THE COCHRANE COLLABORATION

The Cochrane Collaboration, launched in 1992, is a global cooperative organization aimed to produce, update and disseminate systematic reviews of the effect of health care interventions. Reviews are timely updated and the results are disseminated to clinicians, decision-makers, patients.

THE SYSTEMATIC REVIEWS

The principal objective of systematic reviews is to develop information:

- Evidence based
- Easily accessible
- Internationally developed
- Clinically relevant
- Updated

They are useful because size and availability of data are huge and increasing, access to results of research is sometime random, quality of research is heterogeneous and many studies are too small (low statistical power).

They can take into account not only the random variability between different Randomised Controlled Trials (RCT) which are the most powerful research design to evaluate the effectiveness of health care, but also the heterogeneity (temporal, geographic, population, setting…), the different experimental conditions and the quality of RCTs.

They allow to judge:
- Whether there are sufficient evidences of effectiveness of the intervention
- Whether it is necessary to conduct further studies for the evaluation of a treatment and which aspects should be considered

THE COCHRANE REVIEW GROUP ON DRUG AND ALCOHOL

The Cochrane Group on Drug and Alcohol founded in the 1998, has the editorial base in Rome at the Department of Epidemiology of ASL RM E. As part of the Cochrane collaboration, the group is aimed to produce, update and disseminate systematic reviews of trials on the prevention, treatment and rehabilitation of the problematic use of drugs and alcohol.

Different interventions are offered for prevention, treatment and rehabilitation of substance abuse. The choice is often guided by common sense, intuition, experience or ideology and not always by evidence. Clinicians and policy makers need accessible, up to date, objective evidence regarding the effectiveness of interventions.

Our systematic reviews are based on all Randomised Controlled Trials and Controlled Clinical Trials that describe an active intervention (including prevention, treatment and rehabilitation) aimed at reducing the potential for harm or the actual harm directly related to the use of different dependence producing substances.

The group created and maintains a specialised register of trials on the evaluation of effectiveness of treatments. As of August 2009 it contains 6720 references (5107 RCTs and 1628 CCT). The references are systematically searched on the electronic databases (MEDLINE, EMBASE, and PsychInfo). The full text articles are obtained and coded (3908 articles till now).

As of August 2009 the group published 49 reviews, 17 review protocols
THE EDITORIAL PROCESS OF A SYSTEMATIC REVIEW

The systematic reviews are the result of a complex process:
– Formulate a proper question
– Comprehensive data search
– Objective selection and data extraction
– Critical evaluation of primary studies

They provide a priori definition of objectives, search strategy, inclusion criteria, data collection procedures and means of data analysis. All the process is peer reviewed.

Once a review has been completed it is expected the Reviewer will update the review regularly. The Reviewer is asked to review the literature on a regular basis; at least once a year. In cases where new evidence is available the review should be updated. However, in the case where no new evidence exists the date of last update will still be modified to reflect the date of this process. The Trial Search Coordinator performs the search strategy on the group’s specialised register quarterly and forwards the results to the reviewer.

In case of significant changes the peer review process is carried out. The judgement is up to the Coordinating Editor.

Methodological Quality of the studies
The Cochrane Collaboration recommends a specific tool for assessing risk of bias in each included study. This comprises a description and a judgement for each entry in a ‘Risk of bias’ table, where each entry addresses a specific feature of the study.

A ‘Risk of bias’ table is available in RevMan5 for inclusion in a Cochrane review as part of the ‘Table of characteristics of included studies’. For each question-based entry, the judgement (‘Yes’ for low risk of bias; ‘No’ for high risk of bias, or ‘Unclear’) is followed by a text box providing a description of the design, conduct or observations that underlie the judgement.

The risk of bias table is a two-part tool, addressing six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and ‘other issues’). The tool is summarized in Table 8.5.a. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry. This is achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgement of ‘Yes’ indicates low risk of bias, ‘No’ indicates high risk of bias, and ‘Unclear’ indicates unclear or unknown risk of bias.

The domains of sequence generation, allocation concealment and selective outcome reporting should each be addressed in the tool by a single entry for each study. For blinding and for incomplete outcome data, two or more entries may be used because assessments generally need to be made separately for different outcomes (or for the same outcome at different time points). Review authors should try to limit the number of entries used by grouping outcomes, for example, as ‘subjective, or ‘objective’ outcomes for the purposes of assessing blinding; or as ‘patient-reported at 6 months’ or ‘patient-reported at 12 months’ for incomplete outcome data. The same groupings of outcomes will be applied to every study in the review. The final domain (‘other sources of bias’) can be assessed as a single entry for studies as a whole (the default in RevMan).

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REVIEWS AND PROTOCOLS PUBLISHED BY THE COCHRANE GROUP ON DRUG AND ALCOHOL
(Cochrane Library, issue 4.2009)

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**Interventions for which new reviews should be developed**

**Pharmacological interventions for Alcohol abuse and dependence for which new reviews should be published:**
Antipsychotic; Antibiotic; Beta blockers; Anti nausea; Antihypertensive; Sedative, Anxiolytic, Hypnotic; Antidepressant; Hallucinogen; Psychostimulant; Antioxidant; Alcohol antagonist; Antispasmodic; Anti Parkinson; Calcium channel blockers; Interferon; Plant; Aspartate antagonist

**Pharmacological interventions for Cocaine and other psychostimulants abuse and dependence for which new reviews should be developed**
Psychostimulant ; Antihypertensive; Anorexigenic ; Alcohol antagonist ; Anti Parkinson; Opioid antagonist; Aminoacid; Antispasmodic; Mucolytic agent; Pain killer

**Interventions for Polydrug abuse/dependence for which new reviews should be developed**
Pharmacological interventions; Psychosocial interventions

**Other uncovered areas:**
Hallucinogens abuse and dependence; Inhalants
ABSTRACTS OF THE REVIEWS PUBLISHED BY THE GROUP (COCHRANE LIBRARY ISSUE 4, 2008)

OPIATE: MAINTENANCE INTERVENTIONS

[1] METHADONE MAINTENANCE VERSUS NO OPIOID REPLACEMENT THERAPY FOR OPIOID DEPENDENCE

Plain language summary
Methadone maintenance treatment can keep people who are dependent on heroin in treatment programs and reduce their use of heroin. Methadone is the most widely used replacement for heroin in medically-supported maintenance or detoxification programs. Several non-drug detoxification and rehabilitation methods are also used to try and help people withdraw from heroin. However the review found that people have withdrawn from trials when they are assigned to a drug-free program. Consequently, there are no trials comparing methadone maintenance treatment with drug-free methods other than methadone placebo trials, or comparing methadone maintenance with methadone for detoxification only. These trials show that methadone can reduce the use of heroin in dependent people, and keep them in treatment programs.

ABSTRACT
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) 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.

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.

[2] METHADONE MAINTENANCE AT DIFFERENT DOSAGES FOR OPIOID DEPENDENCE

Plain language summary
People who are addicted to opioids have high risks of receiving an overdose of opioid, HIV, hepatitis B and C infections and criminal activity. This has led to a harm reduction treatment approach to drug addiction. Treatment is aimed at a reduction in these risks and relapses to opioid and polysubstance use and promoting psychosocial adjustment. Methadone maintenance treatment is a long-term opioid replacement therapy that is used to manage opioid dependence, reduce illicit opioid use and promote retention in treatment. Taken by mouth and active over 24 to 36 hours, it is an opioid drug that removes the euphoric effects of heroin and reduces withdrawal symptoms as well as being compatible with normal activities at work or school. The review authors identified 22 controlled trials involving a total of 5994 opioid users. In 11 of these trials, all from the USA, 2279 participants were randomised to methadone treatment at different doses or another treatment (buprenorphine or levomethadyl). Treatment was for between seven and 53 weeks. A further 10 controlled trials did not randomly assign the total of 3715 participants to a treatment. These were from various diverse countries and followed opioid users for one to 10 years. Higher doses of methadone (60 to 100 mg/day) were more effective than lower doses (1 to 39 mg/day) in retaining opioid users in therapy and in reducing illicit use of heroin and cocaine during treatment. Side effects of methadone appeared to be similar at the different doses, in one trial only.

The organisation and regulation of methadone maintenance treatment varies widely and some countries have explicit guidelines for programme operation.

**ABSTRACT**

**Background** Methadone maintenance treatment (MMT) is a long term opioid replacement therapy, effective in the management of opioid dependence. Even if MMT at high dosage is recommended for reducing illicit opioid use and promoting longer retention in treatment, at present day “the organisation and regulation of the methadone maintenance treatment varies widely”.

**Objectives** To evaluate the efficacy of different dosages of MMT in modifying health and social outcomes and in promoting patients’ familiar, occupational and relational functioning.

**Search Strategy** We searched: MEDLINE (OVID 1966-2001), EMBASE (1988-2001), ERIC (1988-2001), Psychinfo (1947-2001), Cochrane Controlled Trials Register (CCTR) (1947-2001), Register of the Cochrane Drug and Alcohol Group (CDAG) (1947-2001). The CDAG search strategy was applied together with a specific MESH strategy. Further studies were searched through letters to the authors and check of references.

**Selection criteria** Randomised Controlled Trials (RCT) and Controlled Prospective Studies (CPS) evaluating methadone maintenance at different dosages in the management of opioid dependence. Non-randomised trials were included when proper adjustment for confounding factors was performed at the analysis stage.

**Main results** 22 studies were excluded. 21 studies were included: 11 were RCTs (2279 participants) and 10 were CPSs (3715 participants).

Outcomes: Retention rate - RCTs: High versus low doses at shorter follow-ups: RR=1.36 [1.13,1.63], and at longer ones: RR=1.62 [0.95,2.77].

Opioid use (self reported), times/w - RCTs: high versus low doses WMD= -2.00 [-4.77,0.77] high vs middle doses WMD= -1.89[-3.43, -0.35]

Opioid abstinence, (urine based) at >3-4 w - RCTs: high versus low ones: RR=1.59 [1.16,2.18] high vs middle doses RR=1.51[0.63,3.61]

Cocaine abstinence, (urine based) at >3-4 w - RCTs: high versus low doses RR=1.81 [1.15,2.85]

Overdose mortality - CPSs: high dose versus low dose at 6 years follow up: RR=0.29 [0.02-5.34] high dose vs middle dose at 6 years follow up: RR=0.38 [0.02-9.34] middle dose vs low dose at 6 years follow up: RR=0.57 [0.06-5.06]

**Authors’ conclusions** Methadone dosages ranging from 60 to 100 mg/day are more effective than lower dosages in retaining patients and in reducing use of heroin and cocaine during treatment. To find the optimal dose is a clinical ability, but clinician must consider these conclusions in treatment strategies.

[3] SUBSTITUTION TREATMENT OF INJECTING OPIOID USERS FOR PREVENTION OF HIV INFECTION
Plain language summary
Oral substitution treatment for injecting opioid users reduces drug-related behaviours with a high risk of HIV transmission, but has less effect on sex-related risk behaviours. Injecting drug users are vulnerable to infection with HIV and other blood borne viruses as a result of collective use of injecting equipment as well as sexual behaviour. This review looks at original studies that reported the frequency or prevalence of risk behaviours, or the prevalence of HIV infection related to substitution treatment of opioid dependence to assess the extent to which oral substitution treatment prevents the transmission of HIV infection. It was not possible to accurately estimate the extent of reduction, but it is clear that oral substitution treatment reduces risk behaviours and also actual cases of HIV infection amongst injecting drug users in substitution treatment.

ABSTRACT

Background Injecting drug users are vulnerable to infection with HIV and other blood borne viruses as a result of collective use of injecting equipment as well as sexual behaviour.

Objectives To assess the effect of oral substitution treatment for opioid dependent injecting drug users on rates of HIV infections, and high risk behaviours.

Search Strategy We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and PsycINFO to March 2007. We also searched reference lists of articles, reviews and conference abstracts We also searched reference lists of articles, reviews and conference abstracts.

Selection criteria Studies were required to consider the incidence of risk behaviours, or the incidence of HIV infection related to substitution treatment of opioid dependence. All types of original studies were considered. Two reviewers independently assessed studies for inclusion.

Main results Thirty-three studies, involving 10,400 participants, were included. The majority were not randomised controlled studies and there were problems of confounding and bias. The studies varied in several aspects limiting the extent of quantitative analysis. Studies consistently show that oral substitution treatment for opioid-dependent injecting drug users with methadone or buprenorphine is associated with statistically significant reductions in illicit opioid use, injecting use and sharing of injecting equipment. It is also associated with reductions in the proportion of injecting drug users reporting multiple sex partners or exchanges of sex for drugs or money, but has little effect on condom use. It appears that the reductions in risk behaviours related to drug use do translate into reductions in cases of HIV infection.

Authors’ conclusions Oral substitution treatment for injecting opioid users reduces drug-related behaviours with a high risk of HIV transmission, but has less effect on sex-related risk behaviours. The lack of data from randomised controlled studies limits the strength of the evidence presented in this review.

[4] BUPRENORPHINE MAINTENANCE VERSUS PLACEBO OR METHADONE MAINTENANCE FOR OPIOID DEPENDENCE

Plain language summary
Buprenorphine can reduce heroin use compared with placebo, although it is less effective than methadone. Methadone is widely used as a replacement for heroin in medically-supported maintenance or detoxification programs. Two other drugs are sometimes used to try and help lower use of heroin, specifically buprenorphine and LAAM (lev-o-alpha-acetylmethadol). Buprenorphine is an opioid drug that is not as powerful as heroin and methadone, although the effects of buprenorphine may last longer. Buprenorphine can be taken once every two days. The review of trials found that buprenorphine at medium (8mg - 15mg) and high doses (16mg) can reduce heroin use effectively compared with placebo, although it is less effective than methadone, especially if methadone is prescribed at adequate dose levels of between 60mg and 120mg per day.
**Background** Buprenorphine has been reported as an alternative to methadone for maintenance treatment of opioid dependence, but differing results are reported concerning its relative effectiveness indicating the need for an integrative review.

**Objectives** To evaluate the effects of buprenorphine maintenance against placebo and methadone maintenance in retaining patients in treatment and in suppressing illicit drug use.

**Search Strategy** We searched the following databases up to October 2006: Cochrane Drugs and Alcohol Review Group Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE, Current Contents, Psychlit, CORK, Alcohol and Drug Council of Australia, Australian Drug Foundation, Centre for Education and Information on Drugs and Alcohol, Library of Congress databases, reference lists of identified studies and reviews, authors were asked about any other published or unpublished relevant RCT.

**Selection criteria** Randomised clinical trials of buprenorphine maintenance versus placebo or methadone maintenance.

**Main results** Twenty four studies met the inclusion criteria (4497 participants), all were randomised clinical trials, all but six were double-blind. The method of allocation concealment was not clearly described in the majority (20) of the studies, but where it was reported the methodological quality was good.

Buprenorphine was statistically significantly superior to placebo medication in retention of patients in treatment at low doses (RR=1.50; 95% CI: 1.19 - 1.88), medium (RR=1.74; 95% CI: 1.06 - 2.87), and high doses (RR=1.74; 95% CI: 1.02 - 2.96). The high statistical heterogenity prevented the calculation of a cumulative estimate. However, only medium and high dose buprenorphine suppressed heroin use significantly above placebo.

Buprenorphine given in flexible doses was statistically significantly less effective than methadone in retaining patients in treatment (RR= 0.80; 95% CI: 0.68 - 0.95), but no different in suppression of opioid use for those who remained in treatment.

Low dose methadone is more likely to retain patients than low dose buprenorphine (RR= 0.67; 95% CI: 0.52 - 0.87). Medium dose buprenorphine does not retain more patients than low dose methadone, but may suppress heroin use better. There was no advantage for medium dose buprenorphine over medium dose methadone in retention (RR=0.79; 95% CI:0.64 - 0.99) and medium dose buprenorphine was inferior in suppression of heroin use.

**Authors’ conclusions** Buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is less effective than methadone delivered at adequate dosages.

*[5] LAAM MAINTENANCE VERSUS METHADONE MAINTENANCE FOR HEROIN DEPENDENCE*


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**Plain language summary**

LAAM may be more effective at reducing heroin dependence than methadone, but it is associated with adverse effects, some of which may be life-threatening.

Opiate drugs are used to help people reduce their dependence on heroin (an opiate drug). Methadone needs daily doses, but the effects do not last 24 hours for many people. A dose of LAAM (levomethadyl acetate hydrochloride) works for two or three days. LAAM is not as widely available internationally as methadone, and may be withdrawn from the market because of concerns about life-threatening effects on the heart. The review found that LAAM is more effective than methadone at reducing heroin dependence, but there was not enough evidence from trials to draw conclusions about safety.

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**Abstract**

**Background** LAAM and methadone are both opiate agonists and have been shown to reduce dependence on heroin when given continuously under supervised dosing conditions. LAAM has a long duration of action requiring dosing every two/three days compared to methadone which requires daily dosing. LAAM is not as widely available internationally as methadone, and may be withdrawn from the market following ten cases of life-threatening cardiac arrhythmias and an association with QT prolongation.

**Objectives** To compare the efficacy and acceptability of LAAM maintenance with methadone
maintenance in the treatment of heroin dependence.

**Search Strategy** We searched MEDLINE (January 1966 - August 2000), PsycINFO (1887 - August 2000), EMBASE (January 1985 - August 2000), and Cochrane Controlled Trials Register (Issue 2 2000). We hand searched NIDA monographs until August 2000 and reference lists of articles. The specialised register of trials of the Cochrane Group on Drugs and Alcohol was searched until February 2003.

**Selection criteria** All randomised controlled trials, controlled clinical trials and controlled prospective studies comparing LAAM and methadone maintenance for the treatment of heroin dependence, outcomes of efficacy or acceptability were included.

