TREATMENTS OF SUBSTANCE USE DISORDERS
THE SYSTEMATIC REVIEWS OF THE COCHRANE DRUGS AND ALCOHOL GROUP (CDAG)
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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 SISTEMATIC REVIEWS

The principal objective of systematic reviews is to develop an 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 etherogeneity (temporal, geografic, 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 December 2004 it contains 6195 trials (2817 RCT, 1389 CCT, 1989 other study design)
The references are systematically searched on the electronic databases (MEDLINE, EMBASE, PsychInfo). The full text article are obtained and coded (3039 articles till now).
As of September 2004 the group published 23 reviews, 15 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 perform 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.

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REVIEWS AND PROTOCOLS PUBLISHED BY THE COCHRANE GROUP ON DRUG AND ALCOHOL
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WHAT’S NEW

NEW REVIEWS

Mayet S, Farrell M, Ferri M, Amato, L, Davoli, M Psychosocial treatment for opiate abuse and dependence

NEW PROTOCOLS
Petrie J, Bunn F, Byrne G Parenting programs for preventing tobacco, alcohol and drug abuse in children under 18

Polycarpou A, Papanikolaou P, Contopoulos-Ioannidis DG, Ioannidis JPA. Anticonvulsants for the management of alcohol withdrawal

Ntais C, Pakos E, Panayiotis K, Ioannidis JPA Benzodiazepines for alcohol withdrawal

**REVIEWS SUBSTANTIALLY UPDATED**

Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence

**Reviews**

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2. Buprenorphine for the management of opioid withdrawal
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6. Interventions for prevention of drug use by young people delivered in non-school settings.
7. Neuroelectric stimulation for the management of opioid withdrawal
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11. Treatment for Mandrax (combination of methaqualone, cannabis and tobacco) dependence in adults
12. 12-step type programmes and Alcoholics Anonymous for alcohol dependence
13. Parenting programs for preventing tobacco, alcohol and drug abuse in children under 18
14. Anticonvulsants for the management of alcohol withdrawal
15. Benzodiazepines for alcohol withdrawal

OPIATE: MANAGEMENT OF WITHDRAWAL

[1] OPIOID ANTAGONISTS WITH MINIMAL SEDATION FOR OPIOID WITHDRAWAL
Gowing L., Ali R., White J. Date first publication issue 2, 2000.; Date of the last substantial update issue 2, 2002

Background Managed 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.

Objectives To assess the effectiveness of interventions involving opioid antagonists to induce withdrawal, in combination with medication to ameliorate symptoms but with minimal sedation.

Selection criteria Randomised or quasi-randomised controlled clinical trials or prospective controlled cohort studies that compared antagonist-induced (conscious) withdrawal with other approaches to modify the signs and symptoms of withdrawal in opioid-dependent participants.

Main results Ten studies (5 randomised and 5 non-randomised controlled trials), involving 770 participants, met the inclusion criteria for the review. Treatment regimes using opioid antagonists to induce withdrawal, with minimal sedation, varied in a number of aspects preventing description of a “standard” approach.

Antagonist-induced withdrawal is associated with similar or less overall severity than withdrawal managed primarily with an alpha2 adrenergic agonist. This is probably because of earlier resolution of withdrawal. Peak severity is likely to be higher with antagonist-induced withdrawal and require the use of additional adjunct medications. Withdrawal from methadone may be more severe than withdrawal from heroin, but data are limited.

Antagonist-induced withdrawal appears to be associated with somewhat higher rates of completion of withdrawal and achievement of maintenance doses of naltrexone but there were insufficient data for statistical analyses. The benefit of higher rates of completion of withdrawal is lessened by apparently low rates of retention in subsequent naltrexone maintenance treatment.

Reviewers’ conclusions The use of opioid antagonists combined with alpha2 adrenergic agonists is feasible and probably increases the likelihood of transfer to naltrexone compared to 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.

[2] BUPRENORPHINE FOR THE MANAGEMENT OF OPIOID WITHDRAWAL
Gowing L, Ali R, White J. Date first publication issue 3, 2000; Date of the last substantial update issue 4, 2004

**Background** Managed withdrawal (detoxification) is a necessary step 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 use of buprenorphine to manage the acute phase of opioid withdrawal.

**Selection criteria** Randomised or quasi-randomised controlled clinical trials or prospective controlled cohort studies that compared different buprenorphine regimes, or that compared buprenorphine with another form of treatment (or placebo) to modify the signs and symptoms of withdrawal in participants who were primarily opioid dependent.

