



Loss of treatment benefit when heroin-assisted treatment is stopped after 12 months



Isabelle Demaret, M.P.H. ^{a,b,*}, Etienne Quertemont, Ph.D. ^c, Géraldine Litran, M.A. ^{a,b}, Cécile Magoga, M.A. ^{a,b}, Clémence Deblire, M.A. ^{a,b}, Nathalie Dubois, Ph.D. ^d, Corinne Charlier, Ph.D. ^d, André Lemaître, Ph.D. ^a, Marc Anseau, M.D., Ph.D. ^b

^a Institut des Sciences Humaines et Sociales, Université de Liège B31, Boulevard du Rectorat 7, B-4000, Liège, Belgium

^b Service de Psychiatrie, CHU, Domaine Universitaire du Sart-Tilman B35, B-4000, Liège, Belgium

^c Service de Psychologie, Cognition et Comportement, Université de Liège B32, Boulevard du Rectorat 5, B-4000, Liège, Belgium

^d Service de Toxicologie, CHU, Domaine Universitaire du Sart-Tilman, B35, B-4000, Liège, Belgium

ARTICLE INFO

Article history:

Received 11 November 2015

Received in revised form 13 May 2016

Accepted 6 June 2016

Available online xxxxx

Keywords:

Heroin-assisted treatment

Diacetylmorphine

Treatment duration

Substitution treatment

ABSTRACT

Purpose: In 2013, during a recent heroin-assisted treatment trial, participants in heroin-assisted treatment (HAT) decreased significantly more their street heroin use than participants in oral methadone treatment. After the trial, HAT was discontinued. To examine whether the treatment benefits were sustained three months after the trial, the use of street heroin by the participants was analyzed in a follow-up study.

Results: At the follow-up assessment, street heroin use increased in the experimental group. The two groups no longer showed a significant difference ($p = 0.55$) in the level of street heroin use.

Conclusion: A predetermined and forced end of HAT was followed by a significant increase in the level of street level use.

© 2016 Elsevier Inc. All rights reserved.

1. Introduction

To help heroin-dependent individuals, Belgium - alongside 89% of European countries - offers oral methadone treatment (OMT) (World Health Organization, 2010). However, a proportion of heroin-dependent persons continue to pursue their street heroin use while in OMT. For these individuals, a model of heroin-assisted treatment (HAT) was developed in Switzerland in the nineties (Khan, Khazaal, Thorens, Zullino, & Uchtenhagen, 2014; Perneger, Giner, del Rio, & Mino, 1998; Rehm et al., 2001). In HAT, patients receive medically prescribed diacetylmorphine (DAM) under the supervision of nurses, in an outpatient setting (Demaret, Lemaître, & Anseau, 2012; Ferri, Davoli, & Perucci, 2011). HAT has showed greater efficacy than OMT (Ferri et al., 2011). After the trials, a prolonged HAT was associated with sustained improvement (Blanken, Hendriks, Van Ree, & Van Den Brink, 2010; Guttinger, Gschwend, Schulte, Rehm, & Uchtenhagen, 2003; Oviedo-Joekes, March, Romero, & Perea-Milla, 2010; Verthein et al., 2008).

Abbreviations: HAT, heroin-assisted treatment; OMT, oral methadone treatment; DAM, diacetylmorphine; TADAM, Treatment Assisted by DAM.

* Corresponding author at: Institute for Human and Social Sciences (Université de Liège), Boulevard du Rectorat 7 (B31), B-4000, Liège, Belgium. Tel.: +32 4 366 31 58; fax: +32 4 366 98 08.

E-mail address: isabelle.demaret@ulg.ac.be (I. Demaret).

In Belgium, HAT was accepted and funded by the federal government but only for a period of 12 months and as a clinical trial because prescribing DAM for heroin dependence was (and still is) illegal. This clinical trial has been conducted in Liège, a city where heroin dependence has been particularly problematic. In the urban area of Liège, OMT is widely available and people can freely choose their physician or their treatment centre. In 2007, 3000 people in this area were heroin-dependent, compared to a population of 500,000 inhabitants (Demaret, Herné, Lemaître, & Anseau, 2011).

