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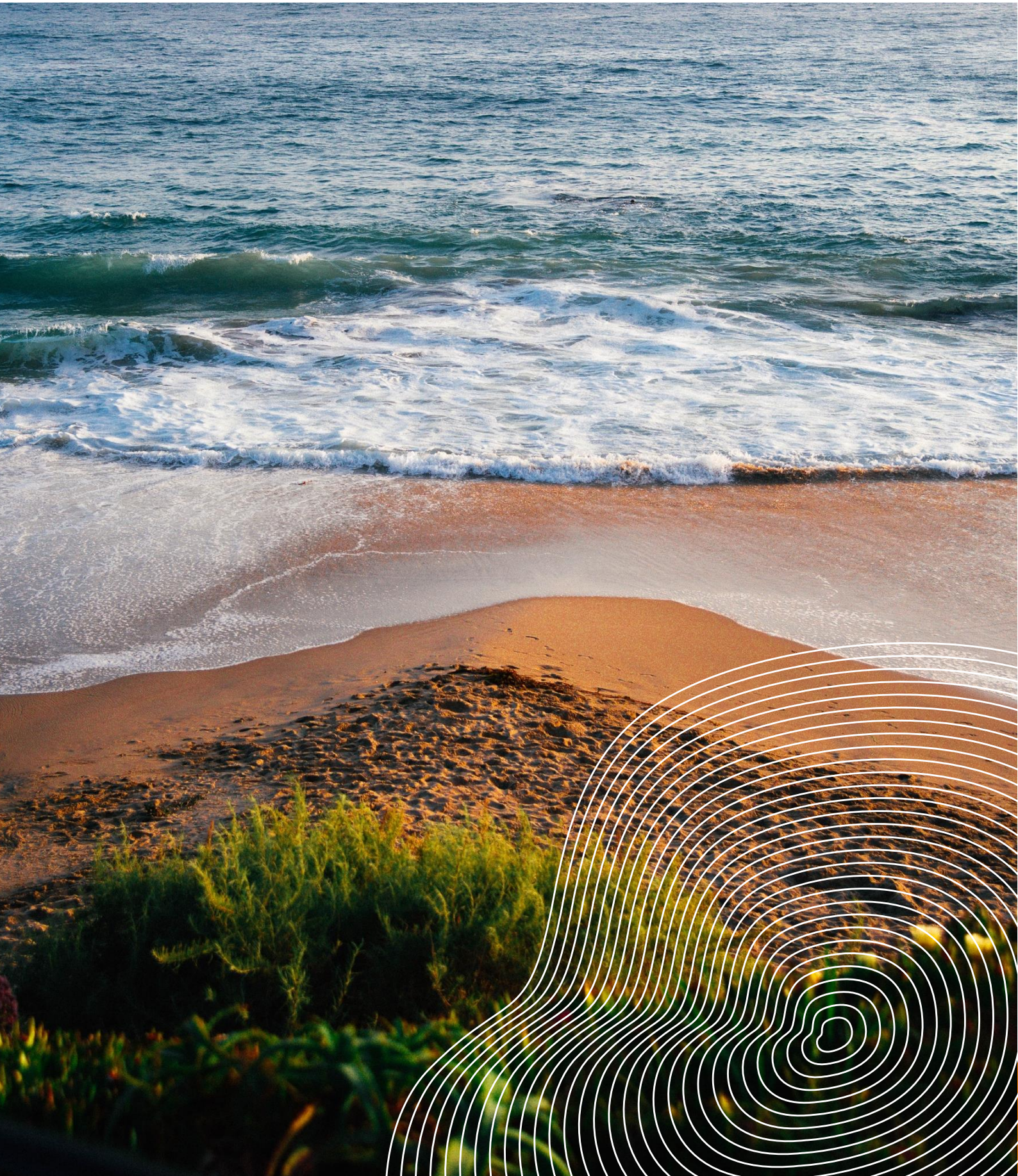
An overview of the evidence for substance use interventions



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An overview of the evidence for substance use interventions

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EXECUTIVE SUMMARY

Background and aims: This report documents the search strategy and findings from an overview of reviews on interventions for substance use. This evidence review was conducted to update the European Monitoring Centre on Drugs and Drug Addiction's (EMCDDA's) evidence on drug demand reduction, treatment, and harm reduction strategies.
Methods: We searched Pubmed for indexed systematic reviews and meta-analyses from 2010 to March 2021 for evidence relating to interventions for illicit substance use. Searches were developed to align with nine topics covered in the EMCDDA's evidence guidelines. Reviews and meta-analyses were included that collated data from randomised controlled trials (RCTs). Evidence from narrative reviews was not included. Evidence statements were extracted from the most recently available comprehensive reviews. Evidence from reviews of cohort studies was included for mortality because evidence from RCTs was insufficient. Data were extracted on evidence for interventions from these reviews (referred to as "evidence statements") and each was provided with a quality rating. Quality ratings were based on GRADE. The original nine search topics were condensed to five topics because of overlapping evidence and/or lack of evidence in some topic areas.
Results: We extracted 70 evidence statements pertaining to 5 topics: interventions to prevent cannabis and other substance use in young people (n = 16), interventions for cannabis use disorder (n = 8), interventions for opioid use disorder (n = 27), interventions for stimulant use disorder (n = 12), and interventions for substance use disorders in prisons (n = 7). Moderate to high quality evidence (n = 24) was largely constrained to substance use prevention interventions, interventions for opioid use disorder (specifically opioid agonist therapy and withdrawal management for opioid use) and stimulant use disorder (psychosocial interventions). Within this, there was good evidence of benefits from universal prevention interventions in schools that target multiple risk behaviours (albeit small effects), opioid agonist treatment, medically-supported opioid withdrawal, and psychosocial interventions for stimulant use disorders.
Conclusions: There is good evidence to support several currently used approaches to preventing illicit substance use in young people and treating substance use disorders. However, much of the evidence for other interventions is low quality, including interventions to address cannabis use disorder, early interventions for substance use in young people, pharmacotherapies for stimulant use disorder, and alternatives to opioid agonist treatment.

ACKNOWLEDGEMENTS

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1 INTRODUCTION

Background

This report documents the search strategy and findings from an overview of reviews on interventions for substance use. This overview was conducted to review and validate the evidence for interventions in the European Response Guide 2021, and update evidence statements in the European Monitoring Centre on Drugs and Drug Addiction's (EMCDDA's) Health and Social Responses to Drug Problems. The review focussed on the domains covered in these evidence guidelines:

- interventions to prevent or delay cannabis use
- treating problematic cannabis use
- treating opioid dependence
- reducing opioid-related deaths
- treatment for problematic stimulant use
- treatment for misuse of medicines
- responses for vulnerable young people
- interventions in schools and colleges
- interventions in prisons and the criminal justice system

Literature searches were undertaken to identify review papers on each of these topics (from 2010 to March 2021). Only illicit substance use was considered. From the identified reviews we extracted a list of evidence statements relevant to each topic, the quality of which was graded using the Cochrane GRADE rating system.

The derived evidence statements were used to review and suggest updates to the EMCDDA evidence guidelines. The evidence statements we report here may therefore differ from those reported by the EMCDDA. The latter have undergone revisions and have been updated to reflect more recent data.

In this report we document the process of conducting the review, and report on the evidence statements we identified and their quality ratings.

2 METHOD

We chose to do an overview of reviews to synthesise current evidence on substance use interventions because this type of review can be conducted quickly, and it provides a user-friendly summary of evidence for policy makers. The unit of analysis in an overview of reviews is review papers rather than individual studies. They are ideally based on systematic reviews and meta-analysis of outcomes of randomised controlled trials of specific interventions for a specific population, and they do not typically include narrative reviews of the evidence.

2.1 Search Strategy

Systematic reviews and meta-analyses published from January 2010 to March 2021 were identified using PubMed. Search terms for each topic in the EMCDDA evidence review were developed using relevant Medical Subject Headings. Searches were restricted to systematic reviews and meta-analyses, as indexed in Pubmed. Search strategies and the date of each search can be found in the appendix of this report (Table S1). We also searched the Cochrane database to locate reviews on each topic area. Table S1 also shows how these original nine searches map onto the five topics in this report.

2.1.1 Data extraction

The titles and abstracts for identified systematic reviews and meta-analyses were exported to excel and reviewed for relevance by one author (PT or NU) and reviewed by a second author (RM). Relevance was based on alignment with the topic area.

Full text papers were obtained for the relevant reviews. Data extracted included: publication details, the population studied, the intervention evaluated, a description of included studies (i.e., the number of trials/participants, types of study design), quality (Cochrane reviews, reviews that included only randomised controlled trials, reviews that included both randomised controlled trials and other study designs), and the study abstract.

We then compiled evidence from systematic reviews and meta-analyses of randomised controlled trials of interventions on each topic. We did not include information from narrative reviews. This was because of the heterogeneity in study designs and outcomes in these reviews, which precluded data

synthesis. Where reviews included both RCTs and other study designs, we extracted evidence based on data specifically from RCTs where possible.

Where more than one review was available on a particular topic, and there was a duplication of evidence, we chose evidence statements based on the most recent comprehensive review available. We also considered the consistency of evidence across reviews and attempted to reconcile disparities in evidence (e.g., by investigating the populations and comparison groups in the included studies). Where evidence was not consistent, a judgement was made regarding the strongest evidence, based on the recency of the review, and on the number and quality of included studies.

2.2 Quality ratings

Where available, evidence statements and their GRADE quality ratings were extracted directly from the review (this was usually the case for Cochrane reviews). However, some GRADE quality ratings needed to be re-assessed to maintain consistency across reviews. Where GRADE quality ratings were not available, the quality of the evidence was assessed using GRADE criteria. Evidence derived from single studies was rated as 'very low quality or insufficient evidence'. Where interventions could not be evaluated using RCTs we have also considered evidence from reviews of cohort studies, the quality of this evidence being graded using the ROBINS-I.

Our system of presenting the quality ratings also included information on the direction of the effect of the intervention (benefit, no effect, or harmful effect). This information was based on the direction of the effect reported by authors. Where the direction of the effect was not reported by the authors it was based on whether there was a significant difference between the intervention and comparison condition and the direction of this statistically significant effect. If the direction of the effect was not reported by the review authors, we report 'no effect' where there was no statistically significant difference between the intervention and comparator groups. We do not report the direction of effect for interventions where there is either very low quality evidence or insufficient evidence.

3 RESULTS

The citations and abstracts for all included reviews can be found in the appendix (Tables S2-S9). To improve presentation of the results we have combined evidence statements for some of the original EMCDDA evidence topics and omitted others. This was done because of considerable overlap in the findings from several topic areas and lack of evidence for others.

3.1 Interpreting the evidence

3.1.1 Key to the quality ratings

Each evidence statement is accompanied by a quality rating (Table 1). This rating system has two dimensions. The first dimension represents the quality of the evidence. This system is based on the Cochrane GRADE rating system:

★★★ High quality evidence
★★ Moderate quality evidence
★ Low quality evidence
? Very low quality evidence or insufficient evidence
Includes cohort evidence based on ROBINS-I

These ratings reflect our certainty or confidence in the evidence. Further information about what each level of evidence represents can be found here. In brief:

Very low quality evidence means that the true effect of the intervention is probably markedly different from the estimate provided, and in this review, it has been combined with insufficient evidence.

Low quality evidence indicates that the true effect of the intervention might be markedly different from the estimate provided. For this reason, we qualify low quality evidence by saying that the intervention 'may' have the nominated effect.

Moderate quality evidence means that we believe the true effect is probably close to the estimated effect.

High quality evidence means that we have a lot of confidence that the true effect is similar to the stated estimate.

The second dimension in the quality rating is the colour of the stars, and this reflects the direction of the intervention's effect. That is, whether the intervention produces a benefit, no or unclear benefit, or potential harm:
GREEN: Benefit, or effect in the intended direction
AMBER: No benefit, or unclear whether the intervention has intended effect
RED: Potential harm, or evidence that the intervention has the opposite effect to that intended (e.g., increasing rather than decreasing drug use)

These two dimensions are combined to provide a single rating that reflects both the quality of the evidence and information on whether the intervention is beneficial, has no clear benefit, or may be potentially harmful (Table 1).

Table 1. Key to the evidence quality ratings

Evidence	Benefit	No clear benefit	Potential harm
High quality	★★★	★★★	★★★
Moderate quality	★★	★★	★★
Low quality	★	★	★
Very low quality or insufficient	?	?	?

As a rule of thumb, moderate and high-quality evidence can be taken as a fair indication that the intervention will produce changes in the indicated direction. However, for interventions with low quality evidence, new evidence may provide different conclusions about whether the intervention is effective. For interventions with very low-quality evidence, or insufficient evidence, additional trials and/or more robust trials of the intervention are needed before conclusions should be drawn about whether the intervention is effective.

3.1.2 Limitations and considerations when interpreting the evidence statements

The evidence statements presented here only cover interventions where (a) there is adequate evidence available from RCTs to assess the impact of an intervention, and (b) where this evidence has been synthesised in a systematic review or meta-analysis. In some cases, even though good evidence may be available from RCTs to demonstrate the benefits of an intervention, it is not included here because the evidence has not been synthesised in a systematic review or meta-analysis.

The quality of evidence for an intervention does not reflect how much of an impact that intervention will have or whether it will be beneficial. For example, there are interventions with high quality evidence of a benefit, but they produce only a very small change in substance use. Where this is the case, we have attempted to qualify statements, however, we urge readers to review the primary reviews to obtain a clearer picture of the magnitude of benefits for a given intervention.

Low quality ratings do not mean that an intervention does not work, but rather that it has not yet been adequately evaluated. In situations where evidence was available from only a single study, or it was low quality (e.g., due to study design limitations), we have assigned a quality rating of very low or insufficient (i.e., '?'). In many situations, we chose not to report on evidence where it was inconclusive or very low quality for the sake of parsimony.

Although it is tempting to combine evidence statements to compare the relative effectiveness of interventions, we urge readers to avoid doing this. Each evidence statement is based on a different set of studies, and therefore

they cannot be directly compared (e.g., if intervention X is better than intervention Y in one evidence statement, and intervention Y is better than intervention Z in a second evidence statement, it may not be valid to assume that intervention X is better than intervention Z).

3.2 Overall findings

We extracted 70 evidence statements pertaining to 5 topics: interventions to prevent cannabis and other substance use in young people (n = 16), interventions for cannabis use disorder (n = 8), interventions for opioid use disorder (n = 27), interventions for stimulant use disorder (n = 12), and interventions for substance use disorders in prisons (n = 7). Moderate to high quality evidence (n = 24) was largely constrained to substance use prevention interventions, interventions for opioid use disorder (specifically opioid agonist therapy and withdrawal management for opioid use) and psychosocial interventions for stimulant use disorder.

The evidence for each specific topic areas is over-viewed in the following sections.

3.3 Interventions to prevent substance use in young people

Most of the available evidence relates to school-based prevention programs (Table 2). The evidence statements for 'broader' prevention interventions are also largely based on interventions carried out in schools or colleges, but also include community-based and family-based interventions (Table 2). Early interventions for substance use in youth are those carried out on populations who are already engaged in substance use (Table 3).

3.3.1 Prevention interventions

Overall, the evidence for school-based drug prevention interventions suggest that they have, at best, small impacts. Importantly, these interventions need to target universal or risk factors, or use a combination of approaches (e.g., including both social competence and social influence) to be beneficial. Brief interventions, or those that focus solely on social influence, do not prevent cannabis use (Table 2).

There is some low-quality evidence that digital interventions may be effective (note that this evidence derives from a combination of interventions delivered both within and outside of the school setting) (Table 2).

Evidence regarding the benefit of interventions outside of schools (e.g., in primary-care settings) is imprecise and inconsistent. Behavioural interventions (e.g., counselling) may produce very small reductions in cannabis use among young people, and some specific types of primary care interventions appear to

be beneficial (e.g., the Familias Unidas intervention), but, overall, they have not been found to reduce illicit drug use (Table 2).

3.3.2 Early interventions

In terms of early interventions for young people already involved in illicit substance use, there is good evidence that brief behavioural interventions do not reduce cannabis use, but they may reduce problems related to substance use (Table 3).

Table 2. Interventions to prevent substance use in young people

Quality Rating	Evidence Statement	Review
	School-based prevention programs	
★★	School programmes based on a combination of social competence and social influence approaches show small but consistent protective effects in preventing substance use (including cannabis use)	Faggiano 2014
★★	Universal school-based interventions targeting multiple risk behaviours produce a small reduction in cannabis use.	MacArthur 2018
★★	School-based programmes based solely on social influence models do not significantly reduce cannabis use more than usual curricula.	Faggiano 2014
★★	Brief school-based interventions do not have a significant effect on cannabis use when compared to providing information only.	Carney 2016
★	Brief school-based interventions may have a very small benefit in reducing substance use compared to assessment only.	Carney 2016
★	Interventions that integrate health education into the academic curricula may produce very small reductions in substance use	Melendez-Torres 2018
?	There is insufficient evidence to confirm that combined universal intervention for students (aged 11–18 years old) and their parents designed to prevent alcohol and/or other drug use may reduce drug use	Newton 2017
?	There is very low quality evidence that the WHO Health Promoting Schools (HPS) framework in improving the health and well-being of students and their academic achievement has no significant effect on substance use.	Langford 2014
	Broader prevention programs∞	
★	Digital prevention interventions may produce a small reduction in cannabis use among young people.	Boumparis 2019
★	Family-based interventions and multisystemic therapy may reduce substance use in young people.	Stockings 2016
★	Behavioural interventions in primary care settings may produce a very small reduction in cannabis use among young people.§	O'Connor 2020

Table 3. Interventions to prevent substance use in young people (continued)

Quality Rating	Evidence Statement	Review
?	There is insufficient evidence to confirm that peer led interventions may reduce cannabis use among youth	MacArthur 2016

Note. Most interventions did not specifically target cannabis use; where available we report on outcomes for both cannabis use and other drug use (but not alcohol use).
∞ Combines the effects of school-based interventions and interventions delivered outside of the school setting.
§ Effects for illicit drugs overall were not consistently observed and overall neither clinically significant nor statistically significant.

Table 4. Early interventions for substance use in young people

Quality Rating	Evidence Statement	Review
★★	Brief behavioural interventions (e.g., motivational interviewing) do not reduce cannabis use in adolescents with problematic substance use, relative to treatment as usual or psychoeducation.	Steele 2020a
★	Brief behavioural interventions (e.g., motivational interviewing) may reduce problems related to substance use in youth with problematic substance use.[#]	Steele 2020a
?	It is unclear whether interventions for street-connected children and young people that promote inclusion and reintegration reduce harms related to substance use.	Coren 2016
?	There is insufficient evidence to confirm the benefits of brief interventions delivered in emergency departments for reducing cannabis use among youth.	Newton 2013

Includes problems related to alcohol use, which was reduced by brief behavioural interventions.

3.4 Interventions for of cannabis use disorder

There is only low-quality evidence available to guide interventions for cannabis use disorder (Table 4). Within this limited body of evidence, the only interventions that may be effective are psychosocial interventions, particularly more intensive psychosocial interventions, and digital treatment interventions. The limited available evidence on pharmacotherapy options (including SSRI antidepressants, the anti-anxiety agent buspirone, and cannabinoids) provides low quality evidence that these do not reduce cannabis use. Cannabinoids were associated with more adverse events, suggesting that they may be harmful.

Table 5. Interventions for cannabis use disorder

Quality Rating	Evidence Statement	Review
	Psychosocial interventions	
★	Psychosocial interventions may reduce cannabis use and related problems, with more intensive interventions (> 4 sessions over > 1 month) producing better outcomes.	Gates 2016
★	Digital treatment interventions may produce a small reduction in cannabis use.	Boumparis 2019
★	Whole-of-community interventions may have no impact on cannabis use.	Stockings 2018
?	There is very low-quality evidence that brief interventions do not reduce cannabis use in health care settings.	Imtiaz 2020
	Pharmacotherapy interventions	
★	Buspirone may not improve treatment outcomes for cannabis use.	Kondo 2020
★	Selective serotonin reuptake inhibitors (SSRIs) may not reduce cannabis use or improve treatment retention.	Kondo 2020
★	Cannabinoids may not reduce cannabis use or increase treatment retention.	Kondo 2020
★	Cannabinoids may be associated with increase adverse health event.	Kondo 2020

3.5 Interventions for opioid use disorder

The evidence for interventions for opioid use disorder is far more substantive than for other drug use disorders (Table 5). Most of this evidence, however, relates to pharmacotherapy interventions, particularly opioid-agonist therapy. There is comparatively little evidence for non-pharmacological interventions which reflects a lack of randomised-controlled trials comparing these interventions to no treatment. Similarly, much of the evidence for buprenorphine is in comparison with methadone maintenance (rather than placebo).

To facilitate interpretation, the evidence on interventions for opioid use has been divided into sections on opioid agonist treatment, antagonist treatments, supervised heroin injection and withdrawal management (Table 5).

3.5.1 Opioid agonist treatment

Overall, there is high quality evidence that opioid agonist treatment is beneficial for opioid use disorder, both in terms of increasing retention in treatment and in reducing illicit opioid use more than other treatments that do not use opioid agonist treatment. There is also evidence that it reduces mortality and crime.

Evidence generally supports the use of buprenorphine as being an effective alternative to methadone, provided dosing is sufficient (≥ 16 mg). There are differences in retention, with methadone generally superior, however, there is some limited evidence that at higher doses of buprenorphine, retention may be the same as for methadone.

The addition of contingency management (which targets abstinence from substance use) can reduce the use of other substances (e.g., cocaine use) among people on opioid-agonist treatment, but it does not further reduce illicit opioid use. The addition of other psychosocial interventions to opioid agonist treatment does not improve retention in opioid agonist treatment or abstinence from opioid use.

3.5.2 Supervised heroin injection

The evidence base for supervised heroin injection is comparatively thin. While there is moderate quality evidence that it improves outcomes when provided in conjunction with opioid agonist treatment, this evidence is specific to people who have long-term heroin use and who have not responded to other treatment. There is insufficient evidence about the impacts of supervised heroin injection on other treatment outcomes (including mortality). There is low-quality evidence suggesting that supervised heroin injection may be associated with more adverse events than opioid agonist treatment.

3.5.3 Antagonist therapies

The evidence for antagonist treatments is specific to oral and implant naltrexone, and is of low quality (Table 6). The limited available evidence suggests that providing oral naltrexone may be no better than providing no treatment or psychotherapy alone. Naltrexone implants may improve treatment retention and reduce opioid use better than no treatment. However, it is more difficult to initiate patients on naltrexone implants (compared to oral naltrexone and buprenorphine combined), and there is low quality evidence that both of these treatment options have similar benefits.

3.5.4 Withdrawal management

There is good evidence that alpha2-adrenergic agonists (e.g., clonidine) reduce the severity of opioid withdrawal in comparison with placebo. However, buprenorphine is superior to alpha2-adrenergic agonists in reducing the severity of withdrawal and increasing completion of withdrawal treatment. Methadone tapering is similarly effective to buprenorphine and other pharmacological treatments for opioid withdrawal, and both may be associated with fewer adverse health events (such as hypotension) than alpha2-adrenergic agonists.

Adding psychosocial treatments to pharmacological opioid withdrawal improves treatment outcomes by reducing dropout and increasing compliance; it also reduces opioid use during treatment.

For pregnant women, there is not enough safety data available to recommend opioid withdrawal; there is low quality evidence showing similar outcomes for both buprenorphine and methadone for pregnant women (see opioid agonist treatment, Table 5).

Table 6. Interventions for opioid use disorder

Quality Rating	Evidence Statement	Review
	Opioid agonist treatment:	
★★★	Methadone is an effective maintenance treatment for opioid use disorder, increasing retention in treatment and reducing heroin use more than treatments that do not use opioid agonist treatments.	Mattick 2009
★★	Buprenorphine (≥ 16 mg) reduces opioid use more than placebo and is similarly effective to methadone at reducing illicit opioid use.	Mattick 2014
★★★	There is usually greater retention in treatment with methadone than buprenorphine[†]	Mattick 2014
★	At fixed high doses of buprenorphine (> 7 mg) retention may be the same as for methadone.	Mattick 2014
★	Buprenorphine maintenance treatment may reduce opioid use in people dependent on pharmaceutical opioids more than withdrawal or psychological treatments.	Nielsen 2016
★★	The addition of CM to opioid agonist treatment can reduce the use of other substances (e.g., cocaine) but not non-prescribed opioid use.	Ainscough 2017
★★[#]	Opioid agonist treatment reduces mortality[‡]	Mattick 2009 Santo 2021
★★	Opioid agonist treatment reduces crime	Mattick 2009
★	Buprenorphine and methadone may be similar in efficacy and safety for pregnant women	Minozzi 2020
★★★	Adding psychosocial interventions to standard opioid agonist treatments does not significantly improve opioid abstinence or retention in opioid agonist treatment.	Amato 2011a
?	There is insufficient evidence to confirm the effectiveness of opioid agonist treatment or pharmacotherapies for opioid detoxification in youth.	Minozzi 2014

Table 5. Interventions for opioid use disorder (continued)

Quality Rating	Evidence Statement	Review
	Supervised heroin injection:	
★★	Supervised heroin injection in addition to flexible doses of methadone can improve treatment retention for people with long-term treatment resistant heroin dependence.	Ferri 2011 Strang 2015
?	There is insufficient evidence about whether supervised heroin injection improves opioid treatment outcomes or mortality.	
★	Supervised heroin injection may be associated with more adverse events than methadone alone.	
	Antagonist treatments:	
★	Oral naltrexone maybe no better than psychotherapy or no treatment in retaining people in treatment or reducing opioid use.	Minozzi 2011
★	Naltrexone implants may produce better retention and reduce opioid use more no treatment, treatment as usual and oral naltrexone.	Larney 2014
★	It may be more difficult to initiate patients on naltrexone implants than oral naltrexone plus buprenorphine.	Jarvis 2018
★	Naltrexone implants may have similar outcomes to oral naltrexone plus buprenorphine, once initiated.	Jarvis 2018
★	Naltrexone may produce similar or greater reductions in mortality risk to opioid agonist treatment during treatment (but not after treatment).	Ma 2019
	Withdrawal management:	
★★	Alpha2-adrenergic agonists (e.g., clonidine) reduce the likelihood of severe withdrawal and increase completion of withdrawal (compared to placebo).	Gowing 2016
★★	Buprenorphine reduces withdrawal severity and increases completion of opioid withdrawal more than clonidine or lofexidine.	Gowing 2017b
★★	There is no difference between buprenorphine and methadone in terms of completing withdrawal.	Gowing 2017b
★★★	Methadone tapering is similarly effective to other pharmacological treatments for opioid withdrawal (both in terms of completing withdrawal and being abstinence at the end of withdrawal).	Amati 2013

Table 5. Interventions for opioid use disorder (continued)

★★	The addition of psychosocial interventions to pharmacological opioid withdrawal improves outcomes (increases compliance, reduces dropout and reduces opioid use during treatment).	Amato 2011b
★	Drop out from adverse effects may be greater for clonidine than buprenorphine (otherwise adverse effects are similarly likely with buprenorphine and clonidine or lofexidine)	Gowing 2017b
★	Hypotension and other adverse effects may be more common with alpha2-adrenergic agonists than methadone tapering (low quality)	Gowing 2016
?	There is not enough safety data available to recommend opioid withdrawal in pregnant women.	Terplan 2018

‡ There is evidence from RCTs that OAT reduces mortality, however, the effects are not statistically significant because of imprecision (mortality being an uncommon outcome). For this reason, we have also used data from cohort studies to support the direction of effect and the quality rating (see Santos et al.* for details) *Santo T, Clark B, Hickman M, Grebely J, Campbell G, Sordo L, Chen A, Tran LT, Bharat C, Padmanathan P, Cousins G, Dupouv J, Kelty E, Muga R, Nosyk B, Min J, Pavarin R, Farrell M, Degenhardt L. The impact of opioid agonist treatment delivered in different settings on all-cause mortality and specific causes of death: A systematic review and meta-analysis. JAMA Psychiatry. 2021: 78(9):979-993

† Low-fixed-doses of methadone (≤ 40 mg) are more likely to retain participants than low-dose buprenorphine (2 - 6 mg), (3 studies, 253 participants, RR 0.67; 95% CI: 0.52 to 0.87). Buprenorphine in flexible doses adjusted to participant need is less effective than methadone in retaining participants in treatment (5 studies, 788 participants, RR 0.83; 95% CI 0.72 to 0.95.)

3.6 Interventions for stimulant use disorders

Evidence for treating stimulant use disorders currently favours psychosocial interventions, with limited evidence available to support pharmacotherapy options (Table 6).

3.6.1 Psychosocial interventions

Overall, the evidence shows that psychosocial interventions (e.g., counselling) increase abstinence from stimulant use compared to no treatment, but amongst the psychosocial treatments, contingency management is the only intervention with good evidence for being superior to 'treatment as usual' (which, in the case of stimulant use disorder, usually consists of case management and available psychosocial supports such as group therapy). In these evaluations, contingency management typically involved reinforcing abstinence from stimulant use with an escalating reinforcement schedule (see Higgins et al. [1, 2] and Petry et al. [3] for details). Contingency management also increases retention in treatment. Twelve-step therapy may outperform treatment as usual, but the quality of evidence for this conclusion is low. Cognitive behavioural therapy may not be superior to treatment as usual.

3.6.2 Pharmacotherapies

Available evidence shows that psychostimulant pharmacotherapies (e.g., dexamphetamine or other prescription stimulants) do not increase retention in treatment, and that antidepressants do not reduce cocaine use. Prescription stimulant use may be associated with a small reduction in cocaine use amongst people with cocaine use disorder, but the quality of evidence for this is low, and the benefit may not extend to meth/amphetamine use. There is insufficient evidence available on the effects of other trialled pharmacotherapies to know whether they are effective.

Table 7. Evidence for the treatment of problematic stimulant use

Quality Rating	Evidence Statement	Review
	Psychosocial interventions:	
★★	Psychosocial interventions increase abstinence from stimulant use compared to no treatment	Minozzi 2016
★★	Contingency management (alone or together with community reinforcement or cognitive behavioural therapy) increases abstinence from stimulants compared to treatment as usual	De Crescenzo 2018
★★	Contingency management (alone or with community reinforcement) increases retention in treatment	De Crescenzo 2018
★	12-step programmes may increase abstinence from stimulant use more than treatment as usual	De Crescenzo 2018
★	Cognitive behavioural therapy may not be superior to treatment as usual in increasing abstinence from stimulant use, but it may improve retention in treatment.	De Crescenzo 2018
	Pharmacological interventions:	
★★	Psychostimulant pharmacotherapies do not improve retention in treatment	Castells 2016
★★	Antidepressant medication does not reduce cocaine use (note - this evidence does not include bupropion)	Chan 2019a, 2019b Pani 2011
★	Prescription stimulants may be associated with a small reduction in cocaine use	Tardelli 2020 Bhatt 2016
★	Prescription stimulants may not reduce meth/amphetamine use	Bhatt 2016
?	There is insufficient evidence to support the use of disulfiram in cocaine use disorder	Pani 2010
?	There is insufficient evidence to support the use of naltrexone in meth/amphetamine use disorders	Lam 2019
?	There is either insufficient data on other medications trialled or low strength evidence that they have no effect on amphetamine use (anticonvulsants, antipsychotics [aripiprazole], opioid antagonists (naltrexone), varenicline and atomoxetine)	Chan 2019b

3.7 Interventions for substance use disorders within prisons

Opioid agonist treatment reduces illicit opioid use whilst people are in prison. It may also reduce the risk of mortality and improve other outcomes (increase community engagement) after release from prison. However, it may not reduce recidivism. There is insufficient evidence to compare benefits of methadone with buprenorphine. Naltrexone may help maintain abstinence from illicit opioid use. Psychosocial interventions in prison may produce a marginal reduction in drug use (Table 7).

Table 8. Evidence for interventions for substance use disorders in prisons

Quality Rating	Evidence Statement	Review
★★	Providing methadone during prison reduces illicit opioid use.	Moore 2019
★	Initiating opioid agonist treatment reduces the risk of death, including drug-related death, after release from prison.	Santo 2021
★	Non-pharmacological interventions (e.g., case management, therapeutic communities) may produce small reductions in drug use and reincarceration among drug-offenders	Perry 2016 Doyle 2019 de Andrade 2018 Galassi 2015
★	Naltrexone may reduce relapse to opioid use (or maintain abstinence from opioid use) among people in the criminal justice system	Bahji 2019
★	Methadone received during incarceration may reduce injection drug use and increases community treatment engagement after prison release	Moore 2019
★	Methadone received during incarceration may not reduce recidivism	Moore 2019
?	There is insufficient evidence to know whether buprenorphine and naltrexone are as effective, or more effective, than either methadone or to placebo, in reducing illicit opioid use after release from prison	Moore 2019

4 DISCUSSION

We found good evidence of benefits for several common interventions for substance use. These included: universal school-based prevention programs (provided these targeted multiple risk behaviours and/or used a combination of approaches), albeit with small intervention effects; opioid agonist treatment (both methadone and buprenorphine); medically supported opioid withdrawal, and psychosocial interventions for stimulant use disorders (when compared to providing no treatment).

We also found good evidence that some interventions were unlikely to have any benefit. Although these findings are potentially very useful in guiding health-providers away from ineffective strategies to address substance use, they need to be interpreted with caution. These null effects can be related to the context in which interventions were delivered and what they were being compared to. For example, although we report that brief behavioural interventions do not reduce cannabis use in adolescents, this was relative to treatment as usual or psycho-education. Therefore, it is not possible to conclude that they would have no beneficial effect compared to not providing any intervention.

There was a poor evidence base for some interventions, including for cannabis use disorders, pharmacotherapy for stimulant use disorders, and early interventions for substance use in young people. Although the evidence for opioid agonist treatments was comprehensive, this was not the case for other interventions for opioid use disorders: there was limited evidence for antagonist treatments, long-acting medications, and the safety of supervised heroin injection.

For some interventions, the evidence was too heterogeneous or imprecise to draw firm conclusions. This was the case for non-school based interventions to reduce substance use in young people (see O'Connor et al. 2020 for a discussion[4]). Because of the substantial variation in the nature of the interventions being assessed, and their impacts, the average null effect of these interventions on illicit drug use is not likely to be an accurate reflection of the potential impact of any specific type of intervention. In this situation it is important to refer to individual studies for more information on which interventions are most effective.

4.1.1 Limitations

This overview of evidence is specific to illicit substance use. Although some interventions had no impact on illicit substance use, they did have beneficial impacts on alcohol use, including some of the interventions to prevent substance use in young people.

Evidence was almost exclusively from high income countries. Hence, the findings may not generalise to low or middle income countries, where contextual factors may impact on the feasibility and integrity of interventions in a way that alters their benefits.

We did not report effect sizes for interventions, because robust estimation of effect sizes requires moderate to high quality data, which was not available for most evidence statements.

We were unable to report evidence for some topics due to a lack of review papers or robust RCTs. This included non-pharmacological community-based treatment options (e.g., residential rehabilitation) and the extra-medical use of prescription medications, where the only robust evidence available related to the use of opioid agonist treatment to treat extra-medical prescription opioid use.

The evolution of treatment impacted the nature of evidence available, in that newer treatment options were compared to current best practice, meaning that for many interventions, there was no data on how they would compare to placebo or no intervention. For example, evidence for buprenorphine was relative to methadone, while long-acting formulations were compared to available oral formulations.

Although our overview used the general methods for conducting an overview of reviews [5], it was less comprehensive in several ways:

- We did not conduct a formal quality assessment of the included reviews.
- We did not use two independent raters to make decisions about which reviews to include, to extract data or to do quality ratings.
- We do not provide a detailed account of our search outcomes, including which papers were included/excluded.
- We do not document all evidence from all included reviews (although this data was extracted as part of the data analysis).

4.1.2 Conclusion

We report on the methods and findings from an overview of interventions for substance use and the quality of the available evidence to support their benefits. Reassuringly, the available evidence supported several commonly used interventions for substance use. This said, there were substantive areas where primary reviews and/or more robust trials are needed to fortify the evidence for substance use interventions. A major limitation of our evidence overview approach is that it could not provide evidence to support decision making about more novel or idiosyncratic interventions, or poorly evaluated interventions, where comprehensive evidence reviews are not available.

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6 APPENDIX

Table S1 Search Terms

Topic area in this report	EMCDDA topic area	Search terms (Pubmed search string)	Date of search
Interventions to prevent substance use in young people	Interventions to prevent or delay cannabis use	Search: (((((cannabis[MeSH Terms]) OR (marijuana abuse[MeSH Terms])) OR (marijuana smoking[MeSH Terms])) OR (cannabinoids[MeSH Terms])) OR (marijuana[Title/Abstract])) OR (cannabi*[Title/Abstract]) Filters: Meta-Analysis, Systematic Review, from 2010 - 2021 Sort by: Most Recent	March 16 2021
	Responses for vulnerable young people	Search: ((((Substance-Related Disorders[MeSH Terms]) OR (Illicit Drugs[MeSH Terms]))) AND (Vulnerable Populations[MeSH Terms])) AND (Young Adult[MeSH Terms]) Filters: Meta-Analysis, Systematic Review, from 2010/1/1 - 2021/4/16 Sort by: Most Recent	April 16 2021
	Interventions in schools and colleges	(Substance-Related Disorders [MeSH Terms] OR Illicit drugs [MeSH Terms] OR Cannabis [MeSH Terms] OR Cocaine [MeSH Terms] OR Heroin [MeSH Terms] OR Marijuana Abuse [MeSH Terms] OR Marijuana Smoking [MeSH Terms] OR Cannabinoids [MeSH Terms] OR Opioid-Related Disorders [MeSH Terms] OR Heroin [MeSH Terms] OR Methamphetamine [MeSH Terms] OR Amphetamines [MeSH Terms] OR Amphetamine-Related Disorders [MeSH Terms] OR Crack Cocaine [MeSH Terms] OR Cocaine-Related Disorders [MeSH Terms] OR N-Methyl-3,4-methylenedioxyamphetamine [MeSH Terms]) AND (Schools [MeSH Terms] OR Universities [MeSH Terms] OR Students [MeSH Terms]) Filters: Meta-Analysis, Systematic Review, from 2010/1/1 - 2021/4/20	April 20 2021
Interventions for cannabis use disorder	Treating problematic cannabis use	Search: (((((cannabis[MeSH Terms]) OR (marijuana abuse[MeSH Terms])) OR (marijuana smoking[MeSH Terms])) OR (cannabinoids[MeSH Terms])) OR (marijuana[Title/Abstract])) OR (cannabi*[Title/Abstract])	

		Filters: Meta-Analysis, Systematic Review, from 2010 - 2021 Sort by: Most Recent	
Interventions for stimulant use disorder	Treatment for problematic stimulant use	Search: ((((((((((methamphetamine[MeSH Terms]) OR (amphetamine[MeSH Terms])) OR (amphetamines[MeSH Terms])) OR (Amphetamine-Related Disorders[MeSH Terms])) OR (methamphetamine[MeSH Terms])) OR (cocaine[MeSH Terms])) OR (crack cocaine[MeSH Terms])) OR (cocaine related disorders[MeSH Terms])) OR (N-Methyl-3,4-methylenedioxyamphetamine[MeSH Terms])) OR (ecstasy[Title/Abstract])) OR (amphetamine*[Title/Abstract])) OR (methamphetamine*[Title/Abstract]) Filters: Meta-Analysis, Systematic Review, from 2010 - 2021 Sort by: Most Recent	March 16 2021
Interventions for opioid use disorder	Treating opioid dependence	(opioid-related disorders[MeSH Terms]) OR (heroin[MeSH Terms])	March 19 2021
	Reducing opioid-related deaths	As above	
	Treatment for misuse of medicines	("prescription drugs"[MeSH Terms] OR "inappropriate prescribing"[MeSH Terms] OR "medical overuse"[MeSH Terms]) AND ((meta-analysis[Filter] OR systematicreview[Filter]) AND (2010/1/1:2021/4/16[pdat]))	March 19 2021
Interventions for substance use disorder in prison	Interventions in prisons and the criminal justice system	Search: ("correctional facilities"[MeSH Terms] OR "prison*"[Title/Abstract]) Filters: Meta-Analysis, Systematic Review, from 2010/1/1 - 2021/3/31	March 31 2021

Table S2 Reviews on interventions to prevent or delay cannabis use

First author	Year	Citation	Abstract
Asevedo E	2014	Asevedo E, Mendes AC, Berk M, Brietzke E. Braz. Systematic review of N-acetylcysteine in the treatment of addictions. J Psychiatry, 36(2):168-75. doi: 10.1590/1516-4446-2013-1244.	Objective: To conduct the first systematic literature review of clinical trials of N-acetylcysteine (NAC) for the treatment of substance abuse disorders and addictive behaviors. Methods: A search of the MEDLINE, Embase and PsycINFO databases was conducted. The inclusion criteria for the review were clinical trials that used NAC in the treatment of a disorder related to substance use and/or addictive behaviors, limited to texts in English, Spanish, or French. The selected studies were evaluated with respect to type of trial, sample size, diagnostic input, intervention, length of follow-up, outcome variables, and results. Results: Nine studies analyzing a total of 165 patients met the eligibility criteria and were included in qualitative analysis. These studies evaluated the role of NAC in cocaine dependence (three studies), cannabis dependence (two studies), nicotine dependence (two studies), methamphetamine addiction (one study), and pathological gambling (one study). Five of these trials were double-blind, randomized, and placebo-controlled. Conclusions: The studies analyzed suggest a potential role for NAC in the treatment of addiction, especially of cocaine and cannabis dependence. These results are concordant with the hypothesis of the involvement of glutamatergic pathways in the pathophysiology of addiction.
Boumparis N	2019	Boumparis N, Loheide-Niesmann L, Blankers M, Ebert DD, Korf D, Schaub MP, Spijkerman R, Tait RJ, Riper H. Short- and long-term effects of digital prevention	Background: Frequent Cannabis use has been linked to a variety of negative mental, physical, and social consequences. We assessed the effects of digital prevention and treatment interventions on Cannabis use reduction in comparison with control conditions. Methods: Systematic review with two separate meta-analyses. Thirty randomized controlled trials met the inclusion criteria for the review, and 21 were included in the meta-analyses. Primary outcome was self-reported Cannabis use at post-treatment and follow-up. Hedges's g was calculated for all

		and treatment interventions for cannabis use reduction: A systematic review and meta-analysis. Drug Alcohol Depend. 2019 Jul 1;200:82-94. doi: 10.1016/j.drugalcdep.2019.03.016. Epub 2019 May 14.	comparisons with non-active control. Risk of bias was examined with the Cochrane risk-of-bias tool. Results: The systematic review included 10 prevention interventions targeting 8138 participants (aged 12 to 20) and 20 treatment interventions targeting 5195 Cannabis users (aged 16 to 40). The meta-analyses showed significantly reduced Cannabis use at post-treatment in the prevention interventions (6 studies, N=2564, g=0.33; 95% CI 0.13 to 0.54, p= 0.001) and in the treatment interventions (17 comparisons, N=3813, g=0.12; 95% CI 0.02 to 0.22, p= 0.02) as compared with controls. The effects of prevention interventions were maintained at follow-ups of up to 12 months (5 comparisons, N=2445, g=0.22; 95% CI 0.12 to 0.33, p < 0.001) but were no longer statistically significant for treatment interventions. Conclusions: Digital prevention and treatment interventions showed small, significant reduction effects on Cannabis use in diverse target populations at post-treatment compared to controls. For prevention interventions, the post-treatment effects were maintained at follow-up up to 12 months later.
Carney T	2016	Carney T, Myers BJ, Louw J, Okwundu CI. Brief school-based interventions and behavioural outcomes for substance-using adolescents. Cochrane Database Syst Rev. 2016 Jan 20;2016(1):CD008969. doi: 10.1002/14651858.CD008969.pub3.	Background: Adolescent substance use is a major problem in and of itself, and because it acts as a risk factor for other problem behaviours. As substance use during adolescence can lead to adverse and often long-term health and social consequences, it is important to intervene early in order to prevent progression to more severe problems. Brief interventions have been shown to reduce problematic substance use among adolescents and are especially useful for individuals who have moderately risky patterns of substance use. Such interventions can be conducted in school settings. This review set out to evaluate the effectiveness of brief school-based interventions for adolescent substance use. Objectives: To evaluate the effectiveness of brief school-based interventions in reducing substance use and other behavioural outcomes among adolescents compared to another intervention or assessment-only conditions.

			Search methods: We conducted the original literature search in March 2013 and performed the search update to February 2015. For both review stages (original and update), we searched 10 electronic databases and six websites on evidence-based interventions, and the reference lists of included studies and reviews, from 1966 to February 2015. We also contacted authors and organisations to identify any additional studies. Selection criteria: We included randomised controlled trials that evaluated the effects of brief school-based interventions for substance-using adolescents. The primary outcomes were reduction or cessation of substance use. The secondary outcomes were engagement in criminal activity and engagement in delinquent or problem behaviours related to substance use. Data collection and analysis: We used the standard methodological procedures outlined by The Cochrane Collaboration, including the GRADE approach for evaluating the quality of evidence. Main results: We included six trials with 1176 adolescents that measured outcomes at different follow-up periods in this review. Three studies with 732 adolescents compared brief interventions (BIs) with information provision only, and three studies with 444 adolescents compared BIs with assessment only. Reasons for downgrading the quality of evidence included risk of bias of the included studies, imprecision, and inconsistency. For outcomes that concern substance abuse, the retrieved studies only assessed alcohol and cannabis. We generally found moderate-quality evidence that, compared to information provision only, BIs did not have a significant effect on any of the substance use outcomes at short-, medium-, or long-term follow-up. They also did not have a significant effect on delinquent-type behaviour outcomes among adolescents. When compared to assessment-only controls, we found low- or very low-quality evidence that BIs reduced cannabis frequency at short-term follow-up in one study (standardised mean difference (SMD) -0.83; 95% confidence interval (CI) -1.14 to -0.53, n =269). BIs also significantly reduced frequency of alcohol use (SMD -0.91; 95% CI -1.21 to -0.61, n = 242), alcohol abuse (SMD

			-0.38; 95% CI -0.7 to -0.07, n = 190) and dependence (SMD -0.58; 95% CI -0.9 to -0.26, n = 190), and cannabis abuse (SMD -0.34; 95% CI -0.65 to -0.02, n =190) at medium-term follow-up in one study. At long-term follow-up, BIs also reduced alcohol abuse (SMD -0.72; 95% CI -1.05 to -0.40, n =181), cannabis frequency (SMD -0.56; 95% CI -0.75 to -0.36, n = 181), abuse (SMD -0.62; 95% CI -0.95 to -0.29, n = 181), and dependence (SMD -0.96; 95% CI -1.30 to -0.63, n = 181) in one study. However, the evidence from studies that compared brief interventions to assessment only conditions was generally of low quality. Brief interventions also had mixed effects on adolescents' delinquent or problem behaviours, although the effect at long-term follow-up on these outcomes in the assessment-only comparison was significant (SMD -0.78; 95% CI -1.11 to -0.45). Authors' conclusions: We found low- or very low-quality evidence that brief school-based interventions may be more effective in reducing alcohol and cannabis use than the assessment-only condition and that these reductions were sustained at long-term follow-up. We found moderate-quality evidence that, when compared to information provision, brief interventions probably did not have a significant effect on substance use outcomes. It is premature to make definitive statements about the effectiveness of brief school-based interventions for reducing adolescent substance use. Further high-quality studies examining the relative effectiveness of BIs for substance use and other problem behaviours need to be conducted, particularly in low- and middle-income countries.
Champion KE	2013	Champion KE, Newton NC, Barrett EL, Teesson M. A systematic review of school-based alcohol and other drug prevention programs facilitated by computers or the	Issues: The use of alcohol and drugs amongst young people is a serious concern and the need for effective prevention is clear. This paper identifies and describes current school-based alcohol and other drug prevention programs facilitated by computers or the Internet. Approach: The Cochrane Library, PsycINFO and PubMed databases were searched in March 2012. Additional materials were obtained from reference lists of papers. Studies were included if they described an Internet- or computer-based prevention program for alcohol or other drugs delivered in schools.

		internet. Drug Alcohol Rev. 2013 Mar;32(2):115-23. doi: 10.1111/j.1465-3362.2012.00517.x. Epub 2012 Oct 8.	Key Findings: Twelve trials of 10 programs were identified. Seven trials evaluated Internet-based programs and five delivered an intervention via CD-ROM. The interventions targeted alcohol, cannabis and tobacco. Data to calculate effect size and odds ratios were unavailable for three programs. Of the seven programs with available data, six achieved reductions in alcohol, cannabis or tobacco use at post intervention and/or follow up. Two interventions were associated with decreased intentions to use tobacco, and two significantly increased alcohol and drug-related knowledge. Conclusion: This is the first study to review the efficacy of school-based drug and alcohol prevention programs delivered online or via computers. Findings indicate that existing computer- and Internet based prevention programs in schools have the potential to reduce alcohol and other drug use as well as intentions to use substances in the future. These findings, together with the implementation advantages and high fidelity associated with new technology, suggest that programs facilitated by computers and the Internet offer a promising delivery method for school-based prevention. [Champion KE, Newton NC, Barrett EL, Teesson M. A systematic review of school-based alcohol and other drug prevention programs facilitated by computers or the Internet.
Champion KE	2016	Champion KE, Newton NC, Teesson M. Prevention of alcohol and other drug use and related harm in the digital age: what does the evidence tell us? Curr Opin Psychiatry. 2016 Jul;29(4):242-9. doi:	Purpose of review: Alcohol and other drug use are major contributors to the global burden of disease. Prevention is critical and evidence is beginning to support the use of online mediums to prevent alcohol and other drug use and harms among adolescents. This study aims to expand the evidence base by conducting a systematic review of recent universal prevention programs delivered by computers and the Internet. Recent findings: A total of 12 papers reporting outcomes from trials of nine universal online prevention programs were identified. Of the identified interventions, five targeted multiple substances, two focused solely on alcohol, one targeted only cannabis and one primarily addressed smoking. The majority of programs were delivered at school; however one was implemented in a primary care setting. Six programs demonstrated significant,

		10.1097/YCO.0000000000000258.	but modest, effects for alcohol and/or other drug use outcomes. Summary: Evidence to support the efficacy of computer and Internet-based prevention programs for alcohol and other drug use and related harms among adolescents is rapidly emerging, demonstrating that online prevention is an area of increasing promise. Further replication work, longer-term trials and attempts to increase the impact are required.
Chiesa A	2014	Chiesa A, Serretti A. Are mindfulness-based interventions effective for substance use disorders? A systematic review of the evidence. Subst Use Misuse. 2014 Apr;49(5):492-512. doi: 10.3109/10826084.2013.770027. Epub 2013 Mar 5.	Mindfulness-based interventions (MBIs) are increasingly suggested as therapeutic approaches for effecting substance use and misuse (SUM). The aim of this article is to review current evidence on the therapeutic efficacy of MBIs for SUM. A literature search was undertaken using four electronic databases and references of retrieved articles. The search included articles written in English published up to December 2011. Quality of included trials was assessed. In total, 24 studies were included, three of which were based on secondary analyses of previously investigated samples. Current evidence suggests that MBIs can reduce the consumption of several substances including alcohol, cocaine, amphetamines, marijuana, cigarettes, and opiates to a significantly greater extent than waitlist controls, non-specific educational support groups, and some specific control groups. Some preliminary evidence also suggests that MBIs are associated with a reduction in craving as well as increased mindfulness. The limited generalizability of the reviewed findings is noted (i.e., small sample size, lack of methodological details, and the lack of consistently replicated findings). More rigorous and larger randomized controlled studies are warranted.
Coren	2016	Coren, E; Hossain, R; Pardo Pardo, J; Bakker, B. Interventions for promoting reintegration and reducing harmful behaviour and	Background: Millions of street-connected children and young people worldwide live or work in street environments. They are vulnerable to many risks, whether or not they remain connected to families of origin, and despite many strengths and resiliencies, they are excluded from mainstream social structures and opportunities. Objectives: Primary research objectives: To evaluate and summarise the effectiveness of interventions for street-connected children and young people that aim to: • promote inclusion and reintegration;

		lifestyles in streetâ€• connected children and young people http://dx.doi.org/10.1002/14651858.CD009927.pub2	• increase literacy and numeracy; • facilitate access to education and employment; • promote mental health, including self esteem; • reduce harms associated with early sexual activity and substance misuse. Secondary research objectives: • To explore whether effects of interventions differ within and between populations, and whether an equity gradient influences these effects, by extrapolating from all findings relevance for low- and middle-income countries (LMICs) (Peters 2004). • To describe other health, educational, psychosocial and behavioural effects, when appropriate outcomes are reported. • To explore the influence of context in design, delivery and outcomes of interventions. • To explore the relationship between numbers of components and duration and effects of interventions. • To highlight implications of these findings for further research and research methods to improve evidence in relation to the primary research objective. • To consider adverse or unintended outcomes. Search methods: We searched the following bibliographic databases, searched for the original review, from inception to 2012, and various relevant nongovernmental and organisational websites: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE and Pre-MEDLINE; EMBASE and EMBASE Classic; Cumulative Index to Nursing and Allied Health Literature (CINAHL); PsycINFO; Education Resource Information Center (ERIC); Sociological Abstracts; Social Services Abstracts; Social Work Abstracts; Healthstar; Latin American Caribbean Health Sciences Literature (LILACS); System for Grey literature in Europe (OpenGrey); ProQuest Dissertations and Theses; EconLit; IDEAS Economics and Finance Research; JOLIS Library Catalog of the holdings of the World Bank Group and International Monetary Fund (IMF) Libraries; British Library for Development Studies (BLDS); Google and Google Scholar. We updated the search in April 2015 for the review update, using the same methods.

			Selection criteria: This review includes data from harm reduction or reintegration intervention studies that used a comparison group study design; all were randomised or quasi-randomised studies. Studies were included if they evaluated interventions provided for street-connected children and young people, from birth to 24 years, in all contexts. Data collection and analysis: Two review authors independently extracted data and assessed risk of bias and other factors presented in the Discussion and Summary quality assessment (Grades of Recommendation, Assessment, Development and Evaluation (GRADE)).We extracted data on intervention delivery, context, process factors, equity and outcomes, and grouped outcomes into psychosocial outcomes, risky sexual behaviours or substance use. We conducted meta-analyses for outcomes where the outcome measures were sufficiently similar. We evaluated other outcomes narratively. Main results: We included 13 studies evaluating 19 interventions from high-income countries (HICs). At update stage (from our 2015 search), one previously included study was removed and three new studies added (since our 2012 search). We found no sufficiently robust evaluations conducted in low- and middle-income countries (LMICs). Study quality overall was low and measurements used by studies variable. Participants were classified as drop-in and shelter-based. No studies measured the primary outcome of reintegration and none reported on adverse effects. We found no consistent results on a range of relevant outcomes within domains of psychosocial health, substance misuse and sexually risky behaviours . Interventions evaluated consisted of time-limited therapeutically based programmes that proved no more effective than standard shelter or drop-in services and other control interventions used for most outcomes in most studies. Favourable changes from baseline were reported for outcomes for most participants following therapy interventions and standard services. We noted considerable heterogeneity between studies and inconsistent reporting of equity data. No studies measured the primary outcome of reintegration or reported on adverse effects. Authors' conclusions: Analysis revealed no consistently significant benefit for focused therapeutic interventions compared with standard services such as drop-in centres, case

			management and other comparable interventions for street-connected children and young people. Commonly available services, however, were not rigorously evaluated. Robust evaluation of interventions, including comparison with no intervention, would establish a more reliable evidence base to inform service implementation. More robust research is needed in LMICs to examine interventions for street-connected children and young people with different backgrounds and service needs.
Coronado-Montoya S	2020	Coronado-Montoya S, Morissette F, Abdel-Baki A, Fischer B, Côté J, Ouellet-Plamondon C, Tremblay L, Jutras-Aswad D. Preventive interventions targeting cannabis use and related harms in people with psychosis: A systematic review. Early Interv Psychiatry. 2020 Dec 6. doi: 10.1111/eip.13081. Online ahead of print.	Aim: While most users will not experience severe adverse health outcomes from cannabis, it can be associated with negative outcomes in people with psychosis. People with psychosis who use cannabis have more severe psychiatric symptoms, higher rates of hospitalization, and diminished psychosocial functioning compared to those who do not use cannabis. Most studies of people with psychotic disorders have focused on cannabis use treatments and only a few on preventive interventions for cannabis. This systematic review aims to evaluate the effectiveness of preventive interventions focusing on cannabis use for people with psychosis. Methods: We searched CINAHL Plus, EBM reviews, EMBASE, MEDLINE, PsycInfo and PubMed databases for controlled studies assessing the effects of preventive interventions on cannabis use and related harms in people with psychosis. We conducted the search using a combination of the following concepts: cannabis, psychosis, intervention and prevention. Risk of bias was assessed. Results: The search yielded 11 460 unique studies. Of these, five studies met our eligibility criteria. None of the studies demonstrated clear efficacy of prevention interventions in reducing cannabis use, and none measured cannabis-related harms. All studies had high risk of bias. Conclusion: The small number of studies and the considerable risk of bias made it difficult to conclude whether any of the existing interventions were promising. With increased acceptance and accessibility of cannabis due to liberalizing cannabis policies, it is imperative to improve the evidence base for preventive interventions, in particular their effectiveness in decreasing the risk of cannabis-related harms in people with psychosis.

