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Pharmacotherapies for cannabis dependence (Review)

Marshall K, Gowing L, Ali R, Le Foll B

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[Intervention Review]

Pharmacotherapies for cannabis dependence

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ABSTRACT

Background

Cannabis is the most prevalent illicit drug in the world. Demand for treatment of cannabis use disorders is increasing. There are currently no pharmacotherapies approved for treatment of cannabis use disorders.

Objectives

To assess the effectiveness and safety of pharmacotherapies as compared with each other, placebo or supportive care for reducing symptoms of cannabis withdrawal and promoting cessation or reduction of cannabis use.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (to 4 March 2014), MEDLINE (to week 3 February 2014), EMBASE (to 3 March 2014) and PsycINFO (to week 4 February 2014). We also searched reference lists of articles, electronic sources of ongoing trials and conference proceedings, and contacted selected researchers active in the area.

Selection criteria

Randomised and quasi-randomised controlled trials involving the use of medications to reduce the symptoms and signs of cannabis withdrawal or to promote cessation or reduction of cannabis use, or both, in comparison with other medications, placebo or no medication (supportive care) in participants diagnosed as cannabis dependent or who were likely to be dependent.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration. Two review authors assessed studies for inclusion and extracted data. All review authors confirmed the inclusion decisions and the overall process.

Main results

We included 14 randomised controlled trials involving 958 participants. For 10 studies the average age was 33 years; two studies targeted young people; and age data were not available for two studies. Approximately 80% of study participants were male. The studies were at low risk of selection, performance, detection and selective outcome reporting bias. Three studies were at risk of attrition bias.

All studies involved comparison of active medication and placebo. The medications included preparations containing tetrahydrocannabinol (THC) (two studies), selective serotonin reuptake inhibitor (SSRI) antidepressants (two studies), mixed action antidepressants (three studies), anticonvulsants and mood stabilisers (three studies), an atypical antidepressant (two studies), an anxiolytic (one

study), a norepinephrine reuptake inhibitor (one study) and a glutamatergic modulator (one study). One study examined more than one medication. Diversity in the medications and the outcomes reported limited the extent that analysis was possible. Insufficient data were available to assess the utility of most of the medications to promote cannabis abstinence at the end of treatment.

There was moderate quality evidence that completion of treatment was more likely with preparations containing THC compared to placebo (RR 1.29, 95% CI 1.08 to 1.55; 2 studies, 207 participants, P = 0.006). There was some evidence that treatment with preparations containing THC was associated with reduced cannabis withdrawal symptoms and craving, but this latter outcome could not be quantified. For mixed action antidepressants compared with placebo (2 studies, 179 participants) there was very low quality evidence on the likelihood of abstinence from cannabis at the end of follow-up (RR 0.82, 95% CI 0.12 to 5.41), and moderate quality evidence on the likelihood of treatment completion (RR 0.93, 95% CI 0.71 to 1.21). For this same outcome there was very low quality evidence for the effects of SSRI antidepressants (RR 0.82, 95% CI 0.44 to 1.53; 2 studies, 122 participants), anticonvulsants and mood stabilisers (RR 0.78, 95% CI 0.42 to 1.46; 2 studies, 75 participants), and the atypical antidepressant, bupropion (RR 1.06, 95% CI 0.67 to 1.67; 2 studies, 92 participants). Available evidence on gabapentin (anticonvulsant) and N-acetylcysteine (glutamatergic modulator) was insufficient for quantitative estimates of their effectiveness, but these medications may be worth further investigation.

Authors' conclusions

There is incomplete evidence for all of the pharmacotherapies investigated, and for many of the outcomes the quality was downgraded due to small sample sizes, inconsistency and risk of attrition bias. The quantitative analyses that were possible, combined with general findings of the studies reviewed, indicate that SSRI antidepressants, mixed action antidepressants, atypical antidepressants (bupropion), anxiolytics (buspirone) and norepinephrine reuptake inhibitors (atomoxetine) are probably of little value in the treatment of cannabis dependence. Preparations containing THC are of potential value but, given the limited evidence, this application of THC preparations should be considered still experimental. Further studies should compare different preparations of THC, dose and duration of treatment, adjunct medications and therapies. The evidence base for the anticonvulsant gabapentin and the glutamatergic modulator N-acetylcysteine is weak, but these medications are also worth further investigation.

PLAIN LANGUAGE SUMMARY

Medications for the treatment of cannabis dependence

Background

Cannabis is the most common illicit drug in the world. Demand by cannabis users for treatment has been increasing in most regions of the world. Currently there are no medications specifically for the treatment of cannabis use. This review sought to assess the effectiveness and safety of medications for the treatment of cannabis dependence.

Search date

We searched the scientific literature in February and March 2014.

Study characteristics

We identified 14 randomised controlled trials (clinical studies where people are allocated at random to one of two or more treatment groups) involving 958 cannabis-dependent participants. Key features of dependent drug use are compulsive use, loss of control over use, and withdrawal symptoms on cessation of drug use. This review included studies where participants were described as dependent or were likely to be dependent based on cannabis use occurring several days a week, or daily.

The average age of participants was 33 years, excluding two studies that targeted young people. Most (80%) study participants were male. Most (10) of the studies were undertaken in the USA, with three occurring in Australia and one in Israel. The studies involved a wide range of medications to reduce the symptoms of cannabis withdrawal and to promote cessation or reduction of cannabis use.

Two studies received study medications from the manufacturing pharmaceutical company but none were funded by pharmaceutical companies.

Key results

The effects for many of the medicines we evaluated in this review were uncertain. Based on the available evidence, antidepressants, bupropion, buspirone and atomoxetine are probably of little value in the treatment of cannabis dependence. Preparations containing

tetrahydrocannabinol (THC), the main psychoactive ingredient of cannabis, are of potential value in the treatment of cannabis dependence, but limitations in the evidence are such that this application of THC preparations should be considered still experimental. Available evidence on gabapentin and N-acetylcysteine suggest that these medications may be worth further investigation, but at this time it is not possible to assess their effectiveness.

Quality of the evidence

The quality of the evidence for many of the outcomes in this review was downgraded because each medication was investigated by only one or two studies, each study involved small numbers of participants, there was some inconsistency in the findings, and a risk of bias due to study participants dropping out of treatment.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Active medication compared with placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Active Medication				
Number abstinent at end of treatment - mixed action antidepressants	**Study population**		**RR 0.82** (0.12 to 5.41)	179 (2 studies)	⊕◯◯◯ **very low**[1,2]	
	250 per 1000	**205 per 1000** (30 to 1000)				
	Moderate					
	233 per 1000	**191 per 1000** (28 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Significant heterogeneity between studies
[2] Studies small (<300 participants in total)

BACKGROUND

Description of the condition

Cannabis is the world's most widely produced, seized and consumed illicit drug (World Drug Report 2013).

The main psychoactive compound in all cannabis products is Δ^9- tetrahydrocannabinol (THC) (EMCDDA Cannabis Drug Profile). The number of cannabis users globally is estimated to range between 2.8% and 5.8% of the world's population (World Drug Report 2013). Prevalence rates of cannabis use vary widely between regions, with the highest prevalence rates in Oceania, the Americas and Africa (World Drug Report 2013). Cannabis use has increased globally, particularly in Asia, since 2009 (World Drug Report 2013) and cannabis is identified as the primary drug of concern for substantial proportions of people in treatment for drug use in Africa, Latin America and the Caribbean, and Oceania (World Drug Report 2013). Cannabis use within some indigenous communities in North America and Australia may be more prevalent than for their non-indigenous counterparts (Beauvais 2004; Clough 2004).

Cannabis use causes significant adverse effects (Budney 2007a). The acute effects of short-term cannabis use (Volkow 2014) include impaired memory (Solowij 2008); impaired motor co-ordination with an associated increased risk of involvement in motor vehicle accidents (Hall 2009); altered judgement; and, in high doses, paranoia and psychosis. Long-term or heavy use of cannabis has been associated with: the development of dependence (Budney 2007a), chronic bronchitis, and increased risk of chronic psychosis disorders in persons with a predisposition for development of such disorders (Volkow 2014). When use is commenced early in adolescence, long-term or heavy cannabis use has also been associated with altered brain development, poor educational outcome, cognitive impairment (Solowij 2008), and diminished life satisfaction and achievement (Gruber 2003).

It has been estimated that some 10% of those who have used cannabis at least once will develop cannabis dependence (Wagner 2002). Based on a large epidemiological survey in the USA, it has been estimated that, among those exposed once to cannabis, 7.0% of males and 5.3% of females will develop cannabis dependence at some point in their life, while 47.4% of males and 32.5% of females will develop cannabis use disorders (abuse or dependence) at some point in their life (Lev-Ran 2013a).

As with other drugs of dependence, the risk of developing dependency is influenced by multiple factors. However, intensive use of cannabis, that is daily or near daily use, is likely to increase the risk of cannabis dependence (EMCDDA 2004). It has been suggested that the earlier initiation of cannabis use (Copeland 2014), use of more potent forms of cannabis (for example the flowering heads of the female cannabis plant), and the greater use of water-pipes may have led to an increased amount of THC consumption by some cannabis users and, therefore, possibly greater rates of cannabis dependence (Hall 2001).

The use of cannabis has consistently been found to be associated with psychotic symptoms (Minozzi 2010) and may be associated with the earlier onset of psychotic illness in some people (Large 2011). Cannabis use and cannabis use disorders have been associated with a range of mental health disorders, such as anxiety and mood disorders (Lev-Ran 2013). These associations were particularly pronounced with bipolar disorder, substance use disorders and specific (antisocial, dependant and histrionic) personality disorders (Lev-Ran 2013).

Estimates of the number of cannabis users experiencing withdrawal are variable (Agrawal 2008; Budney 2006; Chung 2008; Copersino 2006; Cornelius 2008; Hasin 2008). Evidence regarding factors influencing the severity of cannabis withdrawal remains limited, but there is evidence that the total number of cannabis cigarettes smoked is predictive of the intensity of withdrawal during abstinence from cannabis (McClure 2012). Smoking behaviour also appears to be a strong predictor for the severity of cannabis dependence (van der Pol 2014).

General acceptance of a specific cannabis withdrawal syndrome is indicated by the inclusion of diagnostic criteria for cannabis withdrawal in the Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). In the DSM-5 cannabis withdrawal is defined by development of three or more of the following signs and symptoms within approximately one week of cessation of heavy and prolonged cannabis use: (1) irritability, anger or aggression; (2) nervousness or anxiety; (3) sleep difficulty; (4) decreased appetite or weight loss; (5) restlessness; (6) depressed mood; (7) at least one of the following physical symptoms causing significant discomfort: stomach pain, shakiness or tremors, sweating, fever, chills or headache (DSM-5). Onset of symptoms is usually within 24 to 48 hours of abstinence, reaching peak intensity within the first week (Budney 2007a). Symptoms may persist for up three to four weeks (Milin 2008), although there appears to be significant individual variability. The cannabis withdrawal syndrome is not life threatening, nor is it associated with significant medical or psychiatric consequences (Budney 2003).

Demand for treatment for cannabis related disorders has generally increased worldwide over the past decade, albeit with significant regional variation. The World Drug Report gives data on treatment demand in terms of the proportion of treatment services provided for the major drugs of dependence. Cannabis related disorders have dominated demand for drug treatment in Africa over the past 10 years with treatment rates consistently over 60%. Demand for cannabis treatment has grown significantly in some regions, more than doubling in Europe and South America and more than trebling in Oceania (World Drug Report 2013). North America as a whole was the only region to see a decrease in the contribution of cannabis to treatment demand (World Drug Report 2013) but, within the USA, cannabis admissions increased by 32% between 1996 and 2006 (SAMHSA 2008). Increases in the THC content

of cannabis may be a factor in the increasing demand for treatment. In the USA, THC content, as detected in confiscated samples, has increased from about 3% in the 1980s to 12% in 2012 (Volkow 2014). Cannabis users adjust their smoking behaviour when smoking stronger cannabis but the adjustment does not fully compensate for the increased strength (van der Pol 2014). Hence, cannabis users would be expected to be exposed to higher doses of THC as a result of the increasing potency of cannabis preparations. Cannabis users who seek treatment typically have a long history of cannabis use disorder and multiple previous attempts to quit (Copeland 2014).

Description of the intervention

There are currently no accepted pharmacotherapies for the treatment of cannabis withdrawal or cessation (Nordstrom 2007). The identification and development of medications to fill this gap has become an increasing priority among researchers (Vandrey 2009). However, a number of pharmacotherapies have been proposed as possible experimental interventions to attenuate the symptoms and signs of cannabis withdrawal and to promote cessation.

These medications are diverse in nature, encompassing medications that affect cannabinoid receptor systems (for example preparations of THC), medications that affect dopamine pathways, medications that affect the specific symptoms of cannabis withdrawal or that have been used in managing withdrawal from other substances, and medications that affect mental health conditions, such as depression, that may be factors contributing to cannabis use.

How the intervention might work

The proposed pharmacologic interventions may potentially lessen the symptoms and signs of cannabis withdrawal, including craving. The availability of effective pharmacotherapy for cannabis withdrawal may encourage people who are cannabis dependent to enter treatment, and may increase the rates of completion of withdrawal, cessation of cannabis use and entry into relapse prevention treatment.

It has been reported that the experience of cannabis withdrawal symptoms may be a significant obstacle to the achievement of abstinence by people who are cannabis dependent (Budney 2006; Copeland 2001; Hart 2005). Therefore, the effective treatment of the cannabis withdrawal syndrome may promote cessation of cannabis use and provide a first step towards abstinence and recovery.

Why it is important to do this review

As discussed above, there is increasing recognition that cannabis use and dependence is an important public health issue.

Not all cannabis users will need pharmacotherapies to manage withdrawal or support cessation of their use. However, it is important that effective pharmacotherapies are identified for the treatment of cannabis withdrawal, especially in intensive cannabis users who describe withdrawal symptoms on cessation.

We believe that this is the first systematic review of pharmacotherapies for cannabis dependence, and the first review to focus on studies involving people seeking treatment for cannabis use. As such, this review seeks to establish current knowledge on the effectiveness of medications in the treatment of cannabis dependence.

OBJECTIVES

To assess the effectiveness and safety of pharmacotherapies as compared with each other, placebo or no pharmacotherapy (supportive care) for reducing symptoms of cannabis withdrawal and promoting cessation or reduction of cannabis use.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials that provided detailed information on the type and dose of intervention medication used and the characteristics of participants treated.

Types of participants

We included studies that involved participants diagnosed as cannabis dependent or who were likely to be dependent based on reported dose, duration and frequency of use (daily or multiple days per week).

Studies involving participants dependent on, and withdrawing from, both cannabis and nicotine were included, but studies involving participants dependent on and withdrawing from substances other than cannabis and nicotine were excluded. It was intended to use subgroup analyses to assess the impact of concurrent nicotine and cannabis withdrawal on the effectiveness of pharmacotherapies for cannabis withdrawal, but there were insufficient data for such analyses to be undertaken.

Studies undertaken in either inpatient or outpatient settings were included. Studies undertaken in purely research settings, such as residential research laboratory settings, were excluded. Some of these studies provide insight into the effect of different medications on signs and symptoms of cannabis withdrawal and are considered in the discussion section. However, such studies generally

involved participants who were not seeking treatment for cannabis use and cessation of cannabis use was not the goal of the interventions provided, and the nature of outcomes assessed were generally different to those expected of treatment interventions. For these reasons such studies were excluded from this review.

Types of interventions

Experimental interventions involved the administration of medications with the aim of reducing the symptoms and signs of cannabis withdrawal or promoting cessation of cannabis use. Comparison interventions involved the use of different pharmacotherapies, placebo or no pharmacotherapy (supportive care).

