Journal of Urban Health: Bulletin of the New York Academy of Medicine, Vol. 84, No. 4
doi:10.1007/s11524-007-9198-y

Heroin-assisted Treatment (HAT) a Decade Later: A Brief Update on Science and Politics

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ABSTRACT *Since the initial Swiss heroin-assisted treatment (HAT) study conducted in the mid-1990s, several other jurisdictions in Europe and North America have implemented HAT trials. All of these studies embrace the same goal—investigating the utility of medical heroin prescribing for problematic opioid users—yet are distinct in various key details. This paper briefly reviews (initiated or completed) studies and their main parameters, including primary research objectives, design, target populations, outcome measures, current status and—where available—key results. We conclude this overview with some final observations on a decade of intensive HAT research in the jurisdictions examined, including the suggestion that there is a mounting onus on the realm of politics to translate the—largely positive—data from completed HAT science into corresponding policy and programming in order to expand effective treatment options for the high-risk population of illicit opioid users.*

KEYWORDS *Heroin-assisted treatment, Science, Politics, Opioid dependance, Clinical trials*

INTRODUCTION

The phenomenon of illicit opioid use has existed in Western countries for almost a century, and its negative consequences, most importantly, excess mortality, morbidity, and crime, associated with it are well documented.[1–5] In Europe and North America, there are an estimated two to four million illicit heroin users.[6,7] One to two percent of this population prematurely die each year; they contribute to the majority of the existing hepatitis C and a substantial proportion of the HIV disease burden, and—largely driven by their intensive criminal involvement—fuel an overall social cost burden related to illicit drug addiction estimated at billions of dollars per year in countries like the US, Canada, Germany, and others.[8–13]

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In response to the need for providing treatment options for illicit opioid users resistant to available therapeutic opioid maintenance interventions with generally established effectiveness (e.g., oral methadone maintenance treatment [MMT] and oral buprenorphine maintenance treatment [BMT]) and an increasing focus on the public order challenges related to un- or ineffectively treated heroin addiction, half a dozen countries (Canada, Germany, The Netherlands, Spain, Switzerland, and United Kingdom) have embarked on the experimental implementation of medical "heroin-assisted treatment" (HAT) initiatives over the past decades. This series of HAT studies began with the Swiss PROVE study in 1994.[14,15] The main underlying objective of these various HAT trials has been consistently similar: To determine the therapeutic—aiming at individual and/or societal levels—value of medical heroin prescription for high-risk heroin users for whom such benefits cannot be expected or achieved from existing treatment options.[14,16,17] However, each of the studies implemented differed considerably with regard to specific aspects, e.g., target population, nature of interventions, research design (e.g., prospective cohort study, randomized controlled clinical trials [RCT] and measures, and thus has produced distinct and context-specific data and findings). Given that HAT studies in four of the countries have been completed, attention has shifted from the scientific to the sociopolitical level, as the future utilization of HAT based on the scientific evidence provided falls into the realm of political decision making.[18] Below we present a brief update—after an earlier review of HAT studies—on the scientific and sociopolitical state of HAT initiatives in the above countries (Table 1).*

CANADA

The currently ongoing "North American Opiate Medications Initiative" (NAOMI) in Canada, which began recruitment in 2006, is implemented as an RCT in two sites (Montreal and Vancouver); an additional site was planned for Toronto but could not be implemented there. The NAOMI study aims at primary heroin injectors who have had a minimum of two previous unsuccessful treatment (including one MMT) attempts and are not enrolled in treatment at the time of recruitment into the study.[19,20] The trial randomized participants into HAT or MMT—with equal psychosocial interventions—over a 12-month study period, and measures (1) retention and (2) illicit drug use and criminal activity as main outcome indicators. Recruitment into the NAOMI study was initially slower and more difficult than anticipated in both trial sites because of the high-threshold multiple inclusion criteria and the demands that inclusion criteria screening placed on an out-of-treatment population; however, recruitment subsequently improved and was completed in March 2007. All completers, including those randomized into and responding to the HAT arm, are transitioned into regular existing treatment (not HAT) after the experimental phase. The future of HAT in Canada beyond the NAOMI trial is difficult to predict, as the current federal government has generally emphasized a much starker "law and order" approach to addiction problems.