During the randomized controlled trial, street heroin use decreased significantly more in the experimental group with HAT compared to the control group with OMT (Demaret et al., 2015). The modalities of our trial were comparable to the other trials and we included the same target group of persons with heroin dependence and regular street heroin use in spite of a current or previous drug treatment (Ferri et al., 2011; Haasen et al., 2007; March, Oviedo-Joekes, Perea-Milla, Carrasco, & PEPSA Team, 2006; Oviedo-Joekes et al., 2008; Perneger et al., 1998; Strang et al., 2010; van den Brink et al., 2003).

The main difference in our trial was the duration of HAT (limited to 12 months), which was not based upon scientific reasons. The only other trial with a predetermined end of HAT was the Canadian one. A follow-up study of this trial showed that street heroin use rose after the end of HAT, particularly for the group of participants who did not transition voluntarily from DAM to oral methadone (Oviedo-Joekes

et al., 2014). In the Dutch trial, HAT was also discontinued after 12 months, but only during 2 months. This also had a negative impact: 82% of the participants who were completers and responders deteriorated substantially at the end of this discontinuation. After this interruption however, HAT could be pursued with no predefined end point for the participants who deteriorated after the discontinuation (van den Brink et al., 2003).

In this paper, we report the results of a follow-up study and evaluated whether the decrease of street heroin use was sustained three months after the Belgian trial.

2. Methods

2.1. Design

TADAM (Treatment Assisted by DAM) was an open label, randomized controlled trial; it began in January 2011 and ended in January 2013. The Ethics Committee of the University of Liège approved this trial (number 2009/189) on March 16, 2010, including a follow-up after 3 months. After the end of the trial (i.e. at 12 months from treatment start) HAT was stopped in the experimental group and the most appropriate treatment at the time of the transition was offered to each participant. The detailed method and inclusion criteria were as described previously (Demaret et al., 2015).

2.2. Assessments

Every three months from baseline to 15 months, street heroin use and cocaine use were measured by the number of days of use during the previous month, using the European Addiction Severity Index (Kokkevi & Hartgers, 1995). During each assessment, participants also provided a urine sample. In urinalysis (ultra-high-pressure liquid chromatography coupled with mass spectrometry), street heroin use was indicated by the detection of meconin, a metabolite of an opium constituent (noscapine) that is not found in DAM. The presence of benzoylecgonine, a metabolite of cocaine in the sample, revealed cocaine use. In case of discrepancy between self-reported and toxicological data, we replaced the self-reported value by a value based on prior use. At each assessment, physical health was measured by the Maudsley Addiction Profile – Health Symptoms Scale (MAP-HSS) (Marsden et al., 1998); mental health by the total score of the Symptom Check-List (SCL-90-R) (Gosselin & Bergeron, 1993; Pellet, 1997); criminal involvement was characterized by self-reported facts committed or experienced as a victim, during the previous month (Ansseau et al., 2005).

At each assessment, participants who were not (or were no longer) in the HAT centre received a compensation (between 15 and 60 euro depending on the presence of medical examination, blood and urine sample). The research team remained independent from the treatment staff.

2.3. Statistical analysis

Mixed-design analyses of variance (ANOVA), with the experimental group (two levels) as a between-subject factor and time post-inclusion (six levels: baseline, 3, 6, 9, 12 and 15 months post-inclusion) as a within-subject factor, were used for the analyses of continuous data (for self-reported value). The ANOVAs were followed by Newman-Keuls post-hoc comparisons to assess between-group differences. To analyze the level of meconin, Friedman tests for non-parametric repeated measures comparisons were carried out on both groups separately. Non-parametric Spearman correlations were used to examine the association between urinalysis and self-reported values on street heroin use at each assessment. Statistical analyses were performed with STATISTICA 10. Statistical significance was set at $p < 0.05$. Only participants seen at each assessment were included in these analyses.

