AN OVERVIEW OF COCHRANE SYSTEMATIC REVIEWS OF PHARMACOLOGICAL AND PSYCHOSOCIAL TREATMENT OF OPIOID DEPENDENCE

Background paper for the meeting
"1st Consultation on Technical Guidelines for Treatment of Opioid Dependence"
Geneva, 1-4 November 2005

Prepared by

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INTRODUCTION

Rationale for this series of systematic reviews on pharmacological and psychosocial treatments for opiate abuse and dependence

Abuse and dependence on opioid drugs are major health and social issues in many societies. While the prevalence of opioid dependence is generally low, the burden of disease is substantial. The United Nations International Drug Control Programme conservatively estimates that 80 million people worldwide (approximately 1 in 700) currently abuse heroin and other opiate-type substances (UNIDCP 2001). Although opiates are relatively free from long-term adverse health consequences when consumed in a safe manner, they are considered the most harmful of all illicit drugs (UNIDCP 2001), mainly for risks that are consequences of the illegal market. In Europe, the total number of problematic opiate users is estimated to be as many as 1.5 million people (4.0 per 1000 population). The burden to the individual user and the community is shown by a high risk of mortality (Darke 1996;Davoli 1997;Hall 1997) and morbidity (Hagan 2001). Mortality of untreated heroin dependence is consistently estimated at 1-3% per year, at least half of which is due to heroin overdose (Darke 2003;Sporer 1999). Follow-up studies have found that this risk continues for many years after the diagnosis of heroin dependence is made (Haastrup 1984; Hser 1993; Goldstein 1995; Sanchez 1995; Bargagli 2001), indicating that heroin dependence may be regarded as a chronic condition. In fact, opioid addiction is currently defined as a "chronic, relapsing disorder" (Leshner 1998;Dole 1967; Mc Lellan 2000).
Beyond mortality and morbidity, heroin dependence inflicts enormous social and economic costs due to crime, unemployment, relationship breakdown and the cost of law enforcement. In developed countries this has been repeatedly estimated at close to 0.4% of GDP (UNIDCP 2001).

Treatment of drug addiction has been proven to be cost effective (Fletcher 1999; Gossop 2002). Different approaches to assisting dependent heroin users include detoxification and relapse prevention treatment programs (including naltrexone-assisted relapse prevention), therapeutic communities, outpatient drug-free counselling and long-term opiate substitution (or maintenance).
Management of withdrawal symptoms cannot be considered a treatment itself but it is often the first step for many forms of longer-term treatment. A number of different approaches to the management of opioid withdrawal are in use around the world.
Different substances are used also for the management of long-term opioid replacement therapies Substitutive maintenance treatments such as methadone have consistently been shown to enable dependent heroin users to achieve a sustained reduction in their heroin use (Ward 1999; Dole 1969; Yancovitz 1991; Gunne 1981; Simpson 1997; Newman 1979) at least for the duration of the maintenance treatment. The basis of maintenance treatments such as methadone is that by substituting methadone for heroin, users will be more able to regain control over their heroin use. Once on a stable dose, experiences of intoxication or withdrawal are infrequent. The heritability, course and response to medications suggest that people who are opioid dependent will benefit from patterns of treatment similar to those provided to patients with other chronic disorders (e.g. schizophrenia, depression, diabetes), with continuing care and monitoring over time (McLellan 2000; O'Brien 1997). This awareness, in addition to the epidemiological evidence of the drug related risks affecting the addicted population , has promoted the development of the maintenance therapies in opiate addiction treatment (Brettle 1991;Ward 1999). . According to this approach, treatment is aimed at increasing time between relapses of heroin use, and to reduce intensity of relapse, the frequency and length of the relapse (Leshner 1998), overdoses' risk, criminal activity, HIV sero-conversion and finally to promote psychosocial adjustment (Leshner 1998; Ward 1999; Farrell 1994).
As part of the Cochrane collaboration, the Cochrane review group on Drugs and Alcohol (Davoli 2000) produces updates and disseminates systematic reviews of trials on the prevention, treatment and rehabilitation of the problematic use of drugs and alcohol. As of November 1st 2006 the group published 7 reviews on treatments aimed at opioid detoxification and 8 reviews for opiate maintenance interventions.

Details of the methods and results of each review are available in the Cochrane Library (www.thecochranelibrary.com).

Outline of this series of reviews
Various types of interventions have been assessed as treatments for opioid withdrawal and maintenance. In this series of systematic reviews they have been grouped as follows:

Treatments aimed at opioid Detoxification
1. Tapered methadone
2. Buprenorphine
3. Alpha$_2$ Adrenergic Agonists
4. Opioid antagonists associated with minimal sedation
5. Opioid antagonists associated with heavy sedation or anaesthesia
6. Psychosocial and pharmacological treatments
7. Inpatient versus other settings

Treatments aimed at Maintenance for opiod dependence
8. Methadone maintenance
9. Different dosages of methadone maintenance
10. Substitution treatment for injecting opioid users for prevention HIV infection
11. Buprenorphine
12. LAAM
13. Heroin maintenance
14. Naltrexone
15. Psychosocial and pharmacological treatments
16. Psychosocial treatments

Methods

Search strategy: Electronic searches of The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycINFO, using a specific search strategy for each DataBase. Furthermore, scan of references of relevant articles, hand searching and through AMEDEO (http://www.amedeo.com) we obtain weekly emails with bibliographic list about new scientific publications in the field of addiction from the following journals: Lancet, British Medical Journal, Addiction, Alcohol, Alcohol and Alcoholism, Alcoholism and Clinical Experimental Research, American Journal of Drug and Alcohol Abuse, American Journal of Psychiatry, Archives of General Psychiatry, Annals of Epidemiology, Journal of Psychiatric Research, Journal of Substance Abuse Treatment, The American Journal of Medicine, The International Journal of Drug Policy, Journal of Clinical Epidemiology, Journal of Clinical Psychiatry, Journal of Affective Disorders, Biomed Central, Drug and Alcohol Dependence, New England Journal of Medicine. Some of the main electronic sources of ongoing trials (National Research Register, meta-Register of Controlled Trials; Clinical Trials, Trials Central) are searched for ongoing trials. Once the strategy is run on the databases listed below, the bulk of results are checked for relevance using some specific keywords (i.e. surgery, epidural, cancer, pain etc. which tend to interfere with our terms). The remaining references are evaluated by the titles and, when necessary, the abstracts. The full text of the articles is obtained to identify the study design. The studies are coded on the basis of a series of rules developed in collaboration with other Cochrane Groups on mental health which are in the process of creating a common register of trials.
All RCTs and CCTs from the CDAG Specialized Register can be found on the Cochrane Library by doing a search on SR-ADDICTN.

Selection criteria: All Randomised Controlled Trials (RCTs) and Clinical Controlled Trials (CCTs) that describe an active intervention aimed at detoxification or maintenance for opioid abuse/dependence. The inclusion of the other study designs was originally left to the choice of the single authors and later opens to non RCTs only when RCTs were not available

Types of studies: RCT, CCT and CPS

Quality assessment:
For RCT and CCT
- randomisation, i.e. the fact that the treatment/s is/are assigned by chance;

- allocation concealment, in relation to the unawareness of the researcher on the next assignment, to avoid selection bias;
- blinding of those providing and receiving the intervention after the allocation, to avoid performance bias for providers and to avoid contamination, systematic differences in compliance and systematic differences in the placebo effect;
- recording how many patients were lost to follow up in each group and for each outcome measure to estimate the attrition bias;
- blinding of the outcome assessor to avoid detection bias.

For non RCTs
- description of the base population, to estimate the role of selection effects;
- identification and control of all known confounding factors;
- adequate management of the drop-outs.

Data collection: For each study finally selected for inclusion, data extraction was completed when possible directly from the paper independently by two reviewers considering the outcomes and the methodological quality. In case additional information is needed, contact is sought with the authors.

Analysis: Given that most of trials included in the reviews are based on high rates of the events considered and between trials heterogeneity, when metanalysis is possible, the authors used the Relative Risk (RR) with a random effect model to pool the data

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TREATMENTS AIMED AT OPIOID DETOXIFICATION

Review 1.
Methadone at tapered dosages for the management of opioid withdrawal
First published CLIB issue 1, 2002; substantially updated issue 3, 2005

SUMMARY

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.

Main results: 16 trials involving 1187 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) 1.12; 95% CI 0.94 to 1.34 and abstinent 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. 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.

Conclusions: 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.

DESCRIPTION OF STUDIES

Types of studies: All Randomised Controlled Trials and Clinical Controlled Trials on tapered methadone treatment (maximum 30 days) to manage withdrawal from opiates.

Types of interventions:
Experimental interventions: Methadone aimed at the detoxification from opiates, maximum length of treatment: 30 days.
Comparison interventions: Other opioid agonists (LAAM, Buprenorphine, propoxyphene, etc); Adrenergic agonists (clonidine, lofexidine, guanfacine); Opioid antagonists (naltrexone, naloxone); Placebo. All aimed at the detoxification from opiate.

The search strategy resulted in the identification of 49 studies.

Excluded studies: 33 studies did not meet criteria for inclusion in this review
Included studies: 16 studies meet the inclusion criteria for this review (See Table of included studies).

Methodological Quality: 16 RCT, 5/16 studies with an adequate allocation concealment; 13/16 studies were double blind; in 13 studies the investigator or the staff personnel who assessed the outcome measure was blind to treatment allocation

Characteristics of the studies: Duration of trials range 3 to 30 days. The countries in which the 16 studies were conducted are: USA (5), United Kingdom (4), Spain (4), China, Italy and Germany (1 each). 11 trials were conducted with inpatients, five with outpatients.

Characteristics of the participants: 1187 opiate addicts

Comparisons:
- Tapered methadone versus any other pharmacological treatment 16 studies, 1187 participants
- Tapered methadone versus adrenergic agonist 11 studies, 952 participants (Bearn 1996; Camí 1985; Dawe 1995; Gerra 2000; Howells 2002; Jiang 1993; Kleber 1985; San 1990; San 1994; Umbricht 2003; Washton 1989);
- Tapered methadone versus other opioid agonist 4 studies 201 participants; 2 studies (Seifert 2002; Umbricht 2003) compared methadone with buprenorphine, 1 study (Sorensen 1982) with LAAM , 1 study (Tennant 1975) with propoxyphene;
- Tapered methadone versus chlordiazepoxide 1 study, 24 participants;

- Tapered methadone versus placebo 1 study, 22 participants.

Treatment regimes: Methadone: mean starting dose 29 mg/day (range 20 to 58); Adrenergic agonists: clonidine (9 comparisons) mean dose 0.84 mg/day (range 0.12 to 1.35), lofexidine (2 comparisons) mean dose 1.33 mg/day (range 0.60 to 2.00), guanfacine (3 comparisons) mean dose 3.53 mg/day (range 3.00 to 4.00); Buprenorphine. mean dose 2.27 mg/day (range 0.4 to 4.0); LAAM: dosage stated as "parallel to methadone ", the starting dose of methadone in this study was 30 mg; Propoxyphene: starting dose 800 mg/day; Chlordiazepoxide: 200 mg/day.

Outcomes: Completion of treatment; Duration and severity of signs and symptoms of withdrawal; Side effects; Use of primary substance; Abstinent at follow-up;

RESULTS

Completion of treatment
- Tapered methadone versus any other pharmacological treatment, 11 studies, 748 participants: RR 1.12 (CI 95% 0.94 to 1.34), the difference was not statistically significant;
- Tapered methadone versus adrenergic agonist: 7 studies, 577 participants RR 1.09 (CI 95% 0.90 to 1.32), the difference was not statistically significant;
- Tapered methadone versus other opioid agonist: 4 studies, 165 participants RR 1.25 (CI 95% 0.80 to 1.93), the difference was not statistically significant;
- Tapered methadone versus chlordiazepoxide: 1 study, 24 participants RR 1.06 (CI 95% 0.37 to 3.00), the difference was not statistically significant;
- Tapered methadone versus placebo: 1 study, 22 participants RR 3.33 (CI 95% 1.25 to 8.91), in favour of methadone.

Duration and severity of signs and symptoms of withdrawal:
- Tapered methadone versus adrenergic agonist, 11 studies, 748 participants: 5 trials did not find any statistical significant difference in the two groups, 3 trials reported more severe withdrawal symptoms in the adrenergic agonist group but only in some days of the detoxification period, 2 trials reported statistically lower symptoms in methadone group, 1 study reported significant higher symptoms in the methadone group.
- Tapered methadone versus other opioid agonist, 4 studies, 201 participants: methadone versus buprenorphine, 1 study find less withdrawal symptoms in buprenorphine group in the 1° and 2° weeks of treatment and the other did not find any statistical significant difference in the two groups; methadone versus LAAM: withdrawal symptoms were generally higher in the methadone group and this difference was statistically significant on days 8, 12, 15, 16 and 17; methadone versus Propoxyphene: no statistically significant differences were found between the groups.
- Tapered methadone versus chlordiazepoxide: 1 study, 24 participants: few differences between the two groups before day 10, significant higher scores in the chlordiazepoxide group only on day 3; at the end of the study, the scores were higher in the methadone group but not statistically significant.
- Tapered methadone versus placebo: 1 study, 22 participants: higher scores in the placebo groups, 8/11 placebo-treated patients needed to be switched from placebo to methadone because the symptoms experienced.

Side effects
- Tapered methadone versus adrenergic agonist, 8 studies, 608 participants: Regarding the effects on blood pressure, 6 studies reported lower mean blood pressure in participants treated with adrenergic agonists especially in some days of treatment; 1 study reported that more participants treated with clonidine had one or more adverse experiences (18/25 versus 10/25); 1 study no showed significant differences between the groups and scores of MMPI showed in the hysteria scale significant higher scores in methadone group.
- Tapered methadone versus other opioid agonist: 3 studies, 139 participants: comparing methadone versus buprenorphine: 1 study referred that systolic blood pressure decreased significantly in the buprenorphine group during the treatment; methadone versus LAAM: one overdose accident occurred in LAAM group, possibly due to combination with alcohol; methadone versus propoxyphene: only one significant difference could be found between the two treatment groups: 17/36 patients in propoxyphene group compared to 6/36 in methadone reported euphoria.
- Tapered methadone versus chlordiazepoxide: 1 study, 24 participants: in methadone group relative bradycardia is more present in the first days of treatment and the difference with respect to the chlordiazepoxide group became statistically significant on days 4 and 7. Mean pupil size was less in

methadone group during the treatment period and the difference was statistically significant on day 5, similarly mean temperature was lower in this group on day 3.