Dick S	2019	Dick S, Whelan E, Davoren MP, Dockray S, Heavin C, Linehan C, Byrne M. A systematic review of the effectiveness of digital interventions for illicit substance misuse harm reduction in third-level students. BMC Public Health. 2019 Sep 9;19(1):1244. doi: 10.1186/s12889-019-7583-6.	Background: Illicit substance misuse is a growing public health problem, with misuse peaking among 18–25 year olds, and attendance at third-level education identified as a risk factor. Illicit substance misuse has the potential to harm mental and physical health, social relationships, and impact on academic achievements and future career prospects. Digital interventions have been identified as a vehicle for reaching large student populations and circumventing the limited capacity of student health services for delivering face-to-face interventions. Digital interventions have been developed in the area of alcohol and tobacco harm reduction, reporting some effectiveness, but the evidence for the effectiveness of digital interventions targeting illicit substance misuse is lacking. This review aims to systematically identify and critically appraise studies examining the effectiveness of digital interventions for illicit substance misuse harm reduction in third-level students. Methods: We systematically searched ten databases in April 2018 using keywords and database specific terms under the pillars of “mHealth,” “substance misuse,” and “student.” To be eligible for inclusion, papers had to present a measure of illicit substance misuse harm reduction. Included articles were critically appraised and included in the qualitative synthesis regardless of quality. Results: A total of eight studies were included in the qualitative synthesis. Studies reported harm reduction in terms of substance misuse or initiation, as consequences or problems associated with substance misuse, or as correction of perceived social norms. Overall, five out of the eight studies reported at least one positive outcome for harm reduction. The critical appraisal indicated that the study quality was generally weak, predominantly due to a lack of blinding of study participants, and the use of self-reported substance misuse measures. However, results suggest that digital interventions may produce a modest reduction in harm from illicit substance misuse. Conclusions: The results of this review are positive, and support the need for further high-quality research in this

			area, particularly given the success of digital interventions for alcohol and tobacco harm reduction. However, very few studies focused solely on illicit substances, and those that did targeted only marijuana. This suggests the need for further research on the effectiveness of this type of intervention for other illicit substances
Faggiano F	2014	Faggiano F, Minozzi S, Versino E, Buscemi D. Universal school-based prevention for illicit drug use. Cochrane Database Syst Rev. 2014;2014(12):CD003020. doi: 10.1002/14651858.CD003020.pub3. Epub 2014 Dec 1.	Background: Drug addiction is a chronic, relapsing disease. Primary interventions should aim to reduce first use or to prevent the transition from experimental use to addiction. School is the appropriate setting for preventive interventions. Objectives: To evaluate the effectiveness of universal school-based interventions in reducing drug use compared to usual curricular activities or no intervention. Search methods: We searched the Cochrane Drugs and Alcohol Group's Trials Register (September 2013), the Cochrane Central Register of Controlled Trials (2013, Issue 9), PubMed (1966 to September 2013), EMBASE (1988 to September 2013) and other databases. We also contacted researchers in the field and checked reference lists of articles. Selection criteria: Randomised controlled trials (RCT) evaluating school-based interventions designed to prevent illicit drugs use. Data collection and analysis: We used the standard methodological procedures expected by The Cochrane Collaboration. Main results: We included 51 studies, with 127,146 participants. Programmes were mainly delivered in sixth and seventh grade pupils. Most of the trials were conducted in the USA. Social competence approach versus usual curricula or no intervention Marijuana use at < 12 months follow-up: the results favoured the social competence intervention (risk ratio (RR) 0.90; 95% confidence interval (CI) 0.81 to 1.01, four studies, 9456 participants, moderate quality evidence). Seven studies assessed this outcome (no data for meta-analysis): two showed a positive significant effect of intervention, three showed a non-significant effect, one found a significant effect in favour of the control group and one

			found a trend in favour of the control group. Marijuana use at 12+ months: the results favoured the social competence intervention (RR 0.86; 95% CI 0.74 to 1.00, one study, 2678 participants, high quality evidence). Seven studies assessed this outcome (no data for meta-analysis): two showed a significant positive effect of intervention, three showed a non-significant effect, one found a significant effect in favour of the control group and one a trend in favour of the control group. Hard drug use at < 12 months: we found no difference (RR 0.69; 95% CI 0.40 to 1.18, one study, 2090 participants, moderate quality evidence). Two studies assessed this outcome (no data for meta-analysis): one showed comparable results for the intervention and control group; one found a statistically non-significant trend in favour of the social competence approach. Hard drug use at 12+ months: we found no difference (mean difference (MD) -0.01; 95% CI -0.06 to 0.04), one study, 1075 participants, high quality evidence). One study with no data for meta-analysis showed comparable results for the intervention and control group. Any drug use at < 12 months: the results favoured social competence interventions (RR 0.27; 95% CI 0.14 to 0.51, two studies, 2512 participants, moderate quality evidence). One study with 1566 participants provided continuous data showing no difference (MD 0.02; 95% CI -0.05 to 0.09, moderate quality evidence). Social influence approach versus usual curricula or no intervention Marijuana use at < 12 months: we found a nearly statistically significant effect in favour of the social influence approach (RR 0.88; 95% CI 0.72 to 1.07, three studies, 10,716 participants, moderate quality evidence). One study with 764 participants provided continuous data showing results that favoured the social influence intervention (MD -0.26; 95% CI -0.48 to -0.04). Marijuana use at 12+ months: we found no difference (RR 0.95; 95% CI 0.81 to 1.13, one study, 5862 participants, moderate quality evidence). One study with 764 participants provided continuous data and showed nearly statistically significant results in favour of the social influence intervention (MD -0.22; 95% CI -0.46 to 0.02). Of the four studies not providing data for meta-analysis a statistically significant protective effect was only found by one study. Hard drug use at 12+ months: one study not providing data for meta-analysis found a significant protective effect of the

			social influence approach. Any drug use: no studies assessed this outcome. Combined approach versus usual curricula or no intervention: Marijuana use at < 12 months: there was a trend in favour of intervention (RR 0.79; 95% CI 0.59 to 1.05, three studies, 8701 participants, moderate quality evidence). One study with 693 participants provided continuous data and showed no difference (MD -1.90; 95% CI -5.83 to 2.03). Marijuana use at 12+ months: the results favoured combined intervention (RR 0.83; 95% CI 0.69 to 0.99, six studies, 26,910 participants, moderate quality evidence). One study with 690 participants provided continuous data and showed no difference (MD -0.80; 95% CI -4.39 to 2.79). Two studies not providing data for meta-analysis did not find a significant effect. Hard drug use at < 12 months: one study with 693 participants provided both dichotomous and continuous data and showed conflicting results: no difference for dichotomous outcomes (RR 0.85; 95% CI 0.63 to 1.14), but results in favour of the combined intervention for the continuous outcome (MD -3.10; 95% CI -5.90 to -0.30). The quality of evidence was high. Hard drug use at 12+ months: we found no difference (RR 0.86; 95% CI 0.39 to 1.90, two studies, 1066 participants, high quality evidence). One study with 690 participants provided continuous data and showed no difference (MD 0.30; 95% CI -1.36 to 1.96). Two studies not providing data for meta-analysis showed a significant effect of treatment. Any drug use at < 12 months: the results favoured combined intervention (RR 0.76; 95% CI 0.64 to 0.89, one study, 6362 participants). Only one study assessed the effect of a knowledge-focused intervention on drug use and found no effect. The types of comparisons and the programmes assessed in the other two groups of studies were very heterogeneous and difficult to synthesise. Authors' conclusions: School programmes based on a combination of social competence and social influence approaches showed, on average, small but consistent protective effects in preventing drug use, even if some outcomes did not show statistical significance. Some programmes based on the social competence approach also showed protective effects for some outcomes. Since the effects of school-based programmes are small, they

			should form part of more comprehensive strategies for drug use prevention in order to achieve a population-level impact.
Ferri	2013	Ferri, M; Allara, E; Bo, A; Gasparrini, A; Faggiano, F. Media campaigns for the prevention of illicit drug use in young people. http://dx.doi.org/10.1002/14651858.CD009287.pub2	Background: Substance-specific mass media campaigns which address young people are widely used to prevent illicit drug use. They aim to reduce use and raise awareness of the problem. Objectives: To assess the effectiveness of mass media campaigns in preventing or reducing the use of or intention to use illicit drugs amongst young people. Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2013, Issue 1), including the Cochrane Drugs and Alcohol Group's Specialised Register; MEDLINE through PubMed (from 1966 to 29 January 2013); EMBASE (from 1974 to 30 January 2013) and ProQuest Dissertations & Theses A&I (from 1861 to 3 February 2013). Selection criteria: Cluster-randomised controlled trials, prospective and retrospective cohort studies, interrupted time series and controlled before and after studies evaluating the effectiveness of mass media campaigns in influencing drug use, intention to use or the attitude of young people under the age of 26 towards illicit drugs. Data collection and analysis: We used the standard methodological procedures of The Cochrane Collaboration. Main results: We included 23 studies involving 188,934 young people, conducted in the USA, Canada and Australia between 1991 and 2012. Twelve studies were randomised controlled trials (RCT), two were prospective cohort studies (PCS), one study was both a RCT and a PCS, six were interrupted time series and two were controlled before and after (CBA) studies. The RCTs had an overall low risk of bias, along with the ITS (apart from the dimension 'formal test of trend'), and the PCS had overall good quality, apart from the description of loss to follow up by exposure. Self-reported or biomarker-assessed illicit drug use was measured with an array of published and unpublished scales making comparisons difficult. Pooled results of five RCTs (N = 5470) show no effect of media campaign intervention (standardised mean difference (SMD) -0.02; 95% confidence

			interval (CI) -0.15 to 0.12). We also pooled five ITS studies (N = 26,405) focusing specifically on methamphetamine use. Out of four pooled estimates (two endpoints measured in two age groups), there was evidence of a reduction only in past-year prevalence of methamphetamine use among 12 to 17 years old. A further five studies (designs = one RCT with PCS, two PCS, two ITS, one CBA, N = 151,508), which could not be included in meta-analyses, reported a drug use outcome with varied results including a clear iatrogenic effect in one case and reduction of use in another. Authors' conclusions: Overall the available evidence does not allow conclusions about the effect of media campaigns on illicit drug use among young people. We conclude that further studies are needed.
Georgie J M	2016	Georgie J M, Sean H, Deborah M C, Matthew H, Rona C. Peer-led interventions to prevent tobacco, alcohol and/or drug use among young people aged 11-21 years: a systematic review and meta-analysis. Addiction. 2016 Mar;111(3):391-407. doi: 10.1111/add.13224.	Background and Aims: Peer-led interventions may offer a beneficial approach in preventing substance use, but their impact has not yet been quantified. We conducted a systematic review to investigate and quantify the effect of peer-led interventions that sought to prevent tobacco, alcohol and/or drug use among young people aged 11–21 years. Methods Medline, EMBASE, PsycINFO, CINAHL, ERIC and the Cochrane Library were searched from inception to July 2015 without language restriction. We included randomized controlled trials only. Screening and data extraction were conducted in duplicate and data from eligible studies were pooled in a random effects meta-analysis. Results: We identified 17 eligible studies, approximately half of which were school-based studies targeting tobacco use among adolescents. Ten studies targeting tobacco use could be pooled, representing 13 706 young people in 220 schools. Meta-analysis demonstrated that the odds of smoking were lower among those receiving the peer-led intervention compared with control [odds ratio (OR) = 0.78, 95% confidence interval (CI) = 0.62–0.99, P = 0.040]. There was evidence of heterogeneity (I2 = 41%, χ2 15.17, P = 0.086). Pooling of six studies representing 1699 individuals in 66 schools demonstrated that peer-led interventions were also associated with benefit in relation to alcohol use (OR = 0.80, 95% CI = 0.65–0.99, P = 0.036), while three studies (n = 976 students in 38

			schools) suggested an association with lower odds of cannabis use (OR = 0.70, 0.50–0.97, P = 0.034). No studies were found that targeted other illicit drug use. Conclusions: Peer interventions may be effective in preventing tobacco, alcohol and possibly cannabis use among adolescents, although the evidence base is limited overall, and is characterized mainly by small studies of low quality.
MacArthur	2018	MacArthur, G; Caldwell, DM; Redmore, J; Watkins, SH; Kipping, R; White, J; Chittleborough, C; Langford, R; Er, V; Lingam, R; Pasch, K; Gunnell, D; Hickman, M; Campbell, R. Individualâ€• , familyâ€• , and schoolâ€• level interventions targeting multiple risk behaviours in young people. http://dx.doi.org/10.1002/14651858.CD009927.pub2	Background: Engagement in multiple risk behaviours can have adverse consequences for health during childhood, during adolescence, and later in life, yet little is known about the impact of different types of interventions that target multiple risk behaviours in children and young people, or the differential impact of universal versus targeted approaches. Findings from systematic reviews have been mixed, and effects of these interventions have not been quantitatively estimated. Objectives: To examine the effects of interventions implemented up to 18 years of age for the primary or secondary prevention of multiple risk behaviours among young people. Search methods: We searched 11 databases (Australian Education Index; British Education Index; Campbell Library; Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library; Embase; Education Resource Information Center (ERIC); International Bibliography of the Social Sciences; MEDLINE; PsycINFO; and Sociological Abstracts) on three occasions (2012, 2015, and 14 November 2016)). We conducted hand searches of reference lists, contacted experts in the field, conducted citation searches, and searched websites of relevant organisations. Selection criteria: We included randomised controlled trials (RCTs), including cluster RCTs, which aimed to address at least two risk behaviours. Participants were children and young people up to 18 years of age and/or parents, guardians, or carers, as long as the intervention aimed to address involvement in multiple risk behaviours among children and young people up to 18 years of age. However, studies could include outcome data on children > 18 years of age at the time of follow-up. Specifically, we included studies with outcomes collected from those eight to 25 years of age. Further, we included only studies

			with a combined intervention and follow-up period of six months or longer. We excluded interventions aimed at individuals with clinically diagnosed disorders along with clinical interventions. We categorised interventions according to whether they were conducted at the individual level; the family level; or the school level. Data collection and analysis: We identified a total of 34,680 titles, screened 27,691 articles and assessed 424 full-text articles for eligibility. Two or more review authors independently assessed studies for inclusion in the review, extracted data, and assessed risk of bias. We pooled data in meta-analyses using a random-effects (DerSimonian and Laird) model in RevMan 5.3. For each outcome, we included subgroups related to study type (individual, family, or school level, and universal or targeted approach) and examined Effectiveness at up to 12 months' follow-up and over the longer term (> 12 months). We assessed the quality and certainty of evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. Main results: We included in the review a total of 70 eligible studies, of which a substantial proportion were universal school-based studies (n = 28; 40%). Most studies were conducted in the USA (n = 55; 79%). On average, studies aimed to prevent four of the primary behaviours. Behaviours that were most frequently addressed included alcohol use (n = 55), drug use (n = 53), and/or antisocial behaviour (n = 53), followed by tobacco use (n = 42). No studies aimed to prevent self-harm or gambling alongside other behaviours. Evidence suggests that for multiple risk behaviours, universal school-based interventions were beneficial in relation to tobacco use (odds ratio (OR) 0.77, 95% confidence interval (CI) 0.60 to 0.97; n = 9 studies; 15,354 participants) and alcohol use (OR 0.72, 95% CI 0.56 to 0.92; n= 8 studies; 8751 participants; both moderate-quality evidence) compared to a comparator, and that such interventions may be effective in preventing illicit drug use (OR 0.74, 95% CI 0.55 to 1.00; n = 5 studies; 11,058 participants; low-quality evidence) and engagement in any antisocial behaviour (OR 0.81, 95% CI 0.66 to 0.98; n = 13 studies; 20,756 participants; very low-quality evidence) at up to 12 months' follow-up, although there was evidence of moderate to substantial heterogeneity (IM = 49% to 69%).

			Moderate-quality evidence also showed that multiple risk behaviour universal school-based interventions improved the odds of physical activity (OR 1.32, 95% CI 1.16 to 1.50; IM = 0%;n = 4 studies; 6441 participants). We considered observed effects to be of public health importance when applied at the population level. Evidence was less certain for the effects of such multiple risk behaviour interventions for cannabis use (OR 0.79, 95% CI 0.62 to 1.01; P =0.06; n = 5 studies; 4140 participants; IM = 0%; moderate-quality evidence), sexual risk behaviours (OR 0.83, 95% CI 0.61 to 1.12; P = 0.22; n =6 studies; 12,633 participants; IM = 77%; low-quality evidence), and unhealthy diet (OR 0.82, 95% CI 0.64 to 1.06; P = 0.13; n = 3 studies; 6441 participants; IM = 49%; moderate-quality evidence). It is important to note that some evidence supported the positive effects of universal school-level interventions on three or more risk behaviours. For most outcomes of individual- and family-level targeted and universal interventions, moderate- or low-quality evidence suggests little or no effect, although caution is warranted in interpretation because few of these studies were available for comparison (n N 4 studies foreach outcome). Seven studies reported adverse effects, which involved evidence suggestive of increased involvement in a risk behaviour among participants receiving the intervention compared to participants given control interventions. We judged the quality of evidence to be moderate or low for most outcomes, primarily owing to concerns around selection, performance, and detection bias and heterogeneity between studies. Authors' conclusions: Available evidence is strongest for universal school-based interventions that target multiple- risk behaviours, demonstrating that they may be effective in preventing engagement in tobacco use, alcohol use, illicit drug use, and antisocial behaviour, and in improving physical activity among young people, but not in preventing other risk behaviours. Results of this review do not provide strong evidence of benefit for family- or individual-level interventions across the risk behaviours studied. However, poor reporting and concerns around the quality of evidence highlight the need for high-quality

			multiple- risk behaviour intervention studies to further strengthen the evidence base in this field.
Melchior M	2019	Melchior M, Nakamura A, Bolze C, Hausfater F, El Khoury F, Mary-Krause M, Azevedo Da Silva M. Does liberalisation of cannabis policy influence levels of use in adolescents and young adults? A systematic review and meta-analysis. BMJ Open. 2019 Jul 10;9(7):e025880. doi: 10.1136/bmjopen-2018-025880.	Objectives To examine the effect of cannabis policy liberalisation (decriminalisation and legalisation) levels of use in adolescents and young adults. Design Systematic review and meta-analysis. Inclusion criteria: Included studies were conducted among individuals younger than 25 years and quantitatively assessing consequences of cannabis policy change. We excluded articles: (A) exclusively based on participants older than 25 years; (B) only reporting changes in perceptions of cannabis use; (C) not including at least two measures of cannabis use; (D) not including quantitative data; and (E) reviews, letters, opinions and policy papers. PubMed, PsycINFO, Embase and Web of Science were searched through 1 March 2018. Data extraction and synthesis: Two independent readers reviewed the eligibility of titles and abstracts and read eligible articles, and four authors assessed the risk of bias (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies). Extracted data were meta-analysed. The protocol was registered with PROSPERO. Results: 3438 records were identified via search terms and four via citation lists; 2312 were retained after removal of duplicates, 99 were assessed for eligibility and41 were included in our systematic review. 13 articles examined cannabis decriminalisation, 20 examined legalisation for medical purposes and 8 examined legalization for recreational purposes. Findings regarding the consequences of cannabis decriminalisation or legalization for medical purposes were too heterogeneous to be meta-analysed. Our systematic review and meta-analysis suggest a small increase in cannabis use among adolescents and young adults following legalisation of cannabis for recreational purposes (standardised mean difference of 0.03, 95% CI −0.01 to –0.07). Nevertheless, studies characterised by a very low/low risk of bias showed no evidence of changes in cannabis use following policy modifications. Conclusions: Cannabis policy liberalisation does not appear to result in significant changes

			in youths' use, with the possible exception of legalisation for recreational purposes that requires monitoring.
Newton AS	2013	Newton AS, Dong K, Mabood N, Ata N, Ali S, Gokiert R, Vandermeer B, Tjosvold L, Hartling L, Wild TC. Brief emergency department interventions for youth who use alcohol and other drugs: a systematic review. Pediatr Emerg Care. 2013 May;29(5):673-84. doi: 10.1097/PEC.0b013e31828ed325.	Objective: Brief intervention (BI) is recommended for use with youth who use alcohol and other drugs. Emergency departments (EDs) can provide BIs at a time directly linked to harmful and hazardous use. The objective of this systematic review was to determine the effectiveness of ED-based BIs. Methods: We searched 14 electronic databases, a clinical trial registry, conference proceedings, and study references. We included randomized controlled trials with youth 21 years or younger. Two reviewers independently selected studies and assessed methodological quality. One reviewer extracted and a second verified data. We summarized findings qualitatively. Results: Two trials with low risk of bias, 2 trials with unclear risk of bias, and 5 trials with high risk of bias were included. Trials evaluated targeted BIs for alcohol-positive (n = 3) and alcohol/other drug positive youth (n = 1) and universal BIs for youth reporting recent alcohol (n = 4) or cannabis use (n = 1). Few differences were found in favor of ED based BIs, and variation in outcome measurement and poor study quality precluded firm conclusions for many comparisons. Universal and targeted BIs did not significantly reduce alcohol use more than other care. In one targeted BI trial with high risk of bias, motivational interviewing (MI) that involved parents reduced drinking quantity per occasion and high-volume alcohol use compared with MI that was delivered to youth only. Another trial with high risk of bias reported an increase in abstinence and reduction in physical altercations when youth received peer-delivered universal MI for cannabis use. In 2 trials with unclear risk of bias, MI reduced drinking and driving and alcohol-related injuries after the ED visit. Computer-based MI delivered universally in 1 trial with low risk of bias reduced alcohol-related consequences 6 months after the ED visit. Conclusions: Clear benefits of using ED-based BI to reduce alcohol and other drug use and associated injuries or high-risk behaviours remain inconclusive because of variation in assessing outcomes and poor study quality.

Norberg MM	2013	Norberg MM, Kezelman S, Lim-Howe N. Primary prevention of cannabis use: a systematic review of randomized controlled trials. PLoS One. 2013;8(1):e53187. doi: 10.1371/journal.pone.0053187. Epub 2013 Jan 11.	A systematic review of primary prevention was conducted for cannabis use outcomes in youth and young adults. The aim of the review was to develop a comprehensive understanding of prevention programming by assessing universal, targeted, uni-modal, and multi-modal approaches as well as individual program characteristics. Twenty-eight articles, representing 25 unique studies, identified from eight electronic databases (EMBASE, MEDLINE, CINAHL, ERIC, PsycINFO, DRUG, EBM Reviews, and Project CORK), were eligible for inclusion. Results indicated that primary prevention programs can be effective in reducing cannabis use in youth populations, with statistically significant effect sizes ranging from trivial (0.07) to extremely large (5.26), with the majority of significant effect sizes being trivial to small. Given that the preponderance of significant effect sizes were trivial to small and that percentages of statistically significant and non-statistically significant findings were often equivalent across program type and individual components, the effectiveness of primary prevention for cannabis use should be interpreted with caution. Universal multi-modal programs appeared to outperform other program types (i.e, universal uni-modal, targeted multi-modal, targeted unimodal). Specifically, universal multi-modal programs that targeted early adolescents (10–13-year-olds), utilised non-teacher or multiple facilitators, were short in duration (10 sessions or less), and implemented boosters sessions were associated with large median effect sizes. While there were studies in these areas that contradicted these results, the results highlight the importance of assessing the interdependent relationship of program components and program types. Finally, results indicated that the overall quality of included studies was poor, with an average quality rating of 4.64 out of 9. Thus, further quality research and reporting and the development of new innovative programs are required.
O'Connor E	2020	O'Connor E, Thomas R, Senger CA, Perdue L, Robalino S, Patnode C.	IMPORTANCE: Illicit and nonmedical (use in ways other than instructed) drug use is common in adolescents and young adults and increases the risk of harmful outcomes such as injuries, violence, and poorer academic performance. OBJECTIVE: To review the benefits and harms of interventions to prevent illicit and

		Interventions to Prevent Illicit and Nonmedical Drug Use in Children, Adolescents, and Young Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2020 May 26;323(20):2067-2079. doi: 10.1001/jama.2020.1432.	nonmedical drug use in children, adolescents, and young adults to inform the US Preventive Services Task Force. DATA SOURCES: MEDLINE, PubMED, PsycINFO, and the Cochrane Central Register of Controlled Trials (January 1, 2013, to January 31, 2019 [children and adolescents]; January 1,m1992, to January 31, 2019 [young adults <25 years]); surveillance through March 20, 2020.STUDY SELECTION Clinical trials of behavioral counseling interventions to prevent initiation of illicit and nonmedical drug use among young people. DATA EXTRACTION AND SYNTHESIS: Critical appraisal was completed independently by 2 investigators. Data were extracted by 1 reviewer and checked by a second. Random-effects meta-analysis was used to estimate the effect sizes associated with the interventions. MAIN OUTCOMES AND MEASURES: Number of times illicit drugs were used; any illicit drug or any cannabis use. RESULTS: Twenty-nine trials (N = 18 353) met inclusion criteria. Health, social, or legal outcomes such as mental health symptoms, family functioning, consequences of drug use, and arrests were reported in 19 trials and most showed no group differences. The effects on illicit drug use in 26 trials among nonpregnant youth (n = 17 811) were highly variable; the pooled result did not show a clinically important or statistically significant association with illicit drug use (standardized mean difference, −0.08 [95%CI, −0.16 to 0.001]; 24 effects [from 23 studies]; n = 12 801; I2 = 57.0%). The percentage of participants using illicit drugs ranged from 2.3%to 38.6%in the control groups and 2.4%to 33.7%in the intervention groups at 3 to 32 months' follow-up. The median absolute risk difference between groups was–2.8%, favoring the intervention group (range, –11.5%to 14.8%). The remaining 3 trials provided a perinatal home-visiting intervention to pregnant Native American youth. One trial (n=322) found a reduction in illicit drug use at 38 months (eg, cannabis use in the previous month, 10.7%in the intervention group and 15.6%in the control group) but not at earlier follow-up assessments. Across all 29 trials, only 1 trial

			reported on harms and found no statistically significant group differences. CONCLUSIONS AND RELEVANCE: The evidence for behavioral counseling interventions to prevent initiation of illicit and nonmedical drug use among adolescents and young adults was inconsistent and imprecise, with some interventions associated with reduction in use and others associated with no benefit or increased use. Health, social, and legal outcomes were sparsely reported, and few showed improvements.
Patnode CD	2014	Patnode CD, O'Connor E, Rowland M, Burda BU, Perdue LA, Whitlock EP. Primary care behavioral interventions to prevent or reduce illicit drug use and nonmedical pharmaceutical use in children and adolescents: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med. 2014 May 6;160(9):612-20. doi: 10.7326/M13-2064.	Background: Drug use among youths is associated with negative health and social consequences. Even infrequent use increases the risk for serious adverse events by increasing risk-taking behaviors in intoxicated or impaired persons. Purpose: To systematically review the benefits and harms of primary care–relevant interventions designed to prevent or reduce illicit drug use or the nonmedical use of prescription drugs among youths. Data Sources: PubMed, PsycINFO, and the Cochrane Central Register of Controlled Trials through 4 June 2013; MEDLINE through 31 August 2013; and manual searches of reference lists and gray literature. Study Selection: Two investigators independently reviewed 2253 abstracts and 144 full-text articles. English-language trials of primary care–relevant behavioral interventions that reported drug use, health outcomes, or harms were included. Data Extraction: One investigator abstracted data from good- and fair-quality trials into prespecified evidence tables, and a second investigator checked these data. Data Synthesis: Six trials were included, 4 of which examined the effect of the intervention on a health or social outcome. One trial found no effect of the intervention on marijuana-related consequences or driving under the influence of marijuana; 3 trials generally found no reduction in depressed mood at 12 or 24 months. Four of the 5 trials assessing self-reported marijuana use found statistically significant differences favoring the intervention group participants (such as a between-group difference of 0.10 to 0.17 use occasions in the past month). Three trials also reported positive outcomes in nonmedical prescription drug use occasions. Limitations: The body of evidence was small, and there were

			heterogeneous measures of outcomes of limited clinical applicability. Trials primarily included adolescents with little or no substance use. Conclusion: Evidence is inadequate on the benefits of primary care–relevant behavioral interventions in reducing self-reported illicit and pharmaceutical drug use among adolescents.
Porath-Waller AJ	2010	Porath-Waller AJ, Beasley E, Beirness DJ. A meta-analytic review of school-based prevention for cannabis use. Health Educ Behav. 2010 Oct;37(5):709-23. doi: 10.1177/1090198110361315. Epub 2010 Jun 3.	This investigation used meta-analytic techniques to evaluate the effectiveness of school-based prevention programming in reducing cannabis use among youth aged 12 to 19. It summarized the results from 15 studies published in peer-reviewed journals since 1999 and identified features that influenced program effectiveness. The results from the set of 15 studies indicated that these school-based programs had a positive impact on reducing students' cannabis use (d = 0.58, CI: 0.55, 0.62) compared to control conditions. Findings revealed that programs incorporating elements of several prevention models were significantly more effective than were those based on only a social influence model. Programs that were longer in duration (≥15 sessions) and facilitated by individuals other than teachers in an interactive manner also yielded stronger effects. The results also suggested that programs targeting high school students were more effective than were those aimed at middle-school students. Implications for school-based prevention programming are discussed.
Rogers MA	2017	Rogers MA, Lemmen K, Kramer R, Mann J, Chopra V. Internet-Delivered Health Interventions That Work: Systematic Review of Meta-Analyses and Evaluation of Website Availability. J Med Internet Res. 2017	Background: Due to easy access and low cost, Internet-delivered therapies offer an attractive alternative to improving health. Although numerous websites contain health-related information, finding evidence-based programs (as demonstrated through randomized controlled trials, RCTs) can be challenging. We sought to bridge the divide between the knowledge gained from RCTs and communication of the results by conducting a global systematic review and analyzing the availability of evidence-based Internet health programs. Objectives: The study aimed to (1) discover the range of health-related topics that are addressed through Internet-delivered interventions, (2) generate a list of current websites used in the trials which demonstrate a health benefit, and (3) identify gaps in the research

		Mar 24;19(3):e90. doi: 10.2196/jmir.7111.	that may have hindered dissemination. Our focus was on Internet-delivered self-guided health interventions that did not require real-time clinical support. Methods: A systematic review of meta-analyses was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO Registration Number CRD42016041258). MEDLINE via Ovid, PsycINFO, Embase, Cochrane Database of Systematic Reviews, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched. Inclusion criteria included (1) meta-analyses of RCTs, (2) at least one Internet-delivered intervention that measured a health-related outcome, and (3) use of at least one self-guided intervention. We excluded group-based therapies. There were no language restrictions. Results: Of the 363 records identified through the search, 71 meta-analyses met inclusion criteria. Within the 71 meta-analyses, there were 1733 studies that contained 268 unique RCTs which tested self-help interventions. On review of the 268 studies, 21.3% (57/268) had functional websites. These included evidence-based Web programs on substance abuse (alcohol, tobacco, cannabis),mental health (depression, anxiety, post-traumatic stress disorder [PTSD], phobias, panic disorders, obsessive compulsive disorder [OCD]), and on diet and physical activity. There were also evidence-based programs on insomnia, chronic pain, cardiovascular risk, and childhood health problems. These programs tended to be intensive, requiring weeks to months of engagement by the user, often including interaction, personalized and normative feedback, and self-monitoring. English was the most common language, although some were available in Spanish, French, Portuguese, Dutch, German, Norwegian, Finnish, Swedish, and Mandarin. There were several interventions with numbers needed to treat of <5; these included pain ACTION, Mental Health Online for panic disorders, Deprexis, Triple P Online (TPOL), and U Can POOP Too. Hyperlinks of the sites have been listed. Conclusions: A wide range of evidence-based Internet programs are currently available for health-related behaviors, as well as disease prevention and treatment. However, the majority of Internet-delivered health interventions found to be efficacious in RCTs do not

			have websites for general use. Increased efforts to provide mechanisms to host "interventions that work" on the Web and to assist the public in locating these sites are necessary.
Sayegh CS	2017	Sayegh CS, Huey SJ, Zara EJ, Jhaveri K. Follow-up treatment effects of contingency management and motivational interviewing on substance use: A meta-analysis. Psychol Addict Behav. 2017 Jun;31(4):403-414. doi: 10.1037/adb0000277. Epub 2017 Apr 24.	Motivation is an integral factor in substance use treatment and long-term recovery. However, it is unclear what role intrinsic and extrinsic motivation play across different treatment modalities. A meta-analysis (N 84) was performed to estimate the pooled effect size of Motivational Interviewing (MI; primarily targeting intrinsic motivation) and contingency management (CM; primarily targeting extrinsic motivation) at different follow-up periods. Collapsed across all substance types, CM had a significant effect at 3-month follow-up, only. In contrast, MI had a significant effect at 6-month follow-up, only. CM had small and medium effects on multiple substances at 3-month follow-up (i.e., tobacco, marijuana, stimulants, polysubstances), but not at 6-month follow-up. MI had 1 significant medium effect at 3-month follow-up (i.e., marijuana), but several significant small effects at 6-month follow-up (i.e., alcohol, tobacco, polysubstances). This meta-analysis suggests that both CM and MI promote reductions in a range of substances, even several months after the intervention concludes. Further, these results provide some evidence that extrinsically focused CM may produce medium follow-up effects in the short run, but intrinsically focused MI may produce small but durable follow-up effects. However, this interpretation is complicated by the differences between the MI and CM studies that preclude statistical tests comparing effect sizes, and few studies assessed motivation itself. Future researchers should investigate how motivational dynamics impact lasting outcomes in substance use treatment.
Scheim AI	2020	Scheim AI, Maghsoudi N, Marshall Z, Churchill S, Ziegler C, Werb D. Impact evaluations of drug decriminalisation	Objectives: To review the metrics and findings of studies evaluating effects of drug decriminalisation or legal regulation on drug availability, use or related health and social harms globally. Design Systematic review with narrative synthesis. Data sources: We searched MEDLINE, Embase, PsycINFO, Web of Science and six additional databases for publications from 1 January 1970 through 4 October2018.

		and legal regulation on drug use, health and social harms: a systematic review. BMJ Open. 2020 Sep 21;10(9):e035148. doi: 10.1136/bmjopen-2019-035148.	Inclusion criteria: Peer-reviewed articles or published abstracts in any language with quantitative data on drug availability, use or related health and social harms collected before and after implementation of de jure drug decriminalisation or legal regulation. Data extraction and synthesis: Two independent reviewers screened titles, abstracts and articles for inclusion. Extraction and quality appraisal (modified Downs and Black checklist) were performed by one reviewer and checked by a second, with discrepancies resolved by a third. We coded study-level outcome measures into metric groupings and categorised the estimated direction of association between the legal change and outcomes of interest. Results: We screened 4860 titles and 221 full-texts and included 114 articles. Most (n=104, 91.2%) were from the USA, evaluated cannabis reform (n=109, 95.6%) and focussed on legal regulation (n=96, 84.2%). 224 study outcome measures were categorised into 32 metrics, most commonly prevalence (39.5% of studies), frequency (14.0%) or perceived harmfulness (10.5%) of use of the decriminalised or regulated drug; or use of tobacco, alcohol or other drugs (12.3%). Across all substance use metrics, legal reform was most often not associated with changes in use. Conclusions: Studies evaluating drug decriminalisation and legal regulation are concentrated in the USA and on cannabis legalisation. Despite the range of outcomes potentially impacted by drug law reform, extant research is narrowly focussed, with a particular emphasis on the prevalence of use. Metrics in drug law reform evaluations require improved alignment with relevant health and social outcomes.
Steele DW	2020a	Steele DW, Becker SJ, Danko KJ, Balk EM, Adam GP, Saldanha IJ, Trikalinos TA. Brief Behavioral Interventions for Substance Use in	CONTEXT: Adolescents with problematic substance use (SU) are at risk for far-reaching adverse abstract outcomes. OBJECTIVE: Synthesize the evidence regarding the effects of brief behavioral interventions for adolescents (12–20 years) with problematic SU. DATA SOURCES: We conducted literature searches in Medline, the Cochrane Central Register of Controlled Trials, Embase, Cumulative Index to Nursing and Allied Health Literature, and PsycInfo through October 31, 2019. STUDY SELECTION: We screened 33 272 records and citations for interventions in

		Adolescents: A Meta-analysis. Pediatrics. 2020 Oct;146(4):e20200351. doi: 10.1542/peds.2020-0351. Epub 2020 Sep 14.	adolescents with at least problematic SU, retrieved 1831 articles, and selected 22 randomized controlled trials of brief interventions meeting eligibility criteria for meta-analysis. DATA EXTRACTION: We followed Agency for Healthcare Research and Quality guidelines. We categorized brief interventions into components, including motivational interviewing (MI), psychoeducation, and treatment as usual. Outcomes included SU (abstinence, days used per month) for alcohol and cannabis, and substance-related problem scales. Strength of evidence (SoE) was assessed. RESULTS: Both pairwise and network meta-analyses were conducted by using random effects models. Compared to treatment as usual, the use of MI reduces heavy alcohol use days by 0.7 days per month (95% credible interval [CrI]: 21.6 to 0.02; low SoE), alcohol use days by 1.1 days per month (95% CrI 22.2 to 20.3; moderate SoE), and overall substance-related problems by a standardized net mean difference of 0.5 (95% CrI –1.0 to 0; low SoE). The use of MI did not reduce cannabis use days, with a net mean difference of 20.05 days per month (95% CrI: 20.26 to 0.14; moderate SoE). LIMITATIONS: There was lack of consistently reported outcomes and limited available comparisons. CONCLUSIONS: The use of MI reduces heavy alcohol use, alcohol use days, and SU-related problems in adolescents but does not reduce cannabis use days.
Steele DW	2020b	Steele DW, Becker SJ, Danko KJ, Balk EM, Saldanha IJ, Adam GP, Bagley SM, Friedman C, Spirito A, Scott K, Ntzani EE, Saeed I, Smith B, Popp J, Trikalinos TA.	Objectives: This systematic review (SR) synthesizes the literature on behavioral, pharmacologic, and combined interventions for adolescents ages 12 to 20 years with problematic substance use or substance use disorder. We included interventions designed to achieve abstinence, reduce use quantity and frequency, improve functional outcomes, and reduce substance-related harms. Data sources: We conducted literature searches in MEDLINE, the Cochrane CENTRAL Trials Registry, Embase, CINAHL, and PsycINFO to identify primary studies meeting eligibility criteria through November 1, 2019. Review methods. Studies were extracted into the Systematic Review Data Repository. We

		Interventions for Substance Use Disorders in Adolescents: A Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020 May. Report No.: 20-EHC014.	categorized interventions into seven primary intervention components: motivational interviewing (MI), family focused therapy (Fam), cognitive behavioral therapy (CBT), psychoeducation, contingency management (CM), peer group therapy, and intensive case management. We conducted meta-analyses of comparative studies and evaluated the strength of evidence (SoE). The PROSPERO protocol registration number is CRD42018115388. Results: The literature search yielded 33,272 citations, of which 118 studies were included. Motivational interviewing reduced heavy alcohol use days by 0.7 days/month, alcohol use days by 1.2 days/month, and overall substance use problems by a standardized mean difference of 0.5, compared with treatment as usual. Brief MI did not reduce cannabis use days (net mean difference of 0). Across multiple intensive interventions, Fam was most effective, reducing alcohol use days by 3.5 days/month compared with treatment as usual. No intensive interventions reduced cannabis use days. Pharmacologic treatment of opioid use disorder led to a more than 4 times greater likelihood of abstinence with extended courses (2 to 3 months) of buprenorphine compared to short courses (14 to 28 days). Conclusions: Brief interventions: MI reduces heavy alcohol use (low SoE), alcohol use days (moderate SoE), and substance use–related problems (low SoE) but does not reduce cannabis use days (moderate SoE). Nonbrief interventions: Fam may be most effective in reducing alcohol use (low SoE). More research is needed to identify other effective intensive behavioral interventions for alcohol use disorder. Intensive interventions did not appear to decrease cannabis use (low SoE). Some interventions (CBT, CBT+MI, and CBT+MI+CM) were associated with increased cannabis use (low SoE). Both MI and CBT reduce combined alcohol and other drug use (low SoE). Combined CBT+MI reduces illicit drug use (low SoE). Subgroup analyses of interest (male vs. female, racial and ethnic minorities, socioeconomic status, and family characteristics) were sparse, precluding conclusions regarding differential effects. Pharmacological interventions: longer courses of buprenorphine (2–3 months) are more effective than shorter courses (14–28 days) to

			reduce opioid use and achieve abstinence (low SoE). SRs in the college settings support use of brief interventions for students with any use, heavy or problematic use. More research is needed to identify the most effective combinations of behavioral and pharmacologic treatments for opioid, alcohol, and cannabis use disorders.
Stockings E	2016	Stockings E, Hall WD, Lynskey M, Morley KI, Reavley N, Strang J, Patton G, Degenhardt L. Prevention, early intervention, harm reduction, and treatment of substance use in young people. Lancet Psychiatry. 2016 Mar;3(3):280-96. doi: 10.1016/S2215-0366(16)00002-X. Epub 2016 Feb 18.	We did a systematic review of reviews with evidence on the effectiveness of prevention, early intervention, harm reduction, and treatment of problem use in young people for tobacco, alcohol, and illicit drugs (e.g, cannabis, opioids, amphetamines, or cocaine). Taxation, public consumption bans, advertising restrictions, and minimum legal age are effective measures to reduce alcohol and tobacco use, but are not available to target illicit drugs. Interpretation of the available evidence for school-based prevention is affected by methodological issues; interventions that incorporate skills training are more likely to be effective than information provision—which is ineffective. Social norms and brief interventions to reduce substance use in young people do not have strong evidence of effectiveness. Roadside drug testing and interventions to reduce injection-related harms have a moderate-to-large effect, but additional research with young people is needed. Scarce availability of research on interventions for problematic substance use in young people indicates the need to test interventions that are effective with adults in young people. Existing evidence is from high-income countries, with uncertain applicability in other countries and cultures and in subpopulations differing in sex, age, and risk status. Concerted efforts are needed to increase the evidence base on interventions that aim to reduce the high burden of substance use in young people.
Stockings E	2018	Stockings E, Bartlem K, Hall A, Hodder R, Gilligan C, Wiggers J, Sherker S, Wolfenden L. Whole-of-community interventions to	Background and aims Whole-of-community interventions aim to reduce alcohol and other drug (AOD) use and harms by mobilizing community leaders, organizations and policy-makers to respond effectively to AOD use. The aim of this review is to estimate the effectiveness of whole-of-community interventions in reducing population-level harms arising from AOD use. Design A systematic review of electronic databases CENTRAL, Embase, Medline, Medline in Process and PsycINFO was conducted from database inception to August 2017. Eligible trials had a parallel comparison group, implemented

		reduce population-level harms arising from alcohol and other drug use: a systematic review and meta-analysis. Addiction. 2018 Nov;113(11):1984-2018. doi: 10.1111/add.14277. Epub 2018 Jul 5.	interventions in two or more community settings, and reported data on AOD use or harms. Setting Intervention settings included schools, sporting clubs, police and law enforcement agencies, community centres, local media and retail premises. Participants Twenty-four trials from 63 publications were included (n = 249 125 participants). Measurements Outcomes from AOD consumption (quantity and frequency), AOD-related crime and AOD-related accidents, injuries and hospital admissions. Data were pooled using random-effects inverse variance meta-analysis in Review Manager version 5.3. Findings: Risk of bias was mostly high, due to lack of random allocation, selective reporting and significant attrition. Meta-analyses indicated significant reductions in risky drinking [Alcohol Use Disorders Identification Scale (AUDIT) > 8; three trials (7 data points), relative risk (RR) = 0.78, 95% confidence interval (CI) = 0.62–0.99)], but found no impact on past-month alcohol use (five trials, RR = 0.95, 95% CI = 0.89–1.02), binge drinking (five trials, RR = 0.97, 95% CI = 0.89–1.06) or 12-month marijuana use (two trials, RR = 0.98, 95% CI = 0.86–1.11). Narrative synthesis indicated some reductions in AOD-related assault rates and arrests, but were equivocal for quantity of alcohol consumed, 12-month illicit drug use, assault or abuse, motor vehicle accidents and hospital admissions. Conclusions: Interventions to reduce alcohol and other drug use and harms applied to whole communities have resulted so far in small reductions in risky alcohol consumption, but have had little impact upon past month alcohol use, binge drinking or 12-month marijuana use and the studies have been subject to high risk of bias.
Teesson M	2012	Teesson M, Newton NC, Barrett EL. Australian school-based prevention programs for alcohol and other drugs: a systematic review.	Issues: To reduce the occurrence and costs related to substance use and associated harms it is important to intervene early. Although a number of international school-based prevention programs exist, the majority show minimal effects in reducing drug use and related harms. Given the emphasis on early intervention and prevention in Australia, it is timely to review the programs currently trialled in Australian schools. This paper reports the type and efficacy of Australian school-based prevention programs for alcohol and other drugs.

		Drug Alcohol Rev. 2012 Sep;31(6):731-6. doi: 10.1111/j.1465-3362.2012.00420.x. Epub 2012 Feb 17.	Approach: Cochrane, PsychInfo and PubMed databases were searched. Additional materials were obtained from authors, websites and reference lists. Studies were selected if they described programs developed and trialled in Australia that address prevention of alcohol and other drug use in schools. Key Findings. Eight trials of seven intervention programs were identified. The programs targeted alcohol, cannabis and tobacco and most were based on social learning principles. All were universal. Five of the seven intervention programs achieved reductions in alcohol, cannabis and tobacco use at follow up. Conclusion: Existing school-based prevention programs have shown to be efficacious in the Australian context. However, there are only a few programs available, and these require further evaluative research. This is critical, given that substance use is such a significant public health problem. The findings challenge the commonly held view that school-based prevention programs are not effective.

Table S3 Interventions for treating problematic cannabis use

First author	Year	Citation	Abstract
Baker AL	2010	Baker AL, Hides L, Lubman DI. Treatment of cannabis use among people with psychotic or depressive disorders: a systematic review. J Clin Psychiatry. 2010 Mar;71(3):247-54. doi: 10.4088/JCP.09r05119gry.	Objective: This article systematically reviews the evidence from randomized controlled trials (RCTs) for pharmacologic and psychological approaches to the treatment of cannabis use among individuals with psychotic or depressive disorders. Data sources: A systematic literature search was conducted using the PubMed and PsychINFO databases from inception to December 2008. Individual searches in cannabis use (search terms: marijuana, cannabis, marijuana abuse, cannabis abuse, marijuana usage, cannabis usage), mental disorders (search terms: mood disorders, affective disorders, anxiety disorders, anxiety, depressive disorder, depression, psychotic disorders, psychosis, mental disorders), and pharmacotherapy (search terms: medication, drug therapy, pharmacotherapy, psychopharmacology, clinical trials, drug trial, treatment trial) were conducted and limited to humans, adolescents and adults. Study selection: A search combining the individual cannabis use, mental disorder and pharmacotherapy searches produced 1,713 articles (PubMed = 1,398; PsychINFO = 315). Combining the cannabis use and mental disorder searches while limiting them to English articles and RCTs produced a total of 286 articles (PubMed = 228; PsychINFO = 58). From this literature, there were 7 RCTs conducted among mental health clients that reported cannabis use outcomes using pharmacologic or psychological interventions. Data synthesis: While few RCTs have been conducted, there is evidence that pharmacologic and psychological interventions are effective for reducing cannabis use in the short-term among people with psychotic disorders or depression. Conclusions: Although it is difficult to make evidence-based treatment recommendations due to the paucity of research in this area, available studies indicate that effectively treating the mental health disorder with standard pharmacotherapy may be associated with a reduction in cannabis use and that longer or more intensive psychological interventions rather than brief interventions may be required, particularly among heavier users of cannabis and those with more chronic mental disorders. Specific recommendations

			regarding the type and length of specific psychological treatments cannot be made at this time, although motivational interviewing and cognitive-behavioral therapy approaches appear most promising.
Boumparis N	2019	Boumparis N, Loheide-Niesmann L, Blankers M, Ebert DD, Korf D, Schaub MP, Spijkerman R, Tait RJ, Riper H. Short- and long-term effects of digital prevention and treatment interventions for cannabis use reduction: A systematic review and meta-analysis. Drug Alcohol Depend. 2019 Jul 1;200:82-94. doi: 10.1016/j.drugalcdep.2019.03.016. Epub 2019 May 14.	Background: Frequent Cannabis use has been linked to a variety of negative mental, physical, and social consequences. We assessed the effects of digital prevention and treatment interventions on Cannabis use reduction in comparison with control conditions. Methods: Systematic review with two separate meta-analyses. Thirty randomized controlled trials met the inclusion criteria for the review, and 21 were included in the meta-analyses. Primary outcome was self-reported Cannabis use at post-treatment and follow-up. Hedges's g was calculated for all comparisons with non-active control. Risk of bias was examined with the Cochrane risk-of-bias tool. Results: The systematic review included 10 prevention interventions targeting 8138 participants (aged 12 to 20) and 20 treatment interventions targeting 5195 Cannabis users (aged 16 to 40). The meta-analyses showed significantly reduced Cannabis use at post-treatment in the prevention interventions (6 studies, N=2564, g=0.33; 95% CI 0.13 to 0.54, p= 0.001) and in the treatment interventions (17 comparisons, N=3813, g=0.12; 95% CI 0.02 to 0.22, p= 0.02) as compared with controls. The effects of prevention interventions were maintained at follow-ups of up to 12 months (5 comparisons, N=2445, g=0.22; 95% CI 0.12 to 0.33, p < 0.001) but were no longer statistically significant for treatment interventions. Conclusions: Digital prevention and treatment interventions showed small, significant reduction effects on Cannabis use in diverse target populations at post-treatment compared to controls. For prevention interventions, the post-treatment effects were maintained at follow-up up to 12 months later.
Brabete AC	2020	Brabete AC, Greaves L, Hemsing N, Stinson	There is evidence that sex- and gender-related factors are involved in cannabis patterns of use, health effects and biological mechanisms. Women and men report different cannabis

		J. Sex- and Gender-Based Analysis in Cannabis Treatment Outcomes: A Systematic Review. Int J Environ Res Public Health. 2020 Jan 30;17(3):872. doi: 10.3390/ijerph17030872.	use disorder (CUD) symptoms, with women reporting worse withdrawal symptoms than men. The objective of this systematic review was to examine the effectiveness of cannabis pharmacological interventions for women and men and the uptake of sex- and gender-based analysis in the included studies. Two reviewers performed the full-paper screening, and data was extracted by one researcher. The search yielded 6098 unique records—of which, 68 were full-paper screened. Four articles met the eligibility criteria for inclusion. From the randomized clinical studies of pharmacological interventions, few studies report sex-disaggregated outcomes for women and men. Despite emergent evidence showing the influence of sex and gender factors in cannabis research, sex-disaggregated outcomes in pharmacological interventions is lacking. Sex- and gender-based analysis is incipient in the included articles. Future research should explore more comprehensive inclusion of sex- and gender-related aspects in pharmacological treatments for CUD.
Chou R	2020	Chou R, Dana T, Blazina I, Grusing S, Fu R, Bougatsos C. Interventions for Unhealthy Drug Use—Supplemental Report: A Systematic Review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020 Jun. Report No.: 19-05255-EF-2.	Abstract: Background: A U.S. Preventive Services Task Force (USPSTF) report found no consistent evidence that counseling interventions are effective at reducing drug use or improving other health outcomes in populations whose drug use was identified through primary care-based screening with questions about drug use or drug-related risks (i.e., “screen-detected populations”). Evidence from studies of persons seeking or referred for treatment for substance use or with clinical signs or symptoms of substance use (i.e., “treatment-seeking populations”) might also be useful for informing assessments regarding screening in primary care settings. Purpose: This report updates a 2008 USPSTF report on screening for illicit drug use and supplements an updated USPSTF report on screening for any drug use, focusing on the benefits and harms of pharmacotherapy and psychosocial interventions for persons whose drug use was identified when seeking substance use treatment, when presenting with signs or symptoms of drug use, when screened for drug use in primary care or other settings with questions about drug use or drug-related risks, or other means. Data Sources: The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Ovid MEDLINE, Embase, and PsycINFO from inception to September

			2018; surveillance for new literature was conducted through November 22, 2019. Study Selection: We included trials of Food and Drug Administration (FDA)-approved pharmacotherapies for opioid use disorder (methadone, buprenorphine, and naltrexone) and trials of psychosocial interventions for persons engaging in opioid, stimulant, cannabis, and mixed drug or polysubstance use. We also included trials of preemptive prescribing of naloxone in primary care settings as a rescue medication for opioid-related overdose. Trials compared included interventions against placebo, a minimal intervention, waitlist control, or usual care, and evaluated outcomes at >3 months for drug use or other risky behaviors; health, social, and legal consequences of drug use; or harms of treatment. Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF. Data Synthesis (Results): We included a total of 71 trials, with 19 trials of pharmacotherapies and 52 trials of psychosocial interventions. All trials of pharmacotherapies and 25 trials of psychosocial interventions were conducted in treatment-seeking populations. Psychosocial interventions commonly incorporated cognitive-behavioral or motivational interventions and ranged from brief interventions consisting of one or two sessions of no more than one hour to multiple treatment sessions over weeks or months. In most pharmacotherapy trials, drug use counseling was provided to all patients. No study evaluated benefits or harms of pre-emptive naloxone prescribed in primary care settings versus placebo or no naloxone as a rescue medication for opioid-related overdose. In treatment-seeking populations with opioid use disorder, naltrexone (12 trials; relative risk [RR] 0.73, 95% confidence interval [CI] 0.62 to 0.85; number needed to treat [NNT] 5.3) and Interventions for Unhealthy Drug Use iv Pacific Northwest EPC opioid agonist therapy with methadone or buprenorphine (4 trials; RR 0.75, 95% CI 0.59 to 0.82; NNT 2.9) were associated with decreased risk of drug use relapse compared with placebo or no pharmacotherapy. Naltrexone and methadone/buprenorphine therapy were also associated with increased likelihood of retention in substance use treatment (9 trials; RR 1.71, 95% CI

			1.13 to 2.49; NNT 6.7 and 7 trials; RR 2.58, 95% CI 1.78 to 4.59; NNT 2.6; respectively). Evidence on harms of pharmacotherapies was limited, but indicated no increased risk of serious adverse events. Psychosocial interventions were associated with increased likelihood of abstinence from drug use versus control conditions at 3 to 4 months (15 trials, RR 1.60, 95% CI 1.24 to 2.13; NNT 11) and at 6 to 12 months (14 trials; RR 1.25, 95% CI 1.11 to 1.52; NNT 17), based on trials primarily conducted in treatment-seeking populations. Psychosocial interventions were also associated with a greater decrease versus control conditions in the number of drug use days (19 trials; mean difference -0.49 day in the last 7 days, 95% CI -0.85 to -0.13) and a small but statistically significant greater decrease in drug use severity (16 trials; standard mean difference -0.18, 95% CI -0.32 to -0.05) at 3- to 4-month follow-up. There was no difference between psychosocial interventions versus controls on drug use days or severity at longer (6 to 12 month) follow-up. Effects of psychosocial interventions were generally stronger in trials of treatment-seeking than screen-detected populations, trials that evaluated cannabis use than other types of drug use, and trials of more intensive than brief interventions. Few trials evaluated effects of psychosocial interventions for opioid or stimulant use, and estimates were imprecise. Limitations: Limitations included restriction to English-language articles, statistical heterogeneity in pooled analyses, and little evidence on drug-related health, social, or legal outcomes; most trials had methodological limitations. Evidence was lacking on effectiveness of treatments for opioid use disorder related to prescription drug use or stimulant use and evidence was limited for adolescents or pregnant persons. Conclusions: Pharmacotherapy and psychosocial interventions are effective at improving drug use outcomes, but evidence of effectiveness remains primarily derived from trials conducted in treatment-seeking populations. Although the applicability of data from such trials to persons whose drug use is identified through primary care-based screening is uncertain, intervention trials that enrolled patients based on screening identified a spectrum of drug use, ranging from mild drug use to more severe, untreated disease. The applicability of current evidence on drug use interventions to screening might be greater for the subset of

			patients screened in primary care settings with severe, untreated drug use who could utilize pharmacotherapies or more intensive psychosocial interventions.
Cooper K	2015	Cooper K, Chatters R, Kaltenthaler E, Wong R. Psychological and psychosocial interventions for cannabis cessation in adults: a systematic review short report. Health Technol Assess. 2015 Jul;19(56):1-130. doi: 10.3310/hta19560.	Background: Cannabis is the most commonly used illicit drug worldwide. Cannabis dependence is a recognised psychiatric diagnosis, often diagnosed via the Diagnostic and Statistical Manual of Mental Disorders criteria and the International Classification of Diseases, 10th Revision. Cannabis use is associated with an increased risk of medical and psychological problems. This systematic review evaluates the use of a wide variety of psychological and psychosocial interventions, such as motivational interviewing (MI), cognitive–behavioural therapy (CBT) and contingency management. Objective: To systematically review the clinical effectiveness of psychological and psychosocial interventions for cannabis cessation in adults who use cannabis regularly. Data sources: Studies were identified via searches of 11 databases [MEDLINE, EMBASE, Cochrane Controlled Trials Register, Health Technology Assessment (HTA) database, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database, PsycINFO, Web of Science Conference Proceedings Citation Index, ClinicalTrials.gov and metaRegister of Current Controlled Trials] from inception to February 2014, searching of existing reviews and reference tracking. Methods: Randomised controlled trials (RCTs) assessing psychological or psychosocial interventions in a community setting were eligible. Risk of bias was assessed using adapted Cochrane criteria and narrative synthesis was undertaken. Outcomes included change in cannabis use, severity of cannabis dependence, motivation to change and intervention adherence. Results: The review included 33 RCTs conducted in various countries (mostly the USA and Australia). General population studies: 26 studies assessed the general population of cannabis users. Across six studies, CBT (4–14 sessions) significantly improved outcomes (cannabis use, severity of

			dependence, cannabis problems) compared with wait list post treatment, maintained at 9 months in the one study with later follow-up. Studies of briefer MI or motivational enhancement therapy (MET) (one or two sessions) gave mixed results, with some improvements over wait list, while some comparisons were not significant. Four studies comparing CBT (6–14 sessions) with MI/MET (1–4 sessions) also gave mixed results: longer courses of CBT provided some improvements over MI. In one small study, supportive–expressive dynamic psychotherapy (16 sessions) gave significant improvements over one-session MI. Courses of other types of therapy (social support group, case management) gave similar improvements to CBT based on limited data. Limited data indicated that telephone- or internet-based interventions might be effective. Contingency management (vouchers for abstinence) gave promising results in the short term; however, at later follow-ups, vouchers in combination with CBT gave better results than vouchers or CBT alone. Psychiatric population studies: seven studies assessed psychiatric populations (schizophrenia, psychosis, bipolar disorder or major depression). CBT appeared to have little effect over treatment as usual (TAU) based on four small studies with design limitations (both groups received TAU and patients were referred). Other studies reported no significant difference between types of 10-session therapy.
Crippa JA	2012	Crippa JA, Derenusson GN, Chagas MH, Atakan Z, Martín-Santos R, Zuardi AW, Hallak JE. Pharmacological interventions in the treatment of the acute effects of cannabis: a systematic review of literature. Harm	Background: Cannabis intoxication is related to a number of physical and mental health risks with ensuing social costs. However, little attention has been given to the investigation of possible pharmacological interactions in this condition. Objective: To review the available scientific literature concerning pharmacological interventions for the treatment of the acute effects of cannabis. Methods: A search was performed on the Pubmed, Lilacs, and Scielo online databases by combining the terms cannabis, intoxication, psychosis, anxiety, and treatment. The articles selected from this search had their reference lists checked for additional publications related to the topic of the review. Results: The reviewed articles consisted of case reports and controlled clinical trials and are