**Main results** Eighteen studies, (15 RCTs, 3 Controlled prospective studies) met the inclusion criteria for the review. Three were excluded from the meta-analysis due to lack of data on retention, heroin use or mortality. Cessation of allocated medication (11 studies, 1473 participants) was greater with LAAM than with methadone, (RR 1.36, 95%CI 1.07-1.73, p=0.001, NNT=7.7 (or 8)). Non-abstinence was less with LAAM (5 studies, 983 participants; RR 0.81, 95%CI 0.72-0.91, p=0.0003, NNT=9.1 (or 10)). In 10 studies (1441 participants) there were 6 deaths from a range of causes, 5 in participants assigned to LAAM (RR 2.28 (95%CI 0.59-8.9, p=0.2). other relevant outcomes, such as quality of life and criminal activity could not be analysed because of lack of information in the primary studies.

**Authors' conclusions** LAAM appears more effective than methadone at reducing heroin use. More LAAM patients than methadone ceased their allocated medication during the studies, but many transferred to methadone and so the significance of this is unclear. There was no difference in safety observed, although there was not enough evidence to comment on uncommon adverse events.
There was no language or publication year restrictions. We also contacted researchers in the field.

**Selection criteria** Randomised controlled trials of heroin (alone or combined with methadone) maintenance treatment compared with any other pharmacological treatments for heroin dependents.

**Main results** Four trials involving 577 people were included. The studies could not be analysed cumulatively because of heterogeneity of interventions and outcomes. Retention in treatment: no group difference found in two studies; one study involving 96 people found relative risk 2.82 (95% confidence interval 1.70 to 4.68) favouring heroin; another study involving 235 people found relative risk 0.79 (95% confidence interval 0.68 to 0.90) favouring methadone. Relapse to illegal heroin use (self-reported): in one study people using heroin in treatment was 64% (heroin group) and 59% (methadone group); in the other study the relative risk of heroin use was 0.33 (95% confidence interval 0.15 to 0.72) favouring heroin. Criminal offence: one study showed the potential of heroin prescription in reducing the risk of being charged relative risk 0.32 (95% CI 0.14 to 0.78). Social functioning: two studies did not show statistical difference between intervention groups, and two studies considered criminal offence and social functioning as part of a multi domain outcome measure showing improvements among those treated with heroin plus methadone over those on methadone only.

**Authors’ conclusions** No definitive conclusions about the overall effectiveness of heroin prescription is possible. Results favouring heroin treatment come from studies conducted in countries where easily accessible Methadone Maintenance Treatment at effective dosages is available. In those studies heroin prescription was addressed to patients who had failed previous methadone treatments. The present review contains information about ongoing trials which results will be integrated as soon as available.

[7] ORAL NALTREXONE MAINTENANCE TREATMENT FOR OPIOID DEPENDENCE

**Plain language summary**
Methadone treatment is widely used for detoxification or long-term maintenance therapy of opioid users to reduce harm and improve health and social outcomes yet relapses to illicit drug use are common. Naltrexone is an opioid antagonist that has no euphoric effects and could provide a non-addicting treatment for opioid users yet retention rates in treatment are low, making its effectiveness questionable. People such as health professionals, business executives and those who are under probation in the legal system have strong incentives to complete treatment and may be good candidates for naltrexone treatment. Sustained release preparations that reduce the frequency of dosing may make naltrexone treatment more effective. The results of this review show that naltrexone maintenance therapy, alone or in association with psychosocial therapy, was more effective than non-active placebo, alone or with psychosocial therapy, in limiting the use of heroin during treatment. Where naltrexone was compared with non-active placebo, the difference did not reach statistical significance. No clear benefit was shown in terms of retention in treatment, side effects or relapse at follow up. This conclusion is based on 10 controlled studies that randomised 696 participants to naltrexone alone or with psychosocial therapy compared with psychosocial therapy alone or placebo. Participants were opiate addicts after detoxification and were predominantly male with the mean age ranging from 22 and 39 years. Two of the studies (89 participants) evaluated the effectiveness of naltrexone in parolees or probationers. Naltrexone combined with psychosocial therapy was more effective than psychosocial treatment alone for the number of participants re-incarcerated during the study period. The mean length of the trial was six months (range 1 to 10 months). The studies were from diverse countries and used varying dose schedules for naltrexone

**ABSTRACT**

**Background** Research on the clinical application of oral naltrexone agrees on several things. From a pharmacological perspective, naltrexone works. From an applied perspective, however, this medication is not used since the medication compliance and the retention rates are very poor.

**Objectives** To evaluate the effects of naltrexone maintenance treatment versus placebo or other treatments in preventing relapse in opioid addicts after detoxification.
Search Strategy We searched the Cochrane Drugs and Alcohol Group Register of Trials (January 2005), Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library Issue 1, 2005), MEDLINE (1973-first year of naltrexone use in humans- January 2005), EMBASE (1974-January 2005), PsycINFO (OVID-January 1985 to January 2004). We inspected reference lists of relevant articles and we contacted pharmaceutical producers of naltrexone, authors and other Cochrane review groups.

Selection criteria All randomised and controlled clinical trials which focus on the use of naltrexone maintenance treatment versus placebo, or other treatments to reach sustained abstinence from opiate drugs

Main results Ten studies, 696 participants, met the criteria for inclusion in this review. Only two studies described an adequate allocation concealment. The results show that naltrexone maintenance therapy alone or associated with psychosocial therapy is more efficacious than placebo alone or associated with psychosocial therapy in limiting the use of heroin during the treatment (RR 0.72 95% confidence interval 0.58 to 0.90). If we consider only the studies comparing naltrexone with placebo, the difference do not reach the statistical significant, RR 0.79 (95%CI 0.59 to 1.06). With respect to the number of participants re incarcerated during the study period, the naltrexone associated with psychosocial therapy is more effective than the psychosocial treatment alone; RR 0.50 (95%CI 0.27 to 0.91).

No statistically significant benefit was shown in terms of retention in treatment, side effects or relapse results at follow-up for any of the considered comparisons.

Authors' conclusions Unfortunately the studies did not provide an objective evaluation of naltrexone treatment in the field of opioid dependence. The conclusions are also limited due to the heterogeneity of the trials both in the interventions and in the assessment of outcomes.

Plain language summary
The abuse of opioid drugs and drug dependency are major health and social issues. Maintenance treatments with pharmacological agents can help to reduce the risks associated with the use of street drugs for drug addicts who are unable to abstain from drug use. Methadone is effective in retaining patients in treatment and reducing heroin use but re-addiction remains as a substantial challenge. Opiate addicts often have psychiatric problems such as anxiety and depression and may not be able to cope with stress. Psychosocial interventions including psychiatric care, psychotherapy, counselling, and social work services are commonly offered as part of the maintenance programs. Psychological support varies from structured psychotherapies such as cognitive behavioural therapy and supportive-expressive therapy to behavioural interventions and contingency management. This review addressed whether a specific psychosocial intervention provides any additional benefit to pharmacological maintenance treatment. The control intervention was a maintenance program, which routinely offers counselling sessions in addition to pharmacological treatment. Present evidence suggests that adding psychosocial support does not change the effectiveness of retention in treatment. Nor does it result in a clear reduction in opiate use during treatment. Findings on retention in treatment were for 12 different psychosocial interventions including contingency management over 6 to 48 weeks. These conclusions are based on 28 randomised trials involving 2945 opiate addicts, some 66% of whom were male. The average age was 37 years (range 27 to 45). All but two studies were conducted in the USA. The number of participants abstinent at the end of follow up (five trials) and continuous weeks of abstinence (two trials) showed a benefit in favour of the associated treatment. The previous version of this review showed a reduction in opiate use during treatment that was no longer the case with the addition of new studies. The psychosocial interventions are likely to require rigorous assessment of any changes in emotional, interpersonal, vocational and physical health areas of life functioning that may indirectly reduce drug use over longer periods of time.

Abstract
Background Maintenance treatments are effective in retaining patients in treatment and suppressing heroin use. Questions remain regarding the efficacy of additional psychosocial services offered by most maintenance programs.
**Objectives** To evaluate the effectiveness of any psychosocial plus any agonist maintenance treatment versus standard agonist treatment for opiate dependence in respect of retention in treatment, use of substances, health and social status.

**Search Strategy** We searched: Cochrane Drugs and Alcohol Group's Register of Trials (February 2008), Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library issue 1, 2008), MEDLINE (January 1966 to February 2008), EMBASE (January 1980 to February 2008), CINAHL (January 2003-February 2008), PsycINFO (January 1985 to April 2003), reference lists of articles.

**Selection criteria** Randomised studies comparing any psychosocial plus any agonist with any agonist alone intervention for opiate dependence.

**Main results** Twenty eight trials, 2945 participants, were included. These studies considered twelve different psychosocial interventions and three pharmacological maintenance treatments. Comparing any psychosocial plus any maintenance pharmacological treatment to standard maintenance treatment, results do not show benefit for retention in treatment, 23 studies, 2193 participants, Relative Risk (RR) 1.02 (95% CI 0.97 to 1.07), use of opiate during the treatment, eight studies, 681 participants, RR 0.86 (95% CI 0.65 to 1.13), compliance, three studies, MD 0.43 (95% CI -0.05 to 0.92), psychiatric symptoms, four studies, MD 0.02 (-0.19 to 0.23), depression, four studies, MD -1.30 (95% CI -3.31 to 0.72) and results at follow up as number of participants still in treatment at the end of the follow-up, 289 participants, RR 0.91 (95% CI 0.77 to 1.06). In spite of results at follow up as number of participants abstinent at the end of the follow-up, five studies, 232 participants, show a benefit in favour of the associated treatment RR1.15 (95% CI 1.01 to 1.32). The remaining outcomes were analysed only in single studies considering a limited number of participants. Comparing the different psychosocial approaches, results are never statistically significant for all the comparisons and outcomes.

**Authors’ conclusions** Results suggest that adding any psychosocial support to maintenance treatments improve the number of participants abstinent at follow up; no differences for the other outcome measures. Data do not show differences between different psychosocial interventions also for contingency approaches, contrary to all expectations. Duration of the studies was too short to analyse relevant outcomes such as mortality.

[9] **Psychosocial treatment for opiate abuse and dependence**

**Plain language summary**
Currently there is not enough evidence to conclude that psychosocial treatments alone are adequate to treat people with opiate abuse and dependence. Psychosocial interventions alone are offered to people with opiate use disorders indiscriminately across countries; sometimes representing the most prevalent treatment after substitution therapy. Despite its wide use in clinical practice, no systematic review of effectiveness has ever been carried out. This review demonstrated that there was inadequate evidence available to prove the effectiveness of psychosocial interventions alone for the treatment of opiate dependence or that they are superior to any other type of treatment.

**ABSTRACT**

**Background:** Substance dependence is a social and public health problem; therefore it is a priority to develop effective treatments. Previous Cochrane reviews have explored the efficacy of pharmacotherapy for opiate dependence. This current review focuses on the role of psychosocial interventions alone for the treatment of opiate dependence. There is some evidence for the effectiveness of psychosocial interventions, but no systematic review has even been carried out.

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

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

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

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

**Authors’ conclusions** The available evidence has low numbers and is heterogeneous. At present psychosocial treatments alone are not adequately proved treatment modalities or superior to any other type of treatment. It is important to develop a better evidence base for psychosocial interventions to assist in future rationale planning of opioid use drug treatment services.

**[10] Sustained-Release Naltrexone For Opioid Dependence**

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**Plain language summary**
People with opioid dependence require substantial therapeutic effort to keep them drug free. Their use of illicit opioids can be reduced and retention in treatment improved with supervised agonist replacement therapy with methadone, which is a highly addictive drug. Naltrexone is a long-acting, opioid-antagonist that blocks heroin effects. It is used to prevent relapse of both opioid and alcohol dependence. Highly motivated people do best with naltrexone. Most opioid users are sceptical about treatment with naltrexone tablets and many drop out early on. Dropouts can be reduced with supervised tablet taking, offering incentives and using sustained-release naltrexone such as subcutaneous implants or depot injections. There is insufficient evidence from randomised controlled trials to evaluate the effectiveness of sustained-release naltrexone. In the one controlled study that met inclusion criteria, 60 outpatients were randomised to one of three groups that received two sequential depot injections of naltrexone (192 or 384 mg) or placebo injections. The mean dropout time was 48 days with high dose naltrexone compared with 27 days on placebo; an increase in treatment of 21 days (range 11 to 31 days). The lower depot dose gave a lesser benefit. The number retained in treatment at eight weeks did not show a clear difference and ranged from a mean of 68% to 39% of participants in the different groups. ‘Wanting heroin’ did not differ on naltrexone but ‘needing heroin’ scored significantly lower with depot naltrexone compared to placebo. The most prominent adverse effects were general symptoms of fatigue and pain at the injection site. Seventeen reports met inclusion criteria for assessing adverse effects. Seven looked specifically at naltrexone implants for treatment of opioid dependence and wound infection, allergic reaction to the implant and number of implants removed. The majority of the trials did not have a control group and systematic assessment of adverse effects was lacking.

**ABSTRACT**

**Background** Naltrexone is an opioid antagonist which effectively blocks heroin effects. Since opioid dependence treatment with naltrexone tablets suffers from high dropout rates, several depot injections and implants are under investigation. Sustained-release formulations are claimed to be effective, but a systematic review of the literature is lacking.

**Objectives** To evaluate the effectiveness of sustained-release naltrexone for opioid dependence and its adverse effects in different study populations.

**Search strategy** The following databases were searched from their inception to November 2007: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, LILACS, PsycINFO, ISI Web of Science, trial database at http://clinicaltrials.gov, available NIDA
Selection criteria To evaluate effectiveness only RCTs were included. To evaluate safety, any clinical trial reporting adverse effects was assessed. Treatment condition was extended to include alcohol dependent subjects and healthy volunteers.

Main results For effectiveness, one report met inclusion criteria. Two dosages of naltrexone depot injections (192 and 384 mg) were compared to placebo. High-dose significantly increased days in treatment compared to placebo (WMD 21.00, 95% CI 10.68 to 31.32, p<0.0001). High-dose compared to low-dose significantly increased days in treatment (WMD 12.00, 95% CI 1.69 to 22.31, p=0.02). Number of patients retained in treatment did not show significant differences between groups.

For adverse effects, seventeen reports met inclusion criteria analyses, six were RCTs. Side effects were significantly more frequent in naltrexone depot groups compared to placebo. In alcohol dependent samples only, adverse effects appeared to be significantly more frequent in the low-dose naltrexone depot groups compared to placebo (RR 1.18, 95% CI 1.02 to 1.36, p=0.02). In the opioid dependent sample, group differences were not statistically significant. Reports on systematic assessment of side effects and adverse events were scarce.

Authors’ conclusions There is insufficient evidence to evaluate the effectiveness of sustained-release naltrexone for treatment of opioid dependence.

For naltrexone injections, administration site-related adverse effects appear to be frequent, but of moderate intensity and time limited. For a harm-benefit evaluation of naltrexone implants, more data on side effects and adverse events are needed.


Plain language summary
Some women continue to use opioids when they are pregnant. Yet heroin readily crosses the placenta. Opiate dependent women experience a six-fold increase in maternal obstetric complications and give birth to low-weight babies. The newborn may experience narcotic withdrawal (neonatal abstinence syndrome), have development problems, increased neonatal mortality and a 74-fold increased risk of sudden infant death syndrome. Maintenance treatment with methadone provides a steady concentration of opiate in the pregnant woman's blood and so prevents the adverse effects on the fetus of repeated withdrawals. Buprenorphine is also used. They reduce illicit drug use, improve compliance with obstetric care and improve birth weight but are still associated with neonatal abstinence syndrome. The present review found few differences in newborn or maternal outcomes for pregnant opiate-addicted women who were maintained on methadone, buprenorphine or oral slow morphine from a mean gestational age of 23 weeks to delivery. Only three randomised controlled trials satisfied the criteria for the review, two from Austria (outpatients) and one from the USA (inpatients). Two compared methadone with buprenorphine (48 participants) and one compared methadone with oral slow morphine (48 participants). The number of women who dropped out from treatment and the use of primary substance appeared to be the same for methadone and buprenorphine. Oral slow morphine seemed superior to methadone for the number of women who used heroin in their third trimester but without a clear improvement in infant birth weight or duration of neonatal abstinence syndrome. The number of participants in the trials was very small and may not be sufficient to detect differences. Only one study reported on the number of cigarettes the women smoked, a mean of 29 cigarettes per day at enrolment and 14 cigarettes per day at delivery. All the included studies ended immediately after the baby was born. No severe complications were noted.

ABSTRACT
Background The prevalence of opiate use among pregnant women ranges from 1% to 2% to as much as 21%. Heroin crosses the placenta and pregnant opiate dependent women experience a six-fold increase in maternal obstetric complications such as low birth weight, toxaemia, 3rd trimester bleeding, malpresentation, puerperal morbidity, fetal distress and meconium aspiration. Neonatal complications include narcotic withdrawal, postnatal growth deficiency, microcephaly, neurobehavioral problems, increased neonatal mortality and a 74-fold increase in sudden infant death syndrome.
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 on child health status, neonatal mortality, retaining pregnant women in treatment, and reducing use of substances.

Search strategy We searched Cochrane Drugs and Alcohol Group’ Register of Trials (June 2007), PubMed (1966 - June 2007), CINAHL (1982- June 2007), reference lists of relevant papers, sources of ongoing trials, conference proceedings, National focal points for drug research. Authors of included studies and experts in the field were contacted.

Selection criteria Randomised controlled trials enrolling opiate dependent pregnant women.

Main results We found three trials with 96 pregnant women. Two compared methadone with buprenorphine and one methadone with oral slow morphine. For the women there was no difference in drop out rate RR 1.00 (95% CI 0.41 to 2.44) and use of primary substance RR 2.50 (95% CI 0.11 to 54.87) between methadone and buprenorphine, whereas oral slow morphine seemed superior to methadone in abstaining women from the use of heroin RR 2.40 (95% CI 1.00 to 5.77). For the newborns in one trial buprenorphine performed better than methadone for birth weight WMD -530 gr (95% CI -662 to -397), this result is not confirmed in the other trial. For the APGAR score both studies didn’t find significant difference. No differences for NAS measures used. Comparing methadone with oral slow morphine no differences for birth weight and mean duration of NAS. The APGAR score wasn’t considered.

