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Methadone maintenance treatment: A protective factor for cocaine injection in a street-recruited cohort of heroin users☆

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ABSTRACT

Objective: To evaluate the effect of methadone maintenance treatment (MMT) on cocaine use and cocaine injection among heroin users.
Methods: Generalized estimating equations (GEE) were used to examine the association between MMT enrollment (0, <12, ≥12 months) and changes in frequency of cocaine use or injection in two consecutive follow-up visits among heroin users in the Itinere cohort, and to determine whether these changes were independent of equivalent changes in heroin use or injection. Seven multivariate models were constructed, one for each outcome variable on drug use changes.
Results: Of the 992 participants recruited in 2001–2003, 628 (63.3%) had at least one follow-up visit. Of these, 55.8% were enrolled in MMT at baseline and an additional 23.2% initiated MMT during follow-up. In multivariate GEE, changes significantly and positively associated with MMT enrollment were: less cocaine use [MMT < 12 months (OR = 1.70, 95% CI = 1.17–2.48)] and less cocaine injection [MMT ≥ 12 months (OR = 2.98, 95% CI = 1.51–5.89)]. Being on MMT ≥ 12 months was negatively associated with more cocaine use (OR = 0.62, 95% CI = 0.38–0.99) and with more cocaine injection (OR = 0.52, 95% CI = 0.28–0.98). When equivalent changes in heroin were used as a covariate, the MMT effect on less cocaine use was hardly modified (OR = 1.69, 95% CI = 1.07–2.65), and the effect on changes in cocaine injection disappeared.
Conclusion: MMT enrollment is a protective factor against both cocaine use and injection among heroin users. The effect of MMT on cocaine injection appears to be mediated by heroin injection, whereas its effect on cocaine use is more direct.

1. Introduction

Cocaine is frequently used by heroin users (EMCDDA, 2007; Leri et al., 2003). Co-use of these two drugs can occur simultaneously and/or separately, by different routes and in different presentations (hydrochloride or base), and all these patterns can be observed in the same individual (Barrio et al., 1998, 1993; Kreek, 1997; Leri et al., 2004a; Ramírez et al., 2007). It is widely agreed that methadone maintenance treatment (MMT) is beneficial to the health of heroin-dependent patients (Ball and Ross, 1991; Kreek, 1997; WHO, 2009), but its influence on cocaine use remains controversial (Leri et al., 2003).

Findings regarding the effect of methadone on cocaine use have not been consistent. Thus, some studies show a predominance of reduced cocaine use (Borg et al., 1999; DeMaria et al., 2000; Dunteman et al., 1992; Magura et al., 1998; Peles et al., 2006) while others show no effect or a predominance of increased use (Grella et al., 1997; Kosten et al., 1987). In addition, some investigations not specifically intended to evaluate the effect of methadone on cocaine use would also support the hypothesis of a positive effect on the reduction of cocaine use (Chaisson et al., 1989; Hser et al., 1998; Meandzija et al., 1994). All these are clinical studies without a control group of non-treated patients.

☆ Supplementary information on the measures used in this study are available with the online version of this paper. See Appendix A.

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From a pharmacological or neurobiological perspective, it has been suggested that these changes in cocaine use may depend on methadone dose, frequency of use of heroin or cocaine, or pattern of co-use of heroin and cocaine (Borg et al., 1999; Leri et al., 2003; Peles et al., 2006; Stine and Kosten, 1994). With regard to co-use of cocaine and heroin, an important research question not yet answered is whether or not heroin plays an intermediate role in the effect of methadone on cocaine use. Few studies have addressed this issue in humans. In a sample of 526 MMT patients, Dunteman et al. (1992) found that 1 year after admission those patients who stopped using heroin were much more likely to quit using cocaine than were their heroin-using counterparts, and that the odds of using cocaine after admission to MMT were much higher among patients who continued using heroin than among those who did not. These results suggestive of a dependent effect contrast with recent results in animals suggesting that opioid receptors play an important role in the behavioral effects of cocaine (Bilsky et al., 1992; Schroeder et al., 2007), and that methadone has an independent effect on cocaine-seeking behavior in rats (Leri et al., 2004b, 2006, 2009) (Leri et al., 2006; NIDA, 2008).

A separate but related issue is the effect of MMT on cocaine use by injection. Most studies in this field have focused on whether methadone reduces overall injecting behavior among heroin users. In fact, several investigations that have observed the effect of MMT on reducing the frequency of injection of any drug (Avants et al., 2004; Caplehorn and Ross, 1995; Kwiatkowski and Booth, 2001; Thiede et al., 2000; Shah et al., 2006) found that enrollment in MMT predicted shorter time to cessation of injection in both heroin and cocaine injectors. Although this is a relevant issue, there are other important questions that have not yet been answered, for example, whether methadone specifically reduces cocaine injection, and whether this is mediated by the effect of methadone on heroin injection. Both answers are needed to understand the role of MMT in promoting changes toward non-injection routes. It is important to test whether the potential independent effect of methadone on cocaine use also holds for injection of this substance, since it could be subject to modification by some external factors.

Given that cocaine use and its injection are risk factors for HIV infection (Bux et al., 1995; Chaisson et al., 1989; Grella et al., 1995; Leri et al., 2003; Wood et al., 2007), the relationship between MMT and cocaine has important public health implications, especially considering the current epidemic of cocaine use in many countries (EMCDDA, 2007) and the high and growing number of patients in MMT worldwide (EMCDDA, 2006; Krantz and Mehler, 2004; Mesquita et al., 2007).

