

The Andalusian trial on heroin-assisted treatment: A 2 year follow-up

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Abstract

Introduction and Aims. In 2003, a randomised controlled trial comparing injected diacetylmorphine and oral methadone was carried out in Andalusia, Spain. The subsequent follow-up study evaluated the health and drug use status of participants, 2 years after the completion of the trial. **Design and Methods.** This follow-up cohort study was carried out between March and August 2006. Data collected included information on socio-demographics, drug use, health and health-related quality of life. We compared data collected before randomisation and at 2 years for the following three groups: those currently on heroin-assisted treatment (C-HAT), those who have discontinued HAT (D-HAT), and those who have never received HAT (N-HAT). **Results.** From the total 62 randomised participants in 2003, 54 (87%) were interviewed for this study. Participants were distributed as follows: C-HAT 44.4% (24), N-HAT 22.2% (12) and D-HAT 33.3% (18). Illicit heroin use had a statistically significant decrease in the three groups from baseline to 2 years post trial. Mean days of heroin use were 2.42 (SD = 3.02); 6.56 (SD = 9.48) and 13.92 (SD = 12.59) for the C-HAT, D-HAT and N-HAT groups, respectively. Those currently on HAT were the only group that sustained at 2 years, their marked improvement in health after 9 months of treatment during the trial period. **Discussion and Conclusions:** Patients who received HAT showed better outcomes compared with those not on HAT. The results of this study strengthen the evidence showing that HAT can improve and stabilise the health of long-term heroin users with severe comorbidities and high mortality. [Oviedo-Joekes E, March JC, Romero M, Perea-Milla E. The Andalusian trial on heroin assisted treatment: A 2 year follow-up. *Drug Alcohol Rev* 2010;29:75–80]

Key words: opioid dependence, heroin-assisted treatment, cohort follow-up, Spain.

Introduction and aims

The prevalence of heroin use in Europe has been relatively stable in recent years, although heroin remains the main problem drug in those seeking treatment, due to the chronic and relapsing nature of heroin addiction [1]. Methadone maintenance treatment (MMT) has been widely available in the European Union (EU) since the early 1990s, and evaluation of this program in the EU has shown that MMT is effective in the treatment of opioid-dependence, reducing the use of illicit drugs [2,3] and life-threatening comorbidities, such as

HIV transmission [4]. Nevertheless, there remains a sub-sample of opioid-dependent people for whom methadone shows low efficacy, either with high treatment drop out rates or continued use of illicit heroin while in MMT [5,6].

In Spain, as in the EU, the prevalence of heroin use has remained stable since the late 1990s [7]. The consequence of the HIV epidemic in the 1980s, however, has left Spain with an overwhelming number of HIV transmissions among injection heroin users. Current and former injectors continue to show a high prevalence of HIV [8,9] even with widely implementing

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MMT and harm reduction strategies nationwide. Indeed, evidence indicates that 'persistent' heroin users show higher rates of health and social problems, and are at higher risk of being left behind by the health-care system [10].

In the last decade, there have been many initiatives testing alternative formulations of opioid substitution treatments to better attract and retain heroin-dependent people who are currently not reached by the health-care system or who are not effectively treated by other therapies. These clinical studies have proven feasibility and efficacy of agonist substitutive opioids like morphine [11,12], buprenorphine [13,14], codeine [15] and diacetylmorphine (DAM; pharmaceutical grade heroin)[16,17] in the treatment of addiction. These studies aimed to provide indications for tailored treatments to specific patient profiles.

