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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, LMT, 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.

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 &

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Nyswander, 1967; Leshner, 1998; McLellan, Lewis, O'Brien, & Kleber, 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).

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, Breen, 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, &

Table 1
Systematic reviews on the effectiveness of substitution maintenance treatment for opioid dependence from *The Cochrane Library, Issue 4* (2003)

Titles and authors	No. of included studies	No. of participants
"LAAM Maintenance Versus Methadone Maintenance for Heroin Dependence," Clark et al.	17	3766
"Methadone Maintenance Versus No Opioid Replacement Therapy for Opioid Dependence," Mattick et al.	6	954
"Buprenorphine Maintenance Versus Placebo or Methadone Maintenance for Opioid Dependence," Mattick et al.	13	2544
"Heroin Maintenance for Chronic Heroin Dependent," Ferri et al.	4	577
"Methadone Maintenance at Different Dosages for Opioid Dependence," Faggiano et al.	21	5994