Types of outcome measures

Primary outcomes

1. Number of participants abstinent from cannabis at the end of treatment as determined by self-report or urine drug screens, or both
2. Intensity of withdrawal as determined by scores on withdrawal scales, the need for symptomatic medications in addition to the experimental intervention or overall assessments by clinicians and participants
3. Nature, incidence and frequency of adverse effects and whether the planned medication regime was modified in response to adverse effects
4. Completion of scheduled treatment

Secondary outcomes

1. Level of cannabis use at the end of treatment as measured via participant reported level of use or urine drug screens, or both.
2. Number of participants engaged in further treatment following completion of the withdrawal intervention. As discussed in the 'Background' section, treatment of the cannabis withdrawal period may be considered as the first step in treatment, therefore engagement in further relapse prevention treatment may be considered to be a valid outcome of interest.

Search methods for identification of studies

All searches included non-English language literature. No studies were found in languages other than English.

Electronic searches

We searched:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (www.thecochranelibrary.com) to 4 March 2014;
2. MEDLINE (1946 to week 3 February 2014) via Ovid Online;
3. EMBASE (1980 to 3 March 2014) via Ovid Online;
4. PsycINFO (1806 to week 4 February 2014) via Ovid Online.

We developed a search strategy to retrieve references relating to the pharmacologic treatment of cannabis withdrawal. This strategy was adapted to each of the databases listed above.
For details see Appendix 1; Appendix 2; Appendix 3; Appendix 4.
We also searched some of the main electronic sources of ongoing trials:

- Current Controlled Trials (www.controlled-trials.com/);
- ClinicalTrials.gov;
- Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (https://oss-sper-clin.agenziafarmaco.it/);
- Trialsjournal.com.

Searching other resources

We checked the reference lists of relevant review articles and retrieved studies to identify any further studies of interest that were not retrieved by the electronic search. We contacted selected researchers who are active in the area seeking information about unpublished study reports. We also checked conference proceedings likely to contain trials relevant to the review.

Data collection and analysis

Selection of studies

Two authors (KM and LG) independently assessed the titles and abstracts of records retrieved from the systematic search according to the identified inclusion and exclusion criteria. All authors agreed on the inclusion and exclusion decisions. No attempt was made to blind the authors to the names of the study authors, institutions, journal of publication and results when eligibility criteria were applied.

Data extraction and management

Two authors (KM and LG) independently extracted key information from the included studies using a data collection form to record information against the outcome measures (abstinence, intensity of withdrawal, adverse effects, completion of treatment, change in cannabis use, and engagement in follow-up treatment). Data were confirmed by consultation with the other review authors. Key findings of studies were summarized descriptively in the first instance and the capacity for quantitative meta-analysis was considered.
Sufficient information was extracted from reports of included studies to enable assessment of the risk of bias.

Assessment of risk of bias in included studies

The *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) recommends the use of a two-part tool to assess the risk of bias in studies included in Cochrane reviews. This tool addresses the specific domains of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of low, high or unclear risk. Each included study was analysed and described according to these domains. To make these judgements, we used the criteria indicated by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and addressed their applicability to the addiction field.

We considered blinding separately for subjective and objective outcomes. Lack of blinding is a source of serious risk of bias for subjective outcomes but is less significant with objective outcomes, such as completion of treatment and duration of treatment. We only considered incomplete outcome data for the intensity of withdrawal, change in cannabis use, and nature and incidence of adverse effects. Retention in treatment (duration of treatment) and completion of treatment are frequently primary outcome measures in addiction research. See Appendix 5 for the detailed description of the criteria used.

Details of the assessments of risk of bias are included in the Characteristics of included studies.

Measures of treatment effect

Where possible, for dichotomous outcomes (for example number completing treatment) we calculated risk ratios (RR) with 95% confidence intervals (CI). No continuous data were obtained but the intention was to express continuous outcomes as a mean difference where there was a a comparable outcome measure (for example time in treatment) or as a standardized mean difference where there was variability in the outcome measure (for example withdrawal assessment scales).

Unit of analysis issues

One study included in the review involved three treatment arms (two different active medications and placebo). The active medications, compared to placebo, were included in separate subgroups and the calculation of overall totals was suppressed thereby avoiding the unit of analysis error of double-counting participants.

Where urine drug screens were reported in studies, the unit of analysis was the number of study participants and not the number of tests performed.

Dealing with missing data

It was intended to attempt to contact original investigators to request missing data. However, this was not undertaken given the limited capacity for meta-analysis. It was also intended to use sensitivity analysis to assess the impact of different approaches to handling missing data but there were insufficient data for this.

Assessment of heterogeneity

Clinical and methodological heterogeneity was assessed by reviewing the variations between studies in terms of the characteristics of participants included, the interventions and the reported outcomes. Studies were grouped for analyses by the nature of the medication used (experimental intervention). As there was considerable heterogeneity in the types of medications, subgroup but not overall totals were calculated.

We assessed statistical heterogeneity using the Chi^2 test and its P value, by visual inspection of the forest plots. and the I^2 statistic. A P value of the Chi^2 test lower than 0.10 or an I^2 statistic of at least 50% indicated a significant statistical heterogeneity.

Data synthesis

We used Review Manager 5.2 for statistical analyses. In all analyses we used a random-effects model.

Subgroup analysis and investigation of heterogeneity

This review aimed to consider the following potential sources of heterogeneity through subgroup analyses:

1. patterns of cannabis use and the estimated level of THC intake (as indicated by duration and level of use, number of days of use, number of uses per day (frequency), modality of use or route of administration, age at initiation of use);
2. concurrent tobacco smoking;
3. concurrent psychiatric illness and current treatment for a psychiatric illness;
4. the nature of the treatment setting;
5. the nature of adjunct treatment.

None of these analyses were possible due to limitations of the studies that met the inclusion criteria.

Sensitivity analysis

We did not use methodological quality as a criterion for inclusion in this review. We intended to assess the impact of methodological quality through sensitivity analysis. This would have involved considering the overall estimate of effect with studies with a high risk of bias included or excluded. Limitations of data reported by the studies that met the inclusion criteria meant that sensitivity analysis was not possible. However, the risk of bias was discussed in presenting the results.

RESULTS

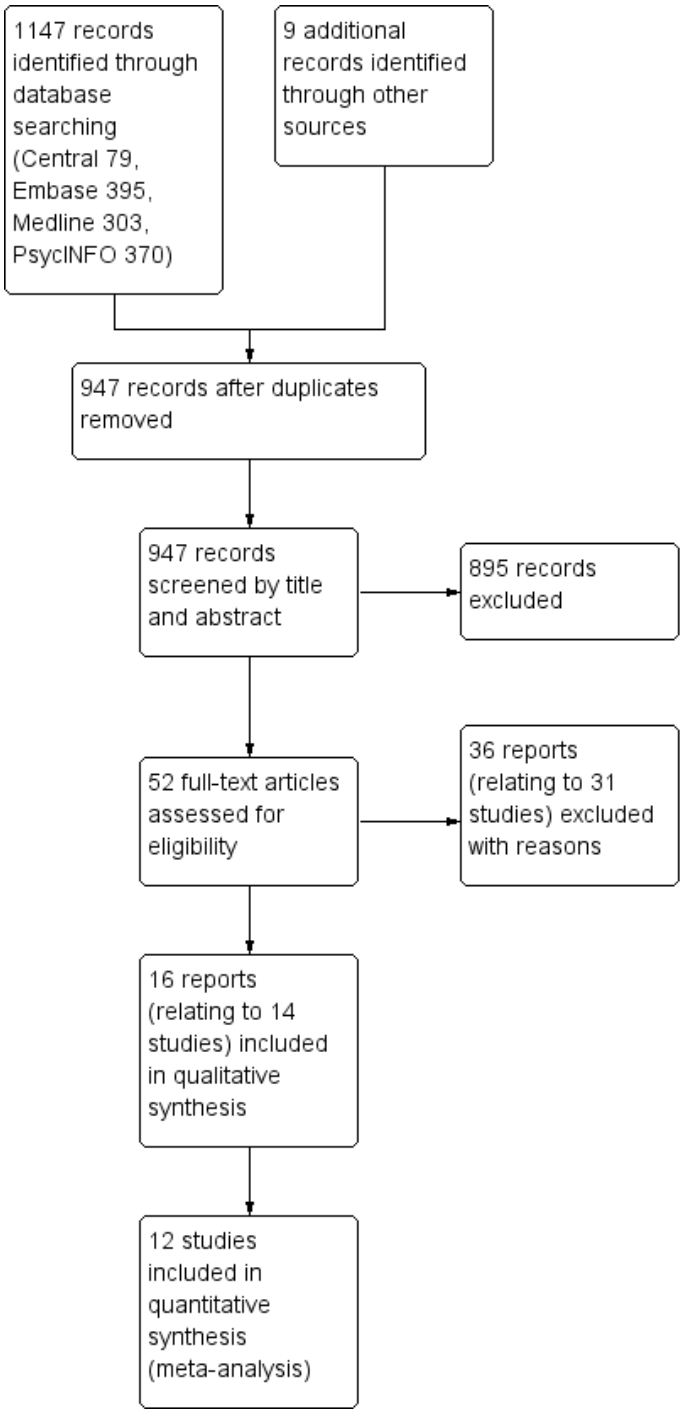
Description of studies

See Characteristics of included studies; Characteristics of excluded studies

Results of the search

Our search strategy identified 947 unique records from which 52 reports, relating to 45 different studies, were identifited as potentially relevant to this review (see Figure 1).

Figure 1. Study flow diagram.



Included studies

Fourteen randomised controlled trials (16 reports) involving 958 participants met the inclusion criteria for this review (see Characteristics of included studies). In total, 500 were treated with active medication and 458 received placebo. In all studies participants were offered some form of psychological therapy in addition to medication (or placebo).

All studies involved a comparison between an active medication and placebo, but the medications investigated by the studies included in this review were diverse. This limited the extent of analysis that was possible.The medications investigated, grouped according to type and mechanism of action, were:

- preparations containing THC, dronabinol (Levin 2011) and nabiximols (Allsop 2014);
- selective serotonin reuptake inhibitor (SSRI) antidepressants fluoxetine (Cornelius 2010), escitalopram (Weinstein 2014);
- mixed action antidepressants (noradrenergic and serotonergic effects), nefazodone (Carpenter 2009), mirtazapine (Frewen 2007), venlafaxine (Levin 2013);
- anticonvulsant and mood stabilisers divalproex sodium (Levin 2004), gabapentin (Mason 2012), lithium (Johnston 2012);
- atypical antidepressant (dopamine reuptake inhibitor and weak norepinephrine reuptake inhibitor) bupropion (Carpenter 2009; Penetar 2012);
- anxiolytic (serotonin 5-HT_{1A} partial agonist) buspirone (McRae-Clark 2009);
- selective norepinephrine reuptake inhibitor atomoxetine (McRae-Clark 2010);
- a supplement promoting glutamate release and modulating N-methyl-D-aspartate (NMDA) receptor, N-acetylcysteine (Gray 2012).

All except two of the studies were undertaken in outpatient settings. Allsop 2014 and Johnston 2012 were primarily studies of cannabis withdrawal, with medication administered in an inpatient (hospital) setting over six to seven days, with follow-up interviews post-discharge.

The majority (10) of the studies were undertaken in the USA, with three studies (Allsop 2014; Frewen 2007; Johnston 2012) in Australia and one study (Weinstein 2014) in Israel. Twelve studies reported the source of funding as (government) research grants, and the funding source was unclear for two studies (Frewen 2007; Johnston 2012). Two studies (Allsop 2014; McRae-Clark 2010) used medications provided by the manufacturing company. Primary researchers associated with six studies declared past associations with pharmaceutical companies. Researchers associated with four studies declared no conflict of interest; no declarations were made for the remaining four studies.

Two studies (Cornelius 2010; Penetar 2012) included participants with cannabis use disorders as well as cannabis dependence, but the majority of participants met diagnostic criteria for cannabis dependence. In the other studies all participants were cannabis dependent.

For 10 studies, the average age of participants was around 33 years; data on age were not provided for two studies (Johnston 2012; Penetar 2012). The target population for the remaining two studies (Cornelius 2010; Gray 2012) was adolescents and young adults. The average age of participants in these studies was 21.1 and 18.9 years, respectively.

Two studies (Johnston 2012; Penetar 2012) did not provide information on the gender of participants; the majority (73% to 92%) of participants in the other 12 studies were male.

Participants in two studies (Cornelius 2010; Levin 2013) had comorbid depression and cannabis use disorders, and in one study (McRae-Clark 2010) participants met diagnostic criteria for attention deficit hyperactivity disorder as well as cannabis dependence.

Excluded studies

Thirty-one studies (36 reports) that were considered potentially relevant to the review and assessed in detail were excluded from the review (see Figure 1 and Characteristics of excluded studies). The reasons for exclusion were: study was exploratory research with participants who were not seeking treatment or participants were not cannabis dependent (14 studies); no treatment comparison (nine studies); cannabis used in combination with other drugs or not the main focus of the treatment intervention (seven studies); no medications (one study); insufficient outcome data (one study). One study was excluded for more than one reason.

Risk of bias in included studies

For summary results of the judged risk of bias across the included studies for each domain, see Figure 2 and Figure 3.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

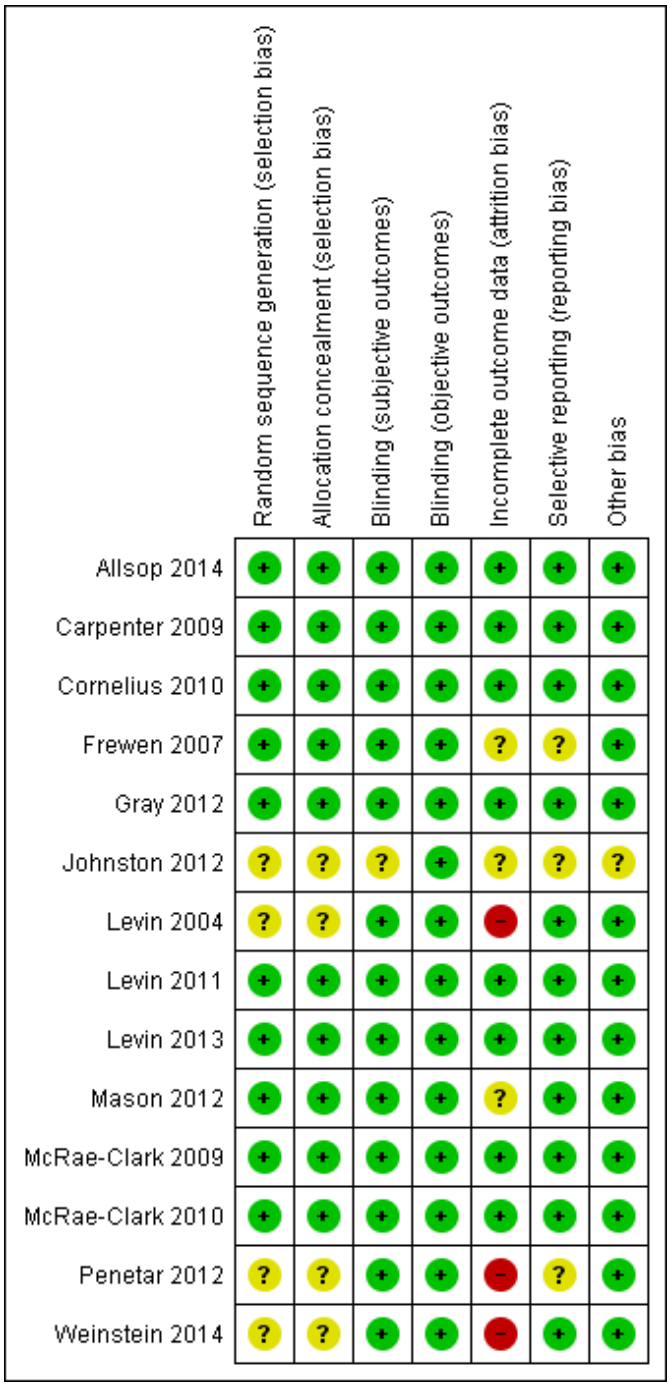
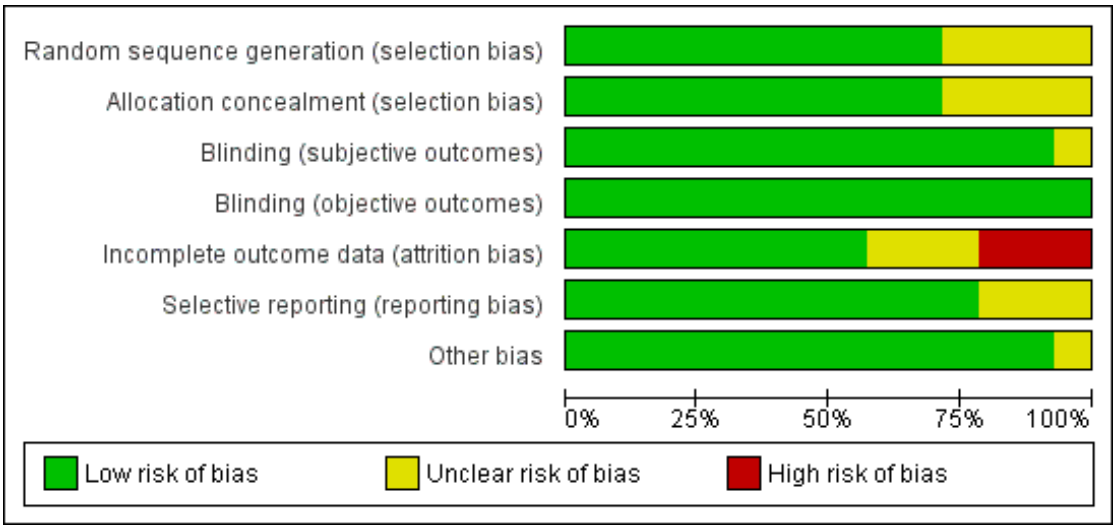


Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

For four studies (Johnston 2012; Levin 2004; Penetar 2012; Weinstein 2014) the risk of bias associated with both sequence generation and concealment of allocation was unclear. All four studies were double-blind and random allocation was stated but the methods of sequence generation and group allocation were not reported. The other studies were assessed as having a low risk of allocation bias.