		Reduct J. 2012 Jan 25;9:7. doi: 10.1186/1477-7517-9-7.	presented according to interventions targeting the physiological, psychiatric, and cognitive symptoms provoked by cannabis. The pharmacological interventions reported in these studies include: beta-blockers, antiarrhythmic agents, antagonists of CB-1 and GABA-benzodiazepine receptors, antipsychotics, and cannabidiol. Conclusion: Although scarce, the evidence on pharmacological interventions for the management of cannabis intoxication suggests that propanolol and rimonabant are the most effective compounds currently available to treat the physiological and subjective effects of the drug. Further studies are necessary to establish the real effectiveness of these two medications, as well as the effectiveness of other candidate compounds to counteract the effects of cannabis intoxication, such as cannabidiol and flumazenil.
Davis ML	2015	Davis ML, Powers MB, Handelsman P, Medina JL, Zvolensky M, Smits JA. Behavioral therapies for treatment-seeking cannabis users: a meta-analysis of randomized controlled trials. Eval Health Prof. 2015 Mar;38(1):94-114. doi: 10.1177/0163278714529970. Epub 2014 Apr 2.	Narrative reviews conclude that behavioral therapies (BTs) produce better outcomes than control conditions for cannabis use disorders (CUDs). However, the strength and consistency of this effect has not been directly empirically examined. The present meta-analysis combined multiple well controlled studies to help clarify the overall impact of behavioral interventions in the treatment of CUDs. A comprehensive literature search produced 10 randomized controlled trials (RCTs; n ¼ 2,027) that were included in the final analyses. Analyses indicated an effect of BTs (including contingency management, relapse prevention, and motivational interviewing, and combinations of these strategies with cognitive behavioral therapy) over control conditions (including waitlist [WL], psychological placebo, and treatment as usual) across pooled outcomes and time points (Hedges' g ¼ 0.44). These results suggest that the average patient receiving a behavioral intervention fared better than 66% of those in the control conditions. BT also outperformed control conditions when examining primary outcomes alone (frequency and severity of use) and secondary outcomes alone (psychosocial functioning). Effect sizes were not moderated by inclusion of a diagnosis (RCTs including treatment-seeking cannabis users who were not assessed for abuse or dependence vs. RCTs including individuals diagnosed as

			dependent), dose (number of treatment sessions), treatment format (either group vs. individual treatment or in-person vs. non-in-person treatment), sample size, or publication year. Effect sizes were significantly larger for studies that included a WL control comparison versus those including active control comparisons, such that BT significantly outperformed WL controls but not active control comparisons.
Gates PJ	2016	Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L. Psychosocial interventions for cannabis use disorder. Cochrane Database Syst Rev. 2016 May 5;2016(5):CD005336. doi: 10.1002/14651858.CD005336.pub4.	Background: Cannabis use disorder is the most commonly reported illegal substance use disorder in the general population; although demand for assistance from health services is increasing internationally, only a minority of those with the disorder seek professional assistance. Treatment studies have been published, but pressure to establish public policy requires an updated systematic review of cannabis-specific treatments for adults. Objectives: To evaluate the efficacy of psychosocial interventions for cannabis use disorder (compared with inactive control and/or alternative treatment) delivered to adults in an out-patient or community setting. Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 6), MEDLINE, EMBASE, PsycINFO, the Cumulaive Index to Nursing and Allied Health Literature (CINAHL) and reference lists of articles. Searched literature included all articles published before July 2015. Selection criteria: All randomised controlled studies examining a psychosocial intervention for cannabis use disorder (without pharmacological intervention) in comparison with a minimal or inactive treatment control or alternative combinations of psychosocial interventions. Data collection and analysis: We used standard methodological procedures as expected by The Cochrane Collaboration. Main results: We included 23 randomised controlled trials involving 4045 participants. A total of 15 studies took place in the United States, two in Australia, two in Germany and one each in Switzerland, Canada, Brazil and Ireland. Investigators delivered treatments over approximately seven sessions (range, one to 14) for approximately 12 weeks (range, one to 56). Overall, risk of bias across studies was moderate, that is, no trial was at high risk of

			selection bias, attrition bias or reporting bias. Further, trials included a large total number of participants, and each trial ensured the fidelity of treatments provided. In contrast, because of the nature of the interventions provided, participant blinding was not possible, and reports of researcher blinding often were unclear or were not provided. Half of the reviewed studies included collateral verification or urinalysis to confirm self-report data, leading to concern about performance and detection bias. Finally, concerns of other bias were based on relatively consistent lack of assessment of non-cannabis substance use or use of additional treatments before or during the trial period. A subset of studies provided sufficient detail for comparison of effects of any intervention versus inactive control on primary outcomes of interest at early follow-up (median, four months). Results showed moderate-quality evidence that approximately seven out of 10 intervention participants completed treatment as intended (effect size (ES) 0.71, 95% confidence interval (CI) 0.63 to 0.78, 11 studies, 1424 participants), and that those receiving psychosocial intervention used cannabis on fewer days compared with those given inactive control (mean difference (MD) 5.67, 95% CI 3.08 to 8.26, six studies, 1144 participants). In addition, low-quality evidence revealed that those receiving intervention were more likely to report point-prevalence abstinence (risk ratio (RR) 2.55, 95% CI 1.34 to 4.83, six studies, 1166 participants) and reported fewer symptoms of dependence (standardised mean difference (SMD) 4.15, 95% CI 1.67 to 6.63, four studies, 889 participants) and cannabis-related problems compared with those given inactive control (SMD 3.34, 95% CI 1.26 to 5.42, six studies, 2202 participants). Finally, very low-quality evidence indicated that those receiving intervention reported using fewer joints per day compared with those given inactive control (SMD 3.55, 95% CI 2.51 to 4.59, eight studies, 1600 participants). Notably, subgroup analyses found that interventions of more than four sessions delivered over longer than one month (high intensity) produced consistently improved outcomes (particularly in terms of cannabis use frequency and severity of dependence) in the short term as compared with low-intensity interventions. The most consistent evidence supports the use of cognitive-behavioural therapy (CBT), motivational enhancement therapy (MET) and

			particularly their combination for assisting with reduction of cannabis use frequency at early follow-up (MET: MD 4.45, 95% CI 1.90 to 7.00, four studies, 612 participants; CBT: MD 10.94, 95% CI 7.44 to 14.44, one study, 134 participants; MET + CBT: MD 7.38, 95% CI 3.18 to 11.57, three studies, 398 participants) and severity of dependence (MET: SMD 4.07, 95% CI 1.97 to 6.17, two studies, 316 participants; MET + CBT: SMD 7.89, 95% CI 0.93 to 14.85, three studies, 573 participants), although no particular intervention was consistently effective at nine-month follow-up or later. In addition, data from five out of six studies supported the utility of adding voucher-based incentives for cannabis-negative urines to enhance treatment effect on cannabis use frequency. A single study found contrasting results throughout a 12-month follow-up period, as post-treatment outcomes related to overall reduction in cannabis use frequency favoured CBT alone without the addition of abstinence-based or treatment adherence-based contingency management. In contrast, evidence of drug counselling, social support, relapse prevention and mindfulness meditation was weak because identified studies were few, information on treatment outcomes insufficient and rates of treatment adherence low. In line with treatments for other substance use, abstinence rates were relatively low overall, with approximately one-quarter of participants abstinent at final follow-up. Finally, three studies found that intervention was comparable with treatment as usual among participants in psychiatric clinics and reported no between-group differences in any of the included outcomes. Authors' conclusions: Included studies were heterogeneous in many aspects, and important questions regarding the most effective duration, intensity and type of intervention were raised and partially resolved. Generalisability of findings was unclear, most notably because of the limited number of localities and homogeneous samples of treatment seekers. The rate of abstinence was low and unstable although comparable with treatments for other substance use. Psychosocial intervention was shown, in comparison with minimal treatment controls, to reduce frequency of use and severity of dependence in a fairly durable manner, at least in the short term. Among the included intervention types, an intensive intervention provided over more than four sessions based on the combination of MET and CBT with

			abstinence-based incentives was most consistently supported for treatment of cannabis use disorder.
Halladay J	2019	Halladay J, Scherer J, MacKillop J, Woock R, Petker T, Linton V, Munn C. Brief interventions for cannabis use in emerging adults: A systematic review, meta-analysis, and evidence map. Drug Alcohol Depend. 2019 Nov 1;204:107565. doi: 10.1016/j.drugalcdep.2019.107565. Epub 2019 Sep 19.	Purpose: This systematic review summarizes and critically appraises the existing literature on brief interventions (BIs) for cannabis use among emerging adults. Methods: Eligible BIs were operationalized as 1–2 sessions focused exclusively on cannabis use for samples with mean ages between 15 and 30. Outcomes related to cannabis use, other substance use, mental health, help-seeking, or functional status were included. Two independent reviewers screened a total of 3638 records, identifying 244 studies for full-text screening. In total, 32 BIs in 26 primary studies with 6318 participants were included. Results: Participants were typically not seeking treatment and using cannabis at least once a month. Most interventions were motivational, single sessions, and delivered in person. Few discussed concurrent psychiatric conditions. Pooling results at 1–3 months post-intervention, BIs compared to passive control slightly reduced symptoms of cannabis use disorder (SMD −0.14 [95% CI −0.26 to −0.01]) and increased the odds of abstinence (OR 1.73 [95% CI 1.13–2.66]). Other outcome results often favored BIs but were not significant. Results of studies comparing types of BIs (k=8) or BIs to longer interventions (k=1) are discussed narratively. Quality assessment suggested low to very low-quality evidence. Conclusions: This review indicates that BIs targeting non-treatment seeking emerging adults result in significant reductions in symptoms of cannabis use disorder and an increased likelihood of cannabis abstinence, however evidence is of low quality.
Hjorthoj CR	2014	Hjorthoj CR, Baker A, Fohlmann A, Nordentoft M. Intervention efficacy in trials targeting	Introduction: Cannabis use disorders are highly prevalent in patients with schizophrenia and other psychoses, and are probably associated with a range of poor outcomes. Several trials have been conducted on this population, the results of which have been summarized in several systematic reviews but never in meta-analyses specifically regarding cannabis use. Methods: PubMed, PsycINFO, EMBASE, and The Cochrane Central Register of Controlled

		cannabis use disorders in patients with comorbid psychosis systematic review and meta-analysis. Curr Pharm Des. 2014;20(13):2205-11. doi: 10.2174/13816128113199990431.	Trials were searched using predefined search terms. We included randomized trials of all types of interventions targeting cannabis use disorders in patients with schizophrenia spectrum disorders. We extracted information on intervention types, efficacy, trial characteristics, and risk of bias. Results: There was no evidence of an effect on frequency of cannabis use, but intervention effects of motivational intervention with or without cognitive behavior therapy were observed on quantity of use and on positive symptoms of schizophrenia. Psychosocial intervention did not have an appreciable effect on negative symptoms. Longer interventions appear to be more efficacious, and efficacy may be better in trials with comparatively few women. Larger trials may be better at establishing effects on positive symptoms. Conclusion: Psychosocial interventions appear moderately efficacious in reducing quantity of cannabis-use and positive symptoms.
Hoch E	2016	Hoch E, Preuss UW, Ferri M, Simon R. Digital Interventions for Problematic Cannabis Users in Non-Clinical Settings: Findings from a Systematic Review and Meta-Analysis. Eur Addict Res. 2016;22(5):233-42. doi: 10.1159/000445716. Epub 2016 May 4.	Background: Existing cannabis treatment programs reach only a very limited proportion of people with cannabis-related problems. The aim of this systematic review and meta-analysis was to assess the effectiveness of digital interventions applied outside the health care system in reducing problematic cannabis use. Methods: We systematically searched the Cochrane Central Register of Controlled Trials (2015), PubMed (2009–2015), Medline (2009–2015), Google Scholar (2015) and article reference lists for potentially eligible studies. Randomized controlled trials examining the effects of internet- or computer-based interventions were assessed. Study effects were estimated by calculating effect sizes (ESs) using Cohen's d and Hedges' g bias-corrected ES. The primary outcome assessed was self-reported cannabis use, measured by a questionnaire. Results: Fifty-two studies were identified. Four studies (including 1,928 participants) met inclusion criteria. They combined brief motivational interventions and cognitive behavioral therapy delivered on line. All studies were of good quality. The pooled mean difference (Δ = 4.07) and overall ES (0.11) give evidence of small effects at 3-month follow-up in favor of digital interventions.

			Conclusions: Digital interventions can help to successfully reduce problematic cannabis use outside clinical settings. They have some potential to overcome treatment barriers and increase accessibility for at-risk cannabis users.
Imtiaz S	2020	Imtiaz S, Roerecke M, Kurdyak P, Samokhvalov AV, Hasan OSM, Rehm J. Brief Interventions for Cannabis Use in Healthcare Settings: Systematic Review and Meta-analyses of Randomized Trials. J Addict Med. 2020 Jan/Feb;14(1):78-88. doi: 10.1097/ADM.0000000000000527.	Objectives: The efficacy of brief interventions for cannabis use was assessed in a systematic review and meta-analyses. Methods: Systematic searches in academic databases were conducted, and reference lists of included studies were reviewed. Randomized trials were included that compared brief interventions with minimal control interventions for improving cannabis-specific outcomes among participants recruited from healthcare settings. Mean differences (MDs) based on change-from-baseline measurements were pooled using random-effects meta-analyses, with stratification by short term (≤3 months) and long term (>3 months). Results: Ten reports from 9 studies were included. Most studies were conducted in the United States, including participants who were adults and were recruited from primary care or emergency departments. There were no significant effects of brief interventions on cannabis-specific Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) scores in the short term (MD -1.27 points; 95% confidence interval [CI] -3.75, 1.21; I 84.40%). The null pattern of findings was also observed for number of days of cannabis use in the past 30 days in the short term (MD -0.22 days; 95% CI -2.27, 1.82; I 60.30%) and long term (MD -0.28 days; 95% CI -2.42, 1.86; I 60.50%). The evidence base for other outcomes not subjected to meta-analyses was limited and mixed. Conclusions: Brief interventions did not result in reductions in cannabis-specific ASSIST scores or number of days of cannabis use, whereas the evidence base for other outcomes was limited and mixed. As such, brief interventions in healthcare settings may not be efficacious for cannabis use.
Kondo KK	2020	Kondo KK, Morasco BJ, Nugent SM, Ayers CK, O'Neil ME, Freeman M,	Across 26 trials, the evidence was largely insufficient. Low-strength evidence was found that selective serotonin reuptake inhibitors (SSRIs) do not reduce cannabis use or improve treatment retention. Low- to moderate-strength evidence was found that buspirone does not improve outcomes and that cannabinoids do not increase abstinence rates (moderate

		Kansagara D. Pharmacotherapy for the Treatment of Cannabis Use Disorder: A Systematic Review. Ann Intern Med. 2020 Mar 17;172(6):398-412. doi: 10.7326/M19-1105. Epub 2020 Mar 3.	SOE), reduce cannabis use (low SOE), or increase treatment retention (low SOE). Across all drug studies, no consistent evidence of increased harm was found.
Montgomery L	2017	Montgomery L, Robinson C, Seaman EL, Haeny AM. A scoping review and meta-analysis of psychosocial and pharmacological treatments for cannabis and tobacco use among African Americans. Psychol Addict Behav. 2017 Dec;31(8):922-943. doi: 10.1037/adb0000326.	The rates of co-occurring cannabis and tobacco use are higher among African Americans relative to other racial/ethnic groups. One plausible approach to treating co-use among African Americans is to examine the effectiveness of treatments for the sole use of cannabis and tobacco to identify effective approaches that might be combined to treat the dual use of these substances. The current meta-analysis sought to include studies that reported cannabis and/or tobacco use outcomes from randomized clinical trials (RCTs) with 100% African American samples. A total of 843 articles were considered for inclusion, 29 were reviewed by independent qualitative coders, and 22 were included in the review. There were no articles on cannabis use treatment with a 100% African American sample, resulting in a need to lower the threshold (60%) and conduct a scoping review of cannabis studies. Preliminary evidence from a small number of studies (k = 7) supports the use of Motivational Interviewing and Cognitive–Behavioral Therapy to treat cannabis use among African Americans, but not Contingency Management. Results from a meta-analysis of 15 tobacco studies found higher rates of smoking abstinence in the treatment condition relative to control conditions overall and across short and long-term follow-up periods. Significant differences in smoking abstinence were also found when examining the effects of pharmacological treatments relative to their control conditions. The clinical and research

			implications of these findings for future psychosocial and pharmacological trials for cannabis and tobacco use and co-use among African Americans are described
Nielsen S	2019	Nielsen S, Gowing L, Sabioni P, Le Foll B. Pharmacotherapies for cannabis dependence. Cochrane Database Syst Rev. 2019 Jan 28;1(1):CD008940. doi: 10.1002/14651858.CD008940.pub3.	Background: Globally, cannabis use is prevalent and widespread. There are currently no pharmacotherapies approved for treatment of cannabis use disorders. This is an update of a Cochrane Review first published in the Cochrane Library in Issue 12, 2014. 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. Search methods: We updated our searches of the following databases to March 2018: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO and Web of Science. Selection criteria: Randomised controlled trials (RCTs) and quasi-RCTs involving the use of medications to treat 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 people diagnosed as cannabis dependent or who were likely to be dependent. Data collection and analysis: We used standard methodological procedures expected by Cochrane. Main results: We included 21 RCTs involving 1755 participants: 18 studies recruited adults (mean age 22 to 41 years); three studies targeted young people (mean age 20 years). Most (75%) participants were male. The studies were at low risk of performance, detection and selective outcome reporting bias. One study was at risk of selection bias, and three studies were at risk of attrition bias. All studies involved comparison of active medication and placebo. The medications were diverse, as were the outcomes reported, which limited the extent of analysis. Abstinence at end of treatment was no more likely with @9-tetrahydrocannabinol (THC) preparations than with placebo (risk ratio (RR) 0.98, 95% confidence interval (CI) 0.64 to 1.52; 305 participants; 3 studies; moderate-quality evidence). For selective serotonin reuptake inhibitor (SSRI) antidepressants, mixed action antidepressants, anticonvulsants and mood stabilisers, buspirone and N-acetylcysteine,

			there was no difference in the likelihood of abstinence at end of treatment compared to placebo (low- to very low-quality evidence). There was qualitative evidence of reduced intensity of withdrawal symptoms with THC preparations compared to placebo. For other pharmacotherapies, this outcome was either not examined, or no significant differences was reported. Adverse effects were no more likely with THC preparations (RR 1.02, 95% CI 0.89 to 1.17; 318 participants; 3 studies) or N-acetylcysteine (RR 0.94, 95% CI 0.71 to 1.23; 418 participants; 2 studies) compared to placebo (moderate-quality evidence). For SSRI antidepressants, mixed action antidepressants, buspirone and N-acetylcysteine, there was no difference in adverse effects compared to placebo (low- to very low-quality evidence). There was no difference in the likelihood of withdrawal from treatment due to adverse effects with THC preparations, SSRIs antidepressants, mixed action antidepressants, anticonvulsants and mood stabilisers, buspirone and N-acetylcysteine compared to placebo (low- to very low-quality evidence). There was no difference in the likelihood of treatment completion with THC preparations, SSRI antidepressants, mixed action antidepressants and buspirone compared to placebo (low- to very low-quality evidence) or with N-acetylcysteine compared to placebo (RR 1.06, 95% CI 0.93 to 1.21; 418 participants; 2 studies; moderate-quality evidence). Anticonvulsants and mood stabilisers appeared to reduce the likelihood of treatment completion (RR 0.66, 95% CI 0.47 to 0.92; 141 participants; 3 studies; low-quality evidence). Available evidence on gabapentin (anticonvulsant), oxytocin (neuropeptide) and atomoxetine was insufficient for estimates of effectiveness. Authors' conclusions: There is incomplete evidence for all of the pharmacotherapies investigated, and for many outcomes the quality of the evidence was low or very low. Findings indicate that SSRI antidepressants, mixed action antidepressants, bupropion, buspirone and atomoxetine are probably of little value in the treatment of cannabis dependence. Given the limited evidence of efficacy, THC preparations should be considered still experimental, with some positive effects on withdrawal symptoms and

			craving. The evidence base for the anticonvulsant gabapentin, oxytocin, and N-acetylcysteine is weak, but these medications are also worth further investigation.
Olmos A	2018	Olmos A, Tirado-Muñoz J, Farré M, Torrens M. The efficacy of computerized interventions to reduce cannabis use: A systematic review and meta-analysis. Addict Behav. 2018 Apr;79:52-60. doi: 10.1016/j.addbeh.2017.11.045. Epub 2017 Dec 7.	Abstract: Background and aims: Cannabis is the most widely consumed illicit drug. Although it is too early to confirm the impact of legalization, the use of cannabis appears to be on the rise in some countries due to its authorization for medical/recreational purposes. Among different types of therapeutic approaches to reduce cannabis use, computerized interventions are becoming a new treatment option. To assess their efficacy, a systematic review and meta-analysis was conducted. Methods: A systematic review and meta-analysis was performed employing randomized controlled clinical trials indexed in MEDLINE and PsycINFO. The principal outcome measure was cannabis use, and the secondary one was the use of other substances during interventions. A subgroup analysis was conducted by length of follow-up, number of sessions, age group, type of analysis, and type of control condition. Results: The meta-analysis included nine studies with 2963 participants. Computerized interventions resulted in significant reductions in the use of cannabis (standardized mean difference [SMD]: −0.19; 95% CI: −0.26, −0.11) and other substances (SMD: −0.27; 95% CI: −0.46, −0.08). Conclusions: Computerized interventions examined in the present study reduced the frequency of cannabis and other substance use. Limitations included the recalculation of dichotomous and continuous data as SMD and the lower number of studies included in the secondary outcome. Computerized interventions could be a viable option to reduce cannabis use.
Roberts	2016	Roberts, NP; Roberts, PA; Jones, N; Bisson, JI. Psychological therapies for	Background" Post-traumatic stress disorder (PTSD) is a debilitating mental health disorder that may develop after exposure to traumatic events. Substance use disorder (SUD) is a behavioural disorder in which the use of one or more substances is associated with heightened levels of distress, clinically significant impairment of functioning, or both. PTSD

		postâ€• traumatic stress disorder and comorbid substance use disorder. http://dx.doi.org/10.1002/14651858.CD010204.pub2	and SUD frequently occur together. The comorbidity is widely recognised as being difficult to treat and is associated with poorer treatment completion and poorer outcomes than for either condition alone. Several psychological therapies have been developed to treat the comorbidity, however there is no consensus about which therapies are most effective. Objectives: To determine the efficacy of psychological therapies aimed at treating traumatic stress symptoms, substance misuse symptoms, or both in people with comorbid PTSD and SUD in comparison with control conditions (usual care, waiting-list conditions, and no treatment) and other psychological therapies. Search methods: We searched the Cochrane Depression, Anxiety and Neurosis Group's Specialised Register (CCDANCTR) all years to 11 March 2015. This register contains relevant randomised controlled trials from the Cochrane Library (all years), MEDLINE (1950 to date), EMBASE (1974 to date), and PsycINFO (1967 to date). We also searched the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov, contacted experts, searched bibliographies of included studies, and performed citation searches of identified articles. Selection criteria: Randomised controlled trials of individual or group psychological therapies delivered to individuals with PTSD and comorbid substance use, compared with waiting-list conditions, usual care, or minimal intervention or to other psychological therapies. Data collection and analysis: We used standard methodological procedures expected by Cochrane. Main results: We included 14 studies with 1506 participants, of which 13 studies were included in the quantitative synthesis. Most studies involved adult populations. Studies were conducted in a variety of settings. We performed four comparisons investigating the effects of psychological therapies with a trauma-focused component and non-trauma-focused interventions against treatment as usual/minimal intervention and other active psychological therapies. Comparisons were stratified for individual- or group-based therapies. All active interventions were based on cognitive behavioural therapy. Our main findings were as

			follows. Individual-based psychological therapies with a trauma-focused component plus adjunctive SUD intervention was more effective than treatment as usual (TAU)/minimal intervention for PTSD severity post-treatment (standardised mean difference (SMD) -0.41; 95% confidence interval (CI) -0.72 to -0.10; 4 studies; n = 405; very low-quality evidence) and at 3 to 4 and 5 to 7 months' follow-up. There was no evidence of an effect for level of drug/alcohol use post-treatment (SMD -0.13; 95% CI -0.41 to 0.15; 3 studies; n = 388; very low-quality evidence), but there was a small effect in favour of individual psychological therapy at 5 to 7 months (SMD -0.28; 95% CI -0.48 to -0.07; 3studies; n = 388) when compared against TAU. Fewer participants completed trauma-focused therapy than TAU (risk ratio (RR) 0.78; 95% CI 0.64 to 0.96; 3 studies; n = 316; low-quality evidence). Individual-based psychological therapy with a trauma-focused component did not perform better than psychological therapy for SUD only for PTSD severity (mean difference (MD) -3.91; 95% CI -19.16 to 11.34; 1 study; n = 46; low-quality evidence) or drug/alcohol use (MD -1.27; 95% CI -5.76 to 3.22; 1 study; n = 46; low-quality evidence). Findings were based on one small study. No effects were observed for rates of therapy completion (RR 1.00; 95% CI 0.74 to 1.36; 1 study; n = 62; low-quality evidence). Non-trauma-focused psychological therapies did not perform better than TAU/minimal intervention for PTSD severity when delivered on an individual (SMD -0.22; 95% CI -0.83 to 0.39; 1 study; n = 44; low-quality evidence) or group basis (SMD -0.02; 95% CI -0.19 to 0.16; 4 studies; n = 513; low-quality evidence). There were no data on the effects on drug/alcohol use for individual therapy. There was no evidence of an effect on the level of drug/alcohol use for group-based therapy (SMD -0.03; 95% CI -0.37 to 0.31; 4 studies; n = 414; very low-quality evidence). A post-hoc analysis for full dose of a widely established group therapy called Seeking Safety showed reduced drug/alcohol use post-treatment (SMD -0.67; 95% CI -1.14 to -0.19; 2 studies; n = 111), but not at subsequent follow-ups. Data on the number of participants completing therapy were not for individual-based therapy. No effects were observed for rates of therapy completion for group-based therapy (RR 1.13; 95% CI 0.88 to

			1.45; 2 studies; n = 217; low-quality evidence). Non-trauma-focused psychological therapy did not perform better than psychological therapy for SUD only for PTSD severity (SMD -0.26; 95% CI -1.29 to 0.77; 2 studies; n = 128; very low-quality evidence) or drug/alcohol use (SMD 0.22; 95% CI -0.13 to 0.57; 2 studies; n = 128; low-quality evidence). No effects were observed for rates of therapy completion (RR 0.91; 95% CI 0.68 to 1.20; 2 studies; n = 128; very low-quality evidence). Several studies reported on adverse events. There were no differences between rates of such events in any comparison. We rated several studies as being at 'high' or 'unclear' risk of bias in multiple domains, including for detection bias and attrition bias. Authors' conclusions: We assessed the evidence in this review as mostly low to very low quality. Evidence showed that individual trauma-focused psychological therapy delivered alongside SUD therapy did better than TAU/minimal intervention in reducing PTSD severity post-treatment and at long term follow-up, but only reduced SUD at long-term follow-up. All effects were small, and follow-up periods were generally quite short. There was evidence that fewer participants receiving trauma-focused therapy completed treatment. There was very little evidence to support use of non-trauma-focused individual- or group-based integrated therapies. Individuals with more severe and complex presentations (e.g. serious mental illness, individuals with cognitive impairment, and suicidal individuals) were excluded from most studies in this review, and so the findings from this review are not generalisable to such individuals. Some studies suffered from significant methodological problems, and some were underpowered, limiting the conclusions that can be drawn. Further research is needed in this area.
Rodríguez A	2018	Rodríguez A, Zavala C. Cannabinoids for the treatment of cannabis abuse disorder. Medwave. 2018 Oct	Introduction: Cannabis stands as the most used illegal drug in the world. Currently there are no pharmacologic alternatives to treat its addiction, so the use of Cannabinoids has been postulated as a therapeutic tool. They would act mainly through decrease in abstinence and craving symptoms but its effectiveness remains unclear. Methods: To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple in-formation

		11;18(6):e7287. doi: 10.5867/medwave.2018.06.7286.	sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. Results and conclusions: We identified seven systematic reviews including 15 studies, of which four were randomized trials. We concluded the use of cannabinoids might result in little or no increase in abstinence at the end of treatment, and it probably increases adverse effects
Tait RJ	2013	Tait RJ, Spijkerman R, Riper H. Internet and computer-based interventions for cannabis use: a meta-analysis. Drug Alcohol Depend. 2013 Dec 1;133(2):295-304. doi: 10.1016/j.drugalcdep.2013.05.012. Epub 2013 Jun 6.	Background: Worldwide, cannabis is the most prevalently used illegal drug and creates demand for prevention and treatment services that cannot be fulfilled using conventional approaches. Computer and Internet-based interventions may have the potential to meet this need. Therefore, we systematically reviewed the literature and conducted a meta-analysis on the effectiveness of this approach in reducing the frequency of cannabis use. Methods: We systematically searched online databases (Medline, PubMed, PsychINFO, Embase) for eligible studies and conducted a meta-analysis. Studies had to use a randomized design, be delivered either via the Internet or computer and report separate outcomes for cannabis use. The principal outcome measure was the frequency of cannabis use. Results: Data were extracted from 10 studies and the meta-analysis involved 10 comparisons with 4125 participants. The overall effect size was small but significant, g = 0.16 (95% confidence interval (CI) 0.09–0.22, P < 0.001) at post-treatment. Subgroup analyses did not reveal significant subgroup differences for key factors including type of analysis (intention-to-treat, completers only), type of control (active, waitlist), age group (11–16, 17+ years), gender composition (female only, mixed), type of intervention (prevention, 'treatment'), guided versus unguided programs, mode of delivery (Internet, computer), individual versus family dyad and venue (home, research setting). Also, no significant moderation effects were found for number of sessions and time to follow-up. Finally, there was no

			evidence of publication bias Conclusions: Internet and computer interventions appear to be effective in reducing cannabis use in the short-term albeit based on data from few studies and across diverse samples
Tatar O	2020	Tatar O, Bastien G, Abdel-Baki A, Huỳnh C, Jutras-Aswad D. A systematic review of technology-based psychotherapeutic interventions for decreasing cannabis use in patients with psychosis. Psychiatry Res. 2020 Jun;288:112940. doi: 10.1016/j.psychres.2020.112940. Epub 2020 Apr 15.	Persistent use of cannabis in persons with psychosis is associated with poor symptomatic and functional outcomes and increased healthcare costs. Face-to-face psychological interventions (e.g., Cognitive Behavioral Therapy- [CBT], Motivation Enhancement Therapy- [MET]) are widely used in treating problematic cannabis use. We aimed to comprehensively review the efficacy of technology-based psychological interventions (TBPIs) in decreasing cannabis use, the design of TBPIs, and TBPI-related preferences in individuals with psychosis. For the systematic review, we searched six major databases from their inception to November 27, 2019. We included empirical articles of quantitative and qualitative methodologies related to TBPIs in individuals with psychosis and cannabis misuse and used narrative synthesis to report results. Only eight articles were found showing that technology-based motivational and psycho-education interventions and cognitive enhancement therapy were minimally efficient in achieving cannabis abstinence or decreasing frequency of use. Qualitative exploratory methods and participatory action research were used to elicit patient and clinician preferences and TBPIs were tailored accordingly to improve cannabis use related outcomes. Research on TBPIs in individuals with psychosis and cannabis misuse is in its early phases. A significant research effort is needed for the development of adapted interventions for CUD to capitalize on the potential of web-based applications.
Walsh H	2020	Walsh H, McNeill A, Purssell E, Duaso M. A systematic review	Background and aims: Tobacco and cannabis are commonly co-used, and evidence for the influence of co-use on quit outcomes for either substance is mixed. We sought to determine the efficacy of tobacco and/or cannabis use interventions delivered to co-users on cannabis

		and Bayesian meta-analysis of interventions which target or assess co-use of tobacco and cannabis in single- or multi-substance interventions. Addiction. 2020 Oct;115(10):1800-1814. doi: 10.1111/add.14993. Epub 2020 Mar 7.	and tobacco use outcomes. Method Systematic review with meta-analysis and narrative review, using five databases and author requests for co-use data. Controlled and uncontrolled intervention studies focusing on treatment of tobacco and/or cannabis use assessing use of both pre- and post-intervention were included. Prevention interventions were excluded. Bayesian meta-analysis was used across four outcome measures: risk ratio for tobacco and cannabis cessation post-intervention separately; standardized mean change for tobacco and cannabis reduction post-intervention separately. Narrative reporting of the same outcome measures in non-randomized clinical trials (non-RCTs) and quality assessment of all included studies were conducted. Results Twenty studies (12 RCTs and eight uncontrolled) were included. Bayesian meta-analysis with informative priors based on existing data of 11 RCTs (six single-substance, five multi-substance interventions) delivered to co-users (n = up to 1117) showed weak evidence for an effect on cannabis cessation [risk ratio (RR) = 1.48, credibility interval (CrI) = 0.92, 2.49, eight studies] and no clear effect on tobacco cessation (RR = 1.10, CrI = 0.68, 1.87, nine studies). Subgroup analysis suggested that multi-substance interventions might be more effective than cannabis-targeted interventions on cannabis cessation (RR = 2.19, CrI = 1.10, 4.36 versus RR = 1.39, CrI = 0.75, 2.74). A significant intervention effect was observed on cannabis reduction (ES = 0.25, CrI = 0.03, 0.45, nine studies) but not on tobacco reduction (ES = 0.16, CrI = 0.14, 0.45, nine studies). Quality of evidence was moderate, although measurement of co-use and cannabis use requires standardization. Uncontrolled studies targeting both cannabis and tobacco use indicated feasibility and acceptability. Conclusions Single and multi-substance interventions addressing tobacco and/or cannabis have not shown a clear effect on either tobacco or cannabis cessation and reduction among co-users. However, dual substance interventions targeting tobacco and cannabis appear feasible
Werneck MA	2018	Werneck MA, Kortas GT, de Andrade AG, Castaldelli-Maia JM. A	Background: About 30% of regular cannabis users report withdrawal symptoms on cessation of prolonged use, such as irritability, insomnia, decreased appetite, depressed mood, anxiety, and restlessness. However, among highly dependent and/or in-treatment

		Systematic Review of the Efficacy of Cannabinoid Agonist Replacement Therapy for Cannabis Withdrawal Symptoms. CNS Drugs. 2018 Dec;32(12):1113-1129. doi: 10.1007/s40263-018-0577-6.	users, the incidence of withdrawal can be even higher, reaching up to 50-95% of individuals. This syndrome was only recognized by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) as a diagnosis with specific criteria in 2013. The treatment options are poor, with high rates of relapse and non-responders. In this scenario, agonist replacement therapy with cannabinoids has demonstrated potential as a promising therapeutic intervention, with a series of studies having been carried out in recent years. Objective: This review sought to summarize trials with cannabinoid agonist replacement therapy for cannabis withdrawal symptoms with the aim of evaluating the efficacy of this pharmacological intervention. Data sources: We entered the following search terms on the PubMed, Web of Science and PsycINFO databases: (marijuana OR marihuana OR cannabis OR THC OR tetrahydrocannabinol OR hashish OR pot) AND (treatment OR medication) AND (withdrawal OR abstinence) AND (dronabinol OR nabilone OR nabiximols OR sativex OR cesamet OR synthetic cannabinoid). The date of the most recent search was September 2017. Study eligibility criteria, participants, and interventions: Original trials, published in English, performed on humans and dealing with cannabis users who were treated for cannabis withdrawal symptoms using synthetic cannabinoids were all included in the present systematic review. Quality and risk of bias across studies were assessed using a Cochrane tool. Study appraisal and synthesis methods: The first, second, and last authors read the abstracts of all studies found in the search (n = 243). The inclusion and exclusion criteria were applied, and 233 articles were excluded. The first and second authors independently developed a data extraction sheet based on the included articles. Results: The present review included ten original articles. Despite the limited number of studies and methodological differences, our findings demonstrate that the use of dronabinol, nabilone, or nabiximols, either alone or in combination with other drugs, shows promise in reducing cannabis withdrawal symptoms, probably with a dose-dependent effect. This has

			also been considered a safe group of medications with good tolerability and few adverse effects.

Table S4 Reviews on treatment for problematic stimulant use

First author	Year	Citation	Abstract
Ameri A	2020	Ameri A, Keshvardoost S, Bahaadinbeigy K. Impact of Mobile Phone-Based Interventions on Methamphetamine Use and High-risk Sexual Behaviors in Men Who Have Sex with Men (MSM): A Systematic Review. Addict Health. 2020 Jan;12(1):58-68. doi: 10.22122/ahj.v12i1.254.	Background: Today, increased use of methamphetamine in homosexual men is associated with high-risk sexual behaviors and (HIV) epidemic. Mobile phone-based interventions are an accessible and rapid method to provide healthcare services to this population. This study aimed to systematically review the effects of mobile phone-based interventions on methamphetamine use and high-risk sexual behaviors in homosexual men. Methods: This systematic review was conducted by two researchers via searching in PubMed, Google Scholar, Web of Science, Scopus, and PsycINFO databases to retrieve the published articles regarding the effects of mobile phone-based interventions on the control of methamphetamine use and high-risk sexual behaviors. Findings: Among 250 unique articles that were retrieved, only five cases met all the inclusion criteria of the study. Accordingly, some of the applied interventions included text messaging (n = 4) and mobile apps (n = 1). In this regard, the use of text messaging significantly decreased the rates of methamphetamine use, condomless anal intercourse (CAI), and HIV transmission among homosexual men. Conclusion: According to the results, short-term interventions based on text messaging could decrease the rates of methamphetamine use and the high-risk sexual behaviors associated with HIV infection in homosexual men. Despite the positive impact of these interventions, long-term follow-ups are required for individuals using methamphetamine in different communities.
AshaRani PV	2020	AshaRani PV, Hombali A, Seow E, Ong WJ, Tan JH, Subramaniam M. Non-pharmacological interventions for	Background: Methamphetamine (METH) use is on the rise globally, with the number of treatment seekers increasing exponentially across the globe. Evidence-based therapies are needed to meet rising treatment needs. This systematic review intends to appraise the existing evidence to identify effective non-pharmaceutical approaches for the treatment of METH use disorder. Methods: Five electronic bibliographic databases-Ovid (Medline), Embase, Cumulative

		methamphetamine use disorder: a systematic review. Drug Alcohol Depend. 2020 Jul 1;212:108060. doi: 10.1016/j.drugalcdep.2020.108060. Epub 2020 May 13.	Index of Nursing and Allied Health Literature (CINAHL), Web of Science and PsycINFO- were searched to identify relevant studies that were published between January 1995 to February 2020. Studies were selected and assessed by two independent reviewers. A systematic review of data from both randomised control trials (RCT) and non-RCTs was conducted to appraise the evidence. Results: A total of 44 studies were included in the review. Behavioural interventions, i.e. cognitive behavioural therapy (CBT), contingency management (CM), exercise, residential rehabilitation based therapies, repetitive transcranial magnetic stimulation (rTMS), and matrix model demonstrated treatment efficacy in promoting abstinence, reducing methamphetamine use or craving in the participants. While CM interventions showed the strongest evidence favouring the outcomes assessed, tailored CBT alone or with CM was also effective in the target population. Conclusions: Behavioural interventions should be considered as the first line of treatment for methamphetamine use disorder. Future studies should address the longevity of the effects, and limitations due to smaller sample sizes and high dropout rates to enable better assessment of evidence.
Bhatt M	2016	Bhatt M, Zielinski L, Baker-Beal L, Bhatnagar N, Mouravska N, Laplante P, Worster A, Thabane L, Samaan Z. Efficacy and safety of psychostimulants for amphetamine and methamphetamine use disorders: a	Background: Amphetamine and methamphetamine use disorders are associated with severe health and social consequences. No pharmacological therapy has been approved for the treatment of these disorders. Psychostimulants can act as maintenance-like therapies for managing substance use among these patients. The aim of this study is to evaluate the literature examining the efficacy and safety of psychostimulant agents for increasing abstinence and treatment retention among patients with amphetamine and methamphetamine use disorders. Methods: We searched MEDLINE, EMBASE, PsycInfo, Cochrane Central, and CINAHL from inception to August 2016. Selection of studies, data extraction, and risk of bias assessment were conducted independently by two reviewers. We conducted meta-analyses to provide a pooled summary estimate for included trials and report the review according to PRISMA guidelines.

		systematic review and meta-analysis. Syst Rev. 2016 Nov 14;5(1):189. doi: 10.1186/s13643-016-0370-x.	Results: We identified and selected 17 studies with 1387 participants. Outcome reporting across trials was inconsistent, and the overall quality of evidence was very low due to high risk of bias and indirectness. A meta-analysis of five trials (642 participants) found no effect of psychostimulants for end-of-study abstinence (odds ratio = 0.97, 95% confidence interval 0.65 to 1.45). Additionally, the pooled estimate from 14 studies (1184 participants) showed no effect of psychostimulants for treatment retention (odds ratio = 1.20, 95% confidence interval = 0.91 to 1.58). The incidence of serious adverse events did not differ between intervention and placebo groups based on qualitative reports from trials. Conclusions: Quantitative analyses showed no effect of psychostimulants for sustained abstinence or treatment retention. We also identified the need for more rigorous studies in this research area with clinician and patient important outcomes
Castells X	2016	Castells X, Cunill R, Pérez-Mañá C, Vidal X, Capellà D. Psychostimulant drugs for cocaine dependence. Cochrane Database Syst Rev. 2016 Sep 27;9(9):CD007380. doi: 10.1002/14651858.CD007380.pub4.	Background: Cocaine dependence is a severe disorder for which no medication has been approved. Like opioids for heroin dependence, replacement therapy with psychostimulants could be an effective therapy for treatment. Objectives: To assess the effects of psychostimulants for cocaine abuse and dependence. Specific outcomes include sustained cocaine abstinence and retention in treatment. We also studied the influence of type of drug and comorbid disorders on psychostimulant efficacy. Search methods: This is an update of the review previously published in 2010. For this updated review, we searched the Cochrane Drugs and Alcohol Group Trials Register, CENTRAL, MEDLINE, Embase and PsycINFO up to 15 February 2016. We hand searched references of obtained articles and consulted experts in the field. Selection criteria: We included randomised parallel group controlled clinical trials comparing the efficacy of a psychostimulant drug versus placebo. Data collection and analysis: We used standard methodological procedures expected by Cochrane. Main results: We included 26 studies involving 2366 participants. The included studies assessed nine drugs: bupropion, dexamphetamine, lisdexamfetamine, methylphenidate,

			modafinil, mazindol, methamphetamine, mixed amphetamine salts and selegiline. We did not consider any study to be at low risk of bias for all domains included in the Cochrane 'Risk of bias' tool. Attrition bias was the most frequently suspected potential source of bias of the included studies. We found very low quality evidence that psychostimulants improved sustained cocaine abstinence (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.05 to 1.77, P = 0.02), but they did not reduce cocaine use (standardised mean difference (SMD) 0.16, 95% CI -0.02 to 0.33) among participants who continued to use it. Furthermore, we found moderate quality evidence that psychostimulants did not improve retention in treatment (RR 1.00, 95% CI 0.93 to 1.06). The proportion of adverse event-induced dropouts and cardiovascular adverse event-induced dropouts was similar for psychostimulants and placebo (RD 0.00, 95% CI -0.01 to 0.01; RD 0.00, 95% CI -0.02 to 0.01, respectively). When we included the type of drug as a moderating variable, the proportion of patients achieving sustained cocaine abstinence was higher with bupropion and dexamphetamine than with placebo. Psychostimulants also appeared to increase the proportion of patients achieving sustained cocaine and heroin abstinence amongst methadone-maintained, dual heroin-cocaine addicts. Retention to treatment was low, though, so our results may be compromised by attrition bias. We found no evidence of publication bias.
Chan B	2019a	Chan B, Kondo K, Freeman M, Ayers C, Montgomery J, Kansagara D. Pharmacotherapy for Cocaine Use Disorder-a Systematic Review and Meta-analysis. J Gen Intern Med. 2019	BACKGROUND: Currently, there are no accepted FDA approved pharmacotherapies for cocaine use disorder, though numerous medications have been tested in clinical trials. We conducted a systematic review and meta-analysis to better understand the effectiveness of pharmacotherapy for cocaine use disorder. METHODS: We searched multiple data sources (MEDLINE, PsycINFO, and Cochrane Library) through November 2017 for systematic reviews and randomized controlled trials (RCTs) of pharmacological interventions in adults with cocaine use disorder. When possible, we combined the findings of trials with comparable interventions and outcome measures in random-effects meta-analyses. We assessed the risk of bias of individual trials and the strength of evidence for each outcome using standardized criteria. Outcomes

		Dec;34(12):2858-2873. doi: 10.1007/s11606-019-05074-8. Epub 2019 Jun 10.	included continuous abstinence (3+ consecutive weeks); cocaine use; harms; and study retention. For relapse prevention studies (participants abstinent at baseline), we examined lapse (first cocaine positive or missing UDS) and relapse (two consecutive cocaine positive or missed UDS′). RESULTS: Sixty-six different drugs or drug combinations were studied in seven systematic reviews and 48 RCTs that met inclusion criteria. Antidepressants were the most widely studied drug class (38 RCTs) but appear to have no effect on cocaine use or treatment retention. Increased abstinence was found with bupropion (2 RCTs: RR 1.63, 95% CI 1.02 to 2.59), topiramate (2 RCTs: RR 2.56, 95% CI 1.39 to 4.73), and psychostimulants (14 RCTs: RR 1.36, 95% CI 1.05 to 1.77), though the strength of evidence for these findings was low. We found moderate strength of evidence that antipsychotics improved treatment retention (8 RCTs: RR 1.33, 95% CI 1.03 to 1.75). DISCUSSION: Most of the pharmacotherapies studied were not effective for treating cocaine use disorder. Bupropion, psychostimulants, and topiramate may improve abstinence, and antipsychotics may improve retention. Contingency management and behavioral interventions along with pharmacotherapy should continue to be explored.
Chan B	2019b	Chan B, Freeman M, Kondo K, Ayers C, Montgomery J, Paynter R, Kansagara D. Pharmacotherapy for methamphetamine/amphetamine use disorder-a systematic review and meta-analysis. Addiction. 2019	Aims: Addiction to methamphetamine/amphetamine (MA/A) is a major public health problem. Currently there are no pharmacotherapies for MA/A use disorder that have been approved for use by the US Food and Drug Administration or the European Medicines Agency. We reviewed the effectiveness of pharmacotherapy for MA/A use disorder to assess the quality, publication bias and overall strength of the evidence. Methods: Systematic review and meta-analysis. We searched multiple data sources (MEDLINE, PsycINFO and Cochrane Library) to April 2019 for systematic reviews (SRs) and randomized controlled trials (RCTs). Included studies recruited adults who had MA/A use disorder; sample sizes ranged from 19 to 229 participants. Outcomes of interest were abstinence, defined as 3 or more consecutive weeks with negative urine drug screens (UDS); overall use, analyzed as the proportion of MA/A negative UDS specimens; and treatment retention. One SR of pharmacotherapies for MA/A use disorder and 17

		Dec;114(12):2122-2136. doi: 10.1111/add.14755. Epub 2019 Sep 12.	additional RCTs met our inclusion criteria encompassing 17 different drugs (antidepressants, antipsychotics, psychostimulants, anticonvulsants and opioid antagonists). We combined the findings of trials with comparable interventions and outcome measures in random-effects meta-analyses. We assessed quality, publication bias and the strength of evidence for each outcome using standardized criteria. Results: There was low-strength evidence from two RCTs that methylphenidate may reduce MA/A use: 6.5 versus 2.8% MA/A-negative UDS in one study (n = 34, P = 0.008) and 23 versus 16% in another study (n = 54, P = 0.047). Antidepressants as a class had no statistically significant effect on abstinence or retention on the basis of moderate strength evidence. Studies of anticonvulsants, antipsychotics (aripiprazole), opioid antagonists (naltrexone), varenicline and atomoxetine provided either low-strength or insufficient evidence of no effect on the outcomes of interest. Many of the studies had high or unclear risk of bias. Conclusions: On the basis of low- to moderate-strength evidence, most medications evaluated for methamphetamine/amphetamine use disorder have not shown a statistically significant benefit. However, there is low-strength evidence that methylphenidate may reduce use.
Chan B	2020	Chan B, Freeman M, Ayers C, Korthuis PT, Paynter R, Kondo K, Kansagara D. A systematic review and meta-analysis of medications for stimulant use disorders in patients with co-occurring opioid use disorders.	Background: Stimulant (cocaine and/or methamphetamine) use has increased among people with opioid use disorder. We conducted a systematic review of medications for stimulant use disorders in this population. Methods: We searched for randomized controlled trials in multiple databases through April 2019, and dual screened studies using pre-specified inclusion criteria. Primary outcomes were abstinence defined as stimulant negative urine screens for ≥3 consecutive weeks; overall use as the proportion of stimulant-negative urine specimens; and retention as the proportion of participants who completed treatment. We rated strength of evidence using established criteria and conducted meta-analyses of comparable interventions and outcomes. Results: Thirty-four trials of 22 medications focused on cocaine use disorder in patients

		Drug Alcohol Depend. 2020 Nov 1;216:108193. doi: 10.1016/j.drugalcdep.2020.108193. Epub 2020 Aug 1.	with opioid use disorder. Most studies enrolled participants stabilized on opioid maintenance therapy, generally methadone. None of the six studies that assessed abstinence found significant differences between groups. We found moderate-strength evidence that antidepressants (desipramine, bupropion, and fluoxetine) worsened retention. There was moderate-strength evidence that disulfiram worsened treatment retention (N = 605, RR 0.86, 95 % CI 0.77 to 0.95). We found low-strength evidence that psychostimulants (mazindol and dexamphetamine) may reduce cocaine use, though the difference was not statistically significant (standard mean difference 0.35 [95 % CI -0.05 to 0.74]). There was only 1 trial for methamphetamine use disorder, which showed insufficient-strength evidence for naltrexone. Conclusions: Co-occurring stimulant/opioid use disorder is an important problem for targeting future research. Medication trials for methamphetamine use disorder are lacking in this population. Most of the medications studied for cocaine use were ineffective, although psychostimulants warrant further study.
De Crescenzo F	2018	De Crescenzo F, Ciabattini M, D'Alò GL, De Giorgi R, Del Giovane C, Cassar C, Janiri L, Clark N, Ostacher MJ, Cipriani A. Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine	Background: Clinical guidelines recommend psychosocial interventions for cocaine and/or amphetamine addiction as first-line treatment, but it is still unclear which intervention, if any, should be offered first. We aimed to estimate the comparative effectiveness of all available psychosocial interventions (alone or in combination) for the short- and long-term treatment of people with cocaine and/or amphetamine addiction. Methods and findings: We searched published and unpublished randomised controlled trials (RCTs) comparing any structured psychosocial intervention against an active control or treatment as usual (TAU) for the treatment of cocaine and/or amphetamine addiction in adults. Primary outcome measures were efficacy (proportion of patients in abstinence, assessed by urinalysis) and acceptability (proportion of patients who dropped out due to any cause) at the end of treatment, but we also measured the acute (12 weeks) and long-term (longest duration of study follow-up) effects of the interventions and the longest duration of abstinence. Odds ratios (ORs) and standardised mean differences were estimated using pairwise and network meta-analysis with random effects. The risk of bias

		addiction: A systematic review and network meta-analysis. PLoS Med. 2018 Dec 26;15(12):e1002715. doi: 10.1371/journal.pmed.1002715. eCollection 2018 Dec.	of the included studies was assessed with the Cochrane tool, and the strength of evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. We followed the PRISMA for Network Meta-Analyses (PRISMA-NMA) guidelines, and the protocol was registered in PROSPERO (CRD 42017042900). We included 50 RCTs evaluating 12 psychosocial interventions or TAU in 6,942 participants. The strength of evidence ranged from high to very low. Compared to TAU, contingency management (CM) plus community reinforcement approach was the only intervention that increased the number of abstinent patients at the end of treatment (OR 2.84, 95% CI 1.24–6.51, P = 0.013), and also at 12 weeks (OR 7.60, 95% CI 2.03–28.37, P = 0.002) and at longest follow-up (OR 3.08, 95% CI 1.33–7.17, P = 0.008). At the end of treatment, CM plus community reinforcement approach had the highest number of statistically significant results in head-to-head comparisons, being more efficacious than cognitive behavioural therapy (CBT) (OR 2.44, 95% CI 1.02–5.88, P = 0.045), non-contingent rewards (OR 3.31, 95% CI 1.32–8.28, P = 0.010), and 12-step programme plus non-contingent rewards (OR 4.07, 95% CI 1.13–14.69, P = 0.031). CM plus community reinforcement approach was also associated with fewer dropouts than TAU, both at 12 weeks and the end of treatment (OR 3.92, P < 0.001, and 3.63, P < 0.001, respectively). At the longest follow-up, community reinforcement approach was more effective than non-contingent rewards, supportive-expressive psychodynamic therapy, TAU, and 12-step programme (OR ranging between 2.71, P = 0.026, and 4.58, P = 0.001), but the combination of community reinforcement approach with CM was superior also to CBT alone, CM alone, CM plus CBT, and 12-step programme plus non-contingent rewards (ORs between 2.50, P = 0.039, and 5.22, P < 0.001). The main limitations of our study were the quality of included studies and the lack of blinding, which may have increased the risk of performance bias. However, our analyses were based on objective outcomes, which are less likely to be biased. Conclusions: To our knowledge, this network meta-analysis is the most comprehensive synthesis of data for psychosocial interventions in individuals with cocaine and/or

			amphetamine addiction. Our findings provide the best evidence base currently available to guide decision-making about psychosocial interventions for individuals with cocaine and/or amphetamine addiction and should inform patients, clinicians, and policy-makers.
Indave BI	2016	Indave BI, Minozzi S, Pani PP, Amato L. Antipsychotic medications for cocaine dependence. Cochrane Database Syst Rev. 2016 Mar 19;3:CD006306. doi: 10.1002/14651858.CD006306.pub3.	Background: Cocaine dependence is often associated with medical, psychological and social problems for individual and public health, generating problems for the community. Users play a role in the spread of infectious diseases such as AIDS, hepatitis and tuberculosis, as well as in crime, violence and neonatal drug exposure. Use of drugs such as antidepressants, anticonvulsants and dopamine agonists to treat cocaine abuse or dependence is not supported by evidence from Cochrane reviews. The use of antipsychotic agents has also been considered, particularly because cocaine can induce hallucinations and paranoia that mimic psychosis. Study characteristics: The review authors identified 14 randomised controlled trials involving 719 adults. One study was conducted in Italy, and the rest in the USA. They involve both inpatient and outpatient settings and had a duration of 14 to 168 days (mean 80 days). Eleven trials randomised participants to receive an antipsychotic drug or placebo using the following antipsychotic medications: risperidone (three studies, 1 to 4 mg/day and one study with injections of long-acting risperidone at a dose of 25 mg/14 days); olanzapine (three studies, 2.5 to 20 mg/day); quetiapine (two studies, 400 and 800 mg/day); lamotrigine (one study, 400 mg/day); reserpine (one study, 50 mg/day). Three trials compared two drugs; olanzapine (10 mg/day) versus haloperidol (10 mg/day), olanzapine (20 mg/day) versus risperidone (9 mg/day) and aripiprazol (10 mg/day) versus ropirinol (4.5 mg/day). Key results: The studies used different instruments or ways to assess the outcomes of interest, limiting the possibility for us to combine the data. When we grouped together all trial results comparing any antipsychotic drug to placebo, we found that antipsychotics slightly increase those who stayed in treatment but they were not effective in reducing cocaine use during treatment (two studies), in sustained abstinence (three studies), or in reducing the urge to consume cocaine (four studies). The single comparisons of each drug

			versus placebo or versus another drug were made in few trials with small sample sizes, limiting the reliability of the results. However, among these comparisons, only quetiapine seemed to perform better than placebo in reducing cocaine use and craving, but results came only from one study with 60 participants. Information was limited on the acceptability of treatment in terms of side effects, abstinence from cocaine use and withdrawal symptoms. Overall, we found no evidence supporting the clinical use of antipsychotic medications in the treatment of cocaine dependence. Quality of the evidence: The major limitations of the studies were the high number of people who withdrew from the m and the lack of clear reporting of the methods used to conduct the studies. Moreover, the number of participants was small, and different ways of measuring and reporting results were used, limiting the possibility for us to combine the data. Overall we judged the quality of the evidence to be moderate for dropouts and low for all the other outcomes considered. The evidence is current up to 15 of July 2015.
Knight R	2019	Knight R, Karamouzian M, Carson A, Edward J, Carrieri P, Shoveller J, Fairbairn N, Wood E, Fast D. Interventions to address substance use and sexual risk among gay, bisexual and other men who have sex with men who use methamphetamine: A systematic review.	Background: Methamphetamine use is common among some populations of gay, bisexual and other men who have sex with men (gbMSM). This study reviewed the status of research on the efficacy of interventions that address harms among gbMSM who use methamphetamine. Methods: We searched MEDLINE, PsycINFO, CINAHL, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Google Scholar to identify publications from inception to October 23, 2017, that assessed an intervention addressing methamphetamine use among gbMSM. Results: Of 1896 potential studies and 935 unique articles screened for inclusion, 28 eligible studies assessed 26 different interventions in the following categories: pharmacological (n = 5); psychosocial (n = 20); harm reduction (n = 1). Given that outcome variables were measured in highly variable ways, we were unable to conduct a meta-analysis of intervention effects. However, 22 studies reported a statistically significant effect on one or more methamphetamine-related outcomes. Among 21 studies that included measures of sexual health-related outcomes, 18 reported a significant effect