**Main results** Thirteen studies (10 RCTs), involving 744 participants, met the criteria for inclusion in the review. Seven studies compared buprenorphine with clonidine; 3 compared buprenorphine with methadone; 1 compared buprenorphine with oxazepam; 2 compared rapid and slow rates of tapering buprenorphine dose; 1 compared 3 different starting doses of buprenorphine.

For groups treated with buprenorphine, withdrawal severity was less than that in groups treated with clonidine; peak severity was similar to those treated with methadone, but withdrawal symptoms may resolve more quickly with buprenorphine. Withdrawal is probably more severe when doses are tapered rapidly following a period of maintenance treatment.

Buprenorphine is associated with fewer adverse effects than clonidine, and completion of withdrawal is significantly more likely with buprenorphine. Buprenorphine and methadone in reducing doses are probably similar in terms of rates of completion of withdrawal, but the evidence is limited. Completion of withdrawal following buprenorphine maintenance treatment may be more likely when doses are reduced gradually.

**Reviewers’ conclusions** Buprenorphine is more effective than clonidine, and of similar effectiveness to methadone, for the management of opioid withdrawal. Many aspects of treatment protocol and relative effectiveness need to be investigated further in order to determine the most effective way of using buprenorphine to manage opioid withdrawal.

Gowing L., Farrell M., Ali R., White J. Date first publication issue 1, 2001; Date of the last substantial update issue 4, 2004

**Background** Withdrawal (detoxification) is necessary prior to drug-free treatment. It may also represent the end point of long-term 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 use of alpha2 adrenergic agonists (clonidine, lofexidine, guanfacine) to manage opioid withdrawal in terms of withdrawal signs and symptoms, completion of treatment and adverse effects.

**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 primarily opioid dependent.

**Main results** Twenty-two studies, involving 1709 participants, were included. Eighteen were randomised controlled trials; for the remaining studies allocation was by participant choice in two, one used alternate allocation and in one the method of allocation was unclear. Twelve 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.
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 in treatment. 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 (low blood pressure, dizziness, dry mouth, lack of energy) than reducing doses of methadone. Lofexidine does not reduce blood pressure to the same extent as clonidine, but is otherwise similar to clonidine.

**Reviewers' conclusions** No significant difference in efficacy was detected for treatment regimes based on the alpha2 adrenergic agonists clonidine and lofexidine, and those based on reducing doses of methadone over a period of around 10 days, for the management of withdrawal from heroin or methadone. Participants stay in treatment longer with methadone regimes and experience less adverse effects. The lower incidence of hypotension makes lofexidine more suited to use in outpatient settings than clonidine. There are insufficient data available to support a conclusion on the efficacy of other alpha2 adrenergic agonists.

[4] **OPIOID ANTAGONISTS UNDER HEAVY SEDATION OR ANAESTHESIA FOR OPIOID WITHDRAWAL**

Gowing L., Ali R., White J. Date first publication issue 1, 2001; Date of the last substantial update issue 1, 2002

**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.

**Selection criteria** Randomised or quasi-randomised controlled trials that compared the administration of opioid antagonists under heavy sedation or anaesthesia with another form of treatment.

**Main results** As yet, no studies have been published comparing treatment regimes involving the administration of opioid antagonists under heavy sedation or anaesthesia with other approaches to detoxification. Treatment regimes for the studies considered for this review varied in the opioid antagonist used, the dose and mode of administration, the anaesthetic agent, duration of anaesthesia and adjunct medications employed. More detailed monitoring of withdrawal is required before any conclusions can be drawn as to what comprises a typical pattern of withdrawal and what factors might influence the pattern. There is only very limited information on referral to ongoing treatment, and relapse to opioid use. Together with the lack of adequate comparisons, this makes it impossible to draw any conclusions about the long-term effectiveness, or the cost-effectiveness, of withdrawal induced by opioid antagonists under heavy sedation or anaesthesia.

**Reviewers' conclusions** Considerably more research evidence will be needed before any conclusions can be drawn regarding the effectiveness of managing withdrawal by administration of opioid antagonists under heavy sedation or anaesthesia. The risk of vomiting during sedation, respiratory depression and cardiac irregularities point to the approach being limited to facilities equipped for intubation, assisted ventilation and a high level of monitoring, and with the capacity to respond to adverse events that might occur. The approach must be regarded as experimental with both risks and benefits remaining uncertain.