Authors’ conclusions We didn’t find any significant difference between the drugs compared both for mother and for child outcomes; the trials retrieved were too few and the sample size too small to make firm conclusion about the superiority of one treatment over another. There is an urgent need of big randomised controlled trials.

[12] Maintenance treatments for opiate dependent adolescents

Plain language summary
It is difficult to draw conclusions about the use of maintenance pharmacological interventions from only two trials. Substance abuse among adolescents (13 to 18 years old) is a serious and growing problem. The most common drugs used by young people worldwide are cannabis and inhalants. Psychostimulants (ecstasy and amphetamines), cocaine, LSD, heroin and other opioids are also used. Many adolescents who use heroin start by snorting it but some progress to injection. Heroin is used sporadically by the majority who use it, but it can become an addictive disorder. In adults, pharmacotherapy is a necessary and acceptable part of effective treatment for opioid dependence. Among adolescents, medications have been used infrequently and a choice has to be made between detoxification and maintenance treatment. The review authors searched the literature and identified two controlled trials from the USA that involved 187 heroin addicts, aged 14 to 21 years; the participants were treated as outpatients. One study of 37 participants compared methadone with LAAM for maintenance treatment. After 16 weeks of maintenance treatment the adolescents were detoxified. The two maintenance treatments gave similar improvements in social functioning. No side effects were reported.

The second trial of 150 adolescents compared buprenorphine and naloxone as maintenance treatment with buprenorphine detoxification over 14 days. The maintenance treatment for nine weeks followed by tapered doses up to 12 weeks seemed to be more effective in retaining patients in treatment but not in reducing the use of drugs of abuse. At one-year follow up, self-reported opioid use was clearly less in the maintenance group and more adolescents were enrolled in other addiction programs. The most common side effect in both groups was headache. No participants left the study because of side effects.

Conducting trials with young people may be difficult for both practical and ethical reasons.

ABSTRACT
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 which systematically assess the effectiveness of the pharmacological maintenance treatment among adolescent.
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 on retaining adolescents in treatment, reducing the use of substances and reducing health and social status.

Search strategy We searched the Cochrane Drugs and Alcohol Group's trials register (August 2008), MEDLINE (January 1966 to August 2008), EMBASE (January 1980 to August 2008), CINHAL (January 1982 to August 2008) and reference lists of articles.

Selection criteria Randomised and controlled clinical trials comparing any maintenance pharmacological interventions alone or associated with psychosocial intervention with no intervention, placebo, other pharmacological intervention included pharmacological detoxification or psychosocial intervention in adolescent (13-18 years).

Main results Two trials involving 187 participants were included. One study compared methadone with LAAM for maintenance treatment lasting 16 weeks after which patients were detoxified, the other compared maintenance treatment with buprenorphine - naloxone with detoxification with buprenorphine. No meta-analysis has been performed because the two studies assessed different comparisons. Maintenance treatment seems more efficacious in retaining patients in treatment but not in reducing patients with positive urine at the end of the study. Self reported opioid use at 1 year follow up was significantly lower in the maintenance group even if both group reported high level of opioid use and more patients in the maintenance group were enrolled in other addiction treatment at 12 month follow up.

Authors' conclusions It is difficult to draft conclusions on the basis of only two trials. One of the possible reason for the lack of evidence could be the difficulty to conduct trial with young people due to practical and ethic reasons.
Plain language summary
Abuse of opioid drugs and dependence on them causes major health and social issues that include transmission of HIV and hepatitis C, increased crime and costs for health care and law enforcement, family disruption and lost productivity. Addicts, particularly those aged 15 to 34 years, are also at higher risk of death. Managed withdrawal (or detoxification) is used as the first step in treatment. Withdrawal symptoms include anxiety, chills, muscle pain (myalgia) and weakness, lethargy and drowsiness and various pharmacological agents can be used to reduce them. Persisting sleep disturbances and drug craving can continue for weeks and months after detoxification and often lead to relapse to opioid use. The number of addicts who complete detoxification tends to be low, and rates of relapse to opioid use following detoxification are high.

For a tapered dose treatment, illicit opioids are substituted with methadone or another agent under medical supervision in decreasing doses. The review authors searched the medical literature and identified 16 controlled trials involving 1187 adult opioid users in various countries. Trial participants were randomised to receive methadone or another pharmacological treatment over 3 to 30 days. The other treatments were adrenergic agonists including clonidine (11 studies), opioid agonists such as buprenorphine and LAAM (four studies) and chlordiazepoxide (one study). In the one study that compared methadone with placebo, withdrawal symptoms were more severe and more drop outs were found in the placebo group. The methadone starting dose ranged from 20 to 58 mg/day (mean 29 mg/day). Withdrawal symptoms were reduced with methadone but the majority of people relapsed to heroin use. There was no clear difference in completion of treatment or abstinence at follow up with the different agents. 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. Treatment with adrenergic agonists was associated with lower mean blood pressure (postural hypotension) than with methadone, from five trials.

ABSTRACT
Background Despite widespread use in many countries the evidence of tapered methadone's efficacy in managing opioid withdrawal has not been systematically evaluated.
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.
Selection criteria All randomised controlled trials which focus on the use of tapered methadone versus all other pharmacological detoxification treatments or placebo for the treatment of opiate withdrawal.
Main results Twenty trials involving 1907 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, relative risk (RR) 1.08 (95% CI 0.95 to 1.24) and results at follow-up RR 1.17 (95% CI 0.72 to 1.92). It was impossible to pool data for the other outcomes but the results of the studies did not show significant differences between the considered treatments. These results were confirmed also when we considered the single comparisons: methadone with: adrenergic agonists (11 studies), other opioid agonists (five studies), anxiolytic (two studies). 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.

[14] BUPRENORPHINE FOR THE MANAGEMENT OF OPIOID WITHDRAWAL

Plain language summary
Buprenorphine is more effective than clonidine or lofexidine, and may have advantages over methadone, for the management of opioid withdrawal.
Dependence on opioid drugs (heroin, methadone) is a major health and social issue in many societies.
Managed withdrawal from opioid dependence is an essential first step for drug-free treatment. This review of trials found that the drug buprenorphine is more effective than clonidine or lofexidine in reducing the signs and symptoms of opioid withdrawal, retaining patients in withdrawal treatment, and supporting the completion of treatment. There is no significant difference in the incidence of adverse effects, but patients treated with buprenorphine may be less likely to drop-out due to adverse effects than is the case with clonidine or lofexidine. There is limited evidence comparing buprenorphine with methadone, but it appears that completion of withdrawal may be more likely with buprenorphine and withdrawal symptoms may resolve more quickly with buprenorphine.

ABSTRACT
Background Managed withdrawal is a necessary step prior to drug-free treatment or as the end point of substitution treatment.
Objectives To assess the effectiveness of interventions involving the use of buprenorphine to manage opioid withdrawal, for withdrawal signs and symptoms, completion of withdrawal and adverse effects.
Search strategy We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2008), MEDLINE (January 1966 to July 2008), EMBASE (January 1985 to 2008 Week 31), PsycINFO (1967 to 7 August 2008) and reference lists of articles.
Selection criteria Randomised controlled trials of interventions involving the use of 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, symptomatic medications or placebo, or different buprenorphine-based regimes.
Main results twenty-two studies involving 1736 participants were included. The major comparisons were with methadone (5 studies) and clonidine or lofexidine (12 studies). Five studies compared different rates of buprenorphine dose reduction.
Severity of withdrawal is similar for withdrawal managed with buprenorphine and withdrawal managed with methadone, but withdrawal symptoms may resolve more quickly with buprenorphine. It appears that completion of withdrawal treatment may be more likely with buprenorphine relative to methadone (RR 1.18; 95% CI 0.93 to 1.49, P = 0.18) but more studies are required to confirm this.
Relative to clonidine or lofexidine, buprenorphine is more effective in ameliorating the symptoms of withdrawal, patients treated with buprenorphine stay in treatment longer (SMD 0.92, 95% CI 0.57 to 1.27, P < 0.001), and are more likely to complete withdrawal treatment (RR 1.64; 95% CI 1.31 to 2.06, P < 0.001). At the same time there is no significant difference in the incidence of adverse effects, but drop-out due to adverse effects may be more likely with clonidine.


Plain language summary
Opioid withdrawal is similar with alpha2-adrenergic agonists and reducing doses of methadone but people stay in treatment longer with methadone and have fewer adverse effects.
Managed withdrawal of opioids, or detoxification, is a required first step for longer-term treatments of opioid
dependence. The signs and symptoms of opioid withdrawal usually begin 6 to 12 hours after the last dose of heroin or morphine and reach peak intensity within two to four days. Most physical withdrawal signs are no longer obvious after 7 to 14 days. The signs and symptoms develop 36 to 48 hours after the last dose of methadone.

Suppression of withdrawal symptoms with methadone and gradual reduction of the methadone dose requires the use of a drug of dependence to treat opioid dependence and there are often governments restrictions on prescription of methadone. Consumers may also dislike of the protracted nature of methadone withdrawal. The alpha2-adrenergic agonist clonidine is used widely as a non-opioid alternative for managing opioid withdrawal. The review authors identified 24 controlled studies, involving 1631 participants who underwent managed withdrawal in 11 different countries. The review focused on alpha2-adrenergic agonists compared to placebo (four studies), reducing doses of methadone (14 studies), and lofexidine compared to clonidine (three studies).

The alpha2-adrenergic agonists clonidine and lofexidine were more effective than placebo in managing withdrawal from heroin or methadone. Despite having adverse effects, they were associated with higher chances of completing treatment.

Comparing reducing doses of methadone to clonidine or lofexidine for the management of withdrawal from opioids, withdrawal signs and symptoms were similar but occurred earlier with the alpha2-adrenergic agonists, within a few days of cessation of the opioid drugs. The chances of completing withdrawal were similar. People stayed in treatment longer with methadone regimes. Clonidine had more adverse effects (low blood pressure, dizziness, dry mouth, lack of energy) than reducing doses of methadone. Lofexidine had less effect on blood pressure than clonidine.

**Abstract**

**Background** Withdrawal is a necessary step prior to drug-free treatment or as the end point of long-term substitution treatment.

**Objectives** To assess the effectiveness of interventions involving the use of alpha2-adrenergic agonists to manage opioid withdrawal.

**Search strategy** We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2008), MEDLINE (January 1966-July 2008), EMBASE (January 1985-2008 Week 31), PsycINFO (1967 to 7 August 2008) and reference lists of articles. We also contacted manufacturers in the field.

**Selection criteria** Controlled trials comparing alpha2-adrenergic agonists 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.

**Main results** Twenty-four studies, involving 1631 participants, were included. Twenty-one were randomised controlled trials. Thirteen studies compared a treatment regime based on an alpha2-adrenergic agonist with one based on reducing doses of methadone. Diversity in study design, assessment and reporting of outcomes limited the extent of quantitative analysis. Alpha2-adrenergic agonists are more effective than placebo in ameliorating withdrawal, and despite higher rates of adverse effects, are associated with significantly higher rates of completion of treatment. For the comparison of alpha2-adrenergic agonist regimes with reducing doses of methadone, there were insufficient data for statistical analysis, but withdrawal intensity appears similar to or marginally greater with alpha2-adrenergic agonists, while signs and symptoms of withdrawal occur and resolve earlier. Participants stay in treatment longer with methadone. No significant difference was detected in rates of completion of withdrawal with adrenergic agonists compared to reducing doses of methadone, or clonidine compared to lofexidine. Clonidine is associated with more adverse effects than reducing doses of methadone. 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 regimes 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.
Plain language summary
Opioid antagonists induce withdrawal by displacing opioids from their receptors. Adrenergic agonists, acting through non-opioid mechanisms, can reduce withdrawal symptoms induced by antagonists. Withdrawal induced by the combination of these substances is more intense early in treatment, but overall severity is less, no difference for completion of treatment.

ABSTRACT
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.
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.

Plain language summary
The potential risks and high cost of using opioid blocking drugs during heavy sedation or anaesthesia to bring on withdrawal outweigh the benefits. Drugs that block opioids are sometimes given to opioid dependent people while they are under heavy sedation or anaesthesia to speed up withdrawal. The review of trials shows that this sort of withdrawal treatment is quicker than withdrawal managed with reducing doses of methadone or clonidine plus symptomatic medications. The intensity of withdrawal experienced with anaesthesia-based approaches is similar to that experienced with similar approaches using only minimal sedation, but there is a significantly increased risk of serious adverse events with anaesthesia-assisted approaches. The lack of additional benefit, and increased risk of harm, suggest that this form of treatment should not be pursued.
ABSTRACT

**Background** Withdrawal (detoxification) is necessary prior to drug-free treatment. It may also represent the end point of long-term opioid replacement treatment such as methadone maintenance. The availability of managed withdrawal is essential to an effective treatment system.

**Objectives** To assess the effectiveness of interventions involving the administration 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 strategy** We searched the Drugs and Alcohol Group register (October 2003), Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 4, 2004), Medline (January 1966 to January 2005), Embase (January 1985 to January 2005), PsycINFO (1967 to January 2005), and Cinahl (1982 to December 2004) and reference lists of studies.

**Selection criteria** Controlled trials comparing antagonist-induced withdrawal under heavy sedation or anaesthesia with another form of treatment, or a different regime of anaesthesia-based antagonist-induced withdrawal.

**Main results** Six studies (five randomised controlled trials) involving 834 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 also 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.

[18] **Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification**


Plain language summary

People who abuse opioid drugs and become dependent on them experience social issues and health risks. Medications such as methadone and buprenorphine are substituted to help dependent drug users detoxify and return to living drug free, by reducing physiological withdrawal symptoms (pharmacological detoxification). Yet psychological symptoms can occur during detoxification and may be distressing. It is often a personal crisis that led to a drug user deciding to detoxify. Furthermore the psychological reasons why a person became addicted are important. They may not be able to cope with stress and have come to expect that using mood modifying illicit substances helps. Even after successful return to a drug-free state, many people return to heroin use and re-addiction is a substantial problem in rehabilitation. The physiological, behavioural and social conditions in an individual's life that made them an opiate addict may still be present when physical dependence on the drug has been eliminated, which makes psychosocial therapy important. Psychosocial treatments include behavioural treatments, counselling and family therapy. The review authors searched the medical literature and found evidence that providing a psychosocial treatment in addition to pharmacological detoxification treatment to adults who are dependent on heroin use is effective in facilitating opioid detoxification. This conclusion is based on eight controlled studies involving 423 adults, about three-quarters men, with an average age of 31 years (28 to 41 years). The studies lasted 16 days to 26 weeks. The addition of a psychosocial treatment to substitution detoxification treatment improved the number of people who completed treatment (relative risk (RR) 1.7), use of opiate (RR 0.82), abstinence from drugs at follow up (RR 2.4), and halved the number of failures to attend clinic absences. The findings of an improved rate of clinical attendance may help in suppressing illicit drug use and provides clinical staff with more opportunities to counsel patients in psychiatric, employment and other drug and non-drug related areas. Variations in the populations who are substance users and use of a wide range of
different psychosocial interventions means that it is difficult to single out particular therapeutic interventions

ABSTRACT

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

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

Search strategy We searched the Cochrane Drugs and Alcohol Group trials register (27 February 2008), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2008), PUBMED (1996 to February 2008); EMBASE (January 1980 to February 2008); CINAHL (January 2003–February 2008); PsycINFO (1985 to April 2003) and reference list of articles.

Selection criteria Randomised controlled trials 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.

Main results Nine studies involving people were included. These studies considered five different psychosocial interventions and two substitution detoxification treatments: Methadone and Buprenorphine. The results show promising benefit from adding any psychosocial treatment to any substitution detoxification treatment in terms of completion of treatment relative risk (RR) 1.68 (95% confidence interval (CI) 1.11 to 2.55), use of opiate RR 0.82 (95% CI 0.71 to 0.93), results at follow-up RR 2.43 (95% CI 1.61 to 3.66), and compliance RR 0.48 (95% CI 0.38 to 0.59).

Authors’ conclusions Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, use of opiate, results at follow-up and compliance. Although a treatment, like detoxification, that exclusively attenuates the severity of opiate withdrawal symptoms can be at best partially effective for a chronic relapsing disorder like opiate dependence, this type of treatment is an essential step prior to longer-term drug-free treatment and it is desirable to develop adjunct psychosocial approaches that might make detoxification more effective. Limitations to this review are imposed by the heterogeneity of the assessment of outcomes. Because of lack of detailed information no meta analysis could be performed to analyse the results related to several outcomes.

Plain language summary

Dependence on opioid drugs, such as heroin, morphine, and codeine, is a serious problem in many societies. Opioids are very difficult to quit using. The first step to quitting is detoxification, which can cause a number of painful symptoms as the drug withdraws from the body. Many people choose an inpatient detoxification program rather than trying to stop using opioids on their own. In an inpatient program, medications such as methadone can ease the symptoms of withdrawal and patients are in a secure, supportive environment with no access to opiates. However, inpatient programs are expensive and can disrupt patients’ lives. An increasing number of outpatient programs are available, providing medication and some support while keeping the drug user in the community. In addition to drop-in programs, there are day centres and even residential facilities which are not staffed 24 hours, unlike inpatient programs. The authors of this review looked for research comparing inpatient and other types of opiate withdrawal programs to see which is more effective. They found only one study from 1975, which had 40 participants. The study suggested inpatient therapy might be more effective than outpatient therapy in the short-term, but all of the inpatients relapsed within three months after detoxification. Since they found only one outdated study which included very few patients, the Cochrane review authors could not conclude whether inpatient treatment is more effective than outpatient or other settings. More research must be done to measure the benefits and costs of inpatient detoxification, especially for more severely dependent users.
**Background** There are a complex range of variables that can influence the course and subjective severity of opioid withdrawal. There is a growing evidence for the effectiveness of a range of medically-supported detoxification strategies, but little attention has been paid to the influence of the setting in which the process takes place.

**Objectives** To evaluate the effectiveness of any inpatient opioid detoxification programme when compared with all other time-limited detoxification programmes on the level of completion of detoxification, the intensity and duration of withdrawal symptoms, the nature and incidence of adverse effects, the level of engagement in further treatment post-detoxification, and the rates of relapse post-detoxification.