Blinding

In one study (Johnston 2012) the risk of bias for subjective outcomes was unclear because the extent of blinding was unclear. Objective outcomes are unlikely to be affected by awareness of group allocation and hence we assessed Johnston 2012 as having a low risk of performance and detection bias in relation to objective outcomes.

All other studies were assessed as having a low risk of performance and detection bias for both subjective and objective outcomes.

Incomplete outcome data

This domain was considered only for the outcomes of intensity of withdrawal, adverse effects and abstinence (or use of cannabis). Completion of treatment was a primary outcome measure for the review. In three studies (Frewen 2007; Johnston 2012; Mason 2012) the risk of attrition bias due to incomplete data was unclear, and three studies (Levin 2004; Penetar 2012; Weinstein 2014) were assessed as being at high risk of attrition bias.

Selective reporting

Frewen 2007 was a secondary analysis of data from a randomised controlled trial and reported some but not all findings from the main study. The full report of the study was not available and hence the risk of reporting bias was unclear. Johnston 2012 was reported as conference abstracts only and insufficient information was available to assess the risk of reporting bias. Penetar 2012 did not discuss adverse effects making it unclear whether adverse effects were systematically assessed during the study.

Other potential sources of bias

In Johnston 2012 the risk of other sources of bias was unclear; all other studies were assessed as being at low risk of other sources of bias, such as recruitment bias, differential amounts of contact time or performance bias in the treatment groups being compared.

Effects of interventions

See: **Summary of findings for the main comparison** Abstinence at end of treatment; **Summary of findings 2** Withdrawal due to adverse effects; **Summary of findings 3** Completion of treatment

Results are presented for the outcomes identified as relevant to this review and then summarised by medication type. Where meta-analysis was possible, only subgroup totals were calculated because of the diversity of the medications that were investigated. The summary of findings tables include results only from those analyses where more than one study provided data.

Cannabis use

The only outcome relating to cannabis use for which meta-analysis was possible was the number of participants abstinent at the end of treatment (Analysis 1.1). These data were available for only four of the medication subgroups (THC preparations, SSRI antidepressants, mixed action antidepressants and anticonvulsants or mood stabilisers), with mixed action antidepressants being the only medication subgroup for which data were obtained from more than one study. There was no significant difference for any of these subgroups in the likelihood of abstinence from cannabis use at the end of treatment for active medication compared to placebo and, because of the small number of studies providing data and the small size of those studies, the quality of evidence in relation to this outcome was considered very low (Summary of findings for the main comparison).

Both studies using preparations containing THC (Allsop 2014; Levin 2011) reported a reduction in cannabis use over time but with no significant group differences. Allsop 2014 reported that weekly cannabis use decreased by an average 19.02 g/day (82%) from baseline to 28-day follow-up, and Levin 2011 reported that the median maximum consecutive days of abstinence was six for the Dronabinol group (interquartile range (IQR) 1 to 13) compared to five for the placebo group (IQR 2 to 16).

In Weinstein 2014 there was a tendency towards participants receiving escitalopram being abstinent at the end of treatment compared to those receiving placebo. However, the high rates of dropout from treatment in this study introduced a high risk of bias for this outcome. Cornelius 2010 compared fluoxetine with placebo and reported that the count of criteria for cannabis abuse or dependence (mean ± SD) at the end of treatment was 3.88 ± 2.51 for those treated with fluoxetine (N = 34) compared to 3.61 ± 1.92 for those receiving placebo (N = 36). There were no significant group by time interactions for cannabis or depression outcomes in this study.

The two studies that reported data on the number of participants abstinent at the end of treatment for mixed action antidepressants compared to placebo had divergent findings (see Analysis 1.1). In Levin 2013 significantly fewer participants treated with venlafaxine were abstinent at the end of treatment compared to participants receiving placebo. In contrast, in Carpenter 2009 there was a tendency towards abstinence being more likely with nefazodone compared to placebo. However, there was no significant difference in the severity of dependence rating (mean ± SD) at the end of treatment for the nefazodone group (2.5 ± 1.4) compared to the placebo group (2.3 ± 1.6). A third study (Frewen 2007) using a mixed action antidepressant (mirtazapine) did not report data suitable for inclusion in the meta-analysis but stated that mirtazapine had no effect on cannabis use, with less than 20% of participants reporting abstinence at day 56.

In addition to the data on abstinence in Analysis 1.1, Levin 2004 reported that at the end of treatment (weeks 7 and 8), participants in the divalproex group reported using cannabis on (mean ± SD) 2.75 ± 3.55 days/week, compared to 1.56 ± 2.34 days/week for the placebo group, and 4.88 ± 7.58 joints/week compared to 0.99 ± 1.18 joints/week for the placebo group. The group by time interaction was not statistically significant. For the anticonvulsant and mood stabiliser gabapentin, Mason 2012 reported a significant reduction in the grams of cannabis smoked per week, by self-report and urinalysis, and in the days of use per week for gabapentin compared to placebo (these data were not reported in a form suitable for inclusion in meta-analysis). Johnston 2012 did not report any data on cannabis use for lithium compared to placebo.

Carpenter 2009 reported no difference between the bupropion and placebo groups in terms of the severity of dependence rating (mean ± SD) at the completion of treatment (2.7 ± 1.5 for N = 40 receiving bupropion compared to 2.3 ± 1.6 for N = 30 receiving placebo).

In McRae-Clark 2009, those receiving buspirone (N = 23) had 45.2% days abstinent during the trial compared to 51.4% for the placebo (N = 27) group. The amount of cannabis used per day was reduced 91% in the buspirone group and 93% in the placebo group. These differences were not statistically significant.

In McRae-Clark 2010, 13 of 19 in the atomoxetine group compared with 9 of 19 in the placebo group had no days with heavy cannabis use during treatment. The atomoxetine group had 60.1 ± 31.5% days with cannabis use compared to 68.1 ± 31.3% for the placebo group (mean ± SD). The authors concluded that atomoxetine may improve some ADHD symptoms but does not reduce cannabis use.

Gray 2012 reported significantly greater likelihood of a negative urine cannabinoid test during treatment for the N-acetyl cysteine group compared to the placebo group (odds ratio 2.4, 95% CI 1.1 to 5.2; P = 0.029). However, there was no significant difference in the percentage of days during treatment with cannabis use, by self-report.

Intensity of withdrawal

Few studies reported data on the intensity of withdrawal, there was variability in the method of assessment of withdrawal, and available data were reported in different ways. As a result, meta-analysis of data on withdrawal intensity was not possible.

The two studies that compared preparations containing THC with placebo found that withdrawal scores decreased over time for both groups but the decrease was greater with the THC preparation than with placebo. Allsop 2014 reported that on average it took 3.1 ± 3.0 days for withdrawal scores to fall below baseline with nabiximols (N = 27) compared with 4.9 ± 3.16 days for placebo (N = 24). Nabiximols reduced the withdrawal score 66% on average from baseline compared to 52% for placebo. The group receiving nabiximols had significantly lower levels of cravings, irritability, anger and aggression. Levin 2011 similarly reported a reduction in the withdrawal discomfort scores for both the dronabinol (N = 79) and placebo (N = 77) groups, but found that participants on dronabinol experienced a significantly greater drop in their withdrawal scores over time.

Frewen 2007 focused on sleep quality and did not report the full assessment of withdrawal intensity during treatment with the mixed action antidepressant mirtazapine compared to placebo. The number of participants in each group was also not reported. In this study the overall difference in sleep between the mirtazapine and placebo groups over time was not significant. Significant improvements were observed for sleep duration and sleep quality but not for sleep disturbances.

Three studies (Johnston 2012; Levin 2004; Mason 2012) compared an anticonvulsant or mood stabiliser with placebo. Levin 2004 reported a reduction in craving over time but with no significant group differences between divalproex (N = 13) and placebo (N = 12). Mason 2012 reported significant reductions in acute withdrawal symptoms with gabapentin (N = 25) compared to placebo (N = 25). Johnston 2012 reported that lithium (N = 19) did not significantly reduce the total scores on the cannabis withdrawal scale relative to placebo (N = 19), but did significantly reduce the items loss of appetite, stomach aches and nightmares or strange dreams.

In Penetar 2012, following cessation of cannabis (days 8 to 21 of the scheduled treatment protocol), withdrawal discomfort scores increased significantly for the placebo group (N = 12) but not the bupropion group (N = 10) based on change from baseline. Craving scores also increased more for the placebo group.

McRae-Clark 2009 reported no significant difference between buspirone (N = 23) and placebo (N = 27) in terms of change in the mean withdrawal checklist score.

McRae-Clark 2010 reported no significant difference between atomoxetine (N = 19) and placebo (N = 19) in terms of change in marijuana craving score.

Adverse effects

Data on the number of participants experiencing any adverse effects (Analysis 1.2) suggested a tendency towards adverse effects being more likely with medication compared to placebo for preparations containing THC, buspirone and atomoxetine, but insufficient data were available to be conclusive. It appeared that the adverse effects experienced did not result in cessation of treatment (Analysis 1.3) and the number of participants withdrawing due to adverse effects was very small. The small number of events and differences between studies resulted in the evidence for this outcome being assessed as very low quality (Summary of findings 2).

Allsop 2014 reported that study participants receiving nabiximols (N = 27) on average experienced 6.96 ± 11.02 adverse effects compared with 5.54 ± 6.70 for those receiving placebo (N = 24). This was consistent with the data shown in Analysis 1.2 from Levin 2011, indicating a somewhat higher likelihood of adverse effects with medication containing cannabinoids compared to placebo.

No data were reported on adverse effects of SSRI antidepressants in a form that was suitable for inclusion in the meta-analysis, but Cornelius 2010 reported no moderate or severe adverse effects with fluoxetine and no participants withdrew from treatment due to adverse effects.

In Carpenter 2009, there was no significant difference in the number of participants experiencing adverse effects with nefazodone (a mixed action antidepressant) compared to placebo, but adverse effects were more likely to be moderate or severe with nefazodone. Diarrhoea was reported to be most common with nefazodone, and gastrointestinal upset with placebo.

No data suitable for inclusion in meta-analyses were reported on the adverse effects of anticonvulsants or mood stabilisers. Levin 2004 noted that medication compliance was low for divalproex, based on blood levels, but it was not clear whether the low rate of compliance was related to adverse effects. For gabapentin compared to placebo, Mason 2012 reported no differences between the groups in the type, number and severity of adverse events reported. For lithium compared to placebo, Johnston 2012 reported no significant difference in the number or severity of adverse effects.

No data suitable for inclusion in meta-analyses were reported on the adverse effects of bupropion, but Carpenter 2009 reported that adverse effects were more likely to be moderate or severe with bupropion compared to placebo. Headaches and nausea were most common with bupropion.

In McRae-Clark 2009, participants receiving buspirone were more likely to experience adverse effects compared to those receiving placebo (RR 1.23, 95% CI 0.99 to 1.53; P = 0.06) (Analysis 1.2). Dizziness was reported more frequently with buspirone. Dry mouth, flushing or sweating and cold-like symptoms were also more frequent with buspirone but the difference was not statistically significant. All adverse effects were noted as being mild to moderate in severity.

In McRae-Clark 2010, all adverse effects were reported as mild to moderate in severity. Sexual dysfunction and gastrointestinal side effects were more common with atomoxetine than placebo.

Gray 2012 reported no significant adverse events and no significant group differences in the occurrence of adverse events for N-acetylcysteine compared with placebo. One participant in the N-acetylcysteine group discontinued medication due to severe heart-

burn.

Completion of treatment

Preparations containing THC were the only medications where completion of the scheduled treatment was more likely with active medication (N = 106) compared to placebo (N = 101) (RR 1.29, 95% CI 1.08 to 1.55; P = 0.006) (Analysis 1.4). The quality of the evidence on completion of treatment was assessed as moderate quality for preparations containing THC and mixed action antidepressants; and very low quality for SSRI antidepressants, anticonvulsants or mood stabilisers, and the atypical antidepressant bupropion (Summary of findings 3).

Allsop 2014 also noted that participants receiving nabiximols remained in treatment for longer than those receiving placebo. Levin 2011 reported that the group receiving dronabinol attended more therapy sessions (8 ± 3.6) than those receiving placebo (6.8 ± 3.8) (mean±SD).

Weinstein 2014 compared an SSRI antidepressant with placebo and reported a high rate of dropout from the study (50%).

While not statistically significant, there was a tendency in Mason 2012 for participants receiving gabapentin to be less likely to complete treatment compared to those receiving placebo. Those receiving gabapentin remained in treatment for an average of 46.8 days compared to 48.7 days for those receiving placebo. Johnston 2012 reported no significant difference in retention rates for lithium compared to placebo.

Summary of effectiveness by medication type

(a) Preparations containing THC

The results of Allsop 2014 and Levin 2011 showed that preparations containing THC were more effective than placebo in reducing cannabis withdrawal symptoms and cravings. The THC preparations were associated with a somewhat higher likelihood of adverse effects, but these adverse effects were not sufficiently severe to cause withdrawal from treatment. Indeed, preparations containing THC were associated with significantly greater likelihood of completing treatment compared to placebo (RR 1.29, 95% CI 1.08 to 1.55; P = 0.006) (Analysis 1.4). However, THC preparations were not associated with increased likelihood of abstinence or a greater reduction in cannabis use.

(b) SSRI antidepressants

Neither of the studies comparing SSRI antidepressants with placebo (Cornelius 2010; Weinstein 2014) reported data on the intensity of withdrawal. No moderate or severe adverse effects were reported. Weinstein 2014 reported a high dropout rate with escitalopram and Cornelius 2010 found no significant difference in rates of completion of treatment for fluoxetine compared to placebo. Both studies reported no significant effect of these medications on cannabis use.