[5] **METHADONE AT TAPERED DOSES FOR THE MANAGEMENT OF OPIOID WITHDRAWAL**

Amato L, Davoli M, Ferri M, Ali R. Date first publication issue 1, 2002; Date of the last substantial update issue 3, 2003

**Background** Despite widespread use in many countries of tapered methadone for detoxification from opiate dependence, the evidence of efficacy to prevent relapse and promote lifestyle change has not been systematically evaluated.
Objectives  To determine whether tapered methadone is effective to manage withdrawal from opioids.

Selection criteria  All randomised controlled trials which focus on the use of tapered methadone (length of treatment max 30 days) versus all other pharmacological detoxification treatments, placebo and different modalities of methadone detoxification programs for the treatment of opiate withdrawal. Trials including patients with additional diagnoses such as benzodiazepine dependence were also eligible.

Main results  20 studies were included in the review, with 1357 people randomised. 10 studies compared methadone with adrenergic agonists, 7 studies compared different modalities of methadone detoxification, 2 studies compared methadone with other opioid agonists, 1 study compared methadone with chlordiazepoxide one with placebo.

The conclusions of the 10 studies that compared methadone with adrenergic agonists showed no substantial clinical difference of the two treatments in terms of retention in treatment, degree of discomfort and detoxification success rates.

The conclusions of the 6 studies that compare different methadone reduction schedules, showed that different types of methadone withdrawal schedule produce different responses in terms of time course of withdrawal, the severity of withdrawal response and possibly in terms of subsequent engagement with treatment.

Regarding the studies that compare methadone with other opioid agonists, in Sorensen 1982 methadyl acetate performed similarly to methadone on most process and outcome measures, while in Tennant 1975, methadone reduced severity of withdrawal and had fewer drop-outs than did a propoxyphene group.

In Drummond 1989, using chlordiazepoxide vs methadone, the results suggest that the two drugs had similar results in terms of overall effectiveness.

San 1992 compared methadone with placebo and found more severe withdrawal and more drop outs in the placebo group.

The results indicate that tapered methadone and other medications used in the included studies are effective in the treatment of the heroin withdrawal syndrome, although symptoms experienced by subjects differed according to the medication used and the program adopted. It seems that regardless of which medication is selected for heroin detoxification, the rates of subsequent heroin abstinence are about equal. This suggests that the medications are similar in terms of overall effectiveness. Improvements were achieved when other services such as counseling and other supporting services were offered contemporaneously with detoxification.

Reviewers’ conclusions  Data from literature are hardly comparable; programs vary widely with regard to duration, design and treatment objectives, impairing the application of meta-analysis. Results of many outcomes could not be summarised because they were presented either in graphical form or provided only statistical tests and p-values. For most studies standard deviation for continuous variables were not provided. The studies included in this review confirm that slow tapering with temporary substitution of long acting opioids, accompanied by medical supervision and ancillary medications can reduce withdrawal severity. Nevertheless the majority of patients relapsed to heroin use. However this cannot be considered a goal for a detoxification as heroin dependence is a chronic, relapsing disorder and the goal of detoxification should be to remove or reduce dependence on heroin in a controlled and human fashion and not a treatment for heroin dependence.

OPIATE: MAINTENANCE TREATMENT

[6] NALTREXONE MAINTENANCE TREATMENT FOR OPIOID DEPENDENCE.
Kirchmayer U., Davoli M., Verster A. Date first publication issue 1, 1999; Date of the last substantial update issue 2, 2003

Background  Despite widespread use of naltrexone maintenance in many countries for more than a decade, the evidence of its effects has not yet been systematically evaluated.

Objectives  To evaluate the effects of naltrexone maintenance treatment in preventing relapse in opioid addicts after detoxification.
Selection criteria All controlled studies of naltrexone; treatment of heroin addicts after detoxification.

Main results Eleven studies met the criteria for inclusion in this review, even if not all of them were randomised. The methodological quality of the included studies varied, but was generally poor. Meta-analysis could be performed to a very low degree only, because the studies and their outcome measures were very heterogeneous. A statistically significant reduction of (re-)incarcerations was found for patients treated with naltrexone and behaviour therapy in respect to those treated with behaviour therapy only. The other outcomes considered in the meta-analysis did not yield any significant results. Final conclusions on whether naltrexone treatment may be considered effective in maintenance therapy cannot be drawn from the clinical trials available so far.

