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Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis

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Abstract

The efficacy of methadone maintenance in opioid addiction was assessed in terms of programme retention rate and reduction of illicit opioid use by means of a meta-analysis of randomised, controlled and double blind clinical trials. The results were compared with interventions using buprenorphine and *levo*-acetylmethadol (LAAM). Trials were identified from the PubMed® database from 1966 to December 1999 using the major medical subject headings 'methadone' and 'randomised controlled trial'. Data for a total of 1944 opioid-dependent patients from 13 studies were analysed. Sixty-four percent of patients received methadone, administered either as fixed or adjusted doses. Thus, 890 patients received $\geqslant 50$ mg/day (high dose group) and 392 were given < 50 mg/day (low dose group). Of 662 controls, 131 received placebo, 350 buprenorphine (265 at doses $\geqslant 8$ mg/day and 85 at doses < 8 mg/day) and 181 LAAM. High doses of methadone were more effective than low doses in the reduction of illicit opioid use (odds ratio [OR] 1.72, 95% confidence interval [CI] 1.26–2.36). High doses of methadone were significantly more effective than low doses of buprenorphine (< 8 mg/day) for retention rates and illicit opioid use, but similar to high doses of buprenorphine ($\geqslant 8$ mg/day) for both parameters. Patients treated with LAAM had more risk of failure of retention than those receiving high doses of methadone (OR 1.92, 95% CI 1.32–2.78). It is proposed that in agonist-maintenance programmes, oral methadone at doses of 50 mg/day or higher is the drug of choice for opioid dependence.

Keywords: Methadone; Opioid use; Buprenorphine; *Levo*-acetylmethadol

1. Introduction

Since Dole and Nyswander (1965) proposed the use of methadone as a substitution treatment for heroin addiction, methadone maintenance treatment has become an extensively used intervention because of its ability to reduce illegal opioid consumption. Later, after the rapid spread of infection with the human immunodeficiency virus (HIV) among intravenous heroin users, it was found that methadone maintenance treatment appeared to reduce the frequency of HIV infection in this population and it became one of the most useful strategies of harm reduction (Ward et al., 1999). At the present time, thousands of patients from many countries are enrolled in methadone treatment programmes. Although the benefits of this therapeutic strategy are well established, relatively few studies have assessed its efficacy in terms of statistically significant differences in outcome measures, so that the role of methadone treatment in opioid dependence is still controversial. On the other hand, many efforts have been made to find alternative drugs to methadone that might be useful in substitution treatment programmes. Opioid agonists, such as *levo*-acetylmethadol (LAAM; Ward et al., 1999), buprenorphine (Ward et al., 1999) and even heroin (Pernerger et al., 1998) have been proposed.

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Meta-analysis, a statistical technique for combining the results of independent studies, is a reliable and recommended approach for drawing definite conclusions from the available evidence on health care interventions (Sacks et al., 1987). Meta-analysis of randomised controlled clinical trials is especially valuable for assessing the efficacy of drug-related interventions. Meta-analysis pools the data of reported trials and presents an objective, quantitative measure of the efficacy of an intervention. Its strength, however, lies in its ability to reduce the type II errors of individual smaller studies and therefore, it increases the level of certainty for or against a given treatment (Dickersin and Berlin, 1992; Walter, 1995). Other important purposes of meta-analysis include resolving of conflicting reports in the literature, investigating variations in treatment effects through stratified analysis, improving the general applicability of known treatment effects, and determining whether or not there is a need for a further major clinical trial.

