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Q2: What interventions are safe and effective for drug withdrawal (cannabis, amphetamines, cocaine, benzodiazepines, and inhalants)?

Background

Cessation of dependent substance use can result in a withdrawal syndrome, which may range in severity from mildly uncomfortable to severely distressing and can result in complications such as seizures, delirium and relapse to drug use. Many medications have been used to treat specific withdrawal symptoms, such as benzodiazepines for insomnia, NSAIDS for muscle aches and so on. Some medications have been used to ameliorate withdrawal symptoms more generally, and these are the subject of this review.

Population/Intervention(s)/ Comparison/Outcome(s) (PICO)

- **Population:** persons dependent on cannabis, stimulants, benzodiazepines of inhalants
- **Interventions:** medication for the treatment of withdrawal
- **Comparison:** placebo or no treatment or treatment as usual
- **Outcomes:**
 - withdrawal severity
 - completion of withdrawal
 - complications of withdrawal
 - drug use

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List of the systematic reviews identified by the search process

A number of reviews have examined pharmacotherapy approaches for cannabis (Benyamina et al 2008; Copeland & Swift, 2009; Budney et al, 2007; Elkashef et al, 2008; Shoptaw et al, 2009; cocaine (x 3 Cochrane reviews). These reviews have identified small numbers of studies using varieties of medications for different drug classes.

Reviews were not GRADEd.

Narrative description of the studies that went into the analysis

Studies for cannabis withdrawal have examined a range of medications, without any licensed medications being identified as consistently improving outcomes in controlled trials.

Studies of cocaine and amphetamine withdrawal have examined a range of medication approaches, including tricyclic antidepressants, SSRIs, dopamine agonists, anticonvulsants and modafinil. To date, there have been no medications shown to consistently improve outcomes for stimulant withdrawal.

Benzodiazepines: a review of controlled studies examining pharmacological approaches to benzodiazepine withdrawal identified 8 RCTs with 458 subjects, all examining different benzodiazepine tapers in outpatient settings, and the potential role of adjunctive medication. Studies supported gradual taper off BZDs (e.g. over a 10-week period) rather than an abrupt cessation of medication (Murphy & Tyrer, 1991; Lemoine et al, 1997), and the use of long-acting over short acting BZDs. Carbamazepine was identified in one small RCT (Schweizer et al, 1991) as a potential adjunct to BZD in alleviating withdrawal discomfort, but did not considerably improve other outcomes (e.g. withdrawal completion). Evidence suggests that psychosocial support assist withdrawal from benzodiazepines.

References

Benyamina A et al (2008). Pharmacotherapy and psychotherapy in cannabis withdrawal and dependence. *Expert Review of Neurotherapeutics*, 8:479-91.

Budney AJ et al (2007). Marijuana Dependence and Its Treatment. *Addiction Science and Clinical Practice*. Available online at <http://www.nida.nih.gov/PDF/ascp/vol4no1/Marijuana.pdf>

Copeland J, Swift W (2009). Cannabis use disorder: epidemiology and management. *International Review of Psychiatry*, 21:96-103.

Elkashef A et al (2008). Marijuana neurobiology and treatment. *Substance Abuse*, 29:17-29.

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Lemoine P, Touchon J, Billardon M (1997). [Comparison of 6 different methods for lorazepam withdrawal. A controlled study, hydroxyzine versus placebo] (in French). *Encéphale*, 23:290 -9.

Murphy SM, Tyrer P (1991). A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence. *The British Journal of Psychiatry*, 158:511-6.

Shoptaw SJ et al (2009). Treatment for amphetamine withdrawal. *Cochrane Database of Systematic Reviews*, (2):CD003021.

Schweizer E et al (1991). Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy. Effects on withdrawal severity and outcome. *Archives of General Psychiatry*, 48:448 -52.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	<p>Studies for cannabis withdrawal have examined a range of medications, without any licensed medications being identified as consistently improving outcomes in controlled trials.</p> <p>Studies of cocaine and amphetamines withdrawal have examined a range of medication approaches, including tricyclic antidepressants, SSRIs, dopamine agonists, anticonvulsants and modafinil. To date, there have been no medications shown to consistently improve outcomes for stimulant withdrawal.</p> <p>Benzodiazepines: a review of controlled studies examining pharmacological approaches to benzodiazepine withdrawal identified 8 RCTs with 458 subjects, all examining different benzodiazepine tapers in outpatient settings, and the potential role of adjunctive medication. Studies supported gradual taper off BZDs (e.g. over a 10-week period) rather than an abrupt cessation of medication (Murphy & Tyrer, 1991; Lemoine et al, 1997, and the use of long-acting over short acting BZDs. Carbamazepine was identified in one small RCT (Schweizer et al, 1991) as a potential adjunct to BZD in alleviating withdrawal discomfort, but did not considerably improve other outcomes (e.g. withdrawal completion).</p>
Summary of the quality of evidence	Quality of evidence not GRADEd, but in general poor quality evidence with few studies, and small sample sizes.

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Balance of benefits versus harms	
Define the values and preferences including any variability and human rights issues	There is a belief that the best intervention for substance withdrawal is "cold turkey". The perspective taken here is that if a person experiencing substance withdrawal symptoms requesting assistance to manage substance withdrawal should receive what support is reasonably available.
Define the costs and resource use and any other relevant feasibility issues	The supportive medications used for the treatment of substance withdrawal are not expensive (benzodiazepines, antiemetics, analgaesics, antidiarrhoeals, and so on).
Recommendation(s)	
<p>Withdrawal from cannabis, cocaine or amphetamines is best undertaken in a supportive environment. No specific medication is recommended for the treatment of withdrawal from these drugs. Strength of recommendation: STANDARD</p> <p>Relief of symptoms (e.g. agitation, sleep disturbance) may be achieved with symptomatic medication for the period of the withdrawal syndrome. Less commonly, depression or psychosis can occur during withdrawal, in these cases the individual needs to be monitored closely and advice sought from relevant specialists, if available. Strength of recommendation: STANDARD</p> <p>Withdrawal from benzodiazepines is best undertaken in a planned (elective) manner, using a gradually tapering dose over 8-12 weeks and with conversion to long-acting benzodiazepines, rather than using short-acting ones. Psychosocial support is helpful for individuals undergoing a tapering regime. Benzodiazepine withdrawal syndrome, if uncontrolled, can be severe; if a severe withdrawal develops (or occurs in an unplanned way on sudden stoppage of these drugs), specialist advice should be obtained regarding starting a high-dose benzodiazepine sedation regime and hospitalization. Strength of recommendation: STRONG</p> <p>In individuals withdrawing from benzodiazepines, the presence of physical comorbidity (such as seizures or chronic pain) or psychiatric comorbidity may be an additional indication for hospitalization. Strength of recommendation: STANDARD</p>	

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Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. No new systematic reviews were found to be relevant .