*In alphabetical order of countries.

TABLE 1 Overview of HAT studies by country

	Canada	Germany	The Netherlands	Spain (Andalusia)	Spain (Catalonia)	Switzerland	United Kingdom
Lead investigator (s)/study period	Schechter, M/ 2005–2008	Naber, D/ 2003–2004	van den Brink, W/1998–2002	March, JC/ 2003–2004	Casas I Brugué, M, Pérez de los Cobos J, Río Meyer, M/ 2004–2006	Rehm, J Uchtenhagen A, Perneger T/ 1994–2006	Strang, J 2006–2008
Design	RCT, multicenter	RCT, multicenter, stratified	2 RCTs, multicenter	RCT	RCT	RCT, prospective cohorts, cohort follow up	RCT, multicenter
Aim/intervention/ main study period	Injected heroin + oral methadone vs. oral methadone/ injected dilaudid + oral methadone vs. oral methadone/ 12 months	Injected heroin (+ oral methadone if requested) vs. oral methadone/ 12 months	Injected heroin + oral methadone vs. oral methadone/ inhaled heroin + oral methadone vs. oral methadone/ 12 months	Injected heroin + oral methadone vs. oral methadone/ 9 months	Oral heroin (IR) vs. oral methadone/ morphine vs. oral methadone	Injected heroin/ oral heroin (IR and SR), oral methadone, oral morphine/2 years (ongoing)	Injected heroin vs. oral methadone/ injected methadone vs. oral methadone/ 6 months
Participants	Opiate-dependent persons, predominantly using injected heroin on regular basis, not responding in the past or currently in MMT. Sample: 246	Heroin addicts, with concomitant health problems, who had not responded sufficiently to methadone treatment or were not reached by the therapeutic system. Sample: 1,032	Heroin-dependent patients in MMT, with severe concomitant problems related to drug misuse, not responding to available treatment. Sample: 549	Regular opioid-injecting people, with severe concomitant problems related to drug misuse, not responding to methadone. Sample: 62	Regular heroin users, not responding to MT in the past, not currently using methadone. Sample: 45	Severe heroin dependent persons to whom other therapies had failed or the health state does not allow another kind of therapy. Sample: 1,273 (247)	Regular injecting heroin users, currently in methadone, who do not benefit from conventional substitution maintenance Treatment Sample: 150
Outcomes	Retention	Improvement by 20% in physical or mental health and 20% reduction of street-heroin use (and no increase in cocaine use).	Improvement by 40% in physical, mental or social health and no increase in cocaine use.	Physical health; Drug related problems; Street drug use; HIV risk behavior; Psycho-social adjustment; Criminal activities.	Retention	Treatment retention	Reduction of illicit heroin and other substance use

	Improvement by 20% in illicit drug use (no deterioration of more than 20% in health or psychosocial measures) Criminal activities				Subjective measures	Improvement in physical, mental and social health	High-risk injecting practices
					Dose response	Permanent abstinence from opiate use	General health and psychosocial functioning Criminal activity Treatment retention Patient satisfaction
Results		Health response: HAT 80%/MMT 74%; OR 1.4 (p=0.023)	Response rate: 56 vs. 31% injected HAT vs. MMT; 50 vs. 27% inhaled HAT vs MMT	HAT/MMT (p): physical health 3.2 (0.034); drug related problems 2.1 (0.004); street heroin use 2.4 (0.02); HIV risk behavior 1.9 (0.004); psychosocial adjustment, no differences; criminal activities 3.2 (0.09)		Retention rate: from 1994 to 2004, 72% of the patients remained in HAT for a year and 58% for 2 years or longer (median retention 2.83 years)	
		Street heroin use: HAT 69%/MMT 55.2; OR 1.9 (p=0.001)	Retention rate: 87 vs. 68% injected HAT vs. MMT; 85 vs. 72% inhaled HAT vs MMT	Retention Rate: 74%/68%		An improvement in physical and mental health was found, and also in social integration	
		Retention rate: HAT 67%/MMT 39%	Discontinuation of heroin resulted in a rapid deterioration in 82% of responders				
		No differences between stratified groups or psychosocial therapies					