**Search strategy** Electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library Issue 2, 2008); MEDLINE (January 1966-May 2008); EMBASE (January 1988-May 2008); PsycInfo (January 1967-May 2008); CINAHL (January 1982-May 2008). In addition the Current Contents, Biological Abstracts, Science Citation Index and Social Sciences Index were searched.

**Selection criteria** Randomised controlled clinical trials comparing inpatient opioid detoxification (any drug or psychosocial therapy) with other time-limited detoxification programmes (including residential units that are not staffed 24 hours per day, day-care facilities where the patient is not resident for 24 hours per day, and outpatient or ambulatory programmes, and using any drug or psychosocial therapy).

**Main results** Only one study met the inclusion criteria. This did not explicitly report the number of participants in each group that successfully completed the detoxification process, but the published data allowed us to deduce that 7 out of 10 (70%) in the inpatient detoxification group were opioid-free on discharge, compared with 11 out of 30 (37%) in the outpatient group. There was very limited data about the other outcomes of interest.

**Authors’ conclusions** This review demonstrates that there is no good available research to guide the clinician about the outcomes or cost-effectiveness of inpatient or outpatient approaches to opioid detoxification.

[20] **DETOXIFICATION TREATMENTS FOR OPIATE DEPENDENT ADOLESCENTS**


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**Plain language summary**

Substance abuse among adolescents (13 to 18 years old) is a serious and growing problem. It is important to identify effective treatments for those who are opioid dependent. For adults, pharmacotherapy is a necessary and acceptable part of effective treatment. Detoxification agents are used to reduce withdrawal symptoms during managed withdrawal but the rate of completion of detoxification tends to be low, and rates of relapse are high. Withdrawal symptoms, particularly drug craving, may continue for weeks and even months after detoxification. The period of recovery from dependence is typically influenced by a range of psychological, social and treatment related factors. Detoxification treatments include methadone, buprenorphine, and alpha2-adrenergic agonists. Medications have been used less frequently in treating substance abuse disorders among adolescents.

The review authors searched the literature for controlled clinical trials investigating pharmacological interventions with or without psychosocial intervention aimed at detoxification in adolescents. They found only two US trials, one comparing 28-day treatment with buprenorphine, using tablets placed under the tongue, to wearing a clonidine patch in 36 opiate dependent adolescents who were treated as outpatients. The trial reported a trend in favour of buprenorphine in reducing the dropout rate but no difference between treatments in the duration and severity of withdrawal symptoms. More participants in the buprenorphine group went on to long-term naltrexone treatment. Side effects were not reported. The other trial compared maintenance treatment vs detoxification treatment: buprenorphine-naloxone maintenance vs buprenorphine detoxification. For drop out the results were in favour of maintenance treatment, as well as for results at follow up; no differences for use of opiate.

Methadone is the most frequently used drug for the treatment of opioid withdrawal yet the review authors did not find any controlled trial using methadone. Conducting trials with young people may be difficult for both practical and ethical reasons.
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 which 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 to no intervention, other pharmacological intervention or psychosocial interventions on completion of treatment, reducing the use of substances and improving health and social status.

Search strategy We searched the Cochrane Central Register of Controlled Trials (August 2008), MEDLINE (January 1966 to August 2008), EMBASE (January 1980 to August 2008), CINHAL (January 1982 to August) and reference lists of articles.

Selection criteria Randomised and 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 (13-18 years).

Main results Two trials involving 190 participants were included. One compares buprenorphine with clonidine for detoxification. No difference was found for drop out: RR 0.45 (95%CI: 0.20 - 1.04) and acceptability of treatment: withdrawal score WMD: 3.97 (95%CI -1.38, 9.32). More participants in the buprenorphine group initiated naltrexone treatment: RR 11.00 [95%CI 1.58, 76.55]. The other compares maintenance treatment vs detoxification treatment: buprenorphine-naloxone maintenance vs 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%CI1.05, 1.76]; no differences for use of opiate.

Authors’ conclusions It is difficult to draft 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 utilized 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.
**ALCOHOL:**

[21] **OPIOID ANTAGONISTS FOR ALCOHOL DEPENDENCE**

**Plain language summary**
Opioid antagonists can decrease alcohol consumption in animals. The review findings support that short-term treatment of naltrexone (NTX) decreases the chance of alcohol relapses for 36% and likely to reduce the chance of returning to drinking for 13%. NTX treatment can lower the risk of treatment withdrawal in alcohol-dependent patients for 28% (NNT = 13). The evidence so far have supported that NTX should be accepted as a short-term treatment for alcoholism. Strategies to improve adherence to NTX treatment, e.g., psychosocial interventions and management of adverse effects, should be concomitantly given. We have not yet known so far how long alcohol-dependent patients who respond to NTX treatment should continue their treatment. Nalmefene has too little evidence to support its clinical use.

**ABSTRACT**

**Background** Opioid antagonists can decrease alcohol consumption in animals. Their harms and benefits have been examined in many clinical trials.

**Objectives** To determine the effectiveness of opioid antagonists in attenuating or preventing the relapses in alcohol dependents in comparison to placebo, other medications and psychosocial treatments.

**Search strategy** The specialised register of the Cochrane Group on Drugs and Alcohol (September 2003); Cochrane Controlled Trials Register (Cochrane Library 2001, issue 4), MEDLINE (1966-October 2001), EMBASE (1980-December 2001), CINHAL (1982 -December 2001). Du Pont Pharmaceutical and Ivax Corporation were contacted for information regarding unpublished trials. The reference lists of the obtained papers were examined.

**Selection criteria** All randomised controlled trials were included. Participants: people with alcohol dependence. Naltrexone (NTX), nalmefene (NMF) and other opioid antagonists with/without other biological or psychosocial treatments were examined.

**Main results** The review included 29 RCTs. Except two of nalmefene, all others investigated NTX. In comparison to placebo, a short-term treatment of NTX significantly decreased the relapse [RR (95% CI) = 0.64 (0.51 to 0.82)] and decrease the return to drinking [RR (95% CI) = 0.87 (0.76 to 1.00). In the respect of acceptability, NTX significantly diminished withdrawal [RR (95% CI) = 0.82 (0.70 to 0.97). While a medium-term treatment of NTX gave no benefit for relapse prevention, it was found to be beneficial on increasing time to first drink and diminishing craving. A medium-term treatment of NTX was superior to acamprosate in reducing relapses, standard drinks and craving. NTX plus an intensive psychosocial treatment (PST) was not superior to NTX plus a simple PST on any short-term outcomes. For a medium-term treatment, NTX plus an intensive PST was superior to NTX plus a simple PST in increasing time to first drink and decreasing craving.

**Authors’ conclusions** The review findings support that short-term treatment of NTX should be accepted as a short-term treatment for alcoholism. Some major limitations of the available evidence include short study duration, small sample sizes and lack of data on psychosocial benefits. Strategies to improve adherence to NTX treatment, e.g., PSTs and management of adverse effects, should be concomitantly given. Due to too little evidence, NMF should have no role for the treatment of alcohol dependence.

[22] **ANTICONVULSANTS FOR ALCOHOL WITHDRAWAL**

**Plain language summary**
There are limited data on anticonvulsants versus placebo for alcohol withdrawal syndrome, while comparisons with other drugs show no clear differences. This Cochrane review summarizes evidence from forty-eight randomised controlled trials evaluating the effectiveness and safety of anticonvulsants in the treatment of alcohol withdrawal symptoms. There are limited data comparing anticonvulsants versus placebo and no clear differences between anticonvulsants.
and other drugs in the rates of therapeutic success. Data on safety outcomes are sparse and fragmented. There is a need for larger, well-designed studies in this field.

ABSTRACT
Background Alcohol withdrawal syndrome is a cluster of symptoms that occurs in alcohol-dependent people after cessation or reduction in alcohol use. This systematic review focuses on the evidence of anticonvulsants’ use in the treatment of alcohol withdrawal symptoms.

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

Search strategy We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2004); MEDLINE (1966 to October 2004); EMBASE (1988 to October 2004) and EU-PSI PSI-Tri database with no language and publication restrictions and references of articles.

Selection criteria All randomized controlled trials examining the effectiveness, safety and overall risk-benefit of an anticonvulsant in comparison with a placebo or other pharmacological treatment or another anticonvulsant were considered.

Main results Forty-eight studies, involving 3610 people were included. Despite the considerable number of randomised controlled trials, there was a variety of outcomes and of different rating scales that led to a limited quantitative synthesis of data. For the anticonvulsant versus placebo comparison, therapeutic success tended to be more common among the anticonvulsant-treated patients (relative risk (RR) 1.32; 95% confidence interval (CI) 0.92 to 1.91), and anticonvulsant tended to show a protective benefit against seizures (RR 0.57; 95% CI 0.27 to 1.19), but no effect reached formal statistical significance. For the anticonvulsant versus other drug comparison, CIWA-Ar score showed non-significant differences for the anticonvulsants compared to the other drugs at the end of treatment (weighted mean difference (WMD) -0.73; 95% CI -1.76 to 0.31). For the subgroup analysis of carbamazepine versus benzodiazepine, a statistically significant protective effect was found for the anticonvulsant (WMD -1.04; 95% CI -1.89 to -0.20), p = 0.02), but this was based on only 260 randomised participants. There was a non-significant decreased incidence of seizures (RR 0.50; 95% CI 0.18 to 1.34) favouring the patients that were treated with anticonvulsants than other drugs, and side-effects tended to be less common in the anticonvulsant-group (RR 0.56; 95% CI 0.31 to 1.02).

Authors’ conclusions It is not possible to draw definite conclusions about the effectiveness and safety of anticonvulsants in alcohol withdrawal, because of the heterogeneity of the trials both in interventions and the assessment of outcomes. The extremely small mortality rate in all these studies is reassuring, but data on other safety outcomes are sparse and fragmented.

[23] BENZODIAZEPINES FOR ALCOHOL WITHDRAWAL

Plain language summary
Benzodiazepines are more effective than placebo against alcohol withdrawal seizures while they have variable profile against other commonly used treatments. This Cochrane review summarizes evidence from fifty-seven randomised controlled trials evaluating the effectiveness and safety of benzodiazepines in the treatment of alcohol withdrawal symptoms. The available data show that benzodiazepines are effective against alcohol withdrawal seizures when compared to placebo. However, there are no prominent differences between benzodiazepines and other drugs in success rates. Data on safety outcomes are sparse and fragmented. There is a need for larger, well-designed studies in this field.

ABSTRACT
Background Alcohol withdrawal syndrome is a cluster of symptoms that occurs in alcohol-dependent people after cessation or reduction in alcohol use. This systematic review focuses on the evidence of benzodiazepines’ use in the treatment of alcohol withdrawal symptoms.

Objectives To evaluate the effectiveness and safety of benzodiazepines in the treatment of alcohol withdrawal.
Search strategy We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4, 2004), MEDLINE (1966 to October 2004) and EU-PSI PSI-Tri database with no language and publication restrictions. We also screened references of retrieved articles.

Selection criteria All randomised controlled trials examining the effectiveness and safety of a benzodiazepine in comparison with a placebo or other pharmacological intervention or other benzodiazepine were considered.

Main results Fifty-seven trials, with a total of 4,051 people were included. Despite the considerable number of randomized controlled trials, there was a very large variety of outcomes and of different rating scales and relatively limited quantitative synthesis of data was feasible. Benzodiazepines offered a large benefit against alcohol withdrawal seizures compared to placebo (relative risk [RR] 0.16; 95% confidence interval [CI] 0.04 to 0.69; p = 0.01). Benzodiazepines had similar success rates as other drugs (RR 1.00; 95% CI 0.83 to 1.21) or anticonvulsants in particular (RR 0.88; 95% CI 0.60 to 1.30) and offered a significant benefit for seizure control against non-anticonvulsants (RR 0.23; 95% CI 0.07 to 0.75; p = 0.02), but not against anticonvulsants (RR 1.99; 95% CI 0.46 to 8.65). Changes in Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scores at the end of treatment were similar with benzodiazepines versus other drugs, although some small studies showed isolated significant differences for other, less commonly, used scales. Data on other comparisons were very limited, thus making quantitative synthesis for various outcomes not very informative.

Authors’ conclusions Benzodiazepines are effective against alcohol withdrawal symptoms, in particular seizures, when compared to placebo. It is not possible to draw definite conclusions about the relative effectiveness and safety of benzodiazepines against other drugs in alcohol withdrawal, because of the large heterogeneity of the trials both in interventions and assessment of outcomes but the available data do not show prominent differences between benzodiazepines and other drugs in success rates.

[24] ALCOHOLICS ANONYMOUS AND OTHER 12-STEP PROGRAMMES FOR ALCOHOL DEPENDENCE

Plain language summary
Alcoholics Anonymous (AA) is self-help group, organised through an international organization of recovering alcoholics, that offers emotional support and a model of abstinence for people recovering from alcohol dependence using a 12-step approach.
As well as AA, there are also alternative interventions based on 12-step type programmes, some self-help and some professionally-led. AA and other 12-step approaches are typically based on the assumption that substance dependence is a spiritual and a medical disease. The available experimental studies did not demonstrate the effectiveness of AA or other 12-step approaches in reducing alcohol use and achieving abstinence compared with other treatments, but there were some limitations with these studies. Furthermore, many different interventions were often compared in the same study and too many hypotheses were tested at the same time to identify factors which determine treatment success.

Abstract
Background Alcoholics Anonymous (AA) is an international organization of recovering alcoholics that offers emotional support through self-help groups and a model of abstinence for people recovering from alcohol dependence, using a 12-step approach. Although it is the most common, AA is not the only 12-step intervention available there are other 12-step approaches (labelled Twelve Step Facilitation (TSF)).
Objectives To assess the effectiveness of AA or TSF programmes compared to other psychosocial interventions in reducing alcohol intake, achieving abstinence, maintaining abstinence, improving the quality of life of affected people and their families, and reducing alcohol associated accidents and health problems.
Search strategy We searched the Specialized Register of Trials of the Cochrane Group on Drugs and Alcohol, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE from 1966, EMBASE from 1980, CINAHL from 1982, PsychINFO from 1967. Searches were updated in February 2005. We also inspected lists of references for relevant studies.
Selection criteria Studies involving adults (>18) of both genders with alcohol dependence attending on a voluntary or coerced basis AA or TSF programmes comparing no treatment, other psychological interventions, 12-step variants.

Main results Eight trials involving 3417 people were included. AA may help patients to accept treatment and keep patients in treatment more than alternative treatments, though the evidence for this is from one small study that combined AA with other interventions and should not be regarded as conclusive. Other studies reported similar retention rates regardless of treatment group. Three studies compared AA combined with other interventions against other treatments and found few differences in the amount of drinks and percentage of drinking days. Severity of addiction and drinking consequence did not seem to be differentially influenced by TSF versus comparison treatment interventions, and no conclusive differences in treatment drop out rates were reported. Included studies did not allow a conclusive assessment of the effect of TSF in promoting complete abstinence.

Authors’ conclusions No experimental studies unequivocally demonstrated the effectiveness of AA or TSF approaches for reducing alcohol dependence or problems. One large study focused on the prognostic factors associated with interventions that were assumed to be successful rather than on the effectiveness of interventions themselves, so more efficacy studies are needed.

[25] PSYCHOTROPIC ANALGESIC NITROUS OXIDE FOR ALCOHOLIC WITHDRAWAL STATES

Plain language summary
Alcoholism is a global problem with approximately 5-10% of the world's population demonstrating alcohol-related diseases. One of the most severe consequences of alcohol dependence is the withdrawal syndrome. This review assessed the effects of psychotropic analgesic nitrous oxide (PAN) in treating alcohol withdrawal. All trials were conducted in in-patient settings although PAN is also administered in outpatient settings. The review found that PAN is as effective as sedatives for managing mild to moderate alcohol withdrawal states. Nonetheless, it does not provide strong evidence in favour of the benefits or harms of using PAN over sedatives in managing acute alcohol withdrawal. Further high quality trials should be done before these findings can be confirmed.

ABSTRACT
Background Alcoholism is a global problem with 5-10% of the world's population demonstrating alcohol-related diseases. One of the most severe consequences of alcohol dependence is the withdrawal syndrome, for which benzodiazepines are the most popular current treatment. An alternative method to benzodiazepine employs psychotropic analgesic nitrous oxide (PAN).

Objectives To assess the effects of PAN for treating alcohol withdrawal states

Search strategy We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2005), MEDLINE, EMBASE, CINAHL (all to May 2005). We scanned Internet web sites, reference lists of relevant articles and abstracts of the international Conferences on Alcoholism. We contacted researchers in the field and industry to identify unpublished trials. No language and publication restrictions.

Selection criteria Randomised controlled trials including voluntary participants dependent on alcohol. PAN was compared to oxygen and/or benzodiazepine regimens.

Main results Five studies, 212 participants, were included. PAN showed improvement of symptoms (RR 1.35; 95% CI 1.01 to 1.79), of the amount and duration of sedative medication and of psychomotor function (WMD -8.71; 95% CI -13.71 to -3.71). At one hour post intervention, no significant differences were found for depression (WMD -2.40; 95% CI -8.70 to 3.89) and anxiety (WMD -3.70; 95% CI -10.53 to 3.12). None of the included studies reported any significant adverse effects of any treatment.

Authors’ conclusions Results indicate that PAN may be an effective treatment of the mild to moderate alcoholic withdrawal state. The rapidity of the therapeutic effect of PAN therapy coupled with the minimal sedative requirements, may enable patients to enter the psychological treatment phase more quickly than those on sedative regimens, accelerating the patients recovery. Our review does not provide strong evidence due to the small sample sizes of the included trials.
Neither does the review indicate any causes for concern that PAN is more harmful than the benzodiazepines. Clinicians wishing to use PAN may initially wish to do so within trial settings. Further high quality trials should be done to confirm these findings and to investigate whether the PAN therapy has fewer adverse effects than other treatments for the alcohol withdrawal states. Studies to investigate the possible cost-effectiveness of PAN by reducing costly hospital admissions and decreasing post administration supervision also need to be performed.


