An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research

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Abstract

Aim: To summarize the major findings of the five Cochrane reviews on substitution maintenance treatments for opioid dependence. Methods: We conducted a narrative and quantitative summary of systematic review findings. There were 52 studies included in the original reviews (12,075 participants, range 577–5894): methadone maintenance treatment (MMT) was compared with methadone detoxification treatment (MDT), no treatment, different dosages of MMT, buprenorphine maintenance treatment (BMT), heroin maintenance treatment (HMT), and L-α-acetylmethadol (LAAM) maintenance treatment (LMT). Measurements: Outcomes considered were retention in treatment, use of heroin and other drugs during treatment, mortality, criminal activity, and quality of life. Findings: Retention in treatment: MMT is more effective than MDT, no treatment, BMT, LAAM, and heroin plus methadone. MMT proved to be less effective than injected heroin alone. High doses of methadone are more effective than medium and low doses. Use of heroin: MMT is more effective than waiting list, less effective than LAAM, and not different from injected heroin. No significant results were available for mortality and criminal activity. Conclusions: These findings confirm that MMT at appropriate doses is the most effective in retaining patients in treatment and suppressing heroin use but show weak evidence of effectiveness toward other relevant outcomes. Future clinical trials should collect data on a broad range of health outcomes and recruit participants from heterogeneous practice settings and social contexts to increase generalizability of results. © 2005 Elsevier Inc. All rights reserved.

Keywords: Methadone maintenance; Buprenorphine; Heroin; LAAM; Cochrane review

1. Introduction

The United Nations International Drug Control Programme (UNIDCP, 2001) conservatively estimates that 80 million people worldwide (approximately 1 in 700) currently abuse heroin and other opiate-type substances. 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.

Mortality of untreated heroin dependence is consistently estimated at 1–3% per year, at least half of which is because of heroin overdose (Darke & Hall, 2003; Sporer, 1999). Follow-up studies have found that this risk continues for many years after the diagnosis of heroin dependence is made (Bargagli, Sperati, Davoli, Forastiere, & Perucci, 2001; Goldstein & Herrera, 1995; Haastrup & Jepsen, 1984; Hser, Anglin, & Power, 1993; Sanchez et al., 1995), indicating that heroin dependence may be regarded as a chronic condition. In fact, opioid addiction is currently defined as a “chronic, relapsing disorder” (Dole &
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).

Different approaches to assisting dependent heroin users include detoxification and relapse prevention treatment programs (including naltrexone-assisted relapse prevention), therapeutic communities, outpatient drug-free counseling, and long-term opiate substitution (or maintenance). Substitutive treatments, such as methadone, have consistently been shown to enable dependent heroin users achieve a sustained reduction in their heroin use (Dole et al., 1969; Gunne & Gronbladh, 1981; Newman & Whitehill, 1979; Simpson, Joe, Dansereau, & Chatham, 1997; Ward, Hall, & Mattick, 1997; Yancovitz et al., 1991), at least for the duration of the maintenance treatment, despite enjoying mixed popularity among heroin users, treatment providers, and policymakers.

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. Although still physically dependent on the maintenance medication, there will be less need to spend time on drug-related activities, and when ready, they may withdraw from the maintenance treatment in an attempt to lead an opiate-free life (Ward et al., 1999). The heritability, course, and response to medications suggest that people who are dependent on opioid 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 et al., 2000; O’Brien, 1997). This awareness, in addition to the epidemiological evidence of the drug-related risks affecting the addicted population (Brettle, 1991; Ward et al., 1999), has promoted the development of the maintenance therapies in opiate-addiction treatment (Brettle, 1991; Ward et al., 1999). According to this approach, treatment is aimed at increasing time between relapses of heroin use and reducing intensity, frequency, and length of relapse (Leshner, 1998), overdoses risk, criminal activity, and HIV seroconversion, and, finally, to promote psychosocial adjustment (Farrell et al., 1994; Leshner, 1998; Ward et al., 1999).

Different substances are used for the management of long-term opioid-replacement therapies.

As part of the Cochrane collaboration, the Cochrane Review Group on Drugs and Alcohol (Davoli & Ferri, 2000) is aimed to produce, update, and disseminate systematic reviews of trials on the prevention, treatment, and rehabilitation of the problematic use of drugs and alcohol. As of November 1, 2003, the group published 19 reviews and 11 review protocols; 5 reviews (Clark et al., 2003; Faggiano, Versino, Vigna-Taglianti, & Lemma, 2003; Ferri, Davoli, & Perucci, 2003; Mattick, Breen, & Kimber, 2003; Mattick, Kimber, & Breen, 2003) focused on efficacy and acceptability of substitutive maintenance treatments for opioid dependence.