TABLE 1 (continued)

	Canada	Germany	The Netherlands	Spain (Andalusia)	Spain (Catalonia)	Switzerland	United Kingdom
Current/ future status of HAT	Trial is in progress in Vancouver and Montreal. Recruitment was completed in March 2007.	300 patients are in follow-up in 7 treatment units. Currently no possibility to admit new patients to HAT.	~400 patients continue to be in HAT in 7 treatment centers; new treatment centers will be opened in 2007 resulting in a total of 800–1,000 treatment slots in 12–15 cities.	Patients receive HAT under compassionate access in one clinic.	Results not published yet.	HAT began on experimental basis (PROVE) in 1994, and has been available as a regular treatment on the basis of governmental decree since 1999.	HAT by GPs available since the 1920s
	After 12 months, HAT participants will be transitioned to available therapies such as MMT.	HAT registration is approved, but federal drug control legislation must be changed.	HAT registration approved in December 2006 (both formulations).	Spanish Government will only consider HAT per approval on the basis of RCTs.		At the end of December 2004, 1273 patients were in HAT in 23 centers.	Few patients receive HAT at low doses and on a take-home basis.
						Oral HAT (tablets) is awaiting approval.	Supervised HAT clinics may become an option.
Additional information	http://www.naomistudy.ca/	http://www.heroinstudie.de	http://www.ccbh.nl	http://www.easp.es/pepsa		http://www.bag.admin.ch/	http://www.iop.kcl.ac.uk/iopweb/departments/home/default.aspx?locator=355&project=10114

GERMANY

The multicenter HAT RCT in Germany was conducted for the primary purpose of a medications approval study between 2003 and 2005, and presented its key results in 2006. The study consisted of several stratified components and aimed at regular injection heroin users both currently in MMT without satisfactory therapeutic response and heroin users not currently in treatment in the previous 6 months (but with a treatment history). In a randomly assigned sample of 1,032 participants, the study compared the benefits of HAT to regular oral MMT as the control intervention over a 12-month trial period. As main outcomes, the study measured changes in health status and illicit heroin use, and found significant improvements in both as well as significantly higher retention rates for the experimental HAT groups (health outcome OR=1.41, 95% CI 1.05–1.89; illicit drug use OR=1.85, 95% CI 1.43–2.40; and retention rate 67 and 40% HAT/MMT, respectively).[21] The study furthermore found no difference on treatment outcomes between the two psychosocial (case management with integrated motivational interviews vs. psycho-education in addition to drug counseling) interventions examined. In addition, a cost–benefit analysis found that HAT produced a net savings balance (€5,966) per patient per year, whereas the costs of MMT remained greater than its calculated savings (minus €2,069) because of its inability to substantially reduce crime and criminal justice system costs.[22] On the basis of the study results, HAT has been approved by the overseeing German Federal Institute for Drugs and Medical Devices. However, future use of HAT would require changes to the federal narcotics control law, which the current German grand coalition government has agreed not to implement currently,[23] and therefore the prospects for HAT as regular treatment in the near future are slim at best.