3. Results

3.1. Participants' characteristics and follow up

Participants' characteristics were described previously (Demaret et al., 2015). Among the 74 participants included in the trial, 13 were excluded from this analysis: in the experimental group, 1 refused to be interviewed, 1 had died and 3 could not be reached at an intermediate assessment; in the control group, 5 refused to be interviewed and 3 could not be reached at an intermediate assessment. 61 (82%) participants were interviewed at each assessment: 31 in the experimental group and 30 in the control group. Of these 61 participants, 2 (one in each group) could not provide a urine sample (they were interviewed in prison) and 2 (both in the experimental group) reported no street heroin use but gave a positive urine sample. The retention rate in substitution treatment was higher for the participants in the experimental group, but the difference was not significant: 30 (97%) versus 26 (87%). The 5 other participants were neither in a substitution treatment, nor abstinent.

3.2. Evolution of the efficacy indicators

Table 1 shows the evolution of efficacy indicators from baseline to 15 months for the 61 patients. Compared to baseline, the decrease of street heroin use at the 15-month assessment was significantly higher in the experimental group than in the control group ($p < 0.001$). MAP-HSS scores also indicated a significantly higher improvement in the experimental group ($p < 0.05$). The other efficacy indicators revealed no significant difference between both groups.

3.3. Other analyses of street heroin use

Newman-Keuls post-hoc tests showed significant differences of street heroin use between the two groups at each assessment (Fig. 1), except at baseline and at the 15-month assessment ($p = 0.55$). Newman-Keuls post-hoc-tests also showed a significant increase of street heroin use in the experimental group between the 12 and 15-month assessments ($p = 0.0052$). Mean levels of meconin (Fig. 2) improved significantly in the experimental group ($\chi^2(5) = 35.01$; $p < 0.00001$) but not in the control group ($\chi^2(5) = 5.59$; $p = 0.35$). Non-parametric Spearman correlations between self-reported values and meconin levels were significant except at baseline (data not shown).

4. Discussion

During the trial, participants in the experimental group showed a decrease of street heroin use significantly more important than in the control group, as in five other trials (Haasen et al., 2007; March et al., 2006; Oviedo-Joekes et al., 2009; Perneger et al., 1998; Strang et al.,

Table 1
Evolution of the efficacy indicators.

Efficacy indicators	Group (n = 61)	T0	T03	T06	T09	T12	T15	P ^a
Street heroin use ^b	DAM	25	6	5	4	8	14	$p = 0.00094$
	METH	28	18	17	18	16	17	
Cocaine use ^b	DAM	3	2	3	2	1	2	$p = 0.83$
	METH	5	5	3	4	2	3	
Criminal involvement ^b	DAM	9	2	3	2	1	2	$p = 0.35$
	METH	8	4	4	5	6	5	
MAP-HSS - total score	DAM	18	13	15	13	16	13	$p = 0.0195$
	METH	19	17	17	17	17	18	
SCL-90-R - total score	DAM	109	75	70	70	71	71	$p = 0.056$
	METH	110	98	92	95	86	94	

^a p for mixed-design analyses of variance (ANOVA).

^b Self-reported data (number of days in past month) complemented with toxicological analysis or registered criminal proceedings.

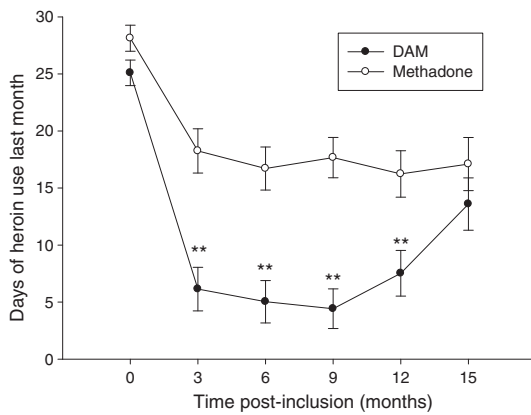


Fig. 1. Improvement in street heroin use at each assessment (self-reported data corrected by toxicological analyses; ** = $p < 0.01$). Vertical bars represent the standard error of the mean value.