(c) Mixed action antidepressants

Three studies were included in this subgroup (Carpenter 2009; Frewen 2007; Levin 2013). Carpenter 2009 found that nefazodone had no significant effect on cannabis withdrawal symptoms. Frewen 2007 reported that mirtazapine improved sleep duration and quality but not sleep disturbances. In Carpenter 2009 there was no significant difference between nefazodone and placebo in the number of participants experiencing adverse effects, but adverse effects were more likely to be moderate or severe with nefazodone. There was no significant difference in rates of completion of treatment for this group of antidepressants compared to placebo. The effect on abstinence varied, with abstinence being significantly less likely with venlafaxine (Levin 2013) and somewhat more likely with nefazodone (Carpenter 2009), while Frewen 2007 reported that mirtazapine had no significant effect on cannabis use.

(d) Anticonvulsants and mood stabilisers

Gabapentin may have ameliorated cannabis withdrawal symptoms (Mason 2012) but it appeared that divalproex did not (Levin 2004), and lithium affected only some symptoms (Johnston 2012). Gabapentin (Mason 2012) and lithium (Johnston 2012) were not associated with adverse effects; information on adverse effects was not reported for divalproex although it was noted that compliance with medication was poor, based on blood levels. Neither medication affected retention in treatment. Gabapentin was associated with reduced cannabis use (Mason 2012) but divalproex was not.

(e) Atypical antidepressant (bupropion)

Bupropion had some capacity to reduce cannabis withdrawal and craving (Penetar 2012). Adverse effects were more likely with bupropion than with placebo. No data were available on rates of completion of treatment. Bupropion had no effect on cannabis dependence.

(f) Anxiolytic (buspirone)

A single study (McRae-Clark 2009) found buspirone to have no effect on cannabis withdrawal symptoms or cannabis use. Adverse effects were more likely with buspirone than with placebo; there were no data on rates of completion of treatment.

(g) Norepinephrine reuptake inhibitor (atomoxetine)

A single study (McRae-Clark 2010) found atomoxetine to have no effect on cannabis withdrawal symptoms, craving or cannabis use. Adverse effects were more likely with atomoxetine; there were no data on rates of completion of treatment.

(h) Glutamatergic modulator (N-acetylcysteine)

A single study (Gray 2012) found that the likelihood of negative urine tests for cannabis during treatment was greater with N-acetylcysteine than with placebo, but these data were not reported against the number of participants. Furthermore, there was no significant difference in self-reported cannabis use. No data were reported on the intensity of withdrawal symptoms or rates of completion of treatment. There was no significant difference between N-acetylcysteine and placebo in terms of adverse effects.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Active medication compared with placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Active Medication				
Number withdrawn due to adverse effects - mixed action antidepressants	**Study population**		**RR 1.44** (0.11 to 18.9)	179 (2 studies)	⊕◯◯◯ **very low**[1,2]	
	11 per 1000	**16 per 1000** (1 to 205)				
	Moderate					
	13 per 1000	**19 per 1000** (1 to 246)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Studies differ in direction of effect without significant heterogeneity
[2] Very few events and small group sizes

Active medication compared with placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Active Medication				
Completion of treatment - THC preparations	**Study population**		**RR 1.29** (1.08 to 1.55)	207 (2 studies)	⊕⊕⊕○ **moderate**[2]	
	614 per 1000	**792 per 1000** (663 to 951)				
	Moderate					
	618 per 1000	**797 per 1000** (667 to 958)				
Completion of treatment - mixed action antidepressants	**Study population**		**RR 0.93** (0.71 to 1.21)	169 (2 studies)	⊕⊕⊕○ **moderate**[2]	
	573 per 1000	**533 per 1000** (407 to 694)				
	Moderate					
	551 per 1000	**512 per 1000** (391 to 667)				
Completion of treatment - SSRI antidepressants	**Study population**		**RR 0.82** (0.44 to 1.53)	122 (2 studies)	⊕○○○ **very low**[1,2,3]	
	790 per 1000	**648 per 1000** (348 to 1000)				
	Moderate					

	766 per 1000	**628 per 1000** (337 to 1000)			
Completion of treatment - anticonvulsant and mood stabiliser	**Study population**		**RR 0.78** (0.42 to 1.46)	75 (2 studies)	⊕○○○ **very low**[2,3]
	405 per 1000	**316 per 1000** (170 to 592)			
	Moderate				
	387 per 1000	**302 per 1000** (163 to 565)			
Completion of treatment - atypical antidepressant (bupropion)	**Study population**		**RR 1.06** (0.67 to 1.67)	92 (2 studies)	⊕○○○ **very low**[2,3]
	429 per 1000	**454 per 1000** (287 to 716)			
	Moderate				
	400 per 1000	**424 per 1000** (268 to 668)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Significant heterogeneity between studies
[2] Studies small (<300 participants in total)
[3] One study at risk of attrition bias

DISCUSSION

Summary of main results

The medications considered by the studies that met the inclusion criteria for this review were diverse in nature. This and variability in the nature of data reported limited the extent of meta-analysis that was possible. In particular, limitations in data on intensity of withdrawal prevented any meta-analysis for this outcome. Obtaining consistent assessments of withdrawal is difficult in the context of clinical treatment, particular when undertaken in outpatient settings. For this reason, the discussion below incorporates some consideration of the findings from studies undertaken in controlled laboratory conditions that provide information on the capacity of the different medications to reduce cannabis withdrawal.

The quality of evidence available for assessment of effectiveness against the defined outcomes was generally very low (see Summary of findings for the main comparison, Summary of findings 2) other than for completion of treatment (preparations containing THC and mixed action antidepressants only) where the quality of the evidence was assessed as moderate (Summary of findings 3).

This section summarises the main results and considers information from studies that were excluded from this review so as to form a more complete view of the effectiveness of medications for the treatment of cannabis dependence.

(a) Preparations containing THC

Preparations containing THC are effective in suppressing cannabis withdrawal symptoms and craving, and are associated with better retention in treatment than placebo, but are not associated with reductions in cannabis use at least in the relatively short time frames of the studies included in this review (Allsop 2014; Levin 2011). The capacity of preparations containing THC to reduce withdrawal discomfort and craving with minimal adverse effects is supported by case reports (Levin 2008; Vandrey 2013) and laboratory studies (Budney 2007; Haney 2004). The use of medications such as lofexidine (Haney 2008) and zolpidem (Haney 2013a) as adjuncts may enhance the effectiveness of THC preparations in attenuating cannabis withdrawal and improving sleep. Effectiveness may also depend on the nature of the cannabinoid preparation used. Nabilone, a synthetic analogue of THC with higher bioavailability than dronabinol, has been used by Haney and colleagues in recent laboratory studies (Haney 2013; Haney 2013a); nabiximols, used by Allsop 2014, is an extract of cannabis containing THC and cannabidiol (another cannabinoid thought to be of therapeutic importance) in a controlled ratio. While the available information indicates that preparations containing THC have considerable potential for the treatment of cannabis dependence, further research is needed to determine the relative effectiveness of different preparations, the value of adjunct medications and therapies, as well as the appropriate duration of treatment before drawing conclusions on the therapeutic value of preparations containing THC.

(b) SSRI antidepressants

In a study of fluoxetine for the treatment of alcohol dependence and comorbid depression, Cornelius 1999 identified a subgroup of study participants who were cannabis users. In this subgroup, fluoxetine treatment was associated with decreased cannabis use relative to placebo. This study provided part of the rationale for the randomised controlled trial comparing fluoxetine and placebo for the treatment of cannabis use disorder and comorbid depression in the adolescents included in this review (Cornelius 2010). In Cornelius 2010 there was no significant difference between fluoxetine and placebo in the effect on cannabis related symptoms, and depressive symptoms improved in both groups. Similarly, Weinstein 2014 found little value for the SSRI escitalopram in the treatment of cannabis dependence. However, these medications may still be of value for the treatment of depression in cannabis users (Findling 2009).

(c) Mixed action antidepressants

The studies that were included in this review found that the mixed action antidepressants nefazodone (Carpenter 2009), mirtazapine (Frewen 2007) and venlafaxine (Levin 2013) are of little value in the treatment of cannabis dependence. In a laboratory study, Haney 2003a found that nefazodone decreased some cannabis withdrawal symptoms (anxiety, muscle pain) but that participants still reported substantial discomfort (irritability, feeling miserable, sleep quality), and also concluded that nefazodone has limited potential in the treatment of cannabis dependence. Similarly, a laboratory study of mirtazapine (Haney 2010) found that mirtazapine improved sleep during abstinence and increased food intake but had no effect on withdrawal symptoms and did not decrease cannabis relapse in the laboratory model. As with SSRI antidepressants, the mixed action antidepressants may be of value in the treatment of depressive symptoms with comorbid substance use disorder but appear to have little value specifically for the treatment of cannabis dependence.

(d) Anticonvulsants and mood stabilisers

Gabapentin (Mason 2012), but not divalproex (Levin 2004), has some capacity to ameliorate cannabis withdrawal symptoms and promote reduction in cannabis use compared to placebo. In a laboratory study divalproex was found to worsen mood and cognitive performance during cannabis withdrawal (associated with the smoking of placebo rather than active cannabis cigarettes) supporting the finding that divalproex is not helpful in the management of cannabis withdrawal. Preliminary studies suggested potential therapeutic value for lithium, particularly with comorbid bipolar

disorder (Geller 1998), but a subsequent randomised controlled trial that was included in this review found that lithium affected only some cannabis withdrawal symptoms and had no effect on retention in treatment (Johnston 2012).

(e) Atypical antidepressant (bupropion)

The studies that were included in this review (Carpenter 2009; Penetar 2012) indicated that bupropion may have some effect on cannabis withdrawal symptoms, but the data were inconclusive. A laboratory study (Haney 2001) found that bupropion was associated with increased ratings of irritability, restlessness, depression and trouble sleeping during the withdrawal phase when study participants were smoking placebo cannabis. The authors concluded that bupropion would not be an effective medication for the treatment of cannabis dependence.

(f) Anxiolytic (buspirone)

Buspirone showed promise in a preliminary study (McRae 2006) but the subsequent randomised controlled trial that was included in this review (McRae-Clark 2009) found it to have little value in the treatment of cannabis dependence. However, it may be useful for the treatment of anxiety in cannabis users.

(g) Norepinephrine reuptake inhibitor (atomoxetine)

Atomoxetine is used for the treatment of attention deficit hyperactivity disorder (ADHD) and the study included in this review (McRae-Clark 2010) investigated the effectiveness of atomoxetine in a population of cannabis users with ADHD. This study found atomoxetine to have little value in the treatment of cannabis dependence, but it may still be useful for the treatment of ADHD in cannabis users. An earlier open label pilot study of atomoxetine for the treatment of cannabis use disorders also found atomoxetine to have limited utility and to be associated with clinically significant gastrointestinal adverse effects.

(h) Glutamatergic modulator (N-acetylcysteine)

This dietary supplement may have some effectiveness in the treatment of cannabis dependence but available data (Gray 2012) were not conclusive.

Overall completeness and applicability of evidence

Studies undertaken to date on pharmacotherapies for cannabis dependence are insufficient to guide clinical practice. There is sufficient evidence to indicate that preparations containing THC and possibly the anticonvulsant gabapentin have therapeutic potential, while further investigation of the atypical antidepressant bupropion and the glutamatergic modulator N-acetylcysteine may be worthwhile. However, the anticonvulsants and mood stabilisers divalproex and lithium, SSRI and mixed action antidepressants, the anxiolytic buspirone and the selective norepinephrine reuptake inhibitor atomoxetine appear to be of little value in the treatment of cannabis dependence. At this point in time, psychological approaches such as motivational enhancement therapy and cognitive-behavioural therapy remain the mainstay of treatment for cannabis use disorders (Copeland 2014; Danovitch 2012).

The studies of preparations containing THC were of relatively short duration, Allsop 2014 administered nabiximols for six days while Levin 2011 administered dronabinol for eight weeks. A minimum of three months of treatment is generally considered necessary for the achievement of sustained behavioural change in people dependent on alcohol and other drugs. Indeed, the Cochrane review of nicotine replacement therapy for smoking cessation, which is a reasonable equivalent to preparations containing THC for cannabis dependence, only includes studies with at least six months follow-up data (Stead 2012). With a longer duration of treatment, in conjunction with psychological therapies focused on relapse prevention, it is possible that an effect on cannabis use may be seen with THC preparations.

Several other medications, including atypical antipsychotics and baclofen, have been explored for potential effects on cannabis use but no studies using these medications met the criteria for inclusion in this review.

The atypical antipsychotics olanzapine and risperidone were compared for the management of psychosis in patients with a history of cannabis use (Akerele 2007; Robinson 2006; Van Nimwegen 2008). The two medications were found to have similar efficacy on psychotic symptoms with no evidence of a differential effect on cannabis craving or use. Another atypical antipsychotic, quetiapine, was compared with placebo in a laboratory study (Cooper 2013). Relative to placebo, quetiapine improved sleep quality but was associated with increased marijuana craving and self-administration during the 'relapse' phase of the laboratory model.

The muscle relaxant and gamma-aminobutyric acid (GABA) derivative baclofen has been suggested to have therapeutic potential on the basis of case reports (Imbert 2014; Subodh 2011). In a laboratory study (Haney 2010), baclofen dose-dependently decreased craving for tobacco and cannabis during a phase of active cannabis smoking but had little effect on mood during abstinence and did not decrease 'relapse' in the laboratory model. Baclofen also worsened cognitive performance regardless of cannabis smoking phase. This suggests that the case reports may not be providing a full picture of the effects of baclofen in cannabis users.

Modafinil is a vigilance promoting drug that is being considered for the treatment of cocaine and methamphetamine dependence. Sugarman 2011 compared modafinil with placebo, alone and in combination with THC, in a laboratory study for a preliminary assessment of the safety of modafinil in combination with a range of doses of THC. While it was concluded that modafinil is safe in combination with THC, there were no data to indicate potential

effectiveness in the treatment of cannabis dependence.

Quality of the evidence

The studies included in this review were small, the quality of evidence was assessed as generally low (see Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3) and the capacity for meta-analysis was limited. As a result, the conclusions of this review should be considered tentative at best. Nonetheless, the review provides an overview of the current status of evidence and points to future directions for research on the development of pharmacotherapies for cannabis dependence.

Potential biases in the review process

Pharmacological approaches to the management of cannabis withdrawal are still in an experimental phase with a diverse array of medications being explored many of which have shown limited effectiveness. Studies with negative or neutral findings are less likely to be published and we identified two studies for which only limited information was available (Frewen 2007; Johnston 2012). It is possible that there are further such studies that we did not locate.

Agreements and disagreements with other studies or reviews

We have identified five recently published reviews of treatments for cannabis dependence (Benyamina 2008; Copeland 2014; Danovitch 2012; Nordstrom 2007; Vandrey 2009). All are in agreement that several pharmacotherapies, in particular preparations of THC, show promise for the treatment of cannabis dependence; but there is currently insufficient evidence to support their broad therapeutic use. These reviews also identify psychotherapies, such as motivational enhancement therapy and cognitive-behavioural therapy, as having demonstrated efficacy in decreasing cannabis use and cannabis related consequences. Hence these reviews support the conclusion that psychological approaches should continue to be the mainstay of treatment for cannabis use disorders, with pharmacotherapies continuing to be experimental.

AUTHORS' CONCLUSIONS

Implications for practice

There is incomplete evidence for all of the pharmacotherapies investigated in this review. Quantitative analysis was not possible for most of the outcomes and was limited for most of the pharmacotherapies investigated. The quality of evidence for many of the outcomes was downgraded due to small sample size, inconsistency and risk of attrition bias. The quantitative analyses that were possible, in combination with the general findings reported by the studies reviewed, indicate that SSRI antidepressants, mixed action antidepressants, atypical antidepressants (bupropion), anxiolytics (buspirone) and norepinephrine reuptake inhibitors (atomoxetine) are probably of little value in the treatment of cannabis dependence. There is moderate quality evidence that completion of treatment is more likely with preparations containing THC compared to placebo (RR 1.29, 95% CI 1.08 to 1.55; 2 studies, 207 participants, P = 0.006), and there is some evidence that treatment with preparations containing THC is associated with reduced cannabis withdrawal symptoms and craving; but there are no data on the effectiveness of THC preparations in promoting abstinence or reduced cannabis use in people who are cannabis dependent. Hence it is concluded that preparations containing THC are of potential value but the limitations in the evidence are such that this application of THC preparations should be considered to still be experimental. The evidence base for the anticonvulsant gabapentin and the glutamatergic modulator N-acetylcysteine is weak and at this time it is not possible to quantitatively estimate their effectiveness.