		Drug Alcohol Depend. 2019 Jan 1;194:410-429. doi: 10.1016/j.drugalcdep.2018.09.023. Epub 2018 Nov 3.	on one or more sexual health-related outcomes, and 15 of those reported a concurrent effect on both drug- and sexual health-related outcomes. Conclusions: This is the first review to provide compelling evidence that integrating interventions to address both drug- and sexual-related harms for gbMSM who use methamphetamine can be efficacious. Future research should focus on identifying differential effects of various intervention approaches by social positioning, as well as prioritize future evaluations of integrated harm reduction interventions (e.g., the distribution of harm reduction kits within sexual health care settings).
Lam L	2019	Lam L, Anand S, Li X, Tse ML, Zhao JX, Chan EW. Efficacy and safety of naltrexone for amfetamine and methamfetamine use disorder: a systematic review of randomized controlled trials. Clin Toxicol (Phila). 2019 Apr;57(4):225-233. doi: 10.1080/15563650.2018.1529317. Epub 2018 Nov 17.	Introduction: Amfetamine and methamfetamine abuse remains a prevalent health problem, increasing the burden on healthcare. Naltrexone, a m-opioid receptor antagonist, has been suggested as a promising treatment for amfetamine and methamfetamine use disorder. Objective: To review the current evidence for the efficacy and safety of naltrexone as a pharmacological treatment for amfetamine and methamfetamine use disorder. The primary outcome was defined as abstinence or reduction of use. Secondary outcomes were, attenuated “positive” subjective effects (e.g., “feel good,” “craving,” etc.) of amfetamine or methamfetamine after naltrexone treatment, adverse events and physiological changes (e.g., blood pressure, heart rate). Methods: This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic literature search was conducted on 2 April 2017, and updated on 31 March 2018. Records were retrieved from databases including PubMed, EMBASE Classic plus EMBASE 1980 via Ovid, and the databases were searched using keywords and/or headings: (naltrexone AND amfetamine AND dependence) OR (naltrexone AND amfetamine AND craving) OR (vivitrol AND amfetamine) OR (revia AND amfetamine) OR (naltrexone AND amfetamine) OR (naltrexone AND methamfetamine dependence) OR (naltrexone AND methamfetamine AND craving) OR (vivitrol AND methamfetamine) OR (revia AND methamfetamine) OR (naltrexone AND ice) OR (naltrexone AND crystal meth) OR (naltrexone AND methamfetamine). Studies investigating the effects of naltrexone on

			amfetamine or methamfetamine use were eligible for inclusion. All studies were rated as low risk of bias using the Cochrane tool for risk of bias. Results: Among 591 identified studies, there were four randomized controlled trials. Two studies investigated the effects of naltrexone on amfetamine use disorder and two on methamfetamine use. Compared to placebo, the abstinence rate was increased significantly ($p < 0.05$) by naltrexone in one of two amfetamine studies, whereas there was no statistical difference in the only study reporting methamfetamine use. In one out of two amfetamine studies, naltrexone significantly attenuated either craving levels or subjective effects (e.g., “want more,” “like effect”) relative to placebo ($p < 0.05$). Additionally, only in one of two methamfetamine studies did naltrexone produce a significant reduction ($p < 0.05$) in craving levels or attenuated subjective effects. Both amfetamine and methamfetamine studies showed good tolerability of naltrexone, with few adverse events seen. Conclusions: There is presently insufficient evidence to support the use of naltrexone in amfetamine and metamfetamine use disorders. There is a compelling need for high-quality studies to further evaluate the potential use of naltrexone.
Ma T	2019	Ma T, Sun Y, Ku Y. Effects of Non-invasive Brain Stimulation on Stimulant Craving in Users of Cocaine, Amphetamine, or Methamphetamine: A Systematic Review and Meta-Analysis. Front Neurosci. 2019 Oct 18;13:1095. doi:	Dopamine system plays a pivotal role in specific kinds of substance use disorders (SUD, i. e., cocaine and methamphetamine use disorders). Many studies addressed whether dopamine-involved craving could be alleviated by non-invasive brain stimulation (NIBS) techniques. Nevertheless, the outcomes were highly inconsistent and the stimulating parameters were highly variable. In the current study, we ran a meta-analysis to identify an overall effect size of NIBS and try to find stimulating parameters of special note. We primarily find 2,530 unduplicated studies in PubMed, Psychology and Behavioral Sciences Collection, PsycARTICLES, PsycINFO, and Google Scholar database involving “Cocaine”/“Amphetamine”/“Methamphetamine” binded with “TMS”/“tDCS”/“non-invasive stimulation” in either field. After visual screening, 26 studies remained. While 16 studies were further excluded due to the lack of data, invalid craving scoring or the absence of sham condition. At last, 16 units of analysis in 12

		10.3389/fnins.2019.01095. eCollection 2019.	eligible studies were coded and forwarded to a random-effect analysis. The results showed a large positive main effect of stimulation (Hedge's g = 1.116, CI = [0.597, 1.634]). Further subgroup analysis found that only high-frequency repetitive transcranial magnetic stimulation (rTMS) could elicit a significant decrease in craving, while the outcome of low-frequency stimulation was relatively controversial. Moreover, univariate meta regression revealed that the number of pulses per session could impose negative moderation toward the intervention. No significant moderation effect was found in types of abuse, overall days of stimulation and other variables of stimulating protocol. In conclusion, this meta-analysis offered a persuasive evidence for the feasibility of using NIBS to remit substance addictive behavior directly based on dopamine system. We also give clear methodological guidance that researchers are expected to use high-frequency, sufficiently segmented rTMS to improve the efficacy in future treatments.
Minozzi S	2015	Minozzi S, Cinquini M, Amato L, Davoli M, Farrell MF, Pani PP, Vecchi S. Anticonvulsants for cocaine dependence. Cochrane Database Syst Rev. 2015 Apr 17;(4):CD006754. doi: 10.1002/14651858.CD006754.pub4.	Background: Cocaine is an illicit drug available as a powder for intranasal or intravenous use or smoked as crack. Short- and long-term use of this drug results in the spread of infectious diseases (for example, AIDS, hepatitis, tuberculosis), crime, violence and prenatal drug exposure. Cocaine dependence is associated with medical and psychosocial complications and is a major public health problem. No proven pharmacological treatment for cocaine dependence is known. Antidepressant, anticonvulsant and dopaminergic medications have all been studied. The present review looked at the efficacy and safety of anticonvulsant drugs for treating cocaine dependence, both as a class and individually. Study characteristics: The review authors searched scientific databases and Internet resources to identify randomised controlled trials (in which participants were allocated at random to any anticonvulsant drug or placebo or another type of drug or non-pharmacological intervention intended to reduce, the use of cocaine). We assessed also dropout from treatment and frequency of side effects .We included people of any gender, age or ethnicity. Key results: The review authors identified 20 studies with 2068 participants, 77% male, with a mean age of 36 years. The mean duration of the trials was 11.8 weeks (range eight

			to 24 weeks). All but two of the trials were conducted in the USA, all with outpatients. The anticonvulsant drugs studied were carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate and vigabatrin. All studies compared anticonvulsants versus placebo. No significant differences were found between placebo and any anticonvulsant in reducing the number of dropouts from treatment, use of cocaine, craving and severity of dependence, depression or anxiety. Side effects were slightly more frequent in the anticonvulsant groups. No current evidence supports the clinical use of anticonvulsant medications for the treatment of cocaine dependence.
Minozzi S	2015	Minozzi S, Amato L, Pani PP, Solimini R, Vecchi S, De Crescenzo F, Zuccaro P, Davoli M. Dopamine agonists for the treatment of cocaine dependence. Cochrane Database Syst Rev. 2015 May 27;2015(5):CD003352 . doi: 10.1002/14651858.CD003352.pub4.	Background: A pharmacological agent with proven efficacy does not exist for treatment of cocaine misuse. Cocaine is an alkaloid derived from the erythroxylon coca leaf that is used as powder for intranasal or intravenous use or as crack, a free-base form which is smoked. Cocaine misuse is a major public health problem because its use can be associated with medical and psychosocial complications including the spread of infectious diseases (such as AIDS, hepatitis and tuberculosis), crime, violence and neonatal drug exposure. In this Cochrane Review we looked at the evidence on the efficacy and acceptability of dopamine agonists as a treatment, used either alone or in combination with any psychosocial intervention, for people addicted to cocaine. Study characteristics: We searched scientific databases and internet resources to identify randomised controlled trials (where participants are allocated at random to any dopamine agonist drug or placebo or another type of drug aimed to reduce use of cocaine. We also assessed dropout from treatment and frequency of side effects. We included adults of any gender, age or ethnicity. Key results: We included 24 studies with 2147 participants, who were all addicted to cocaine. Most were men (82.%)with an average age of 37 years. The mean duration of the included trials was seven weeks (range 1.5 to 16 weeks) Twenty-two studies were conducted in USA, one in Brazil and one in Spain; all but four were outpatients. The included trials studied the following drugs: amantadine, bromocriptine, L dopa/Carbidopa, pergolide, cabergoline hydergine, and pramipexole. All compared

			dopamine agonist versus placebo. Four studies compared amantidine versus antidepressants. No differences were found between the drugs and placebo for any of the outcomes considered: dropout (moderate quality of evidence), abstinence (low quality of evidence), severity of dependence (low quality of evidence), adverse events (moderate quality of evidence). Antidepressants was found to be better than the dopamine agonist amantidine for abstinence, but this was based on two studies with very few participants and low quality of evidence. There is no current evidence supporting the clinical use of dopamine agonist medications in the treatment of cocaine misuse. The evidence is current to 12 January 2015.
Minozzi S	2016	Minozzi S, Saulle R, De Crescenzo F, Amato L. Psychosocial interventions for psychostimulant misuse. The Cochrane database of systematic reviews 2016;9:CD011866-CD	Background: Psychostimulant misuse is a continuously growing medical and social burden. There is no evidence proving the efficacy of pharmacotherapy. Psychosocial interventions could be a valid approach to help patients in reducing or ceasing drug consumption. Objectives: To assess the effects of psychosocial interventions for psychostimulant misuse in adults. Search methods: We searched the Cochrane Drugs and Alcohol Group Specialised Register (via CRSLive); Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; CINAHL; Web of Science and PsycINFO, from inception to November 2015. We also searched for ongoing and unpublished studies via ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/). All searches included non-English language literature. We hand-searched references of topic-related systematic reviews and the included studies. Selection criteria: We included randomised controlled trials comparing any psychosocial intervention with no intervention, treatment as usual (TAU) or a different intervention in adults with psychostimulant misuse or dependence. Data collection and analysis: We used the standard methodological procedures expected by Cochrane.

			Main results: We included a total of 52 trials (6923 participants). The psychosocial interventions considered in the studies were: cognitive behavioural therapy (19 studies), contingency management (25 studies), motivational interviewing (5 studies), interpersonal therapy (3 studies), psychodynamic therapy (1 study), 12-step facilitation (4 studies). We judged most of the studies to be at unclear risk of selection bias; blinding of personnel and participants was not possible for the type of intervention, so all the studies were at high risk of performance bias with regard to subjective outcomes; the majority of studies did not specify whether the outcome assessors were blind. We did not consider it likely that the objective outcomes were influenced by lack of blinding. The comparisons made were: any psychosocial intervention versus no intervention (32 studies), any psychosocial intervention versus TAU (6 studies), and one psychosocial intervention versus an alternative psychosocial intervention (13 studies). Five of included studies did not provide any useful data for inclusion in statistical synthesis. We found that, when compared to no intervention, any psychosocial treatment: reduced the dropout rate (risk ratio (RR): 0.83, 95% confidence interval (CI) 0.76 to −0.91, 24 studies, 3393 participants, moderate quality evidence); increased continuous abstinence at the end of treatment (RR: 2.14, 95% CI 1.27 to −3.59, 8 studies, 1241 participants, low quality evidence); did not significantly increase continuous abstinence at the longest follow-up (RR: 2.12, 95% CI 0.77 to −5.86, 4 studies, 324 participants, low quality evidence); significantly increased the longest period of abstinence: (standardised mean difference (SMD): 0.48, 95% CI 0.34 to 0.63, 10 studies, 1354 participants, high quality evidence). However, it should be noted that the in the vast majority of the studies in this comparison the specific psychosocial treatment assessed in the experimental arm was given in add on to treatment as usual or to another specific psychosocial or pharmacological treatment which was received by both groups. So, many of the control groups in this comparison were not really untreated. Receiving some amount of treatment is not the same as not receiving any intervention, so we could argue that the overall effect of the experimental psychosocial treatment could be smaller if given in add on to TAU or to another intervention than if given to participants not receiving

			any intervention; this could translate to a smaller magnitude of the effect of the psychosocial intervention when it is given in add on. When compared to TAU, any psychosocial treatment reduced dropout rate (RR: 0.72, 95% CI 0.59 to 0.89, 6 studies, 516 participants, moderate quality evidence), did not increase continuous abstinence at the end of treatment (RR: 1.27, 95% CI 0.94 to 1.72, 2 studies, 224 participants, low quality evidence), did not increase longest period of abstinence (MD −3.15 days, 95% CI −10.35 to 4.05, 1 study, 110 participants, low quality evidence). No studies in this comparison assessed the outcome of continuous abstinence at longest follow-up. There were few studies comparing two or more psychosocial interventions, with small sample sizes and considerable heterogeneity in terms of the types of interventions assessed. None reported significant results. None of the studies reported harms related to psychosocial interventions. Authors' conclusions: The addition of any psychosocial treatment to treatment as usual (usually characterised by group counselling or case management) probably reduces the dropout rate and increases the longest period of abstinence. It may increase the number of people achieving continuous abstinence at the end of treatment, although this might not be maintained at longest follow-up. The most studied and the most promising psychosocial approach to be added to treatment as usual is probably contingency management. However, the other approaches were only analysed in a few small studies, so we cannot rule out the possibility that the results were not significant because of imprecision. When compared to TAU, any psychosocial treatment may improve adherence, but it may not improve abstinence at the end of treatment or the longest period of abstinence.
Pani PP	2011	Pani PP, Trogu E, Vecchi S, Amato L. Antidepressants for cocaine dependence and problematic cocaine use.	A pharmacological agent with proven efficacy does not exist for treatment of cocaine dependence. Cocaine is an alkaloid derived from the erythroxylon coca leaf that is used as powder for intranasal or intravenous use or as crack, a free-base form which is smoked. Cocaine dependence is a major public health problem because its use can be associated with medical and psychosocial complications including the spread of infectious diseases (such as AIDS, hepatitis and tuberculosis), crime, violence and neonatal drug exposure.

		Cochrane Database Syst Rev. 2011 Dec 7;(12):CD002950. doi: 10.1002/14651858.CD002950.pub3.	This review looked at the evidence on the efficacy and acceptability of antidepressants alone or in combination with a psychosocial intervention for the treatment of cocaine abuse and dependence. Current evidence from randomised controlled trials does not support the use of antidepressants. Positive results obtained by antidepressants on mood-related outcomes are consistent with the primary effect of antidepressants. They do not seem to be associated with any effect on dropouts from treatment, cocaine use or side effects, which are direct indicators of cocaine abuse and dependence. A total of 37 randomised controlled clinical studies involving 3551 participants were included in the review. All the studies except one took place in the USA; 33 trials were conducted with outpatients in the community or in mental health centres. In 10 trials patients were also treated for opioid dependence with methadone or buprenorphine. The antidepressants included desipramine, fluoxetine and bupropion and the mean duration of the trials was 10.7 weeks. The included studies utilised 43 different rating instruments and differed in design, quality, characteristics of patients, tested medication, services and the treatments delivered.
Pani PP	2010	Pani PP, Trogu E, Vacca R, Amato L, Vecchi S, Davoli M. Disulfiram for the treatment of cocaine dependence. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007024. doi: 10.1002/14651858.CD007024.pub2.	Background: Cocaine dependence is a disorder for which no pharmacological treatment of proven efficacy exists, advances in the neurobiology could guide future medication development. Objectives: To evaluate the efficacy and the acceptability of disulfiram for cocaine dependence. Search strategy: We searched: PubMed, EMBASE, CINAHL (up to January 2008), the Cochrane Central Register of Controlled Trials (CENTRAL-The Cochrane Library, 1, 2009), reference lists of trials, main electronic sources of ongoing trials, conference proceedings. Selection criteria: Randomised and controlled clinical trials comparing disulfiram alone or associated with psychosocial intervention with no intervention, placebo, or other pharmacological intervention for the treatment of cocaine dependence. Data collection and analysis: Three reviewers independently assessed trial quality and

			extracted data. Main results: Seven studies, 492 participants, met the inclusion criteria. Disulfiram versus placebo: no statistically significant results for dropouts but a trend favouring disulfiram, two studies, 87 participants, RR 0.82 (95% CI 0.66 to 1.03). One more study, 107 participants, favouring disulfiram, was excluded from meta-analysis due high heterogeneity, RR 0.34 (95% CI 0.20 to 0.58). For cocaine use, it was not possible to pool together primary studies, results from single studies showed that, one, out of four comparisons, was in favour of disulfiram (number of weeks abstinence, 20 participants, WMD 4.50 (95% CI 2.93 to 6.07).Disulfiram versus naltrexone: no statistically significant results for dropouts but a trend favouring disulfiram, three studies, 131 participants, RR 0.67 (95% CI 0.45 to 1.01). No significant difference for cocaine use was seen in the only study that considered this outcome. Disulfiram versus no pharmacological treatment: for cocaine use: a statistically significant difference in favour of disulfiram, one study, two comparisons, 90 participants: maximum weeks of consecutive abstinence, WMD 2.10 (95% CI 0.69 to 3.51); number of subjects achieving 3 or more weeks of consecutive abstinence, RR 1.88 (95% CI 1.09 to 3.23). Authors' conclusions: There is low evidence, at the present, supporting the clinical use of disulfiram for the treatment of cocaine dependence. Larger randomised investigations are needed investigating relevant outcomes and reporting data to allow comparisons of results between studies. Results from ongoing studies will be added as soon as their results will be available.
Pérez-Mañá C	2013	Pérez-Mañá C, Castells X, Torrens M, Capellà D, Farre M. Efficacy of psychostimulant drugs for amphetamine abuse or dependence.	Amphetamine dependence constitutes a public health problem with many consequences and complications. Amphetamine abuse refers to a maladaptive and hazardous pattern of use considered to be less severe than dependence. To date, no pharmacological treatment has been approved for amphetamine abuse or dependence, and psychotherapy remains the best treatment option. Long-term amphetamine use reduces dopamine levels in the brain. Drugs increasing dopamine and mimicking the effects of amphetamines with lower abuse liability could be used as replacement therapy in amphetamine dependence.

		Cochrane Database Syst Rev. 2013 Sep 2;(9):CD009695. doi: 10.1002/14651858.CD009695.pub2.	Several psychostimulants have been studied recently for this purpose. In this review, the efficacy and safety of psychostimulants for amphetamine abuse or dependence were studied. We found eleven studies enrolling 791 amphetamine-dependent participants and assessing the effects of four different psychostimulants: dexamphetamine, bupropion, methylphenidate and modafinil. Psychosocial interventions were additionally provided to all participants. The studies were conducted in the USA, Australia or Northern Europe, and study length ranged from 8 to 20 weeks. Psychostimulants did not reduce amphetamine use or amphetamine craving and also did not increase sustained abstinence in comparison with placebo. Retention in treatment was similar and low with both treatments. Psychostimulants also did not increase the risk of adverse events that were intense enough to induce dropouts. Research with larger and longer trials is needed to determine whether psychostimulants can be a useful replacement therapy for patients with amphetamine abuse or dependence. The design of future trials should consider the level of dependence at study entry, the potency and the dose of the psychostimulant administered, the length of the trial and the representativeness of included participants.
Ronsley C	2020	Ronsley C, Nolan S, Knight R, Hayashi K, Klimas J, Walley A, Wood E, Fairbairn N. Treatment of stimulant use disorder: A systematic review of reviews. PLoS One. 2020 Jun 18;15(6):e0234809. doi: 10.1371/journal.pone.	Aims: Stimulant use disorder contributes to a substantial worldwide burden of disease, although evidence-based treatment options are limited. This systematic review of reviews aims to: (i) synthesize the available evidence on both psychosocial and pharmacological interventions for the treatment of stimulant use disorder; (ii) identify the most effective therapies to guide clinical practice, and (iii) highlight gaps for future study. Methods: A systematic database search was conducted to identify systematic reviews and meta-analyses. Eligible studies were those that followed standard systematic review methodology and assessed randomized controlled trials focused on the efficacy of interventions for stimulant use disorder. Articles were critically appraised using an assessment tool adapted from Palmeteer et al. and categorized for quality as ‘core’ or ‘supplementary’ reviews. Evidence from the included reviews were further synthesized according to pharmacological or non-pharmacological management themes. Results: Of 476 identified records, 29 systematic reviews examining eleven intervention

		0234809. eCollection 2020.	modalities were included. The interventions identified include: contingency management, cognitive behavioural therapy, acupuncture, antidepressants, dopamine agonists, antipsychotics, anticonvulsants, disulfiram, opioid agonists, N-Acetylcysteine, and psychostimulants. There was sufficient evidence to support the efficacy of contingency management programs for treatment of stimulant use disorder. Psychostimulants, n-acetylcysteine, opioid agonist therapy, disulfiram and antidepressant pharmacological interventions were found to have insufficient evidence to support or discount their use. Results of this review do not support the use of all other treatment options. Conclusions: The results of this review supports the use of contingency management interventions for the treatment of stimulant use disorder. Although evidence to date is insufficient to support the clinical use of psychostimulants, our results demonstrate potential for future research in this area. Given the urgent need for effective pharmacological treatments for stimulant use disorder, high-quality primary research focused on the role of psychostimulant medications for the treatment of stimulant use disorder is needed.
Siefried KJ	2020	Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. CNS Drugs. 2020 Apr;34(4):337-365. doi: 10.1007/s40263-020-00711-x.	Background: Stimulant drugs are second only to cannabis as the most widely used class of illicit drug globally, accounting for 68 million past-year consumers. Dependence on amphetamines (AMPH) or methamphetamine (MA) is a growing global concern. Yet, there is no established pharmacotherapy for AMPH/MA dependence. A comprehensive assessment of the research literature on pharmacotherapy for AMPH/MA dependence may inform treatment guidelines and future research directions. Methods: We systematically reviewed the peer-reviewed literature via the electronic databases PubMed, EMBASE, CINAHL and SCOPUS for randomised controlled trials reported in the English language examining a pharmacological treatment for AMPH/MA dependence or use disorder. We included all studies published to 19 June 2019. The selected studies were evaluated for design; methodology; inclusion and exclusion criteria; sample size; pharmacological and (if included) psychosocial interventions; length of follow-up and follow-up schedules; outcome variables and measures; results; overall conclusions

			and risk of bias. Outcome measures were any reported impact of treatment related to AMPH/MA use. Results: Our search returned 43 studies that met our criteria, collectively enrolling 4065 participants and reporting on 23 individual pharmacotherapies, alone or in combination. Disparate outcomes and measures (n=55 for the primary outcomes) across studies did not allow for meta-analyses. Some studies demonstrated mixed or weak positive signals (often in defined populations, e.g. men who have sex with men), with some variation in efficacy signals dependent on baseline frequency of AMPH/MA use. The most consistent positive findings have been demonstrated with stimulant agonist treatment (dexamphetamine and methylphenidate), naltrexone and topiramate. Less consistent benefits have been shown with the antidepressants bupropion and mirtazapine, the glutamatergic agent riluzole and the corticotropin releasing factor (CRF-1) antagonist pexacerfont; whilst in general, antidepressant medications (e.g. selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs]) have not been effective in reducing AMPH/MA use. Conclusions: No pharmacotherapy yielded convincing results for the treatment of AMPH/MA dependence; mostly studies were underpowered and had low treatment completion rates. However, there were positive signals from several agents that warrant further investigation in larger scale studies; agonist therapies show promise. Common outcome measures should include change in use days. Future research must address the heterogeneity of AMPH/MA dependence (e.g. coexisting conditions, severity of disorder, differences between MA and AMPH dependence) and the role of psychosocial intervention.
Singh M	2016	Singh M, Keer D, Klimas J, Wood E, Werb D. Topiramate for cocaine dependence: a	Aims: To assess the efficacy of topiramate in treating cocaine use disorder (i.e. retention, efficacy, safety and craving re-duction) through a systematic review and meta-analysis. Methods: We searched six scientific databases from inception to 23 December 2014 with no date limits. Data were reviewed, extracted and analysed systematically. Studies were included if they were peer-reviewed randomized control trials with participants meeting

		systematic review and meta-analysis of randomized controlled trials. Addiction. 2016 Aug;111(8):1337-46. doi: 10.1111/add.13328. Epub 2016 Apr 1.	diagnostic criteria for cocaine dependence or cocaine use disorder, with the treatment arm involving topiramate with or without psychosocial intervention, and the control arm involving no intervention or psychosocial intervention with or without placebo. A random-effects meta-analytical model was computed. Results: Five studies met inclusion criteria (n =518). Topiramate was compared with placebo (four studies) and no medication (one study). In a meta-analysis, we observed no significant differences between topiramate and placebo in improving treatment retention risk ratio (RR) = 0.85; 95% confidence interval (CI) = 0.60–1.22, P = 0.38. However, compared with a placebo, use of topiramate was associated with increased continuous abstinence in two of five studies (RR = 2.43; 95% CI = 1.31–4.53, P = 0.005). No differences were observed in frequency of adverse effects reported between topiramate and placebo (RR = 1.06; 95% CI = 0.91–1.23, P =0.48). Topiramate was associated significantly (P < 0.05) with a reduction in craving in only one of five studies. Conclusions: Evidence does not currently support the use of topiramate to improve treatment retention for cocaine use disorder, although it may extend cocaine abstinence with a similar risk of adverse events compared with placebo
Stuart AM	2020	Stuart AM, Baker AL, Denham AMJ, Lee NK, Hall A, Oldmeadow C, Dunlop A, Bowman J, McCarter K. Psychological treatment for methamphetamine use and associated psychiatric symptom outcomes: A	Background: Regular methamphetamine use is associated with increased rates of psychiatric symptoms. Although there has been a substantial body of research reporting on the effectiveness of psychological treatments for reducing methamphetamine use, there is a paucity of research examining the effects of these treatments on co-occurring psychiatric symptoms. We addressed this gap by undertaking a systematic review of the evidence of the effectiveness of psychological treatments for methamphetamine use on psychiatric symptom outcomes in randomized controlled trials. Methods: A narrative synthesis of studies was conducted following the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement to inform methodology. Eight electronic peer-reviewed databases were searched. Ten eligible studies were assessed. Results: Most studies found an overall reduction in levels of methamphetamine use and

		systematic review. J Subst Abuse Treat. 2020 Feb;109:61-79. doi: 10.1016/j.jsat.2019.09.005. Epub 2019 Oct 5.	psychiatric symptoms among samples as a whole. Although brief interventions were effective, there is evidence that more intensive interventions have greater impact on methamphetamine use and/or psychiatric symptomatology. Intervention attendance was variable. Conclusions: The evidence suggests that a variety of psychological treatments are effective in reducing levels of methamphetamine use and improving psychiatric symptoms. Future research should consider how psychological treatments could maximize outcomes in the co-occurring domains of methamphetamine use and psychiatric symptoms, with increasing treatment attendance as a focus
Tardelli VS	2020	Tardelli VS, Bisaga A, Arcadepani FB, Gerra G, Levin FR, Fidalgo TM. Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis. Psychopharmacology (Berl). 2020 Aug;237(8):2233-2255. doi: 10.1007/s00213-020-05563-3. Epub 2020 Jun 29.	Rationale: Agonist-based pharmacologic intervention is an accepted approach in treatment of opioid and tobacco use disorders. Objectives: We conducted a systematic review and meta-analysis to evaluate usefulness of an agonist approach as treatment of (psycho)stimulant use disorder (PSUD). Methods: We reviewed PubMed/Medline, LILACS, and ClinicalTrials.gov databases searching for randomized, double-blind, placebo-controlled, parallel-design studies evaluating outcomes of individuals treated for cocaine- or amphetamine-type substance use disorder. We combined results of all trials that included the following prescription psychostimulants (PPs): modafinil, methylphenidate, or amphetamines (mixed amphetamine salts, lisdexamphetamine, and dextroamphetamine). The combined sample consisted of 2889 patients. Outcomes of interest included the following: drug abstinence (defined as 2–3 weeks of sustained abstinence and the average maximum days of consecutive abstinence), percentage of drug-negative urine tests across trial, and retention in treatment. We conducted random-effects meta-analyses and assessed quality of evidence using the GRADE system. Results: Thirty-eight trials were included. Treatment with PPs increases rates of sustained abstinence [risk ratio (RR) = 1.45, 95% confidence interval (CI) = (1.10, 1.92)] and duration of abstinence [mean difference (MD) = 3.34, 95% CI = (1.06, 5.62)] in patients with PSUD, particularly those with cocaine use disorder (very low-quality evidence).

			Prescription amphetamines were particularly efficacious in promoting sustained abstinence in patients with cocaine use disorder [RR = 2.44, 95% CI = (1.66, 3.58)], and higher doses of PPs were particularly efficacious for treatment of cocaine use disorder [RR = 1.95, 95% CI = (1.38, 2.77)] (moderate quality evidence). Treatment with prescription amphetamines also yielded more cocaine-negative urines [MD = 8.37%, 95% CI = (3.75, 12.98)]. There was no effect of PPs on the retention in treatment. Conclusion: Prescription psychostimulants, particularly prescription amphetamines given in robust doses, have a clinically significant beneficial effect to promote abstinence in the treatment of individuals with PSUD, specifically the population with cocaine use disorder.

Table S5 Reviews on treating opioid dependence and reducing opioid-related deaths

First author	Year	Citation	Abstract
Ainscough TS	2017	Ainscough TS, McNeill A, Strang J, Calder R, Brose LS. Contingency Management interventions for non-prescribed drug use during treatment for opiate addiction: A systematic review and meta-analysis. Drug Alcohol Depend. 2017 Sep 1;178:318-339. doi: 10.1016/j.drugalcdep.2017.05.028. Epub 2017 Jun 24.	Background and aims: Use of non-prescribed drugs during treatment for opiate addiction reduces treatment success, creating a need for effective interventions. This review aimed to assess the efficacy of contingency management, a behavioural treatment that uses rewards to encourage desired behaviours, for treating non-prescribed drug use during opiate addiction treatment. Methods: A systematic search of the databases Embase, PsychInfo, PsychArticles and Medline from inception to March 2015 was performed. Random effects meta-analysis tested the use of contingency management to treat the use of drugs during opiate addiction treatment, using either longest duration of abstinence (LDA) or percentage of negative samples (PNS). Random effects moderator analyses were performed for six potential moderators: drug targeted for intervention, decade in which the study was carried out, study quality, intervention duration, type of reinforcer, and form of opiate treatment. Results: The search returned 3860 papers; 22 studies met inclusion criteria and were meta-analysed. Follow-up data was only available for three studies, so all analyses used end of treatment data. Contingency management performed significantly better than control in reducing drug use measured using LDA (d=0.57, 95% CI: 0.42-0.72) or PNS (d=0.41) (95% CI: 0.28-0.54). This was true for all drugs other than opiates. The only significant moderator was drug targeted (LDA: Q=10.75, p=0.03). Conclusion: Contingency management appears to be efficacious for treating most drug use during treatment for opiate addiction. Further research is required to ascertain the full effects of moderating variables, and longer term effects.
Amato L	2011	Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance	Background: Maintenance treatments are effective in retaining patients in treatment and suppressing heroin use. Questions remain regarding the efficacy of additional psychosocial services. Objectives: To evaluate the effectiveness of any psychosocial plus any agonist maintenance treatment versus standard agonist treatment for opiate dependence

		treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD004147. doi: 10.1002/14651858.CD004147.pub4.	Search methods: We searched the Cochrane Drugs and Alcohol Group trials register (June 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 6, 2011), PUBMED (1996 to 2011); EMBASE (January 1980 to 2011); CINAHL (January 2003 to 2011); PsycINFO (1985 to 2003) and reference list of articles. Selection criteria: Randomised controlled trials and controlled clinical trial comparing any psychosocial plus any agonist with any agonist alone for opiate dependence. Data collection and analysis: Two authors independently assessed trial quality and extracted data. Main results: 35 studies, 4319 participants, were included. These studies considered thirteen different psychosocial interventions. Comparing any psychosocial plus any maintenance pharmacological treatment to standard maintenance treatment, results do not show benefit for retention in treatment, 27 studies, 3124 participants, RR 1.03 (95% CI 0.98 to 1.07), abstinence by opiate during the treatment, 8 studies, 1002 participants, RR 1.12 (95% CI 0.92 to 1.37), compliance, three studies, MD 0.43 (95% CI -0.05 to 0.92), psychiatric symptoms, 3 studies, MD 0.02 (-0.28 to 0.31), depression, 3 studies, MD -1.70 (95% CI -3.91 to 0.51) and results at the end of follow up as number of participants still in treatment, 3 studies, 250 participants, RR 0.90 (95% CI 0.77 to 1.07) and participants abstinent by opioid, 3 studies, 181 participants, RR 1.15 (95% CI 0.98 to 1.36). Comparing the different psychosocial approaches, results are never statistically significant for all the comparisons and outcomes. Authors' conclusions: For the considered outcomes, it seems that adding any psychosocial support to standard maintenance treatments do not add additional benefits. Data do not show differences also for contingency approaches, contrary to all expectations. Duration of the studies was too short to analyse relevant outcomes such as mortality. It should be noted that the control intervention used in the studies included in the review on maintenance treatments, is a program that routinely offers counselling sessions in addition to methadone; thus the review, actually, did not evaluate the question of whether any ancillary psychosocial intervention is needed when methadone maintenance is provided,

			but the narrower question of whether a specific more structured intervention provides any additional benefit to a standard psychosocial support. These interventions probably can be measured and evaluated by employing diverse criteria for evaluating treatment outcomes, aimed to rigorously assess changes in emotional, interpersonal, vocational and physical health areas of life functioning.
Amato L	2011	Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database Syst Rev. 2011 Sep 7;(9):CD005031. doi: 10.1002/14651858.CD005031.pub4.	Background: Different pharmacological approaches aimed at opioid detoxification are effective. Nevertheless a majority of patients relapse to heroin use, and relapses are a substantial problem in the rehabilitation of heroin users. Some studies have suggested that the sorts of symptoms which are most distressing to addicts during detoxification are psychological rather than physiological symptoms associated with the withdrawal syndrome. Objectives: To evaluate the effectiveness of any psychosocial plus any pharmacological interventions versus any pharmacological alone for opioid detoxification, in helping patients to complete the treatment, reduce the use of substances and improve health and social status. Search methods: We searched the Cochrane Drugs and Alcohol Group trials register (June 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 6, 2011), PUBMED (1996 to June 2011); EMBASE (January 1980 to June 2011); CINAHL (January 2003 to June 2008); PsycINFO (1985 to April 2003) and reference list of articles. Selection criteria: Randomised controlled trials and controlled clinical trial which focus on any psychosocial associated with any pharmacological intervention aimed at opioid detoxification. People less than 18 years of age and pregnant women were excluded. Data collection and analysis: Two authors independently assessed trials quality and extracted data. Main results: Eleven studies, 1592 participants, fulfilled the criteria of inclusion and were included in the review. The studies considered five different psychosocial interventions and two pharmacological treatments (methadone and buprenorphine). Compared to any

			pharmacological treatment alone, the association of any psychosocial with any pharmacological was shown to significantly reduce dropouts RR 0.71 (95%CI 0.59 to 0.85), use of opiate during the treatment, RR 0.82 (95% CI 0.71 to 0.93), at follow up RR 0.66 (95% IC 0.53 to 0.82) and clinical absences during the treatment RR 0.48 (95%CI 0.38 to 0.59). Moreover, with the evidence currently available, there are no data supporting a single psychosocial approach. Authors' conclusions: Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, use of opiate, participants abstinent at follow-up and clinical attendance. The evidence produced by this review is limited due to the small number of participants included in the studies, the heterogeneity of the assessment or the lack of detailed outcome information that prevented the possibility of cumulative analysis for several outcomes. Nevertheless it seems desirable to develop adjunct psychosocial approaches that might make detoxification more effective.
Amato L	2013	Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev. 2013 Feb 28;2013(2):CD003409. doi: 10.1002/14651858.CD003409.pub4.	Background: The evidence of tapered methadone's efficacy in managing opioid withdrawal has been systematically evaluated in the previous version of this review that needs to be updated Objectives: To evaluate the effectiveness of tapered methadone compared with other detoxification treatments and placebo in managing opioid withdrawal on completion of detoxification and relapse rate. Search methods: We searched: Cochrane Central Register of Controlled Trials (The Cochrane Library 2012, Issue 4), PubMed (January 1966 to May 2012), EMBASE (January 1988 to May 2012), CINAHL (2003-December 2007), PsycINFO(January 1985 to December 2004),reference lists of articles. Selection criteria: All randomised controlled trials that focused on the use of tapered methadone versus all other pharmacological detoxification treatments or placebo for the treatment of opiate withdrawal. Data collection and analysis: Two review authors assessed the included studies. Any

			doubts about how to rate the studies were resolved by discussion with a third review author. Study quality was assessed according to the criteria indicated in the Cochrane Handbook for Systematic Reviews of Interventions. Main results: Twenty-three trials involving 2467 people were included. Comparing methadone versus any other pharmacological treatment, we observed no clinical difference between the two treatments in terms of completion of treatment, 16 studies 1381 participants, risk ratio RR) 1.08 (95% confidence interval (CI) 0.97 to 1.21); number of participants abstinent at follow-up, three studies, 386 participants RR 0.98 (95% CI 0.70 to 1.37); degree of discomfort for withdrawal symptoms and adverse events, although… Authors' conclusions: Data from literature are hardly comparable; programs vary widely with regard to the assessment of outcome measures, impairing the application of meta-analysis. The studies included in this review confirm that slow tapering with temporary substitution of long- acting opioids, can reduce withdrawal severity. Nevertheless, the majority of patients relapsed to heroin use. It was impossible to pool data for the last two outcomes. These results were confirmed also when we considered the single comparisons: methadone with: adrenergic agonists (11 studies), other opioid agonists (eight studies), anxiolytic (two studies), paiduyangsheng (one study). Comparing methadone with placebo (two studies) more severe withdrawal and more drop-outs were found in the placebo group. The results indicate that the medications used in the included studies are similar in terms of overall effectiveness, although symptoms experienced by participants differed according to the medication used and the program adopted. Authors' conclusions Data from literature are hardly comparable; programs vary widely with regard to the assessment of outcome measures, impairing the application of meta-analysis. The studies included in this review confirm that slow tapering with temporary substitution of long- acting opioids, can reduce withdrawal severity. Nevertheless, the majority of patients relapsed to heroin use.
Bahji A	2019	Bahji A, Cheng B, Gray S, Stuart H.	Introduction: Opioid agonist therapies are effective medications that can greatly improve the quality of life of individuals with opioid use disorder. However, there is significant

		Reduction in mortality risk with opioid agonist therapy: a systematic review and meta-analysis. Acta Psychiatr Scand. 2019 Oct;140(4):313-339. doi: 10.1111/acps.13088.	uncertainty about the risks of cause-specific mortality in and out of treatment. Objective: This systematic review and meta-analysis explored the association between methadone and buprenorphine with cause-specific mortality among opioid-dependent persons. Methods: We searched six online databases to identify relevant cohort studies, calculating all-cause and overdose-specific mortality rates during periods in and out of treatment. We pooled mortality estimates using multivariate random effects meta-analysis of the crude mortality rate per 1000 person-years of follow-up as well as relative risks comparing mortality in vs. out of treatment. Results: A total of 32 cohort studies (representing 150 235 participants,805 423.6 person-years, and 9112 deaths) met eligibility criteria. Crude mortality rates were substantially higher among methadone cohorts than buprenorphine cohorts. Relative risk reduction was substantially higher with methadone relative to buprenorphine when time in-treatment was compared to time out-of-treatment. Furthermore, the greatest mortality reduction was conferred during the first 4 weeks of treatment. Mortality estimates were substantially heterogeneous and varied significantly by country, region, and by the nature of the treatment provider. Conclusion: Precautions are necessary for the safer implementation of opioid agonist therapy, including baseline assessment s of opioid
Carney T	2020	Carney T, Van Hout MC, Norman I, Dada S, Siegfried N, Parry CD. Dihydrocodeine for detoxification and maintenance treatment in individuals with opiate use disorders. Cochrane Database Syst Rev. 2020 Feb	Background: Medical treatment and detoxification from opiate disorders includes oral administration of opioid agonists. Dihydrocodeine (DHC) substitution treatment is typically low threshold and therefore has the capacity to reach wider groups of opiate users. Decisions to prescribe DHC to patients with less severe opiate disorders centre on its perceived safety, reduced toxicity, shorter half-life and more rapid onset of action, and potential retention of patients. This review set out to investigate the effects of DHC in comparison to other pharmaceutical opioids and placebos in the detoxification and substitution of individuals with opiate use disorders. Objectives: To investigate the effectiveness of DHC in reducing illicit opiate use and other health-related outcomes among adults compared to other drugs or placebos used for detoxification or substitution therapy.

		18;2(2):CD012254. doi: 10.1002/14651858.CD012254.pub2.	Search methods: In February 2019 we searched Cochrane Drugs and Alcohol's Specialised Register, CENTRAL, PubMed, Embase and Web of Science. We also searched for ongoing and unpublished studies via ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and Trialsjournal.com. All searches included non-English language literature. We hand-searched references of topic-related systematic reviews and the included studies. Selection criteria: We included randomised controlled trials that evaluated the effect of DHC for detoxification and maintenance substitution therapy for adolescent (aged 15 years and older) and adult illicit opiate users. The primary outcomes were abstinence from illicit opiate use following detoxification or maintenance therapy measured by self-report or urinalysis. The secondary outcomes were treatment retention and other health and behaviour outcomes. Data collection and analysis: We followed the standard methodological procedures that are outlined by Cochrane. This includes the GRADE approach to appraise the quality of evidence. Main results: We included three trials (in five articles) with 385 opiate-using participants that measured outcomes at different follow-up periods in this review. Two studies with 150 individuals compared DHC with buprenorphine for detoxification, and one study with 235 participants compared DHC to methadone for maintenance substitution therapy. We downgraded the quality of evidence mainly due to risk of bias and imprecision. For the two studies that compared DHC to buprenorphine, we found low-quality evidence of no significant difference between DHC and buprenorphine for detoxification at six-month follow-up (risk ratio (RR) 0.59, 95% confidence interval (CI) 0.25 to 1.39; P = 0.23) in the meta-analysis for the primary outcome of abstinence from illicit opiates. Similarly, low-quality evidence indicated no difference for treatment retention (RR 1.29, 95% CI 0.99 to 1.68; P = 0.06). In the single trial that compared DHC to methadone for maintenance substitution therapy, the evidence was also of low quality, and there may be no difference in effects between DHC and

			methadone for reported abstinence from illicit opiates (mean difference (MD) −0.01, 95% CI −0.31 to 0.29). For treatment retention at six months' follow-up in this single trial, the RR calculated with an intention-to-treat analysis also indicated that there may be no difference between DHC and methadone (RR 1.04, 95% CI 0.94 to 1.16). The studies that compared DHC to buprenorphine reported no serious adverse events, while the DHC versus methadone study reported one death due to methadone overdose. Authors' conclusions: We found low-quality evidence that DHC may be no more effective than other commonly used pharmacological interventions in reducing illicit opiate use. It is therefore premature to make any conclusive statements about the effectiveness of DHC, and it is suggested that further high-quality studies are conducted, especially in low- to middle-income countries.
Chou R	2020	Chou R, Dana T, Blazina I, Grusing S, Fu R, Bougatsos C. Interventions for Unhealthy Drug Use—Supplemental Report: A Systematic Review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020 Jun. Report No.: 19-05255-EF-2.	Background: A U.S. Preventive Services Task Force (USPSTF) report found no consistent evidence that counseling interventions are effective at reducing drug use or improving other health outcomes in populations whose drug use was identified through primary care-based screening with questions about drug use or drug-related risks (i.e., “screen-detected populations”). Evidence from studies of persons seeking or referred for treatment for substance use or with clinical signs or symptoms of substance use (i.e., “treatment-seeking populations”) might also be useful for informing assessments regarding screening in primary care settings. Purpose: This report updates a 2008 USPSTF report on screening for illicit drug use and supplements an updated USPSTF report on screening for any drug use, focusing on the benefits and harms of pharmacotherapy and psychosocial interventions for persons whose drug use was identified when seeking substance use treatment, when presenting with signs or symptoms of drug use, when screened for drug use in primary care or other settings with questions about drug use or drug-related risks, or other means. Data Sources: The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Ovid MEDLINE, Embase, and PsycINFO from inception to September 2018; surveillance for new literature was conducted through November 22,

			2019. Study Selection: We included trials of Food and Drug Administration (FDA)-approved pharmacotherapies for opioid use disorder (methadone, buprenorphine, and naltrexone) and trials of psychosocial interventions for persons engaging in opioid, stimulant, cannabis, and mixed drug or polysubstance use. We also included trials of pre-emptive prescribing of naloxone in primary care settings as a rescue medication for opioid-related overdose. Trials compared included interventions against placebo, a minimal intervention, waitlist control, or usual care, and evaluated outcomes at ≥3 months for drug use or other risky behaviors; health, social, and legal consequences of drug use; or harms of treatment. Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF. Data Synthesis (Results): We included a total of 71 trials, with 19 trials of pharmacotherapies and 52 trials of psychosocial interventions. All trials of pharmacotherapies and 25 trials of psychosocial interventions were conducted in treatment-seeking populations. Psychosocial interventions commonly incorporated cognitive-behavioral or motivational interventions and ranged from brief interventions consisting of one or two sessions of no more than one hour to multiple treatment sessions over weeks or months. In most pharmacotherapy trials, drug use counseling was provided to all patients. No study evaluated benefits or harms of preemptive naloxone prescribed in primary care settings versus placebo or no naloxone as a rescue medication for opioid-related overdose. In treatment-seeking populations with opioid use disorder, naltrexone (12 trials; relative risk [RR] 0.73, 95% confidence interval [CI] 0.62 to 0.85; number needed to treat [NNT] 5.3) and opioid agonist therapy with methadone or buprenorphine (4 trials; RR 0.75, 95% CI 0.59 to 0.82; NNT 2.9) were associated with decreased risk of drug use relapse compared with placebo or no pharmacotherapy. Naltrexone and methadone/buprenorphine therapy were also associated with increased likelihood of

			retention in substance use treatment (9 trials; RR 1.71, 95% CI 1.13 to 2.49; NNT 6.7 and 7 trials; RR 2.58, 95% CI 1.78 to 4.59; NNT 2.6; respectively). Evidence on harms of pharmacotherapies was limited, but indicated no increased risk of serious adverse events. Psychosocial interventions were associated with increased likelihood of abstinence from drug use versus control conditions at 3 to 4 months (15 trials, RR 1.60, 95% CI 1.24 to 2.13; NNT 11) and at 6 to 12 months (14 trials; RR 1.25, 95% CI 1.11 to 1.52; NNT 17), based on trials primarily conducted in treatment-seeking populations. Psychosocial interventions were also associated with a greater decrease versus control conditions in the number of drug use days (19 trials; mean difference −0.49 day in the last 7 days, 95% CI −0.85 to −0.13) and a small but statistically significant greater decrease in drug use severity (16 trials; standard mean difference −0.18, 95% CI −0.32 to −0.05) at 3- to 4-month followup. There was no difference between psychosocial interventions versus controls on drug use days or severity at longer (6 to 12 month) followup. Effects of psychosocial interventions were generally stronger in trials of treatment-seeking than screen-detected populations, trials that evaluated cannabis use than other types of drug use, and trials of more intensive than brief interventions. Few trials evaluated effects of psychosocial interventions for opioid or stimulant use, and estimates were imprecise. Limitations: Limitations included restriction to English-language articles, statistical heterogeneity in pooled analyses, and little evidence on drug-related health, social, or legal outcomes; most trials had methodological limitations. Evidence was lacking on effectiveness of treatments for opioid use disorder related to prescription drug use or stimulant use and evidence was limited for adolescents or pregnant persons. Conclusions: Pharmacotherapy and psychosocial interventions are effective at improving drug use outcomes, but evidence of effectiveness remains primarily derived from trials conducted in treatment-seeking populations. Although the applicability of data from such trials to persons whose drug use is identified through primary care-based screening is uncertain, intervention trials that enrolled patients based on screening identified a spectrum of drug use, ranging from mild drug use to more severe, untreated disease. The

			applicability of current evidence on drug use interventions to screening might be greater for the subset of patients screened in primary care settings with severe, untreated drug use who could utilize pharmacotherapies or more intensive psychosocial interventions.
Ferri M	2011	Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. Cochrane Database Syst Rev. 2011 Dec 7;2011(12):CD003410. doi: 10.1002/14651858.CD003410.pub4.	Background: Several types of medications have been used for stabilizing heroin users: Methadone, Buprenorphine and levo-alpha-acetyl-methadol (LAAM.) The present review focuses on the prescription of heroin to heroin-dependent individuals. Objectives: To compare heroin maintenance to methadone or other substitution treatments for opioid dependence regarding: efficacy and acceptability, retaining patients in treatment, reducing the use of illicit substances, and improving health and social functioning. Search methods: A review of the Cochrane Central Register of Trials (The Cochrane Library Issue 1, 2005), MEDLINE (1966 to November 2009), EMBASE (1980 to 2005) and CINAHL until 2005 (on OVID) was conducted. Personal communications with researchers in the field of heroin prescription identified ongoing trials. Selection criteria: Randomised controlled trials of heroin maintenance treatment (alone or combined with methadone) compared with any other pharmacological treatment for heroin-dependent individuals. Data collection and analysis: Two reviewers independently assessed trial quality and extracted data. Main results: Eight studies involving 2007 patients met the inclusion criteria. Five studies compared supervised injected heroin plus flexible dosages of methadone treatment to oral methadone only and showed that heroin helps patients to remain in treatment (valid data from 4 studies, N=1388 Risk Ratio 1.44 (95%CI 1.19-1.75) heterogeneity P=0.03), and to reduce use of illicit drugs. Maintenance with supervised injected heroin has a not statistically significant protective effect on mortality (4 studies, N=1477 Risk Ratio 0.65 (95% CI 0.25-1.69) heterogeneity P=0.89), but it exposes at a greater risk of adverse events related to study medication (3 studies N=373 Risk Ratio 13.50 (95% CI 2.55-71.53) heterogeneity P=0.52). Results on criminal activity and incarceration were not possible to be pooled but where the outcome were measured results of single studies do provide

			evidence that heroin provision can reduce criminal activity and incarceration/imprisonment. Social functioning improved in all the intervention groups with heroin groups having slightly better results. If all the studies comparing heroin provision in any conditions vs any other treatment are pooled the direction of effect remain in favour of heroin. Authors' conclusions: The available evidence suggests an added value of heroin prescribed alongside flexible doses of methadone for long-term, treatment refractory, opioid users, to reach a decrease in the use of illicit substances, involvement in criminal activity and incarceration, a possible reduction in mortality; and an increase in retention in treatment. Due to the higher rate of serious adverse events, heroin prescription should remain a treatment for people who are currently or have in the past failed maintenance treatment, and it should be provided in clinical settings where proper follow-up is ensured.
Ferri M	2013	Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. Cochrane Database Syst Rev. 2013 Jun 5;(6):CD009879. doi: 10.1002/14651858.CD009879.pub2.	Background: Opioid substitution treatments are effective in retaining people in treatment and suppressing heroin use. An open question remains whether slow-release oral morphine (SROM) could represent a possible alternative for opioid-dependent people who respond poorly to other available maintenance treatments. Objectives: To evaluate the efficacy of SROM as an alternative maintenance pharmacotherapy for the treatment of opioid dependence. Search methods: We searched Cochrane Drugs and Alcohol Group's Register of Trials, Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library Issue 3, 2013), MEDLINE (January 1966 to April 2013), EMBASE (January 1980 to April 2013) and reference lists of articles. Selection criteria: Randomised controlled trials (RCTs) and quasi-randomised trials assessing efficacy of SROM compared with other maintenance treatment or no treatment. Data collection and analysis: Two review authors independently selected articles for inclusion, extracted data and assessed risk of bias of included studies. Main results: Three studies with 195 participants were included in the review. Two were cross-over trials and one was a parallel group RCT. The retention in treatment appeared superior to 80% in all the three studies (without significant

			difference with controls). Nevertheless, it has to be underlined that the studies had different durations. One lasted six months, and the other two lasted six and seven weeks. The use of opioids during SROM provision varied from lower to non-statistically or clinically different from comparison interventions, whereas there were no differences as far as the use of other substances was concerned. SROM seemed to be equal to comparison interventions for severity of dependence, or mental health/social functioning, but there was a trend for less severe opiate withdrawal symptoms in comparison with methadone (withdrawal score 2.2 vs. 4.8, P value = 0.06). Morphin using the Beschwerde-Liste (BL); P value < 0.001) and anxiety symptoms (P value = 0.008). Quality of life in people treated with SROM resulted in no significant difference or a worst outcome than in those taking methadone and buprenorphine. Other social functioning measures, such as finances, family and overall satisfaction, scored better in people maintained with the comparison substances than in those maintained with SROM. In particular, people taking methadone showed more favourable values for leisure time (5.4 vs. 3.7, P value <0.001), housing (6.1 vs. 4.7, P value < 0.023), partnerships (5.7 vs. 4.2, P value = 0.034), friend and acquaintances (5.6 vs. 4.4, P value = 0.003), mental health (5.0 vs. 3.4, P value = 0.002) and self-esteem (8.2 vs. 5.7, P value = 0.002) compared to people taking SROM; while people taking buprenorphine obtained better scores for physical health. Medical adverse events were consistently higher in people in SROM than in the comparison groups. None of the studies included people with a documented poor response to other maintenance treatment. Authors' conclusions: The present review did not identify sufficient evidence to assess the effectiveness of SROM for opioid maintenance because only three studies meeting our inclusion criteria have been identified. Two studies suggested a possible reduction of opioid use in people taking SROM. In another study, the use of SROM was associated with fewer depressive symptoms. Retention in treatment was not significantly different among compared interventions while the adverse effects were more frequent with the

			people given SROM. was generally well tolerated and was preferred by a proportion of participants (seven of nine people in one study). Morphine appeared to reduce cravings, depressive symptoms (measured using the Beck Depression Inventory; P value < 0.001), physical complaints (measured
Fink DS	2018	Fink DS, Schleimer JP, Sarvet A, Grover KK, Delcher C, Castillo-Carniglia A, Kim JH, Rivera-Aguirre AE, Henry SG, Martins SS, Cerdá M. Association Between Prescription Drug Monitoring Programs and Nonfatal and Fatal Drug Overdoses: A Systematic Review. Ann Intern Med. 2018 Jun 5;168(11):783-790. doi: 10.7326/M17-3074. Epub 2018 May 8.	Background—Prescription drug monitoring programs (PDMPs) are a key component of the president's Prescription Drug Abuse Prevention Plan to prevent opioid overdoses in the United States. Purpose—To examine whether PDMP implementation is associated with changes in nonfatal and fatal overdoses; identify features of programs differentially associated with those outcomes; and investigate any potential unintended consequences of the programs. Data Sources—Eligible publications from MEDLINE, Current Contents Connect (Clarivate Analytics), Science Citation Index (Clarivate Analytics), Social Sciences Citation Index (Clarivate Analytics), and ProQuest Dissertations indexed through 27 December 2017 and additional studies from reference lists. Study Selection—Observational studies (published in English) from U.S. states that examined an association between PDMP implementation and nonfatal or fatal overdoses. Data Extraction—2 investigators independently extracted data from and rated the risk of bias (ROB) of studies by using established criteria. Consensus determinations involving all investigators were used to grade strength of evidence for each intervention. Data Synthesis—Of 2661 records, 17 articles met the inclusion criteria. These articles examined PDMP implementation only (n = 8), program features only (n = 2), PDMP implementation and program features (n = 5), PDMP implementation with mandated provider review combined with pain clinic laws (n = 1), and PDMP robustness (n = 1). Evidence from 3 studies was insufficient to draw conclusions regarding an association between PDMP implementation and nonfatal overdoses. Low-strength evidence from 10 studies suggested a reduction in fatal overdoses with PDMP implementation. Program features associated with a decrease in overdose deaths included mandatory provider

			review, provider authorization to access PDMP data, frequency of reports, and monitoring of non-scheduled drugs. Three of 6 studies found an increase in heroin overdoses after PDMP implementation. Limitation—Few studies, high ROB, and heterogeneous analytic methods and outcome measurement. Conclusion—Evidence that PDMP implementation either increases or decreases nonfatal or fatal overdoses is largely insufficient, as is evidence regarding positive associations between specific administrative features and successful programs. Some evidence showed unintended consequences. Research is needed to identify a set of “best practices” and complementary initiatives to address these consequences.
Gowing L	2010	Gowing L, Ali R, White JM. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Cochrane Database Syst Rev. 2010 Jan 20;2010(1):CD002022. doi: 10.1002/14651858.CD002022.pub3.	Background: Withdrawal (detoxification) is necessary prior to drug-free treatment or as the end point of long-term substitution treatment. Objectives: To assess the effectiveness of opioid antagonists to induce opioid withdrawal with concomitant heavy sedation or anaesthesia, in terms of withdrawal signs and symptoms, completion of treatment and adverse effects. Search methods: We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2009), Medline (January 1966 to 11 August 2009), Embase (January 1985 to 2009 Week 32), PsycINFO (1967 to July 2009), and reference lists of articles. Selection criteria: Controlled studies of antagonist-induced withdrawal under heavy sedation or anaesthesia in opioid-dependent participants compared with other approaches, or a different regime of anaesthesia-based antagonist-induced withdrawal. Data collection and analysis: One reviewer assessed studies for inclusion, undertook data extraction and assessed quality. Inclusion decisions and the overall process were confirmed by consultation between all authors. Main results: Nine studies (eight randomised controlled trials) involving 1109 participants

			met the inclusion criteria for the review. Antagonist-induced withdrawal is more intense but less prolonged than withdrawal managed with reducing doses of methadone, and doses of naltrexone sufficient for blockade of opioid effects can be established significantly more quickly with antagonist-induced withdrawal than withdrawal managed with clonidine and symptomatic medications. The level of sedation does not affect the intensity and duration of withdrawal, although the duration of anaesthesia may influence withdrawal severity. There is a significantly greater risk of adverse events with heavy, compared to light, sedation (RR 3.21, 95% CI 1.13 to 9.12, P = 0.03) and probably with this approach compared to other forms of detoxification. Authors' conclusions: Heavy sedation compared to light sedation does not confer additional benefits in terms of less severe withdrawal or increased rates of commencement on naltrexone maintenance treatment. Given that the adverse events are potentially life-threatening, the value of antagonist-induced withdrawal under heavy sedation or anaesthesia is not supported. The high cost of anaesthesia-based approaches, both in monetary terms and use of scarce intensive care resources, suggest that this form of treatment should not be pursued.
Gowing L	2014	Gowing L, Farrell MF, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2014 Mar 31;(3):CD002024. doi: 10.1002/14651858.CD002024.pub4.	Background: Withdrawal is a necessary step prior to drug-free treatment or as the endpoint of long-term substitution treatment. Objectives: To assess the effectiveness of interventions involving the use of alpha2-adrenergic agonists compared with placebo, reducing doses of methadone, symptomatic medications or with comparison of different alpha2-adrenergic agonists, for the management of the acute phase of opioid withdrawal. Outcomes included the intensity of signs and symptoms and overall withdrawal syndrome experienced, duration of treatment, occurrence of adverse effects and completion of treatment. Search methods: We searched the Cochrane Central Register of Controlled Trials (Issue 7, 2013), MEDLINE (1946 to July week 4, 2013), EMBASE (January 1985 to August week 1, 2013), PsycINFO (1806 to July week 5, 2013) and reference lists of articles. We also contacted manufacturers in the field.