Meta-analytical procedures have been used to examine the efficacy of methadone as a pharmacological intervention in opiate substance abuse in only three studies (Glanz et al., 1997; Marsch, 1998; Griffith et al., 2000). Glanz and co-workers (1997) carried out a meta-analysis of the reported randomised controlled trials of LAAM versus methadone therapy and found a statistically significant advantage for methadone for retention in treatment. With respect to illicit drug use, the study did not show a significant difference, but a trend in favour of LAAM was observed. However, treatment discontinuance did show a small but statistically significant difference in favour of methadone. The meta-analysis carried out by Marsch (1998) was based on non-drug controlled studies (pre- and post effects or methadone vs no treatment); it analysed the effect of methadone maintenance treatment on illicit opiate use, HIV risk behaviours and criminal activities. In contrast to the report of Glanz et al., (1997) and to the present meta-analysis, retention in treatment was not evaluated. Nevertheless, Marsch (1998) found that the effectiveness of methadone was most apparent in its ability to reduce drug-related criminal behaviours. Methadone had a moderate effect in reducing illicit opiate use and a small to moderate effect in reducing HIV risk behaviours. The third meta-analysis, on contingency management interventions (Griffith et al., 2000), also did not address retention in treatment; the outcome measure of interest was drug use during treatment, as detected through urinalysis. The overall results confirmed that contingency management was effective in reducing supplemental drug use while patients participated in methadone treatment and that methadone dose increases, take-homes as incentives and urine monitoring three times a week were effective in promoting drug-free urines.

The present meta-analysis was conducted to determine the effect of methadone maintenance strategies on the endpoints of retention rate and reduction of illicit opioid use. To assess the influence of methadone on these outcome variables, only double-blind randomised controlled clinical trials in which placebo, buprenorphine or LAAM had been used as the reference drug were selected. Since both drugs are already marketed or will be available at an early date in many countries as an alternative to methadone for substitution treatment, the rationale for selecting trials using buprenorphine or LAAM as control drugs seemed both pertinent and relevant.

2. Methods

2.1. Literature search

Studies eligible for inclusion in the meta-analysis were retrieved from the PubMed® database for 1966 to December 1999 using the major medical subject headings 'Methadone' (all fields) and 'Randomised controlled trial' (publication type). All languages were included. Additional reports were identified from the references lists of retrieved articles, as well as by manual review of the tables of contents of journals on drug of abuse included in the psychiatry and substance abuse subject category listing 1997 of the Journal Citation Reports®. Abstracts of medical meetings were excluded. The Cochrane Library (1999 issue 4) using the word 'methadone' was employed to corroborate completeness of the literature search.

2.2. Selection, extraction, and collection of data

In order to be selected for the study, articles had to fulfil and provide the following information: (1) randomised, controlled, and double-blind clinical trials with methadone as the study drug; (2) length of methadone maintenance treatment $\geqslant 12$ weeks; (3) dose(s) of methadone clearly stated; (4) measures of retention rates in methadone treatment and/or illicit opioid use based on analytical determination of drugs of abuse in urine samples as outcome variables. Trials in which opioid detoxification was a main objective and cross-over trials were excluded.

Data from studies included in the systematic review were extracted independently by two researchers (AM, MF). The following variables were collected: bibliographic reference of the article, first author's name, year of publication, weeks of treatment, control treatment, number of patients in both groups of treatment, doses of methadone and control treatment, retention in treatment at the end of the study period, and illicit opioid use. Some studies used a fixed dose but in others there

was flexible dose titration (see Table 1). In the latter cases, the dose included in the analysis was the mean dose administered at the time of the endpoint evaluation.

The dose of methadone was categorised into two groups: < 50 mg/day (low dose group) and $\geqslant 50$ mg/day (high dose group), because according to the General Accounting Office (GAO, 1990) report of 1990, it is widely accepted that 50 mg is the lowest dose of methadone useful for maintenance interventions. The dose of buprenorphine was categorised in two groups < 8 mg/day (low dose group) and $\geqslant 8$ mg/day (high dose group) taking into account results from a dose–response clinical trial (Ling et al., 1998) and from pharmacokinetic analyses (Kuhlman et al., 1998). The quality of the 13 trials finally included in the meta-analysis was analysed using a validated instrument developed by Jadad et al. (1996) that assesses three critical aspects of a well-designed and well-executed clinical trial, i.e. randomisation, blinding process, and description of withdrawals. Quality scoring ranges from 5 (high quality score) to 1 (low quality score). Open assessments of the items were performed by two of the authors (MF, AM) together.