Implications for research

Preparations containing THC should be investigated further for the treatment of cannabis dependence. The use of nicotine replacement therapies to promote cessation of tobacco smoking provides a parallel context on which to model further research. Further studies should compare the effectiveness of different preparations, doses and duration of treatment, adjunct medications and therapies.

Gabapentin and N-acetylcysteine are also worth further consideration to provide alternative medication approaches, but SSRI and mixed action antidepressants, the atypical antidepressant bupropion, the anxiolytic buspirone and the selective norepinephrine reuptake inhibitor atomoxetine appear to be of limited value in the treatment of cannabis dependence other than for the management of relevant concomitant conditions.

ACKNOWLEDGEMENTS

None

REFERENCES

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allsop 2014

Methods	Double-blind, randomised, placebo-controlled trial. Setting: inpatient (two hospitals), New South Wales, Australia. Funding: research grant (Australian National Health and Medical Research Council), with study drugs provided by manufacturer (GW Pharmaceucticals, UK). Declaration of conflict of interest not published
Participants	N = 51 adults seeking treatment for cannabis use, dependent by DSM-IV-TR. Average age 35; 76% male; 53% unemployed; 25% married or in de facto relationship; on average using 23 g cannabis per day, average duration of use 20 years; 71% also nicotine dependent. Dependence on alcohol or other drugs except nicotine or caffeine and unstable medical or psychiatric conditions were exclusion criteria. Groups well matched apart from differences in baseline withdrawal score and disability scale scores
Interventions	(1) N = 27, nabiximols (cannabis extract, Sativex®), maximum dose 86.4 mg THC, 80 mg cannabidiol; 6 days medication, 3 days washout, or (2) N = 24, placebo. Cognitive-behavioural therapy tailored to inpatient cannabis withdrawal as adjunct intervention. Total 9 days inpatient admission. Follow-up interview after 28 days. Participants compensated AUD 40 for follow-up interviews
Outcomes	Overall withdrawal score, irritability, craving, and depression reported as graphs and results of statistical analyses with imputation for missing data. Number retained in treatment at all time points, median days inpatient stay. Change in amount of cannabis use from baseline to 28-day follow-up
Notes	Withdrawal and craving assessed with Cannabis Withdrawal Scale (19 items on 11-point Likert scale for the previous 24 hours). Drug use by modified timeline follow-back

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent statistician generated a randomization list for each site using random block sizes in Stata, version 11.1 . .."
Allocation concealment (selection bias)	Low risk	Comment: Method of allocation concealment not reported, but generation of lists by independent statistician and use of matching placebos would be expected to provide good control of bias
Blinding (subjective outcomes) All outcomes	Low risk	Quote: "Patients, investigators, and outcome assessors were blind to treatment al-

Allsop 2014 (*Continued*)

		location until all research procedures were complete. Blinding was maintained by the use of a matched placebo ... The success of patient blinding was formally assessed before hospital discharge."
Blinding (objective outcomes) All outcomes	Low risk	Quote: "Patients, investigators, and outcome assessors were blind to treatment allocation until all research procedures were complete. Blinding was maintained by the use of a matched placebo ... The success of patient blinding was formally assessed before hospital discharge."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Statistical methods used to impute missing data and assess data as missing at random
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Carpenter 2009

Methods	Double-blind, randomised, placebo-controlled trial. Setting: outpatient clinic, New York, USA. Funding from research grant (NIDA). One author declared past associations with pharmaceutical companies
Participants	N = 106 participants seeking treatment for problems related to cannabis use, cannabis dependent by DSM-IV and smoking at least 5 cannabis joints per week. Average age 32; 76% male (63% in bupropion group); 34% Caucasian, 28% Hispanic, 27% African-American; 91% employed. Exclusion criteria for the trial included "significant and unstable psychiatric condition", "chronic organic mental disorder" and "DSM-IV dependence criteria for another substance"
Interventions	Placebo for 1 week then (1) N = 36, oral nefazodone, 150 mg/day to maximum 600 mg/day (2) N = 40, oral bupropion-SR 150 mg to maximum of 300 mg/day, or (3) N = 30, oral placebo for 10 weeks. Riboflavin added to medication to monitor adherence. All participants received placebo for 2 weeks after medication phase. Participants attended treatment clinic twice weekly (paid USD 5 for transport costs at each visit); medications dispensed weekly. Weekly individual psychosocial intervention based on coping skills as adjunct therapy. Scheduled duration 13 weeks
Outcomes	Number completing 13 weeks of study, number abstinent at week 10, dependence severity at baseline and week 10 (and improvement), withdrawal symptoms, sleep, HAM-A at baseline and week 10. Total side effects during study

Notes	Cannabis use assessed by self-report and urine toxicology of observed samples provided at each clinic visit, with a cut-off of 100 ng/ml (rather than usual 50 ng/ml) to minimise false positives. Severity of dependence symptoms assessed by Clinical Global Impression (scores from 1 = no pathology, to 7 = extreme pathology). Sleep quality self-reported once a week using the St Mary's Hospital Sleep Questionnaire. Irritability self-reported every other week with the Snaith Irritability Scale (4 items each rated 0 to 3). Hamilton anxiety scale (14 items each rated 0 to 4) administered by clinician every other week. If either urine or self-report data were missing for a given week, it was considered a non-abstinent week

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A research pharmacist who was independent of the research team, conducted the randomization" Comment: Method of sequence generation not reported, but the involvement of an independent pharmacist would be expected to protect against bias
Allocation concealment (selection bias)	Low risk	Quote: "All capsules were prepared at the research pharmacy and looked identical for all three treatment conditions" Comment: although not specifically stated, treatment allocation was likely to have been through medication provided by the research pharmacist making it unlikely that participants or investigators could foresee intervention assignment. Characteristics of participants in three groups similar, except significantly more females in bupropion group
Blinding (subjective outcomes) All outcomes	Low risk	Study stated to have been conducted double-blind, without specification as to whether participants, observers and treating personnel were all blinded to group allocation. However, the provision of active and placebo medications in identical capsules, and the use of urine screening to support self-report data would be expected to be associated with a low risk of bias
Blinding (objective outcomes) All outcomes	Low risk	Study conducted double-blind and these outcomes less likely to be affected by knowledge of treatment allocation. The use of riboflavin to confirm medication adher-

Carpenter 2009 (*Continued*)

		ence would help to reduce the risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was substantial dropout from all three groups, with only 52 of 106 (49%) participants randomised completing the 10-week medication phase and 43% completing the full 13-week trial. Quote: "Survival analysis revealed no statistically significant group differences on treatment retention... there were no differences between those participants who completed the trial and those who did not on demographic indices or baseline substance use measures." Comment: Missing data on cannabis use regarded as indicative of "non-abstinence"; statistical methods used to allow for missing data
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Cornelius 2010

Methods	Double-blind, randomised, placebo-controlled trial. One physician remained non-blinded to handle any potential problems. Setting: outpatient clinic, Pittsburgh, USA. Funding from research grants (NIDA, NIAAA, Veterans Affairs). All authors declared no conflict of interest
Participants	N = 70 adolescents and young adults (aged 14 to 25 at baseline) with comorbid major depression and cannabis use disorder by DSM-IV criteria. Average age 21.1; 61% male; 56% Caucasian, 37% African-American; 94% cannabis dependent, using on average of 76% of days in prior month; 28.6% also alcohol dependent. Bipolar disorder, schizoaffective disorder, schizophrenia, substance abuse or dependence other than alcohol, nicotine or cannabis, history of IV drug use were exclusion criteria
Interventions	(1) N = 34, fluoxetine, 10 mg increasing to 20 mg/day after 2 weeks (2) N = 36, placebo. Nine sessions (delivered at each clinic visit) of manual-based cognitive-behavioural therapy for depression and cannabis use and motivation enhancement therapy for cannabis use as adjunct intervention. Scheduled duration 12 weeks
Outcomes	Severity of abuse or dependence (criteria count), days cannabis used in past week, number completing treatment
Notes	Depressive symptoms rated by observer with Hamilton Rating Scale for Depression and by participants with Beck Depression Inventory. Cannabis use behaviours assessed by timeline follow-back method

Cornelius 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patient randomization was conducted by urn randomization stratified by gender…"
Allocation concealment (selection bias)	Low risk	"Active medication and matching placebo were prepared by the research pharmacy…"
Blinding (subjective outcomes) All outcomes	Low risk	Quote: "The study was conducted in a double-blind fashion, though [one] physician . .. remained non-blinded in order to handle any problems which may have arisen." This suggests it is likely that participants, treating personnel and observers were all blind to group allocation
Blinding (objective outcomes) All outcomes	Low risk	Study conducted double-blind, as indicated above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors note "low percentage of missing data". Missing data handled by carrying forward last observation
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Frewen 2007

Methods	Double-blind, randomised, placebo-controlled trial. Setting: outpatient, Sydney, Australia. Funding: not reported. No declaration of conflict of interest made
Participants	N = 81 adults, seeking treatment for cannabis use, used cannabis in 72 hours prior to assessment interview, dependent by DSM-IV-TR in previous 3 months. Average age 31. 4; 81% male; 78% Australian-born; 64% employed; 92% living in stable accommodation; 63% not in a relationship. Average of 12 years cannabis use; 97% daily smokers; 63% daily tobacco smokers. Psychiatric or medical instability were exclusion criteria. Characteristics of participants similar to characteristics of general population seeking treatment for cannabis use
Interventions	1) Oral mirtazapine 30 mg/day or 2) placebo Weekly individual cognitive-behavioural therapy as adjunct intervention Reimbursement of AUD 30 for expenses at the day 56 interview Scheduled 4 weeks medication, with follow-up 28 days later

Outcomes	Withdrawal symptoms in first seven days related to subsequent cannabis use for groups combined (effect of medication not considered in this analysis). Measures of sleep quality and disruption
Notes	Withdrawal symptoms measured daily for 14 days with the Marijuana Withdrawal Scale (32 items, rated from 0 = "none" to 3 = "severe"). Cannabis use assessed with the drug scale from the Opiate Treatment Index Sleep problems recorded with the Karolinksa Sleep Questionnaire for 7 days, and the Pittsburgh Sleep Quality Index (24 items, global score 0 to 21, with higher scores indicative of poorer sleep) at baseline and days 28 and 56

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomized ... using permuted block randomisation."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was independently assigned by pharmacy staff offsite." " ... the placebo was identically matched in colour, shape, size and taste to the medication." Comment: As independent pharmacy staff controlled the randomization process, it is likely to have prevented investigators and participants from foreseeing allocation assignment
Blinding (subjective outcomes) All outcomes	Low risk	Quote: "All treating physicians, psychologists and research staff were blind to the randomisation until all participants had completed the final research interview."
Blinding (objective outcomes) All outcomes	Low risk	Quote: "All treating physicians, psychologists and research staff were blind to the randomisation until all participants had completed the final research interview."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information available to form a view
Selective reporting (reporting bias)	Unclear risk	Limited study results available
Other bias	Low risk	None apparent

Gray 2012

Methods	Double-blind, randomised, placebo-controlled trial. Setting: outpatient, university clinic, South Carolina, USA. Funding: research grants (NIDA, National Center for Research Resources). Authors declared "no competing interests"
Participants	N = 116 adolescents (age 13 to 21), cannabis-dependent and using cannabis regularly. Average age 18.9 years; 73% male; 83.5% Caucasian; 73.9% enrolled in school. Average 22.6 days with cannabis use in 30 days prior to baseline; 57% smoked tobacco; 13.8% had a psychiatric comorbidity. Dependence on other substances (except nicotine) and unstable psychiatric or medical illness were exclusion criteria
Interventions	(1) N = 58, N-acetylcysteine 1200 mg twice daily or (2) N = 58, placebo. Twice-weekly contingency management and weekly brief (10 minute) individual cessation counselling as adjunct therapies. Initial contingent reward USD 5 (cash) for both adherence and abstinence with amount increased by USD 2 for each successive visit; reward reset to baseline if conditions not met. Seen in clinic weekly. Follow-up 4 weeks after treatment conclusion. Scheduled duration 8 weeks
Outcomes	Likelihood of negative urine test reported as odds ratio and 95% confidence interval. Occurrence of adverse events (number of events and number of participants). Proportion of medication doses consumed, discontinuation of medication due to adverse effects. Number completing treatment, median days in treatment, contingency rewards earned
Notes	Urine cannabinoid testing at all visits. Self-reported cannabis use by timeline follow-back. Medication diaries and weekly pill counts used to determine adherence. Participants lost to follow-up or absent for visits were coded as having a positive urine test

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised in 1:1 parallel group allocation stratified by age and baseline cannabis use. No significant group differences at baseline suggesting appropriate sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "university investigational drug service oversaw randomization, encased medication in identical-appearing capsules, and dispensed them in weekly blister packs..."
Blinding (subjective outcomes) All outcomes	Low risk	Quote: "Participants, investigators and clinical staff remained blind to treatment assignment throughout the study."
Blinding (objective outcomes) All outcomes	Low risk	Quote: "Participants, investigators and clinical staff remained blind to treatment assignment throughout the study."

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data and non-attendance regarded as indicating non-abstinence
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Johnston 2012

Methods	Double-blind, randomised, placebo-controlled trial. Setting: inpatient withdrawal unit; Sydney, Australia. Funding source not reported. No declaration of conflict of interest made
Participants	N = 38 cannabis dependent adults. No other participant characteristics reported
Interventions	(1) N = 19, lithium carbonate, 500 mg bd or (2) N = 19, placebo. Scheduled 7 days inpatient treatment. Follow-up at 14, 30 and 90-days post-discharge
Outcomes	Withdrawal severity by Cannabis Withdrawal Scale; retention; number and severity of adverse effects
Notes	Conference abstracts only - limited data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random allocation stated; method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Random allocation stated; method of allocation concealment not reported
Blinding (subjective outcomes) All outcomes	Unclear risk	Double-blind stated, but adequacy of control for assessment of subjective outcomes (withdrawal severity) unclear
Blinding (objective outcomes) All outcomes	Low risk	Double-blind stated and these outcomes unlikely to be affected by awareness of group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information reported to assess risk
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported to assess risk

Johnston 2012 (*Continued*)

Other bias	Unclear risk	Insufficient information reported to assess risk

Levin 2004

Methods	Double-blind, randomised, placebo-controlled trial. Study included a cross-over phase which was not included in this review due to substantial dropout (> 30%) in the first 2 weeks. Setting: outpatient with two clinic visits per week; New York, USA. Funding: Research grants (NIDA). Declaration of conflict of interest not published
Participants	N = 27 enrolled, N = 25 randomized; cannabis dependent by DSM-IV, using daily. Average age 32; 92% male; 56% Caucasian, 20% Hispanic, 24% African American; average (± SD) joints smoked per week at baseline (1) 28.3 ± 23.2 (2) 19.4 ± 16.4. Dependence on other substances, except caffeine and nicotine, and psychiatric disorder requiring medical intervention were exclusion criteria
Interventions	Two-week single-blind placebo lead-in phase, then (1) N = 13, oral divalproex sodium commenced at 500 mg/day, increasing to maximum of 2 g/day, depending on response, or (2) N = 12, placebo. Medication in 2 doses per day. Weekly individual cognitive-behavioural relapse prevention therapy as adjunct. Scheduled duration 8 weeks (plus subsequent cross-over phase that was excluded from this review)
Outcomes	Outcomes reported for N = 19 who completed 8 weeks of study: frequency and amount of cannabis use and craving score at baseline and weeks 7 and 8; number completing scheduled treatment; number with 2 or more weeks of assumed abstinence
Notes	Urine samples collected and analysed at each visit. Participants reported cannabis use and completed a visual analogue scale of intensity and desire for cannabis each week. Clinician-rated global impression assessment for cannabis use completed weekly. "Strict abstinence" defined as at least one negative urine sample and no self-reported cannabis use for that week. "Assumed abstinence" if patient reported no cannabis use and urine samples had THC-COOH levels at least 50% below the previous week