Use of primary substance

Results as reported in the articles are hardly informative, and data presented as number of positive tests over number of tests cannot be properly analysed through meta-analysis; in fact using tests instead of the subjects as unit of analysis violates the hypothesis of independence among observations, and makes the results of tests done in each patient not independent.

- Tapered methadone versus adrenergic agonists, 1 study, 98 participants: Only 1/11 study, no significant difference was found between the groups.
- Tapered methadone versus other opioid agonists, 2 studies, 133 participants: methadone versus LAAM: proportion of participants using opiates never dropped below 50% for any group at any time, the groups did not differ in the percentage of urine samples that contained opiates overall; methadone versus propoxyphene: number of participants who had opiate negative urine on at least on occasion: 27/36 (75%) in methadone group and 19/36 (53%) in propoxyphene group, the difference is not statistically significant.

Results at follow-up

Abstinent at follow-up

- Tapered methadone versus any other pharmacological treatment, 2 studies 97 participants: numbers of participants abstinent at one month follow-up RR 1.17 (CI 95% 0.72 to 1.92), the difference was not statistically significant. (Figure 1.5)
- Tapered methadone versus Adrenergic agonist: 1 study, 49 participants Kleber 1985: abstinent at one month follow-up: 6/18 in methadone group and 4/15 in the clonidine one; at three months 5/19 in methadone and 4/15 in clonidine groups; at six months 7/18 in methadone and 3/13 in clonidine group. The differences were never statistically significant.
- Tapered methadone versus Other opioid agonist: 2 studies 133 participants: methadone versus LAAM the data were reported for all the participants without distinction between the groups of treatment 24/49 reported that they abstained from heroin >1 day after detoxification, at 3 months 2/49 abstinent, 25/49 sought further treatment and 9/49 enrolled in methadone maintenance treatment; methadone versus propoxyphene: at 1 month follow-up number of abstinent were 15/32 in the methadone group and 13/32 in propoxyphene group, the difference is not statistically significant.

Naloxone challenge

- Tapered methadone versus any other pharmacological treatments, 2 studies 124 participants, both comparing methadone versus adrenergic agonist: 1 study reported rate of participants who accepted and continued naltrexone treatment: in the methadone group 9/34, in clonidine 5 days 17/32, the difference was statistically significant in favour of clonidine; the study of Washton referred data for all the participants without distinction between the groups: of the eight participants who were opiate free at completion of the study, six began treatment with naltrexone.

Reviewers' conclusions

Implications for practice

The conclusions of the 15 studies that compared methadone with other pharmacological treatments aimed at detoxification, showed no substantial clinical difference between the two treatments in terms of completion of treatment, degree of discomfort and results at follow-up. The study that compared tapered methadone with placebo showed more severe withdrawal symptoms and more drop outs in the placebo group. There has been a general pessimism among both clinicians and researchers about the utility of brief detoxification treatment, because many patients soon returned to regular heroin use. This pessimism is probably based on the unrealistic expectation that a brief, inexpensive intervention could dramatically alter the course of a chronic, relapsing disorder like heroin addiction. The investment in methadone detoxification could be justified if more modest goals were being achieved like: the reduction, even temporarily, of the daily heroin dosage, with its consequent reduction of dependence on illegal income and the possibility of reaching drug addicts who would otherwise not have applied for treatment.

Implications for research

The capacity of tapered methadone to ameliorate the signs and symptoms of heroin withdrawal is well known, but further evaluation research is necessary to determine the most cost-effective ways to attain these goals. Conducting trials in the field of drug addiction is more challenging than in other clinical fields. Nevertheless, it would be useful if not essential to follow to ensure that the studies have a random allocation and double blindness and that this is reported in the published papers. To enable comparison and pooling of results standardised criteria for reporting urine analysis results should be used. When different rating

instruments are used researchers should indicate the scores to represent boundaries of mild, moderate and severe withdrawal to allow comparison of results between studies.

Review 2

Buprenorphine for the management of opioid withdrawal

first published CLIB issue 3, 2000; substantially updated issue 4, 2004

SUMMARY

Objectives: To assess the effectiveness of interventions involving the use of buprenorphine to manage opioid withdrawal, in terms of withdrawal signs and symptoms, completion of withdrawal and adverse effects.

Main results: 14 studies involving 784 participants were included. Completion of treatment is significantly more likely with buprenorphine than clonidine RR 1.38 (CI 95% 1.21 to 1.57); no statistically significant difference in rates of completion of treatment for buprenorphine compared to methadone in reducing doses. 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.

Conclusions: Buprenorphine is more effective than clonidine for the management of opioid withdrawal. There appears to be no significant difference between buprenorphine and methadone in terms of completion of treatment, but withdrawal symptoms may resolve more quickly with buprenorphine.

DESCRIPTION OF STUDIES

Types of studies: Randomised and quasi-randomised controlled clinical trials and prospective controlled cohort studies that provided detailed information on the type and dose of drugs used and the characteristics of patients treated.

Types of interventions:
Experimental interventions: studies involved the administration of buprenorphine to ameliorate the signs and symptoms of opioid withdrawal.
Comparison interventions: studies involved the use of reducing doses of methadone, an alpha2 adrenergic agonist, symptomatic medications or placebo, or buprenorphine-based regimes differing in amount, duration, or rate of taper of buprenorphine. Symptomatic medications are defined as benzodiazepines, anti-emetics, anti-diarrhoeas, anti-psychotics, anti-spasmodic, muscle relaxants or non-opioid analgesics, administered in combination as needed, or according to a defined regime.

The search strategy resulted in the identification of 70 different studies, involving the administration of buprenorphine in a context of opioid withdrawal.

Excluded studies: 54 studies did not meet the criteria for inclusion in this review
Included studies: 14 studies involving 784 participants met the inclusion criteria for this review QUALE? (See Table of included studies).

Methodological Quality: 12 RCTs; Methodological quality was not used as a criterion for inclusion in the review. The authors did not report the results of quality assessment, however, where possible, the impact of methodological quality was judged through sensitivity analysis. This involved repeating meta-analyses with studies non RCT being included or excluded from meta-analyses. The only outcome for which sufficient data were available to support sensitivity analyses was completion of treatment for buprenorphine compared to clonidine.

Characteristics of the studies: Duration of treatments range 3-15 days; the countries in which the 14 studies were conducted are not reported. 8 studies inpatient, 6 outpatient treatment setting

Characteristics of the participants: 784 participants withdrawing from heroin or methadone, or both

Comparisons:

- Buprenorphine versus clonidine 7 studies (Cheskin 1994, Fingerhood 2001, Janiri 1994, Lintzeris 2002, Nigam 1993, O'Connor 1997, Umbricht 2003), 545 participants;
- Buprenorphine versus methadone 3 studies (Petitjean 2002, Seifert 2002, Umbricht 2003) 102 participants;
- Different rates of buprenorphine dose reduction 3 studies (Amass 1994, Assadi 2004, Wang 1996) 71 participants;
- Three different starting doses of buprenorphine 1 study (Liu 1997) 60 participants;
- Buprenorphine versus oxazepam 1 study (Schneider 2000) 27 participants.

Treatment regimes: Buprenorphine starting dose range 0.3 mg-10 mg/day; Clonidine starting dose range 0.4-2.7 mg/day; Methadone starting dose range 20-40 mg/day; Oxazepam 90 mg/day.

Outcomes: Completion of treatment; Intensity of withdrawal; Side effects

RESULTS

Completion of treatment
- Buprenorphine versus clonidine 6 studies, 473 participants, RR 1,38 (CI 95% 1,21-1,57) results in favour of buprenorphine (Figure 2.1); if the study with high risk of bias (1 non RCT) was excluded, the result did not change RR 1,32 (CI 95% 1,14-1,52)
- Buprenorphine versus methadone 2 studies, 63 participants, RR 1,14 (CI 95% 0,87-1,50), no statistically significant differences (Figure 2.2)
- Different rates of buprenorphine dose reduction, 1 study, 8 participants reported that rapid drop-out occurred in the rapid taper group once the detoxification phase commenced
- Three different starting doses of buprenorphine, 1 study, 60 participants, no significant difference between the groups
- Buprenorphine versus oxazepam, 1 study, 27 participants 11 out of 15 (73%) treated with buprenorphine and seven of 12 (58%) treated with oxazepam completed treatment. The difference was not statistically significant.

Intensity of withdrawal
- Buprenorphine versus clonidine, 3 studies, 266 participants reported a mean peak withdrawal score. The combined result favours buprenorphine and is statistically significant (standardised mean difference -0.61, 95% confidence interval -0.86 to -0.36, P < 0.001).
- Buprenorphine versus methadone 2 studies, 63 participants; data suggest no, or very little, difference in the severity of withdrawal managed with tapered buprenorphine or tapered methadone.
- Different rates of buprenorphine dose reduction, 3 studies, 71 participants, withdrawal signs and symptoms are more marked when buprenorphine is tapered rapidly, rather than gradually. Muscle aches and insomnia appear to be the main symptoms, with nausea, vomiting, rhino rhea and sweating also occurring in some individuals.
- Three different starting doses of buprenorphine, 1 study, 60 participants, no significant difference between the groups in severity of withdrawal.
- Buprenorphine versus oxazepam, 1 study, 27 participants, and the mean withdrawal score was significantly lower in the buprenorphine group, compared to the oxazepam group, on days three, five and seven. The maximum mean score reported for the buprenorphine group was around 0.7 on day three, compared to 1.2 on days five and seven in the oxazepam group.

Side effects
- Buprenorphine versus clonidine, 5 studies, 277 participants, the data prevent the possibility of pooling the results, but it appears that there are fewer adverse effects when opioid withdrawal is managed with buprenorphine rather than clonidine. In particular clonidine is associated with a higher incidence of symptoms of hypotension (light-headed, dizzy) and lethargy or tiredness, while buprenorphine is associated with a higher incidence of headache and precipitated withdrawal;
- Buprenorphine versus methadone, 1 study, 26 participants reported no severe side effects in either buprenorphine or methadone groups;
- Different rates of buprenorphine dose reduction, 2 studies, 63 participants, one study stated there were none side effects reported and the other reported no significant difference in the total side effects profile of the two groups;
- Buprenorphine versus oxazepam, 1 study, 27 participants reported no severe side effects in either group and no significant differences in blood pressure or heart rate.

Reviewers' conclusions

Implications for practice

Buprenorphine is probably more effective than clonidine in reducing the signs and symptoms of opioid withdrawal and in supporting the completion of withdrawal and is also associated with fewer adverse effects than is clonidine, particularly symptoms of hypotension and lethargy/tiredness.

On the basis of available data, buprenorphine and methadone in tapered doses appear to have similar efficacy in the management of opioid withdrawal, but withdrawal symptoms may resolve more quickly with buprenorphine. However, additional research is required. In particular, information is needed on the extent of rebound withdrawal following cessation of buprenorphine and methadone in tapered doses.

For the management of withdrawal following a period of buprenorphine maintenance treatment, gradual tapering of the dose of buprenorphine appears to be more effective than rapid tapering. Again this is an aspect on which further research is desirable.

Implications for research

Data on the effectiveness of buprenorphine for the management of opioid withdrawal remain limited. Many aspects of treatment protocol, including doses used, as well as frequency, and duration of administration of buprenorphine need to be investigated in order to determine the most effective way of using buprenorphine to manage opioid withdrawal. Effectiveness should be assessed in terms of objective signs and subjective symptoms that are typical of the acute phase of withdrawal, the nature of residual signs and symptoms that are not effectively suppressed by buprenorphine, the occurrence of adverse effects and the completion of withdrawal, assessed using objective criteria such as negative urine tests (particularly for outpatient withdrawal) and/or naloxone challenges. The management of withdrawal following a period of buprenorphine maintenance treatment is another aspect on which information is currently lacking.

Review 3

Alpha2 adrenergic agonists for the management of opioid withdrawal

first published CLIB issue 1, 2001; substantially updated issue 4, 2004

SUMMARY

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

Main results: 22 studies, involving 1709 participants, were included. 13 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. Comparing adrenergic agonist with reducing doses of methadone, for withdrawal intensity 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. 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.

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.

DESCRIPTION OF STUDIES

Types of studies: Randomised, quasi-randomised controlled clinical trials and prospective controlled cohort studies that provided detailed information on the type and dose of drugs used and the characteristics of patients treated.

Types of interventions:
Experimental interventions: Interventions involved the administration of an alpha2 adrenergic agonist (clonidine, lofexidine, guanfacine or guanabenz acetate) as the principal medication to manage the signs and symptoms of acute opioid withdrawal.
Comparison interventions: Interventions involved the use of reducing doses of methadone, symptomatic medications or placebo, or an alpha2 adrenergic agonist regime different to the experimental intervention. Symptomatic medications are defined as benzodiazepines, anti-emetics, anti-diarrhoeal, anti-psychotics, anti-spasmodic, muscle relaxants or non-opioid analgesics, administered in combination as needed or according to a defined regime.

The search strategy resulted in the identification of 62 studies, with treatment regimes involving the administration of alpha2 adrenergic agonists.

Excluded studies: 40 studies did not meet the criteria for inclusion in this review
Included studies: 22 studies, involving 1709 participants, met the inclusion criteria for this review. (See Table of included studies).

Methodological Quality: 18 RCTs, 4 non-randomised controlled trials. Methodological quality was not used as a criterion for inclusion in the review. The authors did not report the results of quality assessment, however, where possible, the impact of methodological quality was judged through sensitivity analysis. This involved repeating meta-analyses with studies non RCT being included or excluded from meta-analyses. The only outcome for which sufficient data were available to support sensitivity analyses was completion of withdrawal for alpha2 adrenergic agonists compared to reducing doses of methadone.

Characteristics of the studies: Duration of trials range 7-10 days. The countries in which the studies were conducted are: United Kingdom (6), Spain and USA (3 each), India and Italy (2 each), Switzerland, China, Taiwan, Germany and Hungary (1 each). 15 studies were conducted with inpatients, 7 with outpatients.

Characteristics of the participants: 904 participants were treated with an alpha2 adrenergic agonist, of these, 488 with clonidine, 301 with lofexidine, 99 with guanfacine, and 16 with tizanidine (a skeletal muscle relaxant with alpha2 adrenergic agonist properties). In 11 studies participants were all withdrawing from heroin, in

nine studies either from methadone, or stabilised on methadone prior to the withdrawal treatment. In 1 study 60% of participants were dependent on heroin and 23% on buprenorphine. In the remaining study participants were withdrawing from either heroin or methadone.