2.3. Data analysis

Logistic regression within a multilevel model framework (Turner et al., 2000) was chosen for the estimation of summary odds ratios (OR) because each study could contribute more than one drug and/or more than one dose and, therefore, the classical approach was not suitable. The proportion of patients retained in the programme and the proportion of illicit opioid users were the dependent variables. In order to obtain a similar positive risk for both outcome variables, retention in treatment was analysed as 'failure in retention'. Studies were considered a random effect that con-

Table 1
Summary of the studies included in the meta-analysis

First author (year)	Drug	Doses (mg/day)	No.	Retention *n* (%)	Illicit opioid use *n* (%)	Weeks
Jaffe et al. (1972)[a]	Methadone	55	15	13 (87)	4 (27)	15
	LAAM	65, Mon–Wed–Fri	19	14 (74)	10 (53)	
Ling et al. (1976)[b]	Methadone	100	142	74 (52)	38 (27)	40
	Methadone	50	146	61 (42)	37 (25)	
	LAAM	80, Mon–Wed–Fri	142	44 (31)	27 (19)	
Panell et al. (1977)[b]	Methadone	100	20	17 (85)		40
	Methadone	50	20	14 (70)		
	LAAM	80, Mon–Wed–Fri	20	12 (60)		
Newman and Whitehill (1979) [a]	Methadone	97	50	38 (76)		32
	Placebo		50	5 (10)		
Johnson et al. (1992)[b]	Methadone	60	54	17 (31)	30 (56)	17
	Methadone	20	55	11 (20)	39 (71)	
	Buprenorphine	8	53	22 (42)	25 (47)	
Strain et al. (1993a)[b]	Methadone	50	84	44 (52)	47 (56)	15
	Methadone	20	82	34 (41)	55 (67)	
	Placebo		81	17 (21)	60 (74)	
Kosten et al. (1993)[b]	Methadone	65	35		17 (49)	24
	Methadone	35	34		16 (47)	
	Buprenorphine	6	28		21 (75)	
	Buprenorphine	2	28		20 (71)	
Banys et al. (1994)[b]	Methadone	80	19	16 (84)		13
	Methadone	40	19	15 (79)		
Strain et al. (1994a)[a]	Methadone	67	27	16 (59)	16 (59)	16
	Buprenorphine	11	24	13 (54)	13 (54)	
Strain et al. (1994b)[a]	Methadone	54	80	45 (56)	38 (48)	16
	Buprenorphine	9	84	47 (56)	46 (55)	
Ling et al. (1996)[b]	Methadone	80	75	39 (52)		26
	Methadone	30	75	30 (40)		
	Buprenorphine	8	75	26 (35)		
Schottenfeld et al. (1997)[b]	Methadone	65	28	18 (64)	13 (46)	24
	Methadone	20	30	14 (47)	21 (70)	
	Buprenorphine	12	29	16 (55)	17 (59)	
	Buprenorphine	4	29	10 (34)	22 (76)	
Strain et al. (1999)[a]	Methadone	90	95	57 (60)	50 (53)	30
	Methadone	46	97	54 (56)	60 (62)	

[a] Flexible dose titration.
[b] Fixed dose.

tributed with two or more drug groups. Dummy variables were included in the models to compare the different drug groups in respect to methadone. Homogeneity of effects was explored including additional random effects for drug groups. When significant, these were retained in the model to account for heterogeneity among studies. Model parameters were estimated with Mlwin using restricted maximum likelihood for final estimates and 95% confidence intervals (CI; Normand, 1999). Methadone at high dose was selected as reference category (OR = 1) for OR calculations.