Details of the methods and results of each review are available in The Cochrane Library.

2. Methods

In this overview, we summarize the major findings of five reviews on substitutive maintenance treatment of opioid dependence (Clark et al., 2003; Faggiano et al., 2003; Ferri et al., 2003; Mattick et al., 2003; Mattick, Kimber et al., 2003), comparing quantitative data where possible.

The five Cochrane reviews on the maintenance treatments for opioid dependence considered for this summary are listed in Table 1. Fifty-two single studies were included in the five reviews, with a total of 12,075 participants (range 577–5894 per review); six studies were in common in two reviews (Johnson, Jaffe, & Fudala, 1992; Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993; Ling, Charuvastra, Kaim, & Klett, 1976; Ling, Wesson, Charuvastra, & Klett, 1996; Schottenfeld, Pakes, Oliveto, Ziedonis, & Kosten, 1997; Strain, Stitzer, Leibson, & Bigelow, 1993), one study was in common in three reviews (Johnson et al., 2000). The maintenance treatments considered in this overview are methadone, buprenorphine, L-α-acetylmethadol (LAAM), and heroin.

All the studies included are randomized clinical trials (RCTs), but 10 studies included in the review on “Methadone Maintenance at Different Dosages for Opioid Dependence” (Faggiano et al., 2003) are controlled perspective studies (CPS) (Caplehorn & Bell, 1991; Caplehorn, Dalton, Cluff, & Petrenas, 1994; Caplehorn, Irwig, & Saunders, 1996; D’Ippoliti, Davoli, Perucci, Pasqualini, &
The outcomes considered in the reviews were retention in treatment, heroin use during treatment, use of other drugs during the treatment, mortality, criminal activity, and quality of life.

Regarding the use of heroin and other substances during treatment, this overview reports only the results based on self-report. Results on urinalysis could not be summarized across all the reviews because their data were incongruous and the number of positive cases was unclear and possibly biased because the results are mainly based on number of positive tests rather than on number of patients with positive tests (Amato, Davoli, Ferri, Growing, & Perucci, 2004).

2.1. Statistical analysis

Dichotomous outcomes (retention in treatment, number of subjects with negative urinalysis) were analyzed calculating relative risk (RR), which expresses uncertainty in each result by the 95% confidence intervals (CI). The RRs from the individual trials were combined through meta-analysis where possible (comparability of intervention between trials) using a random effect model. Heterogeneity of the results was inspected calculating a test of heterogeneity.

3. Results

Results are presented by outcome and treatment comparison.

3.1. Retention in Treatment

MMT is more effective than both tapered methadone and no-medication treatment in retaining patients in treatment (RR 3.86, 95% CI 1.09–13.75; RR 2.50, 95% CI 1.56–3.99), respectively (see Table 2).

When compared with BMT, MMT at flexible doses retained patients better (RR 1.23, 95% CI 1.04–1.44).

