine and lofexidine. Fewer adverse events with lofexidine compared to clonidine, particularly for hypotension.	Whilst lofexidine appears to have a better safety profile than clonidine, it does not have better withdrawal outcomes regarding withdrawal severity or completion rates. Not licensed in Australia and therefore not recommended for use.

Medication	Comparator	Studies	Commentary	Recommendation & evidence level
		guanfacine (Muga 1990; San 1990)		
Methadone	BPN		Considered under Buprenorphine.	
	Alpha-adrenergic agonists		Considered under Alpha-adrenergic agonists.	
Rapid withdrawal using opioid antagonists with minimal sedation (naloxone or naltrexone)	Alpha-adrenergic agonists (clonidine or lofexidine)	Nine studies (5 RCTS). Five inpatient; one study Day 1 inpatient and subsequent outpatient; three studies outpatient	Uncertain whether peak withdrawal induced by opioid antagonists plus clonidine or lofexidine is more severe than withdrawal managed with clonidine or lofexidine alone, or whether the average severity over the withdrawal period is less, as the certainty of the evidence is very low. Moderately severe withdrawal symptoms reported in most studies. Two studies reported significantly higher rates of treatment completion for antagonist-induced withdrawal compared to regimens based on alpha2-adrenergic agonists alone (Arnold-Reed 2005, O'Connor 1995), but in the remaining studies the difference was not significant. The low quality of evidence makes any conclusions on relative rates of completion of detoxification treatment highly uncertain. Delirium or confusional state was reported in 6% (O'Connor 1995) and 8% (Bearn 2001) of first day of naltrexone treatment. AEs not reported in five studies. Clinicians should warn people of the possibility of delirium in the first day of administration of naltrexone, particularly with higher doses (>25mg).	Not recommended given uncertainty as to withdrawal severity, completion rates and severe adverse event rates.

Table 3.7 Summary of evidence and recommendations for management of opioid withdrawal

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient, residential and ambulatory withdrawal setting	Unless inpatient admission is indicated for patient safety reasons (e.g. severe dehydration, comorbid medical, psychiatric or social conditions), there is no clear advantage in an inpatient (or residential) withdrawal setting over an ambulatory setting regarding completion of withdrawal, engagement in post-withdrawal treatment or post-withdrawal substance use, and as such, inpatient withdrawal is not routinely recommended. *Residential withdrawal* settings may be appropriate for those with unsuitable home environments and supports to attempt ambulatory withdrawal, or for those with repeated failure at ambulatory withdrawal attempts. *Ambulatory withdrawal* is a feasible approach for the management of opioid withdrawal, is safe, effective and considerably less expensive when provided within a structured model of care. Ambulatory withdrawal can provide more timely access than residential or inpatient withdrawal, and often has good patient and carer acceptability. It is generally recommended unless there are clinical indications for a residential or inpatient withdrawal setting, such as a history of severe withdrawal.	Ib	Grade C: Satisfactory
Psychosocial interventions			
Psychosocial interventions (counselling, contingency management) in conjunction with pharmacotherapies	Adjunctive psychosocial interventions in addition to medication (e.g. buprenorphine or methadone taper) are effective in terms of completion of treatment, use of opiates, participants abstinent at follow-up and clinical attendance in treatment. It is not possible at this time to identify optimal approaches to psychosocial interventions.	GRADE Moderate to High	Grade C: Satisfactory
Patient information	Provision of structured information to patients is associated with lower withdrawal severity and greater treatment retention.	Ib	Grade D: Poor
Linkages to post-withdrawal treatment services	Structured and assertive linkages to post-withdrawal treatment associated with greater engagement with post-withdrawal treatment.	Ib	Grade D: Poor
Medications			
Tapered doses of opioid agonists			
Buprenorphine or methadone	Effective for managing opiate withdrawal – with higher rates of treatment completion, and reduced withdrawal severity than symptomatic medications. Evidence does not specify optimal treatment duration or dose of agonists. Evidence does not indicate clear advantage of either methadone or buprenorphine.	GRADE Low to Moderate	Grade B: Good

Intervention	Recommendation	Level of evidence	Quality of evidence
Tramadol	May be effective in reducing opioid withdrawal symptoms, however further research required.	Ib	Grade D: Poor
Alpha-adrenergic agonists (high dose clonidine)	Clonidine at doses ≥0.6mg/day is effective in reducing withdrawal symptoms, however its safety profile (hypotension, sedation) limits its utility outside of inpatient hospital settings and is recommended where opioid agonists cannot be used.	GRADE Moderate	Grade B: Good
'Rapid detoxification' using opioid antagonists (naloxone or naltrexone)	Can be used to precipitate the onset (and severity) of opiate withdrawal in conjunction with other medications (e.g. alpha-adrenergic agonists, sedatives), usually in an inpatient setting. Safety concerns regarding severe adverse events (delirium, severe confusion).	GRADE Low	Grade C: Satisfactory
Olanzapine	Single doses of olanzapine (IM) may have a role in the emergency management of opiate withdrawal (e.g. in ED) where an opioid agonist cannot be given.	Ib	Grade D: Poor
Other medications: pregabalin, gabapentin, venlafaxine, diazepam	Evidence is still emerging for the use in the management of opioid withdrawal and cannot be recommended at this time.	Variable according to medication	Grade D: Poor
Physical interventions			
Auricular or traditional Chinese medicine acupuncture during withdrawal episode	Most controlled studies have examined alcohol or opioid withdrawal, and usually as an adjunct to routine care. Meta-analyses indicate there is evidence of a reduction in withdrawal symptoms, cravings and anxiety symptoms, although no differences in completion rates. When individual drug types are examined (e.g. alcohol, opioids, stimulants) there are no benefits of acupuncture on withdrawal symptoms or cravings. The reviewers caution that there are inconsistent findings between studies, poor quality studies and evidence of publication bias, and suggest caution in interpreting evidence.	GRADE Low or Very Low	Grade D: Poor
Exercise for opioid withdrawal	Exercise programs (e.g. jogging, walking) are associated with reductions in withdrawal symptoms, and specific symptoms of anxiety and depression, and should be encouraged in opioid withdrawal.	Ib	Grade D: Poor
Massage therapy during withdrawal	No evidence identified in opioid withdrawal. Limited evidence (extrapolated from alcohol withdrawal RCTs) suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal.	Ib Extrapolated	Grade D: Poor

For classification schemes for categorisation/grading of evidence see Appendices 1 and 2.

Chapter 4. Cannabis

Description of the withdrawal syndrome

DSM-5 criteria for cannabis withdrawal are:

A. Cessation of cannabis use that has been heavy and prolonged (i.e. usually daily or almost daily use over a period of at least a few months)
B. Three (or more) of the following signs and symptoms develop within approximately 1 week after Criterion A:
    1. Irritability, anger, or aggression
    2. Nervousness or anxiety
    3. Sleep difficulty (e.g. insomnia, disturbing dreams)
    4. Decreased appetite or weight loss
    5. Restlessness
    6. Depressed mood
    7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Cannabis withdrawal symptoms may be present within the first 24–48 hours after last use, are most severe in the first two to five days, and generally subside over the first two weeks following cessation. Prolonged withdrawal symptoms (sleep and mood disturbances, cravings) may persist for weeks.[77] A cohort study of n=193 Australian cannabis users undertaking cannabis withdrawal in a NSW inpatient hospital setting [78] identified that recent mental health concerns, but not gender or secondary drug use, corresponded to greater global cannabis withdrawal symptom severity.

Selection of reviews and studies

Systematic reviews

Table 4.1 describes the review articles identified from the search, summarising the type of review, dates, and relevance to our scope. No published systematic review specifically addressed our objective.

The most suitable review as the basis for this rapid review is by.[79] It is contemporary, studies are separately categorised as laboratory studies from clinical trials; and also separate withdrawal interventions from broader cannabis use disorder (CUD) treatment, consistent with the scope of our review. The main concern with this review is that while the search strategy appears comprehensive and 'systematic', its details are not published in the paper. This limitation was addressed by matching studies identified in this review against other systematic reviews noted below. Brezing and Levin provide a narrative review of studies by intervention type, with a focus on medications.

The Gorelick systematic review [80] is also highly relevant to our review, providing a useful and concise summary of the RCTs of cannabis withdrawal management. Gorelick focuses on pharmacological RCTs in clinical populations (not laboratory studies), and hence identifies fewer RCTs than Brezing and Levin.

Several systematic reviews targeted treatment of cannabis use disorder rather than withdrawal intervention outcomes, and hence were not suited to being the 'main review' for this rapid review (e.g. [81-84]) The conclusions from these reviews are examined for consistency with the two main reviews used. Other reviews specifically targeted sleep-related symptoms in withdrawal [85], and cannabinoid agonist medications [86] were also considered in the final recommendations. No review of psychological or physical therapies regarding withdrawal management were identified – although several reviews of psychological interventions for broader CUD, these did not identify studies examining withdrawal intervention.

Relevant papers (or unpublished data) since the review(s)

A review for studies conducted since 2017 (since Brezing and Levin review) indicated that no RCTs had examined pharmacotherapies for cannabis withdrawal. Two studies of 12-week nabiximols compared to placebo in outpatient settings [13, 87] both reported cannabis withdrawal symptoms however in the context of a longer-term 'treatment' paradigm rather than management of a short-term cannabis withdrawal syndrome. While no controlled studies have been reported, several recent case studies of cannabidiol have been reported and are also described.

One unpublished Australian RCT of aerobic exercise for the management of cannabis withdrawal was reported at a national conference [88], and is described.

Table 4.1 Summary of reviews of interventions for cannabis withdrawal

Review authors, title, reference	Date studies reviewed	Type of review	Commentary on review	Evidence grade
Brezing CA, Levin FR. The Current State of Pharmacological Treatments for Cannabis Use Disorder and Withdrawal. Neuropsychopharmacology. 2018;43(1):173–194.	?2017	Search not detailed but 'appears' systematic. Qualitative review	Studies separately categorised as laboratory studies from clinical trials, and also separate withdrawal interventions from broader CUD treatment. Contemporary and preferred review.	
Gorelick DA. Pharmacological treatment of cannabis-related disorders: A narrative review. Current Pharmaceutical Design. 2016;22(42):6409-–19.	April 2016	Systematic review. N=7 RCTs. Qualitative assessment.	Concise review that focuses on withdrawal RCTs of medication approaches in clinical populations. Concise summary of outcomes. Conclusions examined for consistency with main review.	
Werneck MA, Kortas GT, de Andrade A, Castaldelli-Maia JM. A systematic review of the efficacy of cannabinoid agonist replacement therapy for cannabis withdrawal symptoms. CNS Drugs. 2018;2(12):1113–29.	Sept 2017	Systematic review. N=10 RCTs Qualitative assessment	Only examines cannabinoid agonist therapies. Studies include both withdrawal studies and withdrawal measures in longer term CUD treatment. Includes laboratory (n=7) and clinical trials (n=3), although only one clinical RCT of withdrawal treatment (Allsop et al. 2014). Does not add significantly to this review.	
Zhand N and Milin R. What do we know about the pharmacotherapeutic management of insomnia in cannabis withdrawal: A systematic review..American Journal on Addictions. 2018;27(6):453–64.	April 2017	Systematic search & strategy. N=17 RCTs	Studies include withdrawal syndrome as well as sleep specific outcomes, and hence relevant to this review. Pharmacological interventions only examined. Conclusions examined for consistency with main review.	
Nielsen S, Gowing L, Sabioni P, Le Foll B. Pharmacotherapies for cannabis dependence. (2019) Cochrane Database Systematic Reviews. 1:CD008940.	March 2018	Systematic review with meta-analyses for some outcomes. N=21 RCTs	Review pools all withdrawal intervention and CUD studies together, so difficult to interpret their meta-analyses (most studies are 12-week outpatient relapse prevention studies, with an occasional withdrawal study). Conclusions examined for consistency with main review.	
Sabioni P, Le Foll B. Psychosocial and pharmacological interventions for the treatment of cannabis use disorder. F1000Res. 2018 Feb 12;7:173.	?2017	Systematic search described but studies not reported. Narrative review	Global overview with little detail re: studies, their interpretation or rationale for conclusions. Conclusions examined for consistency with main review.	
Balter RE, Cooper ZD, Haney M. Novel Pharmacologic Approaches to Treating Cannabis Use Disorder. Current Addiction Reports. 2014;1(2):137–43.	?2012	Search not described and does not appear to be systematic. Qualitative review	Not systematic search. Superseded by more recent reviews. Does separate withdrawal from cannabis use disorder; focus on medications only. Conclusions examined for consistency with main review.	

Review authors, title, reference	Date studies reviewed	Type of review	Commentary on review	Evidence grade
Chatters R, Cooper K, Day E, Knight M, Lagundoye O, Wong R wt al. Psychological and psychosocial interventions for cannabis cessation in adults: A systematic review. Addiction Research & Theory. 2016;24(2:93–110.	Feb 2014	Systematic review. N=26 RCTs. Qualitative and quantitative (not meta-analysis)	Studies do not include withdrawal intervention, and exclusively reviews longer-term CUD treatment and related outcomes. Not relevant to this review scope.	

Summary of the evidence

4.1 Treatment setting

No controlled studies were identified that compared inpatient to outpatient treatment settings for cannabis withdrawal management. Most controlled studies of cannabis withdrawal have been inpatient (or residential) settings due to their study designs, rather than patient complexity.

Inpatient setting

Cannabis withdrawal is not usually associated with a withdrawal severity that would warrant inpatient hospital admission. Cannabis use is potentially associated with a range of psychiatric (e.g. psychosis, anxiety, depression) or physical (e.g. cardiac arrhythmias, respiratory infections) that may warrant hospital admission, and during which the patient may undergo (non-elective) cannabis withdrawal, that requires management.

Residential withdrawal settings

Residential withdrawal settings may be appropriate for those with unsuitable home environments and supports to attempt withdrawal, or for those with repeated failure at ambulatory withdrawal attempts.

Ambulatory withdrawal

Ambulatory withdrawal is a feasible approach for the management of cannabis withdrawal and is generally recommended.

Table 4.2 Considerations for selection of withdrawal setting for cannabis withdrawal

	Ambulatory	Residential	Inpatient Hospital
Likelihood of severe withdrawal complications	N/A	N/A	N/A
Medical or psychiatric comorbidity	Minor comorbidity	Minor comorbidity	Significant comorbidity. Cannabis withdrawal (e.g. anxiety, physical symptoms) may exacerbate underlying conditions
Other substance use	No heavy drug use	Heavy or unstable use other drugs	Heavy or unstable use other drugs
Social environment	Supportive home environment. Regular monitoring by reliable support people. Good access to outpatient service	Unsupportive home environment or social supports. Poor access to outpatient services	Unsupportive home environment or social supports. Poor access to outpatient services
Previous attempts		Repeated failure at ambulatory withdrawal	Repeated failure at ambulatory withdrawal

*For further details see text.

4.2 Psychosocial Interventions

Counselling/psychosocial interventions during withdrawal

No controlled trials or systematic reviews have examined the impact of psychosocial interventions (e.g. counselling, case management) in the management of cannabis withdrawal.

4.3 Physical therapies

Exercise

In their review of exercise for the treatment of CUD, [89] identified no controlled studies. One uncontrolled trial, [90] reported 10 days of moderate intensity aerobic exercise for 30 minutes resulted in significantly reduced levels of cannabis consumption and daily cravings in 12 non-treatment-seeking individuals, and reduced cannabis use after two weeks. Without a control group, it is impossible to attribute the results to exercise alone.

One unpublished RCT of exercise for the management of cannabis withdrawal is of particular relevance – conducted in an inpatient hospital withdrawal unit in NSW by investigators at University of Sydney. Subjects undergoing cannabis withdrawal were randomised to either active aerobic exercise or stretching (control) 30-minute sessions in n=38 participants. The authors [10] reported that while not effective overall for cannabis withdrawal symptoms (Cannabis Withdrawal Scale global score) or treatment retention (high in both groups), the active exercise group reported fewer sleep problems and less anxiety during the withdrawal episode, highlighting the potential benefits of exercise for these symptoms. The study was likely underpowered to demonstrate global withdrawal outcomes.

Acupuncture, massage therapy.

No controlled studies were identified for the use of acupuncture or massage in the treatment of cannabis withdrawal.

4.4 Medications

On the basis of the current available literature of placebo-controlled trials for CUD, the systematic reviews have largely come to similar conclusions. (see Table 4.3, Brezing and Levin for summary). The evidence following summarises conclusions regarding medication management of cannabis withdrawal episode.

Cannabinoid agonist medications (dronabinol, nabilone, nabiximols) have the strongest evidence base for management of cannabis withdrawal syndrome with regards to reducing global cannabis withdrawal severity.

Haney et al.[91, 92], Budney et al.[93] and Vandrey et al.[94] examined the effects of dronabinol (a synthetic oral THC medication) in human laboratory conditions, demonstrating dronabinol produces dose-dependent reductions in cannabis withdrawal symptoms in cannabis dependent non-treatment seekers. Studies of dronabinol for CUD (12-week placebo controlled RCTs) either alone[95] or in combination with lofexidine[96] suggest reductions in cannabis withdrawal symptoms, although these were long-term outpatient 'maintenance' style studies, and conclusions regarding its efficacy for withdrawal interventions cannot be made from these studies.

Similarly, nabilone, a synthetic THC-like cannabinoid-1 receptor agonist has been shown to reduce cannabis withdrawal, and to reduce cannabis self-administration in non-treatment seeking cannabis dependent users in laboratory conditions[97,98], however studies in clinical populations are lacking.

Nabiximols, a combination THC/cannabidiol (CBD) oromucosal spray, has been examined for cannabis withdrawal management in an Australian inpatient placebo controlled RCT (N=50). Nabiximols was effective in reducing global withdrawal severity. Withdrawal completion rates were high in both placebo and nabiximols groups. There was no difference in relapse rates at one month.

Recent studies of nabiximols as longer-term maintenance models have been examined in outpatient placebo controlled RCTs in Canada [87] and Australia.[13] Both studies showed reduced withdrawal symptoms, although as with the longer-term dronabinol studies [95, 96], conclusions regarding withdrawal management cannot be made from these studies.

In summary, studies in human laboratory and clinical populations suggest that cannabinoid agonists (at CB1 receptors) such as THC (e.g. in nabiximols) and synthetic THC analogues (dronabinol, nabilone) effectively reduce cannabis withdrawal symptoms, and are well tolerated in cannabis users. The rationale is similar to the use of nicotine replacement treatment for management of smoking cessation, or buprenorphine or methadone taper for heroin withdrawal. The quality of the evidence however remains low, given the few studies and participants in clinical studies of treatment seekers undergoing withdrawal treatment. Furthermore, the optimal approach to using cannabinoids for withdrawal has not been examined in detail. As one reviewer concluded: "While these preliminary results are encouraging, there remain many unanswered questions regarding the duration of treatment, tapering, possible rebound effects, etc" (p.458). [85]

While there are promising case reports [99] of high dose cannabidiol (CBD) suppressing cannabis withdrawal, no controlled human trials have been reported.

Medications that may have a role for specific symptom management

While no other medications have been shown to be effective for managing cannabis withdrawal syndrome, there are promising findings with regards to the role of medications for managing specific symptoms during cannabis withdrawal.

Hypnotic GABA-A medications, *zolpidem* and *BZDs* (specifically nitrazepam, improve sleep during withdrawal in clinical populations undergoing cannabis withdrawal (Ib), although caveats regarding the risks of dependence and rebound symptoms with long term sedative use, and the potential for non-medical use must be considered.

Mirtazapine: A laboratory study [100] may assist with increasing appetite and sleep symptoms, but has no impact on mood or anxiety.

While an open-label study (no control group) of *quetiapine* [101] was promising for specific withdrawal symptoms of sleep disturbances, food intake, and weight loss, controlled trials in human laboratory [102] and outpatient clinical settings [103] indicate that quetiapine may be associated with increased cravings and cannabis use than placebo, and is therefore not recommended at this time.

Medications for which there is limited or no evidence for use in cannabis withdrawal

Medications for which there is limited or no evidence to supporting use in cannabis withdrawal include noradrenergic (e.g. venlafaxine) and serotonergic (esclitalopram, buspirone, flouxetine) antidepressants, baclofen, lithium[104], gabapentin[105], topiramate[106], N-acetlcysteine.[107, 108]

Similar conclusions are arrived at by other systematic reviews of the literature, including Gorelick 2016, Nielsen et al. 2018 and Shand & Millin 2018.[80, 82, 85]

Table 4.3 Pharmacological interventions for cannabis withdrawal

(Evidence available for the following classes of medications)

Class of medication	Studies	Commentary	Recommendation & evidence level
Noradrenergic agents			
Bupropion	Haney et al, 2001 (L) Carpentar et al, 2009 (T) Penetar et al, 2012 (T)	"Data from the literature on noradrenergic agents suggest that non-stimulant cognitive and mood-enhancing medications are not promising compounds for the treatment of CUD. At best, they may be used to target some specific symptoms of cannabis withdrawal and at worst, they may cause intolerable side effects, particularly gastrointestinal, and/or exacerbate cannabis use" Brezing & Levin 2017 p.182.	Not recommended
Nefadozone	Haney et al, 2003 (L) Carpentar et al, 2009 (T)		Not recommended
Venlafaxine	Levin et al, 2013 (T)		Not recommended
Atomoxetine	McRae-Clark et al (2010) (T)		Not recommended
Mirtazepine	Haney et al, 2010 (L)		Not recommended, although may assist in symptomatic management of sleep
Serotonergic agents			
Buspironepropion	McRae-Clark et al, 2009 (T) McRae-Clark et al, 2015 (T)	"The work to date exploring antidepressants and atypical anxiolytics appear to have limited value in the treatment of CUD other than for the potential treatment of comorbid conditions or targeting specific symptoms that trouble patients (ie, food intake and sleep)." Brezing & Levin 2017 p.183.	Not recommended
Escitalopram	Weinstein et al, 2014 (T)		Not recommended
Gamma-aminobutyric acid (GABA-A) agents			
Baclofen	Haney et al, 2010 (L)	Little effect on withdrawal	"GABA-A agonist sleep agents and other medications with GABA-A activity, such as gabapentin and topiramate, show promise in the treatment of CUD to target difficulties with sleep as a result of withdrawal and/or maintenance treatment of CUD by decreasing cannabis use, respectively. Larger, fully powered placebo-controlled trials need to be completed." p.184
Zolpidem	Vandrey et al, 2011 (L)	"ER zolpidem attenuated the effects of abstinence on sleep architecture as measured with PSG in addition to improvements in subjective ratings of sleep quality. The authors concluded that it may be useful as an adjunctive medication treatment for CUD." p.184	
Nitrazepam	Allsop et al 2015 (T)	Nitrazepam resulted in better sleep during inpatient withdrawal on the nights it was used (Actigraphy and subjective report).	

Class of medication	Studies	Commentary	Recommendation & evidence level
Gabapentin	Mason et al, 2012 (T)	Some promising effects on withdrawal, but underpowered 12-week outpatient study and limited conclusions can be drawn.	
Cannabinoids			
Dronabinol	Haney et al, 2004 (L) Budney et al, 2007(L) Levin et al, 2011 (T) Levin et al, 2016 (T)	Reduced cannabis withdrawal in laboratory settings, and in long-term outpatient trials – however no trials in clinical setting for withdrawal management.	Not available in Australia. Further research in clinical populations required.
Nabilone	Haney, 2013b (L) Herrmann et al, 2016 (L)	Laboratory studies promising in reducing withdrawal. Awaiting clinical trials.	Not available in Australia. Further research in clinical populations required.
Nabiximols	Allsop et al, 2014 (T/I) Trigo et al 2018 (T) Lintzeris et al 2019 (T)	Effective in placebo-controlled RCT in clinical trial population in inpatient settings. Reduced withdrawal symptoms in outpatient long-term RCTs, however difficult to interpret.	Further research required to corroborate findings and determine optimal dose and duration of treatment.
Others			
Lithium	Johnston et al, 2014 (T/I)	Not effective in management of cannabis withdrawal.	Not recommended
Quetiapine	Cooper et al, 2013 (L)	May assist with specific withdrawal symptoms, including sleep, food intake, and weight loss; but concerns about increases in craving need to be considered.	Not recommended at this stage, and further research required.

Table 4.4 Summary of evidence and recommendations for management of cannabis withdrawal

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient, residential and ambulatory withdrawal setting	No controlled studies were identified comparing withdrawal settings for cannabis withdrawal. Recommendations extrapolated from evidence for alcohol and opioid withdrawal. Inpatient admission is indicated for patient safety reasons in the context of severe comorbid medical or psychiatric conditions. Residential withdrawal settings may be appropriate for those with unsuitable home environments and supports to attempt ambulatory withdrawal, or for those with repeated failure at ambulatory withdrawal attempts. Ambulatory withdrawal is a feasible approach for the management of cannabis withdrawal and is generally recommended.	Extrapolated evidence (Ia (alcohol) and Ib (opioids). Evidence for cannabis: III	Grade D: Poor
Psychosocial interventions			
Psychosocial interventions (structured counselling, case management, provision of information)	No controlled trials examining psychosocial interventions (e.g. counselling, case management, provision of information) in the management of cannabis withdrawal were identified. Evidence extrapolated from evidence for alcohol and opioids. Psychosocial interventions (structured withdrawal counselling, case management) should be incorporated into the management of cannabis withdrawal.	Extrapolated evidence	Grade D: Good Practice Point (GPP)
Patient information	Provision of structured information to patients is associated with lower withdrawal severity and greater treatment retention.	Ib	Grade D: Poor
Linkages to post-withdrawal treatment services	Structured and assertive linkages to post-withdrawal treatment associated with greater engagement with post-withdrawal treatment.	Ib	Grade D: Poor
Medications			
Cannabinoid agonist medications (nabiximols, dronabinol, nabilone)	Studies in human laboratory and clinical populations consistently suggest that cannabinoid agonists (at CB1 receptors) such as THC (e.g. in nabiximols) and synthetic THC analogues (dronabinol, nabilone) effectively reduce cannabis withdrawal symptoms, and are well tolerated in cannabis users. Evidence does not specify optimal treatment duration or dose of agonists, and further research is required to establish optimal medication regimens.	Ib	Grade C: Satisfactory
Hypnotic medications (zolpidem, BZDs	Hypnotic GABA-A medications zolpidem and BZDs (specifically nitrazepam) improve sleep during withdrawal in clinical populations undergoing cannabis withdrawal (Ib), although caveats regarding the risks of dependence and rebound symptoms with long term sedative use, and the potential for non-medical use must be considered.	Ib	Grade C: Satisfactory

Intervention	Recommendation	Level of evidence	Quality of evidence
Mirtazepine	A laboratory study may assist with increasing appetite and sleep symptoms but has no impact on mood or anxiety.	IIb	Grade D: Poor
Other medications	Medications for which there is limited or no evidence supporting their use at this time include noradrenergic (e.g. venlafaxine) and serotonergic (esclitalopram, buspirone, flouxetine) antidepressants, baclofen, lithium, gabapentin, topiramate, N-acetlcysteine, quetiapine, cannabidiol.	Variable according to medication.	Grade D: Poor
Physical Interventions			
Aerobic exercise for cannabis withdrawal	Aerobic exercise programs are associated with reductions in withdrawal symptoms, and specific symptoms of sleep disturbances, anxiety and depression, and should be encouraged in cannabis withdrawal.	Ib	Grade: D Poor
Mind-Body exercise (e.g. yoga)	No controlled studies were identified examining yoga for substance withdrawal (excluding tobacco). Further research recommended.	Nil	Grade: No controlled studies
Massage therapy during withdrawal	Limited evidence suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal.	Extrapolated Ib	Grade D: Poor

For classification schemes for categorisation/grading of evidence see Appendices 1 and 2.