3. Results

A total of 13 studies fulfilled the inclusion criteria and all of them were published since 1972 (Table 1). Fifteen reports (Jaffe et al., 1972; Ling et al., 1976; Newman and Whitehill, 1979; Johnson et al., 1992; Kosten et al., 1993; Strain et al., 1993a,b, 1994a,b; Banys et al., 1994; Stine and Kosten, 1994; Ling et al., 1996; Strain et al., 1996; Schottenfeld et al., 1997; Strain et al., 1999) were retrieved from the PubMed® database, but three of them were repeated (Strain et al., 1993b; Stine and Kosten, 1994; Strain et al., 1996). One article was obtained by review of the articles' reference lists (Panell et al., 1977). No further articles were retrieved through the Cochrane database search. All the studies included in the meta-analysis had a minimal quality score of four points and two of them reach the maximal score (five points).

The total number of opioid-dependent patients included in the 13 studies was 1944, with a range among studies from 34 to 430. Most of the patients were male (80%). The mean age was 34.4 years and Caucasians accounted for the 43% of the total sample. Other baseline characteristics, such as employment status, length of opioid addiction, and number of previous treatments, were not routinely described in all the publications. Sixty-four percent of the patients ($n = 1282$) received methadone. According to the methadone dose administered, 890 patients were considered in the high dose group and 392 in the low dose group. Only in one study (Jaffe et al., 1972), was the mean of all methadone doses considered. Eleven studies compared one or more doses of methadone with placebo or other control drugs (with one or more different doses), but in two studies (Banys et al., 1994; Strain et al., 1999) only two doses of methadone were administered (high, low).

With respect to the 662 controls, the following distribution was recorded: 131 in the placebo group, 350 in the buprenorphine group (265 receiving high dose and 85 receiving low dose), and 181 in the LAAM group. Twelve studies included data on retention failure and nine studies provided data on illicit opioid use measured by random urine testing (Table 1).

3.1. Methadone by dose and versus placebo

When the efficacy of methadone maintenance intervention was analysed, a clear difference between low and high doses was observed (Fig. 1A and 1B). High doses of methadone ($\geqslant 50$ mg/day) were more effective than low doses in reducing illicit opioid use (OR 1.72 [95% CI, 1.26–2.36], $P = 0.0007$). Although the risk of failure in retention in the methadone maintenance programme was higher in the low dose group, statistically significant differences were not found (OR 1.25 [95% CI, 0.94–1.67], $P = 0.13$). Methadone at high dose was better than placebo in terms of failure in retention (OR 8.76 [95% CI, 3.82–20.07], $P < 0.0001$) and positive opioid urines (OR 2.44 [95% CI, 1.35–4.43], $P = 0.0033$). Low dose of methadone was better than placebo in retention but similar in illicit opioid use.

3.2. Methadone versus buprenorphine

Subjects given low doses of buprenorphine showed more risk of illicit drug use than those given high doses of methadone (OR 3.39 [95% CI, 1.87–6.16], $P = 0.0001$). The risk for positive urine testing was similar between high doses of methadone and high doses of buprenorphine (OR 1.08 [95% CI, 0.75–1.57], $P = 0.68$; Fig. 1A). In relation to failure of retention in the programme, subjects treated with low doses of buprenorphine showed more risk of retention failure than those treated with high doses of methadone (OR 2.72 [95% CI, 1.12–6.58], $P = 0.027$). The risk for retention failure was similar between high doses of methadone and high doses of buprenorphine (OR 1.14 [95% CI, 0.83–1.59], $P = 0.042$; Fig. 1B).

3.3. Methadone versus LAAM

Methadone at high doses was similar to LAMM in illicit opioid use (OR 0.72 [95% CI, 0.46–1.11], $P = 0.14$; Fig. 1A), but better in respect to retention in treatment (OR 1.92 [95% CI, 1.1.31–2.81], $P = 0.0008$; Fig. 1B). Methadone at low doses was worse than LAAM with regard to illicit opioid use, but the two treatments showed a similar proportion of failures in retention.