2010) and, as in other trials, this effect was confirmed by urinalysis and cocaine use did not increase. Their scores on the physical (MAP-HSS) and mental (SCL-90-R) health questionnaires also improved significantly more after 12 months, as in other trials (Demaret et al., 2015). At the follow-up assessment, only street heroin use and scores on the MAP-HSS revealed significant improvement in the experimental group. Cocaine use and criminal involvement were low in both groups and the difference of evolution between the groups was never significant during or after the trial.

However, after the end of HAT, street heroin use significantly increased in the experimental group and the difference between the groups was no longer significant with the Newman–Keuls post-hoc tests at the follow-up assessment. In the follow-up studies of other trials, this increase in street heroin use was not found for individuals who could continue HAT. On the contrary, participants in long-term HAT reported less street heroin use than those who stopped HAT (Blanken et al., 2010; Guttinger et al., 2003; Oviedo-Joekes et al., 2010; Verthein et al., 2008). Furthermore, participants who stopped HAT involuntarily showed a particularly important increase of their street heroin use in comparison with participants who stopped voluntarily (Oviedo-joekes et al., 2014).

The worsening of participants' situations following discontinuation of HAT compared to their situations during treatment further supports the idea that a predetermined and abrupt end of HAT leads to a loss of benefits gained during treatment (Demaret et al., 2015). Given this, a forced end of HAT without therapeutic justification can be seen as ethically disputable, even after a 12-month treatment. This deterioration justifies the refusal of heroin-dependent individuals to enter the trial during the recruitment process because of the predetermined end of HAT (Demaret

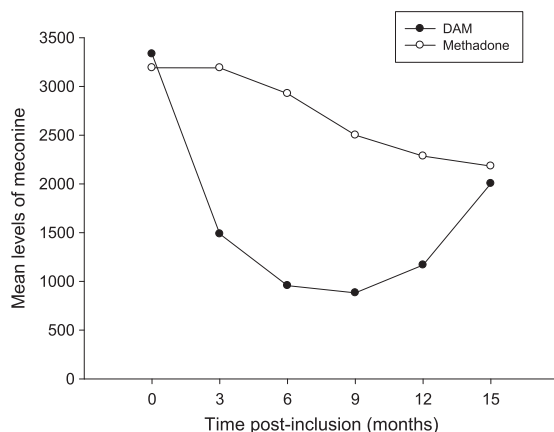


Fig. 2. Levels of meconin at each assessment based on urinalysis.

et al., 2014). These refusals could have been a cause of the lack of power of our primary outcome analysis (Demaret et al., 2015).

Our study limits were the relatively low number of participants and the fact that our trial and the follow-up study were not designed to assess the effect of the forced end of HAT after 12 months. Nonetheless, our conclusions were supported by the results of other trials as seen above.

5. Conclusion

HAT is more effective than OMT for decreasing street heroin use for heroin-dependent individuals who pursue street heroin use in spite of a current or previous OMT. However, three months after a predetermined end of HAT (i.e. without a spontaneous demand by the patient), the use of street heroin increased again to reach levels very close to those observed in the control group. Therefore, HAT should be offered as an open-ended treatment as recommend by the WHO for other opioid treatment (World Health Organization, 2010) and the end of treatment should be a clinical decision based on the evolution of the patient.

Role of funding sources

The TADAM trial was funded at 80% by the Federal Minister of Social Affairs and Public Health. It was also funded by the City and the University of Liège. Only the authors were involved in the collection, analysis, and interpretation of data as in the writing of the report and in the decision to submit the paper for publication. Concerning the trial and manuscript, the authors were independent from the funding sources.

Contributors

Marc Anseau was the principal investigator. He conceived and designed the study with André Lemaître and Isabelle Demaret. They led the interpretation of the data and approved the final report. Isabelle Demaret coordinated the research, the collection of data, the (statistical) analyses, the interpretation and the writing of the report. Géraldine Litran, Cécile Magoga, and Clémence Deblire collected the data. Nathalie Dubois did the medical and toxicological analyses. Corinne Charlier helped for the interpretation of the urine and blood analyses. Etienne Quertemont did the statistical analyses. Isabelle Demaret wrote the final report and, with Etienne Quertemont, drafted this paper. All authors contributed to and have approved the final manuscript.