No statistically significant differences were observed when high doses of methadone were compared with low doses of buprenorphine, although retention in treatment was always higher among methadone patients (RR 1.45, 95% CI 0.94–2.22). Similarly, the other comparisons of low- and
Retention in treatment: Results from studies included in the systematic reviews (The Cochrane Library, Issue 4, 2003)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>No. of subjects</th>
<th>Patients retained in the treatment (%)</th>
<th>Patients retained in the control (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMT vs. MDT</td>
<td>2</td>
<td>340</td>
<td>76</td>
<td>27</td>
<td>3.86 (1.09–13.75)</td>
</tr>
<tr>
<td>MMT vs. no treatment</td>
<td>1</td>
<td>165</td>
<td>52</td>
<td>21</td>
<td>2.50 (1.56–3.99)</td>
</tr>
<tr>
<td>MMT vs. LAAM 3 months</td>
<td>3</td>
<td>464</td>
<td>73</td>
<td>57</td>
<td>2.18 (1.46–3.25)</td>
</tr>
<tr>
<td>MMT vs. LAAM 12 months</td>
<td>6</td>
<td>990</td>
<td>54.5</td>
<td>37</td>
<td>1.43 (1.14–1.78)</td>
</tr>
<tr>
<td>MMT flexible doses vs. BMT flexible doses</td>
<td>6</td>
<td>837</td>
<td>63</td>
<td>53</td>
<td>1.23 (1.04–1.44)</td>
</tr>
<tr>
<td>MMT high doses vs. BMT low doses</td>
<td>2</td>
<td>120</td>
<td>62</td>
<td>42</td>
<td>1.45 (0.94–2.22)</td>
</tr>
<tr>
<td>MMT low dose vs. BMT low doses</td>
<td>2</td>
<td>121</td>
<td>58</td>
<td>42</td>
<td>1.35 (0.94–1.94)</td>
</tr>
<tr>
<td>MMT high doses vs. BMT high doses</td>
<td>5</td>
<td>449</td>
<td>52</td>
<td>41</td>
<td>1.26 (0.99–1.63)</td>
</tr>
<tr>
<td>Low doses of BMT vs. placebo</td>
<td>2</td>
<td>487</td>
<td>58</td>
<td>38</td>
<td>1.24 (1.06–1.45)</td>
</tr>
<tr>
<td>Very high doses of BMT vs. placebo</td>
<td>2</td>
<td>463</td>
<td>54.5</td>
<td>46.5</td>
<td>1.21 (1.02–1.44)</td>
</tr>
<tr>
<td>MMT vs. LAAM at 3 months</td>
<td>3</td>
<td>464</td>
<td>73</td>
<td>57</td>
<td>2.18 (1.46–3.25)</td>
</tr>
<tr>
<td>MMT vs. LAAM at 12 months</td>
<td>6</td>
<td>990</td>
<td>54.5</td>
<td>37</td>
<td>1.43 (1.14–1.78)</td>
</tr>
<tr>
<td>MMT vs. heroin injectable + methadone</td>
<td>1</td>
<td>174</td>
<td>85</td>
<td>72</td>
<td>1.17 (0.99–1.38)</td>
</tr>
<tr>
<td>MMT vs. heroin inhalable + methadone</td>
<td>1</td>
<td>256</td>
<td>87</td>
<td>68</td>
<td>1.27 (1.11–1.46)</td>
</tr>
<tr>
<td>MMT vs. heroin 30–120 mg/day</td>
<td>1</td>
<td>96</td>
<td>25</td>
<td>70</td>
<td>0.35 (0.21–0.59)</td>
</tr>
<tr>
<td>Heroin mean 509 mg/day vs. any other conventional drug treatment</td>
<td>1</td>
<td>51</td>
<td>92.5</td>
<td>92</td>
<td>1.01 (0.86–1.19)</td>
</tr>
<tr>
<td>MMT 60–109 mg vs. 40–59 mg</td>
<td>3</td>
<td>560</td>
<td>57</td>
<td>46</td>
<td>1.23 (1.05–1.45)</td>
</tr>
<tr>
<td>MMT 60–109 mg vs. 1–39 mg</td>
<td>5</td>
<td>496</td>
<td>56</td>
<td>41</td>
<td>1.36 (1.13–1.63)</td>
</tr>
<tr>
<td>MMT &gt;110 mg vs. 40–59 mg</td>
<td>1</td>
<td>80</td>
<td>62.5</td>
<td>37.5</td>
<td>1.67 (1.05–2.66)</td>
</tr>
<tr>
<td>MMT &gt;110 mg vs. 1–39 mg</td>
<td>1</td>
<td>166</td>
<td>52</td>
<td>41</td>
<td>1.26 (0.91–1.75)</td>
</tr>
<tr>
<td>MMT 65–110 mg vs. &lt;30 mg (CPS)</td>
<td>3</td>
<td>713</td>
<td>81</td>
<td>54.5</td>
<td>5.36 (3.62–7.93)</td>
</tr>
<tr>
<td>MMT 30–59 mg vs. &lt;30 mg (CPS)</td>
<td>2</td>
<td>575</td>
<td>63</td>
<td>41</td>
<td>1.77 (1.40–2.25)</td>
</tr>
<tr>
<td>MMT 65–110 mg vs. 30–59 mg (CPS)</td>
<td>2</td>
<td>614</td>
<td>73</td>
<td>63</td>
<td>1.19 (1.06–1.33)</td>
</tr>
</tbody>
</table>