4. Discussion

The present study compared the effectiveness of methadone, buprenorphine and LAAM in long-term treatment in opioid dependence; it showed that methadone administered at doses of $\geqslant 50$ mg/day and buprenorphine $\geqslant 8$ mg were similar in terms of retention in treatment and both were better than LAAM (the probability of failure in retention was almost two-

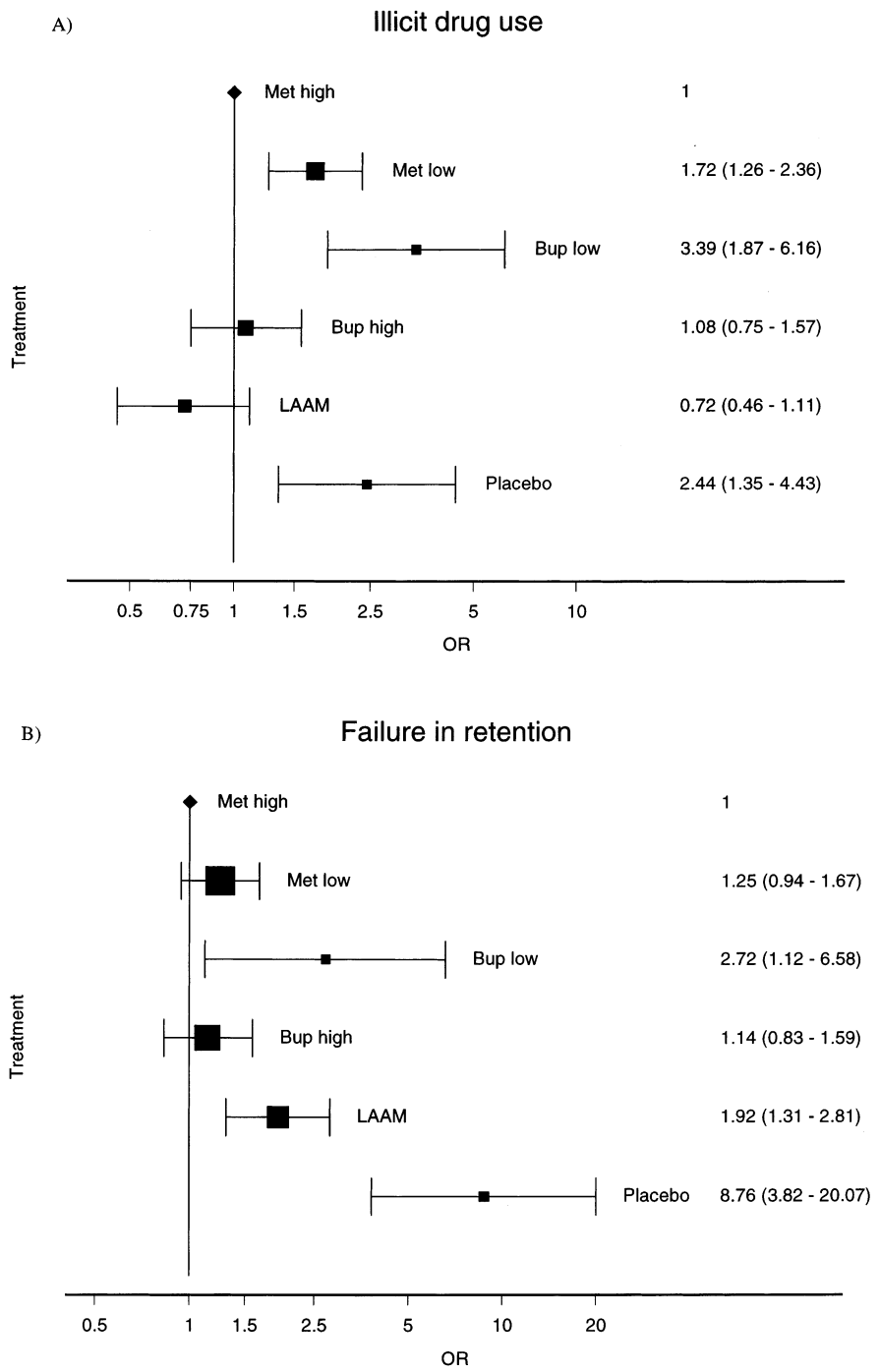

Fig. 1. Pooled effects (odds ratio and 95% confidence intervals) of drug conditions in comparison with high dose methadone on: (A) prevention of illicit opioid use, and (B) on failure in retention in methadone maintenance programmes. The size of the symbols is proportional to the number of subjects included in pooled studies.

fold in relation to methadone). However, the three treatment modalities showed similar efficacy in reducing illicit opioid use. The administration of doses of methadone $\geqslant 50$ mg increased the retention rates (25% less retention failures; OR 1.25) and reduced illicit opioid use by 72% (OR 1.72) as compared with low-dose methadone. In a recent open, randomised clinical trial methadone (high dose from 60 to 100 mg, low dose 20 mg) was administered daily whereas LAAM (75–115 mg) and buprenorphine (16–32 mg) were given three times a week; high-dose methadone, buprenorphine and LAAM substantially reduced the use of illicit opioids as compared with low-dose methadone (Johnson et al., 2000).

Accordingly, the present results confirm previous recommendations that daily doses of methadone higher

than 50 mg increase the efficacy of methadone maintenance (Farrell et al., 1994; Marsch, 1998). It should be noted that, despite this recommendation, the use of methadone at doses lower than 50 mg is not infrequent (D'Aunno and Vaughn, 1992; Strang and Sheridan, 1998). Reasons for under-dosing may reflect some bias in our society against the drug-dependent population, including the fear of iatrogenic addiction by doctors and patients, reluctance to recognise dependence as a medical disorder, or concerns about methadone diversion when given at high doses (Cooper, 1992).