Chapter 5. Benzodiazepines

Description of the withdrawal syndrome

Benzodiazepines (BZDs) are used in the treatment of sleep and anxiety disorders, and despite the fact that they are not recommended for long-term use (i.e. more than two months); they continue to be prescribed for longer periods. Their abuse potential and problematic withdrawal has been well established.

DSM-5 recognises "sedative, hypnotic and anxiolytic use disorder" as a distinct condition and the withdrawal from these medications is described as per the following:

A. Cessation of (or reduction in) sedative, hypnotic, or anxiolytic use that has been heavy and prolonged.

B. Two (or more) of the following, developing within several hours to a few days after Criterion A:

- Autonomic hyperactivity (e.g. sweating or pulse rate greater than 100)
- Hand tremor
- Insomnia
- Nausea or vomiting
- Transient visual, tactile, or auditory hallucinations or illusions
- Psychomotor agitation
- Anxiety
- Grand mal seizures.[3]

C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

The onset and duration of withdrawal symptoms largely depends upon the type of BZD being used. The withdrawal from short-acting BZDs (e.g. temazepam, alprazolam) can occur within 24 hours of last use, whereas the onset from long acting BZDs (e.g. diazepam, clonazepam) may be delayed for several days after last use. The duration of withdrawal is related to the rate of taper, but usually continues for weeks or months, which can complicate management in an acute treatment setting such as inpatient or residential withdrawal unit.

Selection of reviews and studies

Table 5.1 describes the review articles identified from the search, summarising the type of review, dates, and relevance to our scope.

The most recent Cochrane review[109] builds on, and agrees with the previous Cochrane review[110] which have explored the same issue. Other reviews are described in Table 5.1. No recent controlled studies published since the Cochrane reviews were identified.

Table 5.1 Summary of reviews of interventions for benzodiazepine withdrawal

Review authors, title, reference	Date studies reviewed	Type of review	Commentary on review	Evidence Grade
Denis C, Fatseas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Cochrane Database of Systematic Reviews, 2006;(3): CD005194	Oct 2004	Systematic review of eight out of 35 eligible studies that met the Cochrane criteria No meta-analysis conducted	The review is of good quality and includes withdrawal experience. Authors conclude that a gradual taper is more favourable than abrupt cessation of BZDs. They also highlight that Carbamazepine and some SSRIs may have a place in the treatment of BZD withdrawals. All of the studies included in this review are conducted in outpatient settings.	
Lingford-Hughes A. R, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. Journal of Psychopharmacology, 2012;26(7);899–952	? March 2010	Systematic review of 10 RCTs Qualitative assessment No meta-analysis conducted	The review is conducted for the purpose of updating British Association for Psychopharmacology (BAP) guidelines and presented in that context. The authors interpreted evidence in a way that would make practical sense to clinicians and used non-RCTs as well. Both outpatient and inpatient trials are included in this review.	
Baandrup L, Ebdrup BH, Rasmussen JØ, Lindschou J, Gluud C, Glenthøj BY. (Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. 2018; Cochrane Database of Systematic Reviews, (3).	Oct 2017	Systematic review 35 trials with 2295 participants Meta-analysis is conducted where possible and appropriate	The review is of good quality and includes withdrawal experience. Authors concur with the conclusion of the previous Cochrane review that a gradual taper of BZDs is superior to abrupt cessation, and they go on to explore the effects of various drugs on the withdrawal experience. Both outpatient and inpatient trials are included in this review.	
Darker CD, Sweeney BP, Barry JM, Farrell MF, & Donnelly-Swift E., Psychosocial interventions for benzodiazepine harmful use, abuse or dependence. Cochrane Database of Systematic Reviews, 2015; (5):CD009652. .	2014	Systematic review with meta-analysis. 25 RCTs including 1666 people, although not all related to withdrawal managememt.	Cochrane quality review of psychosocial interventions (CBT and motivational interviewing) for management of BZD use disorder.	

Summary of the evidence

5.1 Treatment setting

All of the reviews above indicate that BZD withdrawal management can safely be done in the community. However, polysubstance use, existing comorbidities, and individual vulnerabilities, should be taken into account when deciding on the treatment setting. A brief inpatient admission may also be required for stabilising the patient with a history of high-dose erratic benzodiazpeine use, prior to commencing a gradual taper in the community.

5.2 Psychosocial interventions

A Cochrane review [111] specifically examined the role of psychosocial interventions in the management of BZD use disorders - generally as adjuncts to medication management. The review included a range of studies involving withdrawal using gradual taper, however did not separately undertake meta-analyses for withdrawal related studies. The review identified:

- Moderate quality of evidence that CBT plus taper was more likely to result in successful discontinuation of BZDs within four weeks post treatment compared to taper only (Risk ratio (RR) 1.40, 95%CI 1.05 to 1.86; nine trials, 423 participants) and moderate quality of evidence at three month follow-up (RR 1.51, 95% CI 1.15 - 1.98) in favour of CBT (taper) for 575 participants
- Very low quality of evidence available to assess the effect of motivational interviewing, with different findings across the few studies
- Low quality evidence to support relaxation (versus treatment as usual (TAU)) as an adjunct to gradual taper, at three-month follow-up (RR 2.20, 95% CI 1.23 - 3.94)
- There is emerging evidence to suggest that prescribing interventions (e.g. a tailored GP letter versus a generic GP letter, a standardised interview versus TAU) may be effective in patients with low dose BZD dependence – especially older patients (see Chapter 1 for review).

In summary, the evidence suggests that both CBT and relaxation training – as adjuncts to BZD taper – may be effective in reducing BZD use in the short term (three-month time period).

5.3 Physical therapies

No studies were identified that examined the role of physical therapies (e.g. acupuncture, massage or exercise) in the management of BZD withdrawal, and recommendations are extrapolated from other substances (See Chapter 1).

5.4 Medications

The Cochrane review concluded that a gradual taper of BZDs was preferable to abrupt cessation in the management of BZD withdrawal. The rate and the duration of the gradual BZD taper varied in all studies included in these two reviews from between 10–25% per week/fortnight, with a duration varying between 8–24 weeks. There are two studies[112, 113] suggesting that an inpatient rapid taper over a period of one week may be as safe and effective as the gradual taper, but both of these studies are of poor quality and their results have not been replicated.

The studies that explored the use of pregabalin, captodiame, paroxetine, tricyclic antidepressants, and flumazenil for the management of withdrawal from BZDs, were assessed to be of very low quality.[109] In fact, flumazenil use was associated with serious adverse effects in one study, resulting in that study being prematurely terminated.[114]

As for the management of ongoing anxiety symptoms following the withdrawal from BZDs, the use of carbamazepine, pregabalin, captodiame, paroxetine, and flumazenil were explored, but again the evidence stemming from the studies included in the Cochrane review[109] were found to be of very low quality.

Another systematic review of note, is the British Association for Psychopharmacology guidelines on the pharmacological management of substance use disorders.[115] A panel of experts were asked to perform a systematic review in their fields of expertise, in order to produce the guidelines. The reported search strategy is well aligned with a good systematic review process. The main reason for the inclusion of this review is the distinction that is made between those patients who use their 'therapeutic doses' of BZDs and experience harm; and those patients who misuse or use BZDs illicitly, often at high doses. This distinction may be helpful for practitioners who might use the NSW Drug and Alcohol Withdrawal Clinical Practice Guidelines.[116]

The authors suggest the use of a gradual taper of the BZDs that the patients have been on, prior to switching to a longer-acting BZD if the patient is using 'therapeutic doses'; and there is good evidence that a written information/instruction from the prescriber will facilitate the success of this intervention. There seems to be no evidence for adjunctive or alternative pharmacotherapies for this purpose. As for the management of high dose and/or illicit BZD use, the authors suggest that there is a lack of evidence for the efficacy of BZD maintenance prescribing and hence is not recommended. It is suggested that daily doses of 30mg diazepam would suffice to control the majority of withdrawal symptoms including withdrawal seizures, in high-dose dependent users. The authors signal the potential efficacy of carbamazepine in the management of BZDs in this group, but highlight the poor quality of evidence, for studies exploring this medication.

In summary, all three reviews favour a gradual BZD taper over abrupt cessation of the medications, and refrain from recommending any other pharmacotherapies for the management of BZD withdrawal, as the evidence of their efficacy at this stage, is very poor.

5.5 Special Populations

Older people

Older people are among the most vulnerable when it comes to BZD misuse due to the effect of these medications on cognitive and motor functions, and the fact that they can be implicated in common problems such as falls.

Two recent reviews have examined interventions to reduce BZD use in the elderly[36, 37], including prescribing interventions (patient education, GP letters, medication reviews) and withdrawal approaches (including medication taper and counselling approaches). This subject is reviewed in greater detail in Chapter 1. In summary, the reviews identified it is possible to reduce BZD use in elderly patients using patient education, regular medication reviews, gradual taper and counselling approaches (e.g. CBT, relaxation training). The prevalence of withdrawal symptoms, and the rate and duration of the taper seems to be varied in the studies that were included in this review and needs to be explored in further studies.

Table 5.2 Summary of evidence and recommendations for management of benzodiazepine (BZD) withdrawal

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Setting	All reviews indicate that BZD withdrawal can be safely managed in the community setting. An inpatient admission may be indicated to stabilise a patient with a history of erratic high dose BZD use prior to a gradual taper in the community, or for managing withdrawal from other substances, significant comorbidities, or other vulnerabilities, however rapid dose reductions in a brief inpatient admission (e.g. less than two weeks) is usually not recommended for a patient using moderate or high doses of BZDs (e.g. >10mg oral diazepam equivalent), due to the risk of severe withdrawal symptoms (e.g. seizures, panic) emerging after discharge.	Ib	Grade C: Satisfactory
Psychosocial interventions			
Psychosocial interventions (e.g. CBT), in conjunction with pharmacotherapies	Both CBT (Moderate GRADE evidence) and relaxation training (Low GRADE) are effective in reducing BZD use during withdrawal and in the immediate (three month) post withdrawal period, as adjuncts to BZD taper.	GRADE: Moderate (CBT), Low (relaxation)	Grade C: Satisfactory
Prescribing interventions and patient information	There is emerging evidence to suggest that a tailored general practitioner's letter (for low dose patients (e.g. using <10mg ODE), a standardised interview, or provision of written information/instructions from the prescriber to patients could be effective in patients with low dose long-term BZD use. No evidence to suggest it is effective with patients using high doses/illicit use of BZDs.	Ib	Grade D: Poor
Physical interventions			
Massage therapy during withdrawal	Limited evidence extrapolated from alcohol withdrawal literature suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal. Evidence supports relaxation training (see psychosocial interventions above).	Extrapolated from Alcohol (Ib)	Grade D: Poor

Medications			
Tapered doses of BZDs	Gradual taper more favourable than abrupt cessation or rapid taper. Rate 10%–25% week/fortnight, duration 8–24 weeks. Individually adjusted withdrawal rate – consider: BZD type, dosage, psychosocial/environmental factors etc. Expert panel - British Association for Psychopharmacology Guidelines suggest an initial taper of BZD the patient has been on, prior to transfer to a longer acting BZD, for patients on "therapeutic" doses. BZD dose of 30mg/day (oral diazepam equivalent) is usually adequate as a starting dose for dose reductions for patients with a pattern of erratic high-dose BZD use.	GRADE Moderate to High	Grade B: Good
'Rapid' dose reduction (less than two weeks)	It has been suggested that inpatient rapid taper over one week may be as safe and effective as gradual outpatient taper in two poor quality studies – findings have not been replicated. The main concern with rapid dose reductions is the emergence of severe withdrawal symptoms after cessation of medication, especially for patients taking moderate or high dose BZDs (e.g. ODE 10mg/ day).	IIa	Grade D: Poor
Other medications to manage BZZD withdrawal: • Pregabalin • Captodiame • Paroxetine • Tricyclic antidepressants • Flumazenil	Potential for selective serotonin re-uptake inhibitors (SSRIs) e.g. paroxetine and carbamazepine in treatment of BZD withdrawal. However, all studies of very low quality, therefore, not clinically recommended. Flumenazil – serious adverse effects resulting in the study being prematurely terminated.	GRADE Low	Grade D: Poor
Maintenance BZDs	May be effective for patients dependent on high doses/illicit BZD use, those with repeated failure at attempted withdrawal, however there is insufficient evidence from controlled studies to support 'maintenance' treatment for the management of BZD dependence. Lack of evidence to support efficacy.	IIb	Grade D: Poor
Pharmacological management of anxiety post-withdrawal • Carbamezapine • Pregabalin • Captodiame • Paroxetine • Flumazenil	Emerging evidence for pharmacological management of anxiety, post-BZD withdrawal. Carbamezapine is one of the most promising drugs, but due to low to very low quality of evidence, cannot be clinically recommended at this time. The use of the BZD antagonist flumazenil ('rapid detox') has not been demonstrated to be safe in published studies and is not recommended for use.	Ib	Grade D: Poor

For classification schemes for categorisation/grading of evidence see Appendices 1 and 2.

Chapter 6. Amphetamines and methamphetamine

Description of the withdrawal syndrome

The DSM-5[3] criteria for stimulant withdrawal (including amphetamine-type stimulants, cocaine, and other stimulants) are:

A. Cessation of (or reduction in) prolonged amphetamine-type substance, cocaine, or other stimulant use

B. Dysphoric mood and two (or more) of the following physiological changes, developing within a few hours to several days after Criterion A:
   1. Fatigue
   2. Vivid, unpleasant dreams
   3. Insomnia or hypersomnia
   4. Increased appetite
   5. Psychomotor retardation

C. The signs and symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

While the stimulant class of drugs may have similar psychotropic effects, including improved mood and energy levels, their mechanism of action can be very different.[117] Methamphetamine is the most commonly used illicit amphetamine-type stimulant (excluding MDMA) in Australia at present, although prescription amphetamines are also used illicitly. Methamphetamine is a more potent derivative of amphetamine, with a longer duration of action and more readily crosses the blood-brain barrier than amphetamine.[118] The form of methamphetamine (e.g. crystalline or powder) can influence potency, duration and effect.[117]

Amphetamine withdrawal has distinct phases of symptoms. An early 'crash' phase (12–24 hours following last use) includes exhaustion and fatigue (usually hypersomnia but sometimes insomnia or restless sleep), flat mood, anxiety, agitation, cravings and non-specific aches and pains. The duration of the 'crash' is generally up to two to three days.[119, 120] Following this, the profile of symptoms changes to more characteristic withdrawal symptoms including strong cravings, mood fluctuations, irritability, restlessness, anxiety, agitation, fatigue, muscle tension, increased appetite, and poor concentration. Disturbance of thought (e.g. paranoia, delusions) and perception (e.g. misperceptions, auditory hallucinations) may emerge during the withdrawal syndrome. Peak withdrawal symptoms occur within the first seven days, with symptoms persisting for two to four weeks.[121] This can be followed by what is sometimes called an "extinction" phase, a period of weeks to months following the 'withdrawal' phase, where symptoms can include episodic fluctuation in mood, episodic cravings, and disturbed sleep.[121] While withdrawal from amphetamine has been reported on more extensively, specific characteristics of methamphetamine such as its long duration of action may produce distinct withdrawal features. The withdrawal syndrome specific to methamphetamine has not been characterised in large cohorts.

Assessing amphetamine and methamphetamine withdrawal

A number of scales have been used to assess amphetamine withdrawal symptoms such as the Amphetamine Withdrawal Questionnaire (AWQ)[122] and the Amphetamine Cessation Symptoms Assessment (ACSA). However, these tools have not been validated in MA withdrawal, and there is no correlation between ACSA scores and observer-rated withdrawal severity ($r=0.19$, $p>0.05$).[123]

Selection of reviews and studies

Systematic reviews

The reviews examined for the purposes of this rapid literature review reported on studies for the treatment of withdrawal from amphetamines or MA dependence. An additional limitation in interpreting the reviews is that they predominantly reported on studies with the primary outcomes of abstinence or reduced use, not severity of withdrawal symptoms. Table 6.1 describes the review articles identified in the search, summarising the type of review, dates, and relevance to the scope of work herein. Shoptaw et al. (2009) was the highest quality systematic review identified.

Relevant papers since this review

Since the Shoptaw *et al.* Cohcrane review in 2009, seven reports of six RCTs have been published, all of which report on pharmacotherapies for the treatment of MA withdrawal. These are presented in Table 6.2.

Table 6.1 Summary of reviews on management of amphetamines and methamphetamine (MA) withdrawal

Review title, reference	First author	Date of studies reviewed	Type of review	Commentary on review	Evidence grade
Treatment for amphetamine withdrawal[121]	Shoptaw SJ	1997–2008	Systematic with meta-analysis	Studies directly assess pharmacotherapies for amphetamine withdrawal. Low number of participants across studies (n=125). Strict inclusion criteria and high-level analysis.	
Evidence-based guidelines for the pharmacologic management of methamphetamine dependence, relapse Prevention, chronic methamphetamine-related, and comorbid psychiatric disorders in post-acute settings[124]	Hartel-Petri R	1994–2016	Systematic	Does not include methodology or search strategy. Number of participants not stated and little assessment of risk of bias.	
A review of methamphetamine dependence and withdrawal treatment: a focus on anxiety outcomes[125]	Hellem TL	2008–2015	Narrative	Only reviews one study addressing withdrawal, already assessed in Shoptaw 2008.	
Pharmacotherapy of amphetamine-type stimulant dependence: an update[126]	Brensilver M	2006–2011	Narrative	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	
Pharmacotherapeutic agents in the treatment of methamphetamine dependence[127]	Morley KC	2006–2016	Narrative	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	
Putting the call out for more research: the poor evidence base for treating methamphetamine withdrawal[128]	Pennay AE	1981–2009	Systematic	Gives good overview of MA withdrawal management and is written to follow from Shoptaw 2009. No meta-analysis or literature summary but effectively summarises state of the evidence.	
Cognitive-behavioural treatment for amphetamine-type stimulants (ATS)-use disorders[129]	Harad T	2010–2015	Systematic with meta-analysis	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	

Review title, reference	First author	Date of studies reviewed	Type of review	Commentary on review	Evidence grade
Efficacy of psychostimulant drugs for amphetamine abuse or dependence[130]	Perez-Mana C	2007–2012	Systematic with meta-analysis	Studies do not include withdrawal intervention and only address replacement therapies. Outside the scope of this review.	
Treatments for methamphetamine abuse: a literature review for the clinician[131]	Brackins T	2005–2010	Narrative	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	
Pharmacological approaches to methamphetamine dependence: a focused review[132]	Karila L	2001–2010	Narrative	Studies assess the effectiveness of one pharmacotherapy, groups MA and amphetamine-type stimulants together.	
Psychological treatments for stimulant misuse, comparing and contrasting those for amphetamine dependence and those for cocaine dependence[133]	Vocci FJ	2004–2006	Narrative	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	
Pharmacotherapy of methamphetamine addiction: an update[134]	Elkashef A	1996–2017	Narrative	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	
A systematic review of cognitive and behavioural therapies for methamphetamine dependence[135]	Lee NK	2001–2007	Systematic	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	
Pharmacotherapy for methamphetamine dependence: a review of the pathophysiology of methamphetamine addiction and the theoretical basis and efficacy of pharmacotherapeutic interventions[136]	Rose ME	1990–2007	Narrative	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	

Review title, reference	First author	Date of studies reviewed	Type of review	Commentary on review	Evidence grade
Pharmacotherapy for amphetamine dependence: A systematic review[137]	Lee NK	1998 - 2016	Systematic	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	
Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology, and treatment literature[138]	Courtney KE	2004 - 2013	Narrative	Presents other reviews and clinical trials in the same group for discussion. Lack of specific search strategy (i.e. searched for 'most recent').	
Treatment for amphetamine psychosis[139]	Shoptaw SJ	2005 (one study)	Systematic with meta-analysis	Studies do not include withdrawal intervention and only addresses amphetamine related psychosis. Outside the scope of this review.	
Evidence-based guidelines for the pharmacological management of acute methamphetamine-related disorders and toxicity[140]	Wodarz N	2001–2015	Systematic with meta-analysis	Much of the evidence applied to clinical recommendations and guidelines is derived from low-level evidence (LoE5, mechanism-based reasoning).	
Efficacy and safety of psychostimulants for amphetamine and methamphetamine use disorders: a systematic review and meta-analysis[141]	Bhatt M	2007–2015	Systematic with meta-analysis	Studies do not include withdrawal intervention and only address replacement therapies. Outside the scope of this review.	
A review of psychological and pharmacological treatment options for methamphetamine dependence[142]	Ciketi, S	2000–2009	Systematic	Studies do not include withdrawal intervention and only address dependence. Outside the scope of this review.	

Table 6.2 Additional Randomised Controlled Trials (RCTs) published since selected review (2006) for treatment of methamphetamine (MA) withdrawal

Paper authors, title, reference	Study description	Commentary on paper and main conclusions
Methadone versus buprenorphine		
Ahmadi J, Jahrome LR. Comparing the effect of buprenorphine and methadone in the reduction of methamphetamine craving: a randomised clinical trial. Trials. 2017;18(1):259.	n=40 parallel group RCT, MA dependant (DSM-V), >6 months use, discontinued use before trial. Comparing buprenorphine (8mg/ day) and methadone (40mg/day). Primary endpoint Visual Analogue Scale (VAS) for craving over a 17-day inpatient withdrawal.	Both methadone and buprenorphine significantly reduced cravings over the study period. From Day 10 buprenorphine significantly lowered cravings compared to methadone. There was no control group or follow-up and the study only included men, so generalisability is limited.
Modafinil		
Hester R, Lee N, Pennay A, Nielsen S, Ferris J. The effects of modafinil treatment on neuropsychological and attentional bias performance during 7-day inpatient withdrawal from methamphetamine dependence. Experimental and Clinical Psychopharmacology. 2010;18(6):489-97.	n=19 parallel group RCT, MA dependent (DSM-IV), MA use in last 48 hrs. Comparing tapered modafinil (from 200mg/100mg/day) with placebo over 7 days. Battery of neuropsychological tests administered to all participants.	Significant improvement in immediate verbal memory recall in the treatment arm. No other psychological outcomes were significantly different.
And Lee N, Pennay A, Hester R, McKetin R, Nielsen S, Ferris J. A pilot randomised controlled trial of modafinil during acute methamphetamine withdrawal: Feasibility, tolerability and clinical outcomes. Drug and Alcohol Review. 2013; 32:88-95.	Same study as above. In this report the primary outcome was feasibility and the secondary outcomes included: retention in treatment, withdrawal severity, craving, and sleep scores.	Modafinil is well accepted by MA users and feasible for short-term inpatient withdrawal. However, no difference in any secondary outcome measure was detected between intervention and placebo groups. Study was not sufficiently powered to detect differences, additionally treatment arm had longer duration of MA use and higher rates of polypharmacology use as compared to the placebo arm. Secondary analysis of Hester 2010 (above).
Modafinil versus mirtazapine		
McGregor C, Srisuraoanint M, Mitchell A, Wickes W, White J. 2008. Symptoms and sleep patterns during inpatient treatment of methamphetamine withdrawal:	n=49, MA dependent (DSM-IV), MA use >3 times per week over the last month. Comparing modafinil (400mg/day, n=14) mirtazapine (60mg/day, n=13) and TAU (pericyazine 2.5-	Both treatment arms indicated reduced sensations of craving and withdrawal severity when compared to TAU historical reference

Paper authors, title, reference	Study description	Commentary on paper and main conclusions
A comparison of mirtazapine and modafinil with treatment as usual. Journal of Substance Abuse Treatment. 35:334-43.	10mg/day, n=22, historical controls). Primary outcome withdrawal severity, secondary outcome quality of sleep. 10-day inpatient setting.	group. Modafinil was superior to mirtazapine for the first seven days, however differences were not apparent after that. Mirtazapine arm had improved quality of sleep versus modafinil. Study used control data from a previous trial. The study does not state if allocation was randomised. All treatment arms requested similar amounts of symptomatic (breakthrough/rescue) medications.
NMDA receptor antagonist		
Farahzadi M, Moazen-Zadeh E, Razaghi E, Zarrindast M, Bidaki R, Akhondzadeh S. Riluzole for treatment of men with methamphetamine dependence: A randomised, double-blind, placebo-controlled clinical trial. Journal of Psychopharmacology. 2019;33(3):305–15.	n=40 parallel group RCT, MA dependent (DSM-IV), male. Comparing riluzole (50mg/day) with placebo over 12 weeks. Primary outcome retention in treatment, secondary include abstinence, craving and withdrawal severity.	Treatment arm experienced significantly lower craving and lower levels or withdrawal severity. This study was designed to treat dependence however, and withdrawal outcomes were secondary. Participants were not required to cease methamphetamine use at any point during the study.
Modarresi A, Eslami K, Kouti L, Hassanvand R, Javadi M, Sayyah M. Amantadine reduces persistent fatigue during post-acute withdrawal phase in methamphetamine abstained individuals. Journal of Substance Use. 2018; 23(6); 584–90.	n=35, MA abstinent suffering from withdrawal induced fatigue. Comparing amantadine (100mg/day) or placebo for 4 weeks. Primary outcome fatigue symptoms, secondary outcome abstinence.	While fatigue was significantly lower in the treatment group there was no difference in MA abstinence between arms. This study does not investigate acute withdrawal, nor people withdrawing without persistent fatigue symptoms.
Other medications		
Morabbi M, Razaghi E, Moazen-Zadeh E, Safi-Aghdam H, Zarrindast MR, et al Pexacerfont as a CRF1 antagonist for the treatment of withdrawal symptoms in men with heroin/ methamphetamine dependence: a randomised, double-blind, placebo-controlled clinical trial. International Clinical Psychopharmacology. 2018; 33:111-9.	n=54, parallel group RCT, MA dependent (DSM-IV). Comparing tapered pexacerfont (300mg/200mg/100mg/day) and placebo over three weeks. Primary outcome was abstinence, and secondary outcome was craving.	No difference in abstinence, however there was a reduction in craving levels in the treatment arm. The study did not report MA and heroin independently, so it is not possible to distinguish the effect on MA withdrawal.