Reviewers' conclusions The available trials do not allow a final evaluation of naltrexone maintenance treatment yet. A trend in favour of treatment with naltrexone was observed for certain target groups (particularly people who are highly motivated), as has been previously described in the literature.

[7] LAAM MAINTENANCE VERSUS METHADONE MAINTENANCE FOR HEROIN DEPENDENCE
Clark N, Lintzeris N, Gijsbers A, Whelan G, Dunlop A, Ritter A, Ling W. Date first publication issue 2, 2002,

Background LAAM and methadone are both full mu 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 or 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.

Selection criteria All randomised controlled trials, controlled clinical trials and controlled prospective studies comparing LAAM and methadone maintenance for the treatment of heroin dependence and measuring 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.

Reviewers' 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.

[8] METHADONE MAINTENANCE VERSUS NO OPIOID REPLACEMENT THERAPY FOR OPIOID DEPENDENCE
Mattick RP, Breen C, Kimber J, Davoli M. Date first publication issue 4, 2002; Date of the last substantial update issue 2, 2003

Background Methadone maintenance was the first widely used form of opioid replacement therapy developed 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.

**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** Six studies met the criteria for inclusion in this review, all were randomised clinical trials, two were double-blind. There were a total number of 954 participants. The method of concealment of allocation was inadequate in one study, not clearly described in four studies, but adequate in a sixth study. Based on the meta-analysis, methadone appeared statistically more effective than non-pharmacological approaches in retaining patient in treatment (3 RCTs, RR=3.05; 95%CI: 1.75-5.35) and in the suppression of heroin use (3 RCTs, RR=0.32; 95%CI: 0.23-0.44), but not statistically in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25).

**Reviewers’ 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.

[9] **BUPRENORPHINE MAINTENANCE VS PLACEBO OR METHADONE MAINTENANCE FOR OPIOID DEPENDENCE**

Mattick RP, Kimber J, Breen C, Davoli M. Date first publication issue 4, 2002; Date of the last substantial update issue 3, 2003

**Background** Buprenorphine has recently been reported to be an alternative to methadone and LAAM for maintenance treatment of opioid dependent individuals, 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.

**Selection criteria** Randomised clinical trials of buprenorphine maintenance compared with either placebo or methadone maintenance for opioid dependence.

**Main results** Thirteen studies met the inclusion criteria, all were randomised clinical trials, all but one were double-blind. The method of concealment of allocation was not clearly described in 11 of the studies, otherwise methodological quality was good. Buprenorphine given in flexible doses appeared statistically more effective than methadone in retaining patient in treatment (RR= 0.82; 95% CI: 0.69-0.96). Low dose buprenorphine is not superior to low dose methadone. High dose buprenorphine does not retain more patients than low dose methadone, but may suppress heroin use better. There was no advantage for high dose buprenorphine over high dose methadone in retention (RR=0.79; 95% CI:0.62-1.01), and high dose buprenorphine was inferior in suppression of heroin use. Buprenorphine was statistically significantly superior to placebo medication in retention of patients in treatment at low doses (RR=1.24; 95% CI: 1.06-1.45), high doses (RR=1.21; 95% CI: 1.02-1.44), and very high doses (RR=1.52; 95% CI: 1.23-1.88). However, only high and very high dose buprenorphine suppressed heroin use significantly above placebo.

**Reviewers’ conclusions** Buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is not more effective than methadone at adequate dosages.

[10] **HEROIN MAINTENANCE FOR CHRONIC HEROIN ADDICTS**

Ferri M, Davoli M, Perucci CA. Date first publication issue 3, 2003; Date of the last substantial update issue 4, 2004

**Background** Dependent heroin users are characterised by the persistence of use in spite of the difficulties they experience with health, law, social achievements and personal relationships. The present review will consider maintenance treatment in which the patients enter programs of pharmacological administration tailored to achieve patient stabilisation. Many medications have
been used for this purpose such as: Methadone, Buprenorphine and LAAM. The present review will focus on maintenance treatment through the prescription of heroin.

**Objectives** To assess the efficacy and acceptability of heroin maintenance versus methadone or other substitution treatments for opioid dependence, in retaining patients in treatment; reducing the use of illicit substances and improving health and social functioning.