Self-reported use of heroin during the treatment: Results from studies included in the systematic reviews (The Cochrane Library, Issue 4, 2003)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>No. of subjects</th>
<th>Patients using heroin in the treatment (%)</th>
<th>Patients using heroin in the control (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMT vs. waiting list/no treatment</td>
<td>3</td>
<td>230</td>
<td>37</td>
<td>87</td>
<td>0.32 (0.23–0.44)</td>
</tr>
<tr>
<td>MMT vs. LAAM</td>
<td>4</td>
<td>983</td>
<td>59</td>
<td>48</td>
<td>1.23 (1.10–1.39)</td>
</tr>
<tr>
<td>MMT vs. HMT 30–120 mg/day</td>
<td>1</td>
<td>88</td>
<td>59</td>
<td>64</td>
<td>0.91 (0.66–1.27)</td>
</tr>
<tr>
<td>HMT mean 509 mg/day vs. any other conventional drug treatment</td>
<td>1</td>
<td>48</td>
<td>22</td>
<td>66</td>
<td>0.33 (0.15–0.72)</td>
</tr>
</tbody>
</table>
conducted cannot be properly analyzed. This difficulty in analysis is because using tests (instead of the subjects or patients) as unit of analysis violates the assumption of independence among observations. In fact, the results of tests done in each patient are not independent. This is the reason why here are reported data based on self-report rather than multiple urine tests.

MMT proved to be more effective in reducing heroin use than waiting list/no treatment (RR 0.32, 95% CI 0.23–0.44), whereas it was less effective than LAAM (RR 1.23, 95% CI 1.10–1.39), and no differences were observed when MMT was compared with injected HMT (RR 0.91, 95% CI 0.66–1.27).

MMT did not differ from BMT in the two flexible dose studies (326 participants) that reported data on this outcome. The results are not summarized because the effect size was not considered as a dichotomous variable (use/not use) but as a continuous variable (number of times of heroin use). For all the other comparisons (MMT low doses vs. BMT low doses, MMT high doses vs. BMT high doses, MMT low doses vs. BMT high doses) the five studies (700 participants) that considered this outcome, showed that methadone performed better than buprenorphine in preventing heroin use during treatment especially when high doses were administered. The percentage of participants reporting use of heroin were 19% for the MMT high dose, 23% for BMT high dose, and 29% for BMT low dose, but no overarching meta-analysis was conducted.

Heroin (mean of 509 mg/day) proved to be better than the other conventional drug treatment it was compared with (RR 0.33, 95% CI 0.15–0.72), although the result is based on only one study and there were only 48 participants (see Table 2).

### 3.3. Mortality

It was possible to report data regarding this outcome for 14 of 52 RCTs included in the original reviews (see Table 4).

Although the reduction of mortality rate is an important outcome, not surprisingly, few studies reported this outcome. In fact, death within the time frames of clinical trials is a rare event, even in a high-risk population like opiate users, and to reach the statistical power needed to study mortality, big RCTs or long follow-up periods are required; in fact, most of the evidence on the effectiveness of methadone treatment in reducing mortality comes from observational studies (Bargagli et al., 2001; Frischer et al., 1997; Orti et al., 1996). For all the studies reporting this outcome, the differences were not statistically significant.

Only 1 (Van Ameijden et al., 1999, 498 participants) of the 10 CPS included considered the outcome of patient mortality. There were four deaths in the group treated with low doses (5–55 mg), one death in the group of medium doses (55–70 mg), and no deaths in the group treated with doses of higher than 75 mg. The results of Van Ameijden et al.’s (1999) study are all not statistically significant; nevertheless, all comparisons between dosages showed protective effect for higher dosages, with a possible dose–response relationship.

### 3.4. Criminal activity

The effect of substitution maintenance therapies on criminal activity was not systematically evaluated in the studies included in the considered reviews (see Table 5). It was possible to report data regarding this outcome only for 5 of 52 RCTs included in the original reviews.

Differences that were not statistically significant were observed between MMT and waiting list or HMT. However, the percentage of people involved in criminal activity was lower in methadone treatment groups, suggesting that methadone could be effective in reducing the criminal activities related to heroin use. (UNIDCP, 1997; Hall, 1996).

No significant differences are evident for mean number of criminal activities in the comparison between high