Conflicts of interest

None.

Acknowledgement

We thank each participant; the staff from the HAT centre and from the partner centers; the staff of the University of Liège who always helped us quickly to solve administrative problems; the staff of the policlinic of the Liège University Hospital; the experts of our scientific committee; the researchers from other countries who gave us information and helped us to visit their HAT centers; the staff from these centers; the Psychiatric Platform of Liège who invited us to the meetings of the addiction network of the Province of Liège; the funders of the trial and the Drug Cell of the Federal Public Service of Health, Food Chain Safety and Environment who were in charge of the administrative follow up of the TADAM assessment.

References

- Anseau, M., Gustin, F., Hodiaumont, F., Lemaître, A., Lo Bue, S., Lorant, V., ... Van Deun, P. (2005). *DHCo Délivrance d'héroïne sous contrôle médical : Etude de faisabilité et de suivi*. Gand, Belgique: Academia press.

- Blanken, P, Hendriks, VM, Van Ree, JM, & Van Den Brink, W (2010). Outcome of long-term heroin-assisted treatment offered to chronic, treatment-resistant heroin addicts in the Netherlands. *Addiction*, *105*, 300–308. <http://dx.doi.org/10.1111/j.1360-0443.2009.02754.x>.
- Demaret, I, Herné, P, Lemaître, A, & Anseau, M (2011). Feasibility assessment of heroin-assisted treatment in Liège, Belgium. *Acta Psychiatrica Belgica*, *111*, 3–8.
- Demaret, I, Lemaître, A, & Anseau, M (2012). Staff concerns in heroin-assisted treatment centres. *Journal of Psychiatric and Mental Health Nursing*, *19*, 563–567. <http://dx.doi.org/10.1111/j.1365-2850.2011.01810.x>.
- Demaret, I, Litran, G, Magoga, C, Deblire, C, Dupont, A, De Roubaix, J, ... Anseau, M (2014). Why do heroin users refuse to participate in a heroin-assisted treatment trial? *Heroin Addiction and Related Clinical Problems*, *16*, 41–48.
- Demaret, I, Quertemont, E, Litran, G, Magoga, C, Deblire, C, Dubois, N, ... Anseau, M (2015). Efficacy of heroin-assisted treatment in Belgium: A randomised controlled trial. *European Addiction Research*, *21*, 179–187. <http://dx.doi.org/10.1159/000369337>.
- Ferri, M, Davoli, M, & Perucci, CA (2011). Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database of Systematic Reviews*, *12*, CD003410. <http://dx.doi.org/10.1002/14651858.CD003410.pub4>.
- Gosselin, M, & Bergeron, J (1993). *Evaluation des qualités psychométriques du questionnaire de santé mentale SCL-90-R*. Montréal, QC: RISQ, 87.
- Guttinger, F, Gschwend, P, Schulte, B, Rehm, J, & Uchtenhagen, A (2003). Evaluating long-term effects of heroin-assisted treatment: the results of a 6-year follow-up. *European Addiction Research*, *9*, 73–79. <http://dx.doi.org/10.1159/000068811>.
- Haasen, C, Verthein, U, Degkwitz, P, Berger, J, Krausz, M, & Naber, D (2007). Heroin-assisted treatment for opioid dependence: randomised controlled trial. *The British Journal of Psychiatry*, *191*, 55–62. <http://dx.doi.org/10.1192/bjp.bp.106.026112>.
- Khan, R, Khazaal, Y, Thorens, G, Zullino, D, & Uchtenhagen, A (2014). Understanding Swiss drug policy change and the introduction of heroin maintenance treatment. *European Addiction Research*, *20*, 200–207. <http://dx.doi.org/10.1159/000357234>.
- Kokkevi, A, & Hartgers, C (1995). EuropASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. *European Addiction Research*, *1*, 208–210. <http://dx.doi.org/10.1159/000259089>.
