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Predictors of non-use of illicit heroin in opioid injection maintenance treatment of long-term heroin dependence☆

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HIGHLIGHTS

- We tested opioid injection maintenance treatment for long-term heroin dependence.
- Participants received injectable diacetylmorphine or hydromorphone for 12 months.
- We examined predictors of past-month non-use of illicit heroin during treatment.
- Independent effect of several concurrent factors besides the injection opioid dose.
- This suggests benefits from the clinic that go beyond the provision of medication.

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ABSTRACT

Aims: To investigate baseline and concurrent predictors of non-use of illicit heroin among participants randomized to injectable opioids in the North American Opiate Medication Initiative (NAOMI) clinical trial.
Methods: NAOMI was an open-label randomized controlled trial comparing the effectiveness of injectable diacetylmorphine and hydromorphone for long-term opioid-dependency. Outcomes were assessed at baseline and during treatment (3, 6, 9, 12 months). Days of non-use of illicit heroin in the prior month at each follow-up visit were divided into three categories: Non-use; Low use (1 to 7 days) and High use (8 days or more). Tested covariates were: Sociodemographics, Health, Treatment, Drug use and illegal activities. Mixed-effect proportional odds models with random intercept for longitudinal ordinal outcomes were used to assess the predictors of the non-use of illicit heroin.
Results: 139 participants were included in the present analysis. At each follow-up visit, those with non-use of illicit heroin represented 47.5% to 54.0% of the sample. Fewer days of cocaine use ($p = 0.074$), fewer days engaged in illegal activities at baseline ($p < 0.01$) and at each visit ($p < 0.01$), less money spent on drugs ($p < 0.001$), days with injection opioid or oral methadone treatment ($p < 0.001$) and total mg of injectable opioids taken ($p < 0.001$), independently predicted lower use of illicit heroin.
Conclusions: The independent effect of several concurrent factors besides the injection of opioid dose suggests benefits from the clinic that go beyond the provision of the medication alone. Thus, this supervised model of care presents an opportunity to maximize the beneficial impact of medical and psychosocial components of the treatment on improving outcomes associated with non-use of illicit heroin.

Abbreviations: NAOMI, North American Opiate Medication Initiative; MMT, methadone maintenance treatment; DAM, diacetylmorphine; HDM, hydromorphone.

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1. Introduction

Heroin dependence is a chronic relapsing condition that remains a critical public health problem in Canada and the world. Among long-term users, abstinence from opioids (licit or illicit) is difficult to sustain over time and therefore abstinence-oriented therapies show relatively low efficacy (De Jong, Roozen, van Rossum, Krabbe, & Kerkhof, 2007). Opioid agonist substitution has been shown to be the most effective treatment option (Van den Brink & Haasen, 2006), in particular oral methadone maintenance treatment (MMT) is widely used and accepted in western countries. Although evidence shows that MMT is highly effective (Amato et al., 2005), some opioid dependent individuals are not attracted to or do not benefit from this therapy (Goldstein, Deren, Kang, Des Jarlais, & Magura, 2002; Termorshuizen et al., 2005), relapsing into using illicit street heroin, even while receiving methadone treatment (Best et al., 1999). For individuals for whom at a given time abstinence oriented treatment and oral methadone treatments are not effective, alternative therapeutic options have been tested, such as medically prescribed pharmaceutical-grade heroin (diacetylmorphine, DAM).

Studies in Europe and Canada ascertained the efficacy of supervised medically prescribed DAM in specialized clinics for long-term opioid injectors who continue using street opioids despite the available treatments (Haasen et al., 2007; March, Oviedo-Joekes, Perea-Milla, & Carrasco, 2006; Oviedo-Joekes et al., 2009; Rehm et al., 2001; Strang et al., 2010; van den Brink et al., 2003). Moreover, an independent systematic review of eight randomized clinical trials involving 2007 participants has concluded that treatment with DAM (with or without co-prescribed flexible dosages of methadone), compared to oral methadone, helps patients to remain in treatment and to reduce use of illicit drugs (Ferri, Davoli, & Perucci, 2011). Upon the demonstrated effectiveness of DAM in controlled trials, studies in Europe have explored the response to treatment among those who were eligible to continue receiving it. For example, in the Netherlands, 149 participants in the clinical trials were eligible to continue receiving DAM after finishing the study. Results showed that among those patients retained in treatment, 4-year response rates (a multidomain outcome measure (van den Brink et al., 2003)) were 90% (Blanken, Hendriks, van Ree, & van den Brink, 2010).