**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** 2400 references were obtained and 20 studies were eligible, 4 met the inclusion criteria for a total of 577 patients. The studies included could not be analysed cumulatively because of heterogeneity of interventions and outcomes considered. Two studies compared injected heroin to oral methadone for 1 year (270 patients) but considered different outcomes; one study compared injected heroin and methadone to oral methadone for 6 months (51 patients); and one compared inhaled heroin and methadone to oral methadone for 1 year (235 patients). Retention in treatment: in two studies there was no statistical difference between groups; one study (N=96) had a RR=2.82 (95% CI 1.70-4.68) in favour of heroin; one study (N=235) had a RR 0.79 (95%CI 0.68-0.90) in favour of methadone. Relapse to illegal heroin use, based on self report: in one study the proportion of people still using heroin were 64% in the heroin group, 59% methadone group; in the other study the RR was 0.33 (95%CI 0.15-0.72) in favour of heroin. The remaining studies did not provide the data. Criminal offence: one of the two studies which provided details about this showed the potential of heroin prescription in reducing the risk of being charged RR 0.32 (95% CI 0.14-0.78). Social functioning: the two studies reporting this outcome did not show statistical difference between intervention groups. The two most recent studies considered criminal offence and social functioning as part of a multidomain outcome measure and showed higher improvement among those treated with heroin plus methadone over those on methadone only.

**Reviewers' conclusions** No definitive conclusions about the overall effectiveness of heroin prescription is possible because of non-comparability of the experimental studies available to be included in this review. Results favouring heroin treatment come from studies conducted in countries where the treatment system is comprehensive and easy accessible Methadone Maintenance Treatment at effective dosages is available. In those studies heroin prescription was addressed to patients who had failed previous methadone treatments.

[11] **METHADONE MAINTENANCE AT DIFFERENT DOSAGES FOR OPIOID DEPENDENCE**

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P CA Date first publication issue 3, 2003

**Background** Methadone maintenance treatment (MMT) is a long term opioid replacement therapy, recognised as effective in the management of opioid dependence. Even if MMT at high dosage is recommended as therapy 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 for opioid dependence in modifying health and social outcomes and in promoting patients' familial, occupational and relational functioning.

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

**Main results** 22 studies were excluded from the review. 21 studies were included; of them, 11 were RCTs with 2279 people randomised and 10 were CPSs with 3715 people followed-up. Outcomes: Retention rate - RCTs: High vs 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 vs 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 vs 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 vs low doses RR=1.81 [1.15,2.85]
Overdose mortality - CPSs: high dose vs 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]

**Reviewers’ 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.

**[12] Substitution Treatment of Injecting Opioid Users for Prevention of HIV Infection**
Gowing L., Farrell M, Bornemann R, Ali R., White J.  Date first publication issue 4, 2004

**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.

**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.

**Main results**
Twenty-eight studies, involving 7900 participants, were included. The majority were not randomised controlled studies. Issues of confounding and bias are discussed. The studies varied in several aspects limiting the extent of quantitative analysis.

**Reviewers’ conclusions**
Oral substitution treatment for opioid-dependent injecting drug users 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. The lack of data from randomised controlled studies limits the strength of the evidence presented in this review. However, these findings add to the stronger evidence of effectiveness of substitution treatment on drug use, and treatment retention outcomes shown by other systematic reviews. On this basis, the provision of substitution treatment for opioid dependence in countries with emerging HIV and injecting drug use problems as well as in countries with established populations of injecting drug users should be supported.

**OPIATE: PSYCHOSOCIAL TREATMENTS**

**[13] Psychosocial and Pharmacological Treatments versus Pharmacological Treatments for Opioid Detoxification**
Amato L, Minozi S, Davoli M, Vecchi S, Ferri M, Mayet S Date first publication issue 4, 2004

**Background**
Different pharmacological approaches aimed at opioid detoxification are effective. Nevertheless a majority of patients relapse to heroin use, and relapse to re-addiction is a substantial problem in the rehabilitation of dependent heroin users. Some studies have suggested that the sorts of symptoms which are most distressing to addicts during detoxification are psychological symptoms 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.
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 The searching process resulted in the identification of 77 different studies: 8 studies met inclusion criteria. These studies considered 5 different psychosocial interventions and 2 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 RR 1.68 (95% CI 1.11-2.55), results at follow-up RR 2.43 (95% CI 1.61-3.66), and compliance RR 0.48 (95% CI 0.38-0.59). In respect of the use of heroin during the treatment, the differences were not statistically significant but favoured the combined treatments.