In relation to alternative drugs for opioid maintenance, buprenorphine and LAAM, some points have to be discussed. Both methadone and buprenorphine showed a dose–response relationship and the pattern of response for each substance was similar, i.e. high doses were superior than low doses. When high and low doses of methadone were compared with high and low doses of buprenorphine, high doses of both agents were superior to low doses. In the case of LAAM, the limited number of studies (only three) and the narrow range of doses administered did not allow assessment of differences between doses. Although in terms of effectiveness buprenorphine or LAMM were not better than methadone, they shared some characteristics that could be useful in clinical practice. Buprenorphine and LAAM can be administered every two days (Johnson et al., 1995; Ward et al., 1999) instead of daily, thus reducing the number of attendance to the centre and theoretically allowing the recruitment and control of more patients in each programme, with a decreased risk of diversion. This issue could be relevant in countries with very restrictive take-home dose policies.

In the case of buprenorphine, this drug may be less stigmatising than methadone and can be acceptable for some patients who do not want to take methadone. Other possible advantages are related to its pharmacological properties. The withdrawal symptoms following the abrupt discontinuation of buprenorphine are relatively mild (Fudala et al., 1990; San et al., 1992) and it seems to have a theoretical lower risk of overdose because of its partial agonist properties (Walsh et al., 1994; Cowan et al., 1977). In some countries, such as France, legislation makes it easier to prescribe high-dose, sublingual buprenorphine than methadone (Tignol et al., 1998). The wide use of this substitution therapy has been related to an increased number of buprenorphine-related deaths after the intravenous injection of crushed tablets and the concomitant intake of other psychotropics (especially benzodiazepines; Reynaud et al., 1998; Tracqui et al., 1998a,b).

