Is There a Need for Heroin Substitution Treatment in Vancouver's Downtown Eastside?

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ABSTRACT

The North American Opiate Medication Initiative (NAOMI) was a randomized controlled trial conducted in Vancouver and Montreal comparing heroin substitution treatment (HST) to methadone treatment (MT) for heroin addicts. The HST group had a higher treatment retention rate and lower illicit heroin use than the MT group. Despite the rigour with which the study was designed, systematic flaws have affected the interpretation of the results. In the MT arm, the dose was titrated slowly, contributing to the high early dropout rate. The mean maintenance dose was suboptimal. The investigators did not calculate on-treatment retention rates; by the end of the trial, more subjects were on MT than HST. Life-threatening events were more common in the HST than the MT group. Overall, the only clear advantage of HST over MT was its greater initial treatment attractiveness, resulting in more early drop-outs in the MT group.

HST is intended for treatment-refractory addicts who have no other option but to use street heroin. Yet for most NAOMI subjects, the safest and most cost-effective approach is comprehensive MT or buprenorphine with optimal dosing, flexible program policies, and the provision of integrated primary care and social services. These proven strategies, currently lacking in Vancouver's Downtown Eastside, should be implemented before diverting already insufficient resources to HST, given its risks, cost and uncertain efficacy.

Key words: Heroin prescription; heroin substitution; heroin addiction; methadone maintenance

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The North American Opiate Medication Initiative (NAOMI)¹ conducted in Vancouver and Montreal is the first North American trial to compare the effectiveness of oral methadone and injection heroin for treatment-refractory heroin addicts. NAOMI addresses an important public health concern; many of the estimated 10,000 heroin users in Vancouver's Downtown Eastside (DTES) are not in treatment. In the NAOMI trial, 350 heroin addicts were randomized to heroin substitution treatment (HST) or methadone treatment (MT) in an open label manner.¹ The investigators reported that HST was more effective than MT at reducing illicit opioid use and improving treatment retention. The NAOMI study has generated much interest and its investigators have called for the establishment of HST and hydromorphone clinics in the DTES. Given the significant limitations of the trial, these calls are premature.

The first major flaw in the trial is that the MT subjects received a suboptimal maintenance dose. This may have contributed to the high early drop-out rate and ongoing heroin use. While the subjects' mean maintenance dose (96.0 mg) is reasonable for most methadone programs, it is low for patients who had failed previous methadone treatment and who continue to use heroin. A number of studies have shown that methadone doses of 100 mg or above are more effective than lower doses at reducing heroin use and improving treatment retention.²⁻⁵ The investigators do not describe their clinical criteria for dose titration, a serious oversight for a trial in which the primary outcome depends on individualized dosing.

In one publication, the investigators state that the dose was increased if the patient used heroin more than twice per week.¹ This is neither standard nor evidence-based. In the Ontario and British Columbia methadone guidelines, physicians are advised to increase the dose until withdrawal symptoms and cravings have resolved and regular heroin use has ceased.^{6,7} The trial probably did not use these standard dose criteria since the mean street heroin use was six days per month in the MT group while the mean dose was only 96 mg. The investigators state that there were no differences in "treatment response" between subjects who received daily doses above or below 100 mg (68% vs. 62%, $p=0.63$),⁸ but the study was not powered to detect dose effects, and the dose difference between those over and under 100 mg might have been too small to affect outcome.

Also of concern is that the mean dose in the MT group was only 60 mg/day after 30 days. This is an inappropriately slow titration

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rate for a cohort of heroin users who have previously failed MT, and it may have contributed to the higher early drop-out rate in the MT group (24 vs. 7 subjects by 30 days, $p < 0.0001$). The BC and Ontario guidelines allow a physician to titrate to 90 mg or above by day 30.^{6,7} According to one study, the threshold dose for suppressing heroin use is 70 mg.⁹

Another limitation of the trial is that the investigators did not analyze on-treatment retention rates. Using an Intention to Treat (ITT) analysis, the overall treatment retention rate was 87.8% (101/115) for the HST group, compared to 54.1% (60/111) for the MT group ($p < 0.001$). However this analysis is misleading without an on-treatment analysis. Subjects in the MT group were prohibited from switching to the HST arm, but those assigned to HST could switch to MT in the community. Thus, 23 subjects initially randomized to HST were on MT at the end of the study; most had switched within 9 months of randomization. The ITT analysis assigned them as a success of HST, despite the fact that they were on MT at the end of the study and were on MT for much of the trial's duration.