Reviewers' conclusions Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, 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.

[14] PSYCHOSOCIAL COMBINED WITH AGONIST MAINTENANCE TREATMENTS VERSUS AGONIST MAINTENANCE TREATMENTS ALONE FOR TREATMENT OF OPIOID DEPENDENCE

Amato L, Minozi S, Davoli M, Vecchi S, Ferri M, Mayet S Date first publication issue 4, 2004

Background Methadone maintenance at proper doses is effective in retaining patients in treatment and suppressing heroin use. Questions remain regarding the efficacy of the psychosocial services that are offered by most maintenance programs.

Objectives To evaluate the effectiveness of any psychosocial plus any agonist maintenance treatment versus any agonist treatment alone for opiate dependence in retaining patients in treatment, reducing the use of substances and improving health and social status.

Selection criteria RCTs which focus on any psychosocial plus any agonist compared to any agonist maintenance intervention for opiate dependence. People aged less than 18 and pregnant women were excluded. Psychosocial in combination with antagonist maintenance treatment are excluded too.

Main results The searching process resulted in the identification of 77 different studies: 12 studies met the inclusion criteria. These studies considered 8 different psychosocial interventions and 1 pharmacological treatment: Methadone Maintenance (MMT). The results show additional benefit in adding any psychosocial treatment to standard methadone maintenance treatment in relation to the use of heroin during the treatment RR 0.69 (95% CI 0.53-0.91); no statistically significant additional benefit was shown in terms of retention in treatment RR 0.94 (95% CI 0.85-1.02); and results at follow-up RR 0.90 (95% CI 0.76-1.07).

Reviewers' conclusions The present evidence suggests that adding any psychosocial support to Standard MMT significantly improves the non-use of heroin during treatment. Retention in treatment and results at follow-up are also improved, although this finding did not achieve statistical significance. Insufficient evidence is available on other possible relevant outcomes such as Psychiatric symptoms/psychological distress, Quality of life.

Limitations to this review are imposed by the heterogeneity of the trials both in the interventions and the assessment of outcomes. Results of studies were sometimes in disagreement and because of lack of detailed information no meta analysis could be performed to analyse the results related to the outcomes more often reported as positive results in the single studies. Duration of the studies was also too short to analyse other relevant outcomes such as mortality. In order to study the possible added value of any psychosocial treatment over an already effective treatment such as standard MMT, only big multi site studies could be considered which define experimental
interventions and outcomes in the most standardized way as possible.

[15] **NEW Psychosocial treatment for opiate abuse and dependence**  
Mayet S, Farrell M, Ferri M, Amato, L, Davoli, M. Date first publication issue 1, 2005

**Background:** Substance dependence is a major social and public health problem; therefore it is a priority to develop effective treatments. The treatment of opioid dependence is complex. 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 are many different psychosocial interventions offered to opiate addicts, which are widely spread. 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:** The inclusion criteria for all randomised-controlled trials were that they should focus on psychosocial interventions alone for treating opioid use disorders.

**Main results:** Five studies fit the study criteria. 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 within treatment. This was 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 (standard) therapy. As the studies were heterogeneous, it was not possible to pool the results and perform a meta-analysis.

**Reviewers’ 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. Large-scale randomised trials are required with longer follow up stating methods of randomisation, allocation concealment and blinding. Where possible this should include intention to treat analysis, with power calculations performed prior to the trial. These studies can be designed and delivered to provide usable data for better understanding of this important component of intervention in the field of dependence.

**COCAINE**

[16] **CARBAMAZEPINE FOR COCAINE DEPENDENCE**  
Lima AR, Lima MS, Soares BGO, Farrell M. Date first publication issue 2, 2000; Date of the last substantial update issue 2, 2002

**Background** Cocaine dependence has become a substantial public health problem, developing a significant number of medical, psychological and social problems, including the spread of infectious diseases (e.g. AIDS, hepatitis and tuberculosis), crime, violence and neonatal drug exposure. Although there is no consensus regarding how to treat cocaine dependence, effective pharmacotherapy has a potentially major role to play as part of a broader treatment milieu. The anti-convulsant carbamazepine, a tricyclic medication that is widely used to treat a variety of neurological and psychiatric disorders, has also been used for treatment of cocaine dependence,
although its effectiveness has not been established. **Objectives** To determine whether carbamazepine (CBZ) is effective for the treatment of cocaine dependence.