Comparisons:
- Adrenergic agonist versus methadone, 12 studies (Bearn 1996; Bearn 1998; Beswick 2003; Cami 1985; Gerra 2000; Howells 1999; Jiang 1993; Kleber 1985; San 1990; San 1994; Senay 1983; Washton 1981), 1008 participants;
- Two different alpha2 adrenergic agonists 4 studies (Carnwath 1998; Kahn 1997; Lin 1997; San 1990), 227 participants;
- Adrenergic agonist versus placebo, 2 studies (Benos 1985; Gerra 1995), 102 participants;
- Adrenergic agonist versus meperidine (pethidine), 1 study (Malhotra 1997), 39 participants;
- Adrenergic agonist versus a combination of the anti-depressant mianserin, and the anti-epileptic carbamazepine, 1 study (Bertschy 1997), 32 participants;
- Adrenergic agonist versus a combination of the benzodiazepine chlordiazepoxide, and the neuroleptic chlorpromazine, 1 study (Gupta 1988), 120 participants;
- Adrenergic agonist versus a combination of symptomatic medications, 1 study (Li 2002), 52 participants;
- Tizanidine, a skeletal muscle relaxant with alpha2 adrenergic agonist properties versus symptomatic medications, 1 study (Sos 2000), 26 participants.

Treatment regimes: Adrenergic agonists are typically administered orally as two to four doses per day. Clonidine starting dose 0.1 to 0.2mg/dose increasing to a maximum of around 1.0mg/day, and lofexidine at 0.4 to 0.6mg/dose increasing to a maximum of around 2mg/day. Maximal doses administered two to four days after cessation of opioids, then tapered,

Outcomes: Completion of treatment; Intensity of withdrawal; Side effects

RESULTS

Completion of treatment
- Adrenergic agonist versus methadone, 9 studies, 612participants: RR 0,89 (CI 95% 0,77-1,03), no differences between the treatments ; if the studies with high risk of bias (3 non RCT) were excluded, the result did not change RR 1,05 (CI 95% 0,86-1,27);
- Two different alpha2 adrenergic agonists, 1 study, 50 participants: 17/26 (65%) in lofexidine group and 12/24 (50%) in clonidine, in favour of lofexidine;
- Other comparison: number of participants that completed the treatment: adrenergic agonist versus placebo (1 study, 50 participants) 22/25 (88%) in clonidine group and 11/25 (44%) in placebo, favour clonidine; antidepressant tricyclic (1 study, 32 participants), 10/16 (63%) in clonidine, and 9 /16 (56%) in mianserin-carbamazepine combination group, no difference.

Intensity of withdrawal
- Adrenergic agonist versus methadone, 12 studies, 1008 participants: data were insufficient for statistical comparison and results across studies are confounded by variability in the means of assessment of withdrawal severity, participant characteristics and setting. However, for 11/12 studies the peak withdrawal associated with adrenergic agonist was similar to, or perhaps marginally higher than, peak withdrawal severity associated with methadone. Regarding the signs and symptoms of withdrawal it does appear that neither treatment fully suppresses the aches and pains, sleep disturbances, loss of energy, chills, or anxiety associated with opioid withdrawal.
- Two different alpha2 adrenergic agonists, 4 studies, 102 participants: data available showed a similar effectiveness in terms of overall intensity of withdrawal and the patterns of individual signs and symptoms.
- Other comparison: clonidine more effective and more acceptable then placebo (2 studies, 102 participants), muscle relaxant (1 study, 26 participants), antidepressant tricyclic (1 study, 32 participants), neuroleptic + benzodiazepine (1 study, 120 participants), symptomatic (1 study, 52 participants)

Side effects
- Adrenergic agonist versus methadone, 9 studies, 805 participants: clonidine is associated with more adverse effects than methadone; hypotension is the most significant adverse effect, aside from hypotension, the adverse effects more commonly associated with clonidine than with methadone were dizziness, drowsiness, fatigue, lethargy and dry mouth.
- Two different alpha2 adrenergic agonists, 4 studies 227 participants: hypotension occurs less frequently with lofexidine compared to clonidine treatment, also guanfacine was associated with fewer adverse effects than clonidine.
- Other comparison: clonidine versus placebo (1 study, 50 participants): sedation and dry mouth

approximately twice in clonidine, compared placebo group; clonidine versus antidepressant tricyclic (1 study, 32 participants): significantly lower blood pressure in participants treated with clonidine; clonidine vs neuroleptic+anxiolitic (1 study, 120 participants): 4/60 participants in clonidine and 0/60 in neuroleptic+anxiolitic group recorded severe hypotension (< 90mmHg), extra pyramidal symptoms requiring benzhexol occurred in 38/60, and severe dehydration requiring parenteral fluids occurred in 9/60 participants treated with chlordiazepoxide-chlorpromazine, but none of those treated with clonidine.

Reviewers' conclusions

Implications for practice

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. The overall intensity of withdrawal associated with alpha2 adrenergic agonist treatment appears generally similar to, or perhaps marginally greater than that associated with reducing doses of methadone, and withdrawal occurs at different stages of the treatment regimes. Participants with methadone regimes experience fewer adverse effects. Direct comparison of lofexidine and clonidine indicates that lofexidine is associated with fewer adverse effects, particularly less hypotensive effects. Lofexidine has similar efficacy to clonidine, but is associated with fewer hypotensive side effects. On this basis lofexidine should be preferred, particularly for withdrawal in an outpatient setting.

Implications for research

There remains limited information on the relative efficacy of clonidine, lofexidine and, particularly, guanfacine. These three alpha2 adrenergic agonists should be compared systematically in terms of amelioration of the signs and symptoms of withdrawal, completion of treatment and the occurrence of adverse effects. A further area of potential investigation is the nature of withdrawal signs and symptoms that are not significantly ameliorated by treatment with alpha2 adrenergic agonists. This is - it would be valuable to investigate adjunct medications that address the symptoms that are a problem for patients. These are likely to include sleep disturbances, anxiety and aches and pains, which are suggested by studies included in this review to be incompletely suppressed by both alpha2 adrenergic agonists and reducing doses of methadone. Comparisons between reducing doses of methadone and buprenorphine with alpha2 adrenergic agonists could be improved also.

Review 4

Opioid antagonists with minimal sedation for opioid withdrawal

first published CLIB issue 2, 2000; last substantive update issue 1, 2006. (Under editorial process, confidential)

SUMMARY

Objectives: To assess the effectiveness of interventions involving the administration of opioid antagonists to induce withdrawal, in combination with medications to ameliorate symptoms but with minimal sedation, compare with more established approaches to detoxification (reducing doses of methadone, adrenergic agonists, buprenorphine, and symptomatic medications) or placebo.

Main results: 9 studies with 775 participants, met the inclusion criteria for the review. For completion rate, no differences were found comparing naltrexone plus adrenergic agonist with adrenergic agonist alone both when all study designs were included and when only RCTs were considered (RR 1,11 95% CI 0,85-1.44) as well as when naloxone plus adrenergic agonists were compared with adrenergic agonist alone (RR 1,05 95% CI 0,89-1,24). 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. Delirium may occur following the first dose of opioid antagonist, particularly with higher doses (>25mg naltrexone).

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 treatment 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.

DESCRIPTION OF STUDIES

Types of studies: Randomised, quasi-randomised controlled clinical trials and prospective controlled cohort studies that provided detailed information on the type and dose of drugs used and the characteristics of patients treated.

Types of interventions:
Experimental interventions: studies involved the administration of an opioid antagonist (naloxone, naltrexone or nalmefene) in the first three days of treatment, or within three days of last opioid use in combination with medication to ameliorate the symptoms but with no or minimal sedation.
Comparison interventions: studies involved the use of reducing doses of methadone, alpha2 adrenergic agonist, buprenorphine, symptomatic medications or placebo, or antagonist-based regimes differing in the type or dose regime of opioid antagonist. Symptomatic medications are defined as benzodiazepines, anti-emetics, anti-diarrhoeal, anti-psychotics, anti-spasmodic, muscle relaxants or non-opioid analgesics, administered in combination as needed, or according to a defined regime.

The search strategy resulted in the identification of 40 studies involving the administration of opioid antagonists to induce opioid withdrawal, in combination with medication to ameliorate symptoms, but without significant sedation or anaesthesia.

Excluded studies: 31 studies did not meet the criteria for inclusion in this review
Included studies: 9 studies met the inclusion criteria for this review (See Table of included studies).

Methodological Quality: 5 RCT; 3 non-randomised with participants able to choose which treatment modality they received; and 1 allocated participants consecutively to the treatment regimes being compared. The authors did not report the results of quality assessment, however, where possible, the impact of methodological quality was judged through sensitivity analysis. This involved repeating meta-analyses with studies non RCT being included or excluded from meta-analyses.

Characteristics of the studies: The countries in which the studies were conducted are not reported; 4 studies inpatient, 5 outpatient treatments setting

Characteristics of the participants: 775 participants (range 18-162), in 6 studies all participants were withdrawing from heroin; in the other 3 studies participants were using heroin, methadone, or both. All participants in these studies were stabilised on methadone for three days prior to detoxification.

Comparisons:
- opioid antagonist + adrenergic agonist versus adrenergic agonist alone 7 studies (Bearn 2001, Beswick 2003, Buntwal 2000, Gerra 1995, Gerra 2000, O'Connor 1995, O'Connor 1997) 678 participants;
- opioid antagonist + adrenergic agonist versus placebo 1 study (Gerra 1995) 119 participants;
- opioid antagonist + buprenorphine versus buprenorphine alone 1 study (Umbricht 1999) 60 participants;
- different modalities of initial doses of naltrexone 1 study (Vining 1988) 18 participants.

Treatment regimes:
Naltrexone (7 studies), initial dose range 12.5-14 mg/day; maintenance dose 50 mg/day.
Naloxone (4 studies) initial dose range 0.2-0.8 mg/day
Adrenergic agonists: clonidine (4 studies) initial dose range 0.4-1.05 mg/day; lofexidine (3 studies) initial dose range 1.8-2.0 mg/day, then both tapered in three-four days.
Buprenorphine (1 study) initial dose 24 mg/day, then tapered in four days.
Other than Gerra 1995, all studies report the use of a range of additional adjunct medications, including benzodiazepines, non-steroidal anti-inflammatory drugs (analgesics), anti-emetics and muscle relaxants.

Outcomes: Completion of treatment; Intensity of withdrawal; Side effects.

RESULTS

Completion of treatment
Because the naltrexone and naloxone regimes differ substantially, separate analyses have been undertaken for each of these opioid antagonists.
- Opioid antagonist (naltrexone)+ adrenergic agonist versus adrenergic agonist alone: 4 studies, 330 participants RR 1,26 (CI 95% 0,80-2,00), no statistically significant difference quale?(Figure 4.1);, if the studies with high risk of bias (2 non RCT) were excluded, the result did not change RR 1,11 (CI 95% 0,85-1,44
- Opioid antagonist (naloxone)+ adrenergic agonist versus adrenergic agonist alone: 3 studies, 243 participants RR 1,05 (CI 95% 0,89-1,24) no statistically significant difference ;
- Different modalities of initial doses of naltrexone: 1 study showing no differences between the groups.

Intensity of withdrawal
- Opioid antagonist + adrenergic agonist versus adrenergic agonist alone: 4 studies which results suggest that 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. Delirium may occur following the first dose of opioid antagonist, particularly with higher doses (>25mg naltrexone);
- Opioid antagonist + adrenergic agonist versus placebo: 1 study, participants treated with placebo has score significantly higher than opioid antagonists;
- Opioid antagonist + buprenorphine versus buprenorphine alone: 1 study, withdrawal ratings indicated peak withdrawal severity was similar in the two groups but occurred at different times, on day 2 in the associated group and in day 8 in the other; for both withdrawal symptoms were reported to be of moderate intensity;
- Different modalities of initial doses of naltrexone: 1 study no difference detected between the groups.

Side effects
- Opioid antagonist + adrenergic agonist versus adrenergic agonist alone: 3 studies, one study reported that four of 68 (6%) participants treated with clonidine-naltrexone, but none of 57 treated with clonidine only, experienced mild to moderate delirium on the first day of clonidine-naltrexone treatment. One of 57 treated with clonidine only experienced symptoms of hypotension, but this may have been due to an unrelated medical condition. 1 study reported the development of a "transient, self-limiting confusional state" in two of 26 (8%) of those treated with naltrexone and lofexidine and another reported that one participant in the lofexidine group experienced dizziness and was given a lower dose.

Reviewers' conclusions

Implications for practice
The use of opioid antagonists combined with alpha2 adrenergic agonists is a feasible approach to the management of opioid withdrawal, the withdrawal syndrome associated with this form of treatment is

probably more intense than that associated with withdrawal managed by clonidine or lofexidine alone, but overall severity is less, probably because signs and symptoms of withdrawal resolve more quickly. 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. Patients should be warned of the possibility of delirium in the first day of administration of naltrexone. They should also be informed that withdrawal will be moderately severe and that symptoms such as muscle aches, vomiting and diarrhoea, and insomnia are likely to persist despite medication. To manage such side effects it is desirable to provide a high level of monitoring and support for several hours following administration of the first dose of opioid antagonist.

Implications for research

It would be desirable for withdrawal status to be assessed for sufficient time to record the subsidence of both objective and subjective symptoms. Whatever rating instrument is used, researchers should indicate the scores considered to represent boundaries of mild, moderate and severe withdrawal to enable comparison of studies using different rating instruments. It is also desirable for information to be provided concerning which items contribute most to the withdrawal score and which signs and symptoms are most persistent, and most troubling to participants. The use of adjunct medications, additional to alpha2 adrenergic agonists, appears necessary to control signs and symptoms during peak withdrawal severity. Investigation of the type and doses of adjunct medications required is necessary to the establishment of standard regimes for antagonist-induced withdrawal.

Review 5

Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal

first published CLIB issue 1, 2001; last substantive update issue 1, 2006 (Under editorial process, confidential)

SUMMARY

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.

Main results: 5 studies involving 728 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; 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- 9.12)

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.

DESCRIPTION OF STUDIES

Types of studies: Randomised, quasi-randomised controlled clinical trials and prospective controlled cohort studies that provided detailed information on the type and dose of drugs used and the characteristics of patients treated.