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Twenty-seven participants were enrolled and 25 were randomized." Comment: method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Quote: [participants] "...were randomly assigned to receive either divalproex or a matching placebo." Comment: method of allocation concealment not reported

Levin 2004 (*Continued*)

Blinding (subjective outcomes) All outcomes	Low risk	Quote: "Following randomization, patients received...either divalproex sodium or a placebo using a double-blind design" Comment: use of urine screening to support determination of "abstinence" would be expected to help reduce bias in these outcomes
Blinding (objective outcomes) All outcomes	Low risk	Quote: "Following randomization, patients received...either divalproex sodium or a placebo using a double-blind design" Comment: these outcomes considered unlikely to be affected by knowledge of group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Rates of dropout were similar in the two groups, but there was no discussion of possible differences between those retained and those who dropped out of the study. Cannabis use outcomes were reported only for those who completed treatment
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	The cross-over phase of the trial was excluded from analyses and this review due to high rates of dropout in the first two weeks

Levin 2011

Methods	Randomised, double-blind, placebo-controlled, trial. Randomisation after 1-week placebo lead-in phase. Those who used cannabis less than twice a week during the placebo lead-in phase were not randomised. Setting: outpatient with clinic attendance twice weekly, New York, USA. Funding: research grant (NIDA). One author declared prior associations with pharmaceutical companies
Participants	N = 156 adults seeking outpatient treatment for problems related to cannabis use, dependent by DSM-IV-TR, using cannabis at least 5 days a week in prior 28 days. Average age 38; 82% male; 60% employed full-time, 13% part-time; 31% married. Significant psychiatric condition and dependence on other substances except nicotine were exclusion criteria. No significant group differences in demographic or clinical characteristics at baseline
Interventions	Placebo for 1 week, then 1) N = 79, oral dronabinol, commenced at 10 mg/day, titrated to 20 mg twice a day or the maximum tolerated, or 2) N = 77, placebo. Medication maintained to end of week 8 then tapered over 2 weeks. Weekly individual therapy based on coping skills plus motivational enhancement therapy as adjunct intervention. Participants earned vouchers with value increased by USD 1.50 for each consecutive

	visit, with value reset for non-attendance, and USD 10 for returning their pill bottle and remaining medication. Maximum possible earnings were USD 570. Cash payments of USD 5 to 20 were made at each visit for transport costs
Outcomes	Number achieving 2 weeks abstinence in weeks 7 and 8 and median maximum consecutive days abstinence; number retained in study to week 8; average number of therapy sessions attended; number experiencing any adverse effects, requiring dose reduction, serious adverse events and number withdrawn due to adverse events; withdrawal scores reported as graph and results of statistical modelling; medication compliance
Notes	Cannabis use assessed by timeline follow-back. Urine samples tested at each clinic visit for confirmation of self-report. Withdrawal symptoms assessed twice a week using the Withdrawal Discomfort Score (10 items, scores 0-30). Craving by Marijuana Craving Questionnaire with the 47-item version completed once a month, and the 12-item version weekly. Side effects assessed twice a week using the Modified Systematic Assessment for Treatment and Emergent Events (SAFTEE). Hamilton Anxiety and Depression scales used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomized ... using a fixed block size of 4, stratified by joints used per week…and whether or not they were receiving a psychotropic medication."
Allocation concealment (selection bias)	Low risk	Quote:"A research pharmacist, who was independent of the research team, conducted the randomization."
Blinding (subjective outcomes) All outcomes	Low risk	Quote: "Donabinol...or matching placebo. ..was prepared by the pharmacy...packaged in matching gelatin capsules with lactose filler and an equal amount of riboflavin. All capsules looked identical..." Comment: double-blind stated. Participants may have been able to distinguish the effects of dronabinol, but use of urine screening to support self-report would be expected to reduce risk of bias
Blinding (objective outcomes) All outcomes	Low risk	Double-blind stated. Packaging of medication in identical capsules as above. Objective outcomes less likely to be influenced by awareness of group allocation

Levin 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All analyses were conducted on the intent-to-treat population." "...missing data in weeks 7 and 8 were scored as indicating cannabis use..."
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Levin 2013

Methods	Randomised, double-blind, placebo-controlled trial. Outpatient setting with twice weekly clinic attendance, New York, USA. Funding: research grants (NIDA). Two authors declared prior associations with pharmaceutical companies
Participants	N = 103 seeking treatment for problems related to cannabis use, cannabis dependence and major depressive disorder or dysthymia by DSM-IV. Average age 35; 74% male; 40% working full-time; 18% currently married; average 27.4 days of use in month prior to baseline. No significant group differences on demographic or clinical characteristics at baseline. Physical dependence on substances other than cannabis or nicotine was an exclusion criterion
Interventions	One-week placebo lead-in phase - those who improved as assessed by Clinical Global Impression rating were not randomised. (1) N = 51, venlafaxine-extended release, up to 375 mg on a fixed-flexible schedule or (2) N = 52, placebo. Medication dose titrated over 3 weeks, then maintained for 8 weeks. Weekly individual cognitive behavioural therapy that primarily targeted cannabis use as adjunct intervention. Participants received USD 5 to 20 per visit for transport costs, and USD 10 per week if they returned their pill bottles and any remaining medication. Scheduled duration 12 weeks
Outcomes	Abstinence defined by 2 or more consecutive urine-confirmed abstinent weeks. Improvement in depressive symptoms by Hamilton Depression Rating Scale
Notes	Cannabis use assessed by timeline follow-back. Urine THC levels tested at each visit, with cut-off of 100 ng/ml to decrease the probability of false positives. Side effects assessed weekly using the Modified Systematic Assessment for Treatment and Emergent Events

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomized at the end of the [placebo] lead-in phase using a computer-generated fixed-block size of 4, with a 1: 1 allocation ratio, and stratified by joints used per week...and severity of depression" Comment: similarities of groups at base-

Levin 2013 (*Continued*)

		line suggest adequate method of sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "A research pharmacist, who was independent of the research team, conducted the randomization and maintained the allocation sequence." Venlafaxine or placebo "was prepared by the pharmacy... packaged in matching gelatin capsules with lactose filler." Comment: allocation by pharmacy and identical appearance of medication and placebo would support adequate concealment of allocation
Blinding (subjective outcomes) All outcomes	Low risk	Quote: "Participants, care providers and outcome assessors were kept blinded to the allocation."
Blinding (objective outcomes) All outcomes	Low risk	Quote: "Participants, care providers and outcome assessors were kept blinded to the allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patients who dropped out were significantly younger and less likely to be married, but rates of dropout were similar in the two arms. Those who dropped out without achieving 2 continuous weeks of abstinence were classified as not abstinent
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Mason 2012

Methods	Randomised, double-blind, placebo controlled trial. Setting: outpatient with weekly clinic visits, California, USA. Funding: research grants (NIDA). One author declared past associations with pharmaceutical companies
Participants	N = 50 treatment-seeking volunteers with current cannabis dependence by DSM-IV, smoked cannabis at least once in week prior to randomisation. Average age 33.9 years, 88% male, average 11.6 years of daily cannabis use, smoking an average of 11.0 g/week; 62% employed full-time; 40% married. Abuse or dependence on substances other than cannabis or nicotine, and significant psychiatric disorders were exclusion criteria. No significant group differences on demographic or clinical variables at baseline

Mason 2012 (*Continued*)

Interventions	1) N = 25, oral gabapentin 300 mg, increasing to 1200 mg/day, or 2) N = 25, matched placebo. Abstinence-oriented individual counselling weekly. Scheduled duration 12 weeks
Outcomes	Change in amount of cannabis use, frequency of use and withdrawal symptoms, as graphs and results of statistical tests. Number completing treatment
Notes	Cannabis use by weekly urine toxicology and self-report by timeline follow-back interview. Withdrawal symptoms by Marijuana Withdrawal Checklist. Marijuana Problems Scale completed at baseline and end of treatment (week 12)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "subjects were randomly assigned … in a 1:1 ratio, on the basis of a computer-generated randomization code."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization code was kept by the study pharmacist, who provided subjects with a 1-week supply of medication in a blister card package at each weekly study visit…" Comment: allocation by pharmacy and identical appearance of medication and placebo would support adequate concealment of allocation
Blinding (subjective outcomes) All outcomes	Low risk	Quote: "Subjects, care providers, and those assessing outcomes were blinded to the identity of drug assignment. Gabapentin was purchased and over-encapsulated to match placebo capsules."
Blinding (objective outcomes) All outcomes	Low risk	Quote: "Subjects, care providers, and those assessing outcomes were blinded to the identity of drug assignment. Gabapentin was purchased and over-encapsulated to match placebo capsules."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High rate of dropout. Extent of missing data, and adjustments for missing data unclear
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

McRae-Clark 2009

Methods	Randomised, double-blind, placebo-controlled trial. N = 93 randomised; N = 34 did not receive study drug (21 failed to return for second baseline visit); analysis based on those randomised who received study drug and completed at least one post-baseline visit. Setting: outpatient with clinic visits 1 to 2 times per week, South Carolina, USA. Funding: research grant (NIDA). Two authors declared past associations with pharmaceutical companies
Participants	N = 50 with current cannabis dependence by DSM-IV. Average age 31.6; 90% male; 86% Caucasian; on average used cannabis on 89% of days prior to study entry, using average 3.8 g/day. Dependence on other substances except caffeine or nicotine, history of psychotic disorder, current major depression were exclusion criteria. Treatment groups similar on baseline characteristics
Interventions	(1) N = 23, oral buspirone, initiated at 5 mg twice a day, increased 5 to 10 mg every 3 to 4 days as tolerated to maximum 60 mg per day or (2) N = 27, placebo. Motivational interviewing (3 sessions) as adjunct intervention for first four weeks. Subjects received USD 10 for time and travel associated with study visits. Scheduled duration 12 weeks
Outcomes	Urinalysis data reported as per cent of screens that were negative, not participants with negative screens. Mean change in withdrawal score. Number experiencing any adverse effect. Number completing treatment. Change in reported cannabis use per using day, % days abstinent during study
Notes	Cannabis use by timeline follow-back for 90 days prior to study entry, and weekly throughout the study. Craving by Marijuana Craving Questionnaire, withdrawal, by Marijuana Withdrawal Checklist. Urine drug screens at baseline and weekly during study. Side effects evaluated weekly with open-ended questions. Adjustment for missing data by last observation carried forward

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Urn randomization ...was used to determine treatment assignment. Urn variables used were age ... gender, and [anxiety] score..."
Allocation concealment (selection bias)	Low risk	Quote: [participants] "Randomized at central pharmacy..." "Buspirone and placebo tablets were packaged in identical opaque gelatin capsules with cornstarch."
Blinding (subjective outcomes) All outcomes	Low risk	Double-blind stated. Urinalysis to support self-report data would be expected to reduce bias, although authors noted some inconsistencies between urine screen and self-report data

McRae-Clark 2009 (*Continued*)

Blinding (objective outcomes) All outcomes	Low risk	Double-blind stated and these outcomes considered unlikely to be affected by awareness of group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	High rate of dropout but statistical methods used to adjust for missing data (GEE modelling and last observation carried forward)
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

McRae-Clark 2010

Methods	Randomised, double-blind, placebo-controlled trial; 78 participants were randomised but only 46 received study medication and only 38 returned for at least one post-baseline assessment. Analyses based on this group. Setting: outpatient, South Carolina, USA. Funding: research grants (NIDA), with medication and placebo provided by manufacturer (Eli Lilly and Company). Two authors declared past associations with pharmaceutical companies
Participants	N = 38 adults, cannabis dependence and attention deficit hyperactivity disorder (with age of onset before 12 years of age) by DSM-IV. Average age 29.9 years; 76% male; 92% Caucasian; used cannabis on average 87% of days prior to baseline, using average of 4.1 times per day. Dependence on other substances except caffeine or nicotine, and other psychiatric disorders were exclusion criteria. No significant group differences on baseline characteristics
Interventions	(1) N = 19, oral atomoxetine started at 25 mg, increased to 40 mg in week 2, and to 80 mg in week 3 as tolerated, with further increase to 100 mg/day in week 4 if required, or (2) N = 19, matching placebo. Motivational interviewing (3 sessions) as adjunct intervention. Nominal monetary reimbursement for completion of study assessments. Scheduled duration 12 weeks
Outcomes	Self-reported cannabis use during week 12 (last observation carried forward for participants who did not complete the trial). Number completing treatment. Change in craving scores. Number experiencing adverse effects and type of adverse effects
Notes	Cannabis use self-reported by timeline follow-back weekly and assessed by Clinical Global Impression of Severity and Improvement Scales. Urine drug screens at baseline and then weekly. Medication side effects weekly by standard checklist. Craving by Marijuana Craving Questionnaire. Compliance assessed by patient report and pill count

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

McRae-Clark 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Simple randomization was used to assign treatments to participants using a 1: 1 allocation ratio."
Allocation concealment (selection bias)	Low risk	Quote: "...participants were randomized at the central pharmacy..."
Blinding (subjective outcomes) All outcomes	Low risk	Double-blind stated. Use of matching capsules along with urine screening to validate self-report data would be expected to reduce the risk of bias
Blinding (objective outcomes) All outcomes	Low risk	Double-blind stated and these outcomes unlikely to be affected by awareness of group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	High rates of dropout in both groups. Last observation carried forward and statistical techniques used to allow for missing data
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Penetar 2012

Methods	Randomised, double-blind, placebo-controlled trial. Setting: outpatient with daily clinic attendance Monday to Friday, Harvard Medical School, USA. Funding: research grant (NIDA). Disclosures of interests according to ICMJE criteria were a requirement of publication
Participants	N = 22 treatment seeking, with cannabis abuse or dependence by DSM-IV, with at least 3 years of heavy use (smoking on 5 or more days a week or more than 25 times per month) and with 2 or more negative symptoms in previous quit attempts. Demographic data were provided only for N = 9 who completed the study (5 male, average age 31.2 years, 7 met criteria for dependence). Abuse or dependence on any other drug (including nicotine) was an exclusion criterion
Interventions	Participants used cannabis as usual for 7 days then commenced 1) N = 10, oral bupropion-SR (sustained release) 150 mg/day for days 1 to 3, then 150 mg twice a day or 2) N = 12, placebo. Cannabis use stopped on day 8 (Quit Day). Tobacco and caffeine continued throughout the study. Weekly individual motivational enhancement therapy (3 sessions) as adjunct intervention. Scheduled duration 21 days
Outcomes	Data reported as graphs and results of statistical tests. Relevant outcomes reported were completion of study, change in withdrawal discomfort and change in craving

Notes	Withdrawal by Marijuana Withdrawal Checklist (29 items each rated 0-3). Withdrawal discomfort score calculated from 10 items (max score 30). Drug use, sleep and withdrawal recorded by participants in daily diary. With each medication administration participants consumed identical appearing capsule that contained riboflavin to measure compliance. Urine testing to confirm drug use

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random allocation to treatment group stated, but method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding (subjective outcomes) All outcomes	Low risk	Double-blind stated and "Bupropion tablets were repackaged into gelatin capsules...Placebo consisted of identical appearing gelatin capsules". Use of urine screening to verify self-report expected to reduce risk of bias
Blinding (objective outcomes) All outcomes	Low risk	Double-blind stated, placebo used, and these outcomes less likely to be affected by awareness of group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of dropout and demographics reported only for those who completed treatment. Unclear whether there were differences between the groups, or between those who did and did not complete the study. Unclear how missing data were handled
Selective reporting (reporting bias)	Unclear risk	Data on adverse effects not reported
Other bias	Low risk	None apparent

Weinstein 2014

Methods	Randomised, double-blind, placebo-controlled trial. Setting: outpatient, Tel Aviv, Israel. Funding: research grant (Israeli anti-drug authority). Authors declared no conflict of interest
Participants	N = 52, regular cannabis users, dependent by DSM-IV. Average age 32.7, 75% male. Dependence on other drugs or alcohol and significant psychiatric disorders were exclusion criteria