			Selection criteria: Randomised controlled trials comparing alpha2-adrenergic agonists (clonidine, lofexidine, guanfacine, tizanidine) with reducing doses of methadone, symptomatic medications or placebo, or comparing different alpha2-adrenergic agonists to modify the signs and symptoms of withdrawal in participants who were opioid dependent. Data collection and analysis One review author assessed studies for inclusion and undertook data extraction. All review authors decided on inclusion and confirmed the overall process. Main results: We included 25 randomised controlled trials, involving 1668 participants. Five studies compared a treatment regimen based on an alpha2adrenergic agonist with placebo, 12 with a regimen based on reducing doses of methadone, four with symptomatic medications and five compared different alpha2-adrenergic agonists. Alpha2-adrenergic agonists were more effective than placebo in ameliorating withdrawal in terms of the likelihood of severe withdrawal (risk ratio (RR) 0.32, 95% confidence interval (CI) 0.18 to 0.57, 3 studies, 148 participants). Completion of treatment was significantly more likely with alpha2-adrenergic agonists compared with placebo (RR 1.95, 95% CI 1.34 to 2.84, 3 studies, 148 participants). Alpha2-adrenergic agonists were somewhat less effective than reducing doses of methadone in ameliorating withdrawal symptoms, as measured by the likelihood of severe withdrawal (RR 1.18, 95% CI 0.81 to 1.73, 5 studies, 340 participants), peak withdrawal score (standardised mean difference (SMD) 0.22, 95% CI -0.02 to 0.46, 2 studies, 263 participants) and overall withdrawal severity (SMD 0.13, 95% CI -0.24 to 0.49, 3 studies, 119 participants). These differences were not statistically significant. The signs and symptoms of withdrawal occurred and resolved earlier with alpha2-adrenergic agonists. The duration of treatment was significantly longer with reducing doses of methadone (SMD -1.07, 95% CI -1.31 to -0.83, 3 studies, 310 participants). Hypotensive or other adverse effects were significantly more likely with alpha2-adrenergic agonists (RR 1.92, 95% CI 1.19 to 3.10, 6 studies, 464 participants) but there was no significant difference in rates of completion of withdrawal treatment (RR 0.85, 95% CI 0.69 to 1.05, 9 studies, 659 participants). There were insufficient data for quantitative comparison of

			different alpha2-adrenergic agonists. Available data suggest that lofexidine does not reduce blood pressure to the same extent as clonidine, but is otherwise similar to clonidine. Authors' conclusions Clonidine and lofexidine are more effective than placebo for the management of withdrawal from heroin or methadone. No significant difference in efficacy was detected for treatment regimens based on clonidine or lofexidine, and those based on reducing doses of methadone over a period of around 10 days but methadone is associated with fewer adverse effects than clonidine, and lofexidine has a better safety profile than clonidine.
Gowing L	2016	Gowing L, Farrell M, Ali R, White JM. Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2016 May 3;2016(5):CD002024. doi: 10.1002/14651858.CD002024.pub5.	Background: Withdrawal is a necessary step prior to drug-free treatment or as the endpoint of long-term substitution treatment. Objectives: To assess the effectiveness of interventions involving the use of alpha2-adrenergic agonists compared with placebo, reducing doses of methadone, symptomatic medications, or an alpha2-adrenergic agonist regimen different to the experimental intervention, for the management of the acute phase of opioid withdrawal. Outcomes included the withdrawal syndrome experienced, duration of treatment, occurrence of adverse effects, and completion of treatment. Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1946 to November week 2, 2015), EMBASE (January 1985 to November week 2, 2015), PsycINFO (1806 to November week 2, 2015), Web of Science, and reference lists of articles. Selection criteria: Randomised controlled trials comparing alpha2-adrenergic agonists (clonidine, lofexidine, guanfacine, tizanidine) with reducing doses of methadone, symptomatic medications or placebo, or comparing different alpha2-adrenergic agonists to modify the signs and symptoms of withdrawal in participants who were opioid dependent. Data collection and analysis: We used standard methodological procedures expected by The Cochrane Collaboration. Main results: We included 26 randomised controlled trials involving 1728 participants. Six studies compared an alpha2-adrenergic agonist with placebo, 12 with reducing doses of methadone, four with symptomatic medications, and five compared different alpha2-adrenergic agonists. We assessed 10 studies as having a high risk of bias in at least one of the methodological

			domains that were considered. We found moderate-quality evidence that alpha2-adrenergic agonists were more effective than placebo in ameliorating withdrawal in terms of the likelihood of severe withdrawal (risk ratio (RR) 0.32, 95% confidence interval (CI) 0.18 to 0.57; 3 studies; 148 participants). We found moderate-quality evidence that completion of treatment was significantly more likely with alpha2-adrenergic agonists compared with placebo (RR 1.95, 95% CI 1.34 to 2.84; 3 studies; 148 participants).Peak withdrawal severity may be greater with alpha2-adrenergic agonists than with reducing doses of methadone, as measured by the likelihood of severe withdrawal (RR 1.18, 95% CI 0.81 to 1.73; 5 studies; 340 participants; low quality), and peak withdrawal score (standardised mean difference (SMD) 0.22, 95% CI -0.02 to 0.46; 2 studies; 263 participants; moderate quality), but these differences were not significant and there is no significant difference in severity when considered over the entire duration of the withdrawal episode (SMD 0.13, 95% CI -0.24 to 0.49; 3 studies; 119 participants; moderate quality). The signs and symptoms of withdrawal occurred and resolved earlier with alpha2-adrenergic agonists. The duration of treatment was significantly longer with reducing doses of methadone (SMD -1.07, 95% CI -1.31 to -0.83; 3 studies; 310 participants; low quality). Hypotensive or other adverse effects were significantly more likely with alpha2-adrenergic agonists (RR 1.92, 95% CI 1.19 to 3.10; 6 studies; 464 participants; low quality), but there was no significant difference in rates of completion of withdrawal treatment (RR 0.85, 95% CI 0.69 to 1.05; 9 studies; 659 participants; low quality).There were insufficient data for quantitative comparison of different alpha2-adrenergic agonists. Available data suggest that lofexidine does not reduce blood pressure to the same extent as clonidine, but is otherwise similar to clonidine. Authors' conclusions: Clonidine and lofexidine are more effective than placebo for the management of withdrawal from heroin or methadone. We detected no significant difference in efficacy between treatment regimens based on clonidine or lofexidine and those based on reducing doses of methadone over a period of around 10 days, but methadone was associated with fewer adverse effects than clonidine, and lofexidine has a better safety profile than clonidine.

Gowing L	2017	Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. Cochrane Database Syst Rev. 2017 May 29;5(5):CD002021. doi: 10.1002/14651858.CD002021.pub4.	Background: Managed withdrawal is necessary prior to drug-free treatment. It may also represent the end point of long-term opioid replacement treatment. Objectives: To assess the effectiveness of opioid antagonists in combination with minimal sedation to induce withdrawal, in terms of intensity of withdrawal, adverse effects and completion of treatment. Search strategy: We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2005, which includes the Cochrane Drugs and Alcohol Group register), MEDLINE (January 1966 to August 2005), EMBASE (January 1985 to August 2005), PsycINFO (1967 to August 2005), and CINAHL (1982 to July 2005) and reference lists of articles. Selection criteria: Experimental interventions involved the use of opioid antagonists in combination with minimal sedation to manage withdrawal in opioid-dependent participants compared with other approaches or different opioid antagonist regime. Data collection and analysis: One reviewer assessed studies for inclusion and undertook data extraction and trial quality. Study authors were contacted for additional information. Main results: Nine studies (5 randomised controlled trials), involving 775 participants, met the inclusion criteria for the review. Withdrawal induced by opioid antagonists in combination with an adrenergic agonist is more intense than withdrawal managed with clonidine or lofexidine alone, but the overall severity is less. Limited data showed that antagonist-induced withdrawal may be more severe when the last opioid used was methadone rather than heroin or another short-acting opioid. Delirium may occur following the first dose of opioid antagonist, particularly with higher doses (> 25mg naltrexone). The studies included suggest there is no significant difference in rates of completion of treatment for withdrawal induced by opioid antagonists, in combination with an adrenergic agonist, compared with adrenergic agonist alone. Authors' conclusions: The use of opioid antagonists combined with alpha2 adrenergic agonists is a feasible approach to the management of opioid withdrawal. However, it is unclear whether this approach reduces the duration of withdrawal or facilitates transfer to naltrexone treatment to a greater extent than withdrawal managed primarily with an adrenergic agonist.A high level of monitoring and support is desirable for several hours following administration of opioid

			antagonists because of the possibility of vomiting, diarrhoea and delirium. Further research is required to confirm the relative effectiveness of antagonist-induced regimes, as well as variables influencing the severity of withdrawal, adverse effects, the most effective antagonist-based treatment regime, and approaches that might increase retention in subsequent naltrexone maintenance treatment.
Gowing L	2017	Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev. 2017 Feb 21;2(2):CD002025. doi: 10.1002/14651858.CD002025.pub5.	Background: Managed withdrawal is a necessary step prior to drug-free treatment or as the endpoint of substitution treatment. Objectives: To assess the effects of buprenorphine versus tapered doses of methadone, alpha2-adrenergic agonists, symptomatic medications or placebo, or different buprenorphine regimens for managing opioid withdrawal, in terms of the intensity of the withdrawal syndrome experienced, duration and completion of treatment, and adverse effects. Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 11, 2016), MEDLINE (1946 to December week 1, 2016), Embase (to 22 December 2016), PsycINFO (1806 to December week 3, 2016), and the Web of Science (to 22 December 2016) and hand-searched the reference lists of articles. Selection criteria: Randomised controlled trials of interventions using buprenorphine to modify the signs and symptoms of withdrawal in participants who were primarily opioid dependent. Comparison interventions involved reducing doses of methadone, alpha2-adrenergic agonists (clonidine or lofexidine), symptomatic medications or placebo, and different buprenorphine-based regimens. Data collection and analysis: We used standard methodological procedures expected by Cochrane. Main results We included 27 studies involving 3048 participants. The main comparators were clonidine or lofexidine (14 studies). Six studies compared buprenorphine versus methadone, and seven compared different rates of buprenorphine dose reduction. We assessed 12 studies as being at high risk of bias in at least one of seven domains of methodological quality. Six of these studies compared buprenorphine with clonidine or lofexidine and two with methadone; the other four studies compared different rates of buprenorphine dose reduction. For the comparison of buprenorphine and

			methadone in tapered doses, meta-analysis was not possible for the outcomes of intensity of withdrawal or adverse effects. However, information reported by the individual studies was suggestive of buprenorphine and methadone having similar capacity to ameliorate opioid withdrawal, without clinically significant adverse effects. The meta-analyses that were possible support a conclusion of no difference between buprenorphine and methadone in terms of average treatment duration (mean difference (MD) 1.30 days, 95% confidence interval (CI) −8.11 to 10.72; N = 82; studies = 2; low quality) or treatment completion rates (risk ratio (RR) 1.04, 95% CI 0.91 to 1.20; N = 457; studies = 5; moderate quality). Relative to clonidine or lofexidine, buprenorphine was associated with a lower average withdrawal score (indicating less severe withdrawal) during the treatment episode, with an effect size that is considered to be small to moderate (standardised mean difference (SMD) 0.43, 95% CI −0.58 to −0.28; N = 902; studies = 7; moderate quality). Patients receiving buprenorphine stayed in treatment for longer, with an effect size that is considered to be large (SMD 0.92, 95% CI 0.57 to 1.27; N = 558; studies = 5; moderate quality) and were more likely to complete withdrawal treatment (RR 1.59, 95% CI 1.23 to 2.06; N = 1264; studies = 12; moderate quality). At the same time there was no significant difference in the incidence of adverse effects, but dropout due to adverse effects may be more likely with clonidine (RR 0.20, 95% CI 0.04 to 1.15; N = 134; studies = 3; low quality). The difference in treatment completion rates translates to a number needed to treat for an additional beneficial outcome of 4 (95% CI 3 to 6), indicating that for every four people treated with buprenorphine, we can expect that one additional person will complete treatment than with clonidine or lofexidine. For studies comparing different rates of reduction of the buprenorphine dose, meta-analysis was possible only for treatment completion, with separate analyses for inpatient and outpatient settings. The results were diverse, and we assessed the quality of evidence as being very low. It remains very uncertain what effect the rate of dose taper has on treatment outcome. Authors' conclusions: Buprenorphine is more effective than clonidine or lofexidine for managing opioid withdrawal in terms of severity of withdrawal, duration of withdrawal

			treatment, and the likelihood of treatment completion. Buprenorphine and methadone appear to be equally effective, but data are limited. It remains possible that the pattern of withdrawal experienced may differ and that withdrawal symptoms may resolve more quickly with buprenorphine. It is not possible to draw any conclusions from the available evidence on the relative effectiveness of different rates of tapering the buprenorphine dose. The divergent findings of studies included in this review suggest that there may be multiple factors affecting the response to the rate of dose taper. One such factor could be whether or not the initial treatment plan includes a transition to subsequent relapse prevention treatment with naltrexone. Indeed, the use of buprenorphine to support transition to naltrexone treatment is an aspect worthy of further research. Most participants in the studies included in this review were male. None of the studies reported outcomes on the basis of sex, preventing any exploration of differences related to this variable. Consideration of sex as a factor influencing response to withdrawal treatment would be relevant research for selecting the most appropriate type of intervention for each individual.
Gregory VL Jr	2020	Gregory VL Jr, Ellis RJB. Cognitive-behavioral therapy and buprenorphine for opioid use disorder: A systematic review and meta-analysis of randomized controlled trials. Am J Drug Alcohol Abuse. 2020 Sep 2;46(5):520-530. doi: 10.1080/00952990.20	Background: Recent systematic reviews have questioned the ability of psychosocial intervention to add substantive benefit to buprenorphine therapy. Objectives: The purpose of the present meta-analysis was to test the random effects model (REM) null hypothesis that, for opioid use disorder (OUD) and opioid biological sample outcomes, the summary effect of cognitive-behavioral therapy (CBT) + buprenorphine randomized controlled trials (RCTs) = 0. Methods: A systematic review was conducted searching electronic databases and the reference lists of included studies. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria were used to guide this review and the REM meta-analysis. Results: The initial meta-analytic model (k = 4) was insignificant (REM Hedges' g =.22, Z = 1.27, p =.206, 95% CI: −0.12–0.56) and heterogeneous (I2 = 53.47). A pre-specified categorical moderator analysis explained the heterogeneity via CBT modality. Categorical

		20.1780602. Epub 2020 Sep 22.	moderator analysis (k = 4) showed non-individual CBT RCTs (k = 2) to have a REM Hedges' g summary effect of.598 (p =.006) and individual-CBT RCTs (k = 2) to have a REM Hedges' g summary effect of −0.010 (p = .936). The difference between these two subgroups was significant (Q = 5.85, df = 1, p = .016). Conclusion: The evidence cautiously suggests that for OUD, there may be some benefit to adding non-individual CBT to buprenorphine therapy.
Jarvis BP	2018	Jarvis BP, Holtyn AF, Subramaniam S, Tompkins DA, Oga EA, Bigelow GE, Silverman K. Extended-release injectable naltrexone for opioid use disorder: a systematic review. Addiction. 2018 Jul;113(7):1188-1209. doi: 10.1111/add.14180. Epub 2018 Mar 24.	Aims: To review systematically the published literature on extended-release naltrexone (XR-NTX, Vivitrol®), marketed as a once-per-month injection product to treat opioid use disorder. We addressed the following questions: (1) how successful is induction on XR-NTX; (2) what are adherence rates to XR-NTX; and (3) does XR-NTX decrease opioid use? Factors associated with these outcomes as well as overdose rates were examined. Methods: We searched PubMed and used Google Scholar for forward citation searches of peer-reviewed papers from January 2006 to June 2017. Studies that included individuals seeking treatment for opioid use disorder who were offered XR-NTX were included. Results: We identified and included 34 studies. Pooled estimates showed that XR-NTX induction success was lower in studies that included individuals that required opioid detoxification [62.6%, 95% confidence interval (CI) = 54.5–70.0%] compared with studies that included individuals already detoxified from opioids (85.0%, 95% CI = 78.0–90.1%); 44.2% (95% CI = 33.1–55.9%) of individuals took all scheduled injections of XR-NTX, which were usually six or fewer. Adherence was higher in prospective investigational studies (i.e. studies conducted in a research context according to a study protocol) compared to retrospective studies of medical records taken from routine care (6-month rates: 46.7%, 95% CI = 34.5–59.2% versus 10.5%, 95% CI = 4.6–22.4%, respectively). Compared with referral to treatment, XR-NTX reduced opioid use in adults under criminal justice supervision and when administered to inmates before release. XR-NTX reduced opioid use compared with placebo in Russian adults, but this effect was confounded by differential retention between study groups. XR-NTX showed similar efficacy to

			buprenorphine when randomization occurred after detoxification, but was inferior to buprenorphine when randomization occurred prior to detoxification. Conclusions: Many individuals intending to start extended-release naltrexone (XR-NTX) do not and most who do start XR-NTX discontinue treatment prematurely, two factors that limit its clinical utility significantly. XR-NTX appears to decrease opioid use but there are few experimental demonstrations of this effect.
Klimas J	2019	Klimas J, Gorfinkel L, Giacomuzzi SM, Ruckes C, Socías ME, Fairbairn N, Wood E. Slow release oral morphine versus methadone for the treatment of opioid use disorder. BMJ Open. 2019 Apr 2;9(4):e025799. doi: 10.1136/bmjopen-2018-025799.	Objective: To assess the efficacy of slow release oral morphine (SROM) as a treatment for opioid use disorder (OUD). Design: Systematic review and meta-analysis of randomised controlled trials (RCTs). Data sources: Three electronic databases were searched through 1 May 2018: the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE. We also searched the following electronic registers for ongoing trials: ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, Current Controlled Trials and the EU Clinical Trials Register. Eligibility criteria for selecting studies: We included RCTs of all durations, assessing the effect of SROM on measures of treatment retention, heroin use and craving in adults who met the diagnostic criteria for OUD. Data extraction and synthesis: Two independent reviewers extracted data and assessed risk of bias. Data were pooled using the random-effects model and expressed as risk ratios (RRs) or mean differences with 95% CIs. Heterogeneity was assessed ($\chi 2$ statistic) and quantified (I2 statistic) and a sensitivity analysis was undertaken to assess the impact of particular high-risk trials. Results: Among 1315 records screened and four studies reviewed, four unique randomised trials met the inclusion criteria (n=471), and compared SROM with methadone. In the meta-analysis, we observed no significant differences between SROM and methadone in improving treatment retention (RR=0.98; 95%CI: 0.94 to 1.02, p=0.34) and heroin use (RR=0.96; 95% CI: 0.61 to 1.52, p=0.86). Craving data was not amenable to meta-analysis. Available data implied no differences in adverse events, heroin, cocaine

			or benzodiazepine use. Conclusions: Meta-analysis of existing randomised trials suggests SROM may be generally equal to methadone in retaining patients in treatment and reducing heroin use while potentially resulting in less craving. The methodological quality of the included RCTs was low-to-moderate.
Lagisetty P	2017	Lagisetty P, Klasa K, Bush C, Heisler M, Chopra V, Bohnert A. Primary care models for treating opioid use disorders: What actually works? A systematic review. PLoS One. 2017 Oct 17;12(10):e0186315. doi: 10.1371/journal.pone.0186315. eCollection 2017.	Background: Primary care-based models for Medication-Assisted Treatment (MAT) have been shown to reduce mortality for Opioid Use Disorder (OUD) and have equivalent efficacy to MAT in specialty substance treatment facilities. Objective: The objective of this study is to systematically analyze current evidence-based, primary care OUD MAT interventions and identify program structures and processes associated with improved patient outcomes in order to guide future policy and implementation in primary care settings. Data sources: PubMed, EMBASE, CINAHL, and PsychInfo. Methods: We included randomized controlled or quasi experimental trials and observational studies evaluating OUD treatment in primary care settings treating adult patient populations and assessed structural domains using an established systems engineering framework. Results: We included 35 interventions (10 RCTs and 25 quasi-experimental interventions) that all tested MAT, buprenorphine or methadone, in primary care settings across 8 countries. Most included interventions used joint multi-disciplinary (specialty addiction services combined with primary care) and coordinated care by physician and non-physician provider delivery models to provide MAT. Despite large variability in reported patient outcomes, processes, and tasks/tools used, similar key design factors arose among successful programs including integrated clinical teams with support staff who were often advanced practice clinicians (nurses and pharmacists) as clinical care managers, incorporating patient “agreements,” and using home inductions to make treatment more convenient for patients and providers. Conclusions: The findings suggest that multidisciplinary and coordinated care delivery

			models are an effective strategy to implement OUD treatment and increase MAT access in primary care, but research directly comparing specific structures and processes of care models is still needed
Larney S	2014	Larney S, Gowing L, Mattick RP, Farrell M, Hall W, Degenhardt L. A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence. Drug Alcohol Rev. 2014 Mar;33(2):115-28. doi: 10.1111/dar.12095. Epub 2013 Dec 3.	Introduction and Aims: Naltrexone implants are used to treat opioid dependence, but their safety and efficacy remain poorly understood. We systematically reviewed the literature to assess the safety and efficacy of naltrexone implants for treating opioid dependence. Design and Methods: Studies were eligible if they compared naltrexone implants with another intervention or placebo. Examined outcomes were induction to treatment, retention in treatment, opioid and non-opioid use, adverse events, non-fatal overdose and mortality. Quality of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach. Data from randomised studies were combined using meta-analysis. Data from non-randomised studies were presented narratively. Results: Five randomised trials (n = 576) and four non-randomised studies (n = 8358) were eligible for review. The quality of the evidence ranged from moderate to very low. Naltrexone implants were superior to placebo implants [risk ratio (RR): 0.57; 95% confidence interval (CI) 0.48, 0.68; k = 2] and oral naltrexone (RR: 0.57; 95% CI 0.47, 0.70; k = 2) in suppressing opioid use. No difference in opioid use was observed between naltrexone implants and methadone maintenance (standardised mean difference:−0.33; 95% CI −0.93, 0.26;k = 1); however, this finding was based on low-quality evidence from one study. Discussion: The evidence on safety and efficacy of naltrexone implants is limited in quantity and quality, and the evidence has little clinical utility in settings where effective treatments for opioid dependence are used. Conclusion. Better designed research is needed to establish the safety and efficacy of naltrexone implants. Until such time, their use should be limited to clinical trials.
Ma J	2019	Ma J, Bao YP, Wang RJ, Su MF, Liu MX, Li	Opioid use disorder (OUD) is associated with a high risk of premature death. Medication-assisted treatment (MAT) is the primary treatment for opioid dependence. We

		JQ, Degenhardt L, Farrell M, Blow FC, Ilgen M, Shi J, Lu L. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. Mol Psychiatry. 2019 Dec;24(12):1868-1883. doi: 10.1038/s41380-018-0094-5. Epub 2018 Jun 22.	comprehensively assessed the effects of different MAT-related characteristics on mortality among those with OUD by a systematic review and meta-analysis. The all-cause and overdose crude mortality rates (CMRs) and relative risks (RRs) by treatment status, different type, period, and dose of medication, and retention time were pooled using random effects, subgroup analysis, and meta-regression. Thirty cohort studies involving 370,611 participants (1,378,815 person-years) were eligible in the meta-analysis. From 21 studies, the pooled all-cause CMRs were 0.92 per 100 person-years (95% CI: 0.79–1.04) while receiving MAT, 1.69 (1.47–1.91) after cessation, and 4.89 (3.54–6.23) for untreated period. Based on 16 studies, the pooled overdose CMRs were 0.24 (0.20–0.28) while receiving MAT, 0.68 (0.55–0.80) after cessation of MAT, and 2.43 (1.72–3.15) for untreated period. Compared with patients receiving MAT, untreated participants had higher risk of all-cause mortality (RR 2.56 [95% CI: 1.72–3.80]) and overdose mortality (8.10 [4.48–14.66]), and discharged participants had higher risk of all-cause death (2.33 [2.02–2.67]) and overdose death (3.09 [2.37–4.01]). The all-cause CMRs during and after opioid substitution treatment with methadone or buprenorphine were 0.93 (0.76–1.10) and 1.79 (1.47–2.10), and corresponding estimate for antagonist naltrexone treatment were 0.26 (0–0.59) and 1.97 (0–5.18), respectively. Retention in MAT of over 1-year was associated with a lower mortality rate than that with retention ≤1 year (1.62, 1.31–1.93 vs. 5.31, −0.09–10.71). Improved coverage and adherence to MAT and post-treatment follow-up are crucial to reduce the mortality. Long-acting naltrexone showed positive advantage on prevention of premature death among persons with OUD.
Mattick RP	2009	Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy	Background: Methadone maintenance was the first widely used opioid replacement therapy to treat heroin dependence, and it remains the best-researched treatment for this problem. Despite the widespread use of methadone in maintenance treatment for opioid dependence in many countries, it is a controversial treatment whose effectiveness has been disputed. Objectives: To evaluate the effects of methadone maintenance treatment (MMT)

		for opioid dependence. Cochrane Database Syst Rev 2009	compared with treatments that did not involve opioid replacement therapy (i.e., detoxification, offer of drug-free rehabilitation, placebo medication, wait-list controls) for opioid dependence. Search strategy: We searched the following databases up to Dec 2008: the Cochrane Controlled Trials Register, EMBASE, PubMED, CINAHL, Current Contents, Psychlit, CORK [www. state.vt.su/adap/cork], Alcohol and Drug Council of Australia (ADCA) [www.adca.org.au], Australian Drug Foundation (ADF-VIC) [www.adf.org.au], Centre for Education and Information on Drugs and Alcohol (CEIDA) [www.ceida.net.au], Australian Bibliographic Network (ABN), and Library of Congress databases, available NIDA monographs and the College on Problems of Drug Dependence Inc. proceedings, the reference lists of all identified studies and published reviews; authors of identified RCTs were asked about other published or unpublished relevant RCTs. Selection criteria: All randomised controlled clinical trials of methadone maintenance therapy compared with either placebo maintenance or other non-pharmacological therapy for the treatment of opioid dependence. Data collection and analysis: Reviewers evaluated the papers separately and independently, rating methodological quality of sequence generation, concealment of allocation and bias. Data were extracted independently for meta-analysis and double-entered. Main results: Eleven studies met the criteria for inclusion in this review, all were randomised clinical trials, two were double-blind. There were a total number of 1969 participants. The sequence generation was inadequate in one study, adequate in five studies and unclear in the remaining studies. The allocation of concealment was adequate in three studies and unclear in the remaining studies. Methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self report and urine/hair analysis (6 RCTs, RR = 0.66 95% CI 0.56-0.78), but not statistically different in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25) or mortality (4 RCTs, RR=0.48; 95%CI:

			0.10-2.39). Authors' conclusions: Methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy. It does not show a statistically significant superior effect on criminal activity or mortality.
Mattick RP	2014	Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014 Feb 6;(2):CD002207. doi: 10.1002/14651858.CD002207.pub4.	Background: Buprenorphine maintenance treatment has been evaluated in randomised controlled trials against placebo medication, and separately as an alternative to methadone for management of opioid dependence. Objectives: To evaluate buprenorphine maintenance compared to placebo and to methadone maintenance in the management of opioid dependence, including its ability to retain people in treatment, suppress illicit drug use, reduce criminal activity, and mortality. Search methods We searched the following databases to January 2013: Cochrane Drugs and Alcohol Review Group Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Current Contents, PsycLIT, CORK, Alcohol and Drug Council of Australia, Australian Drug Foundation, Centre for Education and Information on Drugs and Alcohol, Library of Congress, reference lists of identified studies and reviews. We sought published/unpublished randomised controlled trials (RCTs) from authors. Selection criteria Randomised controlled trials of buprenorphine maintenance treatment versus placebo or methadone in management of opioid-dependent persons. Data collection and analysis: We used Cochrane Collaboration methodology. Main results We include 31 trials (5430 participants), the quality of evidence varied from high to moderate quality. There is high quality of evidence that buprenorphine was superior to placebo medication in retention of participants in treatment at all doses examined. Specifically, buprenorphine retained participants better than placebo: at low doses (2 - 6 mg), 5 studies, 1131 participants, risk ratio (RR) 1.50; 95% confidence interval (CI) 1.19 to 1.88; at medium doses (7 - 15 mg), 4 studies, 887 participants, RR 1.74; 95% CI 1.06 to 2.87; and at high doses (≥ 16 mg), 5 studies, 1001 participants, RR 1.82; 95% CI 1.15 to 2.90. However, there is moderate quality of evidence that only high-dose buprenorphine (≥

			16 mg) was more eLective than placebo in suppressing illicit opioid use measured by urinanalysis in the trials, 3 studies, 729 participants, standardised mean difference (SMD) -1.17; 95% CI -1.85 to -0.49, Notably, low-dose, (2 studies, 487 participants, SMD 0.10; 95% CI -0.80 to 1.01), and medium-dose, (2 studies, 463 participants, SMD -0.08; 95% CI -0.78 to 0.62) buprenorphine did not suppress illicit opioid use measured by urinanalysis better than placebo. There is high quality of evidence that buprenorphine in flexible doses adjusted to participant need, was less effective than methadone in retaining participants, 5 studies, 788 participants, RR 0.83; 95% CI 0.72 to 0.95. For those retained in treatment, no difference was observed in suppression of opioid use as measured by urinalysis, 8 studies, 1027 participants, SMD -0.11; 95% CI -0.23 to 0.02 or self-report, 4 studies, 501 participants, SMD -0.11; 95% CI -0.28 to 0.07, with moderate quality of evidence. Consistent with the results in the flexible-dose studies, in low fixed-dose studies, methadone (≤ 40 mg)was more likely to retain participants than low-dose buprenorphine (2 - 6 mg), (3 studies, 253 participants, RR 0.67; 95% CI: 0.52 to 0.87). However, we found contrary results at medium dose and high dose: there was no difference between medium-dose buprenorphine (7 - 15 mg) and medium-dose methadone (40 - 85 mg) in retention, (7 studies, 780 participants, RR 0.87; 95% CI 0.69 to 1.10) or in suppression of illicit opioid use as measured by urines, (4 studies, 476 participants, SMD 0.25; 95% CI -0.08 to 0.58) or self-report of illicit opioid use, (2 studies, 174 participants, SMD -0.82; 95% CI -1.83 to 0.19). Similarly, there was no difference between high-dose buprenorphine (≥ 16 mg) and high-dose methadone (≥85 mg) in retention (RR 0.79; 95% CI 0.20 to 3.16) or suppression of self-reported heroin use (SMD -0.73; 95% CI -1.08 to -0.37) (1 study, 134 participants). Few studies reported adverse events ; two studies compared adverse events statistically, finding no difference between methadone and buprenorphine, except for a single result indicating more sedation among those using methadone. Authors' conclusions: Buprenorphine is an effective medication in the maintenance

			treatment of heroin dependence, retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials. However, compared to methadone, buprenorphine retains fewer people when doses are flexibly delivered and at low fixed doses. If fixed medium or high doses are used, buprenorphine and methadone appear no different in effectiveness (retention in treatment and suppression of illicit opioid use); however, fixed doses are rarely used in clinical practice so the flexible dose results are more relevant to patient care. Methadone is superior to buprenorphine in retaining people in treatment, and methadone equally suppresses illicit opioid use.
McAuley A	2015	McAuley A, Aucott L, Matheson C. Exploring the life-saving potential of naloxone: A systematic review and descriptive meta-analysis of take home naloxone (THN) programmes for opioid users. Int J Drug Policy. 2015 Dec;26(12):1183-8. doi: 10.1016/j.drugpo.2015.09.011. Epub 2015 Oct 1.	Background: The epidemic of drug-related mortality continues to endure. The most common cause of death associated with drugs is overdose and opioids are consistently the substances most prominently involved. As well as efforts to control the availability of illicit drugs and increase engagement in treatment services, the use of naloxone for peer administration has increasingly been championed as a mechanism for addressing the DRD epidemic. Despite increasing adoption and use of take-home naloxone (THN) as a primary response to DRD internationally the evidence base remains limited. Methods: A systematic review and descriptive meta-analysis of the international THN literature was undertaken to determine an effect size for THN programmes. For each study, a proportion of use (PoU) was calculated using the number of 'peer administered uses' and the 'total number of participant/clients' trained and supplied with naloxone with a specific focus on people who use drugs

			(PWUD). This was constrained to a three month period as the lowest common denominator. As a percentage this gives the three month rate of use (per 100 participants). Results: From twenty-five identified THN evaluations, nine studies allowed a PoU to be determined. Overall, the model shows a range of 5.2–13.1 (point estimate 9.2) naloxone uses every three months for every 100 PWUD trained. Conclusion: Our model estimates that around 9% of naloxone kits distributed are likely to be used for peer administration within the first three months of supply for every 100 PWUD trained. Future evaluations should directly compare different training structures to test relative effectiveness and use a series of fixed time periods (3, 6 and 12 months) to determine whether time since training affects rate of naloxone use.
Meader N	2010	Meader N. A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis. Drug Alcohol Depend. 2010	Objectives: The aim of this systematic review was to compare the efficacy of methadone, buprenorphine, clonidine and lofexidine for opioid detoxification. Mixed treatment comparison meta-analyses were used to synthesise the data as it is designed for data-sets where limitations in standard pairwise meta-analyses make comparisons difficult to interpret. Data sources: A systematic search was conducted using the following databases: CENTRAL, CINAHL, Embase, HMIC, Medline and PsycINFO. Review methods: RCTs that included opioid dependent participants over a mean age of 16 receiving opioid detoxification using buprenorphine, methadone, clonidine or lofexidine were included in the systematic review. Included studies were quality assessed and the completion of treatment data was extracted by the author and a research assistant

		Apr 1;108(1-2):110-4. doi: 10.1016/j.drugalcdep.2009.12.008. Epub 2010 Jan 13.	independently. Mixed treatment comparison methods were used to synthesise the data. Results: There were 23 RCTs included in the systematic review (and 20 included in the meta-analysis) comprising a total of 2112 participants. Buprenorphine and methadone were ranked as the most effective methods of opioid detoxification followed by lofexidine and clonidine respectively. Conclusion: Buprenorpine and methadone appear to be the most effective detoxification treatments. While the analysis suggests buprenorphine is the most effective method of detoxification there is some uncertainty on whether it is more effective than methadone and requires further research to confirm this result.
Minozzi S	2011	Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev. 2011 Apr 13;2011(4):CD001333. doi: 10.1002/14651858.CD001333.pub4.	Background: Research on clinical application of oral naltrexone agrees on several things. From a pharmacological perspective, naltrexone works. From an applied perspective, the medication compliance and the retention rates are poor. Objectives: To evaluate the effects of naltrexone maintenance treatment versus placebo or other treatments in preventing relapse in opioid addicts after detoxification. Search methods We searched: Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library issue 6 2010), PubMed (1973- June 2010), CINAHL (1982- June 2010). We inspected reference lists of relevant articles and contacted pharmaceutical producers of naltrexone, authors and other Cochrane review groups. Selection criteria: All randomised controlled clinical trials which focus on the use of naltrexone maintenance treatment versus placebo, or other treatments to reach sustained abstinence from opiate drugs Data collection and analysis: Three reviewers independently assessed studies for inclusion and extracted data. One reviewer carried out the qualitative assessments of the methodology of eligible studies using validated checklists. Main results: Thirteen studies, 1158 participants, met the criteria for inclusion in this review. Comparing naltrexone versus placebo or no pharmacological treatments, no statistically significant difference were noted for all the primary outcomes considered. The

			only outcome statistically significant in favour of naltrexone is re incarceration, RR 0.47 (95%CI0.26-0.84), but results come only from two studies. Considering only studies were patients were forced to adherence a statistical significant difference in favour of naltrexone was found for retention and abstinence, RR 2.93 (95%CI 1.66-5.18). Comparing naltrexone versus psychotherapy, in the two considered outcomes, no statistically significant difference was found in the single study considered. Naltrexone was not superior to benzodiazepines and to buprenorphine for retention and abstinence and side effects. Results come from single studies. Authors' conclusions: The findings of this review suggest that oral naltrexone did not perform better than treatment with placebo or no pharmacological agent with respect to the number of participants re-incarcerated during the study period. If oral naltrexone is compared with other pharmacological treatments such as benzodiazepine and buprenorphine, no statistically significant difference was found. The percentage of people retained in treatment in the included studies is however low (28%). The conclusion of this review is that the studies conducted have not allowed an adequate evaluation of oral naltrexone treatment in the field of opioid dependence. Consequently, maintenance therapy with naltrexone cannot yet be considered a treatment which has been scientifically proved to be superior to other kinds of treatment.
Nielsen S	2016	Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database Syst Rev. 2016 May	Background: There are increasing concerns regarding pharmaceutical opioid harms including overdose and dependence, with an associated increase in treatment demand. People dependent on pharmaceutical opioids appear to differ in important ways from people who use heroin, yet most opioid agonist treatment research has been conducted in people who use heroin. Objectives: To assess the effects of maintenance agonist pharmacotherapy for the treatment of pharmaceutical opioid dependence. Search methods: The search included the Cochrane Drugs and Alcohol Group's Specialised Register of Trials; the Cochrane Central Register of Controlled Trials

		9;(5):CD011117. doi: 10.1002/14651858.CD011117.pub2.	(CENTRAL, 2015, Issue 5); PubMed (January 1966 to May 2015); EMBASE (Ovid) (January 1974 to May 2015); CINAHL (EBSCOhost) (1982 to May 2015); ISI Web of Science (to May 2014); and PsycINFO (Ovid) (1806 to May 2014). Selection criteria: We included randomised controlled trials examining maintenance opioid agonist treatments that made the following two comparisons:1. full opioid agonists (methadone, morphine, oxycodone, levo-alpha-acetylmethadol (LAAM), or codeine) versus different full opioid agonists or partial opioid agonists (buprenorphine) for maintenance treatment and2. full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment (without opioid agonist treatment). Data collection and analysis: We used standard Cochrane methodological procedures. Main results: We identified six randomised controlled trials that met inclusion criteria (607 participants).We found moderate quality evidence from two studies of no difference between methadone and buprenorphine in self reported opioid use (risk ratio (RR) 0.37, 95% confidence interval (CI) 0.08 to 1.63) or opioid positive urine drug tests (RR 0.81, 95% CI 0.56 to 1.18). There was low quality evidence from three studies of no difference in retention between buprenorphine and methadone maintenance treatment (RR 0.69, 95% CI 0.39 to 1.22). There was moderate quality evidence from two studies of no difference between methadone and buprenorphine on adverse events (RR 1.10, 95% CI 0.64 to 1.91).We found low quality evidence from three studies favouring maintenance buprenorphine treatment over detoxification or psychological treatment in terms of fewer opioid positive urine drug tests (RR 0.63, 95% CI 0.43 to 0.91) and self reported opioid use in the past 30 days (RR 0.54, 95% CI 0.31 to 0.93). There was no difference on days of unsanctioned opioid use (standardised mean difference (SMD) -0.31, 95% CI -0.66 to 0.04). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on retention in treatment (RR 0.33, 95% CI 0.23 to 0.47). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on adverse events (RR 0.19, 95% CI 0.06 to 0.57).The main weaknesses in the quality of the data was the use of open-label study

			designs. Authors' conclusions: There was low to moderate quality evidence supporting the use of maintenance agonist pharmacotherapy for pharmaceutical opioid dependence. Methadone or buprenorphine appeared equally effective. Maintenance treatment with buprenorphine appeared more effective than detoxification or psychological treatments. Due to the overall low to moderate quality of the evidence and small sample sizes, there is the possibility that the further research may change these findings.
Nikoo M	2017	Nikoo M, Nikoo N, Anbardan SJ, Amiri A, Vogel M, Choi F, Sepehry AA, Bagheri Valoojerdi AH, Jang K, Schütz C, Akhondzadeh S, Krausz M. Tincture of opium for treating opioid dependence: a systematic review of safety and efficacy. Addiction. 2017 Mar;112(3):415-429. doi: 10.1111/add.13628. Epub 2016 Dec 13.	Background and Aims: Recently, there has been a growing interest in using opium tincture (OT) for treating opioid dependence in certain regions. We aimed to assess the evidence on its safety and efficacy for this indication. Methods: We searched several databases (CENTRAL, Medline, EMBASE, Web of Science, PsychINFO, ProQuest Dissertation and Theses Database, Iran Medex, clinicaltrials.gov and who.int/trialsearch) with no language or publication date limitations. Two reviewers selected randomized controlled trials (RCT), cohort/case–control/cross-sectional studies and case-series on safety or efficacy of OT for treating opioid dependence and then extracted reported measures of mentioned outcomes from selected studies. We used the Effective Public Health Practice Project (EPHPP) Quality Assessment tool for appraisal. Results: From nine selected studies; in three RCTs and one cohort analytical analysis on detoxification, 110 patients were treated with 15–140 morphine equivalents/day (mEq/d) of OT; in four prospective and one retrospective uncontrolled case-series on long-term/maintenance treatment, 570 patients were treated with 100–400 mEq/d of OT. Only two studies on detoxification included a comparison: one concluded equal efficacy of OT and methadone in suppressing withdrawal symptoms (P = 0.32) and the other concluded OT to be less efficacious than buprenorphine/naloxone in suppressing withdrawal [OT = 12.20, 95% confidence interval (CI) = 11.00, 13.40]; control: 5.20 (95% CI = 4.69, 5.71) and craving (OT = 303.0, 95% CI = 144.664, 750.664; control: 0.0) but not significantly different (P = 0.26) in retaining participants in treatment. No major adverse events were

			reported. Conclusions: Conclusive recommendations about the safety and efficacy of opium tincture for treating opioid dependence are not possible
Rahimi-Movaghar A	2013	Rahimi-Movaghar A, Amin-Esmaeili M, Hefazi M, Yousefi-Nooraie R. Pharmacological therapies for maintenance treatments of opium dependence. Cochrane Database Syst Rev. 2013 Jan 31;(1):CD007775. doi: 10.1002/14651858.CD007775.pub2.	Background: Pharmacologic therapies for maintenance treatment of heroin dependence have been used and studied widely. Systematic reviews have demonstrated the effectiveness of such therapies. Opium dependence is associated with less problems and impairments and is less likely to be used by injecting, with consequent reductions in risk of overdose and blood-borne diseases. Although it is a common substance use disorder in many countries, a systematic review of the literature is lacking on the maintenance treatment for opium dependence. Objectives: To evaluate the effectiveness and safety of various pharmacological therapies on maintenance of opium dependence (alone or in combination with psychosocial interventions) compared to no intervention, detoxification, different doses of the same intervention, other pharmacologic interventions and any psychosocial interventions. Search methods: We searched the following sources up to February 2012: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, PsycINFO, regional databases (IMEMR and ASCI), national databases (Iranmedex and Iranpsych), main electronic sources of ongoing trials and reference lists of all relevant papers. Also, we contacted known investigators from some Asian countries to obtain details about unpublished trials. Selection criteria: Randomised controlled clinical trials (RCTs) comparing any maintenance pharmacologic intervention versus no intervention, other pharmacologic or non-pharmacologic intervention for opium dependence. Data collection and analysis: Two reviewers assessed the risks of biases and extracted data, independently. Main results: Three RCTs recruiting 870 opium dependents were included. The studies made different comparisons so it was not possible to pool data. Only retention rate was assessed by the studies. Two studies compared different doses of buprenorphine: in one study, 4 mg/day of buprenorphine was compared with doses of 2 mg/day and 1 mg/day and in another study, 8 mg/day of buprenorphine was compared with doses of 3 mg/day

			and 1 mg/day. Comparisons showed a statistically significant difference between groups; higher doses of buprenorphine increased the probability of retention in treatment. The studies had high risks of biases. In the third study, after a process of detoxification, baclofen (60 mg/day) was compared with placebo for maintenance treatment. The difference in retention rate between groups was high, but it was not statistically significant. Authors' conclusions: It is not possible to conclude about the use of any kind of pharmacologic therapies for maintenance treatment of opium dependence.
Rahimi-Movaghar A	2018	Rahimi-Movaghar A, Gholami J, Amato L, Hoseinie L, Yousefi-Nooraie R, Amin-Esmaeili M. Pharmacological therapies for management of opium withdrawal. Cochrane Database Syst Rev. 2018 Jun 21;6(6):CD007522. doi: 10.1002/14651858.CD007522.pub2.	Background: Pharmacologic therapies for management of heroin withdrawal have been studied and reviewed widely. Opium dependence is generally associated with less severe dependence and milder withdrawal symptoms than heroin. The evidence on withdrawal management of heroin might therefore not be exactly applicable for opium. Objectives: To assess the effectiveness and safety of various pharmacologic therapies for the management of the acute phase of opium withdrawal. Search methods We searched the following sources up to September 2017: CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, regional and national databases (IMEMR, Iranmedex, and IranPsych), main electronic sources of ongoing trials, and reference lists of all relevant papers. In addition, we contacted known investigators to obtain missing data or incomplete trials. Selection criteria: Controlled clinical trials and randomised controlled trials on pharmacological therapies, compared with no intervention, placebo, other pharmacologic treatments, different doses of the same drug, and psychosocial intervention, to manage acute withdrawal from opium in a maximum duration of 30 days. Data collection and analysis: We used the standard methodological procedures expected by Cochrane. Main results: We included 13 trials involving 1096 participants. No pooled analysis was possible. Studies were carried out in three countries, Iran, India, and Thailand, in outpatient and inpatient settings. The quality of the evidence was generally very low. When the mean of withdrawal symptoms was provided for several days, we mainly focused on day 3. The reason for this was that the highest severity of opium withdrawal is

			in the second to fourth day. Comparing different pharmacological treatments with each other, clonidine was twice as good as methadone for completion of treatment (risk ratio (RR) 2.01, 95% confidence interval (CI) 1.69 to 2.38; 361 participants, 1 study, low-quality evidence). All the other results showed no differences between the considered drugs: baclofen versus clonidine (RR 1.06, 95% CI 0.63 to 1.80; 66 participants, 1 study, very low-quality evidence); clonidine versus clonidine plus amantadine (RR 1.03, 95% CI 0.86 to 1.24; 69 participants, 1 study); clonidine versus buprenorphine in an inpatient setting (RR 1.04, 95% CI 0.90 to 1.20; 1 study, 35 participants, very low quality evidence); methadone versus tramadol (RR 0.95, 95% CI 0.65 to 1.37; 1 study, 72 participants, very low-quality evidence); methadone versus methadone plus gabapentin (RR 1.17, 95% CI 0.96 to 1.43; 1 study, 40 participants, low-quality evidence), and tincture of opium versus methadone (1 study, 74 participants, low-quality evidence). Comparing different pharmacological treatments with each other, adding amantadine to clonidine decreased withdrawal scores rated at day 3 (mean difference (MD) -3.56, 95% CI -5.97 to -1.15; 1 study, 60 participants, very low-quality evidence). Comparing clonidine with buprenorphine in an inpatient setting, we found no difference in withdrawal symptoms rated by a physician (MD -1.40, 95% CI -2.93 to 0.13; 1 study, 34 participants, very low-quality evidence), and results in favour of buprenorpine when rated by participants (MD -11.80, 95% CI -15.56 to -8.04). Buprenorphine was superior to clonidine in controlling severe withdrawal symptoms in an outpatient setting (RR 0.35, 95% CI 0.19 to 0.64; 1 study, 76 participants). We found no difference in the comparison of methadone versus tramadol (MD 0.04, 95% CI -2.68 to 2.76; 1 study, 72 participants) and in the comparison of methadone versus methadone plus gabapentin (MD -2.20, 95% CI -6.72 to 2.32; 1 study, 40 participants). Comparing clonidine versus buprenorphine in an outpatient setting, more adverse effects were reported in the clonidine group (1 study, 76 participants). Higher numbers of participants in the clonidine group experienced hypotension at days 5 to 8, headache at days 1 to 8, sedation at days 5 to 8, dizziness and dry mouth at days 1 to 10, and nausea at days 1

			to 9. Sweating was reported in a significantly higher number of participants in the buprenorphine group at days 1 to 10. We found no difference between groups for all the other comparisons considering this outcome. Comparing different dosages of the same pharmacological detoxification treatment, a high dose of clonidine (1 to 1.2 mg/day) did not differ from a low dose of clonidine (0.5 to 0.6 mg/day) in completion of treatment in an inpatient setting (RR 1.00, 95% CI 0.84 to 1.19; 1 study, 68 participants), however a higher number of participants with hypotension was reported in the high-dose group (RR 3.25, 95% CI 1.77 to 5.98). Gradual reduction of methadone was associated with more adverse effects than abrupt withdrawal of methadone (RR 2.25, 95% CI 1.02 to 4.94; 1 study, 20 participants, very low-quality evidence). Authors' conclusions: Results did not support using any specific pharmacological approach for the management of opium withdrawal due to generally very low quality evidence and small or no differences between treatments. However, it seems that opium withdrawal symptoms are significant, especially at days 2 to 4 after discontinuation of opium. All of the assessed medications might be useful in alleviating symptoms. Those who receive clonidine might experience hypotension
Rice D	2020	Rice D, Corace K, Wolfe D, Esmaeilisaraji L, Michaud A, Grima A, Austin B, Douma R, Barbeau P, Butler C, Willows M, Poulin PA, Sproule BA, Porath A, Garber G, Taha S, Garner G, Skidmore B, Moher D, Thavorn	Background: Guidelines recommend that individuals with opioid use disorder (OUD) receive pharmacological and psychosocial interventions; however, the most appropriate psychosocial intervention is not known. In collaboration with people with lived experience, clinicians, and policy makers, we sought to assess the relative benefits of psychosocial interventions as an adjunct to opioid agonist therapy (OAT) among persons with OUD. Methods: A review protocol was registered a priori (CRD42018090761), and a comprehensive search for randomized controlled trials (RCT) was conducted from database inception to June 2020 in MEDLINE, Embase, PsycINFO and the Cochrane Central Register of Controlled Trials. Established methods for study selection and data extraction were used. Primary outcomes were treatment retention and opioid use (measured by urinalysis for opioid use and opioid abstinence outcomes). Odds ratios were

		K, Hutton B. Evaluating comparative effectiveness of psychosocial interventions adjunctive to opioid agonist therapy for opioid use disorder: A systematic review with network meta-analyses. PLoS One. 2020 Dec 28;15(12):e0244401. doi: 10.1371/journal.pone.0244401. eCollection 2020.	estimated using network meta-analyses (NMA) as appropriate based on available evidence, and in remaining cases alternative approaches to synthesis were used. Results: Seventy-two RCTs met the inclusion criteria. Risk of bias evaluations commonly identified study limitations and poor reporting with regard to methods used for allocation concealment and selective outcome reporting. Due to inconsistency in reporting of outcome measures, only 48 RCTs (20 unique interventions, 5,404 participants) were included for NMA of treatment retention, where statistically significant differences were found when psychosocial interventions were used as an adjunct to OAT as compared to OAT-only. The addition of rewards-based interventions such as contingency management (alone or with community reinforcement approach) to OAT was superior to OAT-only. Few statistically significant differences between psychosocial interventions were identified among any other pairwise comparisons. Heterogeneity in reporting formats precluded an NMA for opioid use. A structured synthesis was undertaken for the remaining outcomes which included opioid use (n = 18 studies) and opioid abstinence (n = 35 studies), where the majority of studies found no significant difference between OAT plus psychosocial interventions as compared to OAT-only. Conclusions: This systematic review offers a comprehensive synthesis of the available evidence and the limitations of current trials of psychosocial interventions applied as an adjunct to OAT for OUD. Clinicians and health services may wish to consider integrating contingency management in addition to OAT for OUD in their settings to improve treatment retention. Aside from treatment retention, few differences were consistently found between psychosocial interventions adjunctive to OAT and OAT-only. There is a need for high-quality RCTs to establish more definitive conclusions.
Saulle R	2017	Saulle R, Vecchi S, Gowing L. Supervised dosing with a long-acting opioid medication in the	Background: Opioid dependence (OD) is an increasing clinical and public health problem worldwide. International guidelines recommend opioid substitution treatment (OST), such as methadone and buprenorphine, as first-line medication treatment for OD. A negative aspect of OST is that the medication used can be diverted both through sale on the black market, and the unsanctioned use of medications. Daily supervised administration of

		management of opioid dependence [RM supervised vs. unsupervised dosing]. Cochrane Database Syst Rev. 2017 Apr 27;4(4):CD011983. doi: 10.1002/14651858.CD011983.pub2.	medications used in OST has the advantage of reducing the risk of diversion, and may promote therapeutic engagement, potentially enhancing the psychosocial aspect of OST, but costs more and is more restrictive on the client than dispensing for off-site consumption. Objectives: The objective of this systematic review is to compare the effectiveness of OST with supervised dosing relative to dispensing of medication for off-site consumption. Search methods: We searched in Cochrane Drugs and Alcohol Group Specialised Register and Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, Web of Science from inception up to April 2016. Ongoing and unpublished studies were searched via ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/).All searches included non-English language literature. We hand searched references on topic-related systematic reviews. Selection criteria: Randomised controlled trials (RCTs), controlled clinical trials (CCTs), and prospective controlled cohort studies, involving people who are receiving OST (methadone, buprenorphine) and comparing supervised dosing with dispensing of medication to be consumed away from the dispensing point, usually without supervision. Data collection and analysis: We used the standard methodological procedures expected by Cochrane. Main results: Six studies (four RCTs and two prospective observational cohort studies), involving 7999 participants comparing supervised OST treatment with unsupervised treatment, met the inclusion criteria. The risk of bias was generally moderate across trials, but the results reported on outcomes that we planned to consider were limited. Overall, we judged the quality of the evidence from very low to low for all the outcomes. We found no difference in retention at any duration with supervised compared to unsupervised dosing (RR 0.99, 95% CI 0.88 to 1.12, 716 participants, four trials, low-quality evidence) or in retention in the shortest follow-up period, three months (RR 0.94; 95% CI 0.84 to 1.05; 472 participants, three trials, low-quality evidence). Additional data at 12 months from one

			observational study found no difference in retention between groups (RR 0.94, 95% CI 0.77 to 1.14; n = 300).There was no difference in abstinence at the end of treatment (self-reported drug use) (67% versus 60%, P = 0.33, 293 participants, one trial, very low-quality evidence); and in diversion of medication (5% versus 2%, 293 participants, one trial, very low-quality evidence).Regarding our secondary outcomes, we did not found a difference in the incidence of adverse effects in the supervised compared to unsupervised control group (RR 0.63; 96% CI 0.10 to 3.86; 363 participants, two trials, very low-quality evidence). Data on severity of dependence were very limited (244 participants, one trial) and showed no difference between the two approaches. Data on deaths were reported in two studies. One trial reported two deaths in the supervised group (low-quality evidence), while in the cohort study all-cause mortality was found lower in regular supervision group (crude mortality rate 0.60 versus 0.81 per 100 person-years), although after adjustment insufficient evidence existed to suggest that regular supervision was protective (mortality rate ratio = 1.23, 95% CI = 0.67 to 2.27).No studies reported pain symptoms, drug craving, aberrant opioid-related behaviours, days of unsanctioned opioid use and overdose. Authors' conclusions: Take-home medication strategies are attractive to treatment services due to lower costs, and place less restrictions on clients, but it is unknown whether they may be associated with increased risk of diversion and unsanctioned use of medication. There is uncertainty about the effects of supervised dosing compared with unsupervised medication due to the low and very low quality of the evidence for the primary outcomes of interest for this review. Data on defined secondary outcomes were similarly limited. More research comparing supervised and take-home medication strategies is needed to support decisions on the relative effectiveness of these strategies. The trials should be designed and conducted with high quality and over a longer follow-up period to support comparison of strategies at different stages of treatment. In particular, there is a need for studies assessing in more detail the risk of diversion and safety outcomes of using supervised OST to manage opioid dependence.

Sordo L	2017	Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017 Apr 26;357:j1550. doi: 10.1136/bmj.j1550.	Objective: To compare the risk for all cause and overdose mortality in people with opioid dependence during and after substitution treatment with methadone or buprenorphine and to characterise trends in risk of mortality after initiation and cessation of treatment. Design: Systematic review and meta-analysis. Data sources: Medline, Embase, PsycINFO, and LILACS to September 2016. Study selection: Prospective or retrospective cohort studies in people with opioid dependence that reported deaths from all causes or overdose during follow-up periods in and out of opioid substitution treatment with methadone or buprenorphine. Data extraction and synthesis: Two independent reviewers performed data extraction and assessed study quality. Mortality rates in and out of treatment were jointly combined across methadone or buprenorphine cohorts by using multivariate random effects meta-analysis. Results: There were 19 eligible cohorts, following 122885 people treated with methadone over 1.3-13.9 years and 15831 people treated with buprenorphine over 1.1-4.5 years. Pooled all cause mortality rates were 11.3 and 36.1 per 1000 person years in and out of methadone treatment (unadjusted out-to-in rate ratio 3.20, 95% confidence interval 2.65 to 3.86) and reduced to 4.3 and 9.5 in and out of buprenorphine treatment (2.20, 1.34 to 3.61). In pooled trend analysis, all cause mortality dropped sharply over the first four weeks of methadone treatment and decreased gradually two weeks after leaving treatment. All cause mortality remained stable during induction and remaining time on buprenorphine treatment. Overdose mortality evolved similarly, with pooled overdose mortality rates of 2.6 and 12.7 per 1000 person years in and out of methadone treatment

			(unadjusted out-to-in rate ratio 4.80, 2.90 to 7.96) and 1.4 and 4.6 in and out of buprenorphine treatment. Conclusions: Retention in methadone and buprenorphine treatment is associated with substantial reductions in the risk for all cause and overdose mortality in people dependent on opioids. The induction phase onto methadone treatment and the time immediately after leaving treatment with both drugs are periods of particularly increased mortality risk, which should be dealt with by both public health and clinical strategies to mitigate such risk. These findings are potentially important, but further research must be conducted to properly account for potential confounding and selection bias in comparisons of mortality risk between opioid substitution treatments, as well as throughout periods in and out of each treatment.
Strang J	2015	Strang J, Groshkova T, Uchtenhagen A, van den Brink W, Haasen C, Schechter MT, Lintzeris N, Bell J, Pirona A, Oviedo-Joekes E, Simon R, Metrebian N. Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction†. Br J	Background: Supervised injectable heroin (SIH) treatment has emerged over the past 15 years as an intensive treatment for entrenched heroin users who have not responded to standard treatments such as oral methadone maintenance treatment (MMT) or residential rehabilitation. Aims: To synthesise published findings for treatment with SIH for refractory heroin-dependence through systematic review and meta-analysis, and to examine the political and scientific response to these findings. Method: Randomised controlled trials (RCTs) of SIH treatment were identified through database searching, and random effects pooled efficacy was estimated for SIH treatment. Methodological quality was assessed according to criteria set out by the Cochrane Collaboration. Results: Six RCTs met the inclusion criteria for analysis. Across the trials, SIH treatment improved treatment outcome, i.e., Greater reduction in the use of illicit ‘street’ heroin in patients receiving SIH treatment compared with control groups (most often receiving MMT). Conclusions: SIH is found to be an effective way of treating heroin dependence refractory to standard treatment. SIH may be less safe than MMT and therefore requires more

		Psychiatry. 2015 Jul;207(1):5-14. doi: 10.1192/bjp.bp.114.149195.	clinical attention to manage greater safety issues. This intensive intervention is for a patient population previously considered unresponsive to treatment. Inclusion of this low-volume, high-intensity treatment can now improve the impact of comprehensive healthcare provision.