In a recent study, death rates from overdoses of buprenorphine and methadone in France from 1994 to 1998 were computed. There were an estimated 1.4 more buprenorphine-related deaths than methadone-related deaths. However, 14 times more patients received buprenorphine than methadone. If all patients in France that received either of these drugs had been treated only with methadone, the expected number of deaths would have been 288 instead of 46 (Auriacombe et al., 2001). One possible limitation of our study is that buprenorphine was administered as a liquid in all the studies included in this meta-analysis. The bioavailability of buprenorphine from the tablets seems to be half that from the liquid formulation (Nath et al., 1999). Nevertheless the clinical results in France with tablets seem similar to those reported in clinical trials in US for the liquid formulation (Anonymous, 1999).

With regard to LAAM, our results are less encouraging than those for buprenorphine. Nevertheless, the results of LAAM are based on only three studies where LAAM was administered on a Monday–Wednesday–Friday schedule. Fixed doses of LAAM (80 mg) were administered in two of these studies (Ling et al., 1976; Panell et al., 1977) and, at the present time, 40% higher doses on Fridays are recommended. Therefore, it is possible that the efficacy of LAAM may have been improved if larger doses had been given on Fridays. With respect to the third study (Jaffe et al., 1972) LAAM was given at flexible doses (mean dose 65 mg).

The present findings are similar than those reported by Glanz et al. (1997) in their meta-analysis of randomised controlled clinical trials comparing LAAM and methadone. They included a total of 12 trials and their inclusion/exclusion criteria were wider than ours (e.g. including open, single-blind and detoxification studies). They found a lower, but non-significant, risk for illicit drug use in favour to LAAM, and a significantly higher risk favouring methadone for retention in treatment (Glanz et al., 1997). Our results were similar to theirs. Furthermore, the use of LAAM has some limitations as compared with methadone. It needs a longer period of induction to achieve the maintenance dose and it shows an increased risk of dropout during that period (Jones et al., 1998; Johnson et al., 2000). It is common for patients to need supplemental doses of methadone during the induction period and during the weekends to help them through the long, 72-h inter-dose interval (Rawson et al., 1998). It has recently been shown that LAAM also has some degree of abuse liability, although the gradual onset of effects after oral administration is likely to minimise the risk of abuse by the oral route (Walsh et al., 1998).

Some limitations of the present study have to be mentioned. In accordance with its basic design, only double-blind trials were selected, so that valuable information reported by non-double blinded studies is potentially missing. Another limitation is that we

considered only the effect of medication doses on retention rate and illicit opioid use. We realise that other factors included in the programme, i.e. psychosocial services, also might have an effect on the overall efficacy of a methadone programme (McLellan et al., 1993). On the other hand, given that demographic characteristics and clinical data of patients from the individual studies were not fully reported, the question as to whether outcomes in the various drug and dosing conditions differed for different types of opioid-dependent participants was not analysed. Another limitation is the different length of the follow-up in the studies included. It seems that the largest percentage of drop-outs in methadone programmes occurs during the first months of treatment, with a tendency towards stabilisation thereafter.

The results of this meta-analysis demonstrate that methadone, when administered at doses of 50 mg/day or higher, continues to be the drug of choice for treating opioid dependence in programmes based on agonist-maintenance. The new drugs, buprenorphine or LAAM, do not seem superior to methadone in terms of efficacy. In our opinion, the most important advantage of LAAM and buprenorphine is the '3-days a week schedule' and this may be relevant in case of policies restricting or forbidding take-home methadone. In addition, the newer drugs can be an alternative for some patients who present problems with methadone administration or refuse to take the drug. Although the efficacy of methadone intervention was only assessed in terms of retention in treatment and illegal drug use, other benefits related to decreases in HIV risk behaviour and criminality (Marsch, 1998) and improvements in health-related quality of life already reported for methadone (Torrens et al., 1997, 1999), have yet to be demonstrated for buprenorphine and LAAM.

5. Addendum

On 19 April, 2001 The European Agency for the Evaluation of Medicinal Products published a public statement on the recommendation to suspend the marketing authorization for LAAM in the European Union due to serious and unpredictable cardiotoxicity associated with the use of LAAM (see http://www.emea.eu.int).

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