THE NETHERLANDS

Beginning in 1998, a multicenter study was conducted in the Netherlands to determine the benefits of heroin coprescription (i.e., heroin plus methadone) for a sample of heroin addicts (*N*=549) not responding satisfactorily to MMT.[16] The study consisted of two separate RCTs, namely, an injection heroin and an inhalable heroin trial, each compared to oral MMT alone, over a 12-month study period. The trials showed superior retention for MMT (87% MMT vs. 68% coprescribed injectable heroin; 85% oral MMT vs. 72% coprescribed inhalable heroin), yet demonstrated superior therapeutic benefits in the intent-to-treat analysis for both experimental arms (56 vs. 31% and 50 vs. 27%) compared to MMT on the basis of a multidomain response index, consisting of physical health, mental health, and social functioning (including criminal activity) measures.[24] Furthermore, the discontinuation of HAT resulted in a rapid deterioration in four out of five treatment responders. From a cost-effectiveness perspective, it was demonstrated that HAT was cost-effective according to universal standards of health economics and on a cost–benefit basis resulted in savings of approximately €12,000 per patient per year compared with MMT alone.[25] In 2004, the Dutch government decided to support the approval of HAT as regular addiction treatment alongside other existing interventions (e.g., MMT). In December 2006, the Dutch Medicines Evaluation Board approved both inhalable and injectable heroin as a medicinal product for the treatment of poorly functioning, therapy-resistant heroin addicts who are characterized by daily heroin use; who have not responded to treatment in

at least one, regularly attended methadone maintenance program; and who are currently enrolled in methadone treatment. Currently (mid-2007) about 400 patients are receiving HAT in 9 cities, and it is expected that HAT will eventually become available to 800–1,000 patients in 12–15 cities across The Netherlands.

SPAIN

Two HAT studies were recently completed in Spain. The first one was an RCT implemented in Granada (Andalusia) between 2003 and 2004, examining the efficacy of injection HAT (in combination with methadone) compared to MMT alone in a study sample of *N*=62 over a 9-month study period. The target group was regular opioid injectors with at least two previous MMT episodes and severe health or social problems.[26] The study found no differences in retention rates between experimental and control arm; it found significantly greater improvements for drug-related risk behaviors, illicit heroin use, and health indicators in the experimental group, although both the experimental and control group demonstrated significant intrinsic improvements on key outcome indicators over time. Trial participants continue to receive HAT, and new patients enter to fill out open HAT slots, under compassionate use principles and the umbrella of a follow-up study.

A pharmaceutical efficacy study comparing oral heroin and oral morphine (experimental) with oral methadone (control) prescription in a small sample of inpatient heroin addicts with previous exposure to MMT has been implemented in Barcelona between 2004 and 2006.[27] However, results of this study are currently not yet available.

In reference to the Granada HAT study, the Spanish federal drug control authority did not deem that study's results as conclusive, and is currently not considering HAT for approval as a regular treatment.

SWITZERLAND

The initial Swiss HAT trial ("PROVE" study) was conducted as a prospective cohort study with some 1,000 participants in 18 treatment centers between 1994 and 1996. The multisite study aimed at injecting heroin addicts not effectively reached by other therapies, and demonstrated considerable improvements in illicit heroin and cocaine use, physical and mental health status, criminal activity, and social integration at the end of the 2-year study period.[15] The study also included a small (*N*=51) RCT in one site (Geneva) comparing HAT to other (mainly MMT) therapies, which found substantial improvements for illicit heroin use, health status, and crime among HAT patients.[28] An economic evaluation of the program also found a positive cost–benefit ratio of approximately 1:2.[29] Follow-up monitoring found high long-term retention rates of patients in HAT, yet also documented that substantial numbers of patients shifted to other forms of treatment (e.g., MMT) or into abstinence.[30] Whereas the original PROVE study included an injection morphine component, which proved not feasible, a recent Swiss study demonstrated the feasibility and efficacy of (immediate and slow release) oral heroin (tablet) maintenance as a complementary intervention to prescribed injectable heroin.[31] The initial Swiss HAT studies were criticized for their limited scientific rigor (i.e., not an RCT);[32,33] however, they fulfilled a crucial "ice breaker" function for HAT trials in other countries. After strong public approval of HAT through several referenda, the Swiss federal government established HAT by executive decree as a

regular part of the therapeutic option landscape for heroin addiction treatment in 1999.[34] At the end of 2004, some 1,200 patients were enrolled in HAT in 23 treatment centers across Switzerland.[35]