Table S6 Reviews on treatment for misuse of medicines

First author	Year	Citation	Abstract
Baandrup	2018	Lone Baandrup 1, Bjørn H Ebdrup, Jesper Ø Rasmussen, Jane Lindschou, Christian Gluud, Birte Y Glenthøj. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. Cochrane Database Syst Rev. 2018 Mar 15;3(3):CD011481. doi: 10.1002/14651858.CD011481.pub2.	Background: Prolonged treatment with benzodiazepines is common practice despite clinical recommendations of short-term use. Benzodiazepines are used by approximately 4% of the general population, with increased prevalence in psychiatric populations and the elderly. After long term use it is often difficult to discontinue benzodiazepines due to psychological and physiological dependence. This review investigated if pharmacological interventions can facilitate benzodiazepine tapering. Objectives: To assess the benefits and harms of pharmacological interventions to facilitate discontinuation of chronic benzodiazepine use. Search methods: We searched the following electronic databases up to October 2017: Cochrane Drugs and Alcohol Group's Specialised Register of Trials, CENTRAL, PubMed, Embase, CINAHL, and ISI Web of Science. We also searched ClinicalTrials.gov, the WHO ICTRP, and ISRCTN registry, and checked the reference lists of included studies for further references to relevant randomised controlled trials. Selection criteria: We included randomised controlled trials comparing pharmacological treatment versus placebo or no intervention or versus another pharmacological intervention in adults who had been treated with benzodiazepines for at least two months and/or fulfilled criteria for benzodiazepine dependence (any criteria). Data collection and analysis: We used standard methodological procedures expected by Cochrane. Results: We included 38 trials (involving 2543 participants), but we could only extract data from 35 trials with 2295 participants. Many different interventions were studied, and no single intervention was assessed in more than four trials. We extracted data on 18 different comparisons. The risk of bias was high in all trials but one. Trial Sequential Analysis showed imprecision for all comparisons. For benzodiazepine discontinuation, we found a potential benefit of valproate at end of intervention (1 study, 27 participants; risk ratio (RR) 2.55, 95% confidence interval (CI) 1.08 to 6.03; very low-quality evidence) and of tricyclic

			antidepressants at longest follow-up (1 study, 47 participants; RR 2.20, 95% CI 1.27 to 3.82; low-quality evidence).We found potentially positive effects on benzodiazepine withdrawal symptoms of pregabalin (1 study, 106 participants; mean difference (MD) -3.10 points, 95% CI -3.51 to -2.69; very low-quality evidence), captodiame (1 study, 81 participants; MD -1.00 points, 95% CI -1.13 to -0.87; very low-quality evidence), paroxetine (2 studies, 99 participants; MD -3.57 points, 95% CI -5.34 to -1.80; very low-quality evidence), tricyclic antidepressants (1 study, 38 participants; MD -19.78 points, 95% CI -20.25 to -19.31; very low-quality evidence), and flumazenil (3 studies, 58 participants; standardised mean difference -0.95, 95% CI -1.71 to -0.19; very low-quality evidence) at end of intervention. However, the positive effect of paroxetine on benzodiazepine withdrawal symptoms did not persist until longest follow-up (1 study, 54 participants; MD -0.13 points, 95% CI -4.03 to 3.77; very low-quality evidence).The following pharmacological interventions reduced symptoms of anxiety at end of intervention: carbamazepine (1 study, 36 participants; MD -6.00 points, 95% CI -9.58 to -2.42; very low-quality evidence), pregabalin (1 study, 106 participants; MD -4.80 points, 95% CI -5.28 to -4.32; very low-quality evidence), captodiame (1 study, 81 participants; MD -5.70 points, 95% CI -6.05 to -5.35; very low-quality evidence), paroxetine (2 studies, 99 participants; MD -6.75 points, 95% CI -9.64 to -3.86; very low-quality evidence), and flumazenil (1 study, 18 participants; MD -1.30 points, 95% CI -2.28 to -0.32; very low-quality evidence).Two pharmacological treatments seemed to reduce the proportion of participants that relapsed to benzodiazepine use: valproate (1 study, 27 participants; RR 0.31, 95% CI 0.11 to 0.90; very low-quality evidence) and cyamemazine (1 study, 124 participants; RR 0.33, 95% CI 0.14 to 0.78; very low-quality evidence). Alpidem decreased the proportion of participants with benzodiazepine discontinuation (1 study, 25 participants; RR 0.41, 95% CI 0.17 to 0.99; number needed to treat for an additional harmful outcome (NNTH) 2.3 participants; low-quality evidence) and increased the occurrence of withdrawal syndrome (1 study, 145 participants; RR 4.86, 95% CI 1.12 to 21.14; NNTH 5.9 participants; low-quality evidence). Likewise, magnesium aspartate decreased the proportion of participants discontinuing benzodiazepines (1 study, 144 participants; RR 0.80, 95% CI 0.66

			to 0.96; NNTH 5.8; very low-quality evidence).Generally, adverse events were insufficiently reported. Specifically, one of the flumazenil trials was discontinued due to severe panic reactions. Authors' conclusions: Given the low or very low quality of the evidence for the reported outcomes, and the small number of trials identified with a limited number of participants for each comparison, it is not possible to draw firm conclusions regarding pharmacological interventions to facilitate benzodiazepine discontinuation in chronic benzodiazepine users. Due to poor reporting, adverse events could not be reliably assessed across trials. More randomised controlled trials are required with less risk of systematic errors ('bias') and of random errors ('play of chance') and better and full reporting of patient-centred and long-term clinical outcomes. Such trials ought to be conducted independently of industry involvement.
Darker	2015	Catherine D Darker 1, Brion P Sweeney, Joe M Barry, Michael F Farrell, Erica Donnelly-Swift. Psychosocial interventions for benzodiazepine harmful use, abuse or dependence. Cochrane Database Syst Rev. 2015;(5):CD009652. doi:10.1002/14651858.CD009652.pub2.	Background: Benzodiazepines (BZDs) have a sedative and hypnotic effect upon people. Short term use can be beneficial but long term BZD use is common, with several risks in addition to the potential for dependence in both opiate and non-opiate dependent patients. Objectives: To evaluate the effectiveness of psychosocial interventions for treating BZD harmful use, abuse or dependence compared to pharmacological interventions, no intervention, placebo or a different psychosocial intervention on reducing the use of BZDs in opiate dependent and non-opiate dependent groups. Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL- the Cochrane Library issue 12, 2014) which includes the Cochrane Drugs and Alcohol Group Specialized Register; PubMed (from 1966 to December 2014); EMBASE (from 1988 to December 2014); CINAHL Cumulative Index to Nursing and Allied Health Literature (1982 to September 2013); PsychINFO (1872 to December 2014); ERIC (Education Resources Information Centre, (January 1966 to September 2013); All EBM Reviews (1991 to September 2013, Ovid Interface); AMED (Allied & Alternative Medicine) 1985 to September 2013); ASSIA (Applied Social Sciences Index & Abstracts (1960 to September 2013); LILACS (January 1982 to September 2013); Web of Science (1900 to December 2014);

			Electronic Grey Literature Databases: Dissertation Abstract; Index to Theses. Selection criteria Randomised controlled trials examining the use of a psychosocial intervention to treat BZDs versus pharmacological interventions, no intervention, placebo or a different psychosocial intervention on reducing the use of BZDs in opiate dependent and non-opiate dependent groups. Data collection and analysis: We used the standard methodological procedures outlined in Cochrane Guidelines. Main results: Twenty-five studies including 1666 people met the inclusion criteria. The studies tested many different psychosocial interventions including cognitive behavioural therapy (CBT) (some studies with taper, other studies with no taper), motivational interviewing (MI),letters to patients advising them to reduce or quit BZD use, relaxation studies, counselling delivered electronically and advice provided by a general practitioner (GP). Based on the data obtained, we performed two meta-analyses in this Cochrane review: one assessing the effectiveness of CBT plus taper versus taper only (575 participants), and one assessing MI versus treatment as usual (TAU) (80 participants).There was moderate quality of evidence that CBT plus taper was more likely to result in successful discontinuation of BZDs within four weeks post treatment compared to taper only (Risk ratio (RR) 1.40, 95% confidence interval (CI) 1.05 to 1.86; nine trials, 423 participants) and moderate quality of evidence at three month follow-up (RR 1.51, 95% CI 1.15 to 1.98) in favour of CBT (taper)for 575 participants. The effects were less certain at 6, 11, 12, 15 and 24 months follow-up. The effect of CBT on reducing BZDs by> 50% was uncertain for all time points examined due to the low quality evidence. There was very low quality evidence for the effect on drop-outs at any of the time intervals; post-treatment (RR 1.05, 95% CI 0.66 to 1.66), three month follow-up (RR 1.71, 95% CI0.16 to 17.98) and six month follow-up (RR 0.70, 95% CI 0.17 to 2.88).Based on the very low quality of evidence available, the effect of MI versus TAU for all the time intervals is unclear; post treatment(RR 4.43, 95% CI 0.16 to 125.35; two trials, 34 participants), at three month follow-up (RR 3.46, 95% CI 0.53 to 22.45; four trials,80 participants), six month follow-up (RR 0.14, 95% CI 0.01 to 1.89) and 12 month follow-up (RR

			1.25, 95% CI 0.63 to 2.47).There was very low quality of evidence to determine the effect of MI on reducing BZDs by > 50% at three month follow-up (RR 1.52,95% CI 0.60 to 3.83) and 12 month follow-up (RR 0.87, 95% CI 0.52 to 1.47). The effects on drop-outs from treatment at any of e time intervals between the two groups were uncertain due to the wide CIs; post-treatment (RR 0.50, 95% CI 0.04 to 7.10), three month follow-up (RR 0.46, 95% CI 0.06 to 3.28), six month follow-up (RR 8.75, 95% CI 0.61 to 124.53) and 12 month follow-up(RR 0.42, 95% CI 0.02 to 7.71).The following interventions reduced BZD use - tailored GP letter versus generic GP letter at 12 month follow-up (RR 1.70, 95%CI 1.07 to 2.70; one trial, 322 participants), standardised interview versus TAU at six month follow-up (RR 13.11, 95% CI 3.25 to 52.83; one trial, 139 participants) and 12 month follow-up (RR 4.97, 95% CI 2.23 to 11.11), and relaxation versus TAU at three month follow-up (RR 2.20, 95% CI 1.23 to 3.94).There was insufficient supporting evidence for the remaining interventions. We performed a 'Risk of bias' assessment on all included studies. We assessed the quality of the evidence as high quality for random sequence generation, attrition bias and reporting bias; moderate quality for allocation concealment, performance bias for objective outcomes, and detection bias for objective outcomes; and low quality for performance bias for subjective outcomes and detection bias for subjective outcomes. Few studies had manualised sessions or independent tests of treatment fidelity; most follow-up periods were less than 12 months. Based on decisions made during the implementation of protocol methods to present a manageable summary of the evidence we did not collect data on quality of life, self-harm or adverse events. Authors' conclusions: CBT plus taper is effective in the short term (three month time period) in reducing BZD use. However, this is not sustained at six months and subsequently. Currently there is insufficient evidence to support the use of MI to reduce BZD use. There is emerging evidence to suggest that a tailored GP letter versus a generic GP letter, a standardised interview versus TAU, and relaxation versus TAU could be effective for BZD reduction. There is currently insufficient evidence for other approaches to reduce BZD use.

Nielsen	2016	Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database Syst Rev. 2016 May 9;(5):CD011117. doi: 10.1002/14651858.CD011117.pub2.	Background: Use of pharmaceutical opioids (medicines that are used to treat pain) has increased dramatically in some parts of the world since the mid-1990s. With the increased use, there has been increasing numbers of people seeking treatment for dependence (addiction) on pharmaceutical opioids. Currently, most treatment guidelines are based on research that was conducted in people who were dependent on heroin (a highly addictive opioid). This review sought to compare different opioid agonist maintenance treatments (i.e. treatments such as methadone or buprenorphine that are given for at least 30 days to help the person to reduce their unsanctioned drug use) for the treatment of pharmaceutical opioid dependence. We also compared results from maintenance treatment to short term treatments such as detoxification (removal of the drug from the body) or psychological treatments (e.g. talking therapy, counselling). Study characteristics: We examined the scientific literature up to May 2015. We identified six randomised controlled trials (studies where people were allocated at random to one of two or more treatment or control conditions) involving 607 people who were dependent on pharmaceutical opioids. The people in the study were 77% male and had an average age of 31.6 years. The average duration of the studies comparing different opioid maintenance treatments (three studies that compared methadone to buprenorphine) was 24 weeks, and the average duration of studies comparing a maintenance treatment (three studies with buprenorphine maintenance) to detoxification or psychological treatment was 10 weeks. Five of the six studies were conducted in the US, with one study from Iran. We looked at opioid use and leaving treatment early. Five of the studies were funded by the National Institute of Health (USA), with one study not reporting the funding source. Four studies reported that a drug company provided the medicine. Key results: We found that there is probably little or no difference between how well methadone and buprenorphine worked to keep people in treatment, to reduce opioid use, or side effects. We found that buprenorphine probably keeps more people in treatment, may

			reduce use of opioids, and has fewer side effects compared to detoxification or psychological treatment alone.

Table S7 Reviews on responses for vulnerable young people

First author	Year	Citation	Abstract
Bavarian N	2015	Bavarian N, Flay BR, Ketcham PL, Smit E. The Illicit Use of Prescription Stimulants on College Campuses: A Theory-Guided Systematic Review Health Educ Behav. 2015 Dec;42(6):719-29. doi: 10.1177/1090198115580576. Epub 2015 Jun 1.	The illicit use of prescription stimulants (IUPS) is a substance use behavior that remains prevalent on college campuses. As theory can guide research and practice, we provide a systematic review of the college-based IUPS epidemiological literature guided by one ecological framework, the Theory of Triadic Influence (TTI). We aim to assess prevalence, elucidate the behavior's multi-etiological nature, and discuss prevention implications. Peer-reviewed studies were located through key phrase searches (prescription stimulant misuse and college; "prescription stimulant misuse" and "college"; illicit use of prescription stimulants in college; nonmedical prescription stimulant use in college students) in electronic databases (PubMed, PubMed Central, and EBSCO Host) for the period 2000 to 2013. Studies meeting inclusion criteria had their references reviewed for additional eligible literature. Statistically significant correlates of IUPS in the 62 retrieved studies were organized using the three streams of influence and four levels of causation specified in the TTI. Results show the prevalence of IUPS varies across campuses. Additionally, findings suggest the behavior is multifaceted, as correlates were observed within each stream of influence and level of causation specified by the TTI. We conclude that IUPS is prevalent in, but varies across, colleges, and is influenced by intrapersonal and broader social and societal factors. We discuss implications for prevention and directions for future research.
Benson K	2015	Benson K, Flory K, Humphreys KL, Lee SS. Misuse of stimulant medication among college students: a comprehensive review and meta-analysis	The misuse of stimulant medication among college students is a prevalent and growing problem. The purpose of this review and meta-analysis is to summarize the current research on rates and demographic and psychosocial correlates of stimulant medication misuse among college students, to provide methodological guidance and other ideas for future research, and to provide some preliminary suggestions for preventing and reducing misuse on college campuses. Random-effects meta-analysis found that the rate of stimulant medication misuse among college students was estimated at 17 % (95 % CI [0.13, 0.23], $p < .001$) and identified several psychological variables that differentiated

		Clin Child Fam Psychol Rev. 2015 Mar;18(1):50-76. doi: 10.1007/s10567-014-0177-z.	misusers and nonusers, including symptoms of attention-deficit/hyperactivity disorder, problems associated with alcohol use, and marijuana use. A qualitative review of the literature also revealed that Greek organization membership, academic performance, and other substance use were associated with misuse. Students are misusing primarily for academic reasons, and the most common source for obtaining stimulant medication is peers with prescriptions. Interpretation of findings is complicated by the lack of a standard misuse definition as well as validated tools for measuring stimulant misuse. The relation between stimulant medication misuse and extra curricular participation, academic outcomes, depression, and eating disorders requires further investigation, as do the reasons why students divert or misuse and whether policies on college campuses contribute to the high rates of misuse among students. Future research should also work to develop and implement effective prevention strategies for reducing the diversion and misuse of stimulant medication on college campuses.
Carney T	2016	Carney T, Myers BJ, Louw J, Okwundu CI. Brief school-based interventions and behavioural outcomes for substance-using adolescents Cochrane Database Syst Rev. 2016 Jan 20;2016(1):CD008969. doi: 10.1002/14651858.CD008969.pub3.	Background: Adolescent substance use is a major problem in and of itself, and because it acts as a risk factor for other problem behaviours. As substance use during adolescence can lead to adverse and oKen long-term health and social consequences, it is important to intervene early in order to prevent progression to more severe problems. Brief interventions have been shown to reduce problematic substance use among adolescents and are especially useful for individuals who have moderately risky patterns of substance use. Such interventions can be conducted in school settings. This review set out to evaluate the effectiveness of brief school-based interventions for adolescent substance use. Objectives: To evaluate the effectiveness of brief school-based interventions in reducing substance use and other behavioural outcomes among adolescents compared to another intervention or assessment-only conditions. Search methods: We conducted the original literature search in March 2013 and performed the search update to February 2015. For both review stages (original and update), we searched 10 electronic databases and six websites on evidence-based

			interventions, and the reference lists of included studies and reviews, from 1966 to February 2015. We also contacted authors and organisations to identify any additional studies. Selection criteria: We included randomised controlled trials that evaluated the effects of brief school-based interventions for substance-using adolescents. The primary outcomes were reduction or cessation of substance use. The secondary outcomes were engagement in criminal activity and engagement in delinquent or problem behaviours related to substance use. Data collection and analysis: We used the standard methodological procedures outlined by The Cochrane Collaboration, including the GRADE approach for evaluating the quality of evidence. Main results: We included six trials with 1176 adolescents that measured outcomes at different follow-up periods in this review. Three studies with 732 adolescents compared brief interventions (BIs) with information provision only, and three studies with 444 adolescents compared BIs with assessment only. Reasons for downgrading the quality of evidence included risk of bias of the included studies, imprecision, and inconsistency. For outcomes that concern substance abuse, the retrieved studies only assessed alcohol and cannabis. We generally found moderate-quality evidence that, compared to information provision only, BIs did not have a significant effect on any of the substance use outcomes at short-, medium-, or long-term follow-up. They also did not have a significant effect on delinquent-type behaviour outcomes among adolescents. When compared to assessment-only controls, we found low- or very low-quality evidence that BIs reduced cannabis frequency at short-term follow-up in one study (standardised mean difference (SMD) -0.83; 95% confidence interval (CI) -1.14 to -0.53, n =269). BIs also significantly reduced frequency of alcohol use (SMD -0.91; 95% CI -1.21 to -0.61, n = 242), alcohol abuse (SMD -0.38; 95% CI -0.7 to -0.07, n = 190) and dependence (SMD -0.58; 95% CI -0.9 to -0.26, n = 190), and cannabis abuse (SMD -0.34; 95% CI -0.65 to -0.02, n =190) at medium-term follow-up in one study. At long-term follow-up, BIs also reduced alcohol abuse (SMD -0.72;

			95% CI -1.05 to -0.40, n =181), cannabis frequency (SMD -0.56; 95% CI -0.75 to -0.36, n = 181), abuse (SMD -0.62; 95% CI -0.95 to -0.29, n = 181), and dependence (SMD -0.96; 95% CI -1.30 to -0.63, n = 181) in one study. However, the evidence from studies that compared brief interventions to assessment only conditions was generally of low quality. Brief interventions also had mixed effects on adolescents' delinquent or problem behaviours, although the effect at long-term follow-up on these outcomes in the assessment-only comparison was significant (SMD -0.78; 95% CI -1.11 to -0.45). Authors' conclusions: We found low- or very low-quality evidence that brief school-based interventions may be more effective in reducing alcohol and cannabis use than the assessment-only condition and that these reductions were sustained at long-term follow-up. We found moderate-quality evidence that, when compared to information provision, brief interventions probably did not have a significant effect on substance use outcomes. It is premature to make definitive statements about the effectiveness of brief school-based interventions for reducing adolescent substance use. Further high-quality studies examining the relative effectiveness of BIs for substance use and other problem behaviours need to be conducted, particularly in low- and middle-income countries.
Champion KE	2016	Champion KE, Newton NC, Teesson M. Prevention of alcohol and other drug use and related harm in the digital age: what does the evidence tell us? Curr Opin Psychiatry. 2016 Jul;29(4):242-9. doi: 10.1097/YCO.0000000000000258.	Purpose of review: Alcohol and other drug use are major contributors to the global burden of disease. Prevention is critical and evidence is beginning to support the use of online mediums to prevent alcohol and other drug use and harms among adolescents. This study aims to expand the evidence base by conducting a systematic review of recent universal prevention programs delivered by computers and the Internet. Recent findings A total of 12 papers reporting outcomes from trials of nine universal online prevention programs were identified. Of the identified interventions, five targeted multiple substances, two focused solely on alcohol, one targeted only cannabis and one primarily addressed smoking. The majority of programs were delivered at school; however one was implemented in a primary care setting. Six programs demonstrated significant, but modest, effects for alcohol and/or other drug use outcomes. Summary: Evidence to support the efficacy of computer and Internet-based prevention

			programs for alcohol and other drug use and related harms among adolescents is rapidly emerging, demonstrating that online prevention is an area of increasing promise. Further replication work, longer-term trials and attempts to increase the impact are required.
Champion KE	2013	Champion KE, Newton NC, Barrett EL, Teesson M. A systematic review of school-based alcohol and other drug prevention programs facilitated by computers or the internet Drug Alcohol Rev. 2013 Mar;32(2):115-23. doi: 10.1111/j.1465-3362.2012.00517.x. Epub 2012 Oct 8.	Issues: The use of alcohol and drugs amongst young people is a serious concern and the need for effective prevention is clear. This paper identifies and describes current school-based alcohol and other drug prevention programs facilitated by computers or the Internet. Approach: The Cochrane Library, PsycINFO and PubMed databases were searched in March 2012. Additional materials were obtained from reference lists of papers. Studies were included if they described an Internet- or computer-based prevention program for alcohol or other drugs delivered in schools. Key Findings: Twelve trials of 10 programs were identified. Seven trials evaluated Internet-based programs and five delivered an intervention via CD-ROM. The interventions targeted alcohol, cannabis and tobacco. Data to calculate effect size and odds ratios were unavailable for three programs. Of the seven programs with available data, six achieved reductions in alcohol, cannabis or tobacco use at post intervention and/or follow up. Two interventions were associated with decreased intentions to use tobacco, and two significantly increased alcohol and drug-related knowledge. Conclusion. This is the first study to review the efficacy of school-based drug and alcohol prevention programs delivered online or via computers. Findings indicate that existing computer- and Internet based prevention programs in schools have the potential to reduce alcohol and other drug use as well as intentions to use substances in the future. These findings, together with the implementation advantages and high fidelity associated with new technology, suggest that programs facilitated by computers and the Internet offer a promising delivery method for school-based prevention. [Champion KE, Newton NC, Barrett EL, Teesson M. A systematic review of school-based alcohol and other drug prevention programs facilitated by computers or the Internet.

Coren E	2016	Coren, E; Hossain, R; Pardo Pardo, J; Bakker, B Interventions for promoting reintegration and reducing harmful behaviour and lifestyles in streetâ€• connected children and young people Cochrane Database Syst Rev. 2016 Jan 13;2016(1):CD009823. doi: 10.1002/14651858.CD009823.pub3.	Background: Millions of street-connected children and young people worldwide live or work in street environments. They are vulnerable to many risks, whether or not they remain connected to families of origin, and despite many strengths and resiliencies, they are excluded from mainstream social structures and opportunities. Objectives: Primary research objective: To evaluate and summarise the effectiveness of interventions for street-connected children and young people that aim to: • promote inclusion and reintegration; • increase literacy and numeracy; • facilitate access to education and employment; • promote mental health, including self esteem; • reduce harms associated with early sexual activity and substance misuse. Secondary research objectives: • To explore whether effects of interventions differ within and between populations, and whether an equity gradient influences these effects, by extrapolating from all findings relevance for low- and middle-income countries (LMICs) (Peters 2004). • To describe other health, educational, psychosocial and behavioural effects, when appropriate outcomes are reported. • To explore the influence of context in design, delivery and outcomes of interventions. • To explore the relationship between numbers of components and duration and effects of interventions. • To highlight implications of these findings for further research and research methods to improve evidence in relation to the primary research objective. • To consider adverse or unintended outcomes. Search methods: We searched the following bibliographic databases, searched for the original review, from inception to 2012, and various relevant nongovernmental and organisational websites: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE and Pre-MEDLINE; EMBASE and EMBASE Classic; Cumulative Index to

			Nursing and Allied Health Literature (CINAHL); PsycINFO; Education Resource Information Center (ERIC); Sociological Abstracts; Social Services Abstracts; Social Work Abstracts; Healthstar; Latin American Caribbean Health Sciences Literature (LILACS); System for Grey literature in Europe (Open Grey); ProQuest Dissertations and Theses; EconLit; IDEAS Economics and Finance Research; JOLIS Library Catalog of the holdings of the World Bank Group and International Monetary Fund (IMF) Libraries; British Library for Development Studies (BLDS); Google and Google Scholar. We updated the search in April 2015 for the review update, using the same methods. Selection criteria: This review includes data from harm reduction or reintegration intervention studies that used a comparison group study design; all were randomised or quasi-randomised studies. Studies were included if they evaluated interventions provided for street-connected children and young people, from birth to 24 years, in all contexts. Data collection and analysis: Two review authors independently extracted data and assessed risk of bias and other factors presented in the Discussion and Summary quality assessment (Grades of Recommendation, Assessment, Development and Evaluation (GRADE)).We extracted data on intervention delivery, context, process factors, equity and outcomes, and grouped outcomes into psychosocial outcomes, risky sexual behaviours or substance use. We conducted meta-analyses for outcomes where the outcome measures were sufficiently similar. We evaluated other outcomes narratively. Main results: We included 13 studies evaluating 19 interventions from high-income countries (HICs). At update stage (from our 2015 search), one previously included study was removed and three new studies added (since our 2012 search). We found no sufficiently robust evaluations conducted in low- and middle-income countries (LMICs). Study quality overall was low and measurements used by studies variable. Participants were classified as drop-in and shelter-based. No studies measured the primary outcome of reintegration and none reported on adverse effects. We found no consistent results on a range of relevant outcomes within domains of psychosocial health, substance misuse and sexually risky behaviours . Interventions evaluated consisted of time-limited

			therapeutically based programmes that proved no more effective than standard shelter or drop-in services and other control interventions used for most outcomes in most studies. Favourable changes from baseline were reported for outcomes for most participants following therapy interventions and standard services. We noted considerable heterogeneity between studies and inconsistent reporting of equity data. No studies measured the primary outcome of reintegration or reported on adverse effects. Authors' conclusions: Analysis revealed no consistently significant benefit for focused therapeutic interventions compared with standard services such as drop-in centres, case management and other comparable interventions for street-connected children and young people. Commonly available services, however, were not rigorously evaluated. Robust evaluation of interventions, including comparison with no intervention, would establish a more reliable evidence base to inform service implementation. More robust research is needed in LMICs to examine interventions for street-connected children and young people with different backgrounds and service needs.
Dick S	2019	Dick S, Whelan E, Davoren MP, Dockray S, Heavin C, Linehan C, Byrne M. A systematic review of the effectiveness of digital interventions for illicit substance misuse harm reduction in third-level students BMC Public Health. 2019 Sep 9;19(1):1244. doi:	Background: Illicit substance misuse is a growing public health problem, with misuse peaking among 18–25 year olds, and attendance at third-level education identified as a risk factor. Illicit substance misuse has the potential to harm mental and physical health, social relationships, and impact on academic achievements and future career prospects. Digital interventions have been identified as a vehicle for reaching large student populations and circumventing the limited capacity of student health services for delivering face-to-face interventions. Digital interventions have been developed in the area of alcohol and tobacco harm reduction, reporting some effectiveness, but the evidence for the effectiveness of digital interventions targeting illicit substance misuse is lacking. This review aims to systematically identify and critically appraise studies examining the effectiveness of digital interventions for illicit substance misuse harm reduction in third-level students. Methods: We systematically searched ten databases in April 2018 using keywords and database specific terms under

		10.1186/s12889-019-7583-6.	the pillars of “mHealth,” “substance misuse,” and “student.” To be eligible for inclusion, papers had to present a measure of illicit substance misuse harm reduction. Included articles were critically appraised and included in the qualitative synthesis regardless of quality. Results: A total of eight studies were included in the qualitative synthesis. Studies reported harm reduction in terms of substance misuse or initiation, as consequences or problems associated with substance misuse, or as correction of perceived social norms. Overall, five out of the eight studies reported at least one positive outcome for harm reduction. The critical appraisal indicated that the study quality was generally weak, predominantly due to a lack of blinding of study participants, and the use of self-reported substance misuse measures. However, results suggest that digital interventions may produce a modest reduction in harm from illicit substance misuse. Conclusions: The results of this review are positive and support the need for further high-quality research in this area, particularly given the success of digital interventions for alcohol and tobacco harm reduction. However, very few studies focused solely on illicit substances, and those that did targeted only marijuana. This suggests the need for further research on the effectiveness of this type of intervention for other illicit substances
Faggiano F	2014	Faggiano F, Minozzi S, Versino E, Buscemi D. Universal school-based prevention for illicit drug use Cochrane Database Syst Rev. 2014;2014(12):CD003	Background: Drug addiction is a chronic, relapsing disease. Primary interventions should aim to reduce first use or to prevent the transition from experimental use to addiction. School is the appropriate setting for preventive interventions. Objectives: To evaluate the effectiveness of universal school-based interventions in reducing drug use compared to usual curricular activities or no intervention. Search methods: We searched the Cochrane Drugs and Alcohol Group's Trials Register (September 2013), the Cochrane Central Register of Controlled Trials (2013, Issue 9), PubMed (1966 to September 2013), EMBASE (1988 to September 2013) and other

		020. doi: 10.1002/14651858.CD003020.pub3. Epub 2014 Dec 1.	databases. We also contacted researchers in the field and checked reference lists of articles. Selection criteria: Randomised controlled trials (RCT) evaluating school-based interventions designed to prevent illicit drugs use. Data collection and analysis: We used the standard methodological procedures expected by The Cochrane Collaboration. Main results: We included 51 studies, with 127,146 participants. Programmes were mainly delivered in sixth and seventh grade pupils. Most of the trials were conducted in the USA. Social competence approach versus usual curricula or no intervention Marijuana use at < 12 months follow-up: the results favoured the social competence intervention (risk ratio (RR) 0.90; 95% confidence interval (CI) 0.81 to 1.01, four studies, 9456 participants, moderate quality evidence). Seven studies assessed this outcome (no data for meta-analysis): two showed a positive significant effect of intervention, three showed a non-significant effect, one found a significant effect in favour of the control group and one found a trend in favour of the control group. Marijuana use at 12+ months: the results favoured the social competence intervention (RR 0.86; 95% CI 0.74 to 1.00, one study, 2678 participants, high quality evidence). Seven studies assessed this outcome (no data for meta-analysis): two showed a significant positive effect of intervention, three showed a non-significant effect, one found a significant effect in favour of the control group and one a trend in favour of the control group. Hard drug use at < 12 months: we found no difference (RR 0.69; 95% CI 0.40 to 1.18, one study, 2090 participants, moderate quality evidence). Two studies assessed this outcome (no data for meta-analysis): one showed comparable results for the intervention and control group; one found a statistically non-significant trend in favour of the social competence approach. Hard drug use at 12+ months: we found no difference (mean difference (MD) -0.01; 95% CI -0.06 to 0.04), one study, 1075 participants, high quality evidence). One study with no data for meta-analysis showed comparable results for the intervention and control group. Any drug use at < 12 months: the results favoured social competence interventions (RR

			0.27; 95% CI 0.14 to 0.51, two studies, 2512 participants, moderate quality evidence). One study with 1566 participants provided continuous data showing no difference (MD 0.02; 95% CI -0.05 to 0.09, moderate quality evidence). Social influence approach versus usual curricula or no intervention Marijuana use at < 12 months: we found a nearly statistically significant effect in favour of the social influence approach (RR 0.88; 95% CI 0.72 to 1.07, three studies, 10,716 participants, moderate quality evidence). One study with 764 participants provided continuous data showing results that favoured the social influence intervention (MD -0.26; 95% CI -0.48 to -0.04). Marijuana use at 12+ months: we found no difference (RR 0.95; 95% CI 0.81 to 1.13, one study, 5862 participants, moderate quality evidence). One study with 764 participants provided continuous data and showed nearly statistically significant results in favour of the social influence intervention (MD -0.22; 95% CI -0.46 to 0.02). Of the four studies not providing data for meta-analysis a statistically significant protective effect was only found by one study. Hard drug use at 12+ months: one study not providing data for meta-analysis found a significant protective effect of the social influence approach. Any drug use: no studies assessed this outcome. Combined approach versus usual curricula or no intervention: Marijuana use at < 12 months: there was a trend in favour of intervention (RR 0.79; 95% CI 0.59 to 1.05, three studies, 8701 participants, moderate quality evidence). One study with 693 participants provided continuous data and showed no difference (MD -1.90; 95% CI -5.83 to 2.03). Marijuana use at 12+ months: the results favoured combined intervention (RR 0.83; 95% CI 0.69 to 0.99, six studies, 26,910 participants, moderate quality evidence). One study with 690 participants provided continuous data and showed no difference (MD -0.80; 95% CI -4.39 to 2.79). Two studies not providing data for meta-analysis did not find a significant effect. Hard drug use at < 12 months: one study with 693 participants provided both dichotomous and continuous data and showed conflicting results: no difference for dichotomous outcomes (RR 0.85; 95% CI 0.63 to 1.14), but results in favour of the combined intervention for the continuous outcome (MD -3.10; 95% CI -5.90 to -0.30). The quality of evidence was high. Hard drug use at 12+ months: we found no difference (RR 0.86; 95%

			CI 0.39 to 1.90, two studies, 1066 participants, high quality evidence). One study with 690 participants provided continuous data and showed no difference (MD 0.30; 95% CI -1.36 to 1.96). Two studies not providing data for meta-analysis showed a significant effect of treatment. Any drug use at < 12 months: the results favoured combined intervention (RR 0.76; 95% CI 0.64 to 0.89, one study, 6362 participants). Only one study assessed the effect of a knowledge-focused intervention on drug use and found no effect. The types of comparisons and the programmes assessed in the other two groups of studies were very heterogeneous and difficult to synthesise. Authors' conclusions: School programmes based on a combination of social competence and social influence approaches showed, on average, small but consistent protective effects in preventing drug use, even if some outcomes did not show statistical significance. Some programmes based on the social competence approach also showed protective effects for some outcomes. Since the effects of school-based programmes are small, they should form part of more comprehensive strategies for drug use prevention in order to achieve a population-level impact.
Ferri M	2013	Ferri, M; Allara, E; Bo, A; Gasparrini, A; Faggiano, F Media campaigns for the prevention of illicit drug use in young people Cochrane Database Syst Rev. 2013 Jun 5;(6):CD009287. doi: 10.1002/14651858.CD009287.pub2.	Background: Substance-specific mass media campaigns which address young people are widely used to prevent illicit drug use. They aim to reduce use and raise awareness of the problem. Objectives: To assess the effectiveness of mass media campaigns in preventing or reducing the use of or intention to use illicit drugs amongst young people. Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2013, Issue 1), including the Cochrane Drugs and Alcohol Group's Specialised Register; MEDLINE through PubMed (from 1966 to 29 January 2013); EMBASE (from 1974 to 30 January 2013) and ProQuest Dissertations & Theses A&I (from 1861 to 3 February 2013). Selection criteria: Cluster-randomised controlled trials, prospective and retrospective cohort studies, interrupted time series and controlled before and after studies evaluating the effectiveness of mass media campaigns in influencing drug use, intention to use or the

			attitude of young people under the age of 26 towards illicit drugs. Data collection and analysis: We used the standard methodological procedures of The Cochrane Collaboration. Main results: We included 23 studies involving 188,934 young people, conducted in the USA, Canada and Australia between 1991 and 2012. Twelve studies were randomised controlled trials (RCT), two were prospective cohort studies (PCS), one study was both a RCT and a PCS, six were interrupted time series and two were controlled before and after (CBA) studies. The RCTs had an overall low risk of bias, along with the ITS (apart from the dimension 'formal test of trend'), and the PCS had overall good quality, apart from the description of loss to follow up by exposure. Self-reported or biomarker-assessed illicit drug use was measured with an array of published and unpublished scales making comparisons difficult. Pooled results of five RCTs (N = 5470) show no effect of media campaign intervention (standardised mean difference (SMD) -0.02; 95% confidence interval (CI) -0.15 to 0.12). We also pooled five ITS studies (N = 26,405) focusing specifically on methamphetamine use. Out of four pooled estimates (two endpoints measured in two age groups), there was evidence of a reduction only in past-year prevalence of methamphetamine use among 12 to 17 years old. A further five studies (designs = one RCT with PCS, two PCS, two ITS, one CBA, N = 151,508), which could not be included in meta-analyses, reported a drug use outcome with varied results including a clear iatrogenic effect in one case and reduction of use in another. Authors' conclusions: Overall the available evidence does not allow conclusions about the effect of media campaigns on illicit drug use among young people. We conclude that further studies are needed.
Georgie J M	2016	Georgie J M, Sean H, Deborah M C, Matthew H, Rona C. Peer-led interventions to prevent tobacco,	Background and Aims: Peer-led interventions may offer a beneficial approach in preventing substance use, but their impact has not yet been quantified. We conducted a systematic review to investigate and quantify the effect of peer-led interventions that sought to prevent tobacco, alcohol and/or drug use among young people aged 11–21 years.

		alcohol and/or drug use among young people aged 11-21 years: a systematic review and meta-analysis Addiction. 2016 Mar;111(3):391-407. doi: 10.1111/add.13224.	Methods: Medline, EMBASE, PsycINFO, CINAHL, ERIC and the Cochrane Library were searched from inception to July 2015 without language restriction. We included randomized controlled trials only. Screening and data extraction were conducted in duplicate and data from eligible studies were pooled in a random effects meta-analysis. Results: We identified 17 eligible studies, approximately half of which were school-based studies targeting tobacco use among adolescents. Ten studies targeting tobacco use could be pooled, representing 13 706 young people in 220 schools. Meta-analysis demonstrated that the odds of smoking were lower among those receiving the peer-led intervention compared with control [odds ratio (OR) = 0.78, 95% confidence interval (CI) = 0.62–0.99, P = 0.040]. There was evidence of heterogeneity (I2 = 41%, χ2 15.17, P = 0.086). Pooling of six studies representing 1699 individuals in 66 schools demonstrated that peer-led interventions were also associated with benefit in relation to alcohol use (OR = 0.80, 95% CI = 0.65–0.99, P = 0.036), while three studies (n = 976 students in 38 schools) suggested an association with lower odds of cannabis use (OR = 0.70, 0.50–0.97, P = 0.034). No studies were found that targeted other illicit drug use. Conclusions: Peer interventions may be effective in preventing tobacco, alcohol and possibly cannabis use among adolescents, although the evidence base is limited overall, and is characterized mainly by small studies of low quality.
MacArthur G	2016	MacArthur GJ, Harrison S, Caldwell DM, Hickman M, Campbell R. Peer-led interventions to prevent tobacco, alcohol and/or drug use among young people aged 11–21 years: a systematic	Background and Aims Peer-led interventions may offer a beneficial approach in preventing substance use, but their impact has not yet been quantified. We conducted a systematic review to investigate and quantify the effect of peer-led interventions that sought to prevent tobacco, alcohol and/or drug use among young people aged 11–21 years. Methods Medline, EMBASE, PsycINFO, CINAHL, ERIC and the Cochrane Library were searched from inception to July 2015 without language restriction. We included randomized controlled trials only. Screening and data extraction were conducted in duplicate and data from eligible studies were pooled in a random effects meta-analysis. Results We identified 17 eligible studies, approximately half of which were school-based studies targeting tobacco use among adolescents. Ten studies targeting tobacco use

		review and meta-analysis. Addiction 2016;111:391-407	could be pooled, representing 13 706 young people in 220 schools. Meta-analysis demonstrated that the odds of smoking were lower among those receiving the peer-led intervention compared with control [odds ratio (OR) = 0.78, 95% confidence interval (CI) = 0.62–0.99, P = 0.040]. There was evidence of heterogeneity (I2 = 41%, χ2 15.17, P = 0.086). Pooling of six studies representing 1699 individuals in 66 schools demonstrated that peer-led interventions were also associated with benefit in relation to alcohol use (OR = 0.80, 95% CI = 0.65–0.99, P = 0.036), while three studies (n = 976 students in 38 schools) suggested an association with lower odds of cannabis use (OR = 0.70, 0.50–0.97, P = 0.034). No studies were found that targeted other illicit drug use. Conclusions Peer interventions may be effective in preventing tobacco, alcohol and possibly cannabis use among adolescents, although the evidence base is limited overall, and is characterized mainly by small studies of low quality.
MacArthur G	2018	MacArthur, G; Caldwell, DM; Redmore, J; Watkins, SH; Kipping, R; White, J; Chittleborough, C; Langford, R; Er, V; Lingam, R; Pasch, K; Gunnell, D; Hickman, M; Campbell, R Individual, family, and school level interventions targeting multiple risk behaviours in young people Cochrane Database Syst Rev.	Background: Engagement in multiple risk behaviours can have adverse consequences for health during childhood, during adolescence, and later in life, yet little is known about the impact of different types of interventions that target multiple risk behaviours in children and young people, or the differential impact of universal versus targeted approaches. Findings from systematic reviews have been mixed, and effects of these interventions have not been quantitatively estimated. Objectives: To examine the effects of interventions implemented up to 18 years of age for the primary or secondary prevention of multiple risk behaviours among young people. Search methods: We searched 11 databases (Australian Education Index; British Education Index; Campbell Library; Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library; Embase; Education Resource Information Center (ERIC); International Bibliography of the Social Sciences; MEDLINE; PsycINFO; and Sociological Abstracts) on three occasions (2012, 2015, and 14 November 2016)). We conducted hand searches of reference lists, contacted experts in the field, conducted citation searches, and searched websites of relevant organisations.

		2018 Oct 5;10(10):CD009927. doi: 10.1002/14651858.CD009927.pub2.	Selection criteria: We included randomised controlled trials (RCTs), including cluster RCTs, which aimed to address at least two risk behaviours. Participants were children and young people up to 18 years of age and/or parents, guardians, or carers, as long as the intervention aimed to address involvement in multiple risk behaviours among children and young people up to 18 years of age. However, studies could include outcome data on children > 18 years of age at the time of follow-up. Specifically, we included studies with outcomes collected from those eight to 25 years of age. Further, we included only studies with a combined intervention and follow-up period of six months or longer. We excluded interventions aimed at individuals with clinically diagnosed disorders along with clinical interventions. We categorised interventions according to whether they were conducted at the individual level; the family level; or the school level. Data collection and analysis: We identified a total of 34,680 titles, screened 27,691 articles and assessed 424 full-text articles for eligibility. Two or more review authors independently assessed studies for inclusion in the review, extracted data, and assessed risk of bias. We pooled data in meta-analyses using a random-effects (Der Simonian and Laird) model in Rev Man 5.3. For each outcome, we included subgroups related to study type (individual, family, or school level, and universal or targeted approach) and examined Effectiveness at up to 12 months' follow-up and over the longer term (> 12 months). We assessed the quality and certainty of evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. Main results: We included in the review a total of 70 eligible studies, of which a substantial proportion were universal school-based studies (n = 28; 40%). Most studies were conducted in the USA (n = 55; 79%). On average, studies aimed to prevent four of the primary behaviours. Behaviours that were most frequently addressed included alcohol use (n = 55), drug use (n = 53), and/or antisocial behaviour (n = 53), followed by tobacco use (n = 42). No studies aimed to prevent self-harm or gambling alongside other behaviours. Evidence suggests that for multiple risk behaviours, universal school-based interventions were beneficial in relation to tobacco use (odds ratio (OR) 0.77, 95% confidence interval

			(CI) 0.60 to 0.97; n = 9 studies; 15,354 participants) and alcohol use (OR 0.72, 95% CI 0.56 to 0.92; n= 8 studies; 8751 participants; both moderate-quality evidence) compared to a comparator, and that such interventions may be effective in preventing illicit drug use (OR 0.74, 95% CI 0.55 to 1.00; n = 5 studies; 11,058 participants; low-quality evidence) and engagement in any antisocial behaviour (OR 0.81, 95% CI 0.66 to 0.98; n = 13 studies; 20,756 participants; very low-quality evidence) at up to 12 months' follow-up, although there was evidence of moderate to substantial heterogeneity (IM = 49% to 69%). Moderate-quality evidence also showed that multiple risk behaviour universal school-based interventions improved the odds of physical activity (OR 1.32, 95% CI 1.16 to 1.50; IM = 0%;n = 4 studies; 6441 participants). We considered observed effects to be of public health importance when applied at the population level. Evidence was less certain for the effects of such multiple risk behaviour interventions for cannabis use (OR 0.79, 95% CI 0.62 to 1.01; P =0.06; n = 5 studies; 4140 participants; IM = 0%; moderate-quality evidence), sexual risk behaviours (OR 0.83, 95% CI 0.61 to 1.12; P = 0.22; n =6 studies; 12,633 participants; IM = 77%; low-quality evidence), and unhealthy diet (OR 0.82, 95% CI 0.64 to 1.06; P = 0.13; n = 3 studies; 6441 participants; IM = 49%; moderate-quality evidence). It is important to note that some evidence supported the positive effects of universal school-level interventions on three or more risk behaviours. For most outcomes of individual- and family-level targeted and universal interventions, moderate- or low-quality evidence suggests little or no effect, although caution is warranted in interpretation because few of these studies were available for comparison (n N 4 studies foreach outcome). Seven studies reported adverse effects, which involved evidence suggestive of increased involvement in a risk behaviour among participants receiving the intervention compared to participants given control interventions. We judged the quality of evidence to be moderate or low for most outcomes, primarily owing to concerns around selection, performance, and detection bias and heterogeneity between studies. Authors' conclusions: Available evidence is strongest for universal school-based interventions that target multiple- risk behaviours, demonstrating that they may be effective

			in preventing engagement in tobacco use, alcohol use, illicit drug use, and antisocial behaviour, and in improving physical activity among young people, but not in preventing other risk behaviours. Results of this review do not provide strong evidence of benefit for family- or individual-level interventions across the risk behaviours studied. However, poor reporting and concerns around the quality of evidence highlight the need for high-quality multiple- risk behaviour intervention studies to further strengthen the evidence base in this field.
Melchior M	2019	Melchior M, Nakamura A, Bolze C, Hausfater F, El Khoury F, Mary-Krause M, Azevedo Da Silva M. Does liberalisation of cannabis policy influence levels of use in adolescents and young adults? A systematic review and meta-analysis BMJ Open. 2019 Jul 10;9(7):e025880. doi: 10.1136/bmjopen-2018-025880.	Objectives: To examine the effect of cannabis policy liberalisation (decriminalisation and legalisation) levels of use in adolescents and young adults. Design: Systematic review and meta-analysis. Inclusion criteria: Included studies were conducted among individuals younger than 25 years and quantitatively assessing consequences of cannabis policy change. We excluded articles: (A) exclusively based on participants older than 25 years; (B) only reporting changes in perceptions of cannabis use; (C) not including at least two measures of cannabis use; (D) not including quantitative data; and (E) reviews, letters, opinions and policy papers. PubMed, PsycINFO, Embase and Web of Science were searched through 1 March 2018. Data extraction and synthesis: Two independent readers reviewed the eligibility of titles and abstracts and read eligible articles, and four authors assessed the risk of bias (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies). Extracted data were meta-analysed. The protocol was registered with PROSPERO. Results 3438 records were identified via search terms and four via citation lists; 2312 were retained after removal of duplicates, 99 were assessed for eligibility and41 were included in our systematic review. 13 articles examined cannabis decriminalisation, 20 examined legalisation for medical purposes and 8 examined legalization for recreational purposes. Findings regarding the consequences of cannabis decriminalisation or legalization for medical purposes were too heterogeneous to be meta-analysed. Our systematic review and meta-analysis suggest a small increase in cannabis use among adolescents and

			young adults following legalisation of cannabis for recreational purposes (standardised mean difference of 0.03, 95% CI −0.01 to –0.07). Nevertheless, studies characterised by a very low/low risk of bias showed no evidence of changes in cannabis use following policy modifications. Conclusions: Cannabis policy liberalisation does not appear to result in significant changes in youths' use, with the possible exception of legalisation for recreational purposes that requires monitoring.
Minozzi S	2014	Minozzi S, Amato L, Bellisario C, Davoli M. Maintenance treatments for opiate - dependent adolescents. Cochrane Database Syst Rev. 2014 Jun 24;(6):CD007210. doi: 10.1002/14651858.CD007210.pub3.	Background: The scientific literature examining effective treatments for opioid-dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component. Nevertheless, no reviews have been published that systematically assess the effectiveness of pharmacological maintenance treatment in adolescents. Objectives: To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions for retaining adolescents in treatment, reducing the use of substances and improving health and social status. Search methods: We searched the Cochrane Drugs and Alcohol Group's Trials Register (January 2014), the Cochrane Central Register of Controlled Trials (2014, Issue 1), PubMed (January 1966 to January 2014), EMBASE (January 1980 to January 2014), CINAHL (January 1982 to January 2014), Web of Science (1991 to January 2014) and reference lists of articles. Selection criteria: Randomised and controlled clinical trials of any maintenance pharmacological interventions either alone or associated with psychosocial intervention compared with no intervention, placebo, other pharmacological intervention, pharmacological detoxification or psychosocial intervention in adolescents (13 to 18 years). Data collection and analysis: We used the standard methodological procedures expected by The Cochrane Collaboration. Main results: We included two trials involving 189 participants. One study, with 35

			participants, compared methadone with levo-alpha-acetylmethadol (LAAM) for maintenance treatment lasting 16 weeks, after which patients were detoxified. The other study, with 154 participants, compared maintenance treatment with buprenorphine-naloxone and detoxification with buprenorphine. We did not perform meta-analysis because the two studies assessed different comparisons. In the study comparing methadone and LAAM, the authors declared that there was no difference in the use of a substance of abuse or social functioning (data not shown). The quality of the evidence was very low. No side effects, such as nausea, vomiting, constipation, weakness, or fatigue, were reported by study participants. In the comparison between buprenorphine maintenance and buprenorphine detoxification, maintenance treatment appeared to be more efficacious in retaining patients in treatment (drop-out risk ratio (RR) 0.37; 95% confidence interval (CI) 0.26 to 0.54), but not in reducing the number of patients with a positive urine test at the end of the study (RR 0.97; 95% CI 0.78 to 1.22). Self-reported opioid use at one year follow-up was significantly lower in the maintenance group, even though both groups reported a high level of opioid use (RR 0.73; 95% CI 0.57 to 0.95). More patients in the maintenance group were enrolled in other addiction treatment programmes at 12-month follow up (RR 1.33; 95% CI 0.94 to 1.88). The quality of the evidence was low. No serious side effects attributable to buprenorphine-naloxone were reported by study participants and no patients were removed from the study due to side effect. The most common side effect was headache, which was reported by 16% to 21% of patients in both groups Authors' conclusions: It is difficult to draw conclusions on the basis of only two trials. One of the possible reasons for the lack of evidence could be the difficulty of conducting trials with young people for practical and ethical reasons. There is an urgent need for further randomised controlled trials comparing maintenance treatment with detoxification treatment or psychosocial treatment alone before carrying out studies that compare different pharmacological maintenance treatments. These studies should have long follow-

			up and measure relapse rates after the end of treatment and social functioning (integration at school or at work, family relationships).
Minozzi S	2014	Minozzi S, Amato L, Davoli M. Detoxification treatments for opiate dependent adolescents. Cochrane Database Syst Rev 2009:Cd006749	Background: The scientific literature examining effective treatments for opioid dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component of effective treatments for opioid dependence. Nevertheless, no studies have been published that systematically assess the effectiveness of the pharmacological detoxification among adolescents. Objectives: To assess the effectiveness of any detoxification treatment alone or in combination with psychosocial intervention compared with no intervention, other pharmacological intervention or psychosocial interventions on completion of treatment, reducing the use of substances and improving health and social status. Search methods: We searched the Cochrane Central Register of Controlled Trials (2014, Issue 1), PubMed (January 1966 to January 2014), EMBASE (January 1980 to January 2014), CINHAL (January 1982 to January 2014), Web of Science (1991-January 2014) and reference lists of articles. Selection criteria: Randomised controlled clinical trials comparing any pharmacological interventions alone or associated with psychosocial intervention aimed at detoxification with no intervention, placebo, other pharmacological intervention or psychosocial intervention in adolescents (13 to 18 years). Data collection and analysis: We used standard methodological procedures recommended by The Cochrane Collaboration Main results: Two trials involving 190 participants were included. One trial compared buprenorphine with clonidine for detoxification. No difference was found for drop out: risk ratio (RR) 0.45 (95% confidence interval (CI): 0.20 to 1.04) and acceptability of treatment: withdrawal score mean difference (MD): 3.97 (95% CI -1.38 to 9.32). More participants in the buprenorphine group initiated naltrexone treatment: RR 11.00 (95% CI 1.58 to 76.55), quality of evidence moderate. The other trial compared maintenance treatment versus detoxification treatment: buprenorphine-naloxone maintenance versus buprenorphine

			detoxification. For drop out the results were in favour of maintenance treatment: RR 2.67 (95% CI 1.85, 3.86), as well as for results at follow-up RR 1.36 [95% CI 1.05to 1.76); no differences for use of opiate, quality of evidence low. Authors' conclusions: It is difficult to draw conclusions on the basis of two trials with few participants. Furthermore, the two studies included did not consider the efficacy of methadone that is still the most frequent drug utilised for the treatment of opioid withdrawal. One possible reason for the lack of evidence could be the difficulty in conducting trials with young people due to practical and ethical reasons.
Newton AS	2013	Newton AS, Dong K, Mabood N, Ata N, Ali S, Gokiert R, Vandermeer B, Tjosvold L, Hartling L, Wild TC. Brief emergency department interventions for youth who use alcohol and other drugs: a systematic review Pediatr Emerg Care. 2013 May;29(5):673-84. doi: 10.1097/PEC.0b013e31828ed325.	Objective: Brief intervention (BI) is recommended for use with youth who use alcohol and other drugs. Emergency departments (EDs) can provide BIs at a time directly linked to harmful and hazardous use. The objective of this systematic review was to determine the effectiveness of ED-based BIs. Methods: We searched 14 electronic databases, a clinical trial registry, conference proceedings, and study references. We included randomized controlled trials with youth 21 years or younger. Two reviewers independently selected studies and assessed methodological quality. One reviewer extracted and a second verified data. We summarized findings qualitatively. Results: Two trials with low risk of bias, 2 trials with unclear risk of bias, and 5 trials with high risk of bias were included. Trials evaluated targeted BIs for alcohol-positive (n = 3) and alcohol/other drug positive youth (n = 1) and universal BIs for youth reporting recent alcohol (n = 4) or cannabis use (n = 1). Few differences were found in favour of ED based BIs, and variation in outcome measurement and poor study quality precluded firm conclusions for many comparisons. Universal and targeted BIs did not significantly reduce alcohol use more than other care. In one targeted BI trial with high risk of bias, motivational interviewing (MI) that involved parents reduced drinking quantity per occasion and high-volume alcohol use compared with MI that was delivered to youth only. Another trial with high risk of bias reported an increase in abstinence and reduction in physical altercations when youth received peer-delivered universal MI for cannabis use. In 2 trials

			with unclear risk of bias, MI reduced drinking and driving and alcohol-related injuries after the ED visit. Computer-based MI delivered universally in 1 trial with low risk of bias reduced alcohol-related consequences 6 months after the ED visit. Conclusions: Clear benefits of using ED-based BI to reduce alcohol and other drug use and associated injuries or high-risk behaviours remain inconclusive because of variation in assessing outcomes and poor study quality.
O'Connor E	2020	O'Connor E, Thomas R, Senger CA, Perdue L, Robalino S, Patnode C. Interventions to Prevent Illicit and Nonmedical Drug Use in Children, Adolescents, and Young Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force JAMA. 2020 May 26;323(20):2067-2079. doi: 10.1001/jama.2020.1432.	IMPORTANCE: Illicit and nonmedical (use in ways other than instructed) drug use is common in adolescents and young adults and increases the risk of harmful outcomes such as injuries, violence, and poorer academic performance. OBJECTIVE: To review the benefits and harms of interventions to prevent illicit and nonmedical drug use in children, adolescents, and young adults to inform the US Preventive Services Task Force. DATA SOURCES MEDLINE, PubMED, PsycINFO, and the Cochrane Central Register of Controlled Trials (January 1, 2013, to January 31, 2019 [children and adolescents]; January 1,m1992, to January 31, 2019 [young adults <25 years]); surveillance through March 20, 2020.STUDY SELECTION Clinical trials of behavioral counseling interventions to prevent initiation of illicit and nonmedical drug use among young people. DATA EXTRACTION AND SYNTHESIS: Critical appraisal was completed independently by 2 investigators. Data were extracted by 1 reviewer and checked by a second. Random-effects meta-analysis was used to estimate the effect sizes associated with the interventions. MAIN OUTCOMES AND MEASURES: Number of times illicit drugs were used; any illicit drug or any cannabis use. RESULTS: Twenty-nine trials (N = 18 353) met inclusion criteria. Health, social, or legal outcomes such as mental health symptoms, family functioning, consequences of drug use, and arrests were reported in 19 trials and most showed no group differences. The effects on illicit drug use in 26 trials among nonpregnant youth (n = 17 811) were highly variable;

			the pooled result did not show a clinically important or statistically significant association with illicit drug use (standardized mean difference, −0.08 [95%CI, −0.16 to 0.001]; 24 effects [from 23 studies]; n = 12 801; I2 = 57.0%). The percentage of participants using illicit drugs ranged from 2.3%to 38.6%in the control groups and 2.4%to 33.7%in the intervention groups at 3 to 32 months' follow-up. The median absolute risk difference between groups was–2.8%, favoring the intervention group (range, –11.5%to 14.8%). The remaining 3 trials provided a perinatal home-visiting intervention to pregnant Native American youth. One trial (n=322) found a reduction in illicit drug use at 38 months (eg, cannabis use in the previous month, 10.7%in the intervention group and 15.6%in the control group) but not at earlier follow-up assessments. Across all 29 trials, only 1 trial reported on harms and found no statistically significant group differences. CONCLUSIONS AND RELEVANCE The evidence for behavioral counseling interventions to prevent initiation of illicit and nonmedical drug use among adolescents and young adults was inconsistent and imprecise, with some interventions associated with reduction in use and others associated with no benefit or increased use. Health, social, and legal outcomes were sparsely reported, and few showed improvements.
Patnode CD	2014	Patnode CD, O'Connor E, Rowland M, Burda BU, Perdue LA, Whitlock EP. Primary care behavioral interventions to prevent or reduce illicit drug use and nonmedical pharmaceutical use in children and	Background: Drug use among youths is associated with negative health and social consequences. Even infrequent use increases the risk for serious adverse events by increasing risk-taking behaviors in intoxicated or impaired persons. Purpose: To systematically review the benefits and harms of primary care–relevant interventions designed to prevent or reduce illicit drug use or the nonmedical use of prescription drugs among youths. Data Sources: PubMed, PsycINFO, and the Cochrane Central Register of Controlled Trials through 4 June 2013; MEDLINE through 31 August 2013; and manual searches of reference lists and gray literature. Study Selection: Two investigators independently reviewed 2253 abstracts and 144 full-text articles. English-language trials of primary care–relevant behavioral interventions that reported drug use, health outcomes, or harms were included.