Types of interventions:
Experimental interventions: studies involved the administration of an opioid antagonist (naloxone, naltrexone, nalmefene), with the aim of inducing withdrawal, in conjunction with heavy sedation or anaesthesia.
Comparison interventions: studies involved the use of reducing doses of methadone, an alpha2 adrenergic agonist, buprenorphine, symptomatic medications, opioid antagonists with minimal sedation, or placebo to manage withdrawal, or a different regime of antagonist-induced withdrawal with concomitant heavy sedation or anaesthesia. Symptomatic medications are defined as benzodiazepines, anti-emetics, anti-diarrhoeal, anti-psychotics, anti-spasmodic, muscle relaxants or non-opioid analgesics, administered in combination as needed, or according to a defined regime.

The search strategy resulted in the identification of 38 studies involving the administration of opioid antagonists with concomitant sedation or anaesthesia.

Excluded studies: 33 studies did not meet the criteria for inclusion in this review
Included studies: 5 studies involving 728 participants, met the inclusion criteria for this review (See Table of included studies).
Methodological Quality: 4 RCT, 1 allocated participants consecutively to the treatment.

Characteristics of the studies: The countries in which the studies were conducted are not reported. In all studies antagonist-induced withdrawal was administered in a hospital setting with intensive care facilities. Comparison treatments were provided on an inpatient basis in specialist drug and alcohol clinics. Methadone and clonidine were administered on an outpatient basis.

Participants: 728 participants (range 25-300), in 2 studies all participants were withdrawing from heroin, in other 2 participants were using heroin and/or methadone and in 1 study were withdrawing following methadone maintenance treatment.

Comparisons:

- Antagonist-induced withdrawal under anaesthesia versus methadone, 1 study (Krabbe 2003), 30 participants;
- Antagonist-induced withdrawal under anaesthesia versus clonidine and symptomatic medications, 1 study (McGregor 2002), 101 participants;
- Antagonist-induced withdrawal with differing levels of sedation, 2 studies (Seoane 1997; de Jong 2005), 572 participants;
- Two different anaesthetic agents, 1 study (Kiembaum 2000), 25 participants

Treatment regimes: Two studies used naltrexone to induce withdrawal, 2 used naloxone and 1 used both naloxone and naltrexone. In 4 studies anaesthesia was induced and maintained with propofol, in 1 propofol and methohexital were compared. The duration of anaesthesia was at least four hours in all studies.

Outcomes: Completion of treatment; Intensity of withdrawal; Side effects; Results at follow-up as number of abstinent or number still in treatment with naltrexone

RESULTS

Completion of treatment

- Antagonist-induced withdrawal under anaesthesia versus methadone, 1 study, 30 participants: 9/15 (60%) in methadone group dropped out in the first week, compared to 0/15 in the antagonist-induced withdrawal group;
- Antagonist-induced withdrawal under anaesthesia versus clonidine and symptomatic medications, 1 study, 101 participants: 40/51 (78%) of the antagonist-induced withdrawal and 14/50 (28%) of the clonidine group completed withdrawal and commenced naltrexone treatment (the difference was significant);
- Antagonist-induced withdrawal with differing levels of sedation, 1 study, 300 participants: all participants completed detoxification.

Intensity of withdrawal

- Antagonist-induced withdrawal under anaesthesia versus methadone, 1 study, 30 participants: withdrawal scores for the methadone group were lower than the peak scores for the group receiving antagonist-induced withdrawal. In the methadone group peak withdrawal occurred much later, on day 18, some six days after cessation of methadone and commencement of naltrexone;
- Antagonist-induced withdrawal with differing levels of sedation, 2 studies, 572 participants: in both studies the frequency of individual withdrawal signs similar in the two groups;
- Two different anaesthetic agents, 1 study, 25 participants: Scores rose from baseline levels of 2.5-4.5 to maximums (on the day after anaesthesia) of 16.3±2.1 in the group anaesthetised with propofol and 18.2±2.0 in the group administered methohexital. Withdrawal scores then steadily decreased with scores reducing to a level that was not significantly above baseline on day six for the propofol group and day 14 for the methohexital group. Thus withdrawal symptoms decreased significantly more rapidly in the propofol group. They noted that participants in this group could also be extubated significantly earlier than participants anaesthetised with methohexital.

Side effects

- Antagonist-induced withdrawal with differing levels of sedation, 2 studies, 572 participants RR 3.21, (CI 95% 1.139.12), results show a significantly greater risk of adverse events with heavy, compared to light, sedation ;
- Two different anaesthetic agents, 1 study, 25 participants: large amounts of gastric and rectal discharge after naloxone administration, with high fluid requirements in both groups. One patient required an additional two weeks treatment because of partial subclavian vein thrombosis presumed related to central venous catheter. It was not reported which anaesthetic this patient had received.

Results at follow-up

- Antagonist-induced withdrawal under anaesthesia versus methadone, 1 study, 30 participants: at one-month follow-up, 15/15 participants in the antagonist-induced withdrawal group were abstinent, compared to 6/15 (40%) in methadone group. At three months, the difference was less marked, with 10/15 (67%) of the antagonist-induced withdrawal group and 5/15 (33%) of the tapered methadone group still abstinent by urine screen;
- Antagonist-induced withdrawal under anaesthesia versus clonidine and symptomatic medications, 1 study, 101 participants: at three month follow-up, 8/51 (16%) in the antagonist-induced withdrawal group and 1/50 (2%) in the methadone group were still assuming naltrexone;
- Antagonist-induced withdrawal with differing levels of sedation, 1 study, 272 participants: at one month follow-up, 62.8% of the anaesthesia group and 60% of the comparison minimal sedation group were abstinent and 86.1% and 84.4%, respectively, still using naltrexone;

- Two different anaesthetic agents, 1 study, 25 participants: one in each group used heroin in the two to three weeks after detoxification.

Reviewers' conclusions

Implications for practice

The increased risk of clinically significant adverse events associated with heavy, compared to minimal sedation, make the value of anaesthesia-assisted antagonist-induced withdrawal questionable. Given that the intensity and duration of withdrawal, and rates of completion of withdrawal, are similar for antagonist-induced withdrawal with minimal sedation, this would appear to be a preferable approach to managing withdrawal in those wishing to transfer to naltrexone maintenance treatment. The diversity and small number of studies, limits the strength of conclusions that can be drawn. Antagonist-induced withdrawal is more intense but less prolonged than withdrawal managed by tapered methadone or clonidine plus symptomatic medications, and is associated with significant reductions in the time between opioid use and commencement of naltrexone doses sufficient to block the effects of opioid drugs.

The reported occurrence of vomiting during sedation, respiratory depression and cardiac irregularities point to the approach being limited to facilities equipped for intubations, assisted ventilation and a high level of monitoring, and with the capacity to respond to the adverse events that might occur.

Implications for research

The lack of additional benefit, and increased risk of harm associated with antagonist-induced withdrawal under heavy sedation or anaesthesia, as compared to approaches with minimal sedation, suggests that this form of treatment should not be pursued. Research resources would be better directed towards assessment and development of minimal sedation approaches.

However, if undertaken, any research should explore factors that might influence outcomes. These factors include the nature, dose and route of administration of opioid antagonist; the anaesthetic agent, depth and duration of anaesthesia; the type, dose and timing of adjunct medications; and the nature, dose and timing of last opioid use.

Review 6

Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification

first published CLIB issue 4, 2004

SUMMARY

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.

Main results: 8 studies involving 423 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 RR 1.68 (95% CI 1.11 to 2.55), results at follow-up RR 2.43 (CI 95% 1.61 to 3.66), and compliance RR 0.48 (CI 95% 0.38 to 0.59). With regard to the use of heroin during treatment, the differences were not statistically significant but favoured the combined treatments.

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 outcomes assessed. Because of lack of detailed information no meta analysis could be performed to analyse the results related to several outcomes.

DESCRIPTION OF STUDIES

Type of studies: Randomised controlled trials

Types of interventions:
Experimental interventions: Psychosocial plus pharmacological detoxification interventions of any kind (any psychosocial and any drug)
Comparison interventions: Pharmacological treatments (any drug) for opiate detoxification.

The search strategy resulted in the identification of 77 studies with treatment regimes involving the administration of pharmacological treatment associated with some psychosocial intervention.

Excluded studies: 69 studies did not meet the criteria for inclusion in this review

Included studies: 8 studies, involving 423 participants met the inclusion criteria for this review (See Table of included studies).

Methodological Quality: 8 RCT, 2/8 describes the randomization method; none mention any allocation concealment approach. 6/8 were evaluated as studies with moderate risk of bias for allocation concealment and 2/8 were evaluated as studies with inadequate allocation concealment. This involved repeating meta-analyses with these studies being included or excluded from meta-analyses. All studies but one give information on people who left the study or were lost at follow up.

Characteristics of the studies: Four different psychosocial interventions (two behavioural treatments: Contingency Management, Community Reinforcement; one form of structured counselling: Psychotherapeutic Counselling; one Family Therapy). Two detoxification treatments: Methadone Detoxification Treatment (7 studies) and Buprenorphine Detoxification Treatment (1 study). Seven studies were conducted in USA, 1 in UK. Duration of the trials: range 16 days to 26 weeks.

Characteristics of the participants: 423 opiate addicts: 72% (303) were male. Average age was 31 years (range 28 to 41).

Comparisons:

- Any Psychosocial plus any Pharmacological Intervention versus any Pharmacological alone: 8 studies, 423 participants (Bickel 1997; Hall 1979; Higgins 1984; Higgins 1986; McCaul 1984; Rawson 1983; Robles 2002; Yandoli 2002);
- Any Psychosocial Intervention plus Methadone Detoxification Treatment (MDT) versus MDT alone: 7 studies 384 participants (Hall 1979; Higgins 1984; Higgins 1986; McCaul 1984; Rawson 1983; Robles 2002; Yandoli 2002);
- Contingency Management Approaches plus MDT versus MDT alone: 5 studies (Hall 1979, Higgins 1984, Higgins 1986, McCaul 1984, Robles 2002), 215 participants;
- Family Therapy plus MDT versus MDT alone versus Low Contact: 1 study (Yandoli 2002), 119 participants;
- Psychotherapeutic Counselling plus MDT versus MDT alone: 1 study (Rawson 1983), 50 participants;
- Behavioural Treatment plus Buprenorphine Detoxification Treatment (BDT): one study (Bickel 1997), 39 participants.

Treatment regimes: Information on methadone doses was available for seven out of the eight included studies. The mean starting dose of methadone was 44.5 mg (range 30 to 76.4). Buprenorphine dose range was 2 to 8 mg/day.

Outcomes: Completion of treatment; Use of opioid during the treatment; Abstinent at follow-up; Compliance; Use of other drugs; Mortality

RESULTS

Completion of treatment

- Any Psychosocial plus any Pharmacological Intervention versus any Pharmacological alone: 5 studies, 184 participants: RR 1.68 (CI 95% 1.11 to 2.55), the result is significantly in favour of any psychosocial associated with any pharmacological intervention . We performed a sensitivity analysis excluding the study with inadequate allocation concealment; the result did not change, remaining significantly in favour of the associated treatments RR 2.17 (CI 95% 1.26 to 3.72). This result is also confirmed in the single comparisons

Use of primary substance

- Any Psychosocial plus any Pharmacological Intervention versus any Pharmacological alone: 3 studies 109 participants, RR 0.77 (CI 95% 0.59 to 1.01), in favour of the associated treatment although the difference is not statistically significant. (Figure 7.2).
- In the single comparison the difference became statistically significant in favour of the associated treatment only when Contingency Management Approaches plus MDT is compared with MDT alone: 1 study 20 participants, 5/10 (50%) participants in the associated treatment group with opiate positive urine samples compared to 10/10 (100%) in the methadone alone group, RR 0.50 (CI 95% 0.27 to 0.93).

Abstinent at follow-up

- Psychosocial plus any Pharmacological Intervention versus any Pharmacological alone: 3 studies, 208 participants, RR 2.43 (CI 95% 1.61 to 3.66), in favour of the associated treatments . We performed a sensitivity analysis excluding the study with inadequate allocation concealment from meta-analysis; the result was no longer statistically significant RR 2.03 (CI 95% 0.84 to 4.92).

Compliance measured as Clinic Attendance:

- Psychosocial plus any Pharmacological Intervention versus any Pharmacological alone: 3 studies, 1138 participants: RR 0.48 (CI 95% 0.38 to 0.59), the result is significantly in favour of the associated intervention . This result is also confirmed in the single comparisons.

Use of other drugs

- Behavioural Treatment plus Buprenorphine Detoxification Treatment, 1 study, 39 participants: the data are on subjects with positive urine samples for each substance in both groups. Barbiturates: 9/19 (47%) in the associated treatment compared to 6/20 (30%) in the BDT alone group; Benzodiazepines: 17/19 (89%) in the associated treatment group compared to 15/20 (75%) in the BDT alone group; Cannabinoids: 9/19 (47%) in the associated treatment group compared to 11/20 (55%) in the BDT alone group; Cocaine: 12/19 (63%) in the associated treatment compared to 11/20 (55%) in the BDT alone group. The differences were never statistically significant for any of the substances.

Mortality

- Family Therapy plus MDT versus MDT alone versus Low Contact: 1 study 119 participants: 2/41 (5%) in the associated treatment group had died at 1 year follow-up compared to 0/78 in the MDT alone group; 3/41 (7%) in the associated treatment group had died at 5 year follow-up compared to 2/78 (2.5%) in the MDT alone group.

Reviewers' conclusions

Implications for practice

Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in term of completion of treatment, abstinent 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 form 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.

Implications for research

Limitations to this review are imposed by the heterogeneity of the outcomes assessed. Due to lack of detailed information, it was not possible to perform a meta analysis to analyse the results related to several outcomes.

Problems in generalisation of the results call for further research, where the non standardized way in which specific outcomes are measured and reported.

Review 7

Inpatient versus other settings for detoxification for opioid dependence
first published CLIB issue 2, 2005

SUMMARY

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.

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.

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.

DESCRIPTION OF STUDIES

Type of studies: Randomised controlled clinical trials that compare inpatient treatment (as defined below) with any form of non-residential treatment.

Types of interventions:
Experimental interventions: Inpatient opioid detoxification - any time-limited treatment for opioid dependence where the clearly expressed aim at the outset is detoxification (i.e. becoming opioid-free) and where the patient is resident for 24 hours per day in a facility that also has staff present throughout this period.
Comparison interventions: All 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
- outpatient or ambulatory programmes

The search strategy resulted in the identification of 3 studies

Excluded studies: 2 studies did not meet the criteria for inclusion in this review

Included studies: 1 study, 40 participants, met the inclusion criteria for the review (See Table of included studies).