Plain language summary
Excessive drinking contributes significantly to social problems, physical and psychological illness, injury and death. Hidden effects include increased levels of violence, accidents and suicide. Most alcohol-related harm is caused by excessive drinkers whose consumption exceeds recommended drinking levels, not the drinkers with severe alcohol dependency problems. One way to reduce consumption levels in a community may be to provide a brief intervention in primary care over one to four sessions. This is provided by healthcare workers such as general physicians, nurses or psychologists. In general practice, patients are routinely asked about alcohol consumption during registration, general health checks and as part of health screening (using a questionnaire). They tend not to be seeking help for alcohol problems when presenting. The intervention they are offered includes feedback on alcohol use and harms, identification of high risk situations for drinking and coping strategies, increased motivation and the development of a personal plan to reduce drinking. It takes place within the time-frame of a standard consultation, 5 to 15 minutes for a general physician, longer for a nurse.

A total of 29 controlled trials from various countries were identified, in general practice (24 trials) or an emergency setting (five trials). Participants drank an average of 306 grams of alcohol (over 30 standard drinks) per week on entry to the trial. Over 7000 participants with a mean age of 43 years were randomized to receive a brief intervention or a control intervention, including assessment only. After one year or more, people who received the brief intervention drank less alcohol than people in the control group (average difference 38 grams/week, range 23 to 54 grams). For men (some 70% of participants), the benefit of brief intervention was a difference of 57 grams/week, range 25 to 89 grams (six trials). The benefit was not clear for women. The benefits of brief intervention were similar in the normal clinical setting and in research settings with greater resources. Longer counselling had little additional benefit.

ABSTRACT
Background Many trials reported that brief interventions are effective in reducing excessive drinking. However, some trials have been criticised for being clinically unrepresentative and unable to inform clinical practice.
Objectives To assess the effectiveness of brief intervention, delivered in general practice or based primary care, to reduce alcohol consumption. To assess whether outcomes differ between trials in research settings and those in routine clinical settings.
Search strategy We searched the Cochrane Drug and Alcohol Group specialised register (February 2006), MEDLINE (1966 to February 2006), EMBASE (1980 to February 2006), CINAHL (1982 to February 2006), PsycINFO (1840 to February 2006), Science Citation Index (1970 to February 2006), Social Science Citation Index (1970 to February 2006), Alcohol and Alcohol Problems Science Database (1972 to 2003), reference lists of articles.
Selection criteria Randomised controlled trials, patients presenting to primary care not specifically for alcohol treatment; brief intervention of up to four sessions.
Main results Meta-analysis of 22 RCTs (enrolling 7,619 participants) showed that participants receiving brief intervention had lower alcohol consumption than the control group after follow-up of one year or longer (mean difference: -38 grams/week, 95% CI: -54 to -23), although there was substantial heterogeneity between trials (I² = 57%). Sub-group analysis (8 studies, 2,307 participants) confirmed the benefit of brief intervention in men (mean difference: -57 grams/week, 95% CI: -89 to -25, I² = 56%), but not in women (mean difference: -10 grams/week, 95% CI: -48 to 29, I² = 45%). Meta-regression showed little evidence of a greater reduction in alcohol consumption with longer treatment exposure or among trials which were less clinically representative. Extended intervention was associated with a non-significantly greater reduction in...
alcohol consumption than brief intervention (mean difference = -28, 95%CI: -62 to 6 grams/week, I² = 0%)

**Authors' conclusions** Overall, brief interventions lowered alcohol consumption. When data were available by gender, the effect was clear in men at one year of follow up, but not in women. Longer duration of counselling probably has little additional effect. The lack of evidence of any difference in outcomes between efficacy and effectiveness trials suggests that the current literature is relevant to routine primary care. Future trials should focus on women and on delineating the most effective components of interventions.


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**Plain language summary**

Pregnancy can be seen as a window of opportunity where women may seek treatment for their addictions out of concern for their unborn child. Worldwide estimates of alcohol usage report that a large proportion of women continue to drink during their pregnancy. Light alcohol consumption has not been associated with adverse effects on a woman's baby, while excessive consumption of alcohol has been shown to cause a number of birth defects as well as foetal alcohol syndrome. Alcohol consumption during pregnancy is the most widely recognized cause of severe mental and developmental delay in the baby. Therefore pregnancy is an important point in time to treat women for their alcohol dependence. This review sought to find all trials which compared any psychosocial intervention to other treatment or no treatment for pregnant or postpartum women in alcohol treatment. No articles were found which fit our inclusion criteria; most trials assessed psychosocial interventions to reduce alcohol consumption in pregnant or reproductive age women, not pregnant or post-partum women in alcohol treatment. We defined alcohol treatment as when the authors stated the women were in alcohol treatment or any validated psychosocial intervention for the treatment of alcohol dependence. Control trials need to be performed on this population of women to determine the most effective therapy for pregnant women seeking treatment for their alcohol dependence.

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**ABSTRACT**

**Background** Excessive alcohol use during pregnancy has been associated with adverse maternal and neonatal effects. It is therefore important to develop and evaluate effective interventions during this important time in a woman's life. To our knowledge there have been no systematic reviews of randomised control trials (RCT) in this population.

**Objectives** To evaluate the effectiveness of psychosocial interventions in pregnant women enrolled in alcohol treatment programs for improving birth and neonatal outcomes, maternal abstinence and treatment retention.

**Search strategy** We searched the Cochrane Drugs and Alcohol Group’s Trial register (December 2007); MEDLINE (1950 to 2007); PsycINFO (1806 to 2007); EMBASE (1974 to 2007); CINAHL (1982 to 2007)

**Selection criteria** We sought to include randomised or quasi-randomised studies comparing any psychosocial intervention versus pharmacological interventions or placebo or non-intervention or another psychosocial intervention for treating alcohol dependence in pregnancy.

**Main results** The search strategy identified 958 citations. 17 citations were deemed relevant for full text review, an additional 9 articles were retrieved through hand searching references, for a total of 26 articles. Following full text review no articles met the inclusion criteria. Data extraction and assessment of methodological quality were therefore not possible.

**Authors' conclusions** The review question remains unanswered as there were no randomised control trials found relevant to the topic. There is a need for high quality randomised controlled trials to determine the effectiveness of psychosocial interventions in pregnant women enrolled in alcohol treatment programs.


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**Plain language summary**

Drinking alcohol during pregnancy is common. Yet no safe level of alcohol consumption is known, with no
conclusive evidence on any adverse effects on the unborn child with low levels of alcohol. During pregnancy, more than two units per day or more than four units per drinking session may increase the risk of miscarriage, reduce growth, and impair mental development of the baby. Foetal alcohol syndrome is evident as neurological abnormalities, mental retardation, varying degrees of psychosocial and behavioural problems and characteristic facial dysmorphology that are apparent in adolescents and adults. In some populations alcohol use during pregnancy leads to increased child abuse and neglect or compromised mother-infant attachment and responsiveness. Mothers who consume alcohol are more likely to have postnatal depression and are less likely to attend health facilities for education and medical treatment. Specific interventions need to be put in place to assist pregnant and postpartum women who have alcohol problems. Medicines are given to assist with alcohol treatment by lessening the effects during detoxification. These include benzodiazepines, phenothiazines and chlormethiazole, used to reduce anxiety and insomnia. Anti-depressants may also be given after withdrawal. Disulfiram, naltrexone and acamprosate are used in more severe cases to decrease cravings for alcohol and maintain abstinence. The review authors could not identify any randomised controlled trials (RCTs) evaluating the effectiveness of pharmacologic interventions to improve maternal, birth, and infant outcomes in pregnant women enrolled in alcohol treatment programs.

The main reason for study exclusion was study design; we found trials without a control group or focusing only on outcomes for the newborn baby such as birth weight, length or head circumference. Given the stigma attached to alcohol use in pregnancy, recruitment for outcomes trials is likely to remain difficult, which adversely affects generalizability. Clearly the availability of quality evidence would assist with antepartum decision making by both the physician and mother.

**Abstract**

**Background** Excessive alcohol use during pregnancy has been associated with adverse maternal and neonatal effects. It is therefore important to develop and evaluate effective interventions during this important time in a woman's life. To our knowledge there have been no systematic reviews of randomised control trials (RCT) in this population.

**Objectives** To evaluate the effectiveness of pharmacologic interventions in pregnant women enrolled in alcohol treatment programs for improving birth and neonatal outcomes, maternal abstinence and treatment retention.

**Search strategy** We searched the Cochrane Drugs and Alcohol Group's Trial register (August 2008); MEDLINE (January 1950 to June 2008); EMBASE (January 1974 – August 2008); CINAHL (January 1982-June 2008); PsycInfo (January 1806-June2008), and reference lists of articles.

**Selection criteria** We sought to include randomised or quasi-randomised studies comparing any pharmacologic intervention versus other pharmacologic treatment alone or in association with psychosocial treatment, placebo, non-intervention or psychosocial intervention.

**Main results** The search strategy identified 793 citations. Twenty-three citations were deemed relevant for full text review; an additional ten articles were retrieved through hand searching references, for a total of thirty-three articles. Following full text review no articles met the inclusion criteria. Data extraction and assessment of methodological quality were therefore not possible.

**Authors’ conclusions** The review question remains unanswered as there were no randomised control trials found relevant to the topic. There is a need for high quality research to determine the effectiveness of pharmacologic interventions in pregnant women enrolled in alcohol treatment program.

[29] Brief interventions for heavy alcohol users admitted to general hospital wards.
McQueen J, Howe TE, Allan L, Mains D. First published CLIB 2009, Issue 3.

**Plain language summary**

Heavy or dangerous patterns of drinking alcohol can lead to accidents, injuries, physical and psychiatric illnesses, frequent sickness, absence from employment and social problems. Long term alcohol consumption has harmful effects on almost all organs of the body, particularly the brain and gastro-intestinal system. Healthcare professionals have the opportunity to ask people about how much alcohol they drink and offer brief interventions to heavy drinkers. These brief interventions involve a time limited intervention focusing on changing behaviour. They range from a single session providing information and advice to one to three sessions of motivational interviewing or skills-based counseling involving feedback and discussion.
on responsibility and self efficacy. Different health professionals may give the intervention. Admission to hospital as an inpatient, in general medical wards and trauma centres, provides an opportunity whereby heavy alcohol users are accessible, have time for an intervention, and may be made aware of any links between their hospitalisation and alcohol. The review authors identified 11 randomised controlled trials and controlled clinical trials involving 2441 adults (16 years or older) identified as heavy drinkers in hospital, mainly in the UK and USA. Data extracted from two studies indicated that alcohol consumption could be reduced at one year follow up for people who received brief interventions as inpatients. These people drank significantly less alcohol per week than those in the control groups. A trend was observed towards consuming less grammes of alcohol per week at six months in those receiving the brief intervention. No clear differences were observed between the brief intervention and control groups for self reports of alcohol consumption, laboratory markers (GammaGT), number of binges, death or driving offences. The results of the studies were difficult to combine because of the different measures used to assess alcohol consumption and substantial variations in how the studies were carried out. Control groups received assessment (screening) only or usual care, one with an educational leaflet. Screening involves asking people about their drinking patterns, which may have reduced drinking in the short term, as indicated in some of the studies.

**ABSTRACT**

**Background**  Brief interventions involve a time-limited intervention focusing on changing behaviour. They are often motivational in nature using counselling skills to encourage a reduction in alcohol consumption.

**Objectives**  To determine whether brief interventions reduce alcohol consumption and improve outcomes for heavy alcohol users admitted to general hospital inpatient units.

**Search strategy**  We searched the Cochrane Drug and Alcohol Group Register of Trials (June 2008) the Cochrane Central Register of Controlled Trials (The Cochrane Library 2, 2008), MEDLINE January 1966-June 2008, CINAHL 1982-June 2008, EMBASE 1980-June 2008 using the search strategy developed by the Cochrane Drug and Alcohol Group. We hand searched relevant journals, conference proceedings and contacted experts in the field.

**Selection criteria**  All prospective randomised controlled trials and controlled clinical trials were eligible for inclusion. Participants were adults (16 years or older) admitted to general inpatient hospital care for any reason other than specifically for alcohol treatment and received brief interventions (of up to 3 sessions) compared to no or regular treatment.

**Main results**  Eleven studies involving 2441 participants were included in this review. Three results were non significant and one result was significant mean alcohol consumption per week change scores from baseline (P<0.02).

**Authors’ conclusions**  The evidence for brief interventions delivered to heavy alcohol users admitted to general hospital is still inconclusive. From data extracted from two studies it appears that alcohol consumption could be reduced at one year follow up though further research is recommended. Few studies have been retrieved and the results were difficult to combine because of the different measures used to assess alcohol consumption.
PSYCHOSTIMULANTS: COCAINE and AMPHETAMINES

[30] ANTICONVULSANTS FOR COCAINE DEPENDENCE

Plain language summary
Cocaine is an illicit drug used as a powder for intranasal or intravenous use or smoked as crack. Short and long-term use of this drug spreads infectious diseases (for example AIDS, hepatitis and tuberculosis), crime, violence and prenatal drug exposure. Cocaine dependence has medical and psychosocial complications and is a major public health problem. No proven pharmacological treatment exists for cocaine dependence. Antidepressant, anticonvulsants and dopaminergic medications have all been trialled. The present review looked at the efficacy and safety of anticonvulsant drugs for treating cocaine dependence, as a class and individually. The review authors identified 17 randomised controlled trials involving 1194 participants, 80% male, with a mean age of 36 years. The mean duration of the trials was 11 weeks (range 1 to 24 weeks). All the trials were conducted in USA, 16 as outpatients. Very limited evidence can be drawn from the included trials. No significant differences were found between a placebo and any anticonvulsant in reducing the number of dropouts from treatment, use of cocaine, craving, and severity of dependence, depression or anxiety. Placebo was superior to gabapentin in reducing the number of dropouts from treatment (two studies) and use of cocaine. Gabapentin (one study, 95 participants) and phenytoin (two studies, 56 participants) had a greater number of side effects than the placebo. Although the methodological quality of the included studies was good, the sample sizes were small. Most anticonvulsants were used in single studies. Health effects of various substances of abuse seem to be strongly dependent on social context and the location of the studies could affect the treatment effect. Different rating systems were used and symptoms were not categorised as mild, moderate or severe to allow comparison of results between studies.

ABSTRACT
Background Cocaine dependence is a major public health problem that is characterized by recidivism and a host of medical and psychosocial complications. Although effective pharmacotherapy is available for alcohol and heroin dependence none exists currently for cocaine dependence despite two decades of clinical trials primarily involving antidepressant, anticonvulsant and dopaminergic medications. There has been extensive consideration of optimal pharmacological approaches to the treatment of cocaine dependence with consideration of both dopamine antagonists and agonists. Anticonvulsants have been candidates for the treatment of addiction based on the hypothesis that seizure kindling-like mechanisms contribute to addiction.
Objectives To evaluate the efficacy and the acceptability of anticonvulsants for cocaine dependence.
Selection criteria All randomised controlled trials and controlled clinical trials which focus on the use of anticonvulsants medication for cocaine dependence.
Main results Fifteen studies (1066 participants) met the inclusion criteria for this review: the anticonvulsants drugs studied were carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, valproate. No significant differences were found for any of the efficacy measures comparing any anticonvulsants with placebo. Placebo was found to be superior to gabapentin in diminishing the number of dropouts, two studies, 81 participants, Relative Risk (RR) 3.56 (95% CI 1.07 to 11.82) and superior to phenytoin for side effects, two studies, 56 participants RR 2.12 (95% CI 1.08 to 4.17). All the other single comparisons are not statistically significant.
Authors’ conclusions Although caution is needed when assessing results from a limited number of small clinical trials at present there is no current evidence supporting the clinical use of anticonvulsants medications in the treatment of cocaine dependence. Aiming to answer the urgent demand of clinicians, patients, families, and the community as a whole for an adequate treatment for cocaine dependence, we need to improve the primary research in the field of addictions in order to make the best possible use out of a single study and to investigate the efficacy of other pharmacological agent.
**Plain language summary**
Antidepressants have not been proven to reduce cocaine dependence, although this may be because people commonly stop using the antidepressants too soon. As dependence on cocaine became more common and caused major personal and social problems, several methods have been tried to help reduce dependence. Antidepressants are often tried to help people manage the depression and cravings that occur when people stop using cocaine. The review found that trials have not shown that antidepressants can help reduce cocaine dependence, although this may partly be because many people quit using the antidepressants. It may be that more people might benefit if they were helped to keep using antidepressants, including those who are also dependent on heroin or on methadone programs.

**ABSTRACT**

**Background** The past decade has witnessed a sustained search for an effective pharmacotherapeutic agent for the treatment of cocaine dependence. While administration of cocaine acutely increases intercellular dopamine, serotonin, and norepinephrine levels by blocking their presynaptic reuptake, chronic cocaine abuse leads to down-regulation of monoamine systems. Post-cocaine use depression and cocaine craving may be linked to this down-regulation. Antidepressant pharmacotherapy, by augmenting monoamine levels, may alleviate cocaine abstinence symptomatology, as well as relieving dysphoria and associated craving by general antidepressant action.

**Objectives** To evaluate the efficacy and the acceptability of antidepressants for cocaine dependence.

**Search strategy** We searched Cochrane Drug and Alcohol Group Specialised Register (July 2007), MEDLINE (1966 to July 2007), CINAHL (1982 to July 2007), SCOPUS (July 2007); reference searching; personal communication; conference abstracts; unpublished trials, ongoing trials, relevant web-sites.

**Selection criteria** All randomised controlled trials and controlled clinical trials which focus on the use of any antidepressants for cocaine dependence.

**Main results** 18 studies were included in the review (1177 participants). Positive urine sample for cocaine metabolites was the main efficacy outcome, with no significant results obtained regardless of the type of antidepressant. Compared to other drugs, desipramine performed better but showing just a non significant trend with heterogeneity present as revealed by the chi-square test (8.6, df=3; p=0.04). One single trial showed imipramine performed better than placebo in terms of clinical response according to patient's self-report. A similar rate of patients remaining in treatment was found for both patients taking desipramine or placebo. Results from one single trial suggest fluoxetine patients on SSRIs are less likely to dropout. Similar results were obtained for trials where patients had additional diagnosis of opioid dependence and/or were in methadone maintenance treatment.