The practice of prescribing heroin for dependent individuals is not new [18]; however, the stigma attached to the substance has hampered the implementation of heroin-assisted treatment [19]. After the success of supervised heroin clinics in Switzerland, several countries saw an opportunity to reopen the case of heroin-assisted treatment (HAT) for vulnerable long-term opioid users. In Spain, the dialog to provide HAT started in 1997, but regulations only allowed the use of DAM as an investigational product. Concerns of the Spanish regulatory bodies around prescribing DAM did not differ from those experienced in other countries [20]. They were concerned about patient safety, dispensing feasibility, possibility of drug diversions into the black market, dropouts from other treatments for obtaining 'free heroin', and the possibility of massive migration of heroin users to sites where HAT would be offered. In response to the concerns raised, negotiations over the design and implementation of the study continued for years, until a randomised controlled trial (RCT) was finally approved in 2002. Despite the need and wish of other sites to offer heroin prescription, Andalusia was the only Autonomous Community that overcame the obstacles to carry out a HAT trial.

Evidence gathered in the last decade shows that chronic long-term opioid-dependent people with severe health problems who receive HAT show improvements in health and psychosocial adjustment, and show reduced consumption of illicit opioids [16,17,21–30]. Moreover, data from four RCTs evidenced the superiority of HAT compared with MMT for this highly vulnerable group of patients [31–34].

In 2003, an RCT comparing injected DAM versus MMT was carried out in Andalusia, Spain showing that medically prescribed injected DAM under supervision is feasible and effective in our context [34], yet there remains only one clinic running, under the protection of the compassionate use law. The aim of this paper is to

report the evaluation of the health and drug use among participants in the Andalusian HAT trial, 2 years after the trial's conclusion in 2006.

Design and methods

Participants in the trial included 62 chronic-opioid-dependent people with severe drug-related health problems, randomised to receive either oral Methadone or injected DAM. According to the inclusion criteria, the recruited sample responded to a highly marginalised group of opioid-dependent individuals: mainly male, heroin users for 20 years, mostly unemployed, with high levels of physical and mental health comorbidities [34].

The trial started in 2003; the methodology and results were published elsewhere [34]. All participants randomised to receive injected DAM that completed the 9 month trial period continued receiving it under compassionate use ($n = 23$). Those randomised to MMT that completed the 9 months intervention (21) were offered to switch to DAM after clinical evaluation (i.e. health status, illicit heroin use); a total of 13 (61.9%) patients in this group switched to DAM initially. Thus, 71% (44) of the trial participants received at some point DAM and 29% (18) never did it.

Of the 62 participants of the RCT, at 2 years follow-up, three died, 10 were incarcerated (two outside Andalusia and thus not interviewed), and another three were not possible to find (probably they moved out of the city). Finally, 54 participants, 87% from the total sample randomised in 2003, were interviewed. Among them participants were distributed as follow in relation with their HAT status: 22.2% (12) have never received DAM; 44.4% (24) were still in HAT; and 33.3% (18) discontinued HAT treatment.

Researchers independents of the clinical team, conducted the interviews for this study. Data collection included socio-demographics profile, drug use and health using the following validated questionnaires: the Maudsley Addiction Profile, physical health section (MAP-H)[35]; the Psychiatric sub-scale of the Addiction Severity Index (ASI PSY)[36]; the Opiate Treatment Index, HIV risk behaviours section [37]. Health-related quality of life (HRQL) was measured with the SF12 scale [38]. The interview lasted 40 min.

The study was conducted between March and August 2006, an average of 2.1 years [range interquartile = (1.8–2.2)] after participants' conclusion of the 9 months intervention period. Participants still receiving DAM were contacted at the HAT clinic. Others were tried to be contacted using information from field notes, visiting known meeting-points, and through peers. Participants that were incarcerated were contacted through the collaboration of the Medical Director of the Granada Penitentiary Centre. The study