The Canadian study (NAOMI, North American Opiate Medication Initiative), conducted between 2005 and 2008, was a randomized controlled trial testing the effectiveness of injectable DAM, compared to oral MMT, in the Canadian context (Oviedo-Joekes et al., 2009). After twelve months, 67.0% of the participants receiving DAM responded to treatment (based on a multidomain outcome) compared to 47.8% in the methadone group (RR = 1.40; 95% CI = 1.11–1.77; p = 0.004). The respective addiction treatment retention rates in the DAM and MMT groups were 87.8% and 54.1% (RR of 1.62; CI 95% = 1.35–1.95; $p < 0.001$). Analysis of baseline factors of treatment outcomes at 12 months indicated that after adjusting for these variables, treatment with diacetylmorphine remained the only significant predictor (Oviedo-Joekes et al., 2009). An additional small group in the injection arm received hydromorphone (HDM) on a double blind basis, showing almost identical favorable outcomes when compared with DAM (Oviedo-Joekes, Guh, Brissette, Marsh, et al., 2010).

However, the latter analysis utilized baseline predictors only and focused on the multidomain clinical outcome and retention in the prior two weeks at twelve months. In the present analysis, we consider past month non-use of illicit heroin as the favorable outcome on an ongoing basis through the trial. In clinical practice, correlates of addiction treatment favorable outcomes are important to be taken into consideration when making decisions about starting or continuing an intervention (Ciraulo, Piechniczek-Buczek, & Iscan, 2003). In the case of treatment with diacetylmorphine, several studies have identified long-term outcomes (Blanken et al., 2010; Frick, Wiedermann, Schaub, Uchtenhagen, & Rehm, 2010; Oviedo-Joekes, March, Romero, & Perea-Milla, 2010; Verthein et al., 2008), however, little is known regarding predictors of treatment outcomes. In the present study we aim to investigate baseline and concurrent predictors of non-use of illicit heroin during the 12 month NAOMI study period among participants receiving injectable opioids (either diacetylmorphine or hydromorphone).

2. Methods

NAOMI was an open-label, phase III randomized clinical trial. Participants' profile, study design, methodology and results of the parent study have been published elsewhere (Oviedo-Joekes et al., 2009; Oviedo-Joekes, Guh, Brissette, Marchand, et al., 2010; Oviedo-Joekes, Guh, Marsh, Brissette, et al., 2010; Oviedo-Joekes et al., 2008). Briefly, eligible participants were at least 25 years of age, with a minimum of 5 years of opioid dependence, current daily injection of opioids, at least two prior treatment attempts for opioid dependence (including at least one MMT attempt), and no enrolment in MMT within the prior 6 months. A total of 251 individuals were randomized to receive oral methadone (n = 111) or injectable DAM (n = 115). In addition to the 115 participants receiving DAM, a small group of 25 participants received injectable HDM on a double blind basis with DAM, to detect illicit heroin use in urinalysis (Oviedo-Joekes, Guh, Brissette, Marsh, et al., 2010).

Injectable treatment was provided up to three times daily under the supervision of nursing staff. HDM and DAM doses were prescribed in DAM equivalents, to maintain the blinding (Oviedo-Joekes, Marsh, Guh, Brissette, & Schechter, 2011). The study protocol allowed individualized doses, with a four day titration protocol and a maximum of 400 mg per dose and 1000 mg per day. When a participant was absent for more than 3 consecutive days (9 sessions) and less than or equal to 7 days (21 sessions and under), a third of the prescribed dose plus 25 mg was dispensed at each following dose until the tolerated dose was achieved. When a participant missed more than 7 consecutive days (22 sessions), the prescription was canceled, the induction phase was then restarted as per protocol.

Participants were offered psychosocial services and primary care on site and all services were delivered in a patient-centered fashion (Canada, 2002). Medications were provided for 12 months. Since injectable medications were not licensed for addiction treatment, an additional 3-month period was provided to taper and transition those in the injection group to other treatment modalities (primarily MMT). All participants provided written informed consent and the study was approved by the University of British Columbia/Providence Health Care and Centre de Recherche du Centre Hospitalier de l'université de Montréal research ethics boards.

A research team, independent of the clinic services, obtained outcome evaluations at baseline and follow-up (3, 6, 9, 12 months) using the European Addiction Severity Index (Kokkevi & Hartgers, 1995), the Maudsley Addiction Profile (Marsden et al., 1998) and health related quality of life measures (Brooks, 1996). Data on dose and treatment compliance were obtained from the study clinic database. In this study we included participants who were randomized to the injectable arm to receive either DAM or HDM and did not withdraw their consent (n = 139; DAM = 114; HDM = 25). A prior study has demonstrated that these two groups had similar outcomes, therefore they are combined for the present analysis (Oviedo-Joekes, Guh, Brissette, Marsh, et al., 2010). Treatment effectiveness was defined as days of non-use of illicit heroin in the prior 30 days and, among those receiving hydromorphone, no positive urinalysis for morphine or 6 monoacetylmorphine. Because this was not normally distributed, we chose to divide days of Illicit heroin use in the prior 30 days, at each follow-up visit, into three categories: 1 — Non-use = 0 days in the prior month and no positive morphine or monoacetylmorphine