** Authors’ conclusions** There is no current evidence supporting the clinical use of antidepressants in the treatment of cocaine dependence. Given the high rate of dropouts in this population, clinicians may consider adding psychotherapeutic supportive measures aiming to keep patients in treatment.

**Plain language summary**
There is no evidence supporting the clinical use of dopamine agonists in the treatment of cocaine dependence. Cocaine is a major drug of abuse. Cocaine dependence is a common and serious condition, which has become nowadays a substantial public health problem. There is a wide and well documented range of consequences associated to chronic use of this drug, such as medical, psychological and social problems,
including the spread of infectious diseases. Dopamine agonists have been used for reducing the symptoms the patients experience during the initial period of abstinence from cocaine. The review of trials showed not enough evidence to support this treatment.

**Abstract**

**Background** Cocaine dependence is a common and serious condition, which has become a substantial public health problem. There is a wide and well documented range of consequences associated to chronic use of cocaine, such as medical, psychological and social problems. Therapeutic management of the cocaine addicts includes an initial period of abstinence from the drug. During this phase the subjects may experience, besides the intense craving for cocaine, symptoms such as depression, fatigue, irritability, anorexia, and sleep disturbances. It was demonstrated that the acute use of cocaine may enhance dopamine transmission and chronically it decreases dopamine concentrations in the brain. Pharmacological treatment that affects dopamine could theoretically reduce these symptoms and contribute to a more successful therapeutic approach.

**Objectives** To evaluate the efficacy and acceptability of dopamine agonists for treating cocaine dependence.

**Search strategy** Electronic searches of Cochrane Library, EMBASE, MEDLINE, PsycLIT, Biological Abstracts and LILACS; reference searching; personal communication; conference abstracts; unpublished trials from pharmaceutical industry; book chapters on treatment of cocaine dependence, was performed for the primary version of this review in 2001. Another search of the electronic databases was done in December of 2002 for this update. The specialised register of trials of the Cochrane Group on Drugs and Alcohol was searched until February 2003.

**Selection criteria** The inclusion criteria for all randomised controlled trials were that they should focus on the use of dopamine agonists on the treatment of cocaine dependence.

**Main results** Seventeen studies were included, with 1224 participants randomised. Amantadine, bromocriptine, and pergolide were the drugs evaluated. The main outcomes evaluated were positive urine sample for cocaine metabolites, for efficacy, and retention in treatment, as an acceptability measure. There were no significant differences between interventions, and in trials where participants had primary cocaine dependence or had additional diagnosis of opioid dependence and/or were in methadone maintenance treatment.

**Authors’ conclusions** Current evidence does not support the clinical use of dopamine agonists in the treatment of cocaine dependence. Given the high rate of dropouts in this population, clinicians may consider adding other supportive measures aiming to keep patients in treatment.

**Plain language summary**

There are no effective drugs for the treatment of cocaine dependence, and doctors do not agree on a best method of treatment. More than 400 substance abuse clinics in the USA and Europe offer a treatment for cocaine dependence called auricular acupuncture. In this treatment, needles are usually inserted into five specific points in the ear, but some clinics use only four or three of the points. In this Cochrane review the authors set out to discover whether auricular acupuncture is effective in treating cocaine dependence and whether the number of points used makes a difference. The authors searched the medical literature for studies called randomized controlled trials, in which one group of patients receives a treatment (such as acupuncture) and is compared with a similar group who receives a different treatment or no treatment (the control group). The authors found seven studies with a total of 1433 people. Most of the studies compared acupuncture with ‘sham’ acupuncture in which needles were inserted into random places in the ear but not into the specific points required for treatment. The studies used a variety of acupuncture techniques, using three, four, or five of the treatment points. The studies had a number of problems with the way their results were reported. The authors conclude that there is no evidence that any form of auricular acupuncture is effective for treating cocaine dependence. They recommend that better research be done, since it was difficult for them to draw conclusions from the few available studies.
Background Auricular acupuncture (insertion of acupuncture into a number, usually five, of specific points in the ear) is a widely-used treatment for cocaine dependence.

Objectives To determine whether auricular acupuncture is an effective treatment for cocaine dependence, and to investigate whether its effectiveness is influenced by the treatment regimen.

Search strategy We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2004); MEDLINE (January 1966 to October 2004); EMBASE (January 1988 to October 2004); PsycInfo (1985 to October 2004); CINAHL (1982 to October 2004); SIGLE (1980 to October 2004) and reference lists of articles.

Selection criteria Randomised controlled trials comparing a therapeutic regimen of auricular acupuncture with sham acupuncture or no treatment for reduction of cocaine use in cocaine dependents.

Main results Seven studies with a total of 1,433 participants were included. All were of generally low methodological quality. No differences between acupuncture and sham acupuncture were found for attention RR 1.05 (95% CI 0.89 to 1.23) or acupuncture and no acupuncture: RR 1.06 (95% CI 0.90 to 1.26) neither for any measure of cocaine or other drug use. However, the number of participants included in meta-analyses was low, and power was limited. Moderate benefit or harm is not ruled out by these results. Methodological limitations of the included studies may have also made the results open to bias.

Authors' conclusions There is currently no evidence that auricular acupuncture is effective for the treatment of cocaine dependence. The evidence is not of high quality and is inconclusive. Further randomised trials of auricular acupuncture may be justified.

[34] Antipsychotic Medications for Cocaine Dependence.

Plain language summary Cocaine dependence is often associated with medical, psychological and social problems for the individual and public health problems for the community. Users have a role in the spread of the infectious diseases AIDS, hepatitis and tuberculosis as well as crime, violence and neonatal drug exposure. Medication with antidepressants, anticonvulsants such as carbamazepine, and dopamine agonists to assist in stopping cocaine use is not supported by evidence from Cochrane reviews. Use of antipsychotic agents has also been considered, particularly because cocaine can induce hallucinations and paranoia that mimic psychosis.

When all trial results comparing any antipsychotic drug to placebo were grouped together, antipsychotic drugs did not have any benefit in reducing dependency on cocaine. The review authors identified seven controlled trials involving a total of 293 adults, mean age 40 years. The studies were conducted in USA in both inpatient and outpatient settings and had a duration of 5 to 168 days (mean 61 days). Six trials randomised participants to receive an antipsychotic drug or placebo; the seventh compared olanzapine to haloperidol. The antipsychotic medications used were risperidone (three studies, 1 to 4 mg/day); olanzapine (three studies, 10 mg/day); and haloperidol (two studies, 4 and 10 mg/day). Risperidone treatment reduced the number of people who dropped out from treatment (three studies, 144 participants; relative risk 0.77, range 0.77 to 0.98); in individual studies olanzapine and haloperidol showed better results than placebo but the results come from studies to small to give them conclusive (34 participants) and (31 participants) respectively. Information on acceptability of treatment in terms of side effects, abstinence from cocaine use and withdrawal symptoms was limited. The methodological quality of the small number of identified trials was good but the number of participants was small and a variety of ways of reporting results were used.

Abstract Background Cocaine dependence is a public health problem characterized by recidivism and a host of medical and psychosocial complications. Cocaine dependence remains a disorder for which no pharmacological treatment of proven efficacy exists, although considerable advances in the neurobiology of this addiction could guide future medication development.

Objectives To evaluate the efficacy and the acceptability of antipsychotic medications for cocaine dependence.

Search strategy We searched the following sources: MEDLINE (1966 to October 2006), EMBASE (1980 to October 2006), CINAHL (1982 to October 2006), Cochrane Drug and Alcohol Group Specialised Register (October 2006). We also searched the reference lists of trials, the main
electronic sources of ongoing trials (National Research Register, meta-Register of Controlled Trials; Clinical Trials.gov) and conference proceedings likely to contain trials relevant to the review. All searches included also non-English language literature.

Selection criteria All randomised controlled trials and controlled clinical trials with focus on the use of any antipsyhyotic medication for cocaine dependence

Main results Seven small studies were included (293 participants): the antipsychotic drugs studied were risperidone, olanzapine and haloperidol. No significant differences were found for any of the efficacy measures comparing any antipsychotic with placebo. Risperidone was found to be superior to placebo in diminishing the number of dropouts, four studies, 178 participants, Relative Risk (RR) 0.77 (95% CI 0.77 to 0.98). Most of the included studies did not report useful results on important outcomes such as side effects, use of cocaine during treatment and craving. The results on olanzapine and haloperidol come from studies too small to give conclusive results.

Authors’ conclusions Although caution is needed when assessing results from a limited number of small clinical trials there is no current evidence, at the present, supporting the clinical use of antipsychotic medications in the treatment of cocaine dependence. Furthermore, most of the included studies did not report useful results on important outcomes such as side effects, use of cocaine during the treatment and craving. Aiming to answer the urgent demand of clinicians, patients, families, and the community as a whole for an adequate treatment for cocaine dependence, larger randomised investigations should be designed investigating relevant outcomes and reporting data to allow comparison of results between studies. Moreover some efforts should be done also to investigate the efficacy of other type medications, like anticonvulsant, currently used in clinical practice.

[35] PSYCHOSOCIAL INTERVENTIONS FOR COCAINE AND PSYCHOSTIMULANT AMPHETAMINES RELATED DISORDERS

Plain language summary
Psychosocial interventions for cocaine and psychostimulant amphetamines related disorders
Psychostimulants such as amphetamines and cocaine are used, at least in part, because of their effects on mood, cognition and behaviour. People who abuse or are dependent on them often have a long history of repeated periods of intoxication and of withdrawal and after long-term use they can develop a stereotyped behaviour, paranoia, and aggressive behaviour. Substance use disorders are a major public health problem with high costs for society including related health and relationship problems, absenteeism, loss of productivity and the costs of treatment. Yet knowledge about treatment interventions that impact on maintenance of abstinence remains a challenge. Trials on drug treatments for psychostimulants have high levels of dropouts from the trials and psychosocial interventions may be promising treatments as long as they can help to keep patients in treatment and reduce the use of the psychostimulants. In this review, several comparisons were made of psychosocial treatments but most of them did not show statistically significant differences between interventions, so that the evidence currently available does not have data supporting a single psychosocial treatment approach. The review authors identified 27 randomised controlled studies involving 3663 participants who were dependent on cocaine (crack or intravenous) in all but one Australian trial where oral amphetamine was the psychostimulant used. The other trials took place in the US. The trials lasted from 12 weeks to 9 months and the mean age of participants was 33 years old (range 18 to 65 years). Overall, cognitive behavioural interventions reduced dropouts from treatment and use of cocaine when compared with drug counseling. Behavioural interventions also clearly performed better than clinical management (psychotherapy sessions attended), usual care (lower rates of cocaine users at 1 and 3 months), information and referral (non-attendance). A multimodal intensive intervention was more effective than non-intensive delivery and cognitive behavioural treatments with some form of contingency management (involving the incentive of vouchers that are exchangeable for retail items) also showed benefits. Many of the results come from single studies, which limits their generalizability. The interventions used were variable and different types of cognitive behavioural treatments had overlapping but distinct therapeutic approaches. Simple reduction in the amount of drug used or retention in treatment is not a measure of meaningful changes in lifestyle.
**Background** The consumption of psychostimulants for non-medical reasons probably occurs because of their euphoriant and psychomotor-stimulating properties. Chronic consumption of these agents results in development of stereotyped behaviour, paranoia, and possibly aggressive behaviour. Psychosocial treatments for psychostimulant use disorder are supposed to improve compliance, and to promote abstinence. Evidence from randomised controlled trials in this subject needs to be summarised.

**Objectives** To conduct a systematic review of all RCTs on psychosocial interventions for treating psychostimulant use disorder.

**Search strategy** Electronic searches of Cochrane Library, EMBASE, MEDLINE, and LILACS (to may 2006); reference searching; personal communication; conference abstracts; unpublished trials from pharmaceutical industry; book chapters on treatment of psychostimulants abuse/dependence.

**Selection criteria** All randomised-controlled trials focusing on psychosocial interventions for treating psychostimulants abuse/dependence.

**Main results** Twenty-seven randomised controlled studies (3663 participants) fulfilled inclusion criteria and had data that could be used for at least one of the main comparisons. There was a wide heterogeneity in the interventions evaluated: this did not allow to provide a summary estimate of effect and results cannot be summarised in a clear cut way. The comparisons between different type of Behavioural Interventions showed results in favour of treatments with some form of Contingency management in respect to both reducing drop outs and lowering cocaine use.

**Authors’ conclusions** Overall this review reports little significant behavioural changes with reductions in rates of drug consumption following an intervention. Moreover, with the evidence currently available, there are no data supporting a single treatment approach that is able to comprise the multidimensional facets of addiction patterns and to significantly yield better outcomes to resolve the chronic, relapsing nature of addiction, with all its correlates and consequences.

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**TREATMENT FOR AMPHETAMINE DEPENDENCE AND ABUSE**


**Plain language summary**

Drugs to help end amphetamine dependence are not very helpful, and more research is needed. As amphetamines can produce feelings of euphoria, they are widely manufactured. Dependence on amphetamines is more common than cocaine and heroin dependence combined, and ending dependence on amphetamines can be as difficult as it is for cocaine and heroin. Amphetamines are also prescribed for some health problems, and ongoing use can lead to dependence. The review found there was very little evidence about ways to help end dependence on amphetamines. There is some evidence that the drugs fluoxetine and imipramine can be some help, but not enough to help reduce amphetamine use. More research is needed.

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**ABSTRACT**

**Background** Amphetamine use is of concern because it causes a variety of devastating health physical and neurological consequences, including amphetamine-induced mental disorders.

**Objectives** To investigate risks, benefits and costs of a variety of treatments for amphetamine dependence or abuse.


**Selection criteria** All relevant randomised controlled trials (RCTs) and clinical controlled trials (CCTs) were included. Participants were people with amphetamine dependence or abuse, diagnosed by any set of criteria. Any kinds of biological and psychological treatment both alone and combined were examined. A variety of outcomes, for example, number of treatment responders, score changes, were considered.
Main results Fluoxetine, amlodipine, imipramine and desipramine have been investigated in four randomised-controlled trials. In comparison to placebo, short-term treatment of fluoxetine (40 mg/day) significantly decreased craving. In comparison to imipramine 10 mg/day, medium-term treatment of imipramine 150 mg/day significantly increased the duration of adherence to treatment. All four drugs had no benefits on a variety of outcomes, including amphetamine use.

Authors' conclusions Fluoxetine, amlodipine, imipramine and desipramine have very limited benefits for amphetamine dependence and abuse. Fluoxetine may decrease craving in short-term treatment. Imipramine may increase duration of adherence to treatment in medium-term treatment. Apart from these, no other benefits can be found. This limited evidence suggests that no treatment has been demonstrated to be effective for the treatment of amphetamine dependence and abuse. Although there is a large number of people with amphetamine dependence and abuse worldwide, very few controlled trials in this issue have been conducted. As the previous treatment trials show no promising result, other treatments, both biological and psychosocial, should be further investigated. However, the results of neurotoxic studies of amphetamines are also crucial for the study designs appropriate for further treatment studies for amphetamine dependence and abuse.

[37] TREATMENT FOR AMPHETAMINE PSYCHOSIS

Plain language summary
A minority of individuals who use amphetamines develop full-blown psychosis requiring care at emergency departments or psychiatric hospitals. In such cases, symptoms of amphetamine psychosis commonly include paranoid and persecutory delusions as well as auditory and visual hallucinations in the presence of extreme agitation. More common (about 18%) is for frequent amphetamine users to report psychotic symptoms that are sub-clinical and that do not require high-intensity intervention. Clinical reports suggest the development of amphetamine psychosis and of sub-clinical psychosis symptoms is related to the individual's lifetime history of amphetamine use, i.e., cumulative quantity and frequency of exposure to amphetamines. In one of the only randomised trials of antipsychotic medications for treating amphetamine psychosis, Leelahanaj (2005) reported that olanzapine and haloperidol delivered at clinically relevant doses both showed similar efficacy in resolving psychotic symptoms (93% and 79%, respectively), with olanzapine showing significantly greater safety and tolerability than haloperidol as measured by frequency and severity of extrapyramidal symptoms. These outcomes are consistent with treatments for schizophrenia indicating equivalent efficacy between atypical anti-psychotics and conventional anti-psychotics, mostly haloperidol with older drugs causing more severe side effects (Leucht 1999). While anti-psychotic medications demonstrate efficacy in providing short-term relief when a heavy user of amphetamines experiences psychosis, there is no evidence to guide decisions regarding long-term clinical care using these medications for preventing relapse to psychosis.

ABSTRACT
Background Chronic amphetamine users may have experience of paranoia and hallucination. It has long been believed that dopamine antagonists, such as chlorpromazine, haloperidol, and thioridazine, are effective for the treatment of amphetamine psychosis.

Objectives To evaluate risks, benefits, costs of treatments for amphetamine psychosis.


Selection criteria All randomised controlled and clinical trials (RCTs, CCTs) evaluating treatments (alone or combined) for people with amphetamine psychosis

Main results The comprehensive searches found one randomised controlled trial of treatment for amphetamine psychosis meeting the criteria for considering studies. The study involved 58 participants and compared the efficacy and tolerability of two antipsychotic drugs, olanzapine (a newer antipsychotic) and haloperidol (a commonly used antipsychotic medication used as a control condition), in treating amphetamine-induced psychosis. The results show that both olanzapine and haloperidol at clinically relevant doses were efficacious in resolving psychotic symptoms, with the olanzapine condition showing significantly greater safety and tolerability than the haloperidol control as measured by frequency and severity of extrapyramidal symptoms.
**Authors' conclusions** Only one RCT of treatment for amphetamine psychosis has been published. Outcomes from this trial indicate that antipsychotic medications effectively reduce symptoms of amphetamine psychosis, the newer generation and more expensive antipsychotic medication, olanzapine, demonstrates significantly better tolerability than the more affordable and commonly used medication, haloperidol. There are other two studies that did not meet the inclusion criteria for this review. The results of these two studies show that agitation and some psychotic symptoms may be abated within an hour after antipsychotic injection. Whether this limited evidence can be applied for amphetamine psychotic patients is not yet known. The medications that should be further investigate are conventional antipsychotics, newer antipsychotics and benzodiazepines. However, naturalistic studies of amphetamine psychotic symptoms and the prevalence of relapse to psychosis in the presence of amphetamine, are also crucial for advising the development of study designs appropriate for further treatment studies of amphetamine psychosis.