Paper authors, title, reference	Study description	Commentary on paper and main conclusions
Anderson A, Li S, Markova D, Holmes T, Chiang N, Kahn R, et al. Bupropion for the treatment of methamphetamine dependence in non-daily-users: A randomised, double-blind, placebo-controlled trial. 2015. Drug and Alcohol Dependence. 2015; 150:170-4.	n=204, parallel group RCT, MA dependent (DSM-IV) low use (<30 days/month). Comparing bupropion (150mg/twice daily). Primary outcome abstinence over 12 weeks in an outpatient setting.	Bupropion was not superior to placebo in improving abstinence rates among MA dependent people.

Summary of the evidence

6.1 Treatment setting

There may be circumstances in the withdrawal context that require an inpatient hospital setting for withdrawal from amphetamines or MA; for example, where there are significant comorbidities, such as cardiac complications and psychosis. Although no studies directly randomised to inpatient versus outpatient settings, this should be a clinical judgement based on patient presentation.

Table 6.3 Considerations for selection of withdrawal setting for amphetamine withdrawal

	Ambulatory	Residential	Inpatient Hospital
Likelihood of severe withdrawal complications	N/A	N/A	Potential for severe psychiatric and cardiovascular complications during withdrawal
Medical or psychiatric comorbidity	Minor comorbidity	Minor comorbidity	Significant comorbidity. Stimulant withdrawal (e.g. mental or physical symptoms) may exacerbate underlying conditions
Other substance use	No heavy drug use	Heavy or unstable use of other drugs	Heavy or unstable use of other drugs.
Social environment	Supportive home environment. Regular monitoring by reliable support people. Good access to outpatient service	Unsupportive home environment or social supports. Poor access to outpatient services	Unsupportive home environment or social supports. Poor access to outpatient services
Previous attempts		Repeated failure at ambulatory withdrawal	Repeated failure at ambulatory withdrawal

*For further details see text.

6.2 Psychosocial and physical interventions

While psychosocial therapies (e.g. cognitive behavioural therapy or contingency management) have been associated with better outcomes (i.e. retention, abstinence) in people with methamphetamine use disorder[135] very limited research has investigated complementary interventions alongside pharmacotherapies for the treatment of withdrawal from amphetamines and methamphetamine.

Addressed in Hellem et al., a thrice-weekly aerobic and resistance exercise program has been shown to improve mood in residential inpatients undergoing MA withdrawal, when compared to a physical education course in a single unblinded RCT.[125] In a double-blind RCT Liang et al. measured the effectiveness of transcranial magnetic stimulation (in which a changing magnetic field is used to induce an electric current in a small region of the brain) in men during admission to a Chinese rehabilitation centre.[143] Measures of withdrawal symptoms, sleep, depression and craving were improved compared to control. There was no difference in anxiety. No other controlled trials of psychosocial or physical therapies were identified, and while recommendations may be extrapolated from the withdrawal literature from other substances, more

evidence is needed before recommendations can be made with confidence regarding the role of these interventions in amphetamine-type stimulant withdrawal.

6.3 Medications

There are no evidence-based pharmaceutical treatments for amphetamine or MA withdrawal.[121, 140] Current treatment is mainly supportive.

Symptomatic pharmacotherapy

While the use of symptomatic medication for the treatment of amphetamine/MA withdrawal has not been studied in controlled trials, a number of medications are used to reduce the severity of withdrawal symptoms and acute distress. For example, while there are no data on the use of BZDs (e.g. diazepam) in amphetamine/MA withdrawal, their efficacy in the management of anxiety or agitation due to other causes is well established.

Current clinical practice is not well defined. It includes the short-term use of oral symptomatic medications, such as BZDs (e.g. diazepam) and/or antipsychotics (e.g. olanzapine) to manage agitation and irritability.[124]

Other pharmacotherapies

A number of medications were reviewed in the literature. The authors concluded that no medication has been shown to be effective for the treatment of amphetamine withdrawal.[121] Table 6.4 describes the pharmacotherapies investigated and reported in either the Shoptaw et al review (2009) or a subsequent RCT or review, and provides a recommendation based on the level of available evidence. Classification of evidence and strength of recommendations are defined in Appendix 1.

Amineptine, an atypical antidepressant, which inhibits dopamine reuptake, was found to significantly reduce treatment discontinuation rates and improved overall clinical presentation, but had no effect on withdrawal symptoms or craving as compared to placebo.[121]

Modafinil, an atypical psychostimulant, has been investigated in one small-scale RCT with similar results (reported by Hester et al.[144] and Lee et al.[145]). There was no difference in retention in treatment, withdrawal severity, craving or abstinence at follow up, between groups. *Mirtazepine* is an antidepressant that facilitates the release of central nervous system neurotransmitters including noradrenaline, serotonin, and dopamine thought to be involved in some of the symptoms of methamphetamine withdrawal. The benefits of mirtazapine over placebo for reduction in MA withdrawal symptoms were not clear, as studies yielded mixed results. McGregor et al. assessed withdrawal severity and sleep quality in methamphetamine-dependent participants allocated either open-label modafinil or mirtazapine.[146] Withdrawal severity (assesed using the ACSA) was lower in the modafinil group initially, however this difference disappeared after seven days. Mean hours of sleep were significantly higher in the mirtazapine group, and all subjects requested similar levels of symptomatic medications regardless of treatment group. The paper did not report whether allocation to each treatment group was random or not. When mirtazapine was directly compared with placebo, no differences were found, other than mean hours of sleep were higher in the treatment group[147], also reviewed in Shoptaw et al. 2009.

Burproprion is used as an antidepressant and for the treatment of nicotine dependence. As it has some effect on increasing dopamine levels in the brain, it has been studied in MA withdrawal with conflicting results. Studies have shown no effect on abstinence, suggesting bupropion may be of limited use as an aid for MA withdrawal.[124, 148]

Similarly, both *amantadine*[149] and *pexacerfont*[150] have been trialled as withdrawal aids. Amantadine showed an improvement in fatigue levels of the treatment group[149], and pexacerfont showed statistically significant improvements in craving and withdrawal severity[150], however this difference was small in absolute terms. While *riluzole* has displayed promising results as a method to treat dependence there is yet to be a study that directly assess' its effectiveness in a withdrawal setting.[151]

The effectiveness of the *opioid agonists methadone* and *buprenorphine* have been assessed in one RCT in a psychiatric ward among MA-dependent inpatients.[152] During the first week of the trial, both treatment arms showed similar levels of MA craving during withdrawal. However, from day 10, subjects receiving buprenorphine reported significantly lower levels of craving than those receiving methadone. Assessment of these results is difficult, however, as no control arm was included, and no comparison made to treatment as usual.

Table 6.4 Evidence for pharmacological treatments of withdrawal from amphetamines and methamphetamine

Drug class	Medication	ATS / MA*	Reviewed / reported in	Comment	Level of evidence and Recommendation strength
Antidepressant					
Noradrenergic and specific seritonergic	Mirtazapine	ATS and MA	Reviewed in: Shoptaw et al[121] Brensilver et al.[126] Hartrel-Petri et al.[124] Reported in: McGregor et al.[145] Cruickshank et al.[147]	Reduced hyperarousal and anxiety symptoms associated with ATS withdrawal in one RCT.[121] No reduction in ATS withdrawal symptoms or improvement in retention in one RCT.[121] No reduction in depression/anxiety outcomes during withdrawal in one RCT.[125] Participants randomised to mirtazapine more likely to provide negative urine for MA. May reduce symptoms or withdrawal in one RCT.[128] Lower craving.[146] Reduced hours of sleep.[147] Studies lacked power and effect size to detect a reliable difference in outcomes, primarily focused on abstinence and not withdrawal.	Evidence is contradictory and insufficient to recommend mirtazapine as a treatment for MA withdrawal. Level of evidence: Ia, Ib and IIa Recommendation strength: B
Tricyclic Antidepressant	Amineptine	ATS and MA	Reviewed in: Shoptaw et al.[121]	Did not reduce withdrawal symptoms or craving as compared to placebo in two RCTs.[121]	Amineptine does not show evidence of improvement in withdrawal symptoms. Level of evidence: Ia Recommendation strength: A
	Imipramine	MA	Reviewed in: Hartrel-Petri et al.[124]	May increase retention in treatment.[124]	There is insufficient evidence to recommend imipramine as a treatment option for MA withdrawal. Level of evidence: Ia Recommendation strength: A
Selective Seretonin Reuptake Inhibitor (SSRI)	Sertraline	MA	Reviewed in: Hartrel-Petri et al.[124]	Should not be administered to patients with MA disorder to achieve abstinence.[124]	Shows no evidence of improvement of MA withdrawal. Level of evidence: Ia Recommendation strength: A

Aminoketone	Bupropion	MA	Reviewed in: Hartrel-Petri et al.[124] Reported in: Anderson et al.[147]	In a systematic review of 4 RCTs, data suggested that it may be considered for use in patients with moderate (non-daily) MA use to achieve abstinence.[124] However, a subsequent study found that it does not improve abstinence in patients with low MA use.[148]	Evidence directly contradicted by subsequent trial. Does not recommend. Level of evidence: Ia Recommendation strength: A
Psychostimulants					
Central nervous system stimulant	Dexampheta-mine	MA	Reviewed in: Hartrel-Petri et al.[124] Courtney et al.[138]	Replacement therapies should not be offered unless part of a clinical trial.[124] May reduce craving, but not use.[138]	There is insufficient evidence that dexamphetamine improves withdrawal. Limited evidence that it reduces craving. Level of evidence: Ia Recommendation strength: A
Sympathomimetic-like Agent	Modafinil	MA	Reviewed in: Hartrel-Petri et al.[124] Pennay et al.[128] Karila et al.[132] Reported in: Lee et al.[145] Hester et al.[144]	Should not be administered in post-acute phase.[124] May be effective at reducing the severity of withdrawal symptoms.[128, 132] May reduce craving.[132] No difference in craving.[132] No difference in withdrawal symptom severity.[145] May improve memory.[144]	Evidence is contradictory and insufficient to recommend mirtazapine as a treatment for MA withdrawal. Level of evidence: Ia and IIa Recommendation strength: B
Opioid Antagonist					
	Naltrexone	ATS	Reviewed in: Karila et al.[132]	Reduce subjective effects and craving for people recently abstinent from dexamphetamine.[132]	Does not address MA. There is insufficient evidence to recommend naltrexone for the treatment of amphetamine withdrawal. Level of evidence: Ia Recommendation strength: B

Opioid Agonist					
	Methadone	MA	Reported in: Ahmadi et al.[151]	Reduce craving over time. Less effective than buprenorphine after 10 days.[152]	There is insufficient evidence to suggest that methadone may improve MA withdrawal. Level of evidence: IIb Recommendation strength: C
	Buprenorphine	MA	Reported in: Ahmadi et al.[151]	Reduce craving over time. More effective than methadone past 10 days.[152]	There is insufficient evidence to suggest that buprenorphine may improve MA withdrawal. Level of evidence: IIb Recommendation strength: C
Benzothiazole					
Glutamate Antagonist	Riluzole	MA	Reported in: Farahzadi et al.[151]	Reduced craving.[151]	There is insufficient evidence to recommend riluzole for the treatment of MA withdrawal Level of evidence: Ib Recommendation strength: B
Corticotropin Releasing Factor-1 Antagonist					
	Pexcerfont	MA	Reported in: Morabbi et al.[150]	Reduced craving.[150]	There is insufficient evidence to recommend pexcerfont for the treatment of MA withdrawal. Level of evidence: Ib Recommendation strength: B
Antiviral					
M2 Protein Inhibitor	Amantadine	MA	Reported in: Modarresi et al.[149]	Reduced fatigue in post-acute withdrawal only.[149]	There is insufficient evidence to recommend amantadine for the treatment of MA withdrawal. Level of evidence: Ib Recommendation strength: B

*ATS=Amphetamine-type stimulant, MA=methamphetamine

Table 6.5. Summary of evidence and recommendations for management of withdrawal from amphetamines and methamphetamine

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient admission	Unless inpatient admission is indicated for patient safety reasons (e.g. cardiac complications or psychosis, comorbid medical, psychiatric or social conditions), there is no clear advantage in an inpatient (or residential) withdrawal setting over an ambulatory setting regarding completion of withdrawal, engagement in post-withdrawal treatment or post-withdrawal substance use, and as such, inpatient withdrawal is not routinely recommended.	IV	Grade D: Poor
Psychosocial interventions			
Psychosocial interventions (counselling, contingency management) in conjunction with pharmacotherapies	While psychosocial therapies have been associated with better outcomes in people with amphetamine use disorder, there is little evidence to suggest that these interventions may be effective in the withdrawal setting.	III	Grade D: Poor
Physical interventions			
Exercise	One study identified, examined an aerobic and resistance exercise program for inpatient methamphetamine withdrawal, and reported improved mood. Further research is required, particularly given safety concerns (cardiovascular effects) in these populations.	Ib	Grade D: Poor
Mind-body exercise (e.g. yoga)	No controlled studies were identified examining yoga for substance withdrawal (excluding tobacco). Further research recommended.	Nil	Grade: No controlled studies
Massage therapy during withdrawal	Limited evidence suggests massage therapy effective in reducing withdrawal symptoms and anxiety during withdrawal.	Ib	Grade D: Poor
Medications			
Antidepressants			
Mirtazapine	Contradictory evidence for efficacy of mirtazapine. May reduce hyperarousal and anxiety, reduce craving and lessen symptom severity during withdrawal. May have no effect on any of the above outcomes. May reduce sexual risk taking among men who have sex with men. Evidence highly contradictory and a recommendation cannot be made.	Ia	Grade D: Poor

Intervention	Recommendation	Level of evidence	Quality of evidence
Amineptine	May not reduce withdrawal symptoms or craving as compared to placebo.		
Imipramine	May improve retention in treatment.		
Sertraline	Has demonstrated adverse effects on retention in treatment and abstinence compared with placebo.		
Bupropion	Evidence suggests bupropion may or may not improve abstinence rates.		
Antipsychotics			
Olanzapine	May be effective in managing amphetamine-induced psychosis. May lead to more weight gain compared with haloperidol.	IIa	Grade C: Satisfactory
Haloperidol	May be effective in managing amphetamine-induced psychosis. Associated with a higher rate of acute extrapyramidal motor effects and lower treatment retention compared with olanzapine.		
Quetiapine	As effective as haloperidol in the management of amphetamine induced psychosis.		
Risperidone	Generally, well accepted. May be more effective at managing MA induced psychosis than aripiprazole.		
Aripiprazole	May reduce retention in treatment of patients with amphetamine-induced psychosis. Caution regarding length of treatment is required.		
Benzodiazepines			
Diazepam	While there have been no studies that assess BZDs in the context of amphetamine withdrawal; the underlying mechanism of action and medication effects are well understood and can therefore be used to manage some of the symptoms associated with amphetamine withdrawal. Caution regarding length of treatment and side effects (e.g. disinhibition) is required (see text for further detail).	IV for withdrawal, Ia for symptomatic management	Grade C: Satisfactory: outside of withdrawal context, but symptomatic management
Midazolam			
Lorazepam			

Psychostimulants			
Dexamphetamine	May reduce craving but not use. Insufficient RCT evidence.	IIa	Grade D: Poor
Modafinil	May or may not be effective at reducing withdrawal symptoms and craving. May improve memory.		
Opioid agonists			
Methadone	May reduce craving, however less effective than buprenorphine when length of treatment is greater than 10 days. Unknown if more effective than placebo.	IIa	Grade D: Poor
Buprenorphine	May reduce craving, more effective than methadone when length of treatment is greater than 10 days. Unknown if more effective than placebo.		
Riluzole	May reduce craving during withdrawal.	IIb	Grade D: Poor
Pexcerfont	May reduce craving during withdrawal	IIb	Grade D: Poor
Amantadine	May reduce fatigue in post-acute withdrawal only	IIb	Grade D: Poor

Chapter 7. Cocaine

Description of the withdrawal syndrome

Cocaine is derived from the leaf of erythroxylon coca, and most commonly used as powder, for intranasal or intravenous use, or smoked in its free base form, which is often referred to as 'crack'. Cocaine's effect seems to rely on its ability to increase the availability of monoamines namely dopamine, serotonin and noradrenaline in the brain, which deliver the desired effects of euphoria, increased energy and alertness.

Cocaine use disorder has been recognised by DSM-5 and ICD-10 and the withdrawals from which are characterised as dysphoric mood and two or more additional symptoms:

- Fatigue
- Vivid, unpleasant dreams
- Insomnia or hypersomnia
- Increased appetite
- Psychomotor retardation or agitation.

Selection of reviews and studies

No systematic reviews were identified focusing on the management of cocaine withdrawal. Consensus statements favour the symptomatic treatment of the cocaine withdrawal symptoms, mainly with low dose BZDs and/or low dose atypical sedating antipsychotics if the concern is sleeplessness and agitation. Prolonged periods of dysphoric mood may require antidepressant therapy if the diagnosis is depression.

Summary of the evidence

7.1 Treatment setting

No study examined the relevance of the treatment setting for the management of cocaine withdrawal. Although the withdrawal experience from cocaine is relatively mild and may not warrant an admission, when making a decision on the treatment setting, it is important to consider concomitant drug use, comorbidities, as well as the patient's social circumstances.

7.2 Psychosocial interventions

Various systematic reviews examined the efficacy of psychosocial interventions for the treatment of cocaine dependence.[129, 133, 153] Cocaine withdrawal was not a treatment outcome for any of the studies included in these reviews. Overall, psychosocial interventions appeared to decrease the dropout rates and contribute to a longer period of abstinence compared to the treatment as usual option. The most studied and promising intervention was 'contingency management', however, this approach was not compared head to head with any other psychosocial interventions.

7.3 Physical therapies

A systematic review explored the efficacy of auricular acupuncture for the treatment of cocaine dependence[154], but withdrawal was not one of the outcome measures for the studies included in this review. There was no evidence of efficacy for this intervention in the treatment of cocaine dependence.

7.4 Medications

Several systematic reviews examined the efficacy of various medications such as disulfiram[155], antidepressants[156], antipsychotics[157], psychostimulants[158], anticonvulsants[159] and dopamine agonists[160] for the treatment of cocaine dependence. None of the studies included in these reviews had cocaine withdrawal as a secondary outcome. Evidence for the efficacy of any of the medications used in these studies was poor.

Chapter 8. 3,4-methylene-dioxymethamphetamine (MDMA)

The drug 3,4-methylene-dioxymethamphetamine (MDMA) has been colloquially named as *"ecstasy"* by its users. It is a ring-substituted amphetamine derivative that is also related to the hallucinogenic compound mescaline. The classification of MDMA has been problematic as it is chemically closer to hallucinogens, without producing many hallucinogenic effects. Rather, it increases emotional sensitivity and empathy, with users reporting a loss of inhibitions, reduced anxiety and an increased sense of closeness with other people. As a result, MDMA is often classified among amphetamine type substances.

MDMA dependence has not been recognised in DSM-5 or in ICD-10 at the present time.

The concept of MDMA dependence has been a subject of discussion without a clear conclusion.[161]

Description of the withdrawal syndrome

The research suggests that the most commonly reported withdrawal symptoms are 'feel depressed', `feel tired or weak', `change in appetite', `have trouble concentrating', and `feel anxious, restless, or irritable'.[162] However, national and international organisations list the following as the MDMA withdrawal symptoms, which are likely to be based on its similarities to amphetamine type substances, rather than basing it on any specific research.[163] A cautious approach is needed to ensure that reporting of these symptoms by patients, is not due to withdrawal from concomitant use of other substances such as cannabis:

- Irritability
- Depression
- Sleep problems
- Anxiety
- Memory and attention problems
- Decreased appetite
- Decreased interest in and pleasure from sex.

Selection of reviews and studies

No systematic reviews were identified focusing on the management of MDMA withdrawal.

Summary of the evidence

8.1 Treatment setting

It is unlikely that individuals ceasing prolonged or heavy use of MDMA will experience significant discontinuation effects (symtoms) that warrant inpatient admission. Ambulatory settings are generally recommended, although a residential setting may be appropriate for those without a suitable home environment or supports.

8.2 Psychosocial interventions

Existing research appears to be focusing on the impact of long term MDMA use on cognitive function and memory.[164]

Two reviews on the psychosocial interventions for stimulant use disorders included MDMA in their scope[129, 153] but MDMA withdrawal was not one of the outcomes in any of the studies that were included in the review. Overall, both of these papers concluded that psychosocial interventions improved the retention rates in treatment as well as abstinence rates, but long-term effectiveness of these interventions was not clear.

8.3 Physical Therapies

No evidence is available.

8.4 Medications

There are no reviews on the pharmacological interventions for MDMA withdrawal nor dependence.

The consensus statements that inform the current guidelines nationally and internationally suggest treating the abovementioned symptoms symptomatically i.e. with low dose BZDs or low dose sedating atypical antipsychotics for a brief period of time, if the concern is irritability, anxiety or agitation.

Chapter 9. Gabapentin/ pregabalin

Pregabalin and gabapentin are approved pharmacotherapies for the treatment of some epileptic and pain disorders, and pregabalin has increasingly been used for the treatment of generalised anxiety disorder. Their pharmacology is closely related and both are 3-substituted γ-aminobutyric acid (GABA) derivatives, with GABAmimetic features which are most likely to be associated with a sense of relaxation and euphoria.[165]

Neither pregabalin nor gabapentin dependence is recognised in DSM-5 or in ICD-10 at the present time. The concept of gabapentinoid dependence has been examined, but at this stage the addictive properties have only been described among people with current or past SUDs.[166]

Description of the withdrawal syndrome

Various case reports have suggested a similar set of withdrawal symptoms associated with the abrupt discontinuation of long-term, high-dose gabapentin or pregabalin use.[167-169] It is important to note that this information comes from either single case reports or case series with a maximum of seven patients, not from large case series or RCTs. Nevertheless, all of these reports do describe a consistent set of withdrawal symptoms:

- Diaphoresis
- Tachycardia
- Hypertension
- Tremors
- Diarrhoea
- Agitation
- Paranoia
- Auditory hallucinations
- Mutism
- Self-mutilation
- Suicide attempts.

Case series are subject to publication bias, and it is possible that inidividuals may discontinue heavy or regular use of pregabelin or gabapentin without significant discontinuation effects. More research is required.

Selection of reviews and studies

There are no systematic reviews nor RCTs on the management of gabapentionoid withdrawal.

Summary of the evidence

9.1 Treatment setting

No study examined the relevance of the treatment setting for the management of gabapentinoid withdrawal. However, a narrative review that sought to establish the addiction risk of gabapentinoids, clearly identified that the most vulnerable group of people for misuse of, and overdose from these medications, are people with current and past SUD, and are likely to be on another form of narcotic analgesics or opioid substitution treatment.[166] This would indicate a level of complexity that may necessitate an inpatient withdrawal approach if there are concerns about the feasibility of an outpatient taper. The potential physical and psychiatric complications described during withdrawal suggest a period of close monitoring in a hospital setting may be warranted.

9.2 Psychosocial interventions

There are no reviews nor RCTs on the psychosocial interventions for gabapentinoid withdrawal or dependence.

9.3 Physical therapies

There are no reviews nor RCTs on physical interventions for gabapentinoid withdrawal or dependence.

9.4 Medications

Existing case series and case reports suggest that the most effective way to address the withdrawal symptoms is a slow taper of the medication over 10–14 days, as BZDs alone do not seem to alleviate the withdrawal symptoms.

There are no reviews nor RCTs on the pharmacological interventions for gabapentinoid withdrawal or dependence.

Chapter 10. Gamma-hydroxybutyrate (GHB) gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD)

Gamma-hydroxybutyrate (GHB)/Gamma-butyrolactone (GBL) is commonly known as *"liquid ecstasy"*. GHB is predominantly consumed as a 'party drug' for enjoyment. While endogenous doses of GHB act as a neuromodulator in the GABA system producing stimulant-like effects including euphoria and lower inhibitions, supra-therapeutic doses can readily cross the blood-brain barrier leading to profound CNS and respiratory depression.[170]

Description of the withdrawal syndrome

Cessation of gamma-hydroxybutyrate (GHB) and its precursors among people who use GHB regularly and chronically may result in withdrawal-like symptoms. A well-defined withdrawal syndrome for GHB and its analogues is yet to be established, as evidence regarding GHB withdrawal is limited. Case studies and reviews have noted similarities between withdrawal symptoms of GHB and other CNS depressants such as ethanol or BZDs.[171] While not specific to GHB, DSM-5 lists a number of symptoms associated with withdrawal from sedative, hypnotic or anxiolytic medications including: hyperactivity, tremor, insomnia, nausea or vomiting, hallucinations, psychomotor agitation, anxiety and grand mal seizures.

Available case reports and reviews have noted a range of withdrawal symptoms associated with acute- and long-term GHB withdrawal. Withdrawal has typically been observed after prolonged use or high doses of GHB[172], and may develop after only several days to weeks of daily use.[173] Reported minor symptoms of GHB cessation include: tremor, insomnia, diaphoresis, mild anxiety, nausea and tachycardia.