Interventions	One week "induction" with placebo, then (1) N = 26, escitalopram 10 mg/day, or (2) N = 26 placebo. Medication for 9 weeks, follow-up sessions for further 14 weeks. Blinding broken after 9 weeks; participants able to continue open-label escitalopram use. Participants instructed to stop cannabis use after 4 weeks of medication. Weekly (9 sessions) cognitive-behaviour (relapse prevention) and motivation enhancement therapy in combination with medication. Scheduled duration 9 weeks
Outcomes	Number completing treatment, number abstinent, number reporting not taking medication, results of statistical analyses of withdrawal scores
Notes	Urine samples collected every second week. Questionnaires administered to assess anxiety and depression. Revised Clinical Institute Withdrawal Assessment Scale (CIWA) adapted for assessment of cannabis withdrawal (score of 10 or more indicated significant withdrawal)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "participants were blindly randomized..." Method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "participants were blindly randomized..." Method of allocation concealment not reported
Blinding (subjective outcomes) All outcomes	Low risk	Double-blind stated. Subjective outcomes not reported
Blinding (objective outcomes) All outcomes	Low risk	Double-blind stated and these outcomes unlikely to be affected by awareness of group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	High (50%) rate of dropout. Those who did not complete study were younger, and more likely to be daily alcohol drinkers. Non-completers marginally more depressed, but difference not statistically significant
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akerele 2007	Participants were diagnosed with abuse or dependence on marijuana or cocaine. Data was reported separately for cocaine and marijuana use, but it was not possible to extract data just for those dependent on marijuana. All participants were diagnosed with schizophrenia; the management of substance use in the context of schizophrenia was the main focus of the study
Brown 2013	Secondary analysis of data from a randomised controlled trial comparing two behavioural interventions. No use of medications
Budney 2007	Laboratory study involving non-treatment seeking cannabis users. Not all users were cannabis dependent, and participants were not trying to reduce their cannabis use
Cooper 2013	Laboratory study involving marijuana smokers who were not seeking treatment. Investigation of research model of withdrawal and relapse rather than treatment intervention
Cornelius 1999	Randomised controlled trial comparing fluoxetine and placebo for treatment of alcohol dependence with comorbid major depression. Effect on subgroup with diagnosed marijuana abuse considered as secondary analysis
Cornelius 2008	Reports cannabis withdrawal symptoms in participants entering two separate trials of fluoxetine. No treatment intervention for cannabis dependence
Daynes 1994	No treatment comparison. Unclear if participants are cannabis dependent. Insufficient information on participants and treatment regimes
Findling 2009	Randomised controlled trial comparing fluoxetine and placebo for treatment of depressive symptoms in adolescents with comorbid substance use disorder. Cannabis use reported by 88.2% of participants (41.2% dependent). The emphasis of this study is on the amelioration of depression. Outcome data not reported separately for the subset of cannabis-dependent participants
Geller 1998	Randomised controlled trial comparing lithium and placebo for treatment of adolescents with bipolar disorder and comorbid substance use disorder. Majority of participants were polydrug users - 2 of 25 were dependent on cannabis only
Gillman 2006	Reports the use of nitrous oxide for treatment of withdrawal associated with the smoking of methaqualone combined with cannabis. Unclear how many participants were cannabis dependent. All participants received placebo then analgesic nitrous oxide. Effectiveness assessed only in terms of improvement in withdrawal symptoms
Gray 2010	Open-label single group study investigating the effectiveness of N-Acetylcysteine in promoting cessation of cannabis use. No treatment comparison
Haney 2001	Comparison of bupropion and placebo in terms of effect on mood when administered in conjunction with active or placebo cannabis cigarettes. Laboratory study which aimed to assess the therapeutic potential of buproprion, but not a treatment intervention

(*Continued*)

Haney 2003	Investigation of mechanism of effects of cannabis through comparison of naltrexone and methadone, administered prior to oral THC, and different doses of oral THC administered in combination with naltrexone or placebo. No treatment intervention
Haney 2003a	Laboratory study comparing the effect of nefazodone (450mg/day) and placebo on the acute effects of cannabis, and on cannabis withdrawal symptoms. The study aimed to assess the therapeutic potential of nefazodone in cannabis withdrawal but was not a treatment intervention
Haney 2004	Two separate laboratory-based studies, one assessing THC and the other divalproex, compared to placebo, in terms of effects on cannabis withdrawal. Studies aimed to assess the therapeutic potential of THC and divalproex but were not treatment interventions
Haney 2008	Laboratory study investigating the effect of lofexidine and THC (separately and in combination) compared with placebo on cannabis withdrawal symptoms and a model of cannabis relapse. The study aimed to test the therapeutic potential of lofexidine in cannabis withdrawal but was not a treatment intervention
Haney 2010	Controlled laboratory study investigating the effects of baclofen or mirtazapine on cannabis smoking, craving and withdrawal. Exploratory study of the potential therapeutic value of baclofen and mirtazapine, but not a treatment intervention
Haney 2013	Laboratory study with aim of assessing effect of nabilone on marijuana withdrawal symptoms, and laboratory measure of relapse. The study aimed to test the therapeutic potential of nabilone but was not a treatment intervention
Haney 2013a	Laboratory study investigating the effect of zolpidem and nabilone (separately and in combination) compared with placebo on marijuana withdrawal symptoms and a model of marijuana relapse. The study aimed to test the therapeutic potential of zolpidem in marijuana smokers but was not a treatment intervention
Hart 2002	Laboratory study assessing the effect of oral THC or placebo on smoking of marijuana. Aim of study was to explore therapeutic potential of THC, but not a treatment intervention
Imbert 2014	Reports single case involving the use of baclofen to manage cannabis dependence. No treatment comparison
Levin 2008	Not a controlled study. Two case studies and a review of the use of dronabinol for cannabis dependence
McRae 2006	Open label study of buspirone for treatment of cannabis dependence. No treatment comparison
Robinson 2006	Randomised controlled trial comparing olanzapine and risperidone for treatment of schizophrenia in people with a history of cannabis use disorders. Primary goal of treatment was management of schizophrenia. Comparison of substance use outcomes was secondary. Data on substance use was reported only for those who completed treatment
Subodh 2011	An open label study investigating the use of baclofen for the treatment of cannabis dependence. No treatment comparison
Sugarman 2011	Controlled study assessing the safety of modafinil in combination with THC. While the study contributes to assessment of the therapeutic potential of modafinil, this study did not involve a treatment intervention. Participants were occasional cannabis users (people who were heavy users or dependent were excluded)

(*Continued*)

Tirado 2008	An open label study investigating the use / effect of atomoxetine for the treatment of marijuana dependence. No treatment comparison
Van Nimwegen 2008	Randomised controlled trial comparing olanzapine and risperidone for treatment of schizophrenia. Majority of participants were not using cannabis and cannabis dependence was not assessed
Vandrey 2011	Cross-over study comparing zolpidem and placebo during short (3-day) periods of abstinence from cannabis in terms of sleep parameters. Not a full treatment intervention for cannabis dependence
Vandrey 2013	Comparison of dronabinol and placebo in terms of effect on cannabis withdrawal and subjective effects of smoked cannabis, but without providing a treatment intervention for cannabis dependence
Winstock 2009	An open label study investigating the use of lithium carbonate for the management of cannabis withdrawal. No treatment comparison

DATA AND ANALYSES

Comparison 1. Active medication versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number abstinent at end of treatment	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 THC preparations	1	156	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.56, 2.30]
1.2 Mixed action antidepressants	2	179	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.12, 5.41]
1.3 SSRI antidepressants	1	52	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.68, 8.05]
1.4 Anticonvulsant and mood stabiliser	1	19	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.50, 2.34]
1.5 Buspirone	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 Atomoxetine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.7 N-acetylcysteine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Number experiencing adverse effects	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 THC preparations	1	156	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.90, 1.46]
2.2 Mixed action antidepressants	1	76	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.55, 1.55]
2.3 SSRI antidepressants	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Anticonvulsant and mood stabiliser	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Buspirone	1	50	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.99, 1.53]
2.6 Atomoxetine	1	38	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.95, 1.46]
2.7 N-acetylcysteine	1	116	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.59, 1.34]
3 Number withdrawn due to adverse effects	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 THC preparations	1	156	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 15.31]
3.2 Mixed action antidepressants	2	179	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.11, 18.90]
3.3 SSRI antidepressants	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Anticonvulsant and mood stabiliser	1	50	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.12]
3.5 Buspirone	1	50	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.08, 17.74]
3.6 Atomoxetine	1	38	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 69.31]
3.7 N-acetylcysteine	1	116	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.15]
4 Completion of treatment	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 THC preparations	2	207	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.08, 1.55]
4.2 Mixed action antidepressants	2	169	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.71, 1.21]
4.3 SSRI antidepressants	2	122	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.44, 1.53]
4.4 Anticonvulsant and mood stabiliser	2	75	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.42, 1.46]
4.5 Buspirone	1	50	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.56, 1.77]
4.6 Atomoxetine	1	38	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.60, 2.74]
4.7 N-acetylcysteine	1	116	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.83, 1.51]

4.8 Bupropion	2	92	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.67, 1.67]

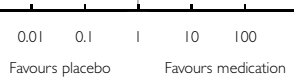
Analysis 1.1. Comparison 1 Active medication versus placebo, Outcome 1 Number abstinent at end of treatment.

Review: Pharmacotherapies for cannabis dependence

Comparison: 1 Active medication versus placebo

Outcome: 1 Number abstinent at end of treatment

Study or subgroup	Medication n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 THC preparations					
Levin 2011	14/79	12/77		100.0 %	1.14 [0.56, 2.30]
Subtotal (95% CI)	**79**	**77**		**100.0 %**	**1.14 [0.56, 2.30]**
Total events: 14 (Medication), 12 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
2 Mixed action antidepressants					
Carpenter 2009	8/36	4/40		48.1 %	2.22 [0.73, 6.76]
Levin 2013	6/51	19/52		51.9 %	0.32 [0.14, 0.74]
Subtotal (95% CI)	**87**	**92**		**100.0 %**	**0.82 [0.12, 5.41]**
Total events: 14 (Medication), 23 (Placebo)					
Heterogeneity: Tau^2 = 1.61; Chi^2 = 7.42, df = 1 (P = 0.01); I^2 =87%					
Test for overall effect: Z = 0.21 (P = 0.83)					
3 SSRI antidepressants					
Weinstein 2014	7/26	3/26		100.0 %	2.33 [0.68, 8.05]
Subtotal (95% CI)	**26**	**26**		**100.0 %**	**2.33 [0.68, 8.05]**
Total events: 7 (Medication), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					
4 Anticonvulsant and mood stabiliser					
Levin 2004	6/10	5/9		100.0 %	1.08 [0.50, 2.34]
Subtotal (95% CI)	**10**	**9**		**100.0 %**	**1.08 [0.50, 2.34]**
Total events: 6 (Medication), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.85)					
5 Buspirone					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Medication), 0 (Placebo)					
Heterogeneity: not applicable					



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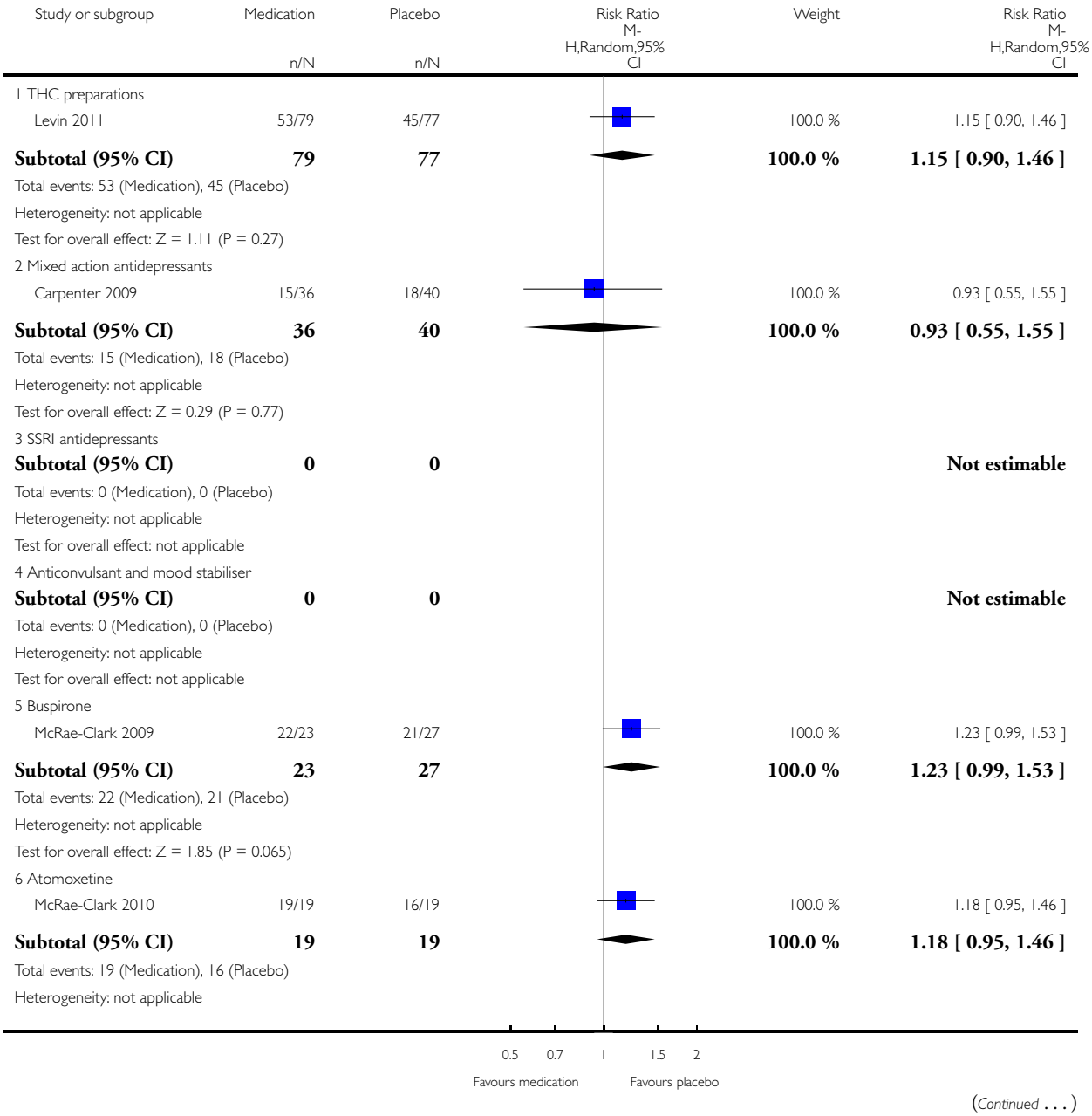
Study or subgroup	Medication n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: not applicable					
6 Atomoxetine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Medication), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
7 N-acetylcysteine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Medication), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 1.36, df = 3 (P = 0.71), I^2 =0.0%					

Analysis 1.2. Comparison 1 Active medication versus placebo, Outcome 2 Number experiencing adverse effects.