[38] **TREATMENT FOR AMPHETAMINE WITHDRAWAL**

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**Plain language summary**
Symptoms of amphetamine withdrawal during the initial days of abstinence from chronic amphetamine use can prompt individuals to return to regular drug use. No medications demonstrate significant effects over placebo in reducing symptoms of acute amphetamine withdrawal.

Amphetamines can make people feel more alert, and are prescribed for problems like depression and attention deficit disorder. Amphetamines can produce euphoria, and so are manufactured for recreational use. Ongoing use can lead to dependence, which can be as hard to recover from as dependence on heroin or cocaine. The only randomized trials of amphetamine withdrawal agents have been of antidepressant drugs (amineptine and mirtazapine). Aminetine was found to have limited benefits, showing improvement only on some subjective effects but is no longer on the market because of concerns over its abuse liability. The benefits of mirtazapine have been less clear based on two randomised controlled trials, with one showing improvements in amphetamine withdrawal symptoms and the other showing no differences in withdrawal outcomes when compared to placebo. More research is needed.

**ABSTRACT**

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

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

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

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

**Main results** Four randomised controlled trials (involving 125 participants) met the inclusion criteria for the review. Two studies found that aminetine significantly reduced discontinuation rates and improved overall clinical presentation, but did not reduce withdrawal symptoms or craving compared to placebo. The benefits of mirtazapine over placebo for reducing amphetamine withdrawal symptoms were not as clear. One study suggested that mirtazapine may reduce hyperarousal and anxiety symptoms associated with amphetamine withdrawal. A more recent study failed to find any benefit of mirtazapine over placebo on retention or on amphetamine withdrawal symptoms.
Authors' conclusions No medication is effective for treatment of amphetamine withdrawal. Amineptine showed reduction in discontinuation rates and improvement in clinical presentation compared to placebo, but had no effect on reducing withdrawal symptoms or craving. In spite of these limited benefits, amineptine is not available for use due to concerns over abuse liability when using the drug. The benefits of mirtazapine as a withdrawal agent are less clear based on findings from two randomised controlled trials: one report showed improvements in amphetamine withdrawal symptoms over placebo; a second report showed no differences in withdrawal symptoms compared to placebo. Further potential treatment studies should examine medications that increase central nervous system activity involving dopamine, norepinephrine and/or serotonin neurotransmitters, including mirtazapine.
ABSTRACT

**Background** Cannabis use disorder is the most common illicit substance use disorder in general population. Despite that, only a minority seek assistance from a health professional, but the demand for treatment is now increasing internationally. Trials of treatment have been published but to our knowledge, there is no published systematic review.

**Objectives** To evaluate the efficacy of psychosocial interventions for cannabis abuse or dependence.

**Search strategy** We searched the Cochrane Central Register of Trials (CENTRAL) The Cochrane Library Issue 3, 2004; MEDLINE (January 1966 to August 2004), PsycInfo (1985 to October 2004), CINAHL (1982 to October 2004), Toxibase (until September 2004) and reference lists of articles. We also contacted researchers in the field.

**Selection criteria** All randomised controlled studies examining a psychotherapeutic intervention for cannabis dependence or abuse in comparison with a delayed-treatment control group or combinations of psychotherapeutic interventions.

**Main results** Six trials involving 1297 people were included. Five studies took place in the United States, one in Australia. Studies were not pooled in meta-analysis because of heterogeneity. The six included studies suggested that counselling approaches might have beneficial effects for the treatment of cannabis dependence. Group and individual sessions of cognitive behavioural therapy (CBT) had both efficacy for the treatment of cannabis dependence and associated problems. CBT produced better outcomes than a brief intervention when CBT was delivered in individual sessions. Two studies suggested that adding voucher-based incentives may enhance treatment when used in combination with other effective psychotherapeutic interventions. Abstinence rates were relatively small overall but favoured the individual CBT 9-session (or more) condition. All included trials reported a statistically significant reductions in frequency of cannabis use and dependence symptoms. But other measures of problems related to cannabis use were not consistently different.

**Authors’ conclusions** The included studies were too heterogeneous and could not allow to draw up a clear conclusion. The studies comparing different therapeutic modalities raise important questions about the duration, intensity and type of treatment. The generalizability of findings is also unknown because the studies have been conducted in a limited number of localities with fairly homogenous samples of treatment seekers. However, the low abstinence rate indicated that cannabis dependence is not easily treated by psychotherapies in outpatient settings.
IATROGENIC USE OF PRESCRIBED DRUGS:

[40] PHARMACOLOGICAL INTERVENTIONS FOR BENZODIAZEPINE MONO-DEPENDENCE MANAGEMENT IN OUTPATIENT SETTINGS


Plain language summary
The improved safety profile of benzodiazepines compared to barbiturates has contributed to a high rate of prescription since the seventies. Prevalence of benzodiazepines use remains important worldwide. Although benzodiazepines are highly effective as short-term treatments for some disorders, they also are potentially addictive drugs. This review has shown that a gradual taper is preferable to abrupt discontinuation of benzodiazepines, and that carbamazepine may be an effective intervention for benzodiazepine gradual taper discontinuation. But, larger controlled studies are needed to confirm carbamazepine's potential benefit, to assess adverse effects and to identify when its clinical use might be most indicated.

ABSTRACT
Background The improved safety profile of benzodiazepines compared to barbiturates has contributed to a high rate of prescription since the seventies. Although benzodiazepines are highly effective for some disorders, they are potentially addictive drugs and they can provide reinforcement in some individuals.

Objectives To evaluate the effectiveness of pharmacological interventions for benzodiazepine mono-dependence.

Search strategy We searched the Cochrane Drugs and Alcohol Group' Register of Trials (October 2004), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2004), MEDLINE (January 1966 to October 2004), EMBASE (January 1988 to October 2004), PsycInfo (1985 to October 2004), CINAHL (1982 to October 2004), Pascal, Toxibase, reference lists of articles.

Selection criteria Randomized trials of benzodiazepines dependence management regardless of type, dose (daily and total) and duration of f therapy and type of therapy.

Main results 753 references were selected and 35 were eligible. Eight met the inclusion criteria for a total of 458 participants. The studies included could not be analysed cumulatively because of heterogeneity of interventions and participants' characteristics. Results support the policy of gradual rather than abrupt withdrawal of benzodiazepine. Progressive withdrawal (over 10 weeks) appeared preferable if compared to abrupt since the number of drop-outs was lower and the procedure judged more favourable by the participants. Short half-life benzodiazepine, associated with higher drop-out rates, did not have higher withdrawal symptoms scores. Switching from short half-life benzodiazepine to long half-life benzodiazepine before gradual taper withdrawal did not receive much support from this review. No benefits of Propanolol, Dothiepin, Buspirone, Progesterone or Hydroxyzine were found for managing benzodiazepine withdrawal or improving benzodiazepine abstinence. Carbamazepine might have promise as an adjunctive medication for benzodiazepine withdrawal, particularly in patients receiving benzodiazepines in daily dosages of 20 mg/d or more of diazepam (or equivalents).

Authors' conclusions All included studies showed that gradual taper was preferable to abrupt discontinuation. The results of this systematic review point to the potential value of carbamazepine as an effective intervention for benzodiazepine gradual taper discontinuation. But, larger controlled studies are needed to confirm carbamazepine's potential benefit, to assess adverse effects and to identify when its clinical use might be most indicated. Other treatment approaches to benzodiazepine discontinuation management should be explored (antidepressants, benzodiazepine receptors modulator).
Plain language summary
There is currently no evidence to determine the best way to treat Mandrax dependence in adults. Dependence and abuse of methaqualone, a type of sedative-hypnotic, is a major public health problem in parts of Africa and India. Treatment is highly variable and takes place in both in-patient and out-patient settings. Despite an extensive search of electronic databases, the internet, relevant conferences and contact with experts in the field, this review identified no randomised controlled trials of the effectiveness of treatment for Mandrax dependence and/or abuse. Currently no evidence exists for using one type of treatment over another.

ABSTRACT
Background Methaqualone is a potent quinazoline, a class of sedative-hypnotics, that has a high potential for abuse. While the oral use of methaqualone (Quaalude, Mandrax) has waned in western countries since the mid-late 1980’s, the practice of smoking methaqualone is a serious public health problem in South Africa, other parts of Africa and India. In the context of diminishing resources devoted to substance abuse treatment in regions affected by methaqualone abuse, it would be desirable to base treatment on the best evidence available. This review aimed to provide health care workers, policy-makers and consumers with the necessary information to make decisions regarding effective treatment of this highly dependence-producing drug.

Objectives To compare the effectiveness of any type of pharmacological or behavioural treatment administered in either an in-patient or out-patient setting compared with either a placebo or no treatment or a waiting list, or with another form of treatment administered in either an in- or out-patient setting.

Search strategy The authors searched the following databases: Cochrane Drugs and Alcohol Group Register of Trials (February 2004); Cochrane Central Register of Controlled Trials (CENTRAL-The Cochrane Library, Issue 2, 2004); MEDLINE (OVID - January 1966 to February 2004), PsycInfo (OVID - January 1967 to February 2004). Relevant conference proceedings and reference lists of relevant articles were hand-searched. Broad Internet searches were conducted and contact made with experts in the field.

Selection criteria All randomised controlled trials and quasi-randomised trials of the effectiveness of treatment programmes (in- or out-patient) for methaqualone dependence and abuse were considered for inclusion in this review.

Data collection and analysis The authors independently assessed study eligibility and quality.

Main results No studies were found that met the inclusion criteria.

Authors’ conclusions To date, no randomized controlled trials appear to have been conducted. Consequently, the effectiveness of inpatient versus outpatient treatment, psychosocial treatment versus no treatment, and pharmacological treatments versus placebo for methaqualone abuse or dependence has yet to be established.
Plain language summary

Therapeutic communities (TCs) are a popular treatment for the rehabilitation of drug users. The results of this review show that there is little evidence that TCs offer significant benefits in comparison with other residential treatment, or that one type of TC is better than another. Prison TC may be better than prison on its own or Mental Health Treatment Programmes to prevent re-offending post-release for inmates.

ABSTRACT

Background Therapeutic communities (TCs) are a popular treatment for the rehabilitation of drug users in the USA and Europe.

Objectives To determine the effectiveness of TC versus other treatments for substance dependents, and to investigate whether effectiveness is modified by client or treatment characteristics.

Search strategy We searched: Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2005); MEDLINE, EMBASE, Psycinfo, CINAHL, SIGLE from their inception to March 2004. Reference lists of studies were scanned.

Selection criteria Randomised controlled trials comparing TC with other treatments, no treatment or another TC.

Main results Seven studies were included. Differences between studies precluded any pooling of data, results are summarised for each trial individually: TC versus community residence: no significant differences for treatment completion; Residential versus day TC: attrition (first two weeks), and abstinence rates at six months significantly lower in the residential treatment group; Standard TC versus enhanced abbreviated TC: number of employed higher in standard TC RR 0.78 (95% CI 0.63, 0.96). Three months versus six months programme within modified TC, and six months versus 12 months programme within standard TC: completion rate higher in the three months programme and retention rate (40 days) significantly greater with the 12 months than 6 months programme.

Two trials evaluated TCs within a prison setting: one reported significantly fewer re-incarcerated 12 months after release from prison in the TC group compared with no treatment, RR 0.68 (95% CI 0.57, 0.81). In the other, people treated in prison with TC compared with Mental Health Treatment Programmes showed significantly fewer re-incarcerations RR 0.28 (95% CI 0.13, 0.63), criminal activity 0.69 (95% CI 0.52, 0.93) and alcohol and drug offences 0.62 (95% CI 0.43, 0.90) 12 months after release from prison.

Authors’ conclusions There is little evidence that TCs offer significant benefits in comparison with other residential treatment, or that one type of TC is better than another. Prison TC may be better than prison on its own or Mental Health Treatment Programmes to prevent re-offending post-release for inmates. However, methodological limitations of the studies may have introduced bias and firm conclusions cannot be drawn due to limitations of the existing evidence.

Plain language summary

Therapeutic communities with aftercare in secure settings may reduced drug misuse and criminal activity. A number of policy directives are aimed at enabling people with drug problems to live healthy, crime free lives. Drug-using offenders naturally represent a socially excluded group who may experience problems in relation to their drug use. A number of studies and previous systematic reviews have considered the effectiveness of drug treatment interventions for drug misusers in the general population, mixed populations of offenders and non-offenders, drug treatment in a specific setting or country with limited outcome measures. This review focuses on drug treatment for offenders across a number of different settings. A
number of studies have been conducted displaying a wide range of outcome measures with varying methodological quality. Little information is provided on the costs and cost-effectiveness of such interventions. Promising results are shown for therapeutic communities with aftercare.

ABSTRACT

Background Drug strategies internationally recognize link between drug use and crime. This review consider interventions for drug-using offenders under the care of the criminal justice system.

Objectives To assess the effectiveness of interventions for drug-using offenders in reducing criminal activity and drug use in the courts, secure establishments and community-based settings.

Search strategy Twenty two electronic databases were searched (1980 to 2004). Internet sites and experts in the field were contacted for further information.

Selection criteria Randomised Controlled Trials designed to reduce, eliminate or prevent relapse in drug using offenders.

Main results Twenty four studies, 8936 participants, met the inclusion criteria. Results show that comparing a court-based community pre-trial release with drugs testing and sanctions versus routine pre-trial, for arrest at 90 days results favoured the comparison group OR 1.33 (95% CI 1.04 to 1.70). Comparing therapeutic community with aftercare with a mental health programme with a waiting list control, considering incarceration at 12 months OR 0.37 (95% CI 0.16 to 0.87), results in favour of the treatment. Comparing intensive supervision with routine parole/probation, for recidivism OR 1.98 (95% CI 1.01 to 3.87) results in favour of comparison group, no statistically significant difference between the groups for arrest OR 1.49 (95% CI 0.88 to 2.51), drug arrest OR 1.10 (95% CI 0.50 to 2.39), conviction OR 0.93 (95% CI 0.55 to 1.58) and incarceration at one year OR 0.88 (95% CI 0.50, 1.54). Comparing intensive supervision and increased surveillance with intensive supervision alone, no statistically significant difference between the groups for recidivism OR 2.09 (95% CI, 0.86 to 5.07), arrest OR 1.22 (95% CI 0.51 to 2.88), drug arrest, OR 1.29 (95% CI 0.35 to 4.85), conviction OR 0.14 (95% CI, 0.22, to 5.91) and incarceration OR 1.30 (95% CI 0.39, to 4.30) at one year.

Authors’ conclusions Limited conclusions can be drawn about the effectiveness of drug treatment programmes for drug-using offenders in the courts or the community. This is partly due to the broad range of studies and the heterogeneity of the different outcome measures presented. Therapeutic communities with aftercare show promising results for the reduction of drug use and criminal activity in drug using offenders. Standardisation of outcome measures and costing methodology would help improve the quality of research conducted in the area.

[44] CASE MANAGEMENT FOR PERSONS WITH SUBSTANCE USE DISORDERS


Plain language summary

Illicit use of drugs such as opioids, cocaine, amphetamines, cannabis and alcohol dependence have health, social and economic complications. Users often have long-term problems in addition to substance abuse.

Case management is a client-centred strategy involving assessment, planning, linking to relevant services and community resources and advocacy. Its intent is to improve the co-ordination and continuity of delivery of services. Brokerage case management sets out to help clients identify their needs and broker services in one or two contacts; intensive case management involves a closer interaction between case manager and client; assertive community treatment (provides assertive outreach and direct counselling services; strengths-based case management focuses on self-direction and the use of informal networks rather than agency resources by applying active outreach. From this review, case management effectively linked people with substance abuse to community and treatment services as compared to treatment as usual or other viable treatment options, such as psycho-education or brief interventions. This conclusion is based on 10 randomised controlled trials involving 3132 participants that compared case management to usual treatment. Two studies compared case management with other specific treatments. Additional analysis of the studies suggested that the use of a manual to guide the delivery of case management could increase linkage. A total of 15 controlled studies that randomised a total of 6694
participants were included in the review. One study was conducted in Europe; all other studies were from North America.

Seven studies with 2391 participants did not find a clear reduction in illicit drug use with case management compared with usual treatment; similarly with alcohol use (two studies). A single, large trial showed that case management for heroin users was superior to psycho-education and drug counselling in reducing drug use. The extent of linkage varied significantly between studies, which is likely to be influenced by the availability of services in the community, the model of case management, how effectively it is applied and its integration in the local network of services.

ABSTRACT

Background Patients with alcohol and other drug use disorders (AOD) frequently have multiple social, physical, and mental health treatment needs, yet have difficulty accessing community services, including drug abuse treatment. One strategy for linking patients with AOD with relevant services is case management, where a single case manager is responsible for linking patients with multiple relevant services.

Objectives To conduct a systematic review of all RCTs on the use of case management for helping drug abusers in or out of treatment. Outcome criteria included successful linkage with other services, illicit drug use outcomes, and a range of related outcomes.


Selection criteria Randomized controlled studies that compared a specific model of case management with either treatment as usual or another treatment model, included only patients with at least one alcohol or drug related problem.

Main results In total, we could extract results from 15 studies. Outcome on illicit drug use was reported from 7 studies with 2391 patients. The effect size for illicit drug use was not significant, and small (standardized mean difference (SMD)=0.12, confidence interval=−0.09,0.29, p=0.20). Substantial heterogeneity was found (I²=69.9%). Linkage to other treatment services was reported in 10 studies with 3132 patients. The effect size for linkage was moderate (SMD=0.42, 95% confidence interval=0.21 to 0.62, p<0.001), but substantial heterogeneity was found (I²=85.2%). Moderator analyses suggested that a part of the heterogeneity found in linkage studies could be explained by the presence or absence of a treatment manual for case management. A single, large trial of case management with two arms, showed that case management was superior to psycho-education and drug counselling in reducing drug use.