- March, JC, Oviedo-Joekes, E, Perea-Milla, E, Carrasco, F, & PEPSA Team (2006). Controlled trial of prescribed heroin in the treatment of opioid addiction. *Journal of Substance Abuse Treatment*, *31*, 203–211. <http://dx.doi.org/10.1016/j.jsat.2006.04.007>.
- Marsden, J, Gossop, M, Stewart, D, Best, D, Farrell, M, Lehmann, P, ... Strang, J (1998). The Maudsley addiction profile (MAP): A brief instrument for assessing treatment outcome. *Addiction*, *93*, 1857–1867.
- Oviedo-Joekes, E, Brissette, S, Marsh, DC, Lauzon, P, Guh, D, Anis, A, & Schechter, MT (2009). Diacetylmorphine versus methadone for the treatment of opioid addiction. *The New England Journal of Medicine*, *361*, 777–786. <http://dx.doi.org/10.1056/NEJMoa0810635>.
- Oviedo-Joekes, E, Guh, D, Marchand, K, Marsh, DC, Lock, K, Brissette, S, ... Schechter, MT (2014). Differential long-term outcomes for voluntary and involuntary transition from injection to oral opioid maintenance treatment. *Substance Abuse Treatment, Prevention, and Policy*, 3–9.
- Oviedo-Joekes, E, March, JC, Romero, M, & Perea-Milla, E (2010). The Andalusian trial on heroin-assisted treatment: A 2 year follow-up. *Drug and Alcohol Review*, *29*, 75–80. <http://dx.doi.org/10.1111/j.1465-3362.2009.00100.x>.
- Oviedo-Joekes, E, Nosyk, B, Brissette, S, Chettiar, J, Schneeberger, P, Marsh, DC, ... Schechter, MT (2008). The North American Opiate Medication Initiative (NAOMI): Profile of participants in North America's first trial of heroin-assisted treatment. *Journal of Urban Health*, *85*, 812–825. <http://dx.doi.org/10.1007/s11524-008-9312-9>.
- Pellet, J (1997). La symptom check-list. In J. D. Guelfi (Ed.), *L'évaluation clinique standardisée en psychiatrie* (pp. 77–85). Paris: Editions Médicales Pierre Fabre.
- Perneger, TV, Giner, F, del Rio, M, & Mino, A (1998). Randomised trial of heroin maintenance programme for addicts who fail in conventional drug treatments. *BMJ*, *317*, 13–18. <http://dx.doi.org/10.1136/bmj.317.7150.13>.
- Rehm, J, Gschwend, P, Steffen, T, Gutzwiller, F, Dobler-Mikola, A, & Uchtenhagen, A (2001). Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: A follow-up study. *Lancet*, *358*, 1417–1420. [http://dx.doi.org/10.1016/S0140-6736\(01\)06529-1](http://dx.doi.org/10.1016/S0140-6736(01)06529-1).
- Strang, J, Metrebian, N, Lintzeris, N, Potts, L, Carnwath, T, Mayet, S, ... Forzisi, L (2010). Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): A randomised trial. *Lancet*, *375*, 1885–1895. [http://dx.doi.org/10.1016/S0140-6736\(10\)60349-2](http://dx.doi.org/10.1016/S0140-6736(10)60349-2).
- van den Brink, W, Hendriks, VM, Blanken, P, Koeter, MWJ, van Zwieten, BJ, & van Ree, JM (2003). Medical prescription of heroin to treatment resistant heroin addicts: Two randomised controlled trials. *BMJ*, *327*, 310. <http://dx.doi.org/10.1136/bmj.327.7410.310>.
- Verthein, U, Bonorden-Kleij, K, Degkwitz, P, Dilg, C, Köhler, WK, Passie, T, ... Haasen, C (2008). Long-term effects of heroin-assisted treatment in Germany. *Addiction*, *103*, 960–968. <http://dx.doi.org/10.1111/j.1360-0443.2008.02185.x>.
- World Health Organization (2010). Atlas on substance use (2010): Resources for the prevention and treatment of substance use disorders. (Retrieved 6 November 2015, from http://www.who.int/substance_abuse/publications/treatment/en/)