Using an on-treatment analysis, by the end of the trial more subjects were on methadone than HST (83 vs. 77). This suggests that in the long run, treatment retention rates may be as high for MT as for HST. This is not surprising, as MT is more accessible and convenient compared to HST, where patients must attend a single clinic for 2-3 injections daily.

Thus the trial's overall results may largely reflect a suboptimal approach to MT. The one clear advantage of HST over MT was treatment attractiveness. Ten patients assigned to the MT group dropped out before receiving a single dose, compared to only one HST subject ($p < 0.005$) (Table 1).^{10,11} This highlights the need to make MT more attractive to heroin addicts, through evidence-based strategies such as optimal dose titration, immediate treatment access and flexible program rules.

The recently published RIOTT trial from the UK addresses some of the concerns about MT dosing in the NAOMI trial.¹² The RIOTT results suggest that there is a group of heroin users who have failed at previous MT and who respond better to HST than to high-dose MT treatment. Unfortunately, NAOMI does not shed light on the size of the treatment-refractory population or their response to HST. NAOMI subjects are more accurately classified as early non-responders, rather than refractory to MT, since they were eligible for NAOMI if they had previously received a methadone dose of only 60 mg for four weeks.

The most important public health message of NAOMI is that there is an urgent need to improve the quality of MT community programs in the DTES. In surveys and qualitative studies, heroin addicts report that the most common reasons for dropping out of methadone treatment are suboptimal doses, rigid program rules, administrative fees, and long waiting lists.¹³ Suboptimal dosing is common in British Columbia MT programs. In a study of 17,000 opioid users on methadone in BC from 1996 to 2007,¹⁴ the overall mean daily dose was <60 mg for 50.5% of patients, <100 mg for an additional 37.3% of patients, and above 100 mg for only 12.4% of patients. The Hazard ratio, a measure of risk of discontinuing MT, was strongly related to the mean dose (see Table 2).¹⁴

Vancouver MT programs face additional problems. The majority of patients receive treatment at fee-for-service clinics, staffed by physicians who may have little training in addiction. The clinics

Table 1. On-treatment Retention

	DAM Group (n=115) (%)	Methadone Group (n=111) (%)	p-value
Dropped out before study began	1/115 (0.8%)	10/111 (9.1%)	Chi sq 7.99 p=0.005
Left assigned treatment day 1-30	7/114 (6.1%) 2 switched to M, 5 dropped out	24/101 (23.8%)	Chi sq 13.5 p<0.0001
Left assigned treatment day 30-month 12	36/107 (33.6%) 27 switched to M, 9 dropped out	18/77 (23.4%)	Chi sq 2.28 p=0.13
Left assigned treatment day 1-month 12	43/114 (37.7%)	42/101 (41.6%)	Chi sq = 0.563 p=0.994
Number of patients on DAM or M by end of trial	77	81 58 from M group, 23 from DAM group	NA

Source: Refs. 10 and 11

DAM=diacetylmorphine; M=methadone; NA=not applicable

Table 2. Hazards Ratio for Methadone Dose and Treatment Discontinuation – BC Methadone Patients, 1996-2007

Mean Dose (mg)	Number of Patients	Hazard Ratio	p-value
<40	6844	1.207	<0.001
40-59	9396	1	Reference
60-79	7468	0.701	<0.001
80-99	4643	0.539	<0.001
100-119	2272	0.441	<0.001
≥120	2033	0.377	<0.001

Adapted from Nosyk et al.¹⁴

usually do not offer on-site primary care. Physicians are not adequately reimbursed for counseling. If counselors are available on site, counselor-patient ratios are too low to provide effective case management. The three government-funded community clinics that provide comprehensive care only treat approximately 500 patients. Buprenorphine is rarely used as it is not included in the provincial formulary, even though it is of comparable effectiveness to methadone. Social services are not well integrated with methadone clinics. Thus, many of the NAOMI study subjects who were judged to have “no options” may not ever have participated in an optimally designed MT or buprenorphine program that embodied the best medical practices.