Authors’ conclusions There is current evidence supporting that case management can enhance linkage with other services. However, evidence that case management reduces drug use or produce other beneficial outcome is not conclusive.

[45] PSYCHOSOCIAL INTERVENTIONS FOR PREGNANT WOMEN IN OUTPATIENT ILlicit DRUG TREATMENT PROGRAMS COMPARED TO OTHER INTERVENTIONS.

Plain language summary
Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions

The effectiveness of psychosocial interventions in pregnant women enrolled in illicit drug treatment programs. Women who use illicit drugs while pregnant are more likely to give birth early and have low weight infants that are at risk of neonatal abstinence syndrome and requiring intensive care. A pregnant woman reduces the risk of these complications by undergoing prenatal drug treatment. Maternal concern for the infant can also motivate her. The length of time on treatment is important. Psychosocial interventions may help to overcome the many barriers to staying in a treatment program and reduce the use of illicit drugs. Contingency management uses positive, supportive reinforcement with, for example, monetary vouchers or giving work and a salary only when abstaining from drug use or attending treatment to change behaviour. Manual based interventions include motivational interviewing with a directive, counselling style.

This systematic review found that contingency management is effective in improving retention of pregnant
women in illicit drug treatment programs but with minimal effects on their abstaining from illicit drugs. Motivational interviewing over three to six sessions may, if anything, lead to poorer retention in treatment. These findings are based on nine controlled trials over 14 days to 24 weeks, five studies used contingency management (346 women) and four studies (266 women) that considered motivational interviewing. All but one took place in the United States. Many of the young women were African American, single, never married or divorced, and unemployed. They were receiving methadone maintenance, using cocaine, or opiate dependent and marijuana and alcohol use was also involved in six studies. In two trials, almost all women were nicotine dependent. No difference in birth outcomes or length of hospital detoxification for the newborns was found, from two studies. None of the included studies stated how the women were referred to treatment. Manual based interventions are less likely to be effective among coerced individuals. It is also unlikely to be used on their own in clinical practice.

ABSTRACT

Background Illicit drug use in pregnancy is a complex social and public health problem. It is important to develop and evaluate effective treatments. There is evidence for the effectiveness of psychosocial in this population; however, to our knowledge, no systematic review on the subject has been undertaken.

Objectives To evaluate the effectiveness of psychosocial interventions in pregnant women enrolled in illicit drug treatment programs on birth and neonatal outcomes, on attendance and retention in treatment, as well as on maternal and neonatal drug abstinence. In short, do psychosocial interventions translate into less illicit drug use, greater abstinence, better birth outcomes, or greater clinic attendance?

Search strategy We searched the Cochrane Drugs and Alcohol Group's trial register (May 2006), the Cochrane Central Register of Trials (Central- The Cochrane Library, Issue 3, 2005); MEDLINE (1.1996-8.2006); EMBASE (1.1996-8.2006); CINAHL (1.1982-8.2006), and reference lists of articles.

Selection criteria Randomised studies comparing any psychosocial intervention versus pharmacological interventions or placebo or non-intervention or another psychosocial intervention for treating illicit drug use in pregnancy.

Main results Nine trials involving 546 pregnant women were included. Five studies considered contingency management (CM), and four studies considered manual based interventions such as motivational interviewing (MI).

The main finding was that contingency management led to better study retention. There was only minimal effect of CM on illicit drug abstinence. In contrast, motivational interviewing led towards poorer study retention, although this did not approach statistical significance. For both, no difference in birth or neonatal outcomes was found, but this was an outcome rarely captured in the studies.

Authors’ conclusions The present evidence suggests that CM strategies are effective in improving retention of pregnant women in illicit drug treatment programs as well as in transiently reducing illicit drug use. There is insufficient evidence to support the use of MI. Overall the available evidence has low numbers and, therefore, it is impossible to accurately assess the effect of psychosocial interventions on obstetrical and neonatal outcomes.

It is important to develop a better evidence base to evaluate psychosocial modalities of treatment in this important population.
PREVENTION

[46] PRIMARY PREVENTION FOR ALCOHOL MISUSE IN YOUNG PEOPLE

Plain language summary
Many studies that have evaluated educational and psychosocial prevention programmes were considered and appraised in this systematic review. A number of programmes showed evidence of ineffectiveness. Those that reported longer-term evaluations (over three years follow-up) were examined in more detail and several promising studies were re-analysed to provide a better indication of the potential impact of the prevention programme. On the basis of this re-analysis, the Strengthening Families Programme (SFP) in particular but also culturally focused skills training appear to offer promise. However, all of the studies included in the review showed some methodological weaknesses and it is therefore necessary to replicate these studies with more robust design and analysis, and across different settings.

ABSTRACT

Background Alcohol misuse is a cause of concern for health services, policy makers, prevention workers, the criminal justice system, youth workers, teachers and parents.

Objectives 1. To identify and summarize rigorous evaluations of psychosocial and educational interventions aimed at the primary prevention of alcohol misuse by young people. 2. To assess the effectiveness of primary prevention interventions over the longer-term (> 3 years).


Selection criteria 1. randomised controlled and non-randomised controlled and interrupted time series designs. 2. educational and psychosocial primary prevention interventions for young people up to 25 years old. 3. alcohol-specific or generic (drugs; lifestyle) interventions providing alcohol outcomes reported. 4. alcohol outcomes: alcohol use, age of alcohol initiation, drinking 5+ drinks on any one occasion, drunkenness, alcohol related violence, alcohol related crime, alcohol related risky behaviour.

Main results 20 of the 56 studies included showed evidence of ineffectiveness. No firm conclusions about the effectiveness of prevention interventions in the short- and medium-term were possible. Over the longer-term, the Strengthening Families Program (SFP) showed promise as an effective prevention intervention. The Number Needed to Treat (NNT) for the SFP over 4 years for three alcohol initiation behaviours (alcohol use, alcohol use without permission and first drunkenness) was 9 (for all three behaviours). One study also highlighted the potential value of culturally focused skills training over the longer-term (NNT=17 over three-and-a-half years for 4+ drinks in the last week).

Authors' conclusions
1. Research into important outcome variables needs to be undertaken. 2. Methodology of evaluations needs to be improved. 3. The Strengthening Families Programme needs to be evaluated on a larger scale and in different settings. 4. Culturally-focused interventions require further development and rigorous evaluation. 5. An international register of alcohol and drug misuse prevention interventions should be established and criteria agreed for rating prevention intervention in terms of safety, efficacy and effectiveness.

[47] SCHOOL-BASED PREVENTION FOR ILLICIT DRUGS’ USE

Plain language summary
Drug addiction is a long-term problem caused by an uncontrollable compulsion to seek drugs. People may
use drugs to seek an effect, to feel accepted by their peers or as a way of dealing with life's problems. Even after undertaking detoxification to reach a drug-free state, many return to opioid use. This makes it important to reduce the number of people first using drugs and to prevent transition from experimental use to addiction. For young people, peers, family and social context are strongly implicated in early drug use. Schools offer the most systematic and efficient way of reaching them. School programs can be designed to provide knowledge about the effects of drugs on the body and psychological effects, as a way of building negative attitudes toward drugs; to build individual self-esteem and self-awareness, working on psychological factors that may place people at risk of use; to teach refusal and social life skills; and to encourage alternative activities to drug use, which instil control abilities.

The review authors found 32 controlled studies, of which 29 were randomised, comparing school-based programs aimed at prevention of substance use with the usual curriculum. The 46,539 students involved were mainly in sixth or seventh grade. Programs that focused on knowledge improved drug knowledge to some degree, in six randomised trials. Social skills programs were more widely used (25 randomised trials) and effectively increased drug knowledge, decision-making skills, self-esteem, resistance to peer pressure, and drug use including of marijuana (RR 0.8) and hard drugs (heroin) (RR 0.5). The programs were mainly interactive and involved external educators in 20 randomised trials. Effects of the interventions on assertiveness, attitudes towards drugs, and intention to use drugs were not clearly different in any of the trials.

Most trials were conducted in the USA and, as a nation's social context and drug policies have a significant influence on the effectiveness of the programs, these results may not be relevant to other countries.

Measures of change were often made immediately after the intervention with very little long-term follow up or investigation of peer influence, social context, and involvement of parents.

ABSTRACT

Background Drug addiction is a chronic, relapsing disease. Primary interventions should be aimed to reduce first use, or prevent the transition from experimental use to addiction. School is the appropriate setting for preventive interventions.

Objectives To evaluate the effectiveness of school-based interventions in improving knowledge, developing skills, promoting change, and preventing or reducing drug use versus usual curricular activities or a different school-based intervention.

Search strategy We searched the Cochrane Drug and Alcohol Group trial register (February 2004), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2004), MEDLINE (1966 to February 2004), EMBASE (1988 to February 2004), and other databases. We also contacted researchers in the field and checked reference lists of articles.

Selection criteria Randomised controlled trials (RCT), case controlled trials (CCT) or controlled prospective studies (CPS) evaluating school-based interventions designed to prevent substance use.

Main results 32 studies (29 RCTs and three CPSs) were included with 46539 participants. Twenty eight were conducted in the USA; most were focused on 6th-7th grade students, and based on post-test assessment.

RCTs
(1) Knowledge versus usual curricula
Knowledge focused programs improve drug knowledge (standardised mean difference (SMD) 0.91; 95% confidence interval (CI) 0.42 to 1.39).

(2) Skills versus usual curricula
Skills based interventions increase drug knowledge (weighted mean difference (WMD) 2.60; 95% CI 1.17 to 4.03), decision making skills (SMD 0.78; CI 95%: 0.46 to 1.09), self-esteem (SMD 0.22; CI 95% 0.03 to 0.40), peer pressure resistance (relative risk (RR) 2.05; CI 95%: 1.24 to 3.42), drug use (RR 0.81; CI 95% 0.64 to 1.02), marijuana use (RR 0.82; CI 95% 0.73 to 0.92) and hard drug use (RR 0.45; CI 95% 0.24 to 0.85).

(3) Skills versus knowledge
No differences are evident.

(4) Skills versus affective
Skills-based interventions are only better than affective ones in self-efficacy (WMD 1.90; CI 95%: 0.25 to 3.55).

Results from CPSs
No statistically significant results emerge from CPSs.
Authors' conclusions Skills based programs appear to be effective in deterring early-stage drug use. The replication of results with well designed, long term randomised trials, and the evaluation of single components of intervention (peer, parents, booster sessions) are the priorities for research. All new studies should control for cluster effect.

[48] INTERVENTIONS FOR PREVENTION OF DRUG USE BY YOUNG PEOPLE DELIVERED IN NON-SCHOOL SETTINGS

Plain language summary
Drug use is widespread among young people including those still at school. Taking drugs is not a medical problem in itself but can affect physical and mental health and social functioning. People may become dependent on drugs, and use of low risk illicit drugs can escalate into use of higher risk drugs. In schools, programs have been introduced to prevent or reduce drug use among young people. Non-school settings for interventions include youth clubs, primary care centres, colleges, with families and in the community. Strategies can target entire populations or be directed at specific groups, often those at high risk.

The review authors identified 17 controlled studies, 9 cluster randomised studies with 253 clusters and 8 individually randomised studies with 1230 participants. All but two of the studies were conducted in the USA. The other studies were in the UK and China. Follow-up periods varied from at completion of the intervention to six years. The studies were too few and each intervention too different to draw any firm conclusions on whether non-school based interventions prevent or reduce drug use by young people. The interventions with suggested benefits need further evaluation before it can be firmly established that they are effective. One of two studies of motivational interviewing suggested that this intervention was beneficial on self-reported cannabis use. Three family interventions (Focus on Families, Iowa Strengthening Families Program and Preparing for the Drug-Free Years) were evaluated, in two separate studies, and may have been beneficial in preventing self-reported cannabis use. The latter two programs were compared to the school-based Life Skills Training program. All of the eight studies of family interventions included contact with parents, in family groups or in separate sessions for parents and their children. Multicomponent community interventions did not have any strong effects on drug use. There were five studies, four of which added the community component to a school drug education program. Education and skills training was not effective in two studies. Many of the studies lacked blinding and had high numbers of participants lost to follow up. No study reported cost outcomes.

ABSTRACT
Background Interventions intended to prevent or reduce use of drugs by young people may be delivered in schools or in other settings. This review aims to summarise the current literature about the effectiveness of interventions delivered in non schools settings.

Objectives (1) - To summarise the current evidence about the effectiveness of interventions delivered in non-school settings intended to prevent or reduce drug use by young people under 25; (2) - To investigate whether interventions' effects are modified by the type and setting of the intervention, and the age of young people targeted; (3) - To identify areas where more research is needed.


Selection criteria Randomised trials that evaluated an intervention targeting drug use by young people under 25 years of age, delivered in a non-school setting, compared with no intervention or another intervention, that reported substantive outcomes relevant to the review.

Main results Seventeen studies, 9 cluster randomised studies, with 253 clusters, 8 individually randomised studies with 1230 participants, evaluating four types of intervention: motivational interviewing or brief intervention, education or skills training, family interventions and multi-component community interventions. Many studies had methodological drawbacks, especially high levels of loss to follow-up. There were too few studies for firm conclusions. One study of motivational interviewing suggested that this intervention was beneficial on cannabis use. Three family interventions (Focus on Families, Iowa Strengthening Families Program and Preparing for the Drug-Free Years), each evaluated in only one study, suggested that they may be beneficial in
preventing cannabis use. The studies of multi component community interventions did not find any strong effects on drug use outcomes, and the two studies of education and skills training did not find any differences between the intervention and control groups.

**Authors’ conclusions** There is a lack of evidence of effectiveness of the included interventions. Motivational interviewing and some family interventions may have some benefit. Cost-effectiveness has not yet been addressed in any studies, and further research is needed to determine whether any of these interventions can be recommended.

**[49] Social Norms Interventions to Reduce Alcohol Misuse in University or College Students.**


Plain language summary

Misuse of alcohol can result in disabilities and death. Alcohol also leads to accidents, fights and unprotected sex. Young people aged 15 to 24 years contribute a high proportion to this burden. University students may not drink as frequently as their non-university peers but they have a tendency to drink excessively when they do. Social norms refer to our perceptions and beliefs about what is 'normal' behaviour. People may believe that their peers drink heavily, which influences their drinking, yet much of peer influence is the result of incorrect perceptions. Normative feedback relies on the presentation of information on these misperceptions, about personal drinking profiles, risk factors, and normative comparisons. Feedback can be given alone or in addition to individual or group counselling.

This systematic review was based on 22 controlled trials involving 7275 college or university students randomly assigned to the social norms intervention or a control group. Interventions delivered using the web or computer, or in individual face-to-face sessions, appeared to reduce alcohol misuse. The evidence was less convincing for group face-to-face sessions. Mailed and group feedback were on the whole no different than with the control intervention. Two large studies showed contradictory results for a social marketing campaign. Only a small number of good quality studies were available for many of the outcomes and analyses, and most of the studies were from the USA. The intensity of the intervention differed between trials as did the control intervention, which was no intervention, educational leaflets or an alcohol educational session. Individual face-to-face feedback typically involved social norms feedback as just one aspect of a broader motivational interviewing intervention. Locations where alcohol outlet density is higher may promote higher consumption through more frequent alcohol promotions and easier access to alcohol, so the effectiveness of an intervention designed to reduce drinking could be expected to be lower in these areas.

**ABSTRACT**

**Background** Drinking is influenced by youth (mis)perceptions of how their peers drink. If misperceptions can be corrected, young people may drink less.

**Objectives** To determine whether social norms feedback reduces alcohol misuse in university or college students.

**Search strategy** Cochrane Drugs and Alcohol Group Register of Trials; Central; MEDLINE; EMBASE; PsycInfo; CINAHL (up to March 2008).

**Selection criteria** RCT or cluster RCT that evaluate social normative intervention with no intervention, alcohol education leaflet or other non-normative feedback intervention

**Main results** Twenty-two studies were included (7,275 participants). Alcohol related problems: Significant reduction with Web/computer feedback (WF) (SMD -0.31 95% CI -0.59 to -0.02), three studies, 278 participants. No significant effect of mailed feedback (MF), individual face-to-face feedback (IFF) or group face-to-face feedback (GFF).

Peak Blood Alcohol Content (BAC) : Significant reduction with WF (SMD -0.77 95% CI -1.25 to -0.28), two studies, 198 participants. No significant effect of MF or IFF.

Drinking Frequency: Significant reduction with WF (SMD -0.38 95% CI -0.63 to -0.13), two studies, 243 participants and IFF (SMD -0.39 95% CI -0.66 to -0.12), two studies, 217 participants. No significant effect of MF.

Drinking Quantity: Significant reduction with WF (SMD -0.35 95% CI -0.51 to -0.18), five studies, 556 participants and GFF (SMD -0.32 95% CI -0.63 to -0.02) three studies, 173 participants. No significant effect of MF or IFF.
Binge drinking: Significant reduction with WF (SMD -0.47 95% CI -0.92 to -0.03) one study, 80 participants, IFF (SMD -0.25 95% CI -0.49 to -0.02) three studies, 278 participants and and GFF (SMD -0.38 95% CI -0.62 to -0.14) four studies, 264 participants. No significant effect for MF. BAC: No significant effect of MF and IFF. Drinking norms: Significant reduction with WF (SMD -0.75 95% CI -0.98 to -0.52) three studies, 312 participants.

Authors’ conclusions WF and IFF are probably effective in reducing alcohol misuse. No direct comparisons of WF against IFF were found, but WF impacted across a broader set of outcomes and is less costly so therefore might be preferred. Significant effects were more apparent for short-term outcomes (up to three months). For mailed and group feedback, and social norms marketing campaigns, the results are on the whole not significant and therefore cannot be recommended.
References of published Reviews


References of the included studies

N.B. The number in square brackets are referred to the review in which the study is included


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