Our study focuses on a community sample of heroin users with highly diverse patterns of cocaine use with respect to the form of presentation of the drug (cocaine hydrochloride or crack), the use of cocaine mixed with heroin, and the route of administration (injected or not). The main objective is to investigate the effect of MMT on changes in the frequency of cocaine use or injection (including cessation of use or injection of this drug) in comparison with users who were not in MMT. We also investigate whether the effects observed in cocaine use or injection are independent of equivalent changes in heroin.

2. Methodology

2.1. Participants

The eligibility criteria were residence in the cities of Barcelona, Madrid or Seville; age 30 years or younger; and having used heroin for at least 12 days in the last 12 months and at least 1 day in the last 3 months. Targeted sampling and chain-referral methods were used for recruitment (Heckathorn, 1997; Watters and Biernacki, 1989). Recruitment from drug dependence treatment services was avoided. Participants signed an informed consent document approved by the Ethics Committee of the Instituto de Salud Carlos III. The cohort included 992 participants recruited between April 2001 and December 2003, and followed up until July 2006. A stipend (18 €) was given at each study visit. Additional details on recruitment procedures and baseline characteristics of participants have been published elsewhere (de la Fuente et al., 2005). Of the participants at baseline, 628 (63.3%) had at least one follow-up visit. Follow-up interviews were scheduled every 12 months, although the actual mean time between interviews was 16.7 months [standard deviation (SD) = 1.9]. The median number of follow-up visits was 2. As compared to participants who had at least one follow-up visit, those who did not return for the second interview were younger ($p = 0.005$), more often homeless or living in unstable housing ($p < 0.001$), and their main source of income more frequently came from marginal or illegal activities ($p = 0.005$). They also used heroin or cocaine more frequently ($p < 0.05$), and the route of heroin administration was more often by injection ($p < 0.05$). However, they did not differ in the frequency of cocaine injection or in the type of heroin or cocaine used.

2.2. Data collection

Computer-assisted personal interviews were conducted. The questionnaire included demographics, information on drug use, self-reported HIV serostatus, and MMT attendance (de la Fuente et al., 2005). At baseline, behavioral questions on drug use and MMT referred to the last 12 months, and in the follow-up visits they referred to the time since the previous interview. Use of heroin and cocaine was investigated separately and in detail. Measures of frequency were included for use of cocaine and heroin in general by different routes of administration, type (hydrochloride or base) of cocaine or heroin most frequently used, and whether they were mainly mixed in the same dose and taken by the same route or used separately. The frequency of injection and use of other routes was obtained by closed, pre-coded questions categorized as: every day, 5–6 days/week, 3–4 days/week, 1–2 days/week, 1–3 days/month, 6–11 days/year, 1–5 days/year, and never. The interviewers received special training to work with these categories accurately as they were standardized and employed throughout the questionnaire with reference to use of other drugs.

2.3. Measures

The primary endpoints (outcomes) of this analysis were changes between two consecutive follow-up visits in the level of cocaine use (any route) and of cocaine injection. The change could be quantitative (from one category of frequency of use or injection to a higher or lower category) or qualitative (from use to non-use, or from injection to non-injection, and vice versa). Three outcomes were designated for changes in cocaine use: more frequent use (More-Use-C), less frequent use (Less-Use-C), and cessation of use (Cess-Use-C), and four outcomes for changes in cocaine injection: initiation or reinitiation of injection (Start-Inj-C); more frequent injection (More-Inj-C); less frequent injection (Less-Inj-C); and cessation of injection (Cess-Inj-C). Changes toward less frequent use or less frequent injection included changes toward cessation of use or cessation of injection, respectively. In addition changes toward more frequency of use or injection included initiation of use or injection. It is also important to note that both the population and the years at risk are different for the study of starting, increasing and decreasing either use or injection (i.e. only those not currently using cocaine are at risk of starting, and those in the highest level of use are not considered when studying increased use). Due to the small number of non-users of cocaine at baseline ($n = 13$), we did not study initiation of cocaine use. The same categories were established for heroin (using an H at the end, e.g., Cess-Use-H).[2]

Because the exact date of the changes studied is unknown, and to avoid instances in which the change occurred before MMT initiation, the values for the exposure factor and covariates were taken for the previous corresponding periods. Thus, for changes between baseline and first follow-up, we considered the 12 months before baseline, and for changes between the first and second follow-up, the period between baseline and first follow-up.

Enrollment in MMT was coded in two categories: (a) in MMT 1–11 months during the last 12 months and (b) in MMT for the last 12 months or longer. This categorization, very similar to that of Chaisson et al. (1989), was used, first, because length of treatment is a predictive factor of drug abuse treatment outcome (Ball and Ross, 1991); second, because a minimum stabilization period of 3–6 months is recommended (Kreek, 1997); and third, because long-term methadone treatment is more likely to have a therapeutic effect on cocaine use (Leri et al., 2003, 2006). Other covariates possibly related with changes in cocaine use or injection were defined the same as in previous studies (Barrio et al., 2007; Bravo et al., 2009). Self-reported HIV serostatus was considered a more appropriate control variable than available laboratory test results, since it is individual knowledge of serostatus that could lead to changes in heroin or cocaine use.

2.4. Analysis

The frequency of changes in heroin or cocaine use and injection incidence rates by person-years of follow-up and their corresponding 95% confidence intervals were

[2] Supplementary tables on the construction of the primary endpoints are available with the online version of this paper. Please see Appendix A.