Table 1. Participants' socio-demographic background

Socio-demographic background	HAT currently 44.4% (n = 24)	HAT in the past 33.3% (n = 18)	Never HAT 22.2% (n = 12)	Total 100% (n = 54)
Age (mean and standard deviation)	39.5 (7.0)	38.4 (3.6)	38.9 (5.5)	39.0 (5.3)
Male	87.5 (21)	83.3 (15)	91.7 (11)	87 (47)
Stable housing ^a	87.5 (21)	76.9 (10)	90 (9)	86.8 (40)
Welfare benefits	41.7 (10)	50.0 (9)	50.0 (6)	46.3 (25)
Working in the last month (regularly or irregular) ^a	54.0 (13)	30.8 (4)	40.0 (4)	32.6 (21)
More that half of the regular acquaintances do not use drugs	58.3 (14)	38.9 (7)	33.3 (4)	46.3 (25)
Engaged in illegal activities in the prior month ^a	8.3 (2)	21.4 (4)	10.0 (1)	12.5 (7)

^aSeven participants in jail were not included in this analysis. HAT, heroin-assisted treatment.

was approved by the Andalusian School of Public Health ethical and research board. Participants signed an informed consent, and were monetary compensated for their time.

Almost all participants were users of heroin mixed with cocaine (speedball) and none reported amphetamine use. The only one participant that reported the use of heroin alone was integrated with the 'heroin combined with cocaine' group. Only one participant reported using cocaine alone, and thus, cocaine use is not presented.

Data analyses were carried out for three groups in relation to their HAT history: currently on HAT (C-HAT), discontinued HAT (D-HAT), never received HAT (N-HAT). Comparisons between baseline outcomes, before randomisation and at 2 years follow-up were made using Wilcoxon Ranks test. Between groups, comparisons of the change from baseline to 2 years were carried out with Kruskal–Wallis Test. Retention in HAT was calculated using a Kaplan–Mayer survival procedure. The analyses were conducted with SPSS 15 [39].

Results

Mean age was 39.02 (SD = 5.26), and 87% of the participants were male. Among them, two (3.7%) were not receiving any treatment, 24 (44.4%) were still receiving DAM, 25 (46.3%) were on MMT and three (5.6%) were drug free. No differences between the C-HAT, D-HAT and N-HAT were found among socio-demographic variables (Table 1), including a drastic reduction in involvement in illegal activities in the prior month (from 58.1% to 12.5%). More important, no differences between these three groups were found among any of the baseline measures obtained before randomisation (data not shown). For those who at some point were on HAT, the mean days receiving DAM were 622.7 (Min = 4; Max = 1100; SD = 359.24) and the

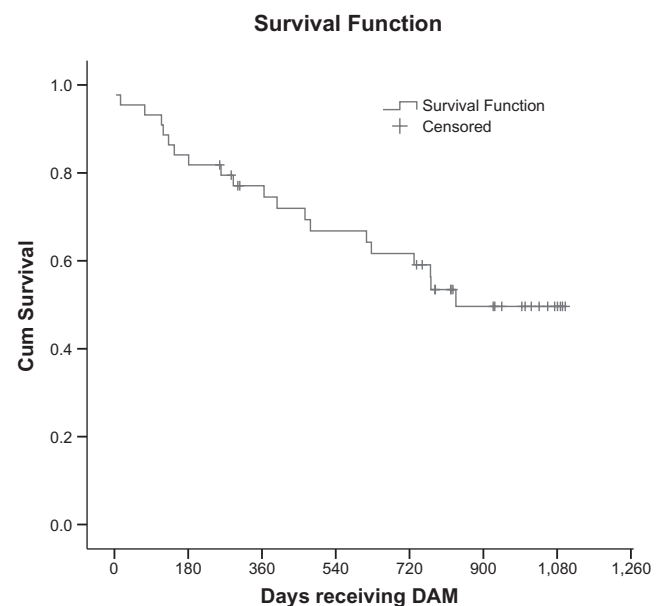


Figure 1. Retention in treatment for participants receiving diacetylmorphine.

retention rate at 3 years was 49.6% (see Figure 1). Participants in HAT visited the clinic twice a day and reported a mean daily dosage of 337.7 mg. of DAM (min. 135; max. 590; SD = 126.1) and 58.9 of MT ($n = 23$; min. 20; max. 110; SD = 25.4). Participants on MMT reported a daily mean dose of 90.1 mg. (min. 8; max. 170; SD = 46.7).

