Pharmacotherapies for cannabis dependence?

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Background

The Cochrane review of pharmacotherapies for cannabis dependence was first published in 2014 [1]. In the past year we have contributed to an update of this review, which is currently in editorial review stage. The new studies that were considered for the update of the review have added to the diversity of medications that have been considered for the treatment of cannabis dependence, but as yet there is not sufficient evidence to support any particular pharmacotherapy.

Aim and methods

This poster provides an overview of the medications that have been trialled as potential pharmacotherapies for cannabis dependence, drawing on the work undertaken to update the Cochrane review. The studies referenced in this poster either met the criteria for inclusion in the updated review, or were consider to be potentially relevant but excluded for some reason.

The table lists the medications that have been tested, grouped by type of medication. The rationale for testing each of the medications is identified as well as the evidence of efficacy. The final column (Future directions) indicates our assessment of the value of further research into the medication as a pharmacotherapy for cannabis dependence, with colour coding to indicate those with some evidence of efficacy (green), those where there is a possibility of efficacy but as yet insufficient evidence to be certain (amber) and those that are of doubtful value in the treatment of cannabis dependence (red).

Medication	Rationale for use	Efficacy	Future directions
THC preparations			
Nabiximols (Sativex®)	Agonist therapy: suppress withdrawal then taper dose. Buccal spray; pharmacokinetics more predictable than oral preparations. Contains cannabidiol which may offer benefits over straight THC [2].	Attenuated withdrawal symptoms and craving more than placebo. [2] Long-term effect on cannabis use unknown.	Equivalent to nicotine replacement therapy – worth further research to determine long-term effects on cannabis use, and therapeutic value of cannabidiol, as well as to compare different THC preparations.
Dronabinol	Orally bioavailable, synthetic form of THC	Improved treatment retention and withdrawal symptoms. [3]	
Nabilone	Synthetic analogue of THC with higher bioavailability than dronabinol. [4]	Attenuated withdrawal in laboratory study, even with once per day dosing. [4] Another laboratory study suggested combination with zolpidem may improve cannabis use outcomes. [5]	
Dronabinol plus lofexidine	Lofexidine added to dampen cannabis withdrawal and craving. Laboratory study found combination improved withdrawal more than either medication alone. [6]	No difference in rates of abstinence from cannabis between dronabinol-lofexidine and placebo groups. [7]	It appears that the addition of lofexidine does not add benefit in treatment context.
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Fluoxetine	Demonstrated efficacy in treating depressive disorder. [8] Previous study [9] for alcohol dependence and depression indicated potential reduction in cannabis use.	Well tolerated in youth with depression and cannabis use disorder, no more effective than placebo for depressive or cannabis-related symptoms. [8, 10]	Not effective specifically for cannabis use disorder.
Vilazodone	Partial 5-HT1A agonist and serotonin receptor inhibitor. Multiple studies implicate cannabinoid interactions with serotonin system. [11]	Vilazodone not more effective than placebo; women had worse cannabis use outcomes than men. [11]	
Escitalopram	Mood disorders common with cannabis use. Negative affect exacerbated during withdrawal. Escitalopram used in moderate depression and anxiety disorders. [12]	High rate of dropout, low rate of abstinence. Inconclusive results. [12]	
Mixed action antidepressants			
Nefazodone	Dual action on serotonin and norepinephrine reuptake, and 5-HT_{2A} receptor antagonist effects. Reduces anxiety and insomnia. No reported abuse potential. [13]	In laboratory study, nefazodone decreased some symptoms but participants still reported discomfort during withdrawal. [14]	Limited value in treatment of cannabis dependence.
Mirtazapine	Noradrenergic and serotonergic antidepressant with sedating properties. [15]	Sleep efficiency and quality improved but not daily sleep disturbances. [15] In laboratory study, improved sleep during abstinence and increased food intake but no effect on withdrawal symptoms. [16]	Limited value, other than for treatment of depression. [17]