		adolescents: a systematic evidence review for the U.S. Preventive Services Task Force Ann Intern Med. 2014 May 6;160(9):612-20. doi: 10.7326/M13-2064.	Data Extraction: One investigator abstracted data from good- and fair-quality trials into prespecified evidence tables, and a second investigator checked these data. Data Synthesis: Six trials were included, 4 of which examined the effect of the intervention on a health or social outcome. One trial found no effect of the intervention on marijuana-related consequences or driving under the influence of marijuana; 3 trials generally found no reduction in depressed mood at 12 or 24 months. Four of the 5 trials assessing self-reported marijuana use found statistically significant differences favoring the intervention group participants (such as a between-group difference of 0.10 to 0.17 use occasions in the past month). Three trials also reported positive outcomes in nonmedical prescription drug use occasions. Limitations: The body of evidence was small, and there were heterogeneous measures of outcomes of limited clinical applicability. Trials primarily included adolescents with little or no substance use. Conclusion: Evidence is inadequate on the benefits of primary care–relevant behavioral interventions in reducing self-reported illicit and pharmaceutical drug use among adolescents.
Porath-Waller AJ	2010	Porath-Waller AJ, Beasley E, Beirness DJ. A meta-analytic review of school-based prevention for cannabis use. Health Educ Behav. 2010 Oct;37(5):709-23. doi: 10.1177/1090198110361315. Epub 2010 Jun 3.	Abstract: This investigation used meta-analytic techniques to evaluate the effectiveness of school-based prevention programming in reducing cannabis use among youth aged 12 to 19. It summarized the results from 15 studies published in peer-reviewed journals since 1999 and identified features that influenced program effectiveness. The results from the set of 15 studies indicated that these school-based programs had a positive impact on reducing students' cannabis use (d = 0.58, CI: 0.55, 0.62) compared to control conditions. Findings revealed that programs incorporating elements of several prevention models were significantly more effective than were those based on only a social influence model. Programs that were longer in duration (≥15 sessions) and facilitated by individuals other than teachers in an interactive manner also yielded stronger effects. The results also suggested that programs targeting high school students were more effective than were

			those aimed at middle-school students. Implications for school-based prevention programming are discussed.
Steele DW	2020	Steele DW, Becker SJ, Danko KJ, Balk EM, Adam GP, Saldanha IJ, Trikalinos TA. Brief Behavioral Interventions for Substance Use in Adolescents: A Meta-analysis Pediatrics. 2020 Oct;146(4):e20200351. doi: 10.1542/peds.2020-0351. Epub 2020 Sep 14.	CONTEXT: Adolescents with problematic substance use (SU) are at risk for far-reaching adverse abstract outcomes. OBJECTIVE: Synthesize the evidence regarding the effects of brief behavioral interventions for adolescents (12–20 years) with problematic SU. DATA SOURCES: We conducted literature searches in Medline, the Cochrane Central Register of Controlled Trials, Embase, Cumulative Index to Nursing and Allied Health Literature, and PsycInfo through October 31, 2019. STUDY SELECTION: We screened 33 272 records and citations for interventions in adolescents with at least problematic SU, retrieved 1831 articles, and selected 22 randomized controlled trials of brief interventions meeting eligibility criteria for meta-analysis. DATA EXTRACTION: We followed Agency for Healthcare Research and Quality guidelines. We categorized brief interventions into components, including motivational interviewing (MI), psychoeducation, and treatment as usual. Outcomes included SU (abstinence, days used per month) for alcohol and cannabis, and substance-related problem scales. Strength of evidence (SoE) was assessed. RESULTS: Both pairwise and network meta-analyses were conducted by using random effects models. Compared to treatment as usual, the use of MI reduces heavy alcohol use days by 0.7 days per month (95% credible interval [CrI]: 21.6 to 0.02; low SoE), alcohol use days by 1.1 days per month (95% CrI 22.2 to 20.3; moderate SoE), and overall substance-related problems by a standardized net mean difference of 0.5 (95% CrI –1.0 to 0; low SoE). The use of MI did not reduce cannabis use days, with a net mean difference of 20.05 days per month (95% CrI: 20.26 to 0.14; moderate SoE). LIMITATIONS: There was lack of consistently reported outcomes and limited available comparisons. CONCLUSIONS: The use of MI reduces heavy alcohol use, alcohol use

			days, and SU-related problems in adolescents but does not reduce cannabis use days.
Stockings E	2016	Stockings E, Hall WD, Lynskey M, Morley KI, Reavley N, Strang J, Patton G, Degenhardt L. -Prevention, early intervention, harm reduction, and treatment of substance use in young people Lancet Psychiatry. 2016 Mar;3(3):280-96. doi: 10.1016/S2215-0366(16)00002-X. Epub 2016 Feb 18.	We did a systematic review of reviews with evidence on the effectiveness of prevention, early intervention, harm reduction, and treatment of problem use in young people for tobacco, alcohol, and illicit drugs (eg, cannabis, opioids, amphetamines, or cocaine). Taxation, public consumption bans, advertising restrictions, and minimum legal age are effective measures to reduce alcohol and tobacco use, but are not available to target illicit drugs. Interpretation of the available evidence for school-based prevention is affected by methodological issues; interventions that incorporate skills training are more likely to be effective than information provision—which is ineffective. Social norms and brief interventions to reduce substance use in young people do not have strong evidence of effectiveness. Roadside drug testing and interventions to reduce injection-related harms have a moderate-to-large effect, but additional research with young people is needed. Scarce availability of research on interventions for problematic substance use in young people indicates the need to test interventions that are effective with adults in young people. Existing evidence is from high-income countries, with uncertain applicability in other countries and cultures and in subpopulations differing in sex, age, and risk status. Concerted eff orts are needed to increase the evidence base on interventions that aim to reduce the high burden of substance use in young people.
Teesson M	2012	Teesson M, Newton NC, Barrett EL. Australian school-based prevention programs for alcohol and other drugs: a systematic review Drug Alcohol Rev. 2012 Sep;31(6):731-	Issues: To reduce the occurrence and costs related to substance use and associated harms it is important to intervene early. Although a number of international school-based prevention programs exist, the majority show minimal effects in reducing drug use and related harms. Given the emphasis on early intervention and prevention in Australia, it is timely to review the programs currently trialled in Australian schools. This paper reports the type and efficacy of Australian school-based prevention programs for alcohol and other drugs. Approach: Cochrane, PsychInfo and PubMed databases were searched. Additional materials were obtained from authors, websites and reference lists. Studies were selected

		6. doi: 10.1111/j.1465-3362.2012.00420.x. Epub 2012 Feb 17.	if they described programs developed and trialled in Australia that address prevention of alcohol and other drug use in schools. Key Findings. Eight trials of seven intervention programs were identified. The programs targeted alcohol, cannabis and tobacco and most were based on social learning principles. All were universal. Five of the seven intervention programs achieved reductions in alcohol, cannabis and tobacco use at follow up. Conclusion. Existing school-based prevention programs have shown to be efficacious in the Australian context. However, there are only a few programs available, and these require further evaluative research. This is critical, given that substance use is such a significant public health problem. The findings challenge the commonly held view that school-based prevention programs are not effective.
Thomas RE	2011	Thomas RE, Lorenzetti D, Spragins W Mentoring adolescents to prevent drug and alcohol use (Review)Cochrane Database Syst Rev. 2011 Nov 9;(11):CD007381. doi: 10.1002/14651858.CD007381.pub2.	Background: Many adolescents receive mentoring. There is no systematic review if mentoring prevents alcohol and drug use. Objectives: Assess effectiveness of mentoring to prevent adolescent alcohol/drug use. Search methods: Cochrane CENTRAL (issue 4), MEDLINE (1950-to July 2011), EMBASE (1980-to July 2011), 5 other electronic and 11 Grey literature electronic databases, 10 websites, reference lists, experts in addictions and mentoring. Selection criteria: Randomised controlled trials (RCTs) of mentoring in adolescents to prevent alcohol/drug use. Data collection and analysis: We identified 2,113 abstracts, independently assessed 233 full-text articles, 4 RCTs met inclusion criteria. Two reviewers independently extracted data and assessed risks of bias. We contacted investigators for missing information. Main results: We identified 4 RCTs (1,194 adolescents). No RCT reported enough detail to assess whether a strong randomisation method was used or allocation was concealed. Blinding was not possible as the intervention was mentoring. Three RCTs provided complete data. No selective reporting. Three RCTs provided evidence about mentoring and preventing alcohol use. We pooled two RCTs (RR for mentoring compared to no intervention = 0.71 (95% CI = 0.57 to 0.90, P value = 0.005). A third RCT found no

			significant differences. Three RCTs provided evidence about mentoring and preventing drug use, but could not be pooled. One found significantly less use of “illegal" drugs," one did not, and one assessed only marijuana use and found no significant differences. One RCT measured “substance use” without separating alcohol and drugs, and found no difference for mentoring.

Table S8 Reviews on interventions in prisons and the criminal justice system

First author	Year	Citation	Abstract
Bahji A	2019	Bahji A, Carlone D, Altomare J. Acceptability and efficacy of naltrexone for criminal justice-involved individuals with opioid use disorder: a systematic review and meta-analysis. Addiction. 2020 Aug;115(8):1413-1425. doi: 10.1111/add.14946. Epub 2020 Jan 17. PMID: 31863669.	Background and aims: Criminal justice-involved individuals carry a disproportionately higher burden of opioid use disorder(OUD) than those not involved with the criminal justice system, and are often unable to access opioid agonist therapies such as methadone and buprenorphine. The opioid receptor antagonist naltrexone (NTX) is effective for the prevention of relapse to OUD and may be more acceptable in criminal justice settings. The objectives of this review were to: (1) provide an overall summary effect across studies for the efficacy and acceptability of oral and injectable NTX for the treatment of OUD among criminal justice-involved individuals and (2) examine systematic variations in study results to explain heterogeneity among study-specific effects. Methods: Systematic review and meta-analysis of 1045 patients across 11 studies (10 randomized controlled trials, one quasi-experimental study). All available outcomes were pooled using random-effects meta-analysis. Subgroup analyses were conducted for oral and injectable naltrexone; meta regression analyses were conducted for socio-demographic and study-level characteristics. Results: NTX improved retention in treatment [risk ratio (RR) = 1.31; 95% confidence interval (CI) = 1.05, 1.63], reduced rates of re-incarceration (RR = 0.70, 95% CI = 0.54–0.92), reduced opioid relapse (RR = 0.63, 95% CI = 0.53–0.76) and improved opioid abstinence (RR = 1.38, 95% CI = 1.16–1.65). While NTX was associated with a greater burden of adverse events overall (RR = 1.49, 95% CI = 1.13–1.95), the findings were inconclusive as to whether or not a difference was present for the number of serious adverse events or overdoses. Conclusions: Naltrexone appears to be efficacious and acceptable for the treatment of opioid use disorder among criminal justice-involved individuals; however, the risk for adverse events must be weighed against the potential benefits.
Bard E	2016	Bard E, Knight M, Plugge E. Perinatal	Background: Women are an increasing minority of prisoners worldwide, and most are of childbearing age. Prisons offer unique opportunities for improving the pregnancy outcomes

		health care services for imprisoned pregnant women and associated outcomes: a systematic review. BMC Pregnancy Childbirth. 2016 Sep 29;16(1):285. doi: 10.1186/s12884-016-1080-z.	of these high-risk women, and no systematic review to date has looked at their care. This systematic review identified studies describing models of perinatal health care for imprisoned women which report maternal and child health and care outcomes. Methods: We systematically searched for literature published between 1980 and April 2014. Studies were eligible if they included a group of imprisoned pregnant women, a description of perinatal health care and any maternal or infant health or care outcomes. Two authors independently extracted data. We described relevant outcomes in prisons (including jails) under models of care we termed PRISON, PRISON+ and PRISON++, depending on the care provided. Where outcomes were available on a comparison group of women, we calculated odds ratios with 95 %confidence intervals. Results: Eighteen studies were reported, comprising 2001 imprisoned pregnant women. Fifteen were in the US, two in the UK and one in Germany. Nine contained a comparison group of women comprising 849 pregnant women. Study quality was variable and outcome reporting was inconsistent. There was some evidence that women in prisons receiving enhanced prison care, PRISON+, were less likely to have inadequate prenatal care (15.4 % vs 30. 7 %, p < 0 · 001), preterm delivery (6.4 % vs 19.0 %, p = 0 · 001) or caesarean delivery (12.9 % vs 26.5 %, p = 0 · 005) compared to women in prisons receiving usual care (PRISON). Women participating in two PRISON++ interventions, that is, interventions which included not only enhanced care in prisons but also coordination of community care on release, demonstrated reductions in long term recidivism rates (summary OR 0 · 37, 95 % CI 0 · 19–0 · 70) compared to pregnant women in the same prisons who did not participate in the intervention. Conclusions: Enhanced perinatal care can improve both short and long-term outcomes but there is a lack of data. Properly designed programmes with rigorous evaluation are needed to address the needs of this vulnerable

			population. The cost to mothers, children and to society of failing to address these important public health issues are likely to be substantial.
Berghuis M	2018	Berghuis M. Reentry Programs for Adult Male Offender Recidivism and Reintegration: A Systematic Review and Meta-Analysis. Int J Offender Ther Comp Criminol. 2018 Oct;62(14):4655-4676. doi: 10.1177/0306624X18778448. Epub 2018 Jun 11.	The aim of this review is to assess the effectiveness of re-entry programs designed to reduce recidivism and ensure successful reintegration among adult, male offenders. Studies were included if they (a) evaluated a re-entry program incorporating elements dealing with the transition from prison to community for adult, male offenders; (b) utilized a randomized controlled design; and (c) measured recidivism as a primary outcome. In addition, secondary outcomes measures of reintegration were also included. The systematic search of 8,179 titles revealed nine randomized controlled evaluations that fulfilled eligibility criteria. The random-effects meta-analysis for rearrest revealed a statistically nonsignificant effect favoring the intervention (odds ratio [OR] = 0.89, 95% confidence interval [CI] [0.74, 1.07]). Similar results were found for reconviction (OR = 0.94, 95% CI [0.77, 1.12]) and reincarceration (OR = 0.90, 95% CI [0.78, 1.05]). Studies reported mixed results of secondary outcomes of reintegration. The results of this review reflect the variability of findings on reducing recidivism. The challenges faced in conducting this review highlight a need for further research and theory development around re-entry programs.
Bi-Mohammed Z	2017	Bi-Mohammed Z, Wright NM, Hearty P, King N, Gavin H. Prescription opioid abuse in prison settings: A systematic review of prevalence, practice and treatment responses. Drug Alcohol Depend. 2017 Feb 1;171:122-131.	Background: To systematically review the quantitative and qualitative evidence base pertaining to the prevalence, practice of, and treatment response to the diversion of prescribed opiates in the prison setting. Methods: Medline, Embase, CINAHL, PsycINFO, Google Scholar, ASSIA and Science Direct databases were searched for papers from 1995 to the present relevant to the abuse of prescribed opiate medication. Identified journals and their reference lists were hand searched for other relevant articles. Of the abstracts identified as relevant, full text papers were retrieved and critiqued against the inclusion criteria for the review. Results: Three hundred and fifty-five abstracts were identified, leading to 42 full-text articles

		doi: 10.1016/j.drugalcdep.2016.11.032. Epub 2016 Dec 14.	being retrieved. Of those, 10 papers were included in the review. Significant differences in abuse behaviours between different countries were reported. However, a key theme emerged from the data regarding a culture of nasal administration of prescribed sublingual buprenorphine within some prisons due to both reduced prevalence of injection within prison and reduced supplies of illicit drugs within prison. The buprenorphine/naloxone preparation appears to be less amenable to abuse. The review highlighted a paucity of empirical research pertaining to both prevalence of the phenomenon and treatment responses. Clinical and research implications: Healthcare providers within prisons need to prescribe opioids in the least abuseable preparation since the risk of abuse is significant, despite widespread processes of supervised dispensing. Prescription medication abuse is not limited to opioids and the predominant drug of abuse in an individual prison can rapidly change according to availability.
de Andrade D	2018	de Andrade D, Ritchie J, Rowlands M, Mann E, Hides L. Substance Use and Recidivism Outcomes for Prison-Based Drug and Alcohol Interventions. Epidemiol Rev. 2018 Jun 1;40(1):121-133. doi: 10.1093/epirev/mxy004.	We conducted a systematic review to examine the substance use and recidivism outcomes of prison-based substance use interventions. We searched public health, criminology, and psychology databases, and conducted forward and backward snowballing methods to identify additional studies. Studies were included if they were published between January 1, 2000 and June 30, 2017; were published in English; and reported substance use and/or recidivism outcomes of prison-based substance use interventions. Studies were reviewed for methodological rigor using the Effective Public Health Practice Project's Quality Assessment Tool for Quantitative Studies. Our search returned 49 studies: 6 were methodologically strong, 20 were moderate, and 23 were weak. Results suggest therapeutic communities are effective in reducing recidivism and, to a lesser extent substance use after release. There is also evidence to suggest that opioid maintenance treatment is effective in reducing the risk of drug use after release from prison for opioid users. Furthermore, care after release from prison appears to enhance treatment effects for both types of interventions. Results provide evidence that policymakers can use to make informed decisions on best-practice approaches when addressing prisoner

			substance dependence and improving long-term outcomes. This comprehensive review highlights the difficulties of conducting quality research in the prison setting and suggests innovative study design for future research.
Degenhardt L	2019	Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, Bruneau J, Altice FL, Henderson G, Rahimi-Movaghar A, Larney S. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. Lancet. 2019 Oct 26;394(10208):1560-1579. doi: 10.1016/S0140-6736(19)32229-9. Epub 2019 Oct 23.	We summarise the evidence for medicinal uses of opioids, harms related to the extra medical use of, and dependence on, these drugs, and a wide range of interventions used to address these harms. The Global Burden of Diseases, Injuries, and Risk Factors Study estimated that in 2017, 40·5 million people were dependent on opioids (95% uncertainty interval 34·3–47·9 million) and 109 500 people (105 800–113 600) died from opioid overdose. Opioid agonist treatment (OAT) can be highly effective in reducing illicit opioid use and improving multiple health and social outcomes—e.g., by reducing overall mortality and key causes of death, including overdose, suicide, HIV, hepatitis C virus, and other injuries. Mathematical modelling suggests that scaling up the use of OAT and retaining people in treatment, including in prison, could avert a median of 7·7% of deaths in Kentucky, 10·7% in Kiev, and 25·9% in Tehran over 20 years (compared with no OAT), with the greater effects in Tehran and Kiev being due to reductions in HIV mortality, given the higher prevalence of HIV among people who inject drugs in those settings. Other interventions have varied evidence for effectiveness and patient acceptability, and typically affect a narrower set of outcomes than OAT does. Other effective interventions focus on preventing harm related to opioids. Despite strong evidence for the effectiveness of a range of interventions to improve the health and wellbeing of people who are dependent on opioids, coverage is low, even in high-income countries. Treatment quality might be less than desirable, and considerable harm might be caused to individuals, society, and the economy by the criminalisation of extra medical opioid use and dependence. Alternative policy frameworks are recommended that adopt an approach based on human rights and public health, do not make drug use a criminal behaviour, and seek to reduce drug-related harm at the population level.
Doyle MF	2019	Doyle MF, Shakeshaft A, Guthrie J, Snijder	Objective: A history of alcohol and other drug (AoD) use is common among men entering prison and often linked to the crime for which they are imprisoned. This is the first

		M, Butler T. A systematic review of evaluations of prison-based alcohol and other drug use behavioural treatment for men. Aust N Z J Public Health. 2019 Apr;43(2):120-130. doi: 10.1111/1753-6405.12884. Epub 2019 Mar 25.	systematic review of prison-based, behavioural AoD treatment programs for more than a decade and the first that reviews the methodological quality of evaluations. This review aims to create an understanding of the quality of research in this field and identify the most effective AoD use treatment for men in prison. Methods: A PRISMA-compliant systematic review of international, peer-reviewed research published between January 1995 and December 2015. The Dictionary for Effective Public Health Practice Project was used to assess the methodological quality of papers. Results: A total of 25 relevant papers were identified, of which 12 were rated as methodologically sound. Four of these measured post-release AoD use and three reported statistically significant reductions in AoD use. Conclusions: Although there is relatively little methodologically strong evidence of the impact of prison-based AoD treatment, and no Australian papers studies, current best-evidence practice is Cognitive behavioural therapy delivered in Therapeutic Community (TC) settings. Implications for public health: Prison-based TC treatment should be available to people in prison who have a history of AoD use.
Erickson M	2019	Erickson M, Shannon K, Sernick A, Pick N, Ranville F, Martin RE, Krüsi A. Women, incarceration and HIV: a systematic review of HIV treatment access, continuity of care and health outcomes across incarceration trajectories. AIDS. 2019 Jan	Objective: The aim of this study was to systematically review the literature on gendered implications of incarceration for HIV outcomes and engagement in care for women living with HIV (WLWH). Design: We systematically searched seven bibliographic databases, for peer-reviewed English-language studies, published between 2007 and 2017 reporting on incarceration, women (transgender inclusive) and HIV. Methods: Articles were included for evaluation if they reported outcomes for at least one of three measures of interest: viral load, antiretroviral therapy (ART) adherence or engagement in care among WLWH along incarceration trajectories. Results: Out of 1119 studies, 24 (2%) met the inclusion criteria. Of these 24 studies, the majority (n¼23) were conducted in the USA, 19 included samples of women and men and seven studies were transgender inclusive. Our review did not reveal clear gender

		27;33(1):101-111. doi: 10.1097/QAD.0000000000002036.	differences in HIV outcomes during periods of incarceration; however, studies reporting post incarceration outcomes demonstrated significant gender disparities in all three outcomes of interest. Following incarceration, women were less likely to be virally suppressed, less likely to achieve optimal ART adherence and less likely to be engaged in care. Conclusion: Despite growing numbers of incarcerated WLWH globally, there is a substantial gap in research examining the impact of incarceration on HIV outcomes for WLWH. Significant gender disparities in HIV outcomes and engagement in care exist along incarceration trajectories for WLWH, especially post incarceration. For improved health outcomes, research is needed to examine the experiences of WLWH throughout incarceration trajectories to develop interventions tailored to the specific needs of WLWH both during and following incarceration.
Finfgeld-Connett D	2011	Finfgeld-Connett D, Johnson ED. Therapeutic substance abuse treatment for incarcerated women. Clin Nurs Res. 2011 Nov;20(4):462-81. doi: 10.1177/1054773811415844. Epub 2011 Jul 19.	The purpose of this qualitative systematic review was to explicate attributes of optimal therapeutic strategies for treating incarcerated women who have a history of substance abuse. An expansive search of electronic databases for qualitative research reports relating to substance abuse treatment for incarcerated women was conducted. Nine qualitative research reports comprised the sample for this review. Findings from these reports were extracted, placed into a data analysis matrix, coded, and categorized. Memos were written and strategies for treating incarcerated women with alcohol problems were identified. Therapeutic effects of treatment programs for incarcerated women with substance abuse problems appear to be enhanced when trust-based relationships are established, individualized and just care is provided, and treatment facilities are separate from the general prison environment.
Galassi A	2015	Galassi A, Mpofu E, Athanasou J. Therapeutic Community Treatment of an Inmate Population with	This systematic literature review maps the evidence for the effectiveness of the therapeutic community interventions (TCI) in reducing re-arrest, re-incarceration or drug misuse following release from prison, including the extent to which these effects are retained over time. The databases searched for the review included PsychINFO, Medline and Scopus and reference lists from relevant articles published between 2007 and 2014. Only quantitative studies that examined the effectiveness of TCI for a prisoner population

		Substance Use Disorders: Post-Release Trends in Re-Arrest, Re-Incarceration, and Drug Misuse Relapse. Int J Environ Res Public Health. 2015 Jun 19;12(6):7059-72. doi: 10.3390/ijerph120607059.	with drug dependence at the time of initial incarceration were considered. Fourteen studies were identified for inclusion in the review. Three-quarters of the studies reported TCI were effective in reducing rates of re-incarceration. About 70% of studies that examined follow-up rates of drug misuse relapse found TCI effective in reducing rates of drug misuse amongst participants. TCI participation reduced re-arrests events in 55% of the studies. Results suggest TCI effective in the short-term rather than longer term for reducing rates of re-incarceration among participants, and to a slightly lesser extent, drug misuse relapse.
Hayhurst KP	2015	Hayhurst KP, Leitner M, Davies L, Flentje R, Millar T, Jones A, King C, Donmall M, Farrell M, Fazel S, Harris R, Hickman M, Lennox C, Mayet S, Senior J, Shaw J. The effectiveness and cost-effectiveness of diversion and aftercare programmes for offenders using class A drugs: a systematic review and economic evaluation.	Methods: Included studies evaluated diversion in adult class A drug-using offenders, in contact with the CJS. The main outcomes were drug use and offending behaviour, and these were pooled using meta-analysis. The economic review included full economic evaluations for adult opiate and/or crack, or powder, cocaine users. An economic decision analytic model, estimated incremental costs per unit of outcome gained by diversion and aftercare, over a 12-month time horizon. The perspectives included the CJS, NHS, social care providers and offenders. Probabilistic sensitivity analysis and one-way sensitivity analysis explored variance in parameter estimates, longer time horizons and structural uncertainty. Results: Sixteen studies met the effectiveness review inclusion criteria, characterised by poor methodological quality, with modest sample sizes, high attrition rates, retrospective data collection, limited follow-up, no random allocation and publication bias. Most study samples comprised US methamphetamine users. Limited meta-analysis was possible, indicating a potential small impact of diversion interventions on reducing drug use [odds ratio (OR) 1.68, 95% confidence interval (CI) 1.12 to 2.53 for reduced primary drug use, and OR 2.60, 95% CI 1.70 to 3.98 for reduced use of other drugs]. The cost-effectiveness

		Health Technol Assess. 2015 Jan;19(6):1-168, vii-viii. doi: 10.3310/hta19060.	review did not identify any relevant studies. The economic evaluation indicated high uncertainty because of variance in data estimates and limitations in the model design. The primary analysis was unclear whether or not diversion was cost-effective. The sensitivity analyses indicated some scenarios where diversion may be cost-effective. Limitations: Nearly all participants (99.6%) in the effectiveness review were American (Californian) methamphetamine users, limiting transfer of conclusions to the UK. Data and methodological limitations mean it is unclear whether or not diversion is effective or cost-effective. Conclusions: High-quality evidence for the effectiveness and cost-effectiveness of diversion schemes is sparse and does not relate to the UK. Importantly this research identified a range of methodological limitations in existing evidence. These highlight the need for research to conceptualise, define and develop models of diversion programmes and identify a core outcome set. A programme of feasibility, pilot and definitive trials, combined with process evaluation and qualitative research is recommended to assess the effectiveness and cost-effectiveness of diversionary interventions in class A drug-using offenders.
Hedrich D	2012	Hedrich D, Alves P, Farrell M, Stöver H, Møller L, Mayet S. The effectiveness of opioid maintenance treatment in prison settings: a systematic review. Addiction. 2012 Mar;107(3):501-17. doi: 10.1111/j.1360-0443.2011.03676.x.	Aims: To review evidence on the effectiveness of opioid maintenance treatment (OMT) in prison and post-release. Methods: Systematic review of experimental and observational studies of prisoners receiving OMT regarding treatment retention, opioid use, risk behaviours, human immunodeficiency virus (HIV)/hepatitis C virus (HCV) incidence, criminality, re-incarceration and mortality. We searched electronic research databases, specialist journals and the EMCDDA library for relevant studies until January 2011. Review conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Results Twenty-one studies were identified: six experimental and 15 observational. OMT was associated significantly with reduced heroin use, injecting and syringe-sharing in prison if doses were adequate. Pre-release OMT was associated significantly with increased treatment entry and retention after release if arrangements

			existed to continue treatment. For other outcomes, associations with pre-release OMT were weaker. Four of five studies found post-release reductions in heroin use. Evidence regarding crime and re-incarceration was equivocal. There was insufficient evidence concerning HIV/HCV incidence. There was limited evidence that pre-release OMT reduces post-release mortality. Disruption of OMT continuity, especially due to brief periods of imprisonment, was associated with very significant increases in HCV incidence. Conclusions Benefits of prison OMT are similar to those in community settings. OMT presents an opportunity to recruit problem opioid users into treatment, to reduce illicit opioid use and risk behaviours in prison and potentially minimize overdose risks on release. If liaison with community-based programmes exists, prison OMT facilitates continuity of treatment and longer-term benefits can be achieved. For prisoners in OMT before imprisonment, prison OMT provides treatment continuity.
Kendall S	2018	Kendall S, Redshaw S, Ward S, Wayland S, Sullivan E. Systematic review of qualitative evaluations of reentry programs addressing problematic drug use and mental health disorders amongst people transitioning from prison to communities. Health Justice. 2018 Mar 2;6(1):4. doi:	Background: The paper presents a systematic review and meta synthesis of findings from qualitative evaluations of community re-entry programs. The programs sought to engage recently released adult prison inmates with either problematic drug use or a mental health disorder. Methods: Seven biomedical and social science databases, Cinahl, Pubmed, Scopus, Proquest, Medline, Sociological abstracts and Web of Science and publisher database Taylor and Francis were searched in 2016 resulting in 2373 potential papers. Abstract reviews left 140 papers of which 8 were included after detailed review. Major themes and subthemes were identified through grounded theory inductive analysis of results from the eight papers. Of the final eight papers the majority (6) were from the United States. In total, the papers covered 405 interviews and included 121 (30%) females and 284 (70%) males. Results: Findings suggest that the interpersonal skills of case workers; access to social support and housing; and continuity of case worker relationships throughout the pre-release and post-release period are key social and structural factors in program success.

		10.1186/s40352-018-0063-8.	Conclusion: Evaluation of community reentry programs requires qualitative data to contextualize statistical findings and identify social and structural factors that impact on reducing incarceration and improving participant health. These aspects of program efficacy have implications for reentry program development and staff training and broader social and health policy and services.
Komalasari R	2021	Komalasari R, Wilson S, Haw S. A systematic review of qualitative evidence on barriers to and facilitators of the implementation of opioid agonist treatment (OAT) programmes in prisons. Int J Drug Policy. 2021 Jan;87:102978. doi: 10.1016/j.drugpo.2020.102978. Epub 2020 Oct 28.	Background: Opioid Agonist Treatment (OAT) programmes are regarded as a gold standard treatment for people living with Opioid Use Disorders (OUDs). However, OAT programmes are often unavailable or poorly implemented in prisons, in spite of the large numbers of people living with OUDs and the high risk of HIV transmission in prison settings. Unusually, this systematic review synthesizes qualitative evidence relating to barriers to, and facilitators of, the implementation of OAT programmes in prisons in high- and low/middle-income countries (LMICs) to provide more nuanced, contextualised understandings of how prison stakeholders perceive and/or experience OAT programmes within different prison settings. Methods: We systematically reviewed six electronic databases for studies published between January 2005 and December 2019 involving prison stakeholders: policy-makers, governors, healthcare staff, prison officers, and prisoners. The search identified 8091 studies, of which only 16 incorporated qualitative methods (including qualitative elements of mixed methods) and met our quality criteria. Four of these studies were conducted in LMICs (Kyrgyzstan, Iran (2) and Indonesia). Results: Findings were organized under three broad themes: (1) perceived benefits of OAT programmes; (2) barriers to the implementation and development of OAT programmes; and (3) treatment processes. Discussion: A lack of a clear understanding of the roles of OAT programmes and doubts regarding their effective- ness for people living with OUDs in prisons are critical barriers to prisoner participation in both high-and LMIC countries. Prison systems, particularly in LMICs, often lack the resources to mitigate problems with implementation. This review highlights an urgent need to develop further qualitative studies into prison OAT

			programmes, employing varied methods to explore such contexts in greater depth and minimize the impact of harms relating to OUDs in prisons.
Larney S	2010	Larney S. Does opioid substitution treatment in prisons reduce injecting-related HIV risk behaviours? A systematic review. Addiction. 2010 Feb;105(2):216-23. doi: 10.1111/j.1360-0443.2009.02826.x.	Objectives: To review systematically the evidence on opioid substitution treatment (OST) in prisons in reducing injecting-related human immunodeficiency virus (HIV) risk behaviours. Methods: Systematic review in accordance with guidelines of the Cochrane Collaboration. Electronic databases were searched to identify studies of prison-based opioid substitution treatment programmes that included assessment of effects of prison OST on injecting drug use, sharing of needles and syringes and HIV incidence. Published data were used to calculate risk ratios for outcomes of interest. Risk ratios were not pooled due to the low number of studies and differences in study designs. Results: Five studies were included in the review. Poor follow-up rates were reported in two studies, and representativeness of the sample was uncertain in the remaining three studies. Compared to inmates in control conditions, for treated inmates the risk of injecting drug use was reduced by 55–75% and risk of needle and syringe sharing was reduced by 47–73%. No study reported a direct effect of prison OST on HIV incidence. Conclusions There may be a role for OST in preventing HIV transmission in prisons, but methodologically rigorous research addressing this question specifically is required. OST should be implemented in prisons as part of comprehensive HIV prevention programmes that also provide condoms and sterile injecting and tattooing equipment.
Lazarus JV	2018	Lazarus JV, Safreed-Harmon K, Hetherington KL, Bromberg DJ, Ocampo D, Graf N, Dichtl A, Stöver H, Wolff H. Health Outcomes for Clients	High levels of drug dependence have been observed in the prison population globally, and the sharing of injecting drug equipment in prisons has contributed to higher prevalence of bloodborne diseases in prisoners than in the general population. Few prison needle and syringe programs (PNSPs) exist. We conducted a systematic review to assess evidence regarding health outcomes of PNSPs. We searched peer-reviewed databases for data relating to needle and syringe programs in prisons. The search methodology was conducted in accordance with accepted guidelines. Five studies met review inclusion criteria, and all presented evidence associating PNSPs with one or more health benefits, but the strength of

		of Needle and Syringe Programs in Prisons. Epidemiol Rev. 2018 Jun 1;40(1):96-104. doi: 10.1093/epirev/mxx019.	the evidence was low. The outcomes for which the studies collectively demonstrated the strongest evidence were prevention of human immunodeficiency virus and viral hepatitis. Few negative consequences from PNSPs were observed, consistent with previous evidence assessments. More research is needed on PNSP effectiveness, and innovative study designs are needed to overcome methodological limitations of previous research. Until stronger evidence becomes available, policymakers are urged to recognize that not implementing PNSPs has the potential to cause considerable harm, in light of what is currently known about the risks and benefits of needle and syringe programs and PNSPs and about the high prevalence of human immunodeficiency virus and viral hepatitis in prisons.
Livingstone N	2013	Livingstone, N; Macdonald, G; Carr, N. Restorative justice conferencing for reducing recidivism in young offenders (aged 7 to 21). Cochrane Database Syst Rev. 2013 Feb 28; 2013(2): CD008898. doi: 10.1002/14651858.CD008898.pub2.	Background: Restorative justice is "a process whereby parties with a stake in a specific offence resolve collectively how to deal with the aftermath of the offence and its implications for the future" (Marshall 2003). Despite the increasing use of restorative justice programmes as an alternative to court proceedings, no systematic review has been undertaken of the available evidence on the effectiveness of these programmes with young offenders. Recidivism in young offenders is a particularly worrying problem, as recent surveys have indicated the frequency of reoffences for young offenders has ranged from 40.2% in 2000 to 37.8% in 2007 (Ministry of Justice 2009) Objectives: To evaluate the effects of restorative justice conferencing programmes for reducing recidivism in young offenders. Search methods: We searched the following databases up to May 2012: CENTRAL, 2012 Issue 5, MEDLINE (1978 to current), Bibliography of Nordic Criminology (1999 to current), Index to Theses (1716 to current), PsycINFO (1887 to current), Social Sciences Citation Index (1970 to current), Sociological Abstracts (1952 to current), Social Care Online (1985 to current), Restorative Justice Online (1975 to current), Scopus (1823 to current), Science Direct (1823 to current), LILACS (1982 to current), ERIC (1966 to current), Restorative Justice Online (4 May 2012), WorldCat (9 May 2012), ClinicalTrials.gov (19 May 2012) and ICTRP (19 May 2012). ASSIA, National Criminal Justice Reference Service and Social

			Services Abstracts were searched up to May 2011. Relevant bibliographies, conference programmes and journals were also searched. Selection criteria: Randomised controlled trials (RCTs) or quasi-RCTs of restorative justice conferencing versus management as usual, in young offenders. Data collection and analysis: Two authors independently assessed the risk of bias of included trials and extracted the data. Where necessary, original investigators were contacted to obtain missing information. Main results: Four trials including a total of 1447 young offenders were included in the review. Results failed to find a significant effect for restorative justice conferencing over normal court procedures for any of the main analyses, including number re-arrested (odds ratio (OR) 1.00, 95% confidence interval (CI) 0.59 to 1.71; P = 0.99), monthly rate of reoffending (standardised mean difference (SMD) -0.06, 95% CI -0.28 to 0.16; P = 0.61), young person's remorse following conference (OR 1.73, 95% CI 0.97 to 3.10; P = 0.06), young person's recognition of wrongdoing following conference (OR 1.97, 95% CI 0.81 to 4.80; P = 0.14), young person's self-perception following conference (OR 0.95, 95% CI 0.55 to 1.63; P = 0.85), young person's satisfaction following conference (OR 0.42, 95% CI 0.04 to 4.07; P = 0.45) and victim's satisfaction following conference (OR 4.05, 95% CI 0.56 to 29.04; P = 0.16). A small number of sensitivity analyses did indicate significant effects, although all are to be interpreted with caution. Authors' conclusions: There is currently a lack of high quality evidence regarding the effectiveness of restorative justice conferencing for young offenders. Caution is urged in interpreting the results of this review considering the small number of included studies, subsequent low power and high risk of bias. The effects may potentially be more evident for victims than offenders. The need for further research in this area is highlighted.
Lowder EM	2018	Lowder EM, Rade CB, Desmarais SL. Effectiveness of Mental Health Courts	Objective: Mental health courts (MHCs) were developed to address the overrepresentation of adults with mental illnesses in the U.S. criminal justice system through diversion into community-based treatment. Research on MHCs has proliferated in recent years, and there is a need to synthesize contemporary literature on MHC effectiveness. The authors

		in Reducing Recidivism: A Meta-Analysis. Psychiatr Serv. 2018 Jan 1;69(1):15-22. doi: 10.1176/appi.ps.201700107. Epub 2017 Aug 15.	conducted a meta-analytic investigation of the effect on criminal recidivism of adult MHC participation compared with traditional criminal processing. Methods: Systematic search of three databases yielded 17 studies (N=16,129) published between 2004 and 2015. Study characteristics and potential moderators (that is, publication type, recidivism outcome, and length and timing of followup) were independently extracted by two of four raters for each study. Two raters coded each study for quality and extracted between-group effect sizes for measures of recidivism (that is, arrest, charge, conviction, and jail time; k=25). Results were synthesized by using random-effects meta-analysis. Heterogeneity and publication bias were also assessed. Results: Results showed a small effect of MHC participation on recidivism (d=–.20) relative to traditional criminal processing. MHCs were most effective with respect to jail time and charge outcomes compared with arrest and conviction, in studies measuring recidivism after MHC exit rather than at entry, and in lower-quality studies compared with moderate- and high-quality studies. Results showed significant heterogeneity in effect sizes across studies (I2=73.33) but little evidence of publication bias. Conclusions: Overall, a small effect of MHC participation on recidivism was noted, compared with traditional criminal processing. Findings suggest the need for research to identify additional sources of variability in the effectiveness of MHCs.
Malta M	2019	Malta M, Varatharajan T, Russell C, Pang M, Bonato S, Fischer B. Opioid-related treatment, interventions, and outcomes among	Background: Worldwide opioid-related overdose has become a major public health crisis. People with opioid use disorder (OUD) are overrepresented in the criminal justice system and at higher risk for opioid-related mortality. However, correctional facilities frequently adopt an abstinence only approach, seldom offering the gold standard opioid agonist treatment (OAT) to incarcerated persons with OUD. In an attempt to inform adequate management of OUD among incarcerated persons, we conducted a systematic review of opioid-related interventions delivered before, during, and after incarceration.

		incarcerated persons: A systematic review. PLoS Med. 2019 Dec 31;16(12):e1003002. doi: 10.1371/journal.pmed.1003002. eCollection 2019 Dec.	Methods and findings: We systematically reviewed 8 electronic databases for original, peer-reviewed literature published between January 2008 and October 2019. Our review included studies conducted among adult participants with OUD who were incarcerated or recently released into the community (90 days post-incarceration). The search identified 2,356 articles, 46 of which met the inclusion criteria based on assessments by 2 independent reviewers. Thirty studies were conducted in North America, 9 in Europe, and 7 in Asia/Oceania. The systematic review included 22 randomized control trials (RCTs), 3 non-randomized clinical trials, and 21 observational studies. Eight observational studies utilized administrative data and included large sample sizes (median of 10,419 [range 2273–131,472] participants), and 13 observational studies utilized primary data, with a median of 140 (range 27–960) participants. RCTs and non-randomized clinical trials included a median of 198 (range 15–1,557) and 44 (range 27–382) participants, respectively. Twelve studies included only men, 1 study included only women, and in the remaining 33 studies, the percentage of women was below 30%. The majority of study participants were middle-aged adults (36–55 years). Participants treated at a correctional facility with methadone maintenance treatment (MMT) or buprenorphine (BPN)/naloxone (NLX) had lower rates of illicit opioid use, had higher adherence to OUD treatment, were less likely to be re-incarcerated, and were more likely to be working 1 year post-incarceration. Participants who received MMT or BPN/NLX while incarcerated had fewer nonfatal overdoses and lower mortality. The main limitation of our systematic review is the high heterogeneity of studies (different designs, settings, populations, treatments, and outcomes), precluding a meta-analysis. Other study limitations include the insufficient data about incarcerated women with OUD, and the lack of information about incarcerated populations with OUD who are not included in published research. Conclusions: In this carefully conducted systematic review, we found that correctional facilities should scale up OAT among incarcerated persons with OUD. The strategy is likely to decrease opioid- related overdose and mortality, reduce opioid use and other risky

			behaviors during and after incarceration, and improve retention in addiction treatment after prison release. Immediate OAT after prison release and additional preventive strategies such as the distribution of NLX kits to at-risk individuals upon release greatly decrease the occurrence of opioid related overdose and mortality. In an effort to mitigate the impact of the opioid-related overdose crisis, it is crucial to scale up OAT and opioid-related overdose prevention strategies(e.g., NLX) within a continuum of treatment before, during, and after incarceration.
Moore KE	2019	Moore KE, Roberts W, Reid HH, Smith KMZ, Oberleitner LMS, McKee SA. Effectiveness of medication assisted treatment for opioid use in prison and jail settings: A meta-analysis and systematic review. J Subst Abuse Treat. 2019 Apr;99:32-43. doi: 10.1016/j.jsat.2018.12.003. Epub 2018 Dec 15.	This study examined the state of the literature on the effectiveness of medication assisted treatment (MAT; methadone, buprenorphine, naltrexone) delivered in prisons and jails on community substance use treatment engagement, opioid use, recidivism, and health risk behaviors following release from incarceration. Randomized controlled trials (RCTs) and quasi-experimental studies published through December 2017 that examined induction to or maintenance on methadone (n=18 studies), buprenorphine (n=3 studies), or naltrexone (n=3 studies) in correctional settings were identified from PsycINFO and PubMed databases. There were a sufficient number of methadone RCTs to meta-analyze; there were too few buprenorphine or naltrexone studies. All quasi-experimental studies were systematically reviewed. Data from RCTs involving 807 inmates (treatment n = 407, control n = 400) showed that methadone provided during incarceration increased community treatment engagement (n=3 studies; OR = 8.69, 95% CI = 2.46; 30.75), reduced illicit opioid use (n=4 studies; OR = 0.22, 95% CI = 0.15; 0.32) and injection drug use (n=3 studies; OR = 0.26, 95% CI = 0.12; 0.56), but did not reduce recidivism (n=4 studies; OR = 0.93, 95% CI = 0.51; 1.68). Data from observational studies of methadone showed consistent findings. Individual review of buprenorphine and naltrexone studies showed these medications were either superior to methadone or to placebo, or were as effective as methadone in reducing illicit opioid use post-release. Results provide the first meta-analytic summary of MATs delivered in correctional settings and support the use of MATs, especially with regard to community substance use treatment engagement and opioid use; additional work is needed to understand the reduction of recidivism and other health risk behaviors.

Pederson SD	2021	Pederson SD, Curley EJ, Collins CJ. A Systematic Review of Motivational Interviewing to Address Substance Use with Justice-Involved Adults. Subst Use Misuse. 2021 Mar 16:1-11. doi: 10.1080/10826084.2021.1887247. Online ahead of print.	Background: Motivational Interviewing (MI) is widely used in substance abuse treatment, possibly due to the short sessions and the treatment's cost-effectiveness. Previous research has established the efficacy of MI among a broad range of populations and outcomes. However, there is a lack of a review of the knowledge about if MI works with justice-involved individuals who have substance use issues. Purpose: This review aimed to examine the extent of the literature on MI as a treatment to decrease rates of substance use for justice-involved individuals. Methods: The databases utilized for the review include Academic Search Complete (EBSCO), PsycINFO, and ProQuest. The dates for the literature inclusion were from 2008 to March 2020. The literature search was initiated in February and was completed in March 2020. Results: Five RCT studies were identified. Studies were conducted using populations during incarceration in prison, prior to release from jail, through probation, and those with DWI charges. However, all of the populations included were actively being monitored for substance use. All five studies found no difference between groups at the latest point in the study, which for most included the follow-up measure. Consideration for potential moderators such as severity and type of substance use, and length of treatment and follow up data are discussed. Conclusion: The results of the review indicated that more standardized and rigorous research is needed for exploring MI with individuals involved with the justice system with the focus of decreasing substance use.
Perdacher E	2019	Perdacher E, Kavanagh D, Sheffield J. Well-being and mental health interventions for Indigenous people in	Background: Indigenous people are overrepresented in prison populations of colonised justice systems, and Indigenous prisoners in these countries are at a particularly high risk of poor mental health and well-being. There is an acute need to ensure the access of these groups to culturally appropriate, evidence-based interventions. Aims: To conduct a systematic review, evaluating quantitative and qualitative evaluations of mental health and well-being interventions designed for Indigenous people in custody.

		prison: systematic review. BJPsych Open. 2019 Nov 4;5(6):e95. doi: 10.1192/bjo.2019.80.	Method: A search of relevant peer-reviewed journal articles to August 2019 was conducted. The focus was on colonised countries under a Western model of justice and health, including Canada, Australia, New Zealand and the USA. The review utilised Scopus, Web of Science, PubMed, PsycNET, EBSCO, Proquest Criminal Justice Database and Informit. Results: Of the 9283 articles initially found, only three quantitative and two qualitative evaluations of mental health or well-being interventions for Indigenous people in custody were identified. None were randomised controlled trials. Culturally based interventions appeared to have high acceptability and potential for increased recovery from trauma, reduced alcohol-related problems and lower reoffending. However, no studies quantitatively assessed mental health or well-being outcomes. Conclusions: As yet there is no high-quality evidence on the impact on mental health and well-being from interventions specifically for Indigenous prisoners, although existing studies suggest programme features that may maximise acceptability and impact. There is a moral, social and practical imperative to build a strong evidence base on this topic.
Perry AE	2019	Perry AE, Martyn-St James M, Burns L, Hewitt C, Glanville JM, Aboaja A, Thakkar P, Santosh Kumar KM, Pearson C, Wright K. Interventions for female drug-using offenders. Cochrane Database Syst Rev. 2019 Dec 13;12(12):CD010910. doi:	Background: This is an updated version of a Cochrane review first published in Issue 3, 2006 (Perry 2006). The review represents one in a family of four reviews focusing on the effectiveness of interventions in reducing drug use and criminal activity for offenders. This specific review considers interventions for female drug-using offenders. Objectives: To assess the effectiveness of interventions for female drug-using offenders in reducing criminal activity, or drug use, or both. Search methods: We searched 14 electronic bibliographic databases up to May 2014 and five additional Website resources (between 2004 and November 2011). We contacted experts in the field for further information. Selection criteria: We included randomised controlled trials (RCTs) designed to reduce, eliminate or prevent relapse of drug use or criminal activity in female drug-using offenders. We also reported data on the cost and cost-effectiveness of interventions. Data collection and analysis: We used standard methodological procedures expected by The Cochrane Collaboration.

		10.1002/14651858.CD010910.pub3.	Main results: Nine trials with 1792 participants met the inclusion criteria. Trial quality and risks of bias varied across each study. We rated the majority of studies as being at 'unclear' risk of bias due to a lack of descriptive information. We divided the studies into different categories for the purpose of meta-analyses: for any psychosocial treatments in comparison to treatment as usual we found low quality evidence that there were no significant differences in arrest rates, (two studies; 489 participants; risk ratio (RR) 0.82, 95% confidence interval (CI) 0.45 to 1.52) or drug use (one study; 77 participants; RR 0.65, 95% CI 0.20 to 2.12), but we found moderate quality evidence that there was a significant reduction in reincarceration, (three studies; 630 participants; RR 0.46, 95% CI 0.34 to 0.64). Pharmacological intervention using buprenorphine in comparison to a placebo did not significantly reduce self-reported drug use (one study; 36 participants; RR 0.58, 95% CI 0.25 to 1.35). No cost or cost-effectiveness evidence was reported in the studies. Authors' conclusions: Three of the nine trials show a positive trend towards the use of any psychosocial treatment in comparison to treatment as usual showing an overall significant reduction in subsequent reincarceration, but not arrest rates or drug use. Pharmacological interventions in comparison to a placebo did not significantly reduce drug use and did not measure criminal activity. Four different treatment comparisons showed varying results and were not combined due to differences in the intervention and comparison groups. The studies overall showed a high degree of heterogeneity for types of comparisons and outcome measures assessed, which limited the possibility to pool the data. Descriptions of treatment modalities are required to identify the important elements for treatment success in drug using female offenders. More trials are required to increase the precision of confidence with which we can draw conclusions about the effectiveness of treatments for female drug-using offenders.
Perry AE	2015	Perry, AE; Neilson, M; Martyn-St James, M; Glanville, JM; Woodhouse, R;	Background: The review represents one in a family of four reviews focusing on a range of different interventions for drug-using offenders. This specific review considers pharmacological interventions aimed at reducing drug use or criminal activity, or both, for illicit drug-using offenders.

		Godfrey, C; Hewitt, C. Pharmacological interventions for drug-using offenders. Cochrane Database Syst Rev. 2013 Dec 19;12(12):CD010862. doi: 10.1002/14651858.CD010862	Objectives: To assess the effectiveness of pharmacological interventions for drug-using offenders in reducing criminal activity or drug use, or both. Search methods: We searched Fourteen electronic bibliographic databases up to May 2014 and five additional Web resources (between 2004 and November 2011). We contacted experts in the field for further information. Selection criteria: We included randomised controlled trials assessing the efficacy of any pharmacological intervention a component of which is designed to reduce, eliminate or prevent relapse of drug use or criminal activity, or both, in drug-using offenders. We also report data on the cost and cost-effectiveness of interventions. Data collection and analysis: We used standard methodological procedures as expected by Cochrane. Main results: Fourteen trials with 2647 participants met the inclusion criteria. The interventions included in this review report on agonistic pharmacological interventions (buprenorphine, methadone and naltrexone) compared to no intervention, other non-pharmacological treatments (e.g. counselling) and other pharmacological drugs. The methodological trial quality was poorly described, and most studies were rated as 'unclear' by the reviewers. The biggest threats to risk of bias were generated through blinding (performance and detection bias) and incomplete outcome data (attrition bias). Studies could not be combined all together because the comparisons were too different. Only subgroup analysis for type of pharmacological treatment were done. When compared to non-pharmacological, we found low quality evidence that agonist treatments are not effective in reducing drug use or criminal activity, objective results (biological) (two studies, 237 participants (RR 0.72 (95% CI 0.51 to 1.00); subjective (self-report), (three studies, 317 participants (RR 0.61 95% CI 0.31 to 1.18); self-report drug use (three studies, 510 participants (SMD: -0.62 (95% CI -0.85 to -0.39). We found low quality of evidence that antagonist treatment was not effective in reducing drug use (one study, 63 participants (RR 0.69, 95% CI 0.28 to 1.70) but we found moderate quality of evidence that they significantly reduced criminal activity (two studies, 114 participants, (RR 0.40, 95% CI 0.21 to 0.74).

			Findings on the effects of individual pharmacological interventions on drug use and criminal activity showed mixed results. In the comparison of methadone to buprenorphine, diamorphine and naltrexone, no significant differences were displayed for either treatment for self report dichotomous drug use (two studies, 370 participants (RR 1.04, 95% CI 0.69 to 1.55), continuous measures of drug use (one study, 81 participants, (mean difference (MD) 0.70, 95% CI -5.33 to 6.73); or criminal activity (one study, 116 participants, (RR 1.25, 95% CI 0.83 to 1.88) between methadone and buprenorphine. Similar results were found for comparisons with diamorphine with no significant differences between the drugs for self report dichotomous drug use for arrest (one study, 825 participants, (RR 1.25, 95% CI 1.03 to 1.51) or naltrexone for dichotomous measures of reincarceration (one study, 44 participants, (RR 1.10, 95% CI 0.37 to 3.26), and continuous outcome measure of crime, (MD -0.50, 95% CI -8.04 to 7.04) or self report drug use (MD 4.60, 95% CI -3.54 to 12.74). Authors' conclusions: When compared to non-pharmacological treatment, agonist treatments did not seem effective in reducing drug use or criminal activity. Antagonist treatments were not effective in reducing drug use but significantly reduced criminal activity. When comparing the drugs to one another we found no significant differences between the drug comparisons (methadone versus buprenorphine, diamorphine and naltrexone) on any of the outcome measures. Caution should be taken when interpreting these findings, as the conclusions are based on a small number of trials, and generalisation of these study findings should be limited mainly to male adult offenders. Additionally, many studies were rated at high risk of bias.
Santo T	2021	Santo Jr , T., Hickman, M., Padmanathan, P., Degenhardt, L., & al., E. (Accepted/In press). The impact of opioid agonist	Importance: Mortality among people with opioid dependence is higher than the general population and a global health burden. Opioid agonist treatment (OAT) is an effective treatment for opioid dependence, however, there has not yet been a systematic review on the relationship between OAT and specific causes of mortality. Objective: To estimate the impact of time in OAT on all-cause and cause-specific mortality. We also examine risk during time periods of treatment, by setting (community and incarceration) and by participant characteristics.

		treatment delivered in different settings on all-cause mortality and specific causes of death: A systematic review and meta-analysis. JAMA Psychiatry.	Data Sources: We searched Embase, MEDLINE, and PsycINFO through January 2020; clinical trial registries, and previous Cochrane reviews. Study Selection: All observational studies that collected data on all-cause or cause-specific mortality among people with opioid dependence in and out-of-OAT were included. Randomised controlled trials (RCTs) were also included. Data Extraction and Synthesis: We followed GATHER, PRISMA, and MOOSE guidelines. Data on study, participant and treatment characteristics were extracted; person-years, and all-cause and cause-specific mortality. Crude mortality rates and rate ratios (RRs) were pooled using random-effects meta-analyses. Main Outcomes: All-cause and cause-specific mortality, overall; by methadone, buprenorphine; setting, and time-period. Results: 15 eligible RCTs, N=3,852 participants; 36 primary cohort studies, N=749,634. Cohort studies found all-cause mortality during OAT more than halved compared to time out-of-OAT (RR=0.47; 95%CI 0.42-0.53). This relationship was consistent by gender, age, location, HIV, or HCV status, and people who inject. Associations were not different for methadone (RR=0.47; 95%CI 0.41-0.54) versus buprenorphine (RR=0.34; 95%CI 0.26-0.45). There was lower risk of drug-related, suicide, alcohol-related, cancer, and cardiovascular mortality during OAT. In the first four weeks of methadone, all-cause mortality and drug-related poisoning was almost double that in the remainder of OAT (not so for buprenorphine). It was six-times higher in the four weeks following OAT cessation, remaining double the rate for the remainder of time out-of-OAT. OAT is strongly associated with a lower risk fo mortality when incarcerated and after release from incarceration, particularly suicide and overdose. Discussion: OAT is associated with a reduction in multiple causes of death. Nonetheless, access remains limited, and coverage too low. Work to improve access globally is likely to have important population-level benefits.
Schwartz RP	2018	Schwartz RP, Mitchell MM, O'Grady KE,	Pharmacotherapy for opioid addiction with methadone, buprenorphine, and naltrexone has proven efficacy in reducing illicit opioid use. These treatments are under-utilized among

		Kelly SM, Gryczynski J, Mitchell SG, Gordon MS, Jaffe JH. Pharmacotherapy for opioid addiction in community corrections. Int Rev Psychiatry. 2018 Oct;30(5):117-135. doi: 10.1080/09540261.2018.1524373. Epub 2018 Dec 6.	opioid addicted individuals on parole, probation, or in drug courts. This paper examines the peer reviewed literature on the effectiveness of pharmacotherapy for opioid addiction of adults under community-based criminal justice supervision in the US. Compared to general populations, there are relatively few papers addressing the separate impact of pharmacotherapy on individuals under community supervision. Tentative conclusions can be drawn from the extant literature. Reasonable evidence exists that illicit opioid use and self-reported criminal behaviour decline after treatment entry, and that these outcomes are as favourable among individuals under criminal justice supervision as the general treatment population. Surprisingly, there is no conclusive evidence regarding the extent to which pharmacotherapy impacts the likelihood of arrest and incarceration among individuals under supervision. However, given the proven efficacy of these three medications in reducing illicit opioid use and the evidence that, in the general population, methadone and buprenorphine treatment are associated with reduction in overdose mortality, the use of all three pharmacotherapies among patients under criminal justice supervision should be expanded while more data are collected on their impact on arrest and incarceration.
Seval N	2020	Seval N, Wurcel A, Gunderson CG, Grimshaw A, Springer SA. The Impact of Medications for Opioid Use Disorder on Hepatitis C Incidence Among Incarcerated Persons: A Systematic Review. Infect Dis Clin North Am. 2020	Hepatitis C virus (HCV) is highly prevalent in the criminal justice system and in persons who inject drugs, particularly opioids. Data on the impact of medications for opioid use disorder (MOUD) are abundant for infectious and non-infectious outcomes but are limited for justice-involved settings. This systematic review and meta-analysis focuses on the impact of MOUD on HCV incidence for persons in prisons and jails. Six studies were included in the qualitative synthesis, of which 4 were included for meta-analysis. A varied MOUD effect on HCV incidence was observed in part due to wide variability in prison and jail risk environments.