Methodological Quality: 1 RCT, participants randomly allocate to different treatment modalities, method of randomisation not described; staff collecting or analysing the outcome data were blinded to the participants' treatment modality.

Characteristics of the participants: All physically dependent on heroin with pharmacological evidence of current drug use through urinalysis or clinical evidence of the opioid withdrawal syndrome. For nearly 75% of the sample this was the first withdrawal treatment experience.

Comparisons:
- Hospital detoxification versus outpatient detoxification. 1 study, (Wilson 1975), 40 participants

Treatment regimes: The hospital detoxification group was supervised by psychiatrists on an open ward of an acute psychiatric treatment service in a general hospital. The detoxification was performed using methadone, not exceed 40mg in any 24-hour period'. No prescribed length of treatment was imposed on the hospital participants, and those who felt stabilised or requested to leave were discharged. The outpatient detoxification group was also supervised by psychiatrist and also received methadone, starting dose 10-20mg, maximum dose 40mg daily on day 2-3, length of treatment fixed 10-day period. Both groups were also offered supportive medication as clinically indicated.

Outcomes: Completion of treatment; Lost at follow-up; Cost of treatment

RESULTS

Completion of treatment

- Hospital detoxification versus outpatient detoxification. 1 study, 40 participants: 7/10 (70%) in the inpatient detoxification group were opioid-free on discharge compared with 11/30 (37%) in the outpatient group. However a number of participants also refused treatment rather than accepting hospitalization (although the exact number is not reported), and so the completion rate in the inpatient sample calculated on an intention-to-treat basis would certainly have been much lower.

Lost at follow-up

- Hospital detoxification versus outpatient detoxification. 1 study, 40 participants:

– hospital sample: 3/10 (30%) were lost to follow-up. Of the remaining 7, 1 resumed heroin use within 24 hours of discharge, 1 within one week, 2 within one month, 2 within two months, and 1 within three months;

– outpatient sample: 10/30 (33%) were lost to follow-up, and 1 patient assigned to the group did not initiate treatment. A further 8 (27%) never stopped using heroin despite receiving methadone. 2 reported return to heroin use within one week of treatment, 5 within two months, and 1 resumed without specifying the time period. Two participants were still heroin-free when last contacted two months after treatment.

Cost of treatment

- Hospital detoxification versus outpatient detoxification. 1 study, 40 participants: average cost of treatment in the outpatient group as US$10 per day or US$100 for a 10-day detoxification programme (including the cost of intake procedures, laboratory work and medications). The average cost of the hospital treatment was US$91 per day or US$496 for a treatment programme with an average patient stay of 5.4 days.

Reviewers' conclusions

Implications for practice

The only real conclusion that can be drawn is that there is very little available research to guide the clinician about the longer-term outcomes or cost-effectiveness of inpatient or outpatient approaches. There is a lack of good quality research evidence available to guide practice in this area. Detoxification is an essential first step in achieving lifelong abstinence, but little attention has been paid to the effect of treatment setting. Given the potential cost of inpatient treatment, it is perhaps surprising that a search of the world literature in this area yielded only two randomised controlled trials, both with significant methodological limitations.

Implications for research

The randomised controlled trial is usually the methodology of choice for determining which treatment option is best. However, in the case of inpatient opioid detoxification there is a problem of equipoise, whereby the patients who theoretically might benefit most from the treatment are often excluded from randomised trials. Furthermore, the few studies that have looked at the effect of setting on detoxification outcomes have involved too few participants to provide sufficient statistical power to detect potential differences. It is important to remember that a failure to detect a difference in these circumstances is not the same as proving that no benefit exists. There is also some evidence that detoxification in an inpatient environment may increase the likelihood of engaging the patient in longer term care, and such a prospective cohort study would be suitable for examining such issues.

MAINTENANCE TREATMENTS FOR OPIOID DEPENDENCE

Review 8

Methadone maintenance versus no opioid replacement therapy for opioid dependence
first published CLIB issue 4, 2002; last substantive update issue 2, 2003

SUMMARY

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.

Main results: Six studies met the criteria for inclusion in this review, all were randomised clinical trials, and two were double-blind. There were a total number of 954 participants. Based on the meta-analysis, methadone appeared statistically significantly 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).

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.

DESCRIPTION OF STUDIES

Type of studies: Clinical controlled trials of MMT against another treatment which does not use opioid replacement therapy.

Types of interventions:
Experimental interventions: MMT interventions even where they also employed other treatments, such as behavioural therapies or outpatient rehabilitation.
Comparison interventions: placebo medication, withdrawal or detoxification (with or without ancillary medication), drug-free rehabilitation treatment (such as therapeutic communities), and no treatment or wait-list controls.

The search strategy resulted in the identification of7 studies

Excluded studies: 1 study did not meet the criteria for inclusion in this review.
Included studies: 6 studies, 954 participants, met the inclusion criteria for the review (See Table of included studies).

Methodological Quality: 6 RCT, double-blind in 2/6 no sufficient data to be confident about the concealment of allocation

Characteristics of the studies: 3 studies were conducted in USA, 1 study each in Sweden, Hong Kong and Thailand; The sample sizes: in 2 studies sample sizes of 32 and 34 respectively, in the other 4 studies sample sizes ranging from 100 to 301.

Characteristics of the participants: 954 participants, 808 (85%) males.

Comparisons:
- MMT vs Methadone detoxification treatment (MDT), 3 studies, 587 participants (Newman 1979; Strain 1993; Vanichseni 1991)
- MMT vs waiting list/no treatment, 3 studies, 367 participants (Dole 1969; Gunne 1981; Yancovitz 1991)

Treatment regimes: Mean dosages of methadone ranged from 74 to 100 mg per day in 4/6 of the included studies: in 1 study was 50 and 20 milligrams per day and in another one was unclear.

Outcomes: Retention in treatment, Use of opiates during the treatment, Criminal activities, Mortality

RESULTS

Retention in treatment

- MMT vs Methadone detoxification treatment (MDT), 3 studies, 505 participants RR= 3.05 (CI 95% 1.75-5.35), results in favour of MMT

Use of opiate (self reported)

- MMT vs waiting list/no treatment, 3 studies, 230 participants RR=0.32 (CI 95% 0.23-0.44), in favour of MMT .

Criminal activities

- MMT vs waiting list/no treatment, 3 studies, 363 participants RR=0.39 (CI 95% 0.12-1,25), no statistically significant difference .

Mortality

- MMT vs Methadone detoxification treatment (MDT), 1 study, 100 participants , 3/50 in MMT group and 1/50 in MDT group died, the difference is not statistically significant
- MMT vs waiting list/no treatment, 2 studies, 335 participants RR=0.15 (CI 95% 0.02-1.18), no statistically significant difference

Reviewers' conclusions

Implications for practice

The implications of the results of the meta-analytic review conducted and reported herein for clinical practice are that methadone maintenance treatment is an effective intervention for the management of heroin dependence. Methadone retains patients in treatment and reduces heroin use. Methadone should be supported as a maintenance treatment for heroin dependence.

Implications for research

Overall there are a relatively limited number of randomised clinical trials on the efficacy of methadone treatment compared to placebo. It does not seem feasible at this stage to conduct further randomised trials of methadone treatment. However, evidence on reduction of criminal activity and mortality from clinical trials is lacking calling for an additional systematic review of observational studies. Moreover, monitoring of the outcome of standard methadone treatment in clinical practice may be important as a research activity to demonstrate its ongoing effectiveness, or to determine whether its effectiveness is being compromised through the reduction of ancillary services or reduction in adequate dose levels. A number of measures (e.g., of other drug use, physical health, and psychological health) were too infrequently and irregularly reported in the literature to be usefully integrated in the quantitative review, but future research might address these important areas.

Review 9.

Methadone maintenance at different dosages for heroin dependence

first published CLIB issue 3, 2000; last substantive update issue 3, 2003

SUMMARY

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.

Main results: 21 studies were included: 11 were RCTs (2279 participants) and 10 were Controlled Prospective studies (CPS) (3715 participants). Retention rate - RCTs: High versus low doses: RR=1.36 (CI 95% 1.13, 1.63), favour high doses. Opioid abstinence, (urine based) RCTs: high versus low ones: RR=1.59 (CI 95% 1.16, 2.18) favour high doses, high vs middle doses RR=1.51(CI 95% 0.63, 3.61), no statistically significant differences. Cocaine abstinence (urine based) RCTs: high versus low doses RR=1.81 (CI 95% 1.15, 2.85), favour high doses. Overdose mortality at 6 years follow up - CPSs: high dose versus low dose: RR=0.29 (CI 95% 0.02-5.34) high dose vs middle dose: RR=0.38 (CI 95% 0.02-9.34), both not statistically significant, middle dose vs low dose: RR=0.57 (CI 95% 0.06-5.06), favour middle doses.

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.

DESCRIPTION OF STUDIES

Types of studies: RCTs, Clinical Controlled Trials (CCT) and the prospective studies evaluating methadone maintenance at different dosages in the management of opioid dependence. CPS were included when proper adjustment for confounding factors was performed at the analysis stage.

The search strategy resulted in the identification of 43 studies.

Excluded studies: 22 studies were excluded from the review, 3 were RCTs, 19 were CPSs;
Included studies: 21 studies were included in the review, 11 RCTs, 10 CPSs (See Table of included studies).

Methodological Quality: 11 studies were RCTs, 9 double blind and 2 single blind, only 1/11 described the method of allocation concealment; 5/11 described the randomisation process. The characteristics of the patients and the inclusion and exclusion criteria were generally well defined in all the studies. The completion of the follow-ups was generally quite high, or it was used an intention to treat analysis. According to these criteria, 5 were evaluated as high quality, 5 as moderate quality and 1 as low quality. 10 studies were CPSs; 6/10 did not present data useful for the inclusion in the metanalysis, because of the statistical model used for the analysis; however, they provided results which can be presented in a narrative way.

Characteristics of the studies: Length of follow-up: RCTs: range 7-52 weeks; CPSs: range 1-10 years. Setting USA (11 RCTs, 1 CPS), Australia (4 CPSs), UK, Switzerland, the Netherlands, Spain, Italy (1 CPS each).
RCTs: High doses=60-109 mg/day; middle dose= 40-59 mg/day; low dose= 1-39 mg/day
CPSs: High doses=>75 mg/day; middle dose= 55-70 mg/day; low dose= 5-55 mg/day

Comparisons:
RCTs: eleven studies and 2279 subjects.

- 60-109 mg/day vs 1-39 mg/day (at 17-26 weeks), 5 studies, 496 participants(Johnson 1992; Johnson 2000; Kosten-Oliveto 1993; Ling 1996; Schottenfeld 1997)
- 60-109 mg/day vs 1-39 mg/day (at 52 weeks), 1 study, 150 participants (Ling 1996)
- 60-109 mg/day vs 40-59 mg/day (at 7-13 weeks), 2 studies 347 participants (Ling 1976; Preston 2000)
- 60-109 mg/day vs 40-59 mg/day (at 27-40 weeks), 3 studies, 560 participants (Goldstein 1973; Ling 1976; Strain 1999)
- 40-59 mg/day vs 1-39 mg/day (at 20 weeks), 1 study, 166 participants (Strain 1993a)
- >110 mg/day vs 40-59 mg/day (at 27 weeks), 1 study, 80 participants (Goldstein 1973)

- >110 mg/day vs 60-109 mg/day (at 27 weeks), 1 study, 80 participants (Goldstein 1973)

CPSs, outcome **"mortality",** one study and 498 subjects (Van Ameijden 1999):
- >75 mg/day vs 5-55 mg/day
- >75 mg/day vs 55-70 mg/day
- 55-70 mg/day vs 5-55 mg/day

CPSs, outcome **"leaving treatment**", three studies and 1202 subjects (D'Ippoliti 1998; Del Rio 1997; Torrens 1996):
- high dose vs middle dose
- middle dose vs low dose
- high dose vs low dose

Outcomes: Retention in treatment, Drug use during treatment (heroin and cocaine), Side effects, Criminal activity, Mortality

RESULTS

Retention in treatment
RCTs
- 60-109 mg/day vs 1-39 mg/day (at 17-26 weeks), 5 studies, 496 participants RR=1.36 (CI 95% 1.13-1.63), in favour of higher dosages ;
- 60-109 mg/day vs 40-59 mg/day (at 7-13 weeks), 2 studies 347 participants RR=1.01 (CI 95% 0.91-1.12), no statistically significant differences ;
- 60-109 mg/day vs 40-59 mg/day (at 27-40 weeks), 3 studies, 560 participants RR=1.23 (CI 95%1.05-1.45), in favour of higher dosages ;
- CPSs: Results from observational studies seems to confirm those from randomised trials: high doses are always protective for leaving treatment.

Drug use during treatment as
n° of opioid abstinent at >3-4 weeks (urine based)
- 60-109 mg/day vs 1-39 mg/day, 3 studies, 237 participants: RR 1.59 (CI 95% 1.16-2.18), in favour of higher dosages ;

n° of cocaine abstinent at >3-4 weeks (urine based)
- 60-109 mg/day vs 1-39 mg/day, 2 studies, 168 participants: RR 1.81 (CI 95% 1.15-2.85), in favour of higher dosages .

Mortality
Only one CPS study, 498 participants, studied the outcome mortality as overdose mortality (6 years follow-up), and in spite of the high number of subjects the results are not statistically significant; nevertheless, all contrasts between dosages showed protective effect for higher dosages, with a clear suggestion of a dose response relationship.

Reviewers' conclusions

Implications for practice
The results of the review support the conclusion that 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. The most important side effect is the risk of increase the use of cocaine, which therefore needs to be carefully surveyed by clinicians.

Implications for research
The main implications for research concern open questions and methodological errors of studies. There are some major outcomes for which data are absent or unsatisfactory: the effect of methadone dose in mortality reduction is the most important one. In general social outcomes are seldom addressed by researchers, and we do not have reliable answer to the question if there is the same dose-response relationship, as found for retention and use of heroin, for criminality or social adjustment. On the methodological point of view, to aid comparison between studies and to simplify synthesis of results, each author should make effort to adopt both outcome indicators and categorisation of outcomes already adopted by other studies. The control of confounding remain the major methodological reason for the exclusion of observational studies. Given that

non-randomised trials are essential to study rare outcomes, such as mortality, researchers should play a major effort to improve the study design particularly in confounding adju

Review 10
Substitution treatment for injecting opioid users for prevention HIV infection
first published CLIB issue 4, 2004

SUMMARY

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

Main results: 28 studies, involving 7900 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. However, 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.