More severe symptoms include hypertension, increased anxiety, and agitation followed by audio/visual hallucinations and paranoid delusions. Seizures, bradycardia, cardiac arrest and renal failure have been described in extreme cases.[172] These symptoms appear to vary between cases and increase in severity according to prior exposure to the drug. Withdrawal symptoms typically begin within 1–12 hours, and have been reported to last up to 21 days[170], with some psychiatric symptoms reported up to six months following cessation.[172] Initial withdrawal is characterised by high craving, profuse sweating, tachycardia and anxiety. From approximately five hours post cessation, psychiatric symptoms such as delusions and hallucinations are characteristic.[174] Patients are expected to make a full recovery, provided they are hospitalised and receive appropriate, timely care.[170]

Assessing withdrawal from GHB, GBL and 1,4BD

There is currently no widely accepted or validated scale for the assessment of withdrawal from GHB or its precursors. Self-developed tools, visual analogue scales and qualitative interviews are common methods of

assessing GHB withdrawal in the literature.[175] Assessment tools for other drugs (e.g. the Clinical Institute Withdrawal Assessment for Alcohol – Revised) have also been employed to examine GHB withdrawal.[176]

Selection of reviews and studies

Table 10.1, describes the review articles identified in the literature search, summarising the type of review, dates, and relevance to the scope of work herein. The available reviews exclusively reported on case studies due to the lack of controlled or observational trials. The only available systematic review relating to management of GHB withdrawal is a case report and systematic review published in 2008.[171]

Table 10.1 Summary of reviews on management of withdrawal from GHB, GBL or 1,4BD

Review title, reference	First author	Date of studies reviewed	Type of review	Commentary on review	Evidence grade
Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review[171]	Wojtowicz JM	1996–2006	Systematic	Systematic search strategy, methods included, studies independently assessed before inclusion. Exclusively case reports. Focused on BZD treatment options.	
Pharmacological treatment of γ-Hydroxybutyrate (GHB) and γ-Butyrolactone (GBL) dependence: Detoxification and relapse prevention[172]	Kamal RM	1998–2016	Narrative	A large number of cases were included in this review. Various pharmacotherapies were examined. Exclusively case reports.	
GHB pharmacology and toxicology: Acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome[177]	Busardò FP	1997–2014	Narrative	Contains limited information on withdrawal. Exclusively case reports. Search strategy or methods not included.	
Management and treatment of gamma butyrolactone withdrawal syndrome: A case report and review[178]	Ghio L	1997–2011	Narrative	Good number of cases included. Investigates a variety of pharmacotherapies. Exclusively case reports. Search strategy or methods not included.	
Acute toxicity and withdrawal syndromes related to gamma-hydroxybutyrate (GHB) and its analogues gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD)[179]	Wood DM	1994–2008	Narrative	Limited investigation into withdrawal. Exclusively case reports. Search strategy or methods not included.	
The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol[170]	Schep LJ	1991–2011	Narrative	Reviews a large number of cases. Broad article with a short section discussing withdrawal. Search strategy included, however does not differentiate between withdrawal and broader GHB literature. Exclusively case reports.	

Review title, reference	First author	Date of studies reviewed	Type of review	Commentary on review	Evidence grade
The neurobiological mechanisms of gamma-hydroxybutyrate dependence and withdrawal and their clinical relevance: a review[180]	Kamal RM	1997–2015	Narrative	Describes the biological pathways of GHB withdrawal in depth. Exclusively case reports. Search strategy or methods not included.	
Treat γ-hydroxybutyrate (GHB) and γ-butyrolactone (GBL) dependence with BZDs first, then with other approaches if BZD-resistant[181]	ADIS Medical Writers	-	Guidelines	Guidelines based on Kamal et al. 2017.[172] Outside scope of this review.	
GHB, GBL and 1,4-BD addiction[182]	Brunt TM	1996–2012	Narrative	Provides little information specific to withdrawal. Exclusively case reports. Search strategy or methods not included.	

Summary of the evidence

10.1 Treatment settings

The potential for severe physical or psychiatric complications following the cessation of heavy and regular GHB use suggests treatment should occur in an inpatient hospital, with regular monitoring. Further research is required.

10.2 Psychosocial interventions

No evidence is available. General principles of psychosocial interventions in withdrawal management are recommended (see Chapter 1).

10.3 Physical therapies

No evidence is available. Exercise is not recommended at this time (further research required) as an intervention during withdrawal due to the risks of cardiovascular complications.

10.4 Medications

There are no evidence-based pharmaceutical treatments for GHB withdrawal.[183] Current reported clinical practice is based on treatment of withdrawal symptoms as necessary.[170]

The existing research literature on GHB withdrawal suggests two primary pharmacological intervention options: high-dose BZDs or titration and tapering of pharmaceutical GHB. High-dose BZDs are commonly considered the primary treatment for GHB withdrawal[170, 172, 177, 179-181], with up to 300mg of diazepine (core element in the structure of BZDs) per day. This is titrated for heavy (>32g/day) GHB use, as suggested by one author.[172]

Titration and tapering with pharmaceutical GHB has also been described in cases of BZD resistance[172], and has been suggested as a possible primary treatment option.[175] Barbiturates such as phenobarbital have also been considered as a primary treatment option[178], and baclofen has recently emerged as a potential treatment option, both as a complementary[184] and stand-alone therapy.[185] In all cases there is no high-level evidence to suggest one treatment over another, and no trialed and validated treatment algorithm.

In Australia, the clinical guidelines for GHB withdrawal available in each state all reference the lack of evidence-based treatments available. The most recent of these (Turning Point, Victoria 2018) acknowledges the lack of evidence in relation to GHB withdrawal management, and does not make any specific recommendations, other than, that specialist advice should be sought in the planning of withdrawal regimes.

Table 10.2 summarises the evidence for pharmacological treatment for GHB/GBL withdrawal.

The review identified the use of a range of medications to manage GHB withdrawal, including: BZDs, antipsychotics, anti-epileptics, and barbiturates. As expected, considering the lack of controlled trials there is no analysis of the relative effectiveness of the proposed treatment options.

The authors concluded that withdrawal from GHB and its analogues results in features similar to other sedative-hypnotic withdrawal syndromes. However, symptoms may be severe, and seizures and death may occur. BZDs are frequently used for initial treatment, and, barbiturates for more severe cases, despite the lack of randomised trials.[171]

A review published in 2016 by Kamal et al. examined 80 published papers.[180] They identified the use of high-dose BZDs as the most common treatment option for GHB withdrawal, with many authors suggesting admission to an ICU in extreme or acute presentations. This review also examines the evidence base for the titration and tapering of pharmaceutical GHB for GHB withdrawal management.[172] Despite not having access to controlled trial data, this approach has led to the generation of practice-based guidelines using sodium oxybate, the sodium salt of GHB, in The Netherlands.[175] The review suggests different approaches for planned and unplanned withdrawal, dependent on dose and psychiatric history. Generally, pharmaceutical GHB titration is suggested for all cases unless there is no history of psychosis or delirium, in which case BZDs are suggested.[172]

While there is no evidence for the use of symptomatic medication in the context of GHB withdrawal, the purpose of these medications in acute withdrawal is to address the associated symptoms and manage acute distress. For example, while there is no data on the use of BZDs (e.g. diazepam) and/or antipsychotics (e.g. olanzapine) in GHB withdrawal, their efficacy in the management of agitation or irritability is well established. However, the use of BZDs should be limited to short-term use given the risk of developing dependency.[186]

Table 10.2 Evidence of pharmacological treatments for management of withdrawal from GHB, GBL 1,4BD

Drug Class	Medication	Reviewed in	Comment	Recommendation and Evidence Level
Benzodiazepines (BZDs)	Undefined	Wojtowicz et al.[171] Kamal et al.[172] Busardò et al.[177] Wood et al.[179] Kamal et al.[180] van Noorden et al.[183]	BZDs are frequently used to treat GHB withdrawal[171, 180] Should not be used if a history of psychoses or resistance is apparent[172] High dose may assist detoxification[177, 179, 183]	Case studies and reports indicate this may be an effective therapy for GHB withdrawal. However, there is no evidence to support this. Evidence Category: IV Recommendation Level: D (directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence)
	Diazepam	Kamal et al.[172]	Successful detoxification with diazepam[172]	Case studies and reports indicate this may be an effective therapy for GHB withdrawal. However, there is no evidence to support this. Evidence Category: IV Recommendation Level: D (directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence)
	Lorazepam	Kuiper et al.[187]	Successful detoxification with lorazepam[187]	Case studies and reports indicate this may be an effective therapy for GHB withdrawal. However, there is no evidence to support this. Evidence Category: IV Recommendation Level: D (directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence)
Barbiturates	Undefined	Wojtowicz et al.[171] Kamal et al.[172] Ghio et al.[178] Wood et al.[179]	Barbiturates may be used for more severe cases or refractory cases.[171] May be used alongside BZDs[172, 179] Should be considered as primary treatment option[178]	Barbiturates may be effective as adjunct therapy to BZDs or as primary therapy. However, there is no evidence to support this. Evidence Category: IV Recommendation Level: D

Drug Class		Medication	Reviewed in	Comment	Recommendation and Evidence Level
					(directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence)
Muscle relaxants	GABA-B antagonist	Baclofen	Schep et al.[170] Beurmanjer et al.[188] Le Tourneau et al.[184] Habibian et al.[185]	Baclofen can be used as an adjunct therapy to BZDs[170] Lower relapse rate in post-acute subjects[188] Reduces seizures and tremors[184] Successful detoxification with baclofen alone[185]	Baclofen may be suitable as adjunct treatment to BZDs. However, there is no evidence to support this. Evidence Category: III and IV Recommendation Level: C (directly based on category III evidence or extrapolated recommendation from category I or II evidence)
CNS depressants	Hydroxybutyrates	GHB	Brunt et al.[182] van Noorden et al.[183] de Jong et al.[189] Dijkstra et al.[175]	Titration of GHB assists successful detoxification [175, 182, 189] Effective where high dose BZDs failed [183]	GHB titration may be an effective primary treatment for GHB withdrawal. It is commonly used when BZD therapy has failed. However, there is no evidence to support this. Evidence Category: III & IV Recommendation Level: C (directly based on category III evidence or extrapolated recommendation from category I or II evidence)

Table 10.3 Summary of evidence and recommendations for management of withdrawal from GHB, GBL, and 1,4BD

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Inpatient admission	Hospital admission required for severe withdrawal, including delirium. ICU may be required. Planned withdrawal from GHB is possible in an outpatient setting in less severe dependence.	IIb	Grade D: Poor
Psychosocial interventions			
Psychosocial interventions (counselling, contingency management) in conjunction with pharmacotherapies	No review or case report has investigated or described psychosocial interventions during GHB withdrawal.	N/A	Grade D: Poor
Physical interventions			
Massage therapy during withdrawal	Limited evidence suggests massage therapy is effective in reducing withdrawal symptoms and anxiety during withdrawal.	Ib	Grade D: Poor
Medications			
Benzodiazepines (BZDs)	BZDs are frequently employed to manage symptoms following GHB cessation, typically with titration and tapering of very high doses. They should not be used if a history of psychosis or resistance is known/apparent. All data in this context (GHB withdrawal) derived entirely from case reports.	IV	Grade D: Poor
Diazepam	Evidence of successful withdrawal from GHB with high-dose diazepam.		
Lorazepam	Evidence of successful withdrawal from GHB with high-dose lorazepam.		
Barbiturates	May be effective as adjunct therapy to BZDs given intravenously in severe cases in inpatient settings. May also be considered as primary treatment option however there is no evidence to support this. All data in this context (GHB withdrawal) derived entirely from case reports.	IV	Grade D: Poor
Baclofen	May be effective as an oral adjunct therapy to BZDs, particularly to help manage seizures and tremors.	IIb	Grade D: Poor
Gamma hydroxybutyrate	Titration and tapering of pharmaceutical GHB (usually as sodium oxybate) may assist in successful GHB detoxification. Particularly effective where high-dose BZDs have failed (one explorative pilot study [n=23]; one observational cohort study [n=274]; case reports).	III	Grade D: Poor
Dexmedetomidine	Dexmedetomidine infusion has shown success during abrupt GHB cessation when BZDs proved ineffective in intensive care settings (review of case series).	IIb	Grade D: Poor

Chapter 11. Methadone to buprenorphine transfer

Both methadone and buprenorphine (BPN) are effective and widely used in the treatment of opioid dependence. Optimising treatment outcomes for individual patients requires some patients to transition from one to the other. In the Australian context, more common reasons for transitioning from methadone to BPN are in response to side effects to methadone, dose not holding (e.g. rapid metabolisers of methadone), or in attempts to withdraw off opioid agonist treatment.[190] It is expected that the introduction of depot BPN treatment will also create increased demand for patients to transfer from methadone to BPN.

However, transitioning from methadone to BPN is complicated by the potential for precipitated withdrawal on commencing BPN — thought to be due to the drug's higher receptor affinity, but lower intrinsic activity (partial agonist) at mu-opioid receptors. This is particularly of concern for patients transferring from higher doses of methadone (e.g. greater than 40–60mg). A number of groups have produced guidelines regarding clinical procedures for transfer between medications.[6, 191-193] The transfer procedures in the Australian guidelines [6] (and consistent with the NSW Guidelines for the Opioid Treatment Program, 2018) were summarised in the table below.[194]

A systematic review of methadone to BPN transfers[195] identified 16 studies reporting on 240 patient transfers–most were uncontrolled studies with few cases, and few studies reported on transfers from high doses (designated as ≥70 mg). Only two RCTs examining different transfer procedures in clinical populations were identified – both conducted in Australia. Breen et al, compared transfer approaches in n=55 patients on 40mg methadone or less who were seeking to transfer to BPN prior to withdrawal off all opioid agonist treatment; and the other by Clarke (2006) examined inpatient transfer approaches on methadone patients between 40mg and 100mg, comparing three separate BPN induction approaches (slow n=9, moderate n=10, rapid n=11). Neither study demonstrated any significant advantages of different approaches.

The Mannelli review identified that transfers from doses below 70mg were feasible using abrupt cessation or taper on an outpatient basis, often with ancillary medications and a 24-hour interval between medications. In contrast, transfers from higher methadone doses usually required inpatient treatment and ancillary medications, and precipitated withdrawal was reported in a substantial minority of cases. The authors concluded *that "due to differences in design and individual variability, a single protocol cannot be formulated"* (p.5).

Since the Mannelli review, an as-yet unpublished systematic review searched the literature for studies on this subject (to 2017) and found no new controlled trials, and indeed few additional studies (17 studies in total). Most studies were observational case series with little harmonisation between studies on how study populations, procedures or outcomes are defined or reported, complicating comparisons across studies. The review attempted meta-analysis of the impact of different variables (e.g. methadone dose, time interval between last methadone dose and first BPN dose, size of first BPN dose, rapidity of BPN dose escalation), and found that successful transfer (on BPN seven days after transfer without experiencing severe precipitated withdrawal) was inversely correlated with methadone dose, and there was a non-significant trend suggesting higher completion rates when the initial BPN dose was delayed at least 24 hours after the last methadone dose. The buprenorphine dosing approach (first dose, total day one or subsequent doses) was less correlated with successful transfer.

Two studies published since these reviews are of relevance to the Australian context. Naumovski and Batey (2015) reported a case series of 29 outpatient transfers from methadone doses of ranging from 43 - 140mg (mean dose 61mg at transfer), and delayed first BPN dose for at least 48 hours (mean COWS of 20 prior to initiating buprenorphine).[196] The authors reported no complications or precipitated withdrawal. Lintzeris and colleagues (2018) implemented and evaluated national Australian guidelines for transferring patients from methadone to BPN in n=33 participants across four services, with 15 cases considered high-dose transfers (from 50mg methadone or more, of which 12 were ≥70mg).[194] The authors reported that no low- or moderate-dose transfers (from less than 50mg methadone) experienced precipitated withdrawal, while three of 15 (20%) of high-dose transfers experienced precipitated withdrawal. The majority of the high-dose transfers (14/15) were conducted in inpatient hospital settings, with an average 2.2 (range 1–3) days. The authors described the guidelines as feasible in specialist settings, however highlighted the need for further research, particularly of the role for the transfers to occur as 'day procedures' without the need for overnight admission.

One other case series published since the 2012 Mannelli review is also of relevance to inpatient procedures.[197] Oretti (2015) reported a case series of seven high-dose inpatient transfers (methadone dose 60–120mg) using clinical procedures broadly consistent with the approach described in the Australian guidelines (sudden cessation of methadone and induction onto BPN approximately 24 hours later). Six of seven patients successfully completed the transfer, and the author confirmed the findings of the Australian guideline evaluation that 'rapid' inpatient transfer can safely occur for most high dose methadone patients without the need for gradual taper to low doses.

A number of alternative approaches to the methadone to BPN transfers have been described. One approach is to transfer the patient from methadone to short-acting opioid medication (e.g. morphine, fentanyl) for several days prior to transferring to BPN. While this approach has been reported as successful in case studies [198], the lack of clinical trials and regulatory issues in such approaches prevent this approach from being recommend at his time. There is also considerable interest in direct methadone to depot BPN transfers – due to the gradual onset of BPN plasma levels with depot injection. Again, clinical trials are required.[198]

Table 11.1 Overview of clinical guidelines for transferring from methadone to buprenorphine (BPN)

Assessment, treatment planning, and patient education - examine patient expectancies, reasons for transfer, and discuss transfer procedures. Identify, and where possible stabilise, any risks for patient safety during the transfer, including unstable substance use, physical, mental health, or social conditions.
Unless urgent transfer required (e.g. severe side effects to methadone), gradually reduce methadone dose until patient starts to experience mild to moderate opioid withdrawal between doses.
Consider treatment setting: inpatient settings recommended for patients transferring from high methadone doses or with significant health comorbidities or unstable social conditions.
Cease methadone and monitor the patient regularly (at least daily) for evidence of opioid withdrawal symptoms. Initiate BPN treatment when patient experiencing moderate opioid withdrawal severity (Clinical Opioid Withdrawal Scale [COWS] >12), at least 24 hours after last methadone dose.
Initiate low-dose BPN treatment (2mg), and monitor hourly for evidence of precipitated withdrawal, preferably using a withdrawal scale (e.g. COWS). Administer further 6mg after one hour. Further doses (4mg or 8mg at a time) are symptom-triggered and continue regular monitoring and dosing until patient comfortable.
On subsequent days, BPN dose from previous day plus additional dose based upon withdrawal severity (symptom-triggered).[194]

Table 11.2 Summary of evidence and recommendations for management of methadone to buprenorphine transfer

Intervention	Recommendation	Level of evidence	Quality of evidence
Setting			
Treatment setting	Transfers from low- to moderate-dose methadone can usually occur in outpatient specialist settings. Transfers from high methadone doses (>50mg) may require a brief inpatient admission for transfer procedures.	III	Grade D: Poor
Psychosocial intervention	No controlled studies but recommended in Australian MATOD and NSW OTP Clinical Guidelines. Patient and carer information and education is an important aspect of treatment planning.	IV	Grade D: GPP (Good Practice Point)
Monitoring	Regularly monitor through transfer process using a structured opiate withdrawal scale (e.g. COWS, SOWS). Review patient regularly throughout transfer process (including daily for first several days of buprenorphine dosing, until dose stable).	IV	Grade D: GPP (Good Practice Point)
Medication	Few controlled trials, most evidence from case series. Discontinue methadone dose and initiate BPN (low dose with incremental dose increases every 1–2 hours until comfortable), with aim of achieving daily buprenorphine dose (usually 16–32mg) within 1–3 days.	III	Grade D: Poor

Discussion

The rapid review of the literature on withdrawal management has highlighted some key principles across the different drugs, and also highlighted some of the key gaps in our knowledge regarding clinical management of withdrawal. Each of the three key questions of the review are addressed below:

Question 1: What have been shown to be the most effective practices for treatment of withdrawal from alcohol and other drugs?

The review highlights that:

A. Withdrawal services should be seen as a 'package of care'

- Withdrawal management involves a combination of psychosocial, physical and pharmacological interventions and effective withdrawal management requires integration of these approaches. Contemporary approaches to withdrawal management require attention to all three dimensions – for example, 'non-medicated' withdrawal services, or withdrawal services without psychosocial supports (e.g. a 'prescription-only' from a GP) should not be considered to be evidence-based.
- Withdrawal services should be seen as part of a continuum of care and should be integrated into a broader care plan that addresses the individual's substance use, health and social issues. While access to withdrawal services should not be conditional upon enrolment in post-withdrawal substance use treatment, the treatment plan should consider ongoing engagement with the patient. Motivation for post-withdrawal treatment should not be considered 'tatic or fixed, and psychosocial interventions (e.g. motivational enhancement) and assertive linkage to post-withdrawal services should be facilitated.
- There are aspects of good clinical practice that are not usually subject to controlled trials yet should still be considered clinical standards of care. These include:
    - Attention to *treatment access* – there is sufficient evidence to highlight that delayed access to withdrawal treatment is associated with poorer outcomes, and a greater emphasis upon earlier engagement is required. This will often mean greater availability of ambulatory withdrawal services, rather than an exclusive reliance on residential/hospital-based services.
    - A *comprehensive clinical assessment* (that includes detailed assessment of substance use, physical, mental and social conditions, legal issues, patient goals and available resources).
    - *Assessment and mitigation of key risks* (e.g. housing, domestic violence, child protection, and overdose risk for those with a history of opioid use, and availability of take-home naloxone interventions for patients and carers).
    - *Care plan* that addresses the patient's substance use, health and psycho-social conditions
    - *Regular monitoring* throughout the withdrawal episode
    - *Transfer of care* documentation and processes consistent with clinical handover principles.

B. Extrapolating across drug classes for psychosocial and physical therapies in withdrawal management

While the evidence for psychosocial and physical interventions has often been accumulated for individual substances (e.g. alcohol or opioid withdrawal), many of the key findings should be extrapolated to other substances. This enables the development of 'standardised' approaches to withdrawal services – irrespective of the drug the individual is withdrawing from. It is not possible at this time to prioritise one psychosocial

counselling approach over another for all substances – principles of motivational enhancement, cognitive behavioural approaches to coping with cravings and withdrawal symptoms, case management and care planning, including assertive approaches to post-withdrawal engagement, should be considered as standard care across drug classes.

The role of physical interventions (e.g. exercise, relaxation strategies such as massage) is still emerging – yet there is considerable evidence that exercise can assist with important symptoms in withdrawal management (e.g. sleep, anxiety, reduced cravings), and as such should be incorporated into withdrawal management services, on an individualised basis. This may require withdrawal services to become better equipped to deliver (or at least incorporate) exercise programs. However, the high rates of physical comorbidities and potential complications of withdrawal require careful patient assessment and tailoring of appropriate exercise programs. Other approaches such as acupuncture have been examined in a number of studies, with insufficient evidence to recommend them for widespread practice. Nevertheless, there may be some patients who benefit from acupuncture.

While the evidence regarding the role of psychoeducation for patients and carers upon withdrawal outcomes remains poor, the limited evidence available is consistent with other principles of consumer health literacy in which patients tend to have better outcomes when more information is available in an accessible form.

The role of structured peer enagagement (e.g. 12-step facilitation) in withdrawal services remains unclear, and further research is required.

C. Developments for particular drug classes

In relation to withdrawal management for specific drugs, there have been few developments in the management of alcohol, opioid or BZD withdrawal in the past decade. Alcohol withdrawal is still underpinned by ensuring appropriate and safe withdrawal setttings, the use of BZDs as the mainstay of medication, and ensuring appropriate monitoring and psychosocial services. Opioid withdrawal is preferentially managed using opioid medications such as buprenorphine, often in an outpatient setting. The introduction of longer acting forms of BPN (e.g. depot products) should also be integrated into withdrawal management settings to enhance post-withdrawal treatment engagement.

The evidence regarding management of cannabis withdrawal is undergoing transformation. Historically, there were few medication options with an established evidence base for this common withdrawal syndrome. More recently, there is increasing evidence to support the use of cannabinoid-agonist medications (e.g. nabiximols), and this is an emerging area of clinical and research practice.

The evidence regarding amphetamine withdrawal remains poor. The high prevalence of significant physical, psychiatric and social problems in patients with methamphetamine dependence will often mean that the settings and withdrawal interventions are shaped by these co-morbidities. It highlights the need for comprehensive assessment as part of entry into withdrawal treatment (ideally, prior to entry), and for care planning with assertive post-withdrawal engagement.

There has been the emergence of a new range of drugs for which we have little evidence and for which we are still developing clinical experience. In particular 'withdrawal' from drugs such as GHB, pregabalin, ketamine, and prescription opioids (for pain management) can pose new challenges for withdrawal services. In particular withdrawal interventions need to occur against the context of the patient's other health conditions and in liaision with community treatment providers. For example, management of the patient who is taking pregabalin or prescription opioids for pain management requires close co-ordination with the

patient's prescribing doctors and pain management services in the community. Similarly, interventions for BZD withdrawal need close collaboration with community prescribers. Withdrawal services need to viewed as a short-term intervention in a longer continuum of care provided by a range of health and welfare services. It is not a stand-alone procedure to be undertaken in isolation of other services.

Question 2: What withdrawal management strategies are the most effective in improving treatment outcomes for the special population groups?

There have been few studies examining special patient populations such as Aboriginal people, LGBTI people, people in custody, or medically unwell populations e.g. those with liver failure, delirium etc. This may reflect the complexity of undertaking clinical trials with some of these patient populations during acute interventions such as withdrawal treatment. Even more obvious is the lack of research that has examined gender differences in withdrawal profiles, management, and outcomes. Most patients attending drug and alcohol services are male, and most pateints enrolled in clinical trials are male. The small numbers of participants in most withdrawal studies prohibits meaningful analysis of subsamples within studies (e.g. based on gender).

For Aboriginal people and LGBTI people, the limited evidence available indicates that services tailored specifically for the population (LGBTI), or which incorporate cultural factors e.g. remaining close to country and family (for Aboriginal people) are more likely to engage these populations in treatment. Further research is required.

There is more research examining withdrawal management in the elderly – most notably for withdrawal from BZDs and alcohol – consistent with the patterns of drugs more commonly used in these populations.

Question 3: What are the differential effects of withdrawal management approaches by setting?

The review identified the importance of treatment setting in withdrawal management. Historically, NSW withdrawal services have emphasised residential or hospital-based approaches. While these are an essential component of the mix of withdrawal services, the over-reliance upon residential/inpatient withdrawal settings – sometimes with no community withdrawal options available for pateints – is neither effective, patient-centred nor resource-efficient. All services should have clinical pathways that ensure that patients have access to the range of withdrawal settings. This is potentially even more important for patients from different cultural backgrounds, and Aboriginal people, where admission to a residential unit can cause cultural difficulties, or where community supports, e.g. remaining close to family and to country, are important to patients. In other contexts, patients may need to be removed from their family or social networks in order to be able to undertake withdrawal. The important factor is that patients have options and pathways – rather than single models of operation.

Areas for further research

Conducting this review has identified several areas where there are critical gaps in our knowledge. The review has highlighted the absence of evidence for most drug classes regarding the use of psychosocial and physical therapies for withdrawal management. Effective withdrawal medications have only been established in controlled trials for alcohol, opioids, and BZDs, with an emerging evidence base for cannabis.

General research themes

Regarding *psychosocial interventions* – greater attention needs to focus on:

- The role of patient (and carer) psychoeducation regarding withdrawal and the longer-term management of substance use disorders

- The role of patient supports – including family, peers, friends and carers – in withdrawal, particularly ambulatory withdrawal services
- The types of psyschosocial interventions that should be incorporated into withdrawal services. The evidence is remarkably poor as to the more effective counselling approaches in withdrawal management. The role of newer approaches, such as mindfulness, remain to be examined in clinical trials in withdrawal management settings.

There is immense potential for *physical therapies* such as exercise and relaxation approaches, and interventions that include mind-body exercise (including yoga). These have largely been unexamined in controlled trials, yet the limited evidence – and evidence from other areas of health – suggest these may have important contributions to patient self-management of symptoms and general health and wellbeing.