UNITED KINGDOM

The context of the British Randomised Injecting Opioid Treatment Trial (RIOTT), which commenced in 2005, is unique in that Britain is the only country in which medical heroin prescribing for addiction treatment purposes has been available before this study (and yet supervision had been minimally utilized in recent years, with only about 300 patients currently provided with regular prescribed heroin).[36,37] The RIOTT study introduces the new modality of supervised injecting to the UK context. In this new setting, it aims to recruit regular injection heroin users currently not sufficiently benefiting from MMT treatment; it consists of two experimental intervention arms, namely, injection heroin and injection methadone treatment,[38] both of which are compared to optimized (oral) MMT in three planned study centers.[39] A total study population of *N*=150 will be randomized into one of the three (two experimental, one control) study arms for a 6-month study period; main outcome indicators consist of illicit heroin and other drug use, health and psychosocial indicators, criminal activity, and treatment retention. It is expected that the outcomes of the RIOTT study—expected for 2009—will inform options and decision making regarding the future of the currently existing HAT and overall opioid maintenance system in Britain.

CONCLUDING REMARKS

A few key conclusions and discussion points regarding the state and future of HAT can be offered based on the above review of completed or ongoing studies.

First, although the basic goal of the different HAT studies is similar, each of the studies is distinct in key aspects, thus limiting direct comparisons and meta-analyses.[40] Although this might be a desirable goal for science, it should be noted that heroin addiction and its consequences occur in distinct real-life environments (including unique cultural and system factors), and interventions need to be devised, measured, and evaluated within these to have authentic relevance for policy and practice.[33,41]

Second, the discussed studies above have demonstrated in several different contexts that the implementation of HAT is feasible, effective, and safe as a therapeutic intervention.[21,24,26,30] This should not be seen as a conclusion that could be taken for granted because many observers expected disastrous consequences from the provision of medical heroin prescription.

Third, even within the contexts of relevant methodological constraints, e.g., the Swiss study relying purely on prospective observational data, and most of the other RCTs comparing HAT outcomes against a control intervention (MMT), which participants have previously either rejected by choice or proven to be ineffective, [32,42] the reviewed HAT studies have demonstrated rather robust and consistently positive therapeutic outcomes on the various indicators chosen for a population of high-risk heroin addicts for whom currently no effective alternative therapies are available. Clearly, this demonstrated effectiveness is at this point limited to short-term outcomes, and long-term examinations ought to follow (albeit Swiss follow-up data present initial positive evidence in this regard).[43] It may very well emerge that HAT's main long-term benefit does not materialize through life-long maintenance,

but by stabilizing and readying many of its patients for other simpler therapeutic interventions or even abstinence.

Fourth, also given the current expansion and diversification of alternative oral opioid maintenance therapies (e.g., buprenorphine and morphine) and considering the complex logistics (on both providers and patients' ends), high costs, and sociopolitical controversy around (especially injection) HAT, the most sensible role of HAT is likely that of an exceptional "last resort" option for heroin addicts who cannot be effectively attracted into or treated in other available therapeutic interventions.[44,45] Granted the above, the primary emerging challenge for science—rather than conducting new and more HAT effectiveness studies—is to provide evidence-based guidelines on how to effectively match existing heroin addict profiles and needs with existing treatment options. This challenge has recently been complicated—in at least some jurisdictions—with the increasing diversification of heroin into poly-opioid (e.g., prescription) use profiles.[46]

Finally, after extensive HAT research efforts over the past decade, the principal onus of action has shifted from the scientific to the political arena in the jurisdictions under study.[12,18] Despite the overall positive results of completed HAT trials undoubtedly justifying some role of HAT in the addiction treatment landscape, authorities in only two countries, Switzerland and the Netherlands, have decisively acted on this issue.[34] In the other countries where HAT studies have been completed, Germany and Spain, political decision makers have resisted to convert the beneficial evidence into the necessary politico-legal framework for a more regular offering of HAT as part of the treatment system. Similar hesitation must be expected for Canada after the completed NAOMI trial, and it is a historical fact that the Australian government stopped a comprehensively prepared HAT study project for political reasons in the mid-1990's.[47] The pressure was primarily on science to produce the evidence basis on HAT—the pressure is now on politics to use the evidence generated in the interest of reduced harms and costs related to the problem of heroin addiction.

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