Conclusions: Oral substitution treatment for injecting opioid users reduces drug-related behaviours with a high risk of HIV transmission, but has little effect on sex-related risk behaviours. The lack of data from randomised controlled studies limits the strength of the evidence presented in this review, but findings concur with previous systematic reviews.

DESCRIPTION OF STUDIES

Types of studies: 2 RCTs, 561 participants; 3 cohort studies, 1180 participants; 2 case control studies, 761 participants; the remaining 20 studies, involving 5393 participants, were other types of descriptive studies. Data on HIV risk behaviour from these studies were either presented with the allocated groups combined, or only one of the groups were relevant to this review. Hence, while these studies commenced as controlled trials, for the purposes of this review they are considered to be descriptive studies.

Types of interventions: Interventions involved the oral administration of full or partial opioid agonists (methadone, buprenorphine, LAAM, codeine or oral morphine) for substitution treatment of opioid dependence. The studies had to consider the frequency of high risk behaviours before and after substitution treatment, it was required that similar data on these behaviours was collected for equivalent periods of time before commencement of treatment, and after a specified period of substitution treatment.

The search strategy resulted in the identification of 28 studies.

Excluded studies: 55 studies were excluded from the review .

Included studies: 28 studies involving around 7900 participants met the inclusion criteria for this review. (See Table of included studies).

Methodological Quality: All of the included studies were assessed for the degree of risk of bias and confounding. With this scale, the higher the overall score the greater the risk of bias and confounding in the study. Only two studies were allocated an overall score of 0, indicating a low level of risk of bias or confounding, an overall score of 1 was allocated to 12 studies, 9 studies were allocated a score of 2, 3 studies received a score of 3 and 2 studies received a score of 4, indicating a high risk of bias and confounding. These ratings of risk of bias and confounding have been used to enter a user-defined order in the data tables. This allows analyses to be displayed in the order of lowest to highest risk of bias and confounding.

Characteristics of the studies: The majority of the studies (21/28) were undertaken in the USA, where primary health care providers are not able to prescribe methadone. Of the remaining studies, 3 were undertaken in the UK, 2 in Australia, 1 in Italy and 1 in Germany. In 20/28 studies, methadone treatment was provided to participants in a specialist drug and alcohol treatment centre; in 1 in the context of a specialist AIDS program; in 1 in a prison setting; in 1 study treatment was provided in both primary health care and specialist drug and alcohol treatment settings with these two settings being compared in one report derived

from this study. In the remaining 5 studies the treatment setting was either not reported or participants were recruited from various sources making identification of setting impossible.

Characteristics of the participants: opioid dependent drug users identified as injecting users, or with a recent history of injecting drug use.

Treatment regimes: for all the studies methadone was the drug used for substitution treatment: average doses 60mg/day or more (10 studies), between 40 and 60mg/day (8 studies), not reported (10 studies).
In 2 studies methadone was provided, for at least one group of participants, in the context of detoxification rather than maintenance: in one the detoxification was scheduled to be completed in 90 days and the other one was designed as an RCT comparing methadone maintenance and 180-day methadone detoxification.

Outcomes: Effect of substitution treatment on: 1. Injecting behaviour as a) prevalence and frequency of injecting use and b) sharing of injecting equipment; 2. Drug use; 3. Sexual behaviour as a) multiple sex partners or commercial sex work and b) unprotected sex; 4. Overall HIV risk; 5. Seroconversion

Comparisons:
- Injecting behaviour as prevalence and frequency of injecting use before treatment vs after a specified period of treatment, 6 studies, 1491 participants (Camacho 1996; Chatham 1999; Dolan 2003; Gossop 2000; King 2000; Magura 1991);
- Injecting behaviour as sharing of injecting equipment before treatment vs after a specified period of treatment, 7 studies, 1726 participants (Camacho 1996; Chatham 1999; Dolan 2003; Gossop 2000; Grella 1996; King 2000; Margolin 2003);
- Opioid use before treatment vs after a specified period of treatment, 7 studies, 1938 participants (Abbott 1998; Avants 1998; Chattam 1999; Dolan 2003; Grella 1996; Margolin 2003; Simpson 1995);
- Cocaine use before treatment vs after a specified period of treatment, 4 studies, 1309 participants (Chattam 1999; Grella 1996; Margolin 2003; Simpson 1995);
- Sexual behaviour as multiple sex partners before treatment vs after a specified period of treatment, 4 studies, 1029 participants (Camacho 1996; Chattam 1999; Grella 1996;King 2000);
- Sexual behaviour as commercial sex work before treatment vs after a specified period of treatment, 2 studies, 525 participants (Grella 1996;King 2000);
- Sexual behaviour as unprotected sex before treatment vs after a specified period of treatment, 6 studies, 1908 participants (Camacho 1996; Chatham 1999; Gossop 2000; Grella 1996; King 2000; Margolin 2003);
- Overall HIV risk before treatment vs after a specified period of treatment, 1 study, 326 participants (Camacho 1996);

Follow-up between 3 and 12 months after entry

RESULTS
- Injecting behaviour as prevalence and frequency of injecting use: 1 controlled study, 129 participants, RR 0.54 (CI 95% 0.41-0.71) favours at follow-up; 5 descriptive studies, 1362 participants: 5/5 studies show a statistically significant decrease in injecting behaviour at follow-up, RR ranged from 0.39 to 0.75;
- Injecting behaviour as sharing of injecting equipment: 1 controlled study, 129 participants, RR 0.38 (CI 95% 0.26-0.56) favours at follow-up; 6 descriptive studies, 1597 participants, in 6/7 studies show statistically significant difference in favour of follow-up, RR ranged from 0.18 to 0.78;
- Opioid use: 1 controlled study, 128 participants, RR 0.31 (CI 95% 0.23-0.42) favours at follow-up; 6 descriptive studies, 1810 participants, 6/6 show a statistically significant difference in favour of follow-up, RR ranged from 0.36 to 0.60;
- Cocaine use: 4 descriptive studies, 1309 participants, 2/4 show a statistically significant difference in favour of follow-up, RR ranged from 0.36 to 0.60;
- Sexual behaviour as multiple sex partners: 4 descriptive studies, 1029 participants, 3/4 show a statistically significant difference in favour of follow-up, RR ranged from 0.39 to 0.76;
- Sexual behaviour as commercial sex work: 2 descriptive studies, 525 participants, 1/2 show a statistically significant difference in favour of follow-up, RR ranged from 0.14 to 0.59;
- Sexual behaviour as unprotected sex: 6 descriptive studies, 1908 participants, 4/6 show a statistically significant difference in favour of follow-up, RR ranged from 0.46 to 1.05;
- Overall HIV risk: 1 descriptive study, 326 participants, RR 0.74 (95% IC 0.68-0.81) .

Reviewers' conclusions

Implications for practice
Following entry into substitution treatment, decrease significantly the proportion of opioid-dependent reporting injecting drug use and the frequency and the levels of sharing of injecting equipment. Similarly,

substitution treatment is associated with reductions in illicit opioid use and with a reduction in the proportion of opioid-dependent reporting multiple sex partners or exchanges of sex for drugs or money. However, substitution treatment has little or no effect on the use of condoms.
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.

Implications for research
Clinical trials of substitution treatments for opioid dependence tend to report only the results of urine screening as an indication of drug use, with specific HIV-risk behaviour data not reported, and probably not collected. Given that preventing the transmission of HIV and other blood-borne viruses is a strong reason for the provision of substitution treatment, such data should be collected and reported for trials of treatment effectiveness. Studies of substitution treatments for opioid dependence tend to monitor, usually through urine screening, use of specific drugs, commonly cocaine, in addition to illicit opioids. It is important to determine changes in patterns of use of a range of drugs associated with substitution treatment for opioid dependence, but to assess sources of HIV risk, what is needed is information on which drugs are being injected by those who continue injecting drug use even whilst receiving substitution treatment.

Review 11

Buprenorphine maintenance versus methadone maintenance for opioid dependence

first published CLIB issue 4, 2002; last substantive update issue 1, 2006 (under editorial process, confidential)

SUMMARY

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

Main results: 23 RCT met the inclusion criteria, buprenorphine in flexible doses is statistically significantly less effective than methadone in retaining patient in treatment (RR= 0.82; 95% CI: 0.72 - 0.94). Low dose methadone is more likely to retain patients than low dose buprenorphine (RR= 0.69; 95% CI: 0.51 - 0.91). 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:0.64 - 0.99), and high dose buprenorphine was inferior in suppression of heroin use. Buprenorphine was statistically significantly superior to placebo in retention of patients in treatment at low doses (RR=1.50; 95% CI: 1.19 - 2.88), high doses (RR=1.74; 95% CI: 1.06 - 2.87), and very high doses (RR=1.74; 95% CI: 1.02 - 2.96). However, only high and very high dose buprenorphine suppressed heroin use significantly above placebo.

Conclusions: Buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is not more effective than methadone delivered at adequate dosages.

DESCRIPTION OF STUDIES

Types of studies: RCTs of buprenorphine maintenance against methadone maintenance or placebo medication in the management of opioid dependence.

Types of interventions:
Experimental interventions: buprenorphine maintenance therapy, using either sublingual tablets or else an ethanol-based solution containing buprenorphine,
Comparison interventions: methadone maintenance therapy or placebo.

The search strategy resulted in the identification of 42 studies.

Excluded studies: 19 studies did not meet the inclusion criteria
Included studies: 23 studies, 4016 participants, were included in this review (See Table of included studies).

Methodological Quality: 23 RCT, 19/23 were conducted under double-blind conditions, 4/23 described an adequate method of concealment of allocation, 0/23 where the concealment method could be defined as clearly inadequate. The outcome measures seemed to be consistent across studies.

Characteristics of the studies: 15/23 studies involved comparisons of methadone and buprenorphine; 8/23 had a placebo-controlled comparison against buprenorphine,

Treatment regimes: 16/23 studies used a fixed dosage of either methadone or buprenorphine, 7/23 studies used flexible doses. Methadone, low doses range 20-35 mg, high dose range 50-80 mg; buprenorphine low dose range 2-5 mg, high dose range 6-16 mg. 8/23 studies compared buprenorphine versus placebo medication, buprenorphine low dose 2-5 mg, high dose 6-16mg, very high >16 mg; placebo was defined as either true placebo (5/9 studies) or a 1mg dose of buprenorphine deemed to be placebo (4/9 studies). The interventions ranged in duration from 2 weeks through to 52 weeks.

Outcomes: Retention in treatment, use of opiate, use of cocaine, use of benzodiazepine, self-reported crime.

Comparisons:
- Flexible doses buprenorphine vs flexible dose methadone, 7 studies, 976 participants (Fischer 1999; Johnson 2000; Lintzeris 2004; Mattick 2003; Petitjean 2001; Strain 1994a; Strain 1994b);
- Low doses buprenorphine (2mg-5mg) vs low doses methadone (20mg-35mg), 5 studies, 598 participants

(Ahmadi 2003a; Johnson 1992; Kosten 1993; Ling 1996; Schottenfeld 1997);
- Low Dose buprenorphine vs high dose methadone (50mg-80 mg), 8 studies, 1064 participants (Ahmadi 2003b; Johnson 1992; Kosten 1993; Ling 1996; Oliveto 1999; Pani 2000; Schottenfeld 1997; Schottenfeld 2005);
- High Dose buprenorphine (6mg-16mg) versus low dose methadone, 5 studies, 469 participants (Ahmadi 2003a; Johnson 1992; Kosten 1993; Ling 1996; Schottenfeld 1997);
- High Dose buprenorphine versus high dose methadone, 7 studies, 708 participants (Johnson 1992; Kosten 1993; Ling 1996; Oliveto 1999; Pani 2000; Scottenfeld 1997; Scottenfeld 2005);
- Low dose buprenorphine maintenance versus placebo, 5 studies, 1131 participants (Ahmadi 2003a; Ahmadi 2003b; Ahmadi 2004; Johnson 1995a; Ling 1998);
- High dose buprenorphine maintenance versus placebo, 4 studies, 887 participants (Ahmadi 2003a; Ahmadi 2004; Johnson 1995a; Ling 1998);
- Very high dose buprenorphine maintenance versus placebo, 4 studies, 728 participants (Fudala 2003; Kakko 2003; Krook 2002; Ling 1998).

RESULTS

Retention in treatment

- Flexibile doses buprenorphine vs flexibile dose metadone, 7 studies, 976 participants, RR 0.82 (CI 95% 0.72-0.94), in favour of methadone
- Low doses buprenorphine vs low doses methadone, 3 studies, 211 participants, RR 0.69 (CI 95% 0.51-0.91), in favour of methadone
- Low Dose buprenorphine vs high dose methadone, 3 studies, 263 participants, RR 0.67 (CI 95% 0.55-0.81), in favour of methadone
- High Dose buprenorphine versus high dose methadone, 7 studies, 708 participants, RR 0.79 (CI 95% 0.64-0.99), in favour of methadone
- Low dose buprenorphine maintenance versus placebo, 5 studies, 1131 participants, RR 1.50 (CI 95% 1.19-1.88), in favour of buprenorphine
- High dose buprenorphine maintenance versus placebo 4 studies, 887 participants, RR 1.74 (CI 95% 1.06-2.87), in favour of buprenorphine
- Very high dose buprenorphine maintenance versus placebo, 4 studies, 728 participants, RR 1.74 (CI 95% 1.02-2.96), in favour of buprenorphine

It was not possible to pool data for the other outcomes measures, but results of the studies show that high dose methadone is superior to low dose buprenorphine in suppressing heroin use and buprenorphine is superior to placebo.

Reviewers' conclusions

Implications for practice

Buprenorphine is an effective treatment for heroin use in a maintenance therapy approach compared with placebo. However, methadone maintenance treatment at high dose is associated with better suppression of heroin use than buprenorphine maintenance treatment. Buprenorphine maintenance should be supported as a maintenance treatment, only where higher doses of methadone cannot be administered. The reasons for not applying the best available treatment should be investigated rather than promoting less effective treatment approaches. Given buprenorphine' different pharmacological properties, it may have advantages in some settings and under some policies where its relative safety and alternate-day administration are useful clinically compared to methadone.

Implications for research

There does not appear to be any need for further randomised control trials of the relative efficacy of methadone compared with buprenorphine. There does appear to be a need to undertake studies which will clarify retention in the first few weeks or months of treatment in buprenorphine versus methadone. One way of addressing this issue would be to compare a standard induction as used in some of the trials reported herein with a rapid induction onto buprenorphine, with the potential to have a further comparison of induction onto methadone. Problems in the methods of induction onto buprenorphine within the trials analysed might partly explain the inferiority of buprenorphine shown in this review. It would be ideal if such a trial were to be conducted under double blind conditions, particularly in terms of the rapid versus standard induction onto buprenorphine. Other outcome measures such as self-reported drug use, criminal activity, physical health, and psychological health which were too infrequently and irregularly reported in the literature to be analysed in the current review could be included in future studies.