**Selection criteria** The inclusion criteria for all randomised controlled trials were that they should focus on the use of carbamazepine drugs versus placebo on the treatment of cocaine dependence. Trials including patients with additional diagnosis such as opiate dependence were also eligible.

**Main results** 5 studies were included in the review, with 455 people randomised. No differences were found regarding positive urine sample for cocaine metabolites. Scores on Spielberg State Anxiety Inventory slightly favoured carbamazepine, but didn't reach statistical significance. Dropouts were high in both groups up to 70% in the placebo group. Less dropout occurred in the carbamazepine group (RR 0.87 95%CI 0.71-1.06). When no retention in treatment was due to side effects no differences were found. The number of participants presenting at least one side effect, reported in Kranzler (Kranzler 1995), was higher in the carbamazepine group (RR 4.33 95% CI 1.45-12.91).

**Reviewers' conclusions** There is no current evidence supporting the clinical use of CBZ in the treatment of cocaine dependence. Larger randomised investigation must be considered taking into account that these time-consuming efforts should be reserved for medications showing more relevant and promising evidence.

**ANTIDEPRESSANT FOR COCAINE DEPENDENCE**

Lima MS, Reisser AAP, Soares BGO, Farrell M. Date first publication issue 4, 2001; Date of the last substantial update issue 2, 2003

**Background** Cocaine dependence is a common and serious condition, which has become a substantial public health problem. 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 conduct a systematic review of all RCTs on the use of antidepressants for treating cocaine dependence.

**Selection criteria** The inclusion criteria for all randomised controlled trials were that they should focus on the use of antidepressants on the treatment of cocaine dependence. Trials including patients with additional diagnosis such as opiate dependence were also eligible.

**Main results** 18 studies were included in the review, with 1177 people randomised. 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.

**Reviewers' 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.

**DOPAMINE AGONISTS FOR COCAINE DEPENDENCE**

Soares BGO, Lima MS, Reisser AAP, Farrell M. Date first publication issue 4, 2001; Date of
Background 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 (e.g. AIDS, hepatitis and tuberculosis), crime, violence and neonatal drug exposure. 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.

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.

Reviewers’ 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.

AMPHETAMINE

[19] TREATMENT FOR AMPHETAMINE ABUSE AND DEPENDENCE
Srisurapanont M, Jarusuraisin N, Kittiratanapaiboon P Date first publication issue 4, 2001

Background The ease of synthesis from inexpensive and readily available chemicals makes possible the wide spread of amphetamine dependence and abuse. Amphetamine use is of concern because it causes a variety of devastating health consequences, including physical and neurological disorders due to amphetamines, amphetamine-induced mental disorders, health consequences of amphetamine use and social consequences of amphetamine use.

Objectives To search and determine 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.

Reviewers’ conclusions The evidence about the treatment for amphetamine dependence and abuse is very limited. It shows that 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, in particular proximal 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.

[20] TREATMENT FOR AMPHETAMINE PSYCHOSIS DISORDER
Srisurapanont M, Kittiratanapaiboon P. Jarusuraisin N. Date first publication issue 4, 2001

Background During the phase of chronic, high-dose consumption of amphetamines, many amphetamine users may have the 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 search and determine risks, benefits, and costs of a variety treatments for amphetamine psychosis.

Selection criteria All relevant randomised controlled trials (RCTs) and clinical trials (CCTs) were included. Participants were people with amphetamine psychosis, diagnosed by any set of criteria. Any kinds of biological and psychological treatments both alone and combined were examined. A variety of outcomes, for example, number of treatment responders, score changes, were considered.

Main results The comprehensive searches found no controlled trials of treatment for amphetamine psychosis meeting the criteria for considering studies.

Reviewers’ conclusions The evidence about the treatment for amphetamine psychosis is very limited. To our knowledge, no controlled trials of treatment for amphetamine psychosis have been carried out. The results of two studies in amphetamine users 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 risks and benefits of giving an antipsychotic injection should be further investigated in amphetamine psychotic patients. Medications that have been used for the treatment of acute exacerbation of schizophrenia should be studied in amphetamine psychotic patients. The medications that may be of interest are conventional antipsychotics, newer antipsychotics and benzodiazepines. However, naturalistic studies of amphetamine psychotic symptoms and course are also crucial for the development of study designs appropriate for further treatment studies of amphetamine psychosis.