Beyond the methodological issues, the NAOMI trial raises serious questions about the safety of HST. There were 16 life-threatening medication-related events (overdoses and seizures) in the HST group, for a rate of 0.16 per patient per year: this is very high for an outpatient, long-term maintenance treatment. There were no such events in the methadone group. The potentially fatal events resolved with on-site treatment, yet non-fatal overdoses and recurrent hypoxia, both on- and off-site, are a concern. Post-dose hypoxemia and clinically significant respiratory depression appears to be common in patients on HST,¹⁵ and may have long-term neurological effects.¹⁶ The investigators point out that HST is safer than street heroin for treatment-refractory patients. However, the large majority of heroin addicts in the DTES are not refractory but lack access to the safer alternative, i.e., optimal and comprehensive MT or buprenorphine.

In addition to being safer than HST, MT is also far less expensive. Heroin is a very expensive drug. Security and health care personnel are required on-site seven days per week at HST clinics. In contrast, methadone can be dispensed at community pharmacies.

In summary, policy-makers should ensure that heroin addicts have rapid access to buprenorphine and methadone treatment, using strategies that have been shown to improve treatment attractiveness and retention, such as optimal dosing, flexible program rules and on-site primary care and counseling.^{17,18} If HST clinics are established, they should be reserved for those who have failed an optimal trial of comprehensive MT.

HST advocates state that they also support methadone treatment. Yet close to \$10 million has been spent on NAOMI, and public and private funds are being raised to fund a hydromorphone and heroin clinic. Meanwhile, over the past ten years there has been little public advocacy or public funds for improved MT, even though it remains suboptimal and dramatically under-resourced. Scarce health care resources should not be diverted towards HST, to the detriment of safer and more cost-effective treatments. As a first step, we recommend an environmental scan to review the state of MT in Vancouver. This should be followed by a public health initiative to improve the quality and accessibility of MT through enhanced training of MT physicians and better integration of MT with primary care, counseling and social services.

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RÉSUMÉ

L'Initiative nord-américaine sur les médicaments opiacés (« NAOMI ») était un essai randomisé contrôlé mené à Vancouver et à Montréal pour comparer le traitement de substitution à l'héroïne (TSH) au traitement à la méthadone (TM) chez les héroïnomanes. Le groupe TSH a eu un taux de rétention en traitement plus élevé et un taux d'utilisation d'héroïne plus bas que le groupe TM. Malgré la rigueur avec laquelle l'étude a été conçue, des défauts systématiques ont influencé l'interprétation des résultats. Dans le groupe TM, la dose a été titrée lentement, contribuant au taux élevé d'abandon précoce. La dose d'entretien moyenne a été sous-optimale. Les chercheurs n'ont pas calculé les taux de rétention en cours de traitement : à la fin de l'étude, il y avait plus de sujets dans le groupe TM que dans le groupe TSH. Les événements mettant la vie en danger ont été plus fréquents dans le groupe TSH que dans le groupe TM. En général, le seul avantage évident du TSH sur le TM a été son plus grand attrait au moment du traitement initial, ce qui a mené à plus d'abandons précoces dans le groupe TM.

Le TSH est destiné aux héroïnomanes réfractaires aux autres traitements et qui n'ont pas d'autre choix que d'utiliser l'héroïne de rue. Mais pour la plupart des sujets de l'étude NAOMI, l'approche la plus sûre et la plus rentable aurait été l'utilisation du TM ou de la buprénorphine avec dosage optimisé, des politiques de programme flexibles, et la prestation de soins de santé primaires et de services sociaux intégrés. Ces stratégies éprouvées, qui ne sont pas largement disponibles dans le quartier Downtown Eastside de Vancouver, devraient être mises en œuvre avant d'affecter des ressources déjà insuffisantes au TSH, compte tenu des risques, des coûts et de l'efficacité incertaine de cette dernière approche.

Mots clés : prescription d'héroïne; substitution à l'héroïne; dépendance à l'héroïne; entretien à la méthadone