Monitoring of withdrawal severity, substance use (in ambulatory settings), and general health during withdrawal are important aspects of care – that have not been examined in this review. It should be noted that whilst established withdrawal scales exist for alcohol, opioids and BZDs, the withdrawal scales for amphetamines, cannabis, and emerging drugs are not ideal.

Another area that warrants attention is the role of *nutrition and nutritional supplements* during withdrawal, particularly for conditions such as alcohol, opioids and amphetamines, which can all affect dietary patterns and nutrition. Further research examining the role of thiamine supplementation in alcohol and other patient populations is required, as well as examination of electrolytes such as magnesium and calcium.

Treatment settings. Further research is required to delineate the role of different withdrawal settings, and decision-making tools to assist patients, clinicans and treatment planners to ensure the best mix of ambulatory, residential and inpatient withdrawal services. Particular attention needs to be given in the NSW service system to establishing more robust ambulatory withdrawal services, and to examine the introduction of home-based models of care. This is consistent with the general trend in healthcare to minimimse or reduce unnecessary hospital admissions and to transfer care to healthcare services in the community. The ability to better engage community providers, including GPs and practice nurses, warrants exploration. The increasing age of our population requires that we also consider the provision of withdrawal services that meet the needs of elderly patients – including within aged care facilities.

Special populations. The research examining the treatment needs of special populations is extremely limited. Some work has examined the needs of elderly patients with alcohol or BZD use problems, but little else. Similarly, the treatment needs regarding withdrawal management for Aboriginal and LGBTQI people, people in custody, and culturally and linguistically diverse (CALD) communities remains poorly researched. Future research should include a range of methodologies to examine these issues, including qualitative and community-informed research, but should not exclude clinical trials.

Drug specific areas of research

Alcohol

Alcohol withdrawal is the most researched and evidence-informed area of clinical pratice of all the drug classes, however there are still areas that require further research. Particular areas include:

- Treatment of DTs, particularly the use of pharmacological management.
- Management of alcohol withdrawal in patients with significant comoribidities including severe liver disease (e.g. cirrhosis), particularly choice of BZD.

- Better understanding of the role of the psychosocial interventions such as patient information, psychosocial interventions and self-help support, in the management of alcohol withdrawal and subsequent treatment engagement.
- While not directly related to the management of alcohol withdrawal, the prevention and management of Wernicke's encephalopathy requires further research to optimise the assessment, prevention and management (including the use of thiamine) in cases of suspected Wernicke's encephalopathy.

Opioids

Treatment approaches for opioid withdrawal are also well researched with a clear evidence base. However, the emergence of new patient populations with dependence to prescribed opioids, usually for pain management, raises new difficulties. The increasing trend to deprescribe opioids for patients, and the advent of prescription-monitoring programs, may result in an increase of patients seeking withdrawal management for their prescription opioid medication use. Often patients have multiple comorbidities including chronic pain, and mental and physical health conditions. Traditional approaches to managing heroin withdrawal may not be adequate to address the range of health problems or conditions that could emerge following withdrawal from long-term opioid treatment. Particular attention is required to examine outcomes associated with withdrawal versus maintenance of opioid treatment in patients dependent on opioid medications with concomitant chronic pain conditions.

The introduction of depot buprenorphine (BPN) medications, and potentially long-acting opioid antagonist formulations, raises new opportunities and challenges that require further research.

Despite 50 years of opioid-agonist treatment with methadone or more recently BPN, research is yet to identify effective strategies that assist suitable patients to withdraw from and cease long-term opioid 'maintenance' treatment. The role of residential and peer support e.g. programs such as 'We Help Ourselves' (WHOs), the role of new depot BPN medications, and the potential of long-acting antagonist formulations, warrant further research. This is an increasingly important issue given the ageing population of patients in methadone programs, and the potential long-term adverse health effects of chronic opioid therapy.

Similarly, while approaches for transferring patients from low and medum doses of methadone to BPN appear well established, transferring patients from higher methadone doses (e.g. >60–80mg) remains poorly researched. Promising areas include the use of bridging short-acting opioids, the role of 'micro-dosing' of BPN (multiple small doses), the potential for transfers using depot BPN (direct from methadone), and the role of opioid antagonists.

Cannabis. The need for more effective and accessible treatment for cannabis dependence is likely to become more important with the emergence of medicinal cannabis treatment in Australia, and changing societal perspectives regarding cannabis use, that is being seen in many countries around the world. At this time, cannabinoid agonist medications, in combination with psychosocial interventions appear to be the most promising avenue, however further research is required to better understand choice of cannabinoids (e.g. THC, CBD ratios), dose and duration of treatment.

Methamphetamine (MA). Our understanding of the nature, time course and severity of MA withdrawal is still emerging. Many of the studies identified examined amphetamine withdrawal or populations with mixed amphetamine, MAs and other stimulants use, and hence there is much still to learn about MA withdrawal charactersitics, and management. Particular attention is needed to better characterise the MA withdrawal syndrome, including duration, and to examine pharmacological treatment of MA withdrawal (e.g. agonist therapies), particularly in the context of comorbid physical and mental health comorbidity.

For the *emerging drugs such as GHB, MDMA and pregabalin*, research is required to better characterise discontinuation effects of stopping frequent use of these drugs; a better understanding of the pharmacological management of withdrawal from these drugs, and a better understanding of the indications for inpatient management.

Conclusion

Withdrawal management is an important component of an alcohol and other drug service profile, and for many people represents an entry point into alcohol and other drugs treatment. Withdrawal offers the opportunity for engagement with patients, and an opportunity to examine the broader range of substances used, health, psychosocial conditions, and legal issues that affect the patient, with the development of a treatment plan to address these factors.

The evidence regarding optimal withdrawal management – while patchy in many areas – is sufficiently robust in most cases to allow the development of evidence-based clinical guidelines. There are 'emerging' drugs (e.g. GHB, ketamine, pregabalin) for which more research and clinical experience is required, however, these drugs still represent a small minority of clinical presentations for withdrawal management.

This review has identified the importance of a 'package of care' for withdrawal management that includes psychosocial, physical and pharmacological interventions, and these should be incorporated into all withdrawal services. The challenge for many withdrawal services and for treatment planners is to ensure that effective services are available, patient-centred, evidence-based and efficient. This necessarily requires a re-examination of the NSW approach, which has historically emphasised residential and hospital-based withdrawal services at the expense of more efficient – and often more patient-centred – ambulatory withdrawal services. An integrated system that matches services to patient needs and enables 'step-up' and 'step down' approaches should make services more accessible and better meet patient needs.

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Appendices

Appendix 1. Evidence classification scheme

Identification and assessment of evidence is best achieved through systematic reviews where all available evidence is assessed for its applicability to the clinical question being considered, reviewing the evidence for bias, and summarising the findings.

The type of evidence required is dependent on the question under consideration. Where efficacy of treatment interventions is the issue, as was the case in this literature review; randomised, controlled trials are most relevant.

The summarised evidence is then categorised based on its susceptibility to bias, which is often related to study design, or analysis of the findings e.g. selection bias (sample is not representative of the population) and confirmation bias (interpreting data to prove a predetermined assumption).

Classification schemes

Category of evidence

Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
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 or clinical experience of respected authorities, or both

Source: Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. British Medical Journal. 1999;318(7183):593-6.[1]

Appendix 2. NHMRC Levels of evidence

Grade	Evidence Description	Recommendation
A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias. All studies consistent. Very large clinical impact. Population/s studied in body of evidence are the same as the target population for the guideline. Directly applicable to Australian healthcare context.	Excellent Body of evidence can be trusted to guide practice. Recommendation based on high quality evidence. Strongly recommended for implementation.
B	One or two level-II studies with a low risk of bias or a SR/several level III studies with a low risk of bias. Most studies consistent and inconsistency may be explained. Substantial clinical impact. Population/s studied in the body of evidence are similar to the target population for the guideline. Applicable to Australian healthcare context with few caveats.	Good Body of evidence can be trusted to guide practice in most situations. Recommendation based on good evidence. Strongly recommended for implementation.
C	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias. Some inconsistency reflecting genuine uncertainty around clinical question. Moderate clinical impact. Population/s studied in body of evidence differ to target population for guideline, but it is clinically sensible to apply this evidence to target population. Probably applicable to Australian healthcare context with some caveats.	Satisfactory Body of evidence provides some support for recommendation(s) but care should be taken in its application. Recommendation based on supportive evidence and a strong theoretical rationale. Recommended for implementation.
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus.	Poor Body of evidence is weak, and recommendation must be applied with caution. Recommendation based on limited, inconsistent or extrapolated evidence. Recommendation supported by expert opinion. Recommended for implementation.
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group.	GPP Evidence limited or non extistent. Recommendation based on current expert opinion and trends in clinical practice. Recommended for implementation.

Source: Coleman K, Norris S, Weston A, Grimmer-Somers K, Hillier S, et al. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: NHMRC 2009. [2]

Appendix 3. Abstracts for key reviews on management of alcohol withdrawal

3.1 Benzodiazepines for alcohol withdrawal

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Editorial group: Cochrane Drugs and Alcohol Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 3, 2010.

Citation: Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD005063. DOI: 10.1002/14651858.CD005063.pub3.

Abstract

Background

Alcohol abuse and dependence represents a serious health problem worldwide with social, interpersonal and legal interpolations. Benzodiazepines have been widely used for the treatment of alcohol withdrawal symptoms. Moreover, it is unknown whether different benzodiazepines and different regimens of administration may have the same merits.

Objectives

To evaluate the effectiveness and safety of benzodiazepines in the treatment of alcohol withdrawal.

Search methods

Cochrane Drugs and Alcohol Group' Register of Trials (December 2009), pubmed, EMBASE, CINAHL (January 1966 to December 2009), econlit (1969 to December 2009). Parallel searches on web sites of health technology assessment and related agencies, and their databases.

Selection criteria

Randomised controlled trials examining effectiveness, safety and risk-benefit of benzodiazepines in comparison with placebo or other pharmacological treatment and between themselves. All patients were included regardless of age, gender, nationality, and outpatient or inpatient therapy.

Data collection and analysis

Two authors independently screened and extracted data from studies.

Main results

Sixty-four studies, 4309 participants, met the inclusion criteria.

Comparing benzodiazepines versus placebo, benzodiazepines performed better for seizures, 3 studies, 324 participants, RR 0.16 (0.04 - 0.69), no statistically significant difference for the other outcomes considered.

Comparing benzodiazepines versus other drugs, there is a trend in favour of benzodiazepines for seizure and delirium control, severe life-threatening side effect, dropouts, dropouts due to side effects and patient's global assessment score. A trend in favour of control group was observed for CIWA-Ar scores at 48 hours and at the end of treatment. The results reach statistical significance only in one study, with 61 participants, results on Hamilton anxiety rating scale favour control MD -1.60 (-2.59 to -0.61)

Comparing different benzodiazepines among themselves, results never reached statistical significance but chlordiazepoxide performed better

Comparing benzodiazepine plus other drug versus other drug, results never reached statistical significance.

In the comparison of fixed-schedule versus symptom-triggered regimens, results from a single study, with 159 participants, favour symptom-triggered regimens MD -1.10 [-3.27, 1.07] for CIWA-Ar scores at the end of treatment. Differences in isolated trials should be interpreted very cautiously.

Authors' Conclusions

Benzodiazepines showed a protective benefit against alcohol withdrawal symptoms, in particular seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with other drugs. Nevertheless, no definite *Conclusions* about the effectiveness and safety of benzodiazepines was possible, because of the heterogeneity of the trials both in interventions and the assessment of outcomes.

3.2 Efficacy and safety of pharmacological interventions for the treatment of the alcohol withdrawal syndrome

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Citation: Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.: CD008537. DOI: 10.1002/14651858.CD008537.pub2.

Abstract

Background

Alcohol abuse and dependence represents a very serious health problem worldwide with major social, interpersonal and legal interpolations. Pharmacological treatments presently used are of uncertain effectiveness and there is even more doubt on the comparative effects and value for money.

Objectives

To summarize Cochrane reviews that assess the effectiveness and safety of pharmacological interventions in the treatment of alcohol withdrawal.

Methods

We searched the Cochrane Database of Systematic Reviews (30 November 2010). Two authors independently screened, extracted data, summarised key characteristics of the included reviews and assessed their quality using AMSTAR; the quality of the evidence was summarised according to the GRADE methodology.

Main Results

Five reviews, 114 studies, 7333 participants, satisfied criteria for inclusions. The outcomes considered were alcohol withdrawal seizures, adverse events and dropouts. Comparing the five treatments with placebo, benzodiazepines performed better for seizures, three studies, 324 participants, RR 0.16 (95% CI 0.04 - 0.69), moderate quality of evidence. Comparing each of the five treatments versus specific class of drugs, benzodiazepines performed better than antipsychotics for seizures, 4 studies, 633 participants, RR 0.24 (95% CI 0.07 - 0.88) high quality of the evidence. Comparing different enzodiazepines and anticonvulsants among themselves, 28 comparisons, results never reached statistical significance but chlordiazepoxide performed better. The quality of evidence was high for 3% of the results, moderate for 28%, low for 48% and very low for 20%.

Authors' Conclusions

Among the treatments considered, benzodiazepines showed a protective benefit against seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with antipsychotics. Nevertheless, no definite *Conclusions* about the effectiveness and safety of benzodiazepines

were possible, because of the heterogeneity of the trials both in interventions and in the assessment of outcomes. Data on potential harms are sparse and fragmented. Results do not provide sufficient evidence in favour of anticonvulsants for the treatment of AWS, but anticonvulsants seem to have limited side effects. There is also not enough evidence of effectiveness and safety of baclofen, because only one study consider this treatment and of GHB for which no strong differences were observed in the comparisons with placebo, benzodiazepines and anticonvulsants.

3.3 Baclofen for alcohol withdrawal

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Citation: Liu J,Wang LN.Baclofen for alcoholwithdrawal.*cochranedatabase of Systematic Reviews* 2017, Issue 8.Art.No.:CD008502. DOI: 10.1002/14651858.CD008502.pub5.

Abstract

Background

Baclofen shows potential for rapidly reducing symptoms of severe alcohol withdrawal syndrome (AWS) in people with alcoholism. Treatment with baclofen is easy to manage and rarely produces euphoria or other pleasant effects or craving for the drug. This is an updated version of the original Cochrane Review published in 2015, Issue 4.

Objectives

To assess the efficacy and safety of baclofen for people with AWS.

Search Methods

We updated our searches of the following databases to March 2017: the Cochrane Drugs and Alcohol Group Specialised Register, CENTRAL, pubmed, Embase, and CINAHL. We also searched registers of ongoing trials. We handsearched the references quoted in the identified trials, and sought information from researchers, pharmaceutical companies, and relevant trial authors about unpublished or uncompleted trials. We placed no restrictions on language.

Selection criteria

We included all randomised controlled clinical trials (rcts) evaluating baclofen versus placebo or any other treatment for people with AWS.We excluded uncontrolled, non-randomised, or quasi-randomised trials. We included both parallel group and cross-over studies.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main Results

We included three rctswith 141 randomised participants. We did not performmeta-analyses due to the different control interventions.

For the comparison of baclofen and placebo (1 study, 31 participants), therewas no significant difference inclinical institutewithdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) scores (very low-quality evidence). For the comparison of baclofen and diazepam (1 study, 37 participants), there was no significant difference in CIWA-Ar scores (very low quality evidence), adverse events (risk difference (RD) 0.00, 95%confidence interval (CI) -0.10 - 0.10; very low quality evidence), dropouts (RD0.00, 95%CI -0.10 - 0.10; very low quality evidence), and dropouts due to adverse events (RD 0.00, 95% CI -0.10 - 0.10; very low quality evidence). For the comparison of baclofen and chlordiazepoxide (1 study, 60 participants), there was no significant difference in CIWA-Ar scores (mean difference (MD) 1.00, 95% CI 0.70 - 1.30; very low quality

evidence), global improvement (MD 0.10, 95% CI -0.03 - 0.23; very low quality evidence), adverse events (RD 2.50, 95% CI 0.88 - 7.10; very low quality of evidence), dropouts (RD 0.00, 95% CI -0.06 - 0.06; very low quality evidence), and dropouts due to adverse events (RD 0.00, 95% CI -0.06 - 0.06; very low quality evidence).

Authors' Conclusions

No *Conclusions* can be drawn about the efficacy and safety of baclofen for the management of alcohol withdrawal because we found insufficient and very low-quality evidence.

3.4 Anticonvulsants for alcohol withdrawal

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Editorial group: Cochrane Drugs and Alcohol Group.

Publication status and date: New search for studies and content updated (*Conclusions* changed), published in Issue 3, 2010. Review content assessed as up-to-date: 29 December 2009.

Citation: Minozzi S, Amato L, Vecchi S, Davoli M. Anticonvulsants for alcohol withdrawal. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD005064. DOI: 10.1002/14651858.CD005064.pub3.

Abstract

Background

Alcohol abuse and dependence represents a most serious health problem worldwide with major social, interpersonal and legal interpolations.

Besides benzodiazepines, anticonvulsants are often used for the treatment of alcohol withdrawal symptoms. Anticonvulsants

Drugs are indicated for the treatment of alcohol withdrawal syndrome, alone or in combination with benzodiazepine treatments. In spite of the wide use, the exact role of the anticonvulsants for the treatment of alcohol withdrawal has not yet bee adequately assessed.

Objectives

To evaluate the effectiveness and safety of anticonvulsants in the treatment of alcohol withdrawal.

Search Methods

We searched Cochrane Drugs and Alcohol Group' Register of Trials (December 2009), pubmed, EMBASE, CINAHL (1966 to December 2009), econlit (1969 to December 2009). Parallel searches on web sites of health technology assessment and related agencies, and their databases.

Selection criteria

Randomised controlled trials (rcts) examining the effectiveness, safety and overall risk-benefit of anticonvulsants in comparison with a placebo or other pharmacological treatment. All patients were included regardless of age, gender, nationality, and outpatient or inpatient therapy.

Data collection and analysis

Two authors independently screened and extracted data from studies.

Main Results

Fifty-six studies, with a total of 4076 participants, met the inclusion criteria. Comparing anticonvulsants with placebo, no statistically significant differences for the six outcomes considered.

Comparing anticonvulsant versus other drug, 19 outcomes considered, results favour anticonvulsants only in the comparison carbamazepine versus benzodiazepine (oxazepam and lorazepam) for alcohol withdrawal symptoms (CIWA-Ar score): 3 studies, 262 participants, MD -1.04 (-1.89 to -0.20), none of the other comparisons reached statistical significance.

Comparing different anticonvulsants no statistically significant differences in the two outcomes considered.

Comparing anticonvulsants plus other drugs versus other drugs (3 outcomes considered), results fromone study, 72 participants, favour paraldehyde plus chloral hydrate versus chlordiazepoxide, for the severe-life threatening side effects, RR 0.12 (0.03 - 0.44).

Authors' Conclusions

Results of this review do not provide sufficient evidence in favour of anticonvulsants for the treatment of AWS. There are some suggestions that carbamazepine may actually be more effective in treating some aspects of alcohol withdrawal when compared to benzodiazepines, the current first-line regimen for alcohol withdrawal syndrome. Anticonvulsants seem to have limited side effects, although adverse effects are not rigorously reported in the analysed trials.

3.5 Symptom-triggered therapy for alcohol withdrawal syndrome: a systematic review and meta-analysis of randomised controlled trials

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Abstract

Background: Benzodiazepines are the standard medication class for treating alcohol withdrawal. Guidelines recommend dosing based on objectively measured symptoms (symptom-triggered therapy) rather than fixed dose regimens. However, the superiority of symptom-triggered therapy has been questioned, and concerns have been raised about its inappropriate use and safety. We aimed to assess whether symptom-triggered therapy is superior to fixed dose schedules in terms of mortality, delirium, seizures, total benzodiazepine dose, and duration of therapy.

Methods: A systematic literature search using Medline, Embase, and the Cochrane Registry through February 2018 was conducted for randomised controlled trials of patients with alcohol withdrawal syndrome comparing fixed dose benzodiazepine schedules to symptom triggered therapy. Risk of bias was assessed using the Cochrane Risk of Bias Tool. Outcomes were pooled using random effects meta-analysis. Heterogeneity was estimated using the I2 statistic. Strength of evidence was assessed using methods outlined by the Agency for Healthcare Research and Quality.

Results: Six studies involving 664 patients were included. There were no deaths and only one seizure in each group. Four studies reported delirium, which occurred in 4 out of 164 patients randomised to symptom-triggered therapy compared to 6 out of 164 randomised to fixed dose therapy (odds ratio, 0.64 [95%CI, 0.17–2.47]). Three studies reported duration of therapy, which was 60.4 h less with symptom-triggered therapy (95% CI, 39.7–81.1 h; p<0.001). Six studies reported total benzodiazepine dosage, which was 10.5 mg in lorazepam-equivalent dosing less with symptom-triggered therapy (95% CI, 7.1–13.9 mg; p=0.011).

Discussion: Moderate strength evidence suggests that symptom-triggered therapy improved duration of therapy and total benzodiazepine dose in specialized detoxification settings of low-risk patients but the applicability of this evidence in general hospital settings is low. There was insufficient evidence for any *Conclusions* about symptom triggered therapy for the major outcomes of mortality, seizure, and delirium in any setting.

3.6 Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses

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Citation: Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. *Cochrane Database of Systematic Reviews* 2010, Issue 2. Art. No.: CD006266. DOI: 10.1002/14651858.CD006266.pub2.

Abstract

Background

Chronic excessive alcohol consumption may lead to dependence, and to alcohol withdrawal syndrome (AWS) in case of abrupt drinking cessation. Gamma-hydroxybutyric acid (GHB) can prevent and suppress withdrawal symptoms, and improve the medium term abstinence rate. However, clear estimates of its beneficial and harmful effects have not been yet established.

Objectives

To evaluate the efficacy and safety of GHB for the treatment of AWS and the prevention of relapse.

Search Methods

We searched the Cochrane Drugs and Alcohol Group's Register of Trials (October 2008), pubmed, EMBASE, CINAHL (January 2005 to October 2008), econlit (1969 to February 2008), and reference lists of retrieved articles.

Selection criteria

Randomised controlled trials (RCT) and Controlled Prospective Studies (CPS) evaluating the efficacy and the safety of GHB versus placebo or other pharmacological treatments.

Data collection and analysis

Three authors independently extracted data and assessed the methodological quality of the studies.

Main Results

Thirteen rcts were included, 11 of which had been conducted in Italy.

For alcohol withdrawal syndrome, comparing GHB 50mg versus placebo, results from 1 study (23 participants) favour GHB for withdrawal symptoms: MD -12.1 (95% CI -15.9 to -8.29), but tolerated side effects were more frequent in the GHB group: RR 16.2 (95% CI 1.04 - 254.9; based on 7 of 11 patients in the GHB group developing transitory vertigo compared to none in the placebo group). In the comparison of GHB 50mg versus Clomethiazole, results from 1 study (21 participants) favour GHB for withdrawal symptoms: MD -3.40 (95% CI -5.09 to -1.71). For GHB 100mg versus Clomethiazole, results from 1 study (98 participants) favour Clomethiazole for side effects: RR 1.84 (95% CI 1.19 - 2.85).

At mid-term, comparing GHB 50mg/day with placebo, 1 study (71 participants, 3 months follow-up) favour GHB for abstinence rate (RR 5.35, 95% CI 1.28 - 22.4), controlled drinking (RR 2.13, 95% CI 1.07 - 5.54), relapses (RR 0.36, 95% CI 0.21 - 0.63), and number of daily drinks (MD -4.60, 95% CI -6.18 to -3.02). On abstinence, GHB performed better than Naltrexone (NTX) (2 studies, 64 participants) (RR 2.59, 95% CI 1.35 - 4.98 at 3 months) and than Disulfiram (1 study, 59 participants) (RR 1.66, 95% CI 0.99 - 2.80 at 12 months, slightly significant). The combination of GHB and NTX was better than NTX for abstinence (RR 12.3, 95% CI 1.79 - 83.9 at 3 months; 1 study, 35 participants). The combination of NTX, GHB and Escitalopram was better than Escitalopram alone for abstinence (RR 2.02 95% CI 1.03 - 3.94 at 3 months; RR 4.58, 95% CI 1.28 - 16.5 at 6 months; 1 study, 23 participants). For Alcohol Craving Scale, results favour GHB over placebo (MD -4.50,

95% CI -5.81 to -3.19 at 3 months; 1 study, 71 participants) and over Disulfiram at 12 months (MD -1.40, 95% CI -1.86 to -0.94, from 1 study with 41 participants).

All other comparisons and outcomes did not show significant differences.

Authors' Conclusions

There is insufficient randomised evidence to be confident of a difference between GHB and placebo, or to determine reliably if GHB is more or less effective than other drugs for the treatment of alcohol withdrawl or the prevention of relapses. The small amount of randomised evidence available suggests that GHB 50mgmay be more effective than placebo in the treatment of AWS, and in preventing relapses and craving in previously detoxified alcoholics during the first 3 months of follow-up. This review does not provide evidence in favour or against GHB compared to benzodiazepines and Clomethiazole for treatment of AWS; but, again based on a small amount of randomised evidence, GHB appears better than NTX and Disulfiram in maintaining abstinence and preventing craving in the medium term (3 to 12months). The review does not provide evidence of a difference in side effects between GHB and benzodiazepines, NTX or Disulfiram. These findings should be considered alongside concerns that have been raised about GHB regarding the risk of developing addiction, and the misuse or abuse of the drug, suggesting the use of GHB only under strict medical surveillance.

Appendix 4. Abstracts for key reviews on management of opioid withdrawal

4.1 Buprenorphine for managing opioid withdrawal

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Citation: Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD002025. DOI: 10.1002/14651858.CD002025.pub5.

Abstract

Background

Managed withdrawal is a necessary step prior to drug-free treatment or as the endpoint of substitution treatment.

Objectives

To assess the effects of buprenorphine versus tapered doses of methadone, alpha2-adrenergic agonists, symptomatic medications or placebo, or different buprenorphine regimens for managing opioid withdrawal, in terms of the intensity of the withdrawal syndrome experienced, duration and completion of treatment, and adverse effects.

Search Methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 11, 2016), MEDLINE (1946 to December week 1, 2016), Embase (to 22 December 2016), psycinfo (1806 to December week 3, 2016), and the Web of Science (to 22 December 2016) and handsearched the reference lists of articles.

Selection criteria

Randomised controlled trials of interventions using buprenorphine to modify the signs and symptoms of withdrawal in participants who were primarily opioid dependent. Comparison interventions involved reducing doses of methadone, alpha2-adrenergic agonists (clonidine or lofexidine), symptomatic medications or placebo, and different buprenorphine-based regimens.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main Results

We included 27 studies involving 3048 participants. The main comparators were clonidine or lofexidine (14 studies). Six studies compared buprenorphine versusmethadone, and seven compared different rates of buprenorphine dose reduction. We assessed 12 studies as being at high risk of bias in at least one of seven domains of methodological quality. Six of these studies compared buprenorphine with clonidine or lofexidine and two with methadone; the other four studies compared different rates of buprenorphine dose reduction.