Venlafaxine	Depression is prevalent in people who are cannabis dependent. Alleviating depression may reduce cannabis use.	Mood improved with no difference between venlafaxine and placebo groups; venlafaxine group experienced more severe withdrawal and more likely to smoke cannabis. [18, 19]	Not effective for treatment of cannabis dependence.
Anticonvulsants and mood stabilisers			
Lithium	Lithium carbonate reduces precipitated withdrawal in rats and humans, possibly by stimulating oxytocin release. Intranasal oxytocin improves sleep architecture, and sleep disturbance may be a factor in relapse. [20]	In randomised controlled trial comparing lithium carbonate to placebo, lithium had “limited efficacy” in improving sleep. [20, 21]	Doubtful value in treatment of cannabis dependence.
Topiramate	Thought to diminish reinforcing effects of cannabis by facilitation of GABA and inhibition of glutamatergic transmission. [22, 23]	Reduced amount of cannabis smoked, without increasing abstinence, but potent side effects, notably cognitive function – major reason for dropout. [22, 23]	Potentially effective if side effects can be managed.
Divalproex sodium	Used for psychiatric disorders characterised by irritability, mood lability and aggression, symptoms that are often associated with cannabis withdrawal. [24]	Frequency and amount of cannabis used, and irritability decreased in divalproex and placebo groups, with no group difference. [24] In laboratory study, divalproex worsened mood and cognitive performance during abstinence. [25]	Doubtful value in treatment of cannabis dependence.
Gabapentin	Calcium channel modulation of GABA; in various disorders gabapentin reduces craving and disturbances in sleep and mood which are persistent in cannabis withdrawal. [26]	Some capacity to ameliorate withdrawal symptoms and promote reduction in cannabis use. [26]	May be worth further research.
Baclofen	GABAB receptor agonist and antispasmodic. [16]	In laboratory study had little effect on mood during abstinence, and worsened cognitive performance in both abstinence and active use phases. [16] Open label study reported common side effects of sedation and lethargy. [27]	Doubtful value in treatment of cannabis dependence.
Atypical antidepressant			
Bupropion	Dopamine reuptake inhibitor and weak norepinephrine reuptake inhibitor [13]. Well tolerated, effective in tobacco smoking cessation [28].	Less withdrawal symptoms and craving and improved retention, compared to placebo [28]. In laboratory study, some aspects of withdrawal worse with bupropion compared to placebo. [29]	Insufficient evidence on cannabis use outcomes in treatment-seeking population. Not supported by laboratory study.
Anxiolytic			
Buspirone	Partial 5-HT1A agonist with little or no abuse potential. [30] Anxiolytic may alleviate cannabis withdrawal and improve cannabis use outcomes. [31]	Promising in initial small trial [31] but in larger study buspirone no more effective than placebo. Women had worse cannabis use outcomes with buspirone. [30]	Little value in the treatment of cannabis dependence.
Other medications			
N-Acetylcysteine	Pro-drug of amino acid cysteine. Modulates glutamatergic neurotransmission. [32]	Promising results in adolescents [32] not replicated in adults [33].	Reason for differing trial findings unclear.
Varenicline	Effective in tobacco smoking cessation. Active at α7 nicotine acetylcholine receptors to which THC binds. Decreases rewarding effects of alcohol and cocaine. [34]	Small scale crossover study suggests varenicline well tolerated, may reduce cannabis craving. [34]	Further research needed.
Atomoxetine	Highly selective inhibitor of presynaptic norepinephrine transporter. Used in treatment of ADHD. [35]	Trial involving adults with ADHD who used cannabis. May improve ADHD symptoms but does not reduce cannabis use. [35]	Little value in the treatment of cannabis dependence.
Oxytocin	Neuropeptide that promotes prosocial behaviours and plays a role in drug-related neuroadaptations [36].	Pilot study only – inconclusive [36].	Worth further research.
Quetiapine	Atypical antipsychotic, shown to improve sleep and decrease anxiety, mood lability and irritability in variety of patient populations. [37]	In laboratory study, quetiapine improved sleep quality, increased caloric intake and decreased weight loss but increased cannabis craving and self-administration during relapse phase. [37]	Doubtful value for treatment of cannabis dependence.
Injectable naltrexone	Some evidence of cross-modulating effects of opioid and cannabinoid systems. [38]	Small, single group study found decreased frequency but not quantity of use. Adjunct medication required for symptoms up to 2 weeks after an injection. [38]	Small study, inconclusive. Doubtful value in treatment of cannabis dependence.

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