Review 12
LAAM maintenance vs methadone maintenance for heroin dependence
first published CLIB issue 2, 2002

SUMMARY

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

Main results: 18 studies, 3766 participants, 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 was greater with LAAM than with methadone, RR 1.36 (95%CI 1.07-1.73). Use of heroin was less with LAAM, RR 0.84 (CI 95% 0.74-0.96). In 10 studies there were 6 deaths from a range of causes, 5 in participants assigned to LAAM RR 2.28 (95%CI 0.59-8.9); other relevant outcomes, such as quality of life and criminal activity could not be analysed because of lack of information in the primary studies.

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.

DESCRIPTION OF STUDIES

Types of studies: All RCT, CCT and CPS comparing LAAM and methadone maintenance for the treatment of heroin dependence, outcomes of efficacy or acceptability were included.

Types of interventions:
Experimental interventions: LAAM, any formulation, any dose (fixed or flexible); any other medication or non pharmacological treatment may be co-administered (including methadone).
Comparison interventions: Methadone, any formulation, any dosage and with any other pharmacological treatments except LAAM.

The search strategy resulted in the identification of 38 studies.

Excluded studies: 20 studies did not meet the inclusion criteria for the review
Included studies: 18 studies, 3766 participants met the inclusion criteria for the review. (See Table of included studies).

Methodological Quality: 15 RCTs and 3 CPSs. 1/18 described the method of randomisation, in no cases did studies report inadequate randomisation techniques. 3/18 stated the method of allocation concealment. 7/18 studies were blinded; 2/18 attempted to follow up patients, failure to conduct "Intention To Treat" analyses and to follow up all patients beyond cessation of the allocated medication was the major limitation of all the studies. Maintenance dose levels and frequency of dispensing were usually not reported adequately. 15/18 studies were included in the meta-analyses.

Characteristics of the studies: All of the studies were conducted in the US in the 1970's apart from recent trials in the US and Australia.

Characteristics of the participants: 8/18 studies were conducted entirely with males as US regulations restricted the use of LAAM in females. In 8/18 studies participants were current dependent street heroin users and in 8/18 methadone maintained volunteers; 1/18 recruited both and in 1/18 patients were already on LAAM and methadone prior to the commencement of the study. The mean age varied from 25 to 26 yrs and the mean duration of heroin use from 5 to 11 yrs. 2/18 studies reported data on employment, rates varied from full employment to approximately 30%. The larger two studies were conducted amongst US war veterans.

Comparisons:

- LAAM alone vs methadone alone, 15 studies, 3572 participants (Freedman 1981; Goldstein 1974; Grevert 1977;Irwin 1976; Johnson 2000; Karp-Gelernter 1982; Lehmann 1976; Ling 1976;Ling 1978; Savage 1976; Senay 1974; Senay 1977; White 2001; Whysner 1978; Zaks 1972);
- LAAM plus methadone vs methadone alone, 2 studies, 179 participants (Ritter 2001 A, Ritter 2001 B);
- Starting with LAAM vs starting with methadone, then switched freely, 1 study, 19 participants (Resnick 1982).

Treatment regimes: 16/18 studies used flexible dosing regimens with dose adjusted by physicians. 18/18 studies LAAM three times weekly. 2/18 studies used fixed doses.

Outcomes: Cessation of allocated medication, use of heroin, mortality.

RESULTS

Cessation of allocated medication

- LAAM alone vs methadone alone, 10 studies, 1454 participants RR 1.36 (CI 95% 1.07-1.73), in favour of methadone

Use of heroin

- LAAM alone vs methadone alone, 3 studies, 808 participants RR 0.71 (CI 95% 0.57-0.0.89), in favour of LAAM
- LAAM plus methadone vs methadone alone, 2 studies, 175 participants RR 1.01 (CI 95% 0.58-1.76), no statistically significant differences

Mortality

Five deaths were reported in patients randomised to LAAM, two were violent, one was due a heroin overdose (during LAAM induction), one due to alcohol induced liver failure, and one was a motor vehicle accident in a patient who had ceased LAAM some months earlier. The one death in the methadone group was due to a brain tumour in a patient with HIV.

Reviewers' conclusions

Implications for practice

Patients considering maintenance treatment with LAAM should be informed that LAAM is an effective medication, that people in research trials have used slightly less heroin than those taking methadone but have possibly ceased LAAM more frequently due to side-effects. The decision to commence LAAM over other maintenance medications should clearly be weighed against the risks of LAAM some of which (including life threatening arrhythmias due to QT prolongation) are not clear at this stage. Given the ease of transfer to LAAM from methadone or buprenorphine, there seems no reason why patients should necessarily commence with LAAM first. For persons in whom methadone and buprenorphine are not effective, LAAM offers an alternative. The as yet unclear risks of LAAM should be weighed against the risks of continued heroin use.

Implications for research

Future research needs to clarify the risks of LAAM treatment, particularly due to QT prolongation, the additional benefit to the community of having both medications available and have to determine if LAAM is more effective than staying on methadone for "methadone failures". Future methadone vs LAAM RCTs should address practical clinical questions, use ITT analyses, follow up all patients and report health outcome measures in a way that can be compared with other studies.

Review 13.

Heroin maintenance for chronic heroin dependents

first published CLIB issue 3, 2003; last substantive update issue 2, 2005

SUMMARY

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.

Main results: 4 trials involving 577 people were included. The studies could not be analysed cumulatively because of heterogeneity of interventions and outcomes. Retention in treatment: 2/2 studies no group differences, 1/4 study favouring heroin and 1/4 favouring methadone. Relapse to illegal heroin use: 1/4 show no differences and 1/4 RR 0.33 (CI 95% 0.15 - 0.72) favouring heroin. Criminal offence: one study showed the potential of heroin prescription in reducing the risk of being charged RR 0.32 (CI 95% 0.14 - 0.78). Social functioning: 2/4 studies did not show statistical difference between intervention groups, and 2/4 studies considered criminal offence and social functioning as part of a multidomain outcome measure showing improvements among those treated with heroin plus methadone over those on methadone only.

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.

DESCRIPTION OF STUDIES

Types of studies: RCTs.

Types of interventions:
Experimental interventions: Maintenance treatment with pharmaceutical heroin alone or in combination with methadone irrespective of dosages, preparation, route of administration, setting and duration of treatment .

Comparison interventions: No intervention, Methadone maintenance, Waiting list for conventional treatments, Any other treatments which are compared against heroin.

The search strategy resulted in the identification of 20 studies.

Excluded studies: 16 studies did not meet the inclusion criteria
Included studies: 4 studies, 577 participants, meet the inclusion criteria (See Table of included studies).

Methodological Quality: 4/4 were RCTs and described the randomisation procedure; in 3/4 the allocation was concealed, in 1 study the treatment providers were aware of the allocation while the patients were not informed about being part of a trial. All the studies reported follow-up information.

Characteristics of the studies: Duration of trial range 6-12 months; Country of origin: Netherlands (2), UK and Switzerland (1 each)

Characteristics of the participants: Heroin addicts, mean addiction career range 2- of 5 years,
aged 18 to 35 years (mean age 23.9), had been in regular contact with a methadone maintenance program.

Comparisons:
- Heroin maintenance vs oral methadone maintenance 1 study, 96 participants (Hartnoll 1980)
- Heroin injectable + methadone (in some cases) vs methadone, 1 study, 51 participants (Perneger 1998)
- Heroin injectable + methadone vs methadone, 1 study, 174 participants (CCBH 2002 a;)
- Heroin inhalable + methadone vs methadone 1 study, 256 participants (CCBH 2002 b)

Treatment regimes: Heroin maintenance range 30-500 mg per day, methadone maintenance range 10-120 mg per day

Outcomes: Retention in treatment, Relapse to street heroin use (self reported), Use of other substances, Death, Criminal activity, Social Functioning

RESULTS

Retention in treatment

- Heroin maintenance vs oral methadone maintenance 1 study, 96 participants, RR 2.82 (CI 95% 1.70-4.68) in favour of heroin maintenance.
- Heroin injectable + methadone (in some cases) vs methadone, 1 study, 51 participants RR 1.01 (CI 95% 0.86-1.19) no differences between groups
- Heroin injectable + methadone vs methadone, 1 study, 174 participants RR 1.17 (95%CI 0.99 to 1.38) not statistically significant
- Heroin inhalable + methadone vs methadone 1 study, 256 participants, RR 0.79 (CI 95% 0.68 to 0.90) in favour of methadone.

Relapse to street heroin use (self reported)

- Heroin maintenance vs oral methadone maintenance 1 study, 88 participants, RR 2.82 (CI 95% 1.70-4.68) in favour of heroin maintenance.
- Heroin injectable + methadone (in some cases) vs methadone, 1 study, 48 participants, RR 0.33 (CI 95% 0.15 to 0.72) in favour of methadone

Death

- Heroin maintenance vs oral methadone maintenance 1 study, 96 participants, 2/44 participants in the heroin group and 1/52 participant in the methadone group died during the treatment. Suicide was considered as the most likely cause.
- Heroin injectable + methadone vs methadone, 1 study, 174 participants, one participant in the heroin group died several hours after discharge from hospitalization for an epileptic seizure treated with opioid antagonist naloxone; the death was reported as a Severe Adverse Events and the section resulted in a natural cause of death.

Criminal activity

- Heroin maintenance vs oral methadone maintenance 1 study, 96 participants: criminal activity as a source of income RR 0.99 (95%CI 0.72-1.34), no statistically significant difference, criminal activity as people arrested RR 0.73 (CI 95% 0.52-1.03) not statistically significant
- Heroin injectable + methadone (in some cases) vs methadone, 1 study, 51 participants: criminal activity as number of participants charged for any reason in the previous six months (before assessment) RR 0.32 (95%CI 0.14- 0.78), in favour of heroin.

Social Functioning

Heroin maintenance vs oral methadone maintenance 1 study, 96 participants: n° of employed at 12 months follow-up RR 0.86 (CI 95% 0.54-1.35) not statistically significant.

Heroin injectable + methadone (in some cases) vs methadone, 1 study, 51 participants: n° of employed at follow-up: RR 1.56 (CI 95% 0.44-5.50) not statistically significant; n° of people with a stable partner RR 1.33 (CI 95% 0.64- 2.79) not statistically significant.

Reviewers' conclusions

Implications for practice

No definitive conclusions about the overall effectiveness of heroin prescription is possible because of non-comparability of the experimental studies available. Heroin use in clinical practice is still a matter of research in most countries. Results favouring heroin treatment come from studies conducted in countries where 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.

Implications for research

Limitations to this review are imposed by the heterogeneity of the trials both in the interventions and the assessment of outcomes. The authors of the largest and most recent studies proposed a composite outcome measure to deal with the complexity of this issue, agreement on the definition of successful outcomes should be sought as well among researchers. Problems in generalisability of the most recent and promising results call for further research, which should be conducted in heterogeneous social contexts (i.e. different patterns of use, different social environment and different offer of treatment strategies). This is confirmed by the many recent proposals for trials in different countries, Germany, Spain and Canada.

Review 14.

Naltrexone maintenance treatment for opioid dependence

first published CLIB issue 1, 1999; last substantive update issue 1, 2006 (Under editorial process, confidential)

SUMMARY

Objectives: To evaluate the effects of naltrexone maintenance treatment versus placebo or other treatments in preventing relapse in opioid addicts after detoxification.

Main results: 10 studies, 696 participants, met the criteria for inclusion in this review. The results show that naltrexone maintenance therapy alone or associated with psychosocial therapy is more efficacious that 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 significance, RR 0.79 (95%CI 0.59-1.06). With respect to the number of participants re-incarcerated during the study period, the naltrexone associate with psychosocial therapy is more effective than the psychosocial treatment alone RR 0.50 (95%CI 0.27-0.91). No statistically significant benefit was shown in terms of retention in treatment, side effects and relapse at follow-up for any of the considered comparisons.

Conclusions: 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.

DESCRIPTION OF STUDIES

Types of studies: All RCTs and CCTs on naltrexone treatment for opioid dependence.

Types of interventions:
Experimental interventions: Treatment with oral naltrexone in any dosage after detoxification alone or in combination with psychosocial treatments
Comparison interventions: Placebo, no intervention, other pharmacological treatments, psychosocial treatments

The search strategy resulted in the identification of 38 studies.

Excluded studies: 27 studies did not meet the criteria for inclusion in this review
Included studies: 10 studies, 696 participants, meet the inclusion criteria. (See Table of included studies).

Methodological Quality: All RCTs, the method of randomizations was described in only one study; 2/10 studies had an adequate allocation concealment, in all the other studies the concealment of allocation was unclear; 7/10 were double-blind.

Characteristics of the studies: The countries in which the studies were conducted are the following: USA: (4 studies), Israel (2 studies), Spain, China, Russian, German (1 study each). Mean duration: six months (range 1 to 10 months)

Comparisons:
Naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy: seven studies , 444 participants (Curran 1976; Guo 2001; Hollister 1978; San 1991; Krupitsky 2004; Lerner 1992; Shufman 1994);
- Naltrexone versus placebo : 4 studies, 329 participants (Curran 1976; Guo 2001; Hollister 1978; San 1991);
- Naltrexone versus psychosocial therapy: 2 studies, 146 participants (Ladewig 1990; Rawson 1979);
- Naltrexone versus naltrexone plus psychosocial therapy, 1 study, 110 participants (Rawson 1979);
- Naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy : 3 studies, 115 participants (Krupitsky 2004; Lerner 1992; Shufman 1994);

- Naltrexone plus psychosocial therapy versus psychosocial therapy alone: 2 studies, 177 participants (Cornish 1977; Rawson 1979);

Treatment regimes: Naltrexone dosage: three times weekly application: 4 studies (100-100-150 mg three studies and 50-50-50 one study); twice weekly application (100- 150 mg): 2 studies; 50 mg every day: 1 study; six days application but the dose is not specified: 1 study; 100 mg for five days and 150 mg on Saturday: 1 study and one study do not specify the doses and the frequency of administration. All trials were conducted on outpatient's basis.