---

### Table 4

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of studies</th>
<th>No. of subjects</th>
<th>Deceased in the treatment (%)</th>
<th>Deceased in the control (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMT vs. waiting list/no treatment</td>
<td>2</td>
<td>335</td>
<td>0</td>
<td>3.5</td>
<td>0.15 (0.02–1.018)</td>
</tr>
<tr>
<td>MMT vs. MDT</td>
<td>1</td>
<td>100</td>
<td>6</td>
<td>2</td>
<td>3.00 (0.32–27.87)</td>
</tr>
<tr>
<td>MMT vs. LAAM</td>
<td>10</td>
<td>1515</td>
<td>0.1</td>
<td>0.6</td>
<td>0.34 (0.07–1.69)</td>
</tr>
<tr>
<td>MMT vs. HMT 30–120 mg/day</td>
<td>1</td>
<td>96</td>
<td>2</td>
<td>4.5</td>
<td>0.40 (0.04–4.27)</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. studies</th>
<th>No. subjects</th>
<th>People involved in criminal activity in the treatment (%)</th>
<th>People involved in criminal activity in the control (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMT vs. waiting list/no treatment</td>
<td>3</td>
<td>363</td>
<td>3</td>
<td>12</td>
<td>0.39 (0.12–1.25)</td>
</tr>
<tr>
<td>MMT vs. HMT 30–120 mg/day</td>
<td>1</td>
<td>88</td>
<td>72</td>
<td>52</td>
<td>1.37 (0.97–1.93)</td>
</tr>
<tr>
<td>MMT vs. HMT 30–120 mg/day</td>
<td>1</td>
<td>88</td>
<td>65</td>
<td>64</td>
<td>1.01 (0.74–1.38)</td>
</tr>
</tbody>
</table>
maximum effectiveness. Low dosages of methadone may govern governments are advised to encourage higher doses to gain methadone treatment in clinical practice, and clinicians and the world, which might negatively affect the effectiveness of than those used in routine clinical practice in some parts of methadone is dependent on dose: High doses of methadone and suppressing heroin use. They also show that efficacy of methadone are associated with better retention in treatment and less heroin use. Doses of methadone used in RCTs are probably higher than those used in routine clinical practice in some parts of the world, which might negatively affect the effectiveness of methadone treatment in clinical practice, and clinicians and governments are advised to encourage higher doses to gain maximum effectiveness. Low dosages of methadone may lead to the effectiveness being compromised.

For instance, in Italy, the mean doses of maintenance therapy is 40 mg/day (EMCCDA Annual Report, 2003), whereas the best average dose and a dose where clinical effects are likely to be more obvious is 60 mg.

The main outcomes considered in the studies included in the systematic reviews were retention in treatment and illicit use of heroin. These outcomes could be considered as intermediate steps of treatment for heroin-addicted patients. Because observational studies showed high rates of mortality in heroin-addicted patients (Bargagli et al., 2001; Davoli et al., 1997), especially early after discharge from treatment (Bird & Hutchinson, 2003; Strang et al., 2003), the ability of a treatment in retaining people in treatment should be reported as a proxy of effectiveness.

The illicit use of heroin is very often associated with risk behaviors, because substance-abusing persons spend most of their time finding, buying, and taking the drug, establishing a vicious circle in which heroin becomes the principal interest. In this context, substance-abusing persons are likely to be involved in criminal activities. The reduction of the illicit use of heroin then should promote physical, social, and behavioral changes toward social reintegration.

The preferred data related to the abstinence from street heroin use, one of the most reliable outcomes to evaluate the effectiveness of treatments for opioid dependence, are based on urinalysis for drug metabolites, because they are more objective than self-report or collateral reports. Unfortunately, it was impossible to summarize data on urinalysis because of the way in which these data were reported in the original studies. This is a recurring problem in the effort to conduct a meta-analysis of urine test results (Amato et al., 2004).

4. Discussion

Data from systematic reviews show that MMT is the most effective treatment in retaining patients in treatment and suppressing heroin use. They also show that efficacy of methadone is dependent on dose: High doses of methadone are associated with better retention in treatment and less heroin use.

Evidence is lacking on reduction of mortality from clinical trials showing a need for additional studies on this outcome, although many observational studies showed a reduction of the mortality rate in opiate-addicted patients in maintenance treatment. (Hickman et al., 2003; Mattick & Degenhardt, 2003; Oliver & Keen, 2003). The mortality rate for regular heroin users is 13 times greater than for the general population (Hulse, English, Milne, & Holman, 1999); the cumulative risk of death among heroin users is 29% by age 40 years and of 53% by age 50 years (Davoli et al., 1997). Despite the fact that death represents the more relevant effect of abuse and the more reliable outcome measurable in population studies, mortality is rarely reported in RCTs of treatment of opioid dependence and is seldom taken into account to assess the efficacy of treatments. The large majority of studies resort to surrogate outcomes to circumvent the difficulty of long-term mortality follow-up. The issue of association between intermediate and surrogate indicators and the actual outcome of interest (i.e., quality and duration of life) could be extremely relevant in the interpretation and generalization of the results of these studies.

Because observational studies showed high rates of mortality in heroin-addicted patients (Bargagli et al., 2001; Davoli et al., 1997), especially early after discharge from treatment (Bird & Hutchinson, 2003; Strang et al., 2003), the ability of a treatment in retaining people in treatment should be reported as a proxy of effectiveness.

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References