For the comparison of buprenorphine and methadone in tapered doses, meta-analysis was not possible for the outcomes of intensity of withdrawal or adverse effects. However, information reported by the individual studies was suggestive of buprenorphine and methadone having similar capacity to ameliorate opioid withdrawal, without clinically significant adverse effects. The meta-analyses that were possible support a conclusion of no difference between buprenorphine and methadone in terms of average treatment duration (mean difference (MD) 1.30 days, 95% confidence interval (CI) -8.11 - 10.72; N=82; studies=2; low quality) or treatment completion rates (risk ratio (RR) 1.04, 95% CI 0.91 - 1.20; N=457; studies=5; moderate quality).

Relative to clonidine or lofexidine, buprenorphinewas associatedwith a lower averagewithdrawal score (indicating less severewithdrawal) during the treatment episode, with an effect size that is considered to be small to moderate (standardised mean difference (SMD) −0.43, 95% CI −0.58 to −0.28; N=902; studies=7; moderate quality). Patients receiving buprenorphine stayed in treatment for longer, with an effect size that is considered to be large (SMD 0.92, 95% CI 0.57-1.27; N=558; studies=5; moderate quality) and were more likely to complete withdrawal treatment (RR 1.59, 95% CI 1.23-2.06; N=1264; studies=12; moderate quality). At the same time there was no significant difference in the incidence of adverse effects, but dropout due to adverse effects may be more likely with clonidine (RR 0.20, 95% CI 0.04-1.15; N=134; studies=3; low quality). The difference in treatment completion rates translates to a number needed to treat for an additional beneficial outcome of 4 (95% CI 3 to 6), indicating that for every four people treated with buprenorphine, we can expect that one additional person will complete treatment than with clonidine or lofexidine.

For studies comparing different rates of reduction of the buprenorphine dose, meta-analysis was possible only for treatment completion, with separate analyses for inpatient and outpatient settings. The results were diverse, and we assessed the quality of evidence as being very low. It remains very uncertain what effect the rate of dose taper has on treatment outcome.

Authors' Conclusions

Buprenorphine is more effective than clonidine or lofexidine for managing opioid withdrawal in terms of severity of withdrawal, duration of withdrawal treatment, and the likelihood of treatment completion.

Buprenorphine and methadone appear to be equally effective, but data are limited. It remains possible that the pattern of withdrawal experienced may differ and that withdrawal symptoms may resolve more quickly with buprenorphine.

It is not possible to draw any *Conclusions* from the available evidence on the relative effectiveness of different rates of tapering the buprenorphine dose. The divergent findings of studies included in this review suggest that there may be multiple factors affecting the response to the rate of dose taper. One such factor could be whether or not the initial treatment plan includes a transition to subsequent relapse prevention treatment with naltrexone. Indeed, the use of buprenorphine to support transition to naltrexone treatment is an aspect worthy of further research.

Most participants in the studies included in this review were male. None of the studies reported outcomes on the basis of sex, preventing any exploration of differences related to this variable. Consideration of sex as a factor influencing response to withdrawal treatment would be relevant research for selecting the most appropriate type of intervention for each individual.

4.2 Opioid antagonists with minimal sedation for opioid withdrawal

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Citation: Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No.: CD002021. DOI: 10.1002/14651858.CD002021.pub4.

Abstract

Background

Managed withdrawal is a necessary step prior to drug-free treatment or as the endpoint of long-term substitution treatment.

Objectives

To assess the effects of opioid antagonists plus minimal sedation for opioid withdrawal. Comparators were placebo as well as more established approaches to detoxification, such as tapered doses of methadone, adrenergic agonists, buprenorphine and symptomatic medications.

Search Methods

We updated our searches of the following databases to December 2016: CENTRAL, MEDLINE, Embase, psycinfo and Web of Science. We also searched two trials registers and checked the reference lists of included studies for further references to relevant studies.

Selection criteria

We included randomised and quasi-randomised controlled clinical trials along with prospective controlled cohort studies comparing opioid antagonists plus minimal sedation versus other approaches or different opioid antagonist regimens for withdrawal in opioid dependent participants.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main Results

Ten studies (6 randomised controlled trials and 4 prospective cohort studies, involving 955 participants) met the inclusion criteria for the review. We considered 7 of the 10 studies to be at high risk of bias in at least one of the domains we assessed.

Nine studies compared an opioid antagonist-adrenergic agonist combination versus a treatment regimen based primarily on an alpha2- adrenergic agonist (clonidine or lofexidine). Other comparisons (placebo, tapered doses of methadone, buprenorphine) made by included studies were too diverse for any meaningful analysis. This review therefore focuses on the nine studies comparing an opioid antagonist (naltrexone or naloxone) plus clonidine or lofexidine versus treatment primarily based on clonidine or lofexidine.

Five studies took place in an inpatient setting, two studies were in outpatients with day care, two used day care only for the first day of opioid antagonist administration, and one study described the setting as outpatient without indicating the level of care provided.

The included studies were heterogeneous in terms of the type of opioid antagonist treatment regimen, the comparator, the outcome measures assessed, and the means of assessing outcomes. As a result, the validity of any estimates of overall effect is doubtful, therefore we did not calculate pooled results for any of the analyses.

The quality of the evidence for treatment with an opioid antagonist-adrenergic agonist combination versus an alpha2-adrenergic agonist is very low. Two studies reported data on peak withdrawal severity, and four studies reported data on the average severity over the period of withdrawal. Peak withdrawal induced by opioid antagonists in combination with an adrenergic agonist appears to be more severe than withdrawal managed with clonidine or lofexidine alone, but the average severity over the withdrawal period is less. In some situations, antagonist-induced withdrawal may be associated with significantly higher rates of treatment completion compared to withdrawal managed with adrenergic agonists. However, this result was not consistent across studies, and the extent of any benefit is highly uncertain.

We could not extract any data on the occurrence of adverse events, but two studies reported delirium or confusion following the first dose of naltrexone. Delirium may be more likely with higher initial doses and with naltrexone rather than naloxone (which has a shorter half-life), but we could not confirm this from the available evidence.

Insufficient data were available to make any *Conclusions* on the best duration of treatment.

Authors' Conclusions

Using opioid antagonists plus alpha2-adrenergic agonists is a feasible approach for managing opioid withdrawal. However, it is unclear whether this approach reduces the duration of withdrawal or facilitates transfer to naltrexone treatment to a greater extent than withdrawal managed primarily with an adrenergic agonist.

A high level of monitoring and support is desirable for several hours following administration of opioid antagonists because of the possibility of vomiting, diarrhoea and delirium.

Using opioid antagonists to induce and accelerate opioid withdrawal is not currently an active area of research or clinical practice, and the research community should give greater priority to investigating approaches, such as those based on buprenorphine, that facilitate the transition to sustained-release preparations of naltrexone.

4.3 Alpha2-adrenergic agonists for the management of opioid withdrawal

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Citation: Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No.: CD002024. DOI: 10.1002/14651858.CD002024.pub5.

Abstract

Background

Withdrawal is a necessary step prior to drug-free treatment or as the endpoint of long-term substitution treatment.

Objectives

To assess the effectiveness of interventions involving the use of alpha2-adrenergic agonists compared with placebo, reducing doses of methadone, symptomatic medications, or an alpha2-adrenergic agonist regimen different to the experimental intervention, for the management of the acute phase of opioid withdrawal.Outcomes included the withdrawal syndrome experienced, duration of treatment, occurrence of adverse effects, and completion of treatment.

Search Methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1946 - November week 2, 2015), EMBASE (January 1985 - November week 2, 2015), psycinfo (1806 - November week 2, 2015), Web of Science, and reference lists of articles.

Selection criteria

Randomised controlled trials comparing alpha2-adrenergic agonists (clonidine, lofexidine, guanfacine, tizanidine) with reducing doses of methadone, symptomatic medications or placebo, or comparing different alpha2-adrenergic agonists to modify the signs and symptoms of withdrawal in participants who were opioid dependent.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration.

Main Results

We included 26 randomised controlled trials involving 1728 participants. Six studies compared an alpha2-adrenergic agonist with placebo, 12 with reducing doses of methadone, four with symptomatic medications, and five compared different alpha2-adrenergic agonists. We assessed 10 studies as having a high risk of bias in at least one of the methodological domains that were considered. We found moderate-quality evidence that alpha2-adrenergic agonists were more effective than placebo in ameliorating withdrawal in terms of the likelihood of severe withdrawal (risk ratio (RR) 0.32, 95% confidence interval (CI) 0.18 to 0.57; 3 studies; 148 participants). We found moderate-quality evidence that completion of treatment was significantly more likely with alpha2-adrenergic agonists compared with placebo (RR 1.95, 95% CI 1.34 - 2.84; 3 studies; 148 participants).

Peak withdrawal severity may be greater with alpha2-adrenergic agonists than with reducing doses of methadone, as measured by the likelihood of severe withdrawal (RR 1.18, 95% CI 0.81 - 1.73; 5 studies; 340 participants; low quality), and peak withdrawal score (standardised mean difference (SMD) 0.22, 95% CI - 0.02 - 0.46; 2 studies; 263 participants; moderate quality), but these differences were not significant and there is no significant difference in severity when considered over the entire duration of the withdrawal episode (SMD0.13, 95%CI -0.24 - 0.49; 3 studies; 119 participants; moderate quality). The signs and symptoms of withdrawal occurred and resolved earlier with alpha2-adrenergic agonists. The duration of treatment was significantly longer with reducing doses of methadone (SMD -1.07, 95% CI -1.31 to -0.83; 3 studies; 310 participants; low quality). Hypotensive or other adverse effects were significantly more likely with alpha2-adrenergic agonists (RR 1.92, 95% CI 1.19 - 3.10; 6 studies; 464 participants; low quality), but there was no

Significant difference in rates of completion of withdrawal treatment (RR 0.85, 95% CI 0.69 - 1.05; 9 studies; 659 participants; low quality).

There were insufficient data for quantitative comparison of different alpha2-adrenergic agonists. Available data suggest that lofexidine does not reduce blood pressure to the same extent as clonidine, but it is otherwise similar to clonidine.

Authors' Conclusions

Clonidine and lofexidine are more effective than placebo for the management of withdrawal from heroin or methadone. We detected no significant difference in efficacy between treatment regimens based on clonidine or lofexidine and those based on reducing doses of methadone over a period of around 10 days, but methadone was associated with fewer adverse effects than clonidine, and lofexidine has a better safety profile than clonidine.

4.4 Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification

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Citation: Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD005031. DOI: 10.1002/14651858.CD005031.pub4.

Abstract

Background

Different pharmacological approaches aimed at opioid detoxification are effective. Nevertheless, a majority of patients relapse to heroin use, and relapses are a substantial problem in the rehabilitation of heroin users.

Some studies have suggested that the sorts of symptoms which are most distressing to addicts during detoxification are psychological rather than physiological symptoms associated with the withdrawal syndrome.

Objectives

To evaluate the effectiveness of any psychosocial plus any pharmacological interventions versus any pharmacological alone for opioid detoxification, in helping patients to complete the treatment, reduce the use of substances and improve health and social status.

Search Methods

We searched the Cochrane Drugs and Alcohol Group trials register (June 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (thecochrane Library Issue 6, 2011), PUBMED(1996-June 2011); EMBASE (January 1980-June 2011);CINAHL (January 2003-June 2008); psycinfo (1985-April 2003) and reference list of articles.

Selection criteria

Randomised controlled trials and controlled clinical trial which focus on any psychosocial associated with any pharmacological intervention aimed at opioid detoxification. People less than 18 years of age and pregnant women were excluded.

Data collection and analysis

Two authors independently assessed trials quality and extracted data.

Main Results

Eleven studies, 1592 participants, fulfilled the criteria of inclusion and were included in the review. The studies considered five different psychosocial interventions and two pharmacological treatments (methadone and buprenorphine). Compared to any pharmacological treatment alone, the association of any psychosocial with any pharmacological was shown to significantly reduce dropouts RR 0.71 (95% CI 0.59 to 0.85), use of opiate during the treatment, RR 0.82 (95% CI 0.71-0.93), at follow up RR 0.66 (95% IC 0.53-0.82) and clinical absences during the treatment RR 0.48 (95%CI 0.38-0.59). Moreover, with the evidence currently available, there are no data supporting a single psychosocial approach.

Authors' Conclusions

Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, use of opiate, participants abstinent at follow-up and clinical attendance. The evidence produced by this review is limited due to the small number of participants included in the studies, the heterogeneity of the assessment or the lack of detailed outcome information that prevented the possibility of cumulative analysis for several outcomes. Nevertheless, it seems desirable to develop adjunct psychosocial approaches that might make detoxification more effective.

4.5 Methadone at tapered doses for the management of opioid withdrawal

Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD003409. DOI: 10.1002/14651858.CD003409.pub4.

Abstract

Background

The evidence of tapered methadone's efficacy in managing opioid withdrawal has been systematically evaluated in the previous version of this review that needs to be updated.

Objectives

To evaluate the effectiveness of tapered methadone compared with other detoxification treatments and placebo in managing opioid withdrawal on completion of detoxification and relapse rate.

Search Methods

We searched: Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2012, Issue 4), pubmed (January 1966 to May 2012), EMBASE (January 1988 to May 2012), CINAHL (2003- December 2007), psycinfo (January 1985 to December 2004), reference lists of articles.

Selection criteria

All randomised controlled trials that focused on the use of tapered methadone versus all other pharmacological detoxification treatments or placebo for the treatment of opiate withdrawal.

Data collection and analysis

Two review authors assessed the included studies. Any doubts about how to rate the studies were resolved by discussion with a third review author. Study quality was assessed according to the criteria indicated in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main Results

Twenty-three trials involving 2467 people were included. Comparing methadone versus any other pharmacological treatment, we observed no clinical difference between the two treatments in terms of completion of treatment, 16 studies 1381 participants, risk ratio (RR) 1.08 (95% confidence interval (CI) 0.97 to 1.21); number of participants abstinent at follow-up, three studies, 386 participants RR 0.98 (95% CI 0.70 to 1.37); degree of discomfort for withdrawal symptoms and adverse events, although it was impossible to pool data for the last two outcomes. These results were confirmed also when we considered the single comparisons: methadone with: adrenergic agonists (11 studies), other opioid agonists (eight studies), anxiolytic (two studies), paiduyangsheng (one study). Comparing methadone with placebo (two studies) more severe withdrawal and more drop-outs were found in the placebo group.

The results indicate that the medications used in the included studies are similar in terms of overall effectiveness, although symptoms experienced by participants differed according to the medication used and the program adopted.

Authors' Conclusions

Data from literature are hardly comparable; programs vary widely with regard to the assessment of outcome measures, impairing the application of meta-analysis. The studies included in this review confirm that slow tapering with temporary substitution of long- acting opioids, can reduce withdrawal severity. Nevertheless, the majority of patients relapsed to heroin use.

4.6 Psychosocial treatment for opiate abuse and dependence

Soraya Mayet[1], Michael Farrell[2], Marica Ferri[3], Laura Amato[4], Marina Davoli[4]

Citation: Mayet S, farrellm, ferrim, Amato L,Davoli M. Psychosocial treatment for opiate abuse and dependence. *Cochranedatabase of Systematic Reviews* 2004, Issue 4. Art. No.: CD004330. DOI: 10.1002/14651858.CD004330.pub2.

Abstract

Background

Substance dependence is a social and public health problem; therefore it is a priority to develop effective treatments. Previous Cochrane reviews have explored the efficacy of pharmacotherapy for opiate dependence. This current review focuses on the role of psychosocial interventions alone for the treatment of

opiate dependence. There is some evidence for the effectiveness of psychosocial interventions, but no systematic review has even been carried out.

Objectives

To assess the efficacy and acceptability of psychosocial interventions alone for treating opiate use disorders.

Search strategy

Electronic searches of databases: Cochrane drugs and Alcohol Group Register of Trials (21 January 2004); Cochrane Central Register of Controlled Trials (CENTRAL-The Cochrane Library, Issue 1, 2004); MEDLINE (1966-2003), LILACS (1982-2003), EMBASE (1980-2003), psycinfo (1872-2003). In addition reference searching, personal communication, conference abstracts, unpublished trials, book chapters on treatment of opioid dependence.

Selection criteria

Randomised controlled trials comparing psychosocial interventions alone versus pharmacological interventions or placebo or non-intervention for treating opioid use disorders.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data.

Main Results

Five trials involving 389 participants were included. These analysed Contingency Management, Brief Reinforcement Based Intensive Outpatient Therapy coupled with contingencymanagement, Cue Exposure therapy, Alternative programformethadonemaintenance Treatment Program Drop-outs (MMTP) and Enhanced Outreach-Counselling Program. All the treatments were studied against the control (standard) treatment; therefore it was not possible to identify which type of psychosocial therapy was most effective.

The main findings were that both Enhanced Outreach Counselling and Brief Reinforcement Based Intensive Outpatient Therapy coupled with Contingency Management had significantly better outcomes than standard therapy regarding relapse to opioid use, re-enrolment in treatment and retention in treatment. At 1-month and 3- month follow up the effects of Reinforcement Based Intensive Outpatient Therapy were not sustained. There was no further follow up of the enhancedoutreach Counselling group. The Alternative Program for MMTP Drop-outs and the behavioural therapies of Cue Exposure and Contingency Management alone were no better than the control. As the studies were heterogeneous, it was not possible to pool the results and perform a meta-analysis.

Authors' Conclusions

The available evidence has low numbers and is heterogeneous. At present psychosocial treatments alone are not adequately proved treatment modalities or superior to any other type of treatment.

It is important to develop a better evidence base for psychosocial interventions to assist in future rationale planning of opioid use drug treatment services.

Appendix 5. Abstracts for key reviews on management of benzodiazepine withdrawal

5.1 Pharmacological interventions for benzodiazepine

Discontinuation in chronic benzodiazepine users

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Citation: Baandrup L, Ebdrup BH, Rasmussen JØ, Lindschou J, Gluud C, Glenthøj BY. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD011481.

DOI: 10.1002/14651858.CD011481.pub2.

Abstract

Background

Prolonged treatment with benzodiazepines is common practice despite clinical recommendations of short-term use. Benzodiazepines are used by approximately 4% of the general population, with increased prevalence in psychiatric populations and the elderly. After long-term use it is often difficult to discontinue benzodiazepines due to psychological and physiological dependence. This review investigated if pharmacological interventions can facilitate benzodiazepine tapering.

Objectives

To assess the benefits and harms of pharmacological interventions to facilitate discontinuation of chronic benzodiazepine use.

Search Methods

We searched the following electronic databases up to October 2017: Cochrane Drugs and Alcohol Group's Specialised Register of Trials, CENTRAL, pubmed, Embase, CINAHL, and isiweb of Science.We also searched clinicaltrials.gov, the WHO ICTRP, and ISRCTN registry, and checked the reference lists of included studies for further references to relevant randomised controlled trials.

Selection criteria

We included randomised controlled trials comparing pharmacological treatment versus placebo or no intervention or versus another pharmacological intervention in adults who had been treated with benzodiazepines for at least two months and/or fulfilled criteria for benzodiazepine dependence (any criteria).

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main Results

We included 38 trials (involving 2543 participants), but we could only extract data from 35 trials with 2295 participants. Many different interventions were studied, and no single intervention was assessed in more

than four trials. We extracted data on 18 different comparisons. The risk of bias was high in all trials but one. Trial Sequential Analysis showed imprecision for all comparisons.

For benzodiazepine discontinuation, we found a potential benefit of valproate at end of intervention (1 study, 27 participants; risk ratio (RR) 2.55, 95% confidence interval (CI) 1.08 to 6.03; very low-quality evidence) and of tricyclic antidepressants at longest follow-up (1 study, 47 participants; RR 2.20, 95% CI 1.27 to 3.82; low-quality evidence).

We found potentially positive effects on benzodiazepine withdrawal symptoms of pregabalin (1 study, 106 participants; mean difference (MD) -3.10 points, 95% CI -3.51 to -2.69; very low-quality evidence), captodiame (1 study, 81 participants; MD -1.00 points, 95% CI -1.13 to -0.87; very low-quality evidence), paroxetine (2 studies, 99 participants; MD -3.57 points, 95% CI -5.34 to -1.80; very low-quality evidence), tricyclic antidepressants (1 study, 38 participants;MD -19.78 points, 95%CI -20.25 to -19.31; very low-quality evidence), and flumazenil (3 studies, 58 participants; standardised mean difference -0.95, 95% CI -1.71 to -0.19; very low-quality evidence) at end of intervention. However, the positive effect of paroxetine on benzodiazepine withdrawal symptoms did not persist

Until longest follow-up (1 study, 54 participants; MD -0.13 points, 95% CI -4.03 to 3.77; very low-quality evidence).

The following pharmacological interventions reduced symptoms of anxiety at end of intervention: carbamazepine (1 study, 36 participants; MD -6.00 points, 95% CI -9.58 to -2.42; very low-quality evidence), pregabalin (1 study, 106 participants; MD -4.80 points, 95% CI -5.28 to -4.32; very low-quality evidence), captodiame (1 study, 81 participants; MD -5.70 points, 95% CI -6.05 to -5.35; very low-quality evidence), paroxetine (2 studies, 99 participants;MD -6.75 points, 95% CI -9.64 to -3.86; very low-quality evidence), and flumazenil (1 study, 18 participants; MD -1.30 points, 95% CI -2.28 to -0.32; very low-quality evidence).

Two pharmacological treatments seemed to reduce the proportion of participants that relapsed to benzodiazepine use: valproate (1 study, 27 participants; RR 0.31, 95%CI 0.11 to 0.90; very low-quality evidence) and cyamemazine (1 study, 124 participants; RR 0.33, 95% CI 0.14 to 0.78; very low-quality evidence). Alpidem decreased the proportion of participants with benzodiazepine discontinuation (1 study, 25 participants; RR 0.41, 95% CI 0.17 to 0.99; number needed to treat for an additional harmful outcome (NNTH) 2.3 participants; low-quality evidence) and increased the occurrence of withdrawal syndrome (1 study, 145 participants; RR 4.86, 95% CI 1.12 to 21.14; NNTH 5.9 participants; low-quality evidence). Likewise, magnesium aspartate decreased the proportion of participants discontinuing benzodiazepines (1 study, 144 participants; RR 0.80, 95% CI 0.66 to 0.96; NNTH 5.8; very low-quality evidence).

Generally, adverse events were insufficiently reported. Specifically, one of the flumazenil trials was discontinued due to severe panic reactions.

Authors' Conclusions

Given the low or very low quality of the evidence for the reported outcomes, and the small number of trials identified with a limited number of participants for each comparison, it is not possible to draw firm *Conclusions* regarding pharmacological interventions to facilitate benzodiazepine discontinuation in chronic benzodiazepine users. Due to poor reporting, adverse events could not be reliably assessed across trials. More randomised controlled trials are required with less risk of systematic errors ('bias') and of random errors ('play of chance') and better and full reporting of patient-centred and long-term clinical outcomes. Such trials ought to be conducted independently of industry involvement.

Appendix 6. Abstracts for key reviews on management of amphetamine withdrawal

6.1 Putting the call out for more research: The poor evidence base for treating methamphetamine withdrawal

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Abstract

Issues. Treatment seeking for methamphetamine withdrawal is low in Australia. Insufficient knowledge regarding the withdrawal syndrome of methamphetamine and the appropriate management of these symptoms may be a contributing factor to the low treatment attendance.

Approach. A systematic review was performed using a range of electronic databases.

Key Findings. Common methamphetamine withdrawal symptoms include symptoms relating to depression, agitation, cognitive impairment and fatigue. These symptoms may last anywhere from a few days to a few months. Methamphetamine withdrawal is most commonly undertaken in an outpatient setting, and psychosocial interventions remain the primary treatment approach in Australia. Two withdrawal scales (Amphetamine Withdrawal Questionnaire and Amphetamine Cessation Symptom Assessment) have been validated for the assessment of methamphetamine withdrawal. Only a small number of medications for methamphetamine withdrawal have been investigated, and to date no medications stand out over the others.

Implications. Current recommendations for methamphetamine withdrawal tend to be based on clinical opinion and subsequently vary between settings. More research in the area is essential to ensure the development of more targeted, timely and effective withdrawal treatment interventions.

Conclusion. The review exposed a lack of well-conducted research targeted towards the management of methamphetamine withdrawal. Further research is essential, and should focus on understanding the nature of methamphetamine withdrawal, its duration, course and effective treatment.[Pennay AE, Lee NK. Putting the call out for more research: The poor evidence base for treating methamphetamine withdrawal. Drug Alcohol Rev 2010]

6.2 Treatment for amphetamine withdrawal

Cochrane Systematic Review - Intervention Version published: 15 April 2009

Steven J Shoptaw, Uyen Kao, Keith Heinzerling, Walter Ling

Abstract

Background

Few studies examined treatments for amphetamine withdrawal, although it is a common problem among amphetamine users. Its symptoms, in particular intense craving, may be a critical factor leading to relapse to amphetamine use. In clinical practice, medications for cocaine withdrawal are commonly used to manage amphetamine withdrawal although the pharmacodynamic and pharmacokinetic properties of these two illicit substances are different.

Objectives

To assess the effectiveness of pharmacological alone or in combination with psychosocial treatment for amphetamine withdrawals on discontinuation rates, global state, withdrawal symptoms, craving, and other outcomes.

Search Methods

MEDLINE (1966 - 2008), CINAHL (1982 - 2008), PsycINFO (1806 - 2008), CENTRAL (Cochrane Library 2008 issue 2), references of obtained articles.

Selection criteria

All randomised controlled and clinical trials evaluating pharmacological and or psychosocial treatments (alone or combined) for people with amphetamine withdrawal symptoms.

Data collection and analysis

Two authors evaluated and extracted data independently. The data were extracted from intention-to-treat analyses. The Relative Risk (RR) with the 95% confidence interval (95% CI) was used to assess dichotomous outcomes. The Weighted Mean Difference (WMD) with 95% CI was used to assess continuous outcomes.

Main Results

Four randomised controlled trials (involving 125 participants) met the inclusion criteria for the review. Two studies found that amineptine significantly reduced discontinuation rates and improved overall clinical presentation, but did not reduce withdrawal symptoms or craving compared to placebo. The benefits of mirtazapine over placebo for reducing amphetamine withdrawal symptoms were not as clear. One study suggested that mirtazapine may reduce hyperarousal and anxiety symptoms associated with amphetamine withdrawal. A more recent study failed to find any benefit of mirtazapine over placebo on retention or on amphetamine withdrawal symptoms.