Review: Pharmacotherapies for cannabis dependence

Comparison: 1 Active medication versus placebo

Outcome: 2 Number experiencing adverse effects



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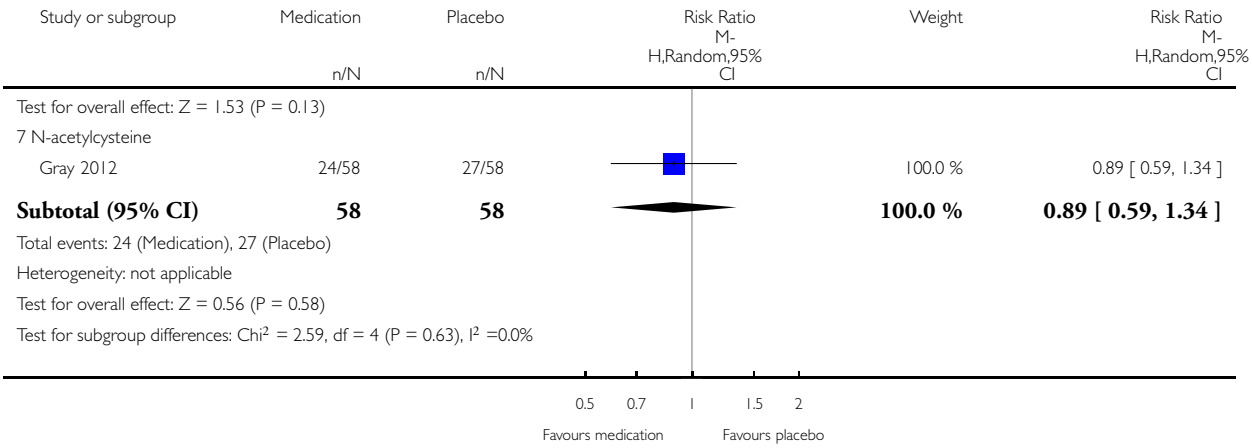
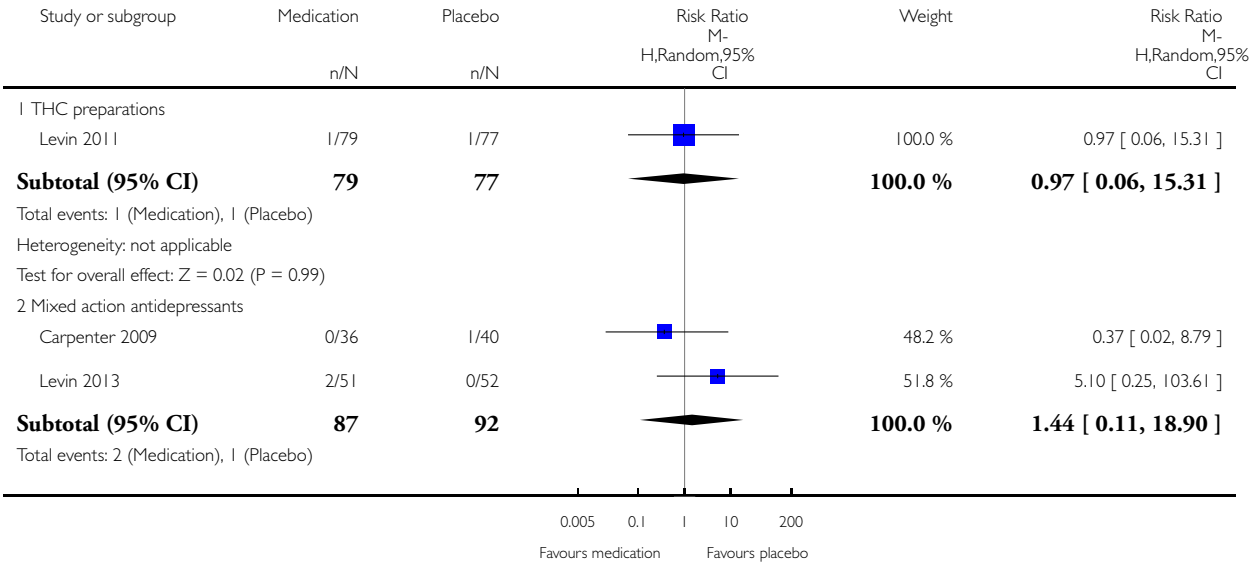


Analysis 1.3. Comparison 1 Active medication versus placebo, Outcome 3 Number withdrawn due to adverse effects.

Review: Pharmacotherapies for cannabis dependence

Comparison: 1 Active medication versus placebo

Outcome: 3 Number withdrawn due to adverse effects



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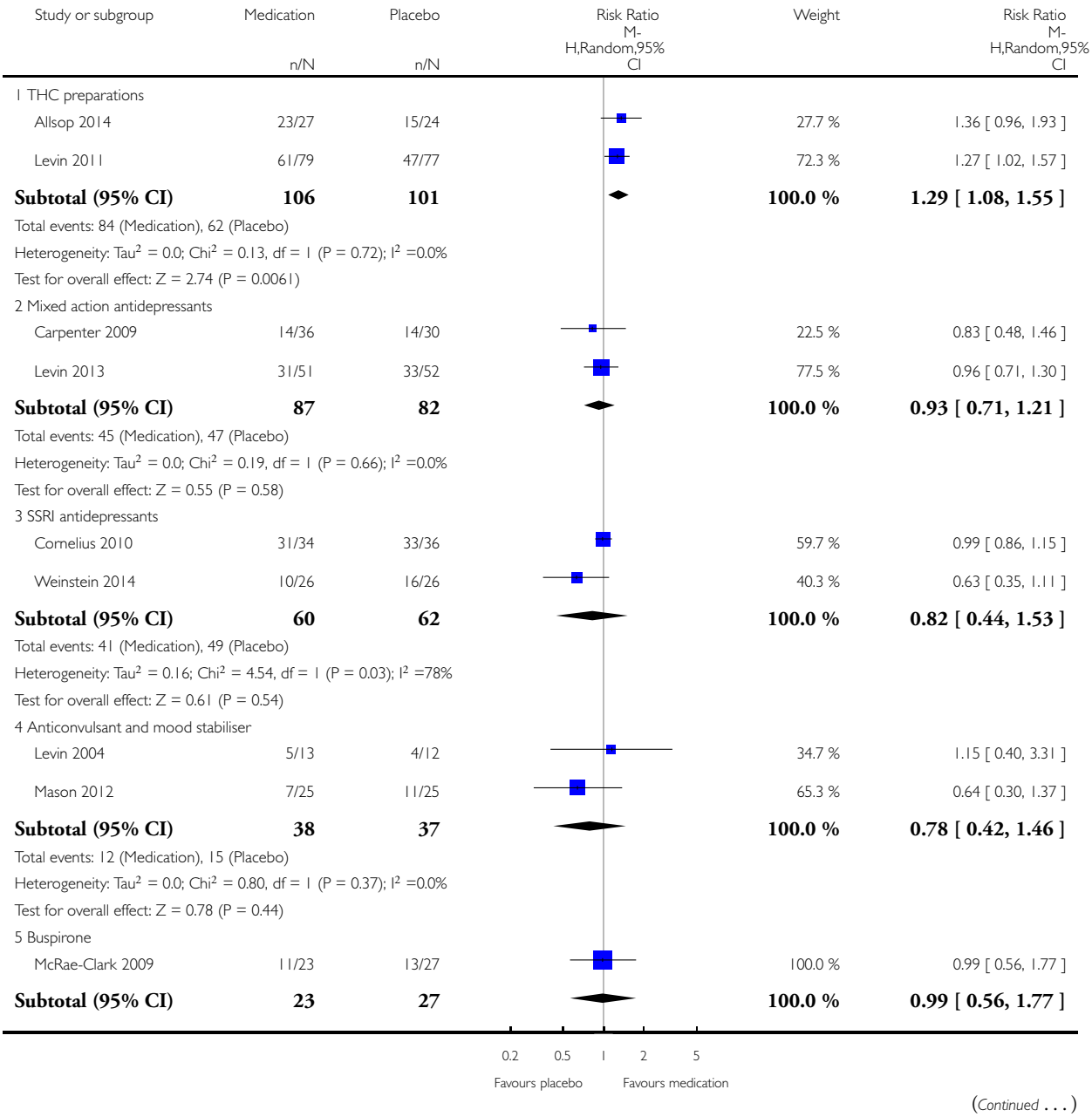
Study or subgroup	Medication n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.97; Chi² = 1.39, df = 1 (P = 0.24); I² =28%					
Test for overall effect: Z = 0.28 (P = 0.78)					
3 SSRI antidepressants					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Medication), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Anticonvulsant and mood stabiliser					
Mason 2012	1/25	1/25		100.0 %	1.00 [0.07, 15.12]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**1.00 [0.07, 15.12]**
Total events: 1 (Medication), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
5 Buspirone					
McRae-Clark 2009	1/23	1/27		100.0 %	1.17 [0.08, 17.74]
Subtotal (95% CI)	**23**	**27**		**100.0 %**	**1.17 [0.08, 17.74]**
Total events: 1 (Medication), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.91)					
6 Atomoxetine					
McRae-Clark 2010	1/19	0/19		100.0 %	3.00 [0.13, 69.31]
Subtotal (95% CI)	**19**	**19**		**100.0 %**	**3.00 [0.13, 69.31]**
Total events: 1 (Medication), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
7 N-acetylcysteine					
Gray 2012	1/58	0/58		100.0 %	3.00 [0.12, 72.15]
Subtotal (95% CI)	**58**	**58**		**100.0 %**	**3.00 [0.12, 72.15]**
Total events: 1 (Medication), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: Chi² = 0.58, df = 5 (P = 0.99), I² =0.0%					

Analysis 1.4. Comparison 1 Active medication versus placebo, Outcome 4 Completion of treatment.

Review: Pharmacotherapies for cannabis dependence

Comparison: 1 Active medication versus placebo

Outcome: 4 Completion of treatment



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Study or subgroup	Medication n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 11 (Medication), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
6 Atomoxetine					
McRae-Clark 2010	9/19	7/19		100.0 %	1.29 [0.60, 2.74]
Subtotal (95% CI)	**19**	**19**		**100.0 %**	**1.29 [0.60, 2.74]**
Total events: 9 (Medication), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.51)					
7 N-acetylcysteine					
Gray 2012	37/58	33/58		100.0 %	1.12 [0.83, 1.51]
Subtotal (95% CI)	**58**	**58**		**100.0 %**	**1.12 [0.83, 1.51]**
Total events: 37 (Medication), 33 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
8 Bupropion					
Carpenter 2009	18/40	14/30		79.5 %	0.96 [0.58, 1.61]
Penetar 2012	5/10	4/12		20.5 %	1.50 [0.55, 4.13]
Subtotal (95% CI)	**50**	**42**		**100.0 %**	**1.06 [0.67, 1.67]**
Total events: 23 (Medication), 18 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.58, df = 1 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					
Test for subgroup differences: Chi^2 = 6.82, df = 7 (P = 0.45), I^2 =0.0%					

APPENDICES

Appendix 1. Search strategy for CENTRAL via The Cochrane Library online

1. (cannabis or marihuana or marijuana) near/2 (abuse or addiction or smoking or dependence):ti,ab,kw
2. MeSH descriptor: [Marijuana Abuse] explode all trees
3. MeSH descriptor: [Marijuana Smoking] explode all trees
4. MeSH descriptor: [Substance Withdrawal Syndrome] explode all trees
5. MeSH descriptor: [Metabolic Detoxication, Drug] explode all trees
6. MeSH descriptor: [Drug Therapy] explode all trees
7. detoxification or detoxication or withdrawal:ti,ab,kw
8. #1 or #2 or #3
9. #4 or #5 or #6 or #7
10. #8 and #9

Appendix 2. Search strategy for MEDLINE via Ovid Online

1. (cannabis or mari#uana).mp.
2. exp cannabis/
3. exp marijuana abuse/
4. exp marijuana smoking/
5. withdrawal.mp.
6. exp substance withdrawal syndrome/
7. (detoxifi$ or desintoxi$ or disintoxi$ or disintossi$).mp.
8. exp Metabolic Detoxication, Drug/
9. exp Drug Therapy
10. 1 or 2 or 3 or 4
11. 5 or 6 or 7 or 8 or 9
12. 10 and 11
13. randomized controlled trial.pt
14. controlled clinical trial.pt
15. randomized.ab
16. placebo.ab
17. randomly.ab
18. trial.ab
19. groups.ab
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. (animals not (humans and animals)).sh.
22. 20 not 21
23. 12 and 22

Appendix 3. Search strategy for EMBASE via Ovid Online

1. (cannabis or mari#uana).mp.
2. cannabis addiction/
3. drug withdrawal/
4. withdrawal syndrome/
5. drug detoxification/ or detoxification/
6. (detoxifi$ or desintoxi$ or disintoxi$ or disintossi$).mp.
7. drug therapy/
8. 1 or 2
9. 3 or 4 or 5 or 6 or 7

10. randomized controlled trial/
11. controlled clinical trial/
12. randomized.ab.
13. placebo.ab.
14. randomly.ab.
15. trial.ab.
16. groups.ab.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 8 and 9
19. 17 and 18
20. limit 19 to human

Appendix 4. Search strategy for PsycINFO via Ovid Online

1. exp cannabis/
2. marijuana usage/
3. (cannabis or mari#uana) .mp.
4. exp Drug Dependency/
5. exp. Drug Abuse/
6. 4 or 5
7. 1 or 2 or 3
8. 6 and 7
9. exp Drug Withdrawal/
10. exp. Detoxification/
11. exp Drug Therapy/
12. (detoxifi$ or desintoxi$ or disintoxi$ or disintossi$).mp.
13. 9 or 10 or 11 or 12
14. 8 and 13
15. limit 14 to human

Appendix 5. Criteria for risk of bias assessment

Item	Judgment	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk

(*Continued*)

2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following method was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear risk	Insufficient information to permit judgement of low or high risk This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement
3. Blinding of participants , providers and outcome assessor (performance and detection bias) Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding of participants , providers and outcome assessor and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants providers and outcome assessor attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk;
4. Blinding of participants , providers and outcome assessor (performance and detection bias) Subjective outcomes	Low risk	Blinding of participants , providers and outcome assessor and unlikely that the blinding could have been broken;
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants, providers and outcome assessor attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk;
5. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or drop out	Low risk	No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;

(*Continued*)

		For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group);
6 Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk	Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear risk	Insufficient information to permit judgement of low or high risk

(*Continued*)

7. Other bias	Low risk	Potential confounding factors identified but evenly distributed between groups Study ceased early but with no indications of selection bias Interventions delivered consistently.
	High risk	Potential confounding factors unequally distributed between groups Study ceased early with risk of selection bias. Differences in aspects of delivery of interventions. Mandatory treatment.
	Unclear risk	Confounding possible but not able to be assessed. Study ceased early and unable to determine possible bias. Unclear if delivery of interventions was equivalent.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the review concept and design. Kushani Marshall and Linda Gowing undertook literature searches, assessed studies for inclusion, and wrote a first draft of the text. Bernard Le Foll and Robert Ali provided comments at all stages of the review.

DECLARATIONS OF INTEREST

Dr Le Foll is performing clinical research evaluating the utility of nabiximols for cannabis dependence treatment using drug supplies donated by GW Pharma. The research is supported by the Centre for Addiction and Mental Health, the Canadian Institute of Health Research (CSU 115548) and the National Institute On Drug Abuse of the National Institutes of Health (R21DA031906).

SOURCES OF SUPPORT

Internal sources

- DASSA-WHO Collaborating Centre in the Treatment of Drug and Alcohol Problems, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol focused on the management of cannabis withdrawal. When it became clear that very few studies considered withdrawal as a distinct phase, the review was broadened to include interventions to support cessation or reduction of cannabis use as well as management of withdrawal symptoms. The broadening of the review made the specification of "the portion of the scheduled treatment episode that is completed on average" less relevant; hence this was dropped from the review.

The original protocol stipulated the inclusion of studies that involve participants who are diagnosed according to DSM-IV or ICD-10 criteria as cannabis dependent, or where dependence is likely based on reported dose, duration and frequency of use (daily or multiple days per week). Given the qualifier of "where dependence is likely" the specification of DSM-IV or ICD-10 criteria would not have resulted in the exclusion of any included studies and was dropped from the methods of the review in the interests of simplicity.

The approach to heterogeneity specified in the protocol (use of a random-effects model in the presence of statistical heterogeneity) was changed based on statistical advice received in the interim. The routine use of a random-effects model is preferred and was the approach used for the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [therapeutic use]; Antidepressive Agents [therapeutic use]; Dronabinol [therapeutic use]; Marijuana Abuse [*drug therapy]; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [therapeutic use]

MeSH check words

Adult; Female; Humans; Male