Outcomes: Retention in treatment, Use of heroin as number of participants with positive urinalysis at the end of the study and self report data, Relapse at follow up, Side effects, Criminal activity

RESULTS

Retention in treatment as number of participants retained at the end of the study

Naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy: 5 studies, 203 participants, RR 1.08 (95% IC 0.74 to 1.57) no statistically significant;

- Naltrexone versus placebo, 2 studies, 88 participants, RR 0.50 (CI 95% 0.20 to 1.24) no statistically significant;
- Naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy, 3 studies, 115 participants, RR 1.38 (95% IC 0.90- 2.10), no statistically significant difference;
- Naltrexone versus naltrexone plus psychosocial therapy, 1 study, 43 participants, RR 0.94 (CI 95% 0.59-1.48) no statistically significant difference;
- Naltrexone plus psychosocial therapy versus psychosocial therapy alone: 1 study, 51 participants, RR 1.50 (95% IC 0.73-3.07), no statistically significant difference

Use of heroin as number of participants with positive urine samples at the end of the study:

- Naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy: 6 studies, 249 participants, RR 0,72 (CI 95% 0.58 to 0.90) in favour of naltrexone
- Naltrexone versus placebo, 3 studies, 134 participants, RR 0.79 (95% IC 0.59 to 1.06) the difference is not statistically significant but there is a trend in favour of naltrexone.
- Naltrexone versus psychosocial therapy, 1 study 19 participants, RR 0.71 (95% IC 0.28- 1.82), no statistically significant difference.
- Naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy, 3 studies, 115 participants, RR 0.66 (95% IC 0.47-0.92), in favour of naltrexone**.**

Results at follow up as number of participants relapsed at follow up

- Naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy, 2 studies, 81 participants, RR 0.94 (CI 95% 0.67 to 1.34) no statistically significant difference
- Naltrexone versus placebo, 1 study, 50 participants, RR 1.07 (95% IC 0.71- 1.60) no statistically significant difference.
- Naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy, 1 study, 31 participants, RR 0.75 (CI 95% 0.39- 1.45) no statistically significant difference
- Naltrexone versus psychosocial therapy, 1 study, 38 participants, RR 0.65 (95% IC 0.19-2.22) no statistically significant difference.
- Naltrexone versus naltrexone plus psychosocial therapy, 1 study, 43 participants, RR 1.16 (CI 95% 0.29-4.57) no statistically significant difference.
- Naltrexone plus psychosocial therapy versus psychosocial therapy alone, 1 study, 35 participants, RR 1.50 (CI 95% 0.55- 4.06) no statistically significant difference

Side effects as number of participants with at least one side effect

- Naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy : three studies (Curran 1976; Guo 2001; Krupitsky 2004) 139 participants, RR 1.21 (95%IC 0.81 to 1.81), no statistically significant difference, but there is a trend in favour of placebo
- Naltrexone versus placebo, 2 studies, 87 participants RR 0.96 (CI 95% 0.65-1.42), no statistically significant difference.
- Naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy, 1 study RR 2.47 (CI 95% 0.74- 8.28) no statistically significant difference
- Naltrexone versus psychosocial therapy, 1 study, 19 participants, RR 0.83 (CI 95% 0.34-2.02) no statistically significant difference.

Re-incarceration as number of participants re incarcerated during the study

- Naltrexone versus psychosocial therapy, 1 study, 38 participants, RR 0.65 (CI 95% 0.26-1.65) no statistically significant difference but there is a trend in favour of the naltrexone treatment.
- Naltrexone plus psychosocial therapy versus psychosocial therapy alone, 2 studies, 86 participants RR 0.50 (CI 95% 0.27- 0.91), in favour of naltrexone.

Reviewers' conclusions

Implications for practice

Naltrexone maintenance therapy associated with psychosocial therapy is effective in limiting the use heroin during the treatment With respect to the number of participants re-incarcerated during the study period, naltrexone associated with psychosocial therapy is more effective than the psychosocial treatment alone. No statistically significant benefit was shown in terms of retention in treatment , side effects and results at follow-up for any of the considered comparisons. Consequently, maintenance therapy with naltrexone cannot yet be considered a treatment which has been scientifically proved to be superior to other kinds of treatment. Naltrexone may be an efficacious adjuvant in therapy, especially for participants who fear severe consequences in case they do not stop taking opioids indefinitely. This target group consists of health-care professionals, who might lose their job or parolees who risk re-incarceration. Other highly motivated addicts may profit from naltrexone treatment.

Implications for research

Limitations to this review are imposed by the heterogeneity of the trials both in the interventions and the assessment of outcomes. In the case of antagonist treatment, randomization is difficult as the participant can find out easily (with one heroin injection) about his/her study medication (verum or placebo). As a consequence, in many studies the type of medication is self-selected and where blinding is done, drop-out in the placebo group is much higher than in the naltrexone group. Given that selective drop-out seems to be difficult to avoid, the comparability of naltrexone and placebo groups is limited. As a consequence, the investigators may try different methods (such as money reward systems) but the variety of individually designed and non-compatible studies limits combination of studies and makes meta-analysis almost impossible.

Review 15.

Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence

first published CLIB issue 4, 2004

SUMMARY

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

Main results: 12 trials, 981 participants were included. The studies considered eight different psychosocial interventions and one 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 Relative Risk 0.69 (95% confidence interval 0.53 to 0.91); no statistically significant additional benefit was shown in terms of retention in treatment relative risk 0.94 (95% confidence interval 0.85 to 1.02); and results at follow-up relative risk 0.90 (95% confidence interval 0.76 to 1.07).

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.

DESCRIPTION OF STUDIES

Types of studies: Randomised controlled trials

Types of interventions:
Experimental interventions: Psychosocial plus agonist maintenance interventions of any kind (any psychosocial and any drug)
Comparison interventions: Any agonist treatments for opiate maintenance therapy.

The search strategy resulted in the identification of 77 studies.

Excluded studies:. 65 studies did not meet the criteria for inclusion in this review.
Included studies: 12 studies met the inclusion criteria for this review (See Table of included studies).

Methodological Quality: 12 RCTs, 2/12 studies describe the randomization method; 0/12 mention any allocation concealment approach; 2/12 were double blind. All but one study were evaluated as studies with moderate risk of bias. 1/12 was evaluated as a study without allocation concealment; 11/12 give information on people who left the study or were lost at follow-up.

Characteristics of the studies: The studies considered 8 different psychosocial interventions and 1 pharmacological maintenance treatment: Methadone Maintenance Treatments; the 8 psychosocial interventions considered in the 12 included studies were: behavioural treatments (4 studies), psychoanalytic oriented treatments (2 studies), one form of structured counselling (1 study), a Short Term Interpersonal Psychotherapy (1 study). All the included studies were conducted in USA; Duration of the trials: range 2-8 months;

Characteristics of the participants: 981 opiate addicts: 81% (794) were male. Average age was 36 years (range 27 to 41).

Comparisons:

- Any psychosocial intervention plus Methadone Maintenance Treatment (MMT) versus MMT: 12 studies, 981 participants (Abbott 1998; Abrahms 1979; Iguchi 1997; Khatami 1982; McLellan 1993; Milby 1978; Preston 2000; Rounsaville 1983; Stitzer 1992; Thornton 1987; Woody 1983; Woody 1995);

- Any behavioural intervention plus MMT versus Standard MMT : 8 studies, 645 participants ((Abbott 1998; Abrahms 1979; Iguchi 1997; Khatami 1982; Milby 1978; Preston 2000; Stitzer 1992; Woody 1983 arm 2);
- Any psychoanalytic oriented interventions plus MMT versus Standard MMT, 3 studies, 211 participants (Thornton 1987; Woody 1983 arm 1; Woody 1995);
- Short term Interpersonal Therapy plus MMT vs Standard MMT: 1 study, 72 participants (Rounsaville 1983);
- Enhanced Methadone Services plus MMT vs Standard MMT vs only MMT: 1 study, 92 participants (McLellan 1993);

Treatment regimes: Information on methadone doses were available for 8 out of 12, the mean methadone dose was 50.7 mg/day.

Outcomes: Retention in treatment, Use of opiate, Results at follow-up as number of participants still in treatment at the end of the follow-up and as number of participants abstinent at the end of the follow-up, Compliance, Craving, Psychiatric symptoms/psychological distress, Quality of life, Severity of dependence.

RESULTS

Retention in treatment as number of participants retained at the end of the study:
- Any Psychosocial interventions plus MMT versus Standard MMT, 8 studies, 510 participants, RR 0.94 (CI 95% 0.85 - 1.02), no statistically significant difference.
- The difference remain not significant for all the other comparisons

Use of opiate as number of participants with consecutive positive urinalysis for at least three weeks:
- Any Psychosocial plus MMT vs Standard MMT, 5 studies, 388 participants, RR 0.69 (CI 95% 0.53 - 0.91), the difference was statistically significant in favour of Psychosocial treatments associated with MMT.
- This difference became not significant only in the comparison Psychoanalytic oriented interventions plus MMT versus Standard MMT, 2 studies, 127 participants, RR 0.83 (CI 95% 0.47 -1.45)

Results at follow-up

as number of participants still in treatment at the end of the follow-up.
- Any Psychosocial plus MMT versus Standard MMT, 3 studies, 250 participants RR 0.90 (CI 95% 0.76 - 1.07), no statistically significant difference.
- The difference remain not significant for all the other comparisons

as number of participants abstinent at the end of the follow-up
- Any Psychosocial plus MMT versus Standard MMT, 2 studies, 108 participants, RR 0.88 (CI 95% 0.67 - 1.15), no statistically significant difference.
- The difference remain not significant for all the other comparisons

For all the outcomes it was impossible to pool the data

Reviewers' conclusions

Implications for practice

The findings of this review suggest that adding any psychosocial support to Standard MMT improves the non-use of heroin during treatment without a statistically significant effect on retention in treatment and results at follow-up. Insufficient evidence is available on other possible relevant outcomes such as Psychiatric symptoms/psychological distress, Quality of life and Severity of dependence.

Implications for research

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 the 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 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 possible.

Review 16.

Psychosocial treatments for opiate abuse and dependence
first published CLIB issue 1, 2005

SUMMARY

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

Main results: 5 trials involving 389 participants were included. 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.

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.

DESCRIPTION OF STUDIES

Types of studies: RCTs that described an active psychosocial intervention for reducing the harm related to opioid use.

Types of interventions:
Experimental interventions: Any psychosocial treatment as long as it is validated or described by the study's author, allowing repetition. The intervention should not included any drug.
Comparison interventions: Other psychosocial treatment, Pharmacological Interventions, Placebo, Non-intervention.

The search strategy resulted in the identification of 16 studies.

Excluded studies: 11 studies did not the inclusion criteria for this review
Included studies: 5 studies meet the inclusion criteria (See Table of included studies).

Methodological Quality: 5 RCTs, 4/5 report the method utilized, the allocation concealment was not adequately described in all trials. 1/5 studies adopted a single-blind procedure, no information on blinding was provided in the other studies; 2/5 carried out intention to treat analysis, 1/5 used intention to treat analysis where possible and 2/5 did not use intention to treat analysis. The outcome reporting varied within the studies preventing the possibility of pooling data.

Characteristics of the studies: Study sizes range 41 -175 participants, duration range 2 weeks - 9 months, 4/5 studies were conducted in an outpatients setting and 4/5 in USA, 1 in UK. The psychosocial interventions considered were: 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.

Characteristics of the participants: 389 opioid users, mean age 36 years 74% male, 59% of the participants were of African American origin.

Comparisons:

- Enhanced outreach counselling program versus brief standard referral protocol, 1 study, 41 participants (Zanis 1996);
- Reinforcement-Based intensive outpatient treatment (RBT) versus Standard community treatment resources, 1 study, 52 participants (Gruber 2000);
- Contingency management (Voucher Reinforcement) versus control, 1 study, 52 participants (Katz 2002)
- Cue exposure therapy versus control, 1 study, 48 participants (Dawe 1993);
- Alternative program for MMTP drop-outs versus control, 1 study, 175 participants (Goldstein 2001).

Outcomes: Use of opiate, Craving, Retention in treatment, Compliance, Relapse at follow-up, Mortality, Physical Health, Quality of life

RESULTS

- enhanced outreach counselling program versus brief standard referral protocol, 1 study 41 participants: re-enrolment back into treatment services RR 0.27 (CI 95% 0.14 -0.52), in favour of the treatment;
- Reinforcement-based intensive outpatient treatment (RBT) versus standard community treatment resources, 1 study, 52 participants: number of dropouts in the first month follow up RR 0.47 (CI 95% 0.29 - 0.77) in favour of the treatment, however this was not maintained by the three month follow up RR 0.99 (CI 95% 0.77 - 1.26).
- Contingency management (voucher reinforcement) versus control, 1 study, 52 participants: no significant difference between the groups for abstinence of one week, two weeks or four weeks, numbers of drop outs, relapse to opioid and cocaine use and the number of research or counselling sessions attended in the first three months;
- Cue exposure therapy versus control, 1 study, 48 participants: no difference between the groups for relapse to opioid use at six weeks and six months follow up;
- Alternative program for MMTP drop-outs versus control, 1 study, 175 participants: there was a trend for the intervention group to improve re-entry back into treatment services, however this was not significant.

Reviewers' conclusions

Implications for practice

The evidence available does not allow an objective evaluation as there is little reliable evidence and the available data is on a very small scale. At present psychosocial treatments alone are not adequately proved treatment modalities or superior to any other type of treatment. There is no data to support psychosocial interventions alone at present. There is no available cost benefit information available. The high attrition rates are very important in substance abuse treatment and this should be a main outcome of any forthcoming research.

Implications for research

Large randomised trials with longer follow ups, to examine whether psychosocial interventions alone help patients with opioid use disorders are needed. The questions that should be raised are whether one psychosocial intervention is more effective than another? Does the effectiveness depend upon personality factors, psychiatric co-morbid diagnosis, length of therapy time, severity of illicit drug use or any other factors? The randomised trials should clearly state the method of randomisation, allocation concealment, blinding where possible, perform intention to treat analysis, with power calculations performed prior to the trial. More pragmatic studies can be designed and delivered that provide usable data for better understanding this important component of intervention in the field of dependence. Globally great emphasis is placed on the vital role of psychosocial treatments for the management of opioid dependence. Indeed in many parts of the world far greater value is attributed to psychosocial treatments than to pharmacological approaches to opioid dependence. However this is despite a dearth of good evidence on the overall value of psychosocial treatments. Policy makers need to ensure that a better evidence base is developed around psychosocial treatment to assist in the future rationale planning of interventions for opioid dependence.

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