Authors' Conclusions

No medication is effective for treatment of amphetamine withdrawal. Amineptine showed reduction in discontinuation rates and improvement in clinical presentation compared to placebo, but had no effect on reducing withdrawal symptoms or craving. In spite of these limited benefits, amineptine is not available for use due to concerns over abuse liability when using the drug. The benefits of mirtazapine as a withdrawal agent are less clear based on findings from two randomised controlled trials: one report showed improvements in amphetamine withdrawal symptoms over placebo; a second report showed no differences in withdrawal symptoms compared to placebo. Further potential treatment studies should examine medications that increase central nervous system activity involving dopamine, norepinephrine and/or serotonin neurotransmitters, including mirtazapine.

Appendix 7. Abstracts for key reviews on management of GHB withdrawal

7.1 Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review

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Abstract

1,4-butanediol (1,4-BD) is an industrial solvent that is metabolized to gamma-hydroxybutyrate (GHB), a gamma-aminobutyric acid agonist and central nervous system depressant. GHB and its analogues are popular drugs of abuse. Withdrawal from these agents is characterized by autonomic instability and altered mental status. We report a case of withdrawal from 1,4-BD lasting 6 days and complicated by new onset of seizures and rhabdomyolysis. In addition, we conducted a systematic review of the English literature pertaining to withdrawal from GHB, 1,4-BD and gamma-butyrolactone (GBL). Data collected from source articles included last use prior to symptom onset, clinical features on presentation, duration of symptoms and outcome. Twenty-seven studies with 57 episodes of withdrawal were included. Thirty-six cases (63%) involved GHB, 3 cases (5%) involved 1,4-BD and 18 (32%) involved GBL. The most common patient symptoms were tremor (67%), hallucinations (63%), tachycardia (63%) and insomnia (58%). Seizures and rhabdomyolysis each occurred in 7% of cases, but only 1 death occurred. Emergency physicians must consider withdrawal from these agents when patients present with clinical features suggestive of a sedative-hypnotic withdrawal syndrome.

Appendix 8. Abstracts for Key Reviews on Psychosocial Intervention

J Subst Abuse Treat. 2015 May;52:31-9. doi: 10.1016/j.jsat.2014.11.009. Epub 2014 Dec 3.

8.1 Patient and program factors that bridge the detoxification-treatment gap: a structured evidence review.

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Abstract

Although completion of detoxification (detox) and a successful transition from detox to substance use disorder (SUD) treatment and/or mutual-help groups are associated with better SUD outcomes, many patients do not complete detox or do not receive SUD care following detox. The purpose of this structured evidence review, summarizing data extraction on a yield of 26 articles, is to identify patient, program, and system factors associated with the outcomes of completion of alcohol detox and successful transitions from alcohol detox to SUD treatment and mutual-help group participation. The review found wide variability among studies in the rates at which patients complete a detox episode (45 to 95%) and enter SUD treatment or mutual-help groups after detox (14 to 92%). Within program factors, behavioral practices that contribute to both detox completion and transitioning to SUD care after detox entail involving the patient's family and utilising motivational-based approaches. Such practices should be targeted at younger patients, who are less likely to complete detox. Although more studies using a randomised controlled trial design are needed, the evidence suggests that barriers to detox completion and transition to SUD care can be overcome to improve patient outcomes.

Cochrane Database Syst Rev. 2011 Sep 7;(9):CD005031. doi: 10.1002/14651858.CD005031.pub4.

8.2 Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification

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Abstract

Background:

Different pharmacological approaches aimed at opioid detoxification are effective. Nevertheless a majority of patients relapse to heroin use, and relapses are a substantial problem in the rehabilitation of heroin users. Some studies have suggested that the sorts of symptoms which are most distressing to addicts during detoxification are psychological rather than physiological symptoms associated with the withdrawal syndrome.

OBJECTIVES:

To evaluate the effectiveness of any psychosocial plus any pharmacological interventions versus any pharmacological alone for opioid detoxification, in helping patients to complete the treatment, reduce the use of substances and improve health and social status.

SEARCH STRATEGY:

We searched the Cochrane Drugs and Alcohol Group trials register (June 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 6, 2011), PUBMED (1996 to June 2011); EMBASE (January 1980 to June 2011); CINAHL (January 2003 to June 2008); PsycINFO (1985 to April 2003) and reference list of articles.

SELECTION CRITERIA:

Randomised controlled trials and controlled clinical trial which focus on any psychosocial associated with any pharmacological intervention aimed at opioid detoxification. People less than 18 years of age and pregnant women were excluded.

DATA COLLECTION AND ANALYSIS:

Two authors independently assessed trials quality and extracted data.

MAIN Results:

Eleven studies, 1592 participants, fulfilled the criteria of inclusion and were included in the review. The studies considered five different psychosocial interventions and two pharmacological treatments (methadone and buprenorphine). Compared to any pharmacological treatment alone, the association of any psychosocial with any pharmacological was shown to significantly reduce dropouts RR 0.71 (95% CI 0.59 to 0.85), use of opiate during the treatment, RR 0.82 (95% CI 0.71 to 0.93), at follow up RR 0.66 (95% IC 0.53 to 0.82) and clinical absences during the treatment RR 0.48 (95%CI 0.38 to 0.59). Moreover, with the evidence currently available, there are no data supporting a single psychosocial approach.

AUTHORS' CONCLUSIONS:

Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, use of opiate, participants abstinent at follow-up and clinical attendance. The evidence produced by this review is limited due to the small number of participants included in the studies, the heterogeneity of the assessment or the lack of detailed outcome information that prevented the possibility of cumulative analysis for several outcomes. Nevertheless it seems desirable to develop adjunct psychosocial approaches that might make detoxification more effective

Cochrane Database Syst Rev. 2015;(5):CD009652.

8.3 Psychosocial interventions for benzodiazepine harmful use, abuse or dependence.

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Abstract

Background:

Benzodiazepines (BZDs) have a sedative and hypnotic effect upon people. Short term use can be beneficial but long term BZD use is common, with several risks in addition to the potential for dependence in both opiate and non-opiate dependent patients.

OBJECTIVES:

To evaluate the effectiveness of psychosocial interventions for treating BZD harmful use, abuse or dependence compared to pharmacological interventions, no intervention, placebo or a different

psychosocial intervention on reducing the use of BZDs in opiate dependent and non-opiate dependent groups.

SEARCH Methods:

We searched the Cochrane Central Register of Controlled Trials (CENTRAL- the Cochrane Library issue 12, 2014) which includes the Cochrane Drugs and Alcohol Group Specialized Register; PubMed (from 1966 to December 2014); EMBASE (from 1988 to December 2014); CINAHL Cumulative Index to Nursing and AlliedHealth Literature (1982 to September 2013); PsychINFO (1872 to December 2014); ERIC (Education Resources Information Centre, (January 1966 to September 2013); All EBM Reviews (1991 to September 2013, Ovid Interface); AMED (Allied & Alternative Medicine) 1985 to September 2013); ASSIA (Applied Social Sciences Index & abstracts (1960 to September 2013); LILACS (January 1982 to September 2013);Web of Science (1900 to December 2014);Electronic Grey Literature Databases: Dissertation Abstract Index to Theses.

SELECTION CRITERIA:

Randomised controlled trials examining the use of a psychosocial intervention to treat BZDs versus pharmacological interventions, no intervention, placebo or a different psychosocial intervention on reducing the use of BZDs in opiate dependent and non-opiate dependent groups.

DATA COLLECTION AND ANALYSIS:

We used the standard methodological procedures outlined in Cochrane Guidelines.

MAIN Results:

Twenty-five studies including 1666 people met the inclusion criteria. The studies tested many different psychosocial interventions including cognitive behavioural therapy (CBT) (some studies with taper, other studies with no taper), motivational interviewing (MI),letters to patients advising them to reduce or quit BZD use, relaxation studies, counselling delivered electronically and advice provided by a general practitioner (GP). Based on the data obtained, we performed two meta-analyses in this Cochrane review: one assessing the effectiveness of CBT plus taper versus taper only (575 participants), and one assessing MI versus treatment as usual (TAU) (80 participants).There was moderate quality of evidence that CBT plus taper was more likely to result in successful discontinuation of BZDs within four weeks post treatment compared to taper only (Risk ratio (RR) 1.40, 95% confidence interval (CI) 1.05 to 1.86; nine trials, 423 participants) and moderate quality of evidence at three month follow-up (RR 1.51, 95% CI 1.15 to 1.98) in favour of CBT (taper)for 575 participants. The effects were less certain at 6, 11, 12, 15 and 24 months follow-up. The effect of CBT on reducing BZDs by >50% was uncertain for all time points examined due to the low quality evidence. There was very low quality evidence for the effect on drop-outs at any of the time intervals; post-treatment (RR 1.05, 95% CI 0.66 to 1.66), three month follow-up (RR 1.71, 95% CI0.16 to 17.98) and six month follow-up (RR 0.70, 95% CI 0.17 to 2.88).Based on the very low quality of evidence available, the effect of MI versus TAU for all the time intervals is unclear; post treatment(RR 4.43, 95% CI 0.16 to 125.35; two trials, 34 participants), at three month follow-up (RR 3.46, 95% CI 0.53 to 22.45; four trials,80 participants), six month follow-up (RR 0.14, 95% CI 0.01 to 1.89) and 12 month follow-up (RR 1.25, 95% CI 0.63 to 2.47).There was very low quality of evidence to determine the effect of MI on reducing BZDs by >50% at three month follow-up (RR 1.52,95% CI 0.60 to 3.83) and 12 month follow-up (RR 0.87, 95% CI 0.52 to 1.47). The effects on drop-outs from treatment at any of e time intervals between the two groups were uncertain due to the wide CIs; post-treatment (RR 0.50, 95% CI 0.04 to 7.10), three month follow-up (RR 0.46, 95% CI 0.06 to 3.28), six month follow-up (RR 8.75, 95% CI 0.61 to 124.53) and 12 month follow-up(RR 0.42, 95% CI 0.02 to 7.71).The following interventions reduced BZD use - tailored GP letter versus generic GP letter at 12 month follow-up (RR 1.70, 95%CI 1.07 to 2.70; one trial, 322 participants), standardised interview versus TAU at six month follow-up (RR 13.11, 95% CI 3.25 to 52.83; one trial, 139 participants) and 12 month follow-up (RR 4.97, 95% CI 2.23 to 11.11), and relaxation versus TAU at three month follow-up (RR 2.20, 95% CI 1.23 to 3.94).There was insufficient supporting evidence for the remaining interventions.We performed a 'Risk of bias' assessment on all included studies. We assessed the quality of the evidence as high quality for

random sequence generation, attrition bias and reporting bias; moderate quality for allocation concealment, performance bias for objective outcomes, and detection bias for objective outcomes; and low quality for performance bias for subjective outcomes and detection bias for subjective outcomes. Few studies had manualised sessions or independent tests of treatment fidelity; most follow-up periods were less than 12 months.Based on decisions made during the implementation of protocol methods to present a manageable summary of the evidence we did not collect data on quality of life, self-harm or adverse events.

AUTHORS' CONCLUSIONS:

CBT plus taper is effective in the short term (three month time period) in reducing BZD use. However, this is not sustained at six months and subsequently. Currently there is insufficient evidence to support the use of MI to reduce BZD use. There is emerging evidence to suggest that a tailored GP letter versus a generic GP letter, a standardised interview versus TAU, and relaxation versus TAU could be effective for BZD reduction. There is currently insufficient evidence for other approaches to reduce BZD use.

Appendix 9. Abstracts for key reviews on physical therapies

9.1 Systematic review of acupuncture for the treatment of alcohol withdrawal syndrome

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(http:// dx. doi. org/ 10. 1136/acupmed- 2016- 011283).

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To cite: Liu X, Qin Z, Zhu X, et al. Acupunct Med 2018;36:275–283.

Original paper

Abstract

Background Acupuncture has been used as a potential therapy for alcohol withdrawal syndrome (AWS), but evidence for its effects on this condition is limited.

Objective To assess the effects and safety of acupuncture for AWS.

Data sources Central Register of Controlled Trials (CENTRAL), PubMed, Embase, the Cochrane Library, PsycINFO, Chinese Biomedicine Literature (CBM), China National Knowledge Infrastructure (CNKI) and Wan-Fang Database were searched from their inception to August 2016.

Study eligibility criteria Randomised controlled trials (RCTs) of drug plus acupuncture or acupuncture alone for the treatment of AWS were included.

Data collection and analysis Continuous data were expressed as mean difference (MD) with 95% confidence intervals (95% CI). Dichotomous data were expressed as risk ratio (RR) with 95% CI.

Results Eleven RCTs with 875 participants were included. In the acute phase, two trials reported no difference between drug plus acupuncture and drug plus sham acupuncture in the reduction of craving for alcohol; however, two positive trials reported that drug plus acupuncture was superior to drug alone in the alleviation of psychological symptoms. In the protracted phase, one trial reported acupuncture was superior to sham acupuncture in reducing the craving for alcohol, one trial reported no difference between acupuncture and drug (disulfiram), and one trial reported acupuncture was superior to sham acupuncture for the alleviation of psychological symptoms. Adverse effects were tolerable and not severe.

Conclusion There was nosignificant difference between acupuncture (plus drug) and sham acupuncture (plus drug) with respect to the primary outcome measure of craving for alcohol among participants with AWS, and no difference in completion rates (pooled results). There was limited evidence from individual trials that acupuncture may reduce alcohol craving in the protracted phase and help alleviate psychological symptoms; however, given concerns about the quantity and quality of included studies, further large-scale and well-conducted RCTs are needed.

Drug Alcohol Depend. 2016 Jun 1;163:1-15. doi: 10.1016/j.drugalcdep.2016.02.034. Epub 2016 Mar 3.

9.2 Acupuncture for substance use disorders: A systematic review and meta-analysis

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Abstract

Background:

This systematic review aims to estimate the effects of acupuncture for adults with substance use disorders (SUDs).

Methods:

We searched 7 electronic databases and bibliographies of previous studies to identify eligible randomised trials. Two independent reviewers screened citations, extracted data, and assessed risks of bias. We performed random effects meta-analyses. We assessed quality of evidence using the GRADE approach.

Results:

We included 41 studies with 5,227 participants. No significant differences were observed between acupuncture and comparators (passive controls, sham acupuncture, treatment as usual, and active interventions) at post-intervention for relapse (SMD -0.12; 95%CI -0.46 to 0.22; 10 RCTs), frequency of substance use (SMD -0.27; -2.67 to 2.13; 2 RCTs), quantity of substance use (SMD 0.01; -0.40 to 0.43; 3 RCTs), and treatment dropout (OR 0.82; 0.63 to 1.09; 22 RCTs). We identified a significant difference in favor of acupuncture versus comparators for withdrawal/craving at post-intervention (SMD -0.57, -0.93 to -0.20; 20 RCTs), but we identified evidence of publication bias. We also identified a significant difference in favor of acupuncture versus comparators for anxiety at post-intervention (SMD -0.74, -1.15 to -0.33; 6 RCTs). Results for withdrawal/craving and anxiety symptoms were not significant at longer follow-up. Safety data (12 RCTs) suggests little risk of serious adverse events, though participants may experience slight bleeding or pain at needle insertion sites.

CONCLUSIONS:

Available evidence suggests no consistent differences between acupuncture and comparators for substance use. Results in favor of acupuncture for withdrawal/craving and anxiety symptoms are limited by low quality bodies of evidence.

PLoS One. 2014 Oct 16;9(10):e110728. doi: 10.1371/journal.pone.0110728. eCollection 2014.

9.3 Impact of physical exercise on substance use disorders: a meta-analysis

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Abstract

OBJECTIVE:

The goal of this meta-analysis was to examine whether long-term physical exercise could be a potential effective treatment for substance use disorders (SUD).

Methods:

The PubMed, Web of Science, Elsevier, CNKI and China Info were searched for randomised controlled trials (RCT) studies in regards to the effects of physical exercise on SUD between the years 1990 and 2013. Four main outcome measures including abstinence rate, withdrawal symptoms, anxiety, and depression were evaluated.

Results:

Twenty-two studies were integrated in the meta-analysis. The results indicated that physical exercise can effectively increase the abstinence rate (OR=1.69 (95% CI: 1.44, 1.99), z=6.33, p<0.001), ease withdrawal

symptoms (SMD=-1.24 (95% CI: -2.46, -0.02), z=-2, p<0.05), and reduce anxiety (SMD=-0.31 (95% CI: -0.45, -0.16), z = -4.12, p<0.001) and depression (SMD = -0.47 (95% CI: -0.80, -0.14), z=-2.76, p<0.01). The physical exercise can more ease the depression symptoms on alcohol and illicit drug abusers than nicotine abusers, and more improve the abstinence rate on illicit drug abusers than the others. Similar treatment effects were found in three categories: exercise intensity, types of exercise, and follow-up periods.

CONCLUSIONS:

The moderate and high-intensity aerobic exercises, designed according to the Guidelines of American College of Sports Medicine, and the mind-body exercises can be an effective and persistent treatment for those with SUD.

Alcohol Alcohol. 2018 Nov 1;53(6):719-727. doi: 10.1093/alcalc/agy066.

9.4 Integrated treatment at the first stage: increasing motivation for alcohol patients with comorbid disorders during inpatient detoxification

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Abstract

Aims:

Co-occurring mental disorders can complicate the detoxification treatment process and outcome. The aim of this study is to examine whether a brief psychoeducational group counseling session during detoxification treatment can increase the motivation for and utilisation of subsequent treatments.

Short summary:

Interventions increased utilisation of post-detoxification treatment and reduced alcohol-related readmissions. Higher depression or trauma scores were associated with higher rates of utilisation of treatment.

Methods:

Patients received either a brief manualised group intervention on the interrelation of alcohol use disorder (AUD) and major depression (MD) or AUD and post-traumatic stress disorder (PTSD) or a cognitive training session (control group). Of the 784 patients treated in the study period, 171 participants were quasi-randomly allocated to groups. Self-reported motivation was measured before and after intervention, transition into AUD treatment and readmissions were collected after detoxification treatment.

Results:

Participating in any of the intervention groups increased the utilisation of AUD treatment after inpatient detoxification ($\chi 2=6.15$, P=0.02) and decreased readmissions 6 months after discharge ($\chi 2=7.46$, P=0.01). Depression and trauma scores moderated the effect: associations with the utilisation of post-detoxification treatment were found in participants with higher depression (OR=5.84, 95% CI=1.17-29.04) or trauma scores (OR=10.17, 95% CI=1.54-67.1).

Conclusions:

An integrated intervention approach for dual diagnosis at the beginning of the treatment can increase motivation for continued AUD treatment. Especially affected dual diagnosis patients can benefit from this treatment.

Alcohol Clin Exp Res. 2016 Sep;40(9):2011-9. doi: 10.1111/acer.13163. Epub 2016 Aug 4.

9.5 Cognitive bias modification training during inpatient alcohol detoxification reduces early relapse: A randomized controlled trial

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Abstract

Background:

Relapse is common in alcohol-dependent individuals and can be triggered by alcohol-related cues in the environment. It has been suggested that these individuals develop cognitive biases, in which cues automatically capture attention and elicit an approach action tendency that promotes alcohol seeking. The study aim was to examine whether cognitive bias modification (CBM) training targeting approach bias could be delivered during residential alcohol detoxification and improve treatment outcomes.

Methods:

Using a 2-group parallel-block (ratio 1:1) randomised controlled trial with allocation concealed to the outcome assessor, 83 alcohol-dependent inpatients received either 4 sessions of CBM training where participants were implicitly trained to make avoidance movements in response to pictures of alcoholic beverages and approach movements in response to pictures of nonalcoholic beverages, or 4 sessions of sham training (controls) delivered over 4 consecutive days during the 7-day detoxification program. The primary outcome measure was continuous abstinence at 2 weeks postdischarge. Secondary outcomes included time to relapse, frequency and quantity of alcohol consumption, and craving. Outcomes were assessed in a telephonic follow-up interview.

Results:

Seventy-one (85%) participants were successfully followed up, of whom 61 completed all 4 training sessions. With an intention-to-treat approach, there was a trend for higher abstinence rates in the CBM group relative to controls (69 vs. 47%, p=0.07); however, a per-protocol analysis revealed significantly higher abstinence rates among participants completing 4 sessions of CBM relative to controls (75 vs. 45%, p=0.02). Craving score, time to relapse, mean drinking days, and mean standard drinks per drinking day did not differ significantly between the groups.

CONCLUSIONS:

This is the first trial demonstrating the feasibility of CBM delivered during alcohol detoxification and supports earlier research suggesting it may be a useful, low-cost adjunctive treatment to improve treatment outcomes for alcohol-dependent patients.

Appendix 10. Abstracts for special populations

10A Aboriginal people

10A1 Aboriginal and Torres Strait Islander health services report, 2010-11: OATSIH services reporting - key Results

Release Date: 04 Oct 2012

Author: AIHW

Key Findings:

Primary health care

In 2010-11, Aboriginal and Torres Strait Islander primary health-care services, funded by the Office for Aboriginal and Torres Strait Islander Health (OATSIH), provided 2.5 million episodes of health care to about 428,000 clients. Compared with 2009-10, there was a 4% increase in episodes of care and a 1% decrease in the number of clients reported. More than three-quarters of clients (77% or 331,000) were Aboriginal or Torres Strait Islander.

About 5,500 full-time equivalent (FTE) staff, including 3,600 FTE health staff and 1,900 FTE managerial, administrative, support and other staff, worked and were paid by their service. This is 14% higher than in the previous year. These staff were assisted in the delivery of primary healthcare by 193 FTE visiting health professionals paid for by other organisations.

Aboriginal or Torres Strait Islander people held more than half (54%) of the FTE positions.

Substance use

In 2010-11, Aboriginal and Torres Strait Islander stand-alone substance use services (funded by OATSIH) provided treatment and assistance for substance use issues to about 28,600 clients, an increase of 9% compared with 2009-10. More than three-quarters of clients (76% or 21,600) were Aboriginal or Torres Strait Islander.

About 880 FTE staff from a variety of health (490 FTE) and managerial, administrative, support and other staff (390 FTE) worked at and were paid by their service. These staff were assisted in the delivery of substance use treatment by 51 FTE visiting health professionals paid for by other organisations.

Aboriginal or Torres Strait Islander people held more than half (61%) of the 880 FTE positions.

Bringing Them Home and Link Up counselling

In 2010-11, Bringing Them Home and Link Up counselling services (funded by OATSIH) provided counselling to about 11,800 clients, an increase of about 10% compared with 2009-10. Most (92% or 10,900) clients were Aboriginal or Torres Strait Islander.

These services reported 44,400 client contacts, which is 22% lower than in the previous year, 2009-10.

A total of 142 counsellors (124 FTE) were employed by the counselling services. Most services (83%) had at least one Aboriginal or Torres Strait Islander counsellor.

Data quality

The majority of 2010-11 OSR questionnaires received had one or more of the following data quality issues: missing data, inappropriate data provided for a question, or lack of coherence of data from two or more questions. These issues were resolved in consultation with the services submitting the data.

10A.2 Culture in treatment for Aboriginal Australian men in New South Wales residential drug and alcohol rehabilitation

Thesis - Doctor of Psychology (Clinical), School of Psychology, 2013.

Berry, Stacey L., Culture in treatment for Aboriginal Australian men in New South Wales residential drug and alcohol rehabilitation services, Doctor of Psychology (Clinical) thesis, School of Psychology, University of Wollongong, 2013. https://ro.uow.edu.au/theses/3758

Abstract

Aboriginal people are one of the populations most in need of mental health and drug and alcohol services within Australia, although it has been questioned whether treatment programs are adequately sensitive to and inclusive of relevant aspects of Aboriginal culture. The primary *Objectives* of the research were to investigate 1) which cultural activities were offered in residential drug and alcohol rehabilitation programs for Aboriginal Australian menof service providers and service users, and 3) whether cultural engagement predicted outcomes.

Study 1 assessed the feasibility of collecting outcome data from a residential drug and alcohol rehabilitation program, and the usability of a recently developed Aboriginal-specific measure of empowerment, the Growth and Empowerment Measure (GEM: Haswell et al. 2010). Study 1 also explored consumer perceptions of the helpfulness of cultural activities within the treatment program. Participants were 57 Aboriginal and 46 non-Aboriginal males attending one residential drug and alcohol rehabilitation service in New South Wales (NSW), Australia. Results from Study 1 identified the need for more specific measures of cultural engagement (Study 2) and informed the design of Study 3.

Study 2 examined the views of service providers regarding the cultural activities offered within treatment programs for Aboriginal Australians. Participants were the managers of five residential drug and alcohol rehabilitation services in NSW. Study 2 also describes the development and content validation of a measure of cultural engagement for use with Aboriginal Australians, the Aboriginal Cultural Engagement Survey (ACES: Berry, Crowe, & Deane, 2012). Development involved the participation of the Aboriginal community in four phases, and results demonstrate excellent content validity both at the item level (all items above .80) and full scale level (.98).

Study 3 assessed the outcomes of empowerment and mental health for Aboriginal males attending residential drug and alcohol rehabilitation services. The association between outcomes and cultural engagement, both in everyday life and while in drug and alcohol treatment, were also investigated. Study 3 examined the preferences of service users regarding the cultural activities offered in treatment programs, including their perceived relevance and helpfulness. Participants were 101 Australian Aboriginal male clients attending five residential drug and alcohol rehabilitation services in NSW. Results of hierarchical multiple regression analysis indicate that cultural engagement in everyday life significantly predicted empowerment but not other measures of mental health. Cultural engagement undertaken within treatment programs was not associated with empowerment or mental health. Potential explanations for the differential effects of cultural engagement are considered. The opinions of service users are presented, including the desire for treatment programs to provide more education regarding history/heritage and more time on Country. Recommendations are made regarding ways to enhance the effectiveness of cultural activities within drug and alcohol rehabilitation programs.

10A.3 Indigenous residential treatment programs for drug and alcohol problems: Current status and options for improvement

M. Brady

Discussion PAPER NO. 236. Centre for Aboriginal Economic Policy Research

Summary

Commonwealth-funded residential rehabilitation programs for Indigenous problem drinkers or drug users were established in the 1970s as community controlled organisations that were separate from Aboriginal Medical Services and independent of State drug and alcohol units. Structural and political factors during their development and growth have meant that many such programs are now poorly networked with

sources of professional advice and other types of therapeutic community. They remain wedded to a single treatment regime and are insulated from change. On the other hand, some offer a range of vocational a skills-based activities as well as providing referrals for effective counselling.

Trends in Indigenous drug and alcohol misuse are changing, with a decline in alcohol use and an increase in opiate use as the principal drug problem for those receiving services. Residential programs need to be informed and competent in order to respond to these changes. Fruitful avenues to pursue in order to improve their knowledge base and perspectives include providing better training for board members as well as facilitating exchanges with other, non-Indigenous therapeutic communities. Collaboration in quality improvement reviews, closer partnerships with local State drug and alcohol services and non-government organisation networks, and mandatory participation in the many available in-service training programs would contribute to achieving these goals.