Difference between and within groups are shown in Table 2. Illicit heroin use in the prior month from baseline to 2 years post trial decreased statistically significant in the three groups. Mean days of use were 2.42 (SD = 3.02) for the C-HAT group; 6.56 (SD = 9.48) for the D-HAT group and 13.92 (SD = 12.59) in the N-HAT group. Between groups comparisons showed that the group currently in HAT used illicit heroin significantly less days in the prior month than the other two groups at follow-up.

Table 2. Group comparisons from baseline to 2 year follow-up

Variable	HAT currently		HAT in the past		Never HAT		<i>P</i> ^a
	Baseline	2 years	Baseline	2 years	Baseline	2 years	
Illicit heroin ^{b,c}	26.8 (7.1)	2.4 (3.0)*	27.3 (5.5)	6.6 (9.5)*	25.6 (9.3)	13.9 (12.6)*	0.001
Cannabis ^b	12.3 (13.3)	10.3 (12.4)	17.6 (11.8)	9.6 (11.3)	15.5 (14.4)	18.8 (14.5)	0.042
Binge drinking ^b	3.3 (8.5)	0.8 (2.3)	3.9 (7.9)	1.7 (3.6)	3.2 (8.5)	3.4 (8.7)	0.433
Illicit benzodiazepines ^b	3.5 (7.3)	1.3 (4.5)	7.1 (10.1)	3.4 (9.7)	7.6 (12.5)	4.4 (9.1)	0.471
OTI HIV risk ^d	10.9 (3.7)	2.8 (7.1)*	12.5 (6.3)	7.2 (7.9)	10.8 (5.7)	9.6 (10.0)	0.045
MAP Health ^d	23.5 (15.7)	20.0 (11.9)	22.9 (10.4)	27.9 (14.9)	23.8 (11.5)	29.6 (17.3)	0.091
SF12 Physical Health ^d	40.5 (10.4)	44.6 (10.2)	44.0 (10.4)	38.4 (13.6)	44.3 (9.2)	45.8 (8.7)	0.152
SF12 Mental Health ^d	30.5 (13.2)	40.1 (12.6)*	30.6 (12.2)	26.8 (11.8)	33.8 (13.4)	32.9 (10.9)	0.004
ASI Psychiatric Composite Score ^d	0.5 (0.2)	0.3 (0.2)*	0.5 (0.2)	0.5 (0.3)	0.5 (0.2)	0.4 (0.2)	0.030

* $P < 0.05$, within groups comparisons Wilcoxon Ranks Test. Mean and standard deviations in brackets are shown. ^aBetween groups comparisons for follow-up scores with Kruskal–Wallis Test. ^bNumber of days of use during the prior month. ^cAlways combined with cocaine; this include one participant that use heroin alone. ^dAll questions referred to the prior month. HAT, heroin-assisted treatment. ASI, Addiction Severity Index; MAP, Maudsley Addiction Profile; OTI, Opiate Treatment Index.

The two groups that at some point received HAT decreased the use of cannabis from baseline to 2 years, contrary to those who never received HAT. This difference between these groups was statistically significant. Also, the C-HAT and D-HAT groups decreased binge alcohol use but not the N-HAT group. The use of non-prescribed benzodiazepines decreased in the three groups; however, this was not statistically significant.

The three groups show a decrease in HIV risk behaviour. Those who received HAT at some point, however, experienced a more significant decrease in their scores, from 10.92 (SD = 3.66) to 2.79 (SD = 7.1) and from 12.45 (SD = 6.28) to 7.22 (SD = 7.86) in the current and past HAT groups, respectively.

Only the participants who continued receiving HAT had improved scores from baseline to follow-up in the MAP-H scale, the ASI psychiatric composite score and the SF12 health-related quality of life, both physical and mental health. Both within and between groups comparisons showed statistically significant differences in the ASI PSY and SF12 scores for this group.