		Sep;34(3):559-584. doi: 10.1016/j.idc.2020.06.011.	
Shaw J	2015	Shaw J, Downe S, Kingdon C. Systematic mixed-methods review of interventions, outcomes and experiences for imprisoned pregnant women. J Adv Nurs. 2015 Jul;71(7):1451-63. doi: 10.1111/jan.12605. Epub 2015 Jan 6.	Aims. To review published studies reporting maternity experiences and outcomes for pregnant incarcerated women and their babies. Background: Numbers of women in prison have increased in many countries. Imprisoned women who are pregnant are particularly vulnerable and marginalised. Little is known about their maternity care experiences, or outcomes. Design: Systematic mixed-methods review using a segregated approach. Data sources: The Cochrane Library, CINAHL, EMBASE, MEDLINE Psych INFO and PubMed were searched using the terms 'mother' and 'prison', (January 1995–July 2012). From July 2012–May 2014 possible new studies were identified through scrutiny of 50 relevant journal contents pages via Zetoc. Results: Seven studies met the review criteria and quality standards, all from the USA or UK. Four of the studies were quantitative; two were qualitative; and one used mixed methods. None reported the outcomes of an intervention. Examination of the quantitative data identified a complex picture of potential harms and benefits for babies born in prison. Qualitative data revealed the unique needs of childbearing women in prison, as they continuously negotiate being an inmate, becoming a mother, complex social histories and the threat of losing their baby, all coalescing with opportunities for transformation offered by pregnancy. Conclusions. There is very limited published data on the experiences and outcomes of childbearing women in prison. There appear to be no good quality intervention studies examining the effectiveness of interventions to improve wellbeing in the short or longer term for these women and their babies.
Sugarman OK	2020	Sugarman OK, Bachhuber MA,	Incarceration poses significant health risks for people involved in the criminal justice system. As the world's leader in incarceration, the United States incarcerated population is at higher

		Wennerstrom A, Bruno T, Springgate BF. Interventions for incarcerated adults with opioid use disorder in the United States: A systematic review with a focus on social determinants of health. PLoS One. 2020 Jan 21;15(1):e0227968. doi: 10.1371/journal.pone.0227968. eCollection 2020.	risk for infectious diseases, mental illness, and substance use disorder. Previous studies indicate that the mortality rate for people coming out of prison is almost 13 times higher than that of the general population; opioids contribute to nearly 1 in 8 post-release fatalities overall, and almost half of all overdose deaths. Given the hazardous intersection of incarceration, opioid use disorder, and social determinants of health, we systematically reviewed recent evidence on interventions for opioid use disorder (OUD) implemented as part of United States criminal justice system involvement, with an emphasis on social determinants of health (SDOH). We searched academic literature to identify eligible studies of an intervention for OUD that was implemented in the context of criminal justice system involvement (e.g., incarceration or parole/probation) for adults ages 19 and older. From 6,604 citations, 13 publications were included in final synthesis. Most interventions were implemented in prisons (n = 6 interventions), used medication interventions (n = 10), and did not include SDOH as part of the study design (n = 8). Interventions that initiated medication treatment early and throughout incarceration had significant, positive effects on opioid use outcomes. Evidence supports medication treatment administered throughout the period of criminal justice involvement as an effective method of improving post-release outcomes in individuals with criminal justice involvement. While few studies included SDOH components, many investigators recognized SDOH needs as competing priorities among justice-involved individuals. This review suggests an evidence gap; evidence-based interventions that address OUD and SDOH in the context of criminal justice involvement are urgently needed.
Troy V	2018	Troy V, McPherson KE, Emslie C, Gilchrist E. The Feasibility, Appropriateness, Meaningfulness, and Effectiveness of	Children whose parents are involved in the criminal justice system (CJS) are at increased risk of developing social, emotional, and behavioural difficulties and are more likely than their peers to become involved in the CJS themselves. Parenting behaviour and parent-child relationships have the potential to affect children's outcomes with positive parenting practices having the potential to moderate some of the negative outcomes associated with parental involvement in the CJS. However, many parents in the CJS may lack appropriate role models to support the development of positive parenting beliefs and practices.

		Parenting and Family Support Programs Delivered in the Criminal Justice System: A Systematic Review. J Child Fam Stud. 2018;27(6):1732-1747. doi: 10.1007/s10826-018-1034-3. Epub 2018 Mar 1.	Parenting programs offer an opportunity for parents to enhance their parenting knowledge and behaviours and improve relationships with children. Quantitative and qualitative evidence pertaining to the implementation and effectiveness of parenting programs delivered in the CJS was included. Five databases were searched and a total of 1145 articles were identified of which 29 met the review inclusion criteria. Overall, programs were found to significantly improve parenting attitudes; however, evidence of wider effects is limited. Additionally, the findings indicate that parenting programs can be meaningful for parents. Despite this, a number of challenges for implementation were found including the transient nature of the prison population and a lack of parent-child contact. Based on these findings, recommendations for the future development and delivery of programs are discussed.
Werb D	2016	Werb D, Kamarulzaman A, Meacham MC, Rafful C, Fischer B, Strathdee SA, Wood E. The effectiveness of compulsory drug treatment: A systematic review. Int J Drug Policy. 2016 Feb;28:1-9. doi: 10.1016/j.drugpo.2015.12.005. Epub 2015 Dec 18.	Background: Despite widespread implementation of compulsory treatment modalities for drug dependence, there has been no systematic evaluation of the scientific evidence on the effectiveness of compulsory drug treatment. Methods: We conducted a systematic review of studies assessing the outcomes of compulsory treatment. We conducted a search in duplicate of all relevant peer-reviewed scientific literature evaluating compulsory treatment modalities. The following academic databases were searched: PubMed, PAIS International, Proquest, PsycINFO, Web of Science, Soc Abstracts, JSTOR, EBSCO/Academic Search Complete, REDALYC, SciELO Brazil. We also searched the Internet, and article reference lists, from database inception to July 15th, 2015. Eligibility criteria are as follows: peer-reviewed scientific studies presenting original data. Primary outcome of interest was post-treatment drug use. Secondary outcome of interest was post-treatment criminal recidivism. Results: Of an initial 430 potential studies identified, nine quantitative studies met the

			inclusion criteria. Studies evaluated compulsory treatment options including drug detention facilities, short (i.e., 21-day) and long-term (i.e., 6 months) inpatient treatment, community-based treatment, group-based outpatient treatment, and prison-based treatment. Three studies (33%) reported no significant impacts of compulsory treatment compared with control interventions. Two studies (22%) found equivocal results but did not compare against a control condition. Two studies (22%) observed negative impacts of compulsory treatment on criminal recidivism. Two studies (22%) observed positive impacts of compulsory inpatient treatment on criminal recidivism and drug use. Conclusion: There is limited scientific literature evaluating compulsory drug treatment. Evidence does not, on the whole, suggest improved outcomes related to compulsory treatment approaches, with some studies suggesting potential harms. Given the potential for human rights abuses within compulsory treatment settings, non-compulsory treatment modalities should be prioritized by policymakers seeking to reduce drug-related harms.
Woodhouse R	2016	Woodhouse R, Neilson M, Martyn-St James M, Glanville J, Hewitt C, Perry AE. Interventions for drug-using offenders with co-occurring mental health problems: a systematic review and economic appraisal. Health Justice. 2016 Sep 13;4(1):10. doi: 10.1186/s40352-016-	Background: Drug-using offenders with co-occurring mental health problems are common in the criminal justice system. A combination of drug use and mental health problems makes people more likely to be arrested for criminal involvement after release compared to offenders without a mental health problem. Previous research has evaluated interventions aimed broadly at those with a drug problem but rarely with drug use and mental health problems. This systematic review considers the effectiveness of interventions for drug-using offenders with co-occurring mental health problems. Methods: We searched 14 electronic bibliographic databases up to May 2014 and five Internet resources. The review included randomised controlled trials designed to reduce, eliminate, or prevent relapse of drug use and/or criminal activity. Data were reported on drug and crime outcomes, the identification of mental health problems, diagnoses and resource information using the Drummond checklist. The systematic review used standard methodological procedures as prescribed by the Cochrane

		0041-y. eCollection 2016 Dec.	collaboration. Results: Eight trials with 2058 participants met the inclusion criteria. These evaluated: case management (RR, 1.05, 95 %CI 0.90 to 1.22, 235 participants), motivational interviewing and cognitive skills, (MD-7.42, 95 % CI-0.20.12 to 5.28, 162 participants) and interpersonal psychotherapy (RR 0.67, 95 % CI 0.3 to 1.5, 38 participants). None of these trials reported significant reductions in self-report drug misuse or crime. Four trials evaluating differing therapeutic community models showed reductions in re-incarceration (RR 0.28, 95 % CI 0.13 to 0.63, 139 participants) but not re-arrest (RR 1.65, 95 % CI 0.83 to 3.28, 370 participants) or self-report drug use (RR 0.73, 95 % CI 0.53 to 1.01, 370 participants). Mental health problems were identified across the eight trials and 17 different diagnoses were described. Two trials reported some resource information suggesting a cost-beneficial saving when comparing therapeutic communities to a prison alternative. Conclusions: Overall, the studies showed a high degree of variation, warranting a degree of caution in the interpretation of the magnitude of effect and direction of benefit for treatment outcomes. Specifically, tailored interventions are required to assess the effectiveness of interventions for drug-using offenders with co-occurring mental health problems
Wright NM	2011	Wright NM, Sheard L, Adams CE, Rushforth BJ, Harrison W, Bound N, Hart R, Tompkins CN. Comparison of methadone and buprenorphine for opiate detoxification (LEEDS trial): a randomised controlled	Background: Many opiate users require prescribed medication to help them achieve abstinence, commonly taking the form of a detoxification regime. In UK prisons, drug users are nearly universally treated for their opiate use by primary care clinicians, and once released access GP services where 40%of practices now treat drug users. There is a paucity of evidence evaluating methadone and buprenorphine (the two most commonly prescribed agents in the UK) for opiate detoxification. Aim: To evaluate whether buprenorphine or methadone help to achieve drug abstinence at completion of a reducing regimen for heroin users presenting to UK prison health care for detoxification. Design: Open-label, pragmatic, randomised controlled trial in three prison primary

		trial. Br J Gen Pract. 2011 Dec;61(593):e772-80. doi: 10.3399/bjgp11X613106.	healthcare departments in the north of England. Method: Prisoners (n = 306) using illicit opiates were recruited and given daily sublingual buprenorphine or oral methadone, in the context of routine care, over a standard reduced regimen of not more than 20 days. The primary outcome measure was abstinence from illicit opiates at 8 days post detoxification, as indicated by urine test (self-report/clinical notes where urine sample was not feasible). Secondary outcomes were also recorded. Results: Abstinence was ascertained for 73.7%at 8 days post detoxification (urine sample = 52.6%, self-report = 15.2%, clinical notes = 5.9%). There was no statistically significant difference in the odds of achieving abstinence between methadone and buprenorphine (odds ratio [OR] = 1.69; 95% confidence interval [CI] = 0.81 to 3.51; P = 0.163). Abstinence was associated solely with whether or not the participant was still in prison at that time (15.22 times the odds; 95%CI = 4.19 to 55.28). The strongest association for lasting abstinence was abstinence at an earlier time point. Conclusion: There is equal clinical effectiveness between methadone and buprenorphine in achieving abstinence from opiates at 8 days post detoxification within prison.

Table S9 Reviews for interventions in schools and colleges

First author	Year	Citation	Abstract
Bavarian N	2015	Bavarian N, Flay BR, Ketcham PL, Smit E. The Illicit Use of Prescription Stimulants on College Campuses: A Theory-Guided Systematic Review. Health Educ Behav. 2015 Dec;42(6):719-29. doi: 10.1177/1090198115580576. Epub 2015 Jun 1.	The illicit use of prescription stimulants (IUPS) is a substance use behavior that remains prevalent on college campuses. As theory can guide research and practice, we provide a systematic review of the college-based IUPS epidemiological literature guided by one ecological framework, the Theory of Triadic Influence (TTI). We aim to assess prevalence, elucidate the behavior's multi-etiological nature, and discuss prevention implications. Peer-reviewed studies were located through key phrase searches (prescription stimulant misuse and college; "prescription stimulant misuse" and "college"; illicit use of prescription stimulants in college; nonmedical prescription stimulant use in college students) in electronic databases (PubMed, PubMed Central, and EBSCO Host) for the period 2000 to 2013. Studies meeting inclusion criteria had their references reviewed for additional eligible literature. Statistically significant correlates of IUPS in the 62 retrieved studies were organized using the three streams of influence and four levels of causation specified in the TTI. Results show the prevalence of IUPS varies across campuses. Additionally, findings suggest the behavior is multifaceted, as correlates were observed within each stream of influence and level of causation specified by the TTI. We conclude that IUPS is prevalent in, but varies across, colleges, and is influenced by intrapersonal and broader social and societal factors. We discuss implications for prevention and directions for future research.
Benson K	2015	Benson K, Flory K, Humphreys KL, Lee SS. Misuse of stimulant medication among college students: a comprehensive review and meta-analysis.	The misuse of stimulant medication among college students is a prevalent and growing problem. The purpose of this review and meta-analysis is to summarize the current research on rates and demographic and psychosocial correlates of stimulant medication misuse among college students, to provide methodological guidance and other ideas for future research, and to provide some preliminary suggestions for preventing and reducing misuse on college campuses. Random-effects meta-analysis found that the rate of stimulant medication misuse among college students was estimated at 17 % (95 % CI [0.13, 0.23], p < .001) and identified several psychological variables that differentiated

		Clin Child Fam Psychol Rev. 2015 Mar;18(1):50-76. doi: 10.1007/s10567-014-0177-z.	misusers and nonusers, including symptoms of attention-deficit/hyperactivity disorder, problems associated with alcohol use, and marijuana use. A qualitative review of the literature also revealed that Greek organization membership, academic performance, and other substance use were associated with misuse. Students are misusing primarily for academic reasons, and the most common source for obtaining stimulant medication is peers with prescriptions. Interpretation of findings is complicated by the lack of a standard misuse definition as well as validated tools for measuring stimulant misuse. The relation between stimulant medication misuse and extra curricular participation, academic outcomes, depression, and eating disorders requires further investigation, as do the reasons why students divert or misuse and whether policies on college campuses contribute to the high rates of misuse among students. Future research should also work to develop and implement effective prevention strategies for reducing the diversion and misuse of stimulant medication on college campuses.
Carney T	2016	Carney T, Myers BJ, Louw J, Okwundu CI. Brief school-based interventions and behavioural outcomes for substance-using adolescents. Cochrane Database Syst Rev. 2016 Jan 20;2016(1):CD008969. doi: 10.1002/14651858.CD008969.pub3.	Background: Adolescent substance use is a major problem in and of itself, and because it acts as a risk factor for other problem behaviours. As substance use during adolescence can lead to adverse and often long-term health and social consequences, it is important to intervene early in order to prevent progression to more severe problems. Brief interventions have been shown to reduce problematic substance use among adolescents and are especially useful for individuals who have moderately risky patterns of substance use. Such interventions can be conducted in school settings. This review set out to evaluate the effectiveness of brief school-based interventions for adolescent substance use. Objectives: To evaluate the effectiveness of brief school-based interventions in reducing substance use and other behavioural outcomes among adolescents compared to another intervention or assessment-only conditions. Search methods: We conducted the original literature search in March 2013 and performed the search update to February 2015. For both review stages (original and update), we searched 10 electronic databases and six websites on evidence-based

			interventions, and the reference lists of included studies and reviews, from 1966 to February 2015. We also contacted authors and organisations to identify any additional studies. Selection criteria: We included randomised controlled trials that evaluated the effects of brief school-based interventions for substance-using adolescents. The primary outcomes were reduction or cessation of substance use. The secondary outcomes were engagement in criminal activity and engagement in delinquent or problem behaviours related to substance use. Data collection and analysis: We used the standard methodological procedures outlined by The Cochrane Collaboration, including the GRADE approach for evaluating the quality of evidence. Main results: We included six trials with 1176 adolescents that measured outcomes at different follow-up periods in this review. Three studies with 732 adolescents compared brief interventions (BIs) with information provision only, and three studies with 444 adolescents compared BIs with assessment only. Reasons for downgrading the quality of evidence included risk of bias of the included studies, imprecision, and inconsistency. For outcomes that concern substance abuse, the retrieved studies only assessed alcohol and cannabis. We generally found moderate-quality evidence that, compared to information provision only, BIs did not have a significant effect on any of the substance use outcomes at short-, medium-, or long-term follow-up. They also did not have a significant effect on delinquent-type behaviour outcomes among adolescents. When compared to assessment-only controls, we found low- or very low-quality evidence that BIs reduced cannabis frequency at short-term follow-up in one study (standardised mean difference (SMD) -0.83; 95% confidence interval (CI) -1.14 to -0.53, n =269). BIs also significantly reduced frequency of alcohol use (SMD -0.91; 95% CI -1.21 to -0.61, n = 242), alcohol abuse (SMD -0.38; 95% CI -0.7 to -0.07, n = 190) and dependence (SMD -0.58; 95% CI -0.9 to -0.26, n = 190), and cannabis abuse (SMD -0.34; 95% CI -0.65 to -0.02, n =190) at medium-term follow-up in one study. At long-term follow-up, BIs also reduced alcohol abuse (SMD -0.72;

			95% CI -1.05 to -0.40, n =181), cannabis frequency (SMD -0.56; 95% CI -0.75 to -0.36, n = 181), abuse (SMD -0.62; 95% CI -0.95 to -0.29, n = 181), and dependence (SMD -0.96; 95% CI -1.30 to -0.63, n = 181) in one study. However, the evidence from studies that compared brief interventions to assessment only conditions was generally of low quality. Brief interventions also had mixed effects on adolescents' delinquent or problem behaviours, although the effect at long-term follow-up on these outcomes in the assessment-only comparison was significant (SMD -0.78; 95% CI -1.11 to -0.45). Authors' conclusions: We found low- or very low-quality evidence that brief school-based interventions may be more effective in reducing alcohol and cannabis use than the assessment-only condition and that these reductions were sustained at long-term follow-up. We found moderate-quality evidence that, when compared to information provision, brief interventions probably did not have a significant effect on substance use outcomes. It is premature to make definitive statements about the effectiveness of brief school-based interventions for reducing adolescent substance use. Further high-quality studies examining the relative effectiveness of BIs for substance use and other problem behaviours need to be conducted, particularly in low- and middle-income countries.
Champion KE	2013	Champion KE, Newton NC, Barrett EL, Teesson M. A systematic review of school-based alcohol and other drug prevention programs facilitated by computers or the internet. Drug Alcohol Rev. 2013 Mar;32(2):115-23. doi:	Issues: The use of alcohol and drugs amongst young people is a serious concern and the need for effective prevention is clear. This paper identifies and describes current school-based alcohol and other drug prevention programs facilitated by computers or the Internet. Approach. The Cochrane Library, PsycINFO and PubMed databases were searched in March 2012. Additional materials were obtained from reference lists of papers. Studies were included if they described an Internet- or computer-based prevention program for alcohol or other drugs delivered in schools. Key Findings. Twelve trials of 10 programs were identified. Seven trials evaluated Internet-based programs and five delivered an intervention via CD-ROM. The interventions targeted alcohol, cannabis and tobacco. Data to calculate effect size and odds ratios were unavailable for three programs. Of the seven programs with available data, six achieved reductions in alcohol, cannabis or tobacco use at post intervention and/or follow up. Two interventions were associated with decreased

		10.1111/j.1465-3362.2012.00517.x. Epub 2012 Oct 8.	intentions to use tobacco, and two significantly increased alcohol and drug-related knowledge. Conclusion. This is the first study to review the efficacy of school-based drug and alcohol prevention programs delivered online or via computers. Findings indicate that existing computer- and Internet based prevention programs in schools have the potential to reduce alcohol and other drug use as well as intentions to use substances in the future. These findings, together with the implementation advantages and high fidelity associated with new technology, suggest that programs facilitated by computers and the Internet offer a promising delivery method for school-based prevention. [Champion KE, Newton NC, Barrett EL, Teesson M. A systematic review of school-based alcohol and other drug prevention programs facilitated by computers or the Internet.
Champion KE	2016	Champion KE, Newton NC, Teesson M. Prevention of alcohol and other drug use and related harm in the digital age: what does the evidence tell us? Curr Opin Psychiatry. 2016 Jul;29(4):242-9. doi: 10.1097/YCO.0000000000000258.	Purpose of review: Alcohol and other drug use are major contributors to the global burden of disease. Prevention is critical and evidence is beginning to support the use of online mediums to prevent alcohol and other drug use and harms among adolescents. This study aims to expand the evidence base by conducting a systematic review of recent universal prevention programs delivered by computers and the Internet. Recent findings A total of 12 papers reporting outcomes from trials of nine universal online prevention programs were identified. Of the identified interventions, five targeted multiple substances, two focused solely on alcohol, one targeted only cannabis and one primarily addressed smoking. The majority of programs were delivered at school; however one was implemented in a primary care setting. Six programs demonstrated significant, but modest, effects for alcohol and/or other drug use outcomes. Summary: Evidence to support the efficacy of computer and Internet-based prevention programs for alcohol and other drug use and related harms among adolescents is rapidly emerging, demonstrating that online prevention is an area of increasing promise. Further replication work, longer-term trials and attempts to increase the impact are required.
Dick S	2019	Dick S, Whelan E, Davoren MP, Dockray	Background: Illicit substance misuse is a growing public health problem, with misuse peaking among 18–25 year olds, and attendance at third-level education identified as a

		S, Heavin C, Linehan C, Byrne M. A systematic review of the effectiveness of digital interventions for illicit substance misuse harm reduction in third-level students. BMC Public Health. 2019 Sep 9;19(1):1244. doi: 10.1186/s12889-019-7583-6.	risk factor. Illicit substance misuse has the potential to harm mental and physical health, social relationships, and impact on academic achievements and future career prospects. Digital interventions have been identified as a vehicle for reaching large student populations and circumventing the limited capacity of student health services for delivering face-to-face interventions. Digital interventions have been developed in the area of alcohol and tobacco harm reduction, reporting some effectiveness, but the evidence for the effectiveness of digital interventions targeting illicit substance misuse is lacking. This review aims to systematically identify and critically appraise studies examining the effectiveness of digital interventions for illicit substance misuse harm reduction in third-level students. Methods: We systematically searched ten databases in April 2018 using keywords and database specific terms under the pillars of “mHealth,” “substance misuse,” and “student.” To be eligible for inclusion, papers had to present a measure of illicit substance misuse harm reduction. Included articles were critically appraised and included in the qualitative synthesis regardless of quality. Results: A total of eight studies were included in the qualitative synthesis. Studies reported harm reduction in terms of substance misuse or initiation, as consequences or problems associated with substance misuse, or as correction of perceived social norms. Overall, five out of the eight studies reported at least one positive outcome for harm reduction. The critical appraisal indicated that the study quality was generally weak, predominantly due to a lack of blinding of study participants, and the use of self-reported substance misuse measures. However, results suggest that digital interventions may produce a modest reduction in harm from illicit substance misuse. Conclusions: The results of this review are positive, and support the need for further high-quality research in this area, particularly given the success of digital interventions for alcohol and tobacco harm reduction. However, very

			few studies focused solely on illicit substances, and those that did targeted only marijuana. This suggests the need for further research on the effectiveness of this type of intervention for other illicit substances
Faggiano F	2014	Faggiano F, Minozzi S, Versino E, Buscemi D. Universal school-based prevention for illicit drug use. Cochrane Database Syst Rev. 2014;2014(12):CD003020. doi: 10.1002/14651858.CD003020.pub3. Epub 2014 Dec 1.	Background: Drug addiction is a chronic, relapsing disease. Primary interventions should aim to reduce first use or to prevent the transition from experimental use to addiction. School is the appropriate setting for preventive interventions. Objectives: To evaluate the effectiveness of universal school-based interventions in reducing drug use compared to usual curricular activities or no intervention. Search methods: We searched the Cochrane Drugs and Alcohol Group's Trials Register (September 2013), the Cochrane Central Register of Controlled Trials (2013, Issue 9), PubMed (1966 to September 2013), EMBASE (1988 to September 2013) and other databases. We also contacted researchers in the field and checked reference lists of articles. Selection criteria: Randomised controlled trials (RCT) evaluating school-based interventions designed to prevent illicit drugs use. Data collection and analysis: We used the standard methodological procedures expected by The Cochrane Collaboration. Main results: We included 51 studies, with 127,146 participants. Programmes were mainly delivered in sixth and seventh grade pupils. Most of the trials were conducted in the USA. Social competence approach versus usual curricula or no intervention Marijuana use at < 12 months follow-up: the results favoured the social competence intervention (risk ratio (RR) 0.90; 95% confidence interval (CI) 0.81 to 1.01, four studies, 9456 participants, moderate quality evidence). Seven studies assessed this outcome (no data for meta-analysis): two showed a positive significant effect of intervention, three showed a non-significant effect, one found a significant effect in favour of the control group and one found a trend in favour of the control group. Marijuana use at 12+ months: the results favoured the social competence intervention (RR 0.86; 95% CI 0.74 to 1.00, one study,

			2678 participants, high quality evidence). Seven studies assessed this outcome (no data for meta-analysis): two showed a significant positive effect of intervention, three showed a non-significant effect, one found a significant effect in favour of the control group and one a trend in favour of the control group. Hard drug use at < 12 months: we found no difference (RR 0.69; 95% CI 0.40 to 1.18, one study, 2090 participants, moderate quality evidence). Two studies assessed this outcome (no data for meta-analysis): one showed comparable results for the intervention and control group; one found a statistically non-significant trend in favour of the social competence approach. Hard drug use at 12+ months: we found no difference (mean difference (MD) -0.01; 95% CI -0.06 to 0.04), one study, 1075 participants, high quality evidence). One study with no data for meta-analysis showed comparable results for the intervention and control group. Any drug use at < 12 months: the results favoured social competence interventions (RR 0.27; 95% CI 0.14 to 0.51, two studies, 2512 participants, moderate quality evidence). One study with 1566 participants provided continuous data showing no difference (MD 0.02; 95% CI -0.05 to 0.09, moderate quality evidence). Social influence approach versus usual curricula or no intervention Marijuana use at < 12 months: we found a nearly statistically significant effect in favour of the social influence approach (RR 0.88; 95% CI 0.72 to 1.07, three studies, 10,716 participants, moderate quality evidence). One study with 764 participants provided continuous data showing results that favoured the social influence intervention (MD -0.26; 95% CI -0.48 to -0.04). Marijuana use at 12+ months: we found no difference (RR 0.95; 95% CI 0.81 to 1.13, one study, 5862 participants, moderate quality evidence). One study with 764 participants provided continuous data and showed nearly statistically significant results in favour of the social influence intervention (MD -0.22; 95% CI -0.46 to 0.02). Of the four studies not providing data for meta-analysis a statistically significant protective effect was only found by one study. Hard drug use at 12+ months: one study not providing data for meta-analysis found a significant protective effect of the social influence approach. Any drug use: no studies assessed this outcome. Combined approach versus usual curricula or no intervention Marijuana use at < 12 months: there

			was a trend in favour of intervention (RR 0.79; 95% CI 0.59 to 1.05, three studies, 8701 participants, moderate quality evidence). One study with 693 participants provided continuous data and showed no difference (MD -1.90; 95% CI -5.83 to 2.03). Marijuana use at 12+ months: the results favoured combined intervention (RR 0.83; 95% CI 0.69 to 0.99, six studies, 26,910 participants, moderate quality evidence). One study with 690 participants provided continuous data and showed no difference (MD -0.80; 95% CI -4.39 to 2.79). Two studies not providing data for meta-analysis did not find a significant effect. Hard drug use at < 12 months: one study with 693 participants provided both dichotomous and continuous data and showed conflicting results: no difference for dichotomous outcomes (RR 0.85; 95% CI 0.63 to 1.14), but results in favour of the combined intervention for the continuous outcome (MD -3.10; 95% CI -5.90 to -0.30). The quality of evidence was high. Hard drug use at 12+ months: we found no difference (RR 0.86; 95% CI 0.39 to 1.90, two studies, 1066 participants, high quality evidence). One study with 690 participants provided continuous data and showed no difference (MD 0.30; 95% CI -1.36 to 1.96). Two studies not providing data for meta-analysis showed a significant effect of treatment. Any drug use at < 12 months: the results favoured combined intervention (RR 0.76; 95% CI 0.64 to 0.89, one study, 6362 participants). Only one study assessed the effect of a knowledge-focused intervention on drug use and found no effect. The types of comparisons and the programmes assessed in the other two groups of studies were very heterogeneous and difficult to synthesise. Authors' conclusions/l School programmes based on a combination of social competence and social influence approaches showed, on average, small but consistent protective effect in preventing drug use, even if some outcomes did not show statistical significance. Some programmes based on the social competence approach also showed protective effect for some outcomes. Since the effects of school-based programmes are small, they should form part of more comprehensive strategies for drug use prevention in order to achieve a population-level impact.

Flynn AB	2015	Flynn AB, Falco M, Hocini S. Independent Evaluation of Middle School-Based Drug Prevention Curricula: A Systematic Review. JAMA Pediatr. 2015 Nov;169(11):1046-52. doi: 10.1001/jamapediatrics.2015.1736.	IMPORTANCE: Lack of robust program evaluation has hindered the effectiveness of school-based drug abuse prevention curricula overall. Independently evaluated randomized controlled trials (RCTs) of universal, middle school-based drug abuse prevention curricula are the most useful indicators of whether such programs are effective or ineffective. OBJECTIVE: To conduct a systematic review identifying independently evaluated RCTs of universal, middle school-based drug abuse prevention curricula; extract data on study quality and substance use outcomes; and assess evidence of program effectiveness. EVIDENCE REVIEW: Psyclnfo, Educational Resources Information Center, Science Citation Index, Social Science Citation Index, Cumulative Index to Nursing and Allied Health Literature, MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched between January 1,1984, and March 15, 2015. Search terms included variations of drug, alcohol, tobacco, and marijuana use, as well as school, prevention, and effectiveness. Studies included in the review were RCTs carried out by independent evaluators of universal school-based drug prevention curricula available for dissemination in the United States that reported alcohol, tobacco, marijuana, or other drug use outcomes. Two researchers extracted data on study quality and outcomes independently using a data extraction form and met to resolve disagreements. FINDINGS: A total of 5071 publications were reviewed, with 13 articles meeting final inclusion criteria. Of the 13 articles, 6 RCTs of 4 distinct school-based curricula were identified for inclusion. Outcomes were reported for 42 single-drug measures in the independent RCTs, with just 3 presenting statistically significant ($P < .05$) differences between the intervention group and the control group. One program revealed statistically significant positive effects at final follow-up (Lions-Quest Skills for Adolescence). CONCLUSIONS AND RELEVANCE: The results of our review demonstrate the dearth of independent research that appropriately evaluates the effectiveness of universal, middle school-based drug prevention curricula. Independent evaluations show little evidence of

			effectiveness for widely used programs. New methods may be necessary to approach school-based adolescent drug prevention.
Gulliver A	2015	Gulliver A, Farrer L, Chan JK, Tait RJ, Bennett K, Calear AL, Griffiths KM. Technology-based interventions for tobacco and other drug use in university and college students: a systematic review and meta-analysis. Addict Sci Clin Pract. 2015 Feb 24;10(1):5. doi: 10.1186/s13722-015-0027-4.	Background: University students have high levels of tobacco and other drug use, yet they are unlikely to seek traditional care. Technology-based interventions are highly relevant to this population. This paper comprises a systematic review and meta-analysis of published randomized trials of technology-based interventions evaluated in a tertiary (university/college) setting for tobacco and other drug use (excluding alcohol). It extends previous reviews by using a broad definition of technology. Methods: PubMed, PsycInfo, and the Cochrane databases were searched using keywords, phrases, and MeSH terms. Retrieved abstracts (n = 627) were double screened and coded. Included studies met the following criteria: (1) the study was a randomized trial or a randomized controlled trial (RCT); (2) the sample was composed of students attending a tertiary (e.g., university, college) institution; (3) the intervention was either delivered by or accessed using a technological device or process (e.g., computer/internet, telephone, mobile short message services [SMS]); (4) the age range or mean of the sample was between 18 and 25 years; and (5) the intervention was designed to alter a drug use outcome relating to tobacco or other drugs (excluding alcohol). Results: A total of 12 papers met inclusion criteria for the current review. The majority of included papers examined tobacco use (n = 9; 75%), two studies targeted marijuana use (17%); and one targeted stress, marijuana, alcohol, and tobacco use. A quantitative meta-analysis was conducted on the tobacco use studies using an abstinence outcome measure (n = 6), demonstrating that the interventions increased the rate of abstinence by 1.5 times that of controls (Risk Ratio [RR] = 1.54; 95% Confidence Interval [CI] = 1.20–1.98). Across all 12 studies, a total of 20 technology-based interventions were reviewed. A range of technology was employed in the interventions, including stand-alone computer programs (n = 10), internet (n = 5), telephone (n = 3), and mobile SMS (n = 2). Conclusions: Although technological interventions have the potential to reduce drug use in tertiary students, very few trials have been conducted, particularly for substances other

			than tobacco. However, the improvement shown in abstinence from tobacco use has the potential to impact substantially on morbidity and mortality.
Hale DR	2014	Hale DR, Fitzgerald-Yau N, Viner RM. A systematic review of effective interventions for reducing multiple health risk behaviors in adolescence. Am J Public Health. 2014 May;104(5):e19-41. doi: 10.2105/AJPH.2014.301874. Epub 2014 Mar 13.	We systematically searched 9 biomedical and social science databases (1980–2012) for primary and secondary interventions that prevented or reduced 2 or more adolescent health risk behaviors (tobacco use, alcohol use, illicit drug use, risky sexual behavior, aggressive acts). We identified 44 randomized controlled trials of universal or selective interventions and were effective for multiple health risk behaviors. Most were school based, conducted in the United States, and effective for multiple forms of substance use. Effects were small, in line with findings for other universal prevention programs. In some studies, effects for more than 1 health risk behavior only emerged at long-term follow-up. Integrated prevention programs are feasible and effective and may be more efficient than discrete prevention strategies.
Langford R	2014	Langford R, Bonell CP, Jones HE, Pouliou T, Murphy SM, Waters E, Komro KA, Gibbs LF, Magnus D, Campbell R. The WHO Health Promoting School framework for improving the health and well-being of students and their academic	Background: The World Health Organization's (WHO's) Health Promoting Schools (HPS) framework is an holistic, settings-based approach to promoting health and educational attainment in school. The effectiveness of this approach has not been previously rigorously reviewed. Objectives: To assess the effectiveness of the Health Promoting Schools (HPS) framework in improving the health and well-being of students and their academic achievement. Search methods: We searched the following electronic databases in January 2011 and again in March and April 2013: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, CINAHL, Campbell Library, ASSIA, Biblio Map, CAB Abstracts, IBSS, Social Science Citation Index, Sociological Abstracts, TRo PHI, Global Health Database, SIGLE, Australian Education Index, British Education Index, Education Resources Information Centre, Database of Education Research, Dissertation

		achievement. Cochrane Database Syst Rev. 2014 Apr 16;(4):CD008958. doi: 10.1002/14651858.CD008958.pub2.	Express, Index to Theses in Great Britain and Ireland,ClinicalTrials.gov, Current controlled trials, and WHO International Clinical Trials Registry Platform. We also searched relevant websites, hand searched reference lists, and used citation tracking to identify other relevant articles. Selection criteria. We included cluster-randomised controlled trials where randomisation took place at the level of school, district or other geographical area. Participants were children and young people aged four to 18 years, attending schools or colleges. In this review, we define HPS interventions as comprising the following three elements: input to the curriculum; changes to the school's ethos or environment or both; and engagement with families or communities, or both. We compared this intervention against schools that implemented either no intervention or continued with their usual practice, or any programme that included just one or two of the above mentioned HPS elements. Data collection and analysis: At least two review authors identified relevant trials, extracted data, and assessed risk of bias in the trials. We grouped different types of interventions according to the health topic targeted or the approach used, or both. Where data permitted, we performed random-effects meta-analyses to provide a summary of results across studies. Main results: We included 67 eligible cluster trials, randomising 1443 schools or districts. This is made up of 1345 schools and 98 districts. The studies tackled a range of health issues: physical activity (4), nutrition (12), physical activity and nutrition combined (18), bullying (7), tobacco(5), alcohol (2), sexual health (2), violence (2), mental health (2), hand-washing (2), multiple risk behaviours (7), cycle-helmet use (1),eating disorders (1), sun protection (1), and oral health (1). The quality of evidence overall was low to moderate as determined by the GRADE approach. 'Risk of bias's assessments identified methodological limitations, including heavy reliance on self-reported data and high attrition rates for some studies. In addition, there was a lack of long-term follow-up data for most studies. We found positive effects for some interventions for: body mass index (BMI), physical activity, physical fitness, fruit and vegetable intake, tobacco use, and being

			bullied. Intervention effects were generally small but have the potential to produce public health benefits at the population level. We found little evidence of effectiveness for standardised body mass index (zBMI) and no evidence of effectiveness for fat intake, alcohol use, drug use, mental health, violence and bullying others; however, only a small number of studies focused on these latter outcomes. It was not possible to meta-analyse data on other health outcomes due to lack of data. Few studies provided details on adverse events or outcomes related to the interventions. In addition, few studies included any academic, attendance or school-related outcomes. We therefore cannot draw any clear conclusions as to the effectiveness of this approach for improving academic achievement.
Lize SE	2017	Lize SE, Iachini AL, Tang W, Tucker J, Seay KD, Clone S, DeHart D, Browne T. A Meta-analysis of the Effectiveness of Interactive Middle School Cannabis Prevention Programs. Prev Sci. 2017 Jan;18(1):50-60. doi: 10.1007/s11121-016-0723-7.	This meta-analysis examines the effectiveness of interactive middle school-based drug prevention programs on adolescent cannabis use in North America, as well as program characteristics that could moderate these effects. Interactive programs, compared to more didactic, lecture style programs, involve participants in skill-building activities and focus on interaction among participants. A systematic literature search was conducted for English-language studies from January 1998 to March 2014. Studies included evaluations using random assignment or a quasi-experimental design of interactive school-based substance use prevention programs delivered to adolescents (aged 12-14) in North American middle schools (grades 6-8). Data were extracted using a coding protocol. The outcomes of interest were post-treatment cannabis use, intent to use, and refusal skills compared across intervention and control groups. Effect sizes (Cohen's d) were calculated from continuous measures, and dichotomous measures were converted to the d index. A total of 30 studies yielding 23 independent samples were included. The random effects pooled effect size for cannabis use (k = 21) was small ([Formula: see text]= -0.07, p < 0.01) and favorable for the prevention programs. The pooled effect sizes for intention to use (k = 3) and refusal skills (k = 3) were not significant. Moderator analyses indicated significant differences in program effectiveness between instructor types, with teachers found to be most effective ([Formula: see text]= -0.08, p = 0.02). The findings provide further support

			for the use of interactive school-based programs to prevent cannabis use among middle school students in North America.
MacArthur G	2018	MacArthur G, Caldwell DM, Redmore J, Watkins SH, Kipping R, White J, Chittleborough C, Langford R, Er V, Lingam R, Pasch K, Gunnell D, Hickman M, Campbell R. Individual-, family-, and school-level interventions targeting multiple risk behaviours in young people. Cochrane Database Syst Rev. 2018 Oct 5;10(10):CD009927. doi: 10.1002/14651858.CD009927.pub2.	Background: Engagement in multiple risk behaviours can have adverse consequences for health during childhood, during adolescence, and later in life, yet little is known about the impact of different types of interventions that target multiple risk behaviours in children and young people, or the differential impact of universal versus targeted approaches. Findings from systematic reviews have been mixed, and effects of these interventions have not been quantitatively estimated. Objectives: To examine the effects of interventions implemented up to 18 years of age for the primary or secondary prevention of multiple risk behaviours among young people. Search methods: We searched 11 databases (Australian Education Index; British Education Index; Campbell Library; Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library; Embase; Education Resource Information Center (ERIC); International Bibliography of the Social Sciences; MEDLINE; PsycINFO; and Sociological Abstracts) on three occasions (2012, 2015, and 14 November 2016)). We conducted hand searches of reference lists, contacted experts in the field, conducted citation searches, and searched websites of relevant organisations. Selection criteria: We included randomised controlled trials (RCTs), including cluster RCTs, which aimed to address at least two risk behaviours. Participants were children and young people up to 18 years of age and/or parents, guardians, or carers, as long as the intervention aimed to address involvement in multiple risk behaviours among children and young people up to 18 years of age. However, studies could include outcome data on children > 18 years of age at the time of follow-up. Specifically, we included studies with outcomes collected from those eight to 25 years of age. Further, we included only studies with a combined intervention and follow-up period of six months or longer. We excluded interventions aimed at individuals with

			clinically diagnosed disorders along with clinical interventions. We categorised interventions according to whether they were conducted at the individual level; the family level; or the school level. Data collection and analysis We identified a total of 34,680 titles, screened 27,691 articles and assessed 424 full-text articles for eligibility. Two or more review authors independently assessed studies for inclusion in the review, extracted data, and assessed risk of bias. We pooled data in meta-analyses using a random-effects (Der Simonian and Laird) model in Rev Man 5.3. For each outcome, we included subgroups related to study type (individual, family, or school level, and universal or targeted approach) and examined effectiveness at up to 12 months' follow-up and over the longer term (> 12 months). We assessed the quality and certainty of evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. Main results: We included in the review a total of 70 eligible studies, of which a substantial proportion were universal school-based studies (n = 28; 40%). Most studies were conducted in the USA (n = 55; 79%). On average, studies aimed to prevent four of the primary behaviours. Behaviours that were most frequently addressed included alcohol use (n = 55), drug use (n = 53), and/or antisocial behaviour (n = 53), followed by tobacco use (n = 42). No studies aimed to prevent self-harm or gambling alongside other behaviours. Evidence suggests that for multiple risk behaviours, universal school-based interventions were beneficial in relation to tobacco use (odds ratio (OR) 0.77, 95% confidence interval (CI) 0.60 to 0.97; n = 9 studies; 15,354 participants) and alcohol use (OR 0.72, 95% CI 0.56 to 0.92; n= 8 studies; 8751 participants; both moderate-quality evidence) compared to a comparator, and that such interventions may be effective in preventing illicit drug use (OR 0.74, 95% CI 0.55 to 1.00; n = 5 studies; 11,058 participants; low-quality evidence) and engagement in any antisocial behaviour(OR 0.81, 95% CI 0.66 to 0.98; n = 13 studies; 20,756 participants; very low-quality evidence) at up to 12 months' follow-up, although there was evidence of moderate to substantial heterogeneity (I2 = 49% to 69%). Moderate-quality evidence also showed that multiple risk behaviour universal school-based interventions improved the odds of physical activity (OR 1.32, 95% CI 1.16 to 1.50;

			I2 = 0%; n = 4 studies; 6441 participants). We considered observed effects to be of public health importance when applied at the population level. Evidence was less certain for the effects of such multiple risk behaviour interventions for cannabis use (OR 0.79, 95% CI 0.62 to 1.01; P = 0.06; n = 5 studies; 4140 participants; I2 = 0%; moderate-quality evidence), sexual risk behaviours (OR 0.83, 95% CI 0.61 to 1.12; P = 0.22; n = 6 studies; 12,633 participants; I2 = 77%; low-quality evidence), and unhealthy diet (OR 0.82, 95% CI 0.64 to 1.06; P = 0.13; n = 3 studies; 6441 participants; I2 = 49%; moderate-quality evidence). It is important to note that some evidence supported the positive effects of universal school-level interventions on three or more risk behaviours. For most outcomes of individual- and family-level targeted and universal interventions, moderate- or low-quality evidence suggests little or no effect, although caution is warranted in interpretation because few of these studies were available for comparison (n ≤ 4 studies for each outcome). Seven studies reported adverse effects, which involved evidence suggestive of increased involvement in a risk behaviour among participants receiving the intervention compared to participants given control interventions. We judged the quality of evidence to be moderate or low for most outcomes, primarily owing to concerns around selection, performance, and detection bias and heterogeneity between studies
Melendez-Torres GJ	2018	Melendez-Torres GJ, Tancred T, Fletcher A, Thomas J, Campbell R, Bonell C. Does integrated academic and health education prevent substance use? Systematic review and meta-analyses. Child Care Health Dev. 2018	Background: Prevention of substance (alcohol, tobacco, illegal/legal drug) use in adolescents is a public health priority. As the scope for school-based health education is constrained in school timetables, interventions integrating academic and health education have gained traction in the UK and elsewhere, though evidence for their effectiveness remains unclear. We sought to syn-the size the effectiveness of interventions integrating academic and health education for the prevention of substance use. Methods: We searched 19 databases between November and December 2015, among other methods. We included randomized trials of interventions integrating academic and health education targeting school students aged 4–18 and reporting substance use outcomes. We excluded interventions for specific health-related subpopulations (e.g., children with behavioural difficulties). Data were extracted independently in duplicate.

		Jul;44(4):516-530. doi: 10.1111/cch.12558. Epub 2018 Feb 15.	Outcomes were synthesized by school key stage (KS) using multilevel meta-analyses, for substance use, overall and by type. Results: We identified 7 trials reporting substance use. Interventions reduced substance use generally in years 7–9 (KS3) based on 5 evaluations (d = −0.09, 95% CI [−0.17, −0.01],I2= 35%), as well as in years 10–11 (KS4) based on 3 evaluations (−0.06, [−0.09, −0.02];I2= 0%). Interventions were broadly effective for reducing specific alcohol, tobacco, and drug use in both KS groups. Conclusions: Evidence quality was highly variable. Findings for years 3–6 and 12–13 could not be meta-analysed, and we could not assess publication bias. Interventions appear to have a small but significant effect reducing substance use. Specific methods of integrating academic and health education remain poorly understood.
Newton NC	2017	Newton NC, Champion KE, Slade T, Chapman C, Stapinski L, Koning I, Tonks Z, Teesson M. A systematic review of combined student- and parent-based programs to prevent alcohol and other drug use among adolescents. Drug Alcohol Rev. 2017 May;36(3):337-351. doi: 10.1111/dar.12497. Epub 2017 Mar 23.	Issues. Alcohol and other drug use among adolescents is a serious concern, and effective prevention is critical. Research indicates that expanding school-based prevention programs to include parenting components could increase prevention outcomes. This paper aims to identify and describe existing combined student- and parent-based programs for the prevention of alcohol and other drug use to evaluate the efficacy of existing programs. Approach: The PsycINFO, Medline, Central Register of Controlled trials and Cochrane databases were searched in April 2015 and additional articles were obtained from reference lists. Studies were included if they evaluated a combined universal intervention for students (aged 11–18 years old) and their parents designed to prevent alcohol and/or other drug use, and were delivered in a school-based setting. Risk of bias was assessed by two independent reviewers. Because of the heterogeneity of the included studies, it was not possible to conduct a meta-analysis and a qualitative description of the studies was provided. Key Findings. From a total of 1654 screened papers, 22 research papers met inclusion criteria, which included 13 trials of 10 programs. Of these, nine programs demonstrated

			significant intervention effects in terms of delaying or reducing adolescent alcohol and/or other drug use in at least one trial. Conclusion. This is the first review of combined student- and parent-based interventions to prevent and reduce alcohol and other drug use. Whilst existing combined student- and parent-based programs have shown promising results, key gaps in the literature have been identified and are discussed in the context of the development of future prevention programs.
Onrust SA	2016	Onrust SA, Otten R, Lammers J, Smit F. School-based programmes to reduce and prevent substance use in different age groups: What works for whom? Systematic review and meta-regression analysis. Clin Psychol Rev. 2016 Mar;44:45-59. doi: 10.1016/j.cpr.2015.11.002. Epub 2015 Dec 15.	Background: Findings from systematic reviews and meta-analyses about the effectiveness of school-based programmes to prevent or reduce substance abuse are inconclusive. We hypothesise that in order to be effective, programmes have to be aligned with the developmental stages of the intended target group (childhood, early, middle, or late adolescence). The present study provides an overview of universal and targeted programmes, while distinguishing four age groups and examining which intervention characteristics are the effective components for the respective groups. Methods: Databases were searched for controlled studies of school-based programmes, evaluating their effectiveness on either smoking, alcohol or drug use. Multivariate meta-regression analysis was used to analyse the associations between effects and programme characteristics. Results: Our meta-analysis evaluates 288 programmes with a total of 436,180 participants. The findings support our hypothesis that specific aspects of the school-based programmes are effective in some developmental stages, but not for other age groups. The differences in effectiveness are systematically related to psychological and cognitive needs and capacities. Discussion: Our findings highlight the importance of considering a developmental perspective when designing and offering school-based prevention programmes. The various developmental stages offer different possibilities and opportunities for the reduction and prevention of substance use.

Porath-Waller AJ	2010	Porath-Waller AJ, Beasley E, Beirness DJ. A meta-analytic review of school-based prevention for cannabis use. Health Educ Behav. 2010 Oct;37(5):709-23. doi: 10.1177/1090198110361315. Epub 2010 Jun 3.	Abstract: This investigation used meta-analytic techniques to evaluate the effectiveness of school-based prevention programming in reducing cannabis use among youth aged 12 to 19. It summarized the results from 15 studies published in peer-reviewed journals since 1999 and identified features that influenced program effectiveness. The results from the set of 15 studies indicated that these school-based programs had a positive impact on reducing students' cannabis use (d = 0.58, CI: 0.55, 0.62) compared to control conditions. Findings revealed that programs incorporating elements of several prevention models were significantly more effective than were those based on only a social influence model. Programs that were longer in duration (≥15 sessions) and facilitated by individuals other than teachers in an interactive manner also yielded stronger effects. The results also suggested that programs targeting high school students were more effective than were those aimed at middle-school students. Implications for school-based prevention programming are discussed.
Porath-Waller AJ	2010	Porath-Waller AJ, Beasley E, Beirness DJ. A meta-analytic review of school-based prevention for cannabis use. Health Educ Behav. 2010 Oct;37(5):709-23. doi: 10.1177/1090198110361315. Epub 2010 Jun 3.	This investigation used meta-analytic techniques to evaluate the effectiveness of school-based prevention programming in reducing cannabis use among youth aged 12 to 19. It summarized the results from 15 studies published in peer-reviewed journals since 1999 and identified features that influenced program effectiveness. The results from the set of 15 studies indicated that these school-based programs had a positive impact on reducing students' cannabis use (d = 0.58, CI: 0.55, 0.62) compared to control conditions. Findings revealed that programs incorporating elements of several prevention models were significantly more effective than were those based on only a social influence model. Programs that were longer in duration (≥15 sessions) and facilitated by individuals other than teachers in an interactive manner also yielded stronger effects. The results also suggested that programs targeting high school students were more effective than were those aimed at middle-school students. Implications for school-based prevention programming are discussed.
Pöttgen S	2016	Pöttgen S, Samkange-Zeeb F,	Objective: The aim of this study is to provide a current overview of the effectiveness of school-based interventions on prevention and/or reduction of substance use among

		Brand T, Steenbock B, Pischke CR. [Effectiveness of School-based Interventions to Prevent and/or Reduce Substance Use among Primary and Secondary School Pupils: A Review of Reviews]. Gesundheitswesen. 2016 Apr;78(4):230-6. doi: 10.1055/s-0035-1547275. Epub 2015 Mar 25.	children and adolescents aged 5-19 years. Methods: A systematic literature search was conducted in PubMed, Cochrane Library, Campbell Collaboration, NICE and ERIC. Systematic reviews and meta-analyses published between 2007 and 2013 were included in the analysis. 2 reviewers assessed the quality of the identified review articles and extracted the data. Results: 14 review articles of moderate to good quality fulfilled the a-priori defined inclusion criteria. Capacity-promoting interventions, e. g., those focusing on strengthening self-confidence and peer resistance, show promising evidence of effectiveness. Multi-component and multi-level interventions are more suitable for the prevention of alcohol and cannabis consumption. Findings on the prevention of tobacco consumption are inconsistent. The effectiveness of knowledge-based interventions is limited. The long-term effectiveness of smoke-free competitions cannot be conclusively evaluated as the findings are discrepant. Conclusions: School-based interventions should include capacity-promoting components and should address further levels beyond the individual, for example, organisational changes of the school setting. Further research is needed, in particular on the effectiveness of multi-component and multi-level interventions for the prevention of tobacco consumption.
Shackleton N	2016	Shackleton N, Jamal F, Viner R, Dickson K, Hinds K, Patton G, Bonell C. Systematic review of reviews of observational studies of school-level effects on sexual health, violence and substance use. Health	For three decades there have been reports that the quality of schools affects student health. The literature is diverse and reviews have addressed different aspects of how the school environment may affect health. This paper is the first to synthesise this evidence using a review of reviews focusing on substance-use, violence and sexual-health. Twelve databases were searched. Eleven included reviews were quality-assessed and synthesised narratively. There is strong evidence that schools' success in engaging students is associated with reduced substance use. There is little evidence that tobacco-control policies and school sexual-health clinics on their own are associated with better outcomes.

		Place. 2016 May;39:168-76. doi: 10.1016/j.healthplace.2016.04.002. Epub 2016 Apr 25.	
Stockings E	2016	Stockings E, Hall WD, Lynskey M, Morley KI, Reavley N, Strang J, Patton G, Degenhardt L. Prevention, early intervention, harm reduction, and treatment of substance use in young people. Lancet Psychiatry. 2016 Mar;3(3):280-96. doi: 10.1016/S2215-0366(16)00002-X. Epub 2016 Feb 18.	We did a systematic review of reviews with evidence on the effectiveness of prevention, early intervention, harm reduction, and treatment of problem use in young people for tobacco, alcohol, and illicit drugs (eg, cannabis, opioids, amphetamines, or cocaine). Taxation, public consumption bans, advertising restrictions, and minimum legal age are effective measures to reduce alcohol and tobacco use, but are not available to target illicit drugs. Interpretation of the available evidence for school-based prevention is affected by methodological issues; interventions that incorporate skills training are more likely to be effective than information provision-which is ineffective. Social norms and brief interventions to reduce substance use in young people do not have strong evidence of effectiveness. Roadside drug testing and interventions to reduce injection-related harms have a moderate-to-large effect, but additional research with young people is needed. Scarce availability of research on interventions for problematic substance use in young people indicates the need to test interventions that are effective with adults in young people. Existing evidence is from high-income countries, with uncertain applicability in other countries and cultures and in subpopulations differing in sex, age, and risk status. Concerted efforts are needed to increase the evidence base on interventions that aim to reduce the high burden of substance use in young people.
Tancred T	2018	Tancred T, Paparini S, Melendez-Torres GJ, Thomas J, Fletcher A, Campbell R, Bonell C. A systematic review and	Background: Schools can play an important role in promoting health. However, many education policies and institutions are increasingly emphasising academic attainment targets, which appear to be diminishing the time available for health education lessons. Interventions that integrate both health and academic learning may present an ideal solution, simultaneously addressing health education and academic development. The theories of change underlying these interventions are therefore of interest but are poorly

		synthesis of theories of change of school-based interventions integrating health and academic education as a novel means of preventing violence and substance use among students. Syst Rev. 2018 Nov 13;7(1):190. doi: 10.1186/s13643-018-0862-y.	studied. Methods: A systematic review of evaluations of interventions that integrate academic and health education for reduced substance use and/or violence was carried out. As part of this, reports describing theory were assessed for quality and data extracted. Theoretical data were synthesised within and across individual interventions using reciprocal translation and meta-ethnographic line of argument synthesis to produce an overall theory of change for interventions that integrate health and academic education to prevent substance use and violence. Results: Forty-eight reports provided theoretical descriptions of 18 interventions. An overarching theory that emerged was that eroding 'boundaries' at multiple and mutually reinforcing levels-by integrating academic and health education, by transforming relationships between teachers and students, by generalising learning from classrooms to the wider school environment and by ensuring consistent messages from schools and families-is intended to lead to the development of a community of engaged students oriented towards pro-social behaviour and away from substance use, violence and other risk behaviours. Conclusions: Eroding 'boundaries' between health and academic education, teachers and students, classrooms and the wider school and schools and families were seen to be the most critical to establishing new frameworks of family, classroom or school organisation that are conducive to promoting both academic and social-emotional outcomes. Whether such interventions are feasible to implement and effective in reducing risk behaviours will be examined in other reports arising from the review.
Teesson M	2012	Teesson M, Newton NC, Barrett EL. Australian school-based prevention programs for alcohol and other drugs: a	Issues: To reduce the occurrence and costs related to substance use and associated harms it is important to intervene early. Although a number of international school-based prevention programs exist, the majority show minimal effects in reducing drug use and related harms. Given the emphasis on early intervention and prevention in Australia, it is timely to review the programs currently trialled in Australian schools. This paper reports

		systematic review. Drug Alcohol Rev. 2012 Sep;31(6):731-6. doi: 10.1111/j.1465-3362.2012.00420.x. Epub 2012 Feb 17.	the type and efficacy of Australian school-based prevention programs for alcohol and other drugs. Approach: Cochrane, PsychInfo and PubMed databases were searched. Additional materials were obtained from authors, websites and reference lists. Studies were selected if they described programs developed and trialled in Australia that address prevention of alcohol and other drug use in schools. Key Findings: Eight trials of seven intervention programs were identified. The programs targeted alcohol, cannabis and tobacco and most were based on social learning principles. All were universal. Five of the seven intervention programs achieved reductions in alcohol, cannabis and tobacco use at follow up. Conclusion: Existing school-based prevention programs have shown to be efficacious in the Australian context. However, there are only a few programs available, and these require further evaluative research. This is critical, given that substance use is such a significant public health problem. The findings challenge the commonly held view that school-based prevention programs are not effective.