10A.4 Healing at Home: Developing a Model for Ambulatory Alcohol "Detox" in an Aboriginal Community Controlled Health Service

Brett, J., Dawson, A., Ivers, R., Lawrence, L., Barclay, S. & Conigrave, K. (2017). Healing at Home: Developing a Model for Ambulatory Alcohol "Detox" in an Aboriginal Community Controlled Health Service. International Journal of Indigenous Health, 12(1), 24-38.

Abstract

Indigenous Peoples who have been colonized typically face a greater burden of injury, disease, and social disruption associated with alcohol use (Kirmayer, Brass, & Tait, 2000). However, they often also encounter many barriers to accessing treatment for alcohol use disorders (Gray, Stearne, Wilson, & Doyle, 2010).

Aboriginal and Torres Strait Islander Australians (here described as Aboriginal Australians) experience 3-8 times the prevalence of alcohol-related illness, injury, and death than the general population (Calabria, Doran, Vos, Shakeshaft, & Hall, 2010). But their barriers to treatment access for alcohol dependence include transport difficulties, fear of discrimination, and lack of culturally secure services

(Brett et al. 2016; Conigrave et al. 2012; Gray, Stearne, et al. 2010; Teasdale et al. 2008).

10A.5 Outpatient alcohol withdrawal management for Aboriginal and Torres Strait Islander peoples

Brett, Jonathan; Lawrence, Leanne; Ivers, Rowena and Conigrave, Katherine. Outpatient alcohol withdrawal management for Aboriginal and Torres Strait Islander peoples [online]. Australian Family Physician, Vol. 43, No. 8, Aug 2014: 563-566.

Abstract: *Background*: There is concern from within Aboriginal and Torres Strait Islander communities about the lack of access to alcohol withdrawal management ('detox') services. Outpatient detox is described within national Australian guidelines as a safe option for selected drinkers. However, uncertainly exists as to how suited Aboriginal and Torres Strait Islander peoples are to this approach. Methods: Consultations were conducted with stakeholders of four health services providing outpatient detox for Aboriginal and Torres Strait Islander peoples in NSW. Thematic analysis was performed to determine elements perceived as important for success. Results: Key themes that emerged were individual engagement, flexibility, assessment of suitability, Aboriginal staff and community engagement, practical support, counselling, staff education and support, coping with relapse and contingency planning. Discussion: There is a need to improve access to alcohol detox services for Aboriginal and Torres Strait Islander peoples. The outpatient setting seems to be a feasible and safe environment to provide this kind of service for selected drinkers.

10A.5 The acceptability to Aboriginal Australians of a family-based intervention to reduce alcohol-related harms.

Calabria B, Clifford A, Shakeshaft A, Allan J, Bliss D, Doran C.

Drug Alcohol Rev. 2013 May;32(3):328-32. doi: 10.1111/j.1465-3362.2012.00525.x. Epub 2012 Nov 1.

Abstract

INTRODUCTION AND AIMS:

Cognitive-behavioural interventions that use familial and community reinforcers in an individual's environment are effective for reducing alcohol-related harms. Such interventions have considerable potential to reduce the disproportionately high burden of alcohol-related harm among Aboriginal Australians if they can be successfully tailored to their specific needs and circumstances. The overall aim of this paper is to describe the perceived acceptability of two cognitive-behavioural interventions, the Community Reinforcement Approach (CRA) and Community Reinforcement and Family Training (CRAFT), to a sample of Aboriginal people.

DESIGN AND *Methods*:

Descriptive survey was administered to 116 Aboriginal people recruited through an Aboriginal Community Controlled Health Service and a community-based drug and alcohol treatment agency in rural New South Wales, Australia.

Results:

Participants perceived CRA and CRAFT to be highly acceptable for delivery in their local Aboriginal community. Women were more likely than men to perceive CRAFT as highly acceptable. Participants expressed a preference for counsellors to be someone they knew and trusted, and who has experience working in their local community. CRA was deemed most acceptable for delivery to individuals after alcohol withdrawal and CRAFT for people who want to help a relative/friend start alcohol treatment. There was a preference for five or more detailed sessions.

Discussion AND *CONCLUSIONS*:

Findings of this study suggest that CRA and CRAFT are likely to be acceptable for delivery to some rural Aboriginal Australians, and that there is potential to tailor these interventions to specific communities.

10A.6 A gendered analysis of Canadian Aboriginal individuals admitted to inpatient substance abuse detoxification: a three-year medical chart review

Callaghan RC, Cull R, Vettese LC, Taylor L.

Am J Addict. 2006 Sep-Oct;15(5):380-6.

Abstract

This study examined gender differences within a sample of Canadian Aboriginal individuals admitted to an inpatient, hospital-based substance abuse detoxification program. Even though alcohol was the most frequent primary drug of detoxification for both genders, women received proportionately higher rates of cocaine or opiate detoxification diagnoses. In addition to a younger age, females reported higher rates of physical and sexual abuse. Women were also administered antidepressants, antibiotic medication protocols, and more medical evaluation tests. It appears that Canadian Aboriginal women have a diverse set of psychological and medical needs. This study demonstrates the need for detoxification programs to address the substantial rates of intravenous drug use and the associated risk of infectious disease (eg, Hepatitis C, HIV) among this treatment-seeking population.

10A.7 Assessment of the Need for Perth-Based Aboriginal Substance Misuse Services: A Report Prepared for the Noongar Alcohol and Substance Abuse Service

Stearne, A. (2002).

National Drug Research Institute, Curtin University of Technology, Perth.

This is a needs assessment of substance misuse services in the Perth metropolitan area (Perth Noongar ATSIC region) for Aboriginal substance users and their families. The report was commissioned by the Noongar Alcohol and Substance Abuse Service (NASAS) to provide a guide for the service needs of their clients. The report found that the current services in Perth were not able to completely meet the needs of Aboriginal clients and further services are required in Perth, particularly residential-based programs.

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10A.8 Factors associated with pretreatment and treatment dropouts: comparisons between Aboriginal and non-Aboriginal clients admitted to medical withdrawal management

Xin Li, Huiying Sun, David C Marsh, and Aslam H Anis; Harm Reduction Journal *2013 10:38*

Abstract

Background

Addiction treatment faces high pretreatment and treatment dropout rates, especially among Aboriginals. In this study we examined characteristic differences between Aboriginal and non-Aboriginal clients accessing an inpatient medical withdrawal management program, and identified risk factors associated with the probabilities of pretreatment and treatment dropouts, respectively.

Methods

2231 unique clients (Aboriginal = 451; 20%) referred to Vancouver Detox over a two-year period were assessed. For both Aboriginal and non-Aboriginal groups, multivariate logistic regression analyses were conducted with pretreatment dropout and treatment dropout as dependent variables, respectively.

Results

Aboriginal clients had higher pretreatment and treatment dropout rates compared to non-Aboriginal clients (41.0% vs. 32.7% and 25.9% vs. 20.0%, respectively). For Aboriginal people, no fixed address (NFA) was the only predictor of pretreatment dropout. For treatment dropout, significant predictors were: being female, having HCV infection, and being discharged on welfare check issue days or weekends. For non-Aboriginal clients, being male, NFA, alcohol as a preferred substance, and being on methadone maintenance treatment (MMT) at referral were associated with pretreatment dropout. Significant risk factors for treatment dropout were: being younger, having a preferred substance other than alcohol, having opiates as a preferred substance, and being discharged on weekends.

Conclusions

Our results highlight the importance of social factors for the Aboriginal population compared to substance-specific factors for the non-Aboriginal population. These findings should help clinicians and decision-makers to recognize the importance of social supports especially housing and initiate appropriate services to improve treatment intake and subsequent retention, physical and mental health outcomes and the cost-effectiveness of treatment.

10A.9 Identity, opportunity and hope: an Aboriginal model for alcohol (and other drug) harm prevention and intervention

Nichols, F (2002).

PhD Thesis, Curtin University, Perth, Australia.

Abstract

The fieldwork for this study was conducted in the West Kimberley region of Western Australia between 1997 and 1999. Qualitative and quantitative information provided by 170 Aboriginal participants enabled an exploration of the context and patterns of Aboriginal alcohol use; Aboriginal perceptions of the alcohol issue, existing interventions, research findings, 'culture' and its role in prevention and intervention; and participants' incorporation of these perceptions into an Aboriginal model for alcohol misuse prevention, intervention and evaluation. Findings were based on the results of individual and focus group interviews, serial model-planning focus groups, documentary data and observation.

Study findings generally suggest that in addition to self-determination and support components, 'cultural context' retains an important role for many remote area Aboriginal people. The findings from a small sub-sample tentatively suggest that 'cultural' disruption, in addition to the socio-economic consequences of colonisation and dispossession, may play an important role in alcohol misuse. Consequently, it appears that in combination with self-determination and support components, the strengthening of a locally-defined 'cultural' context may have an important role in alcohol misuse prevention and intervention - an approach frequently unrepresented in existing symptom-focused models and one inviting further investigation. The model developed by study participants expands significantly on existing symptom-focused approaches through a comprehensive life-enhancement focus on aspects of identity, opportunity and hope. This approach adds depth and meaning to understandings of cultural appropriateness and of culturally relevant models for substance misuse prevention and intervention.

10B People in custody

10B.1 Drug and alcohol use and treatment for Australian Indigenous and non-Indigenous prisoners: demand reduction strategies

Dolan K, Rodas A, Bode A.

Int J Prison Health. 2015;11(1):30-8. doi: 10.1108/IJPH-02-2014-0005.

Abstract

PURPOSE:

The purpose of this paper is to compare the use of drugs and alcohol by Indigenous and non-Indigenous prisoners and examine relevant treatment in Australian prisons.

DESIGN/METHODOLOGY/APPROACH:

Prison authorities were surveyed about alcohol and drug use by prisoners prior to and during imprisonment and drug and alcohol treatment programs in prison. The literature was review for information on alcohol and drug use and treatment in Australian prisons.

FINDINGS:

In 2009, over 80 percent of Indigenous and non-Indigenous inmates smoked. Prior to imprisonment, many Indigenous and non-Indigenous inmates drank alcohol at risky levels (65 vs 47 percent) and used illicit drugs (over 70 percent for both groups). Reports of using heroin (15 vs 21 percent), ATS (21 vs 33 percent), cannabis (59 vs 50 percent) and injecting (61 vs 53 percent) were similarly high for both groups. Prison-based programs included detoxification, Opioid Substitution Treatment, counselling and drug free units, but access was limited especially among Indigenous prisoners.

RESEARCH LIMITATIONS/IMPLICATIONS:

Drug and alcohol use was a significant issue in Australian prisons. Prisoners were over five times more likely than the general population to have a substance use disorder. Imprisonment provides an important opportunity for rehabilitation for offenders. This opportunity is especially relevant to Indigenous prisoners who were more likely to use health services when in prison than in the community and given their vast over representations in prison populations.

PRACTICAL IMPLICATIONS:

Given the effectiveness of treatment in reducing re-offending rates, it is important to expand drug treatment and especially culturally appropriate treatment programs for Indigenous inmates.

ORIGINALITY/VALUE:

Very little is known about Indigenous specific drug and alcohol programs in Australian prisons.

10B.2 Reduction of opiate withdrawal symptoms with use of clonidine in a county jail

Fresquez-Chavez KR, Fogger S.

J Correct Health Care. 2015 Jan;21(1):27-34. doi: 10.1177/1078345814557630. Epub 2014 Nov 26.

Abstract

Increasingly, addicted inmates admitted to jail in New Mexico are in the process of opiate withdrawal. While the standard for opiate detoxification is a narcotic taper, correctional policy restricts opiate use for safety reasons. An alternative for withdrawal is a supportive intervention with clonidine, a non-opiate. Could clonidine be beneficial for acute opiate withdrawal symptoms in this population? Fifty-five inmates (37 male and 18 female) volunteered to participate in assessing clonidine for the reduction of withdrawal symptoms. Symptoms were assessed with the Subjective Opiate Withdrawal Scale and treated with a standard clonidine protocol. Clonidine significantly decreased the mean scores at 1 and 4 hours after medication use. Clonidine for opiate withdrawal reduces symptoms when opiate-assisted detoxification is not available.

10B.3 Prison based detoxification for opioid dependence: a randomised double blind controlled trial of lofexidine and methadone

Howells C, Allen S, Gupta J, Stillwell G, Marsden J, Farrell M. Drug Alcohol Depend. 2002 Jul 1;67(2):169-76.

Abstract

This paper reports results from the first controlled trial of opioid withdrawal treatment in the UK using lofexidine in a prison setting. Seventy-four opioid dependent male inmates at a Southern England prison were randomised to receive either methadone (the standard prison treatment) or lofexidine using a randomised double-blind design. No significant statistical difference between the treatment groups was found in relation to the primary variable of severity of withdrawal symptoms (effect size=0.12). No discernible difference was found in the sitting blood pressure or heart rate of the two groups during the trial. These results provide support for the use of lofexidine for the management of opioid detoxification in the prison setting.

10B.4 Subjective effects of prisoners using buprenorphine for detoxification

Johnstone A, Duffy T, Martin C. Int J Prison Health. 2011;7(4):52-65. doi: 10.1108/17449201111256907.

Abstract

PURPOSE:

Buprenorphine (Subutex) was piloted in two Scottish prisons between 2004 and 2006 and consequently used within other penal establishments in Scotland. This 2007 qualitative study aimed to explore the use of Subutex and its associated effects on 14 participants on detoxification programmes.

DESIGN/METHODOLOGY/APPROACH:

All participants were male, aged from 21 to 44 years with prison sentences ranging from a few months to life imprisonment. Buprenorphine was unavailable to female prisoners at the time of this study. Participants were recruited from seven Scottish prisons. All 14 participants were on detoxification programmes, each was prescribed Subutex, and each was selected from a larger investigation that included both those undergoing detoxification and maintenance (n=21). All participants had previously also used methadone on previous detoxification programmes.

FINDINGS:

It can be concluded that the majority of detoxification participants within this study indicated that Subutex was a more effective treatment than methadone as it helped reduce craving, eased the process of withdrawal and improved sleeping patterns. In addition, the majority of participants noted higher levels of motivation and the ability to set goals towards obtaining an improved quality of life.

ORIGINALITY/VALUE:

This study provides an alternative perspective to the use of Subutex within prison settings, when compared with results from previous quantitative studies reported. The study also highlights inconsistencies drawn from studies in this area, which may be an artefact of study design. It is recommended that further qualitative studies be conducted to explore further this alternative perspective. Finally, the issue of methodological approach taken should be addressed within the context of a related, but independent, research forum.

10B.5 Cannabis use, dependence and withdrawal in indigenous male inmates

Bernadette Rogerson, Susan P. Jacups & Nerina Caltabiano

Abstract

Background:

No studies have investigated cannabis withdrawal in indigenous or incarcerated populations, and there is currently no standard treatment for cannabis withdrawal in Australian prisons.

Aims:

This cross sectional survey examines cannabis use, dependence and involuntary (abrupt cessation) withdrawal in incarcerated indigenous males for the purpose of improving clinical management.

Methods:

101 consenting inmates (18–40 years) from an Australian correction centre were interviewed. Demographic characteristics, lifetime cannabis use (LCU), severity of dependence, cannabis withdrawal symptoms, psychological well-being and alcohol use were measured and compared using univariate and multivariate analyses.

Results:

Cannabis withdrawal symptoms were reported in 57% of current cannabis users compared with 16% of non-users ($p < 0.01$), indicating detectable cannabis dependence and withdrawal in a unique indigenous inmate population. Multivariate analysis revealed statistically significant associations between LCU and cannabis dependence (OR = 8.1; 95% CI: 2.2–29.1) when controlling for psychological well-being and alcohol consumption.

Conclusions:

Upon admission to a correction centre, cannabis users should be assessed and monitored for physical and psychological symptoms of withdrawal.

Implications:

Routine cannabis withdrawal monitoring will maximise staff and inmate safety. This improvement to policy will ensure appropriate risk management of staff and inmates.

10B.6 Incarceration and opioid withdrawal: The experiences of methadone patients and out-of-treatment heroin users

Shannon Gwin Mitchell, Ph.D., Sharon M. Kelly, Ph.D., Barry S. Brown, Ph.D.,Heather Schacht Reisinger, Ph.D., James A. Peterson, Ed.D.,Adrienne Ruhf, Michael H. Agar, Ph.D., and Robert P. Schwartz, M.D.

J Psychoactive Drugs. 2009 Jun; 41(2): 145–152.

doi: 10.1080/02791072.2009.10399907

Abstract

Both heroin-addicted individuals and methadone maintenance patients are likely to face untreated opioid withdrawal while incarcerated. Limited research exists concerning the withdrawal experiences of addicted inmates and their impact on individuals' attitudes and plans concerning drug abuse treatment. In the present study, 53 opioid dependent adults (32 in methadone treatment and 21 out-of-treatment) were interviewed in an ethnographic investigation of withdrawal experiences during incarceration. When treatment for opioid withdrawal was unavailable, detoxification experiences were usually described as negative and were often associated with a variety of unhealthy behaviors designed to relieve withdrawal symptoms. Negative methadone withdrawal experiences also negatively influenced participants' receptivity to seeking methadone treatment upon release. A minority of participants took a positive view of their withdrawal experience and saw it as an opportunity to detox from heroin or discontinue methadone. Findings support the importance of providing appropriate opioid detoxification and/or maintenance therapy to opioid dependent inmates.

10C The Elderly

10C.1 Interventions for reducing benzodiazepine use in older people: meta-analysis of randomised controlled trials

Gould RL, Coulson MC, Patel N, Highton-Williamson E, Howard RJ.

Br J Psychiatry. 2014 Feb;204(2):98-107. doi: 10.1192/bjp.bp.113.126003.

Abstract

Background:

The use of benzodiazepines has been advised against in older people, but prevalence rates remain high.

AIMS:

To review the evidence for interventions aimed at reducing benzodiazepine use in older people.

METHOD:

We conducted a systematic review, assessment of risk of bias and meta-analyses of randomised controlled trials of benzodiazepine withdrawal and prescribing interventions.

Results:

Ten withdrawal and eight prescribing studies met the inclusion criteria. At post-intervention, significantly higher odds of not using benzodiazepines were found with supervised withdrawal with psychotherapy (odds ratio (OR)=5.06, 95% CI 2.68-9.57, P<0.00001) and withdrawal with prescribing interventions (OR=1.43, 95% CI 1.02-2.02, P=0.04) in comparison with the control interventions treatment as usual (TAU), education placebo, withdrawal with or without drug placebo, or psychotherapy alone. Significantly higher odds of not using benzodiazepines were also found for multifaceted prescribing interventions (OR=1.37, 95% CI 1.10-1.72, P=0.006) in comparison with control interventions (TAU and prescribing placebo).

CONCLUSIONS:

Supervised benzodiazepine withdrawal augmented with psychotherapy should be considered in older people, although pragmatic reasons may necessitate consideration of other strategies such as medication review.

10C.2 Managing alcohol withdrawal in the elderly

Kraemer KL, Conigliaro J, Saitz R. Drugs Aging. 1999 Jun;14(6):409-25.

Abstract

The alcohol withdrawal syndrome is common in elderly individuals who are alcohol dependent and who decrease or stop their alcohol intake. While there have been few clinical studies to directly support or refute the hypothesis that withdrawal symptom severity, delirium and seizures increase with advancing age, several observational studies suggest that adverse functional and cognitive complications during alcohol withdrawal do occur more frequently in elderly patients. Most elderly patients with alcohol withdrawal symptoms should be considered for admission to an inpatient setting for supportive care and management. However, elderly patients with adequate social support and without significant withdrawal symptoms at presentation, comorbid illness or past history of complicated withdrawal may be suitable for outpatient management. Although over 100 drugs have been described for alcohol withdrawal treatment, there have been no studies assessing the efficacy of these drugs specifically in elderly patients. Studies in younger patients support benzodiazepines as the most efficacious therapy for reducing withdrawal symptoms and the incidence of delirium and seizure. While short-acting benzodiazepines, such as oxazepam and lorazepam, may be appropriate for elderly patients given the risk for excessive sedation from long-acting benzodiazepines, they may be less effective in preventing seizures and more prone to produce discontinuation symptoms if not

tapered properly. To ensure appropriate benzodiazepine treatment, dose and frequency should be individualised with frequent monitoring, and based on validated alcohol withdrawal severity measures. Selected patients who have a history of severe or complicated withdrawal symptoms may benefit from a fixed schedule of benzodiazepine provided that medication is held for sedation. beta-Blockers, clonidine, carbamazepine and haloperidol may be used as adjunctive agents to treat symptoms not controlled by benzodiazepines. Lastly, the age of the patient should not deter clinicians from helping the patient achieve successful alcohol treatment and rehabilitation.

10C.3 Identifying and managing acute alcohol withdrawal in the elderly

Letizia M, Reinbolz M. Geriatr Nurs. 2005 May-Jun;26(3):176-83.

Abstract

In the elderly population, alcohol-related problems may be misinterpreted as normal consequences of aging. However, alcohol is a commonly abused substance among older adults, and age-related changes predispose these patients to a greater sensitivity to its effects. All older patients should be screened for alcohol dependence and abuse on admission to an acute care facility. If identified, the plan of care must include close observation for acute alcohol withdrawal and prompt intervention if it occurs.

10C.4 A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people

Reeve E, Ong M, Wu A, Jansen J, Petrovic M, Gnjidic D.

Eur J Clin Pharmacol. 2017 Aug;73(8):927-935. doi: 10.1007/s00228-017-2257-8. Epub 2017 Apr 30.

Abstract

PURPOSE:

Benzodiazepines are effective medicines for insomnia and anxiety but are commonly used beyond recommended treatment time frames, which may lead to adverse drug events. The aim of this systematic review was to critically evaluate the success of interventions used to reduce benzodiazepines and 'Z-drug' use, and the impact of these interventions on clinical outcomes in older adults.

Methods:

A search was conducted in PubMed, Embase, Informit, International Pharmaceutical Abstracts, Scopus, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL. Studies conducted in older adults (≥65 years) and published between January 1995 and July 2015 were included. Two authors independently reviewed all articles for eligibility and extracted the data.

Results:

Seven studies of benzodiazepines and Z-drug withdrawal were identified. Benzodiazepine discontinuation rates were 64.3% in one study that employed pharmacological substitution with melatonin and 65.0% in a study that employed general practitioner-targeted intervention. Mixed interventions including patient education and tapering (n=2), pharmacological substitution with psychological support (n=1) and tapering with psychological support (n=1) yielded discontinuation rates between 27.0 and 80.0%. Five studies measured clinical outcomes following benzodiazepine discontinuation. Most (n=4) observed no difference in prevalence of withdrawal symptoms or sleep quality, while one study reported decline in quality of life in those who continued taking benzodiazepine vs. those who discontinued over 8 months.

CONCLUSIONS:

Current evidence shows that benzodiazepine withdrawal is feasible in the older population, but withdrawal rates vary according to the type of intervention. As the benefits and sustainability of these interventions are unclear, further studies should be conducted to assess this.

10C.5 Evaluation of a symptom-triggered protocol approach to the management of alcohol withdrawal syndrome in older adults

Taheri ADahri K, Chan P, Shaw M, Aulakh A, Tashakkor A.

J Am Geriatr Soc. 2014 Aug;62(8):1551-5. doi: 10.1111/jgs.12932. Epub 2014 Jun 24.

Abstract

OBJECTIVES:

To evaluate whether implementation of symptom-triggered administration of a benzodiazepine protocol reduces the severity (total cumulative dose), duration, and complications of alcohol withdrawal syndrome (AWS).

DESIGN:

Retrospective health record review.

SETTING:

Tertiary care center in Vancouver, Canada.

PARTICIPANTS:

Individuals aged 70 and older admitted to the Acute Care for Elders and Acute Medicine Unit wards with diagnostic codes for AWS from 2008 to 2012.

MEASUREMENTS:

Median duration and cumulative dose of benzodiazepine treatment, number of severe AWS complications, severe benzodiazepine-associated adverse effects, and need for adjunct therapy.

Results:

Thirty-three participants in the preprotocol group and 30 in the protocol-implemented group met the inclusion criteria. Median duration of benzodiazepine treatment decreased from 96 hours (interquartile range (IQR) 72-120 hours) in the preprotocol period to 48 hours (IQR 0-108 hours; P=.04), and median cumulative benzodiazepine dose administered decreased from 9 mg (IQR 5-19.8 mg) to 3 mg (IQR 0-10 mg; P=.001). Statistically significantly lower incidence of severe AWS complications (P=.007) and adjunct therapy use (P=.02) was seen in the protocol-implemented group.

CONCLUSION:

A symptom-triggered protocol for dosing of benzodiazepine therapy in the management of AWS in individuals aged 70 and older significantly reduced the total duration of benzodiazepine use, cumulative benzodiazepine dose, and use of adjunctive medications in the treatment of AWS.

10D LGBTI people

10D.1 Methamphetamine treatment outcomes among gay men attending a LGBTI-specific treatment service in Sydney, Australia

Lea T, Kolstee J, Lambert S, Ness R, Hannan S, Holt M.

PLoS One. 2017 Feb 16;12(2):e0172560. doi: 10.1371/journal.pone.0172560. eCollection 2017.

Abstract

Gay and bisexual men (GBM) report higher rates of methamphetamine use compared to heterosexual men, and thus have a heightened risk of developing problems from their use. We examined treatment outcomes among GBM clients receiving outpatient counseling at a lesbian, gay, bisexual, transgender and intersex (LGBTI)-specific, harm reduction treatment service in Sydney, Australia. GBM receiving treatment for methamphetamine use from ACON's Substance Support Service between 2012-15 (n=101) were interviewed at treatment commencement, and after 4 sessions (n=60; follow-up 1) and 8 sessions (n=32; follow-up 2). At each interview, clients completed measures of methamphetamine use and dependence, other substance

use, injecting risk practices, psychological distress and quality of life. The median age of participants was 41 years and 56.4% identified as HIV-positive. Participants attended a median of 5 sessions and attended treatment for a median of 112 days. There was a significant reduction in the median days of methamphetamine use in the previous 4 weeks between baseline (4 days), follow-up 1 (2 days) and follow-up 2 (2 days; p=.001). There was a significant reduction in the proportion of participants reporting methamphetamine dependence between baseline (92.1%), follow-up 1 (78.3%) and follow-up 2 (71.9%, p<.001). There were also significant reductions in psychological distress (p<.001), and significant improvements in quality of life (p< .001). Clients showed reductions in methamphetamine use and improved psychosocial functioning over time, demonstrating the potential effectiveness of a LGBTI-specific treatment service.