[21] TREATMENT FOR AMPHETAMINE WITHDRAWAL
Srisurapanont M, Kittiratanapaiboon P. Jarusuraisin N. Date first publication issue 4, 2001

Background Amphetamine withdrawal has been less studied although it is a common problem with a prevalent rate of 87% among amphetamine users. Its symptoms, in particular intense craving, may be a critical factor leading to relapse of amphetamine use. In clinical practice, treatment for cocaine withdrawal has been recommended for the management of amphetamine withdrawal although the pharmacodynamic and pharmacokinetic properties of these two substances are not the same.

Objectives To search and determine risks, benefits, and costs of a variety of treatments for the management of amphetamine withdrawal.

Selection criteria All relevant randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were included. Participants were people with amphetamine withdrawal, diagnosed by any set of criteria. Any kinds of biological and psychological treatments both alone and combined were examined. A variety of outcomes, for example, number of treatment responders, score changes, were considered.
Main results The results of two studies have shown some benefits of amineptine in the treatment of amphetamine withdrawal. Those benefits can be seen in the respects of discontinuation rate and global state, as measured by Clinical Global Impression Scale. However, no direct benefit of amineptine on amphetamine withdrawal symptoms or craving was shown.

Reviewers' conclusions The evidence about the treatment for amphetamine withdrawal is very limited. Amineptine has limited benefits on some amphetamine withdrawal symptoms. Due to a number of reports of amineptine abuse, it has been withdrawn from the market for a few years. At present, no available treatment has been demonstrated to be effective in the treatment of amphetamine withdrawal. The medications that should be considered for further treatment studies may be those with the propensities to increase dopamine, norepinephrine and/or serotonin activities of the brain. Naturalistic studies of amphetamine withdrawal symptoms and course are also crucial for the development of study designs appropriate for further treatment studies of amphetamine withdrawal.

ALCOHOL

[22] OPIOID ANTAGONISTS FOR ALCOHOL DEPENDENCE
Srisurapanont M, Jarusuraisin N, Kittiratanapaiboon P. Date first publication issue 3, 2000; Date of the last substantial update issue 1, 2005

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 recommencement of alcohol consumption in patients with alcohol dependence in comparison to placebo, other medications and psychosocial treatments. In addition, discontinuation rate, death, patient satisfaction, functioning, health-related quality of life and economic outcomes were also evaluated.

Selection criteria All relevant randomised controlled trials (RCTs) were included. Participants were people with alcohol dependence. Naltrexone (NTX), nalmefene (NMF) and other opioid antagonists with/without other biological or psychosocial treatments were examined. Two primary outcomes were number of participants with relapses (including those who return to heavy drinking) and number of participants who return to drinking. Other outcomes of interest were time to first drink, percentage or number of drinking days, number of standard drinks, craving, percentage or number of days or episodes of heavy drinking, amount of alcohol consumed, discontinuation rate, patient satisfaction, impaired function, health-related quality of life, economic and death.

Main results The review included 29 RCTs presented in 36 articles. Except two RCTs 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 was likely to decrease the return to drinking [RR (95% CI) = 0.87 (0.76 to 1.00)]. In the respect of acceptability, NTX treatment significantly diminished treatment withdrawal [RR (95% CI) = 0.82 (0.70 to 0.97)]. While a medium-term treatment of NTX gave no benefit in the respect of relapse prevention, it was found to be beneficial on two of four secondary outcomes by 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 primary and secondary 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.

Reviewers' conclusions The review findings support that short-term treatment of NTX decreases the chance of alcohol relapses for 36% (number-needed-to-treat or NNT = 7) and likely to reduce the chance of returning to drinking for 13% (NNT = 12). In comparison to placebo group, NTX treatment can lower the risk of treatment withdrawal in alcohol-dependent patients for 28% (NNT = 13). Some major limitations of the available evidence include short study duration in many trials, small sample sizes in most trials and lack of data on psychosocial benefits. In conclusion, NTX should be accepted as a short-term treatment for alcoholism. Strategies to improve adherence to NTX treatment, eg, PSTs 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. Due to too little evidence, NMF should have no role for the treatment of alcohol dependence.

[23] **PRIMARY PREVENTION FOR ALCOHOL MISUSE IN YOUNG PEOPLE**
Foxcroft DR, Ireland D, Lister-Sharp DJ, Lowe G, Breen R. Date first publication issue 3, 2002;

**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, drunkeness, 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 drunkeness) 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).

**Reviewers’ conclusions:** 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.
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References of published Protocols