Discussion and conclusions

This study evaluated the psychosocial status, illicit heroin use, health and health-related quality of life among participants in the Andalusian heroin trial, 2 years after the completion of the trial. Those who were currently in HAT, had terminated or never received HAT showed a decrease in illegal activities, illicit heroin use and HIV risk behaviours. However, participants still receiving DAM had the most significant improvement. Moreover, those currently in HAT are the only group who showed improvement in health and HRQL.

Two other studies have published follow-up results, the Swiss cohort study [40], and the German RCT [41]. The Swiss study followed-up a cohort of 366 patients on average 6.3 years after treatment initiation. At that time, 148 patients were still or have re-entered HAT (40%). Results showed a marked reduction in illicit drug use among those who were still on HAT or have terminated treatment. As in our study, the reduction in illicit heroin use was higher among those who were still in treatment. In addition, participants from both groups were able to maintain the general social improvements gained in the first year of treatment. However, the reduction on illegal income was higher among those retained in HAT (from 53.8% to 9.8%) compared with those who terminated the treatment (from 42.2% to 11.6%). This was not statistically significant. These findings are similar to our results, where the number of days involved in illegal activities decreased among all groups at 2 years follow-up. The German 2 year follow-up study evaluated the long-term effects of HAT comparing patients who were randomised to HAT at the beginning of the trial to those randomised to methadone that switched to heroin [41]. After 2 years, patients that switched from methadone to heroin achieved similar results in health and illicit drug use as those treated with heroin since the beginning. These finding supports the idea that the marked improvement observed in the first months of HAT can be long-term sustained.

The results of our study should be cautiously analysed and context framed. The main limitation is the small sample size that prevents further analysis of the main outcomes. Also, this is a highly selected sub-sample of opioid-dependent individuals: mainly male,

who have used heroin for 20 years and are socially excluded, with high levels of physical and mental health comorbidities. Finally, it should be noted that during the HAT trial period, the clinic had a multidisciplinary team dedicated almost full time to the patients. After the last patient finished the 9 month trial period, at the end of 2004, the HAT clinic management was organised as a regular program [34]. From then psychosocial patients' needs were referred to the available services in the community. In 2007, the Andalusian authorities received approval from the Central Government for new (re)admissions, but until the middle of 2007 the clinic ran following the trial protocol. Thus, as per protocol, participants who did not attend the clinic for five consecutive days or 40 non-consecutive days were discontinued from treatment. After a participant was dismissed, s/he could no longer restart the program (as per the RCT protocol). This placed a tremendous burden on patients who attended the clinic 325 days per year. Therefore, it is important to stress that the group of non-retained patients were discontinued for a variety of reasons and represent a mixed group who were not merely 'non-responders'.

In 2005, 59.9% of the Spanish population indicated that the medical administration of heroin to solve the drug problem was 'a very important measure' [42]. However, the current National law does not allow heroin prescription beyond clinical research in RCTs. This places researchers, clinicians and administrations in a contradictory position: Why would we engage in a RCT to answer a question that five other studies have already provided? If we know HAT is effective, why would we ask this severely affected population to participate in a RCT? Why would we support a treatment that can only be provided through 'compassionate' use?

Urgent measures are needed to make available other substitution options, aside from methadone, in order to attract and retain opioid users into treatment. HAT clinics are highly controversial and expensive, and as a result, few administrations and research teams pursue its approval and implementation. In Andalusia, supervised HAT clinics did not move forward mostly owing to the drastic decline of heroin injectors (less than 10% are mainly injectors). Thus, research in this Autonomous Community (and possibly others to join) is now focused in non-injected opioids for substitution, capable of being integrated in the MMT system.

The results of this study make evident that HAT has a role in the addiction treatment system for a small group of severely affected opioid-dependent individuals. This study also strengthens the importance of HAT in the stabilisation and improvement of physical and mental health of a group of long-term heroin users with severe comorbidities and high mortality. The impact on

the health-care system would be drastic if this cohort remains untreated [10].

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