Is There a Need for Heroin Substitution Treatment in Vancouver's Downtown Eastside? Yes There Is, and in Many Other Places Too

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ABSTRACT

The prescription of medically-supervised diacetylmorphine, the active ingredient in heroin, to individuals with treatment-refractory opioid dependence is a controversial and often politically charged subject. Just as methadone maintenance was opposed in the 1960s by some treatment providers who preferred abstinence-based therapies, heroin-assisted therapy is now being opposed by some methadone treatment providers – this despite the fact that the effectiveness of heroin-assisted treatment has been demonstrated in no less than six randomized trials in Switzerland, the Netherlands, Spain, Germany, Canada and the UK. The North American Opiate Medication Initiative (NAOMI) trial in Canada clearly showed heroin-assisted therapy to be superior to methadone in individuals with chronic, treatment-refractory heroin addiction both in terms of retention in addiction treatment and clinical response. An international internal review panel, three Research Ethics Boards, the CIHR RCT review panel, the Therapeutic Products Directorate of Health Canada, and several journal peer-reviewers reviewed the NAOMI trial. Nevertheless, authors of a commentary in this issue of CJPH find fault with the trial in terms of methadone prescribing, use of intention-to-treat analysis, safety and cost. We take this opportunity to respond to the numerous misconceptions and errors in their commentary.

Key words: Heroin addiction; heroin; methadone; randomized controlled trial

La traduction du résumé se trouve à la fin de l'article.

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When methadone maintenance treatment (MMT) for heroin addiction was first introduced in the 1960s, there was considerable opposition to this advance, particularly from some existing addiction treatment providers who promoted abstinence-based therapies.^{1,2} It is thus not without historical irony that the introduction of heroin maintenance treatment is currently being opposed by some existing methadone providers who promote methadone-based therapies. For the North American Opiate Medication Initiative (NAOMI) trial, this opposition occurred before, during and after the study in the form of articles;³ letters to ethics committees, provincial medical colleges and medical journals;⁴ and the commentary in this issue of CJPH.⁵

The commentary states: "The first major flaw in the trial is that the MMT subjects received a suboptimal maintenance dose". It appears the authors confuse the issue of maximum allowable dose and mean or median dose. NAOMI provided individualized doses without a dose cap, the approach recommended in the literature on the issue of dose and outcome. In practice, the dose prescribed is limited by several factors: some patients respond well to doses less than 100 mg/day, for example, because of very slow clearance, and would be killed by forcing them to take 100 mg/day or more; some patients refuse dose increases because of fear of difficulty getting off a high dose or because they want to be able to feel the effect of street heroin when used in addition to methadone; missed appointments limit the potential to increase doses safely; and treatment interruptions necessitate re-titration from low doses. Forcing patients to take a dose above what they will tolerate or accept is at best paternalistic rather than patient-centered, resulting in

increased patient drop-out, and at worst dangerous, resulting in patient death. Doses above 100 mg were often prescribed in NAOMI but only when it was safe to do so and acceptable to the patient who was being treated. The authors correctly note that there were no differences in treatment response between NAOMI subjects who received daily doses above or below 100 mg (68% vs. 62%, $p=0.63$), supporting the fact that each patient was receiving an optimized dose for their circumstances. The commentary notes that patients retained in MMT used heroin a mean of 6 days per month (although the median was only 1 to 2 days), suggesting the doses were inadequate. However, this is a common finding. For example, the RIOTT study,⁶ to which the authors appear to give greater credence than NAOMI, reported that only about 10% of subjects retained on oral methadone were abstinent of street heroin at the study's endpoint. One way to reduce illicit heroin use to zero in MMT study participants would be to withdraw anyone from the MMT group who chooses to use street heroin, even if only very occasionally. It is this kind of punitive programming that undermines the effectiveness of MMT and is hardly in keeping with the flexible program rules that the authors appear to advocate.

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Another of their arguments against the NAOMI results is that the MMT titration rate was too slow. This is misguided on two fronts. First, while higher dose has been linked to better outcomes, there is little or no literature that more rapid titration leads to better response. The overwhelming evidence on titration concerns the risk of overdose death when titration rates are too fast. As per the BC and Ontario guidelines for MMT, in the NAOMI study, patients in the methadone arm received an initial dose between 15 to 40 mg on days 1 to 3. Afterwards, if the patient so wished and there were no clinical contraindications, the dose could be increased from 5 mg to 10 mg once or twice a week to a maximum dose of 60 mg. Once the 60 mg level was reached, doses could be increased from 10 mg to 15 mg each week or two, if the patient so wished and there were no clinical contraindications. These procedures are in compliance with the guideline recommendation to “Start low–go slow dosing” in part because patients are at a high risk of death from methadone overdose in the first two weeks of methadone treatment in amounts as little as 30-50 mg.

Second, a dose of 90 mg after 30 days, to which the commentary refers, is more accurately characterized as the maximum possible dose. In order to reach this as a mean dose for a large number of patients at 30 days, one would have to enforce the maximum rate of titration on all patients without respect for their choice, clinical response or safety, or else one would have to titrate some patients more quickly than the guidelines allow, increasing the risk of methadone overdose.

The authors comment on the use of Intention-to-treat (ITT) analysis. Randomization ensures an even distribution of patient characteristics between groups, and differences in the outcomes can then be attributed to the treatment effect. As stated in CONSORT,⁷ ITT analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by random assignment and which may reflect non-adherence to the protocol.

Interpretations of results derived from on-treatment analysis (as appears in Table 1 of the commentary) are thus seriously flawed, but can provide some useful information in conventional drug trials. In such trials, it is generally considered a treatment failure when a patient goes off the study medication. However, in the case of NAOMI, the potential bias is much greater because heroin patients were *encouraged* to switch to methadone if and when they were willing to do so, and all patients were encouraged to stop drugs altogether. These are positive clinical outcomes that are completely unlike a patient stopping their medication in, say, a cardiology trial. To consider those who switched to methadone as retained in the group allocated to methadone, as these authors did, introduces a fatal bias into their analysis. What the NAOMI results show is that once patients are attracted into heroin treatment and are stabilized, a significant number become ready to switch to methadone, a treatment they might not otherwise have considered at all.

The authors comment on the safety of heroin without critical thought. It is certainly true that serious adverse events (SAEs) were more frequent in the heroin group. But it is important to remember that this group was under far more intensive study surveillance (2 to 3 extended clinic visits every day) than the methadone group. If someone in the heroin group experienced an overdose, it was witnessed at the clinic, treated immediately, and recorded by study staff. Overdoses on street heroin in the methadone group were not similarly recorded. The authors state “there were no such events in

the methadone group”, but in fact we have no count of how many illicit heroin overdoses there were in the MMT group. We do know there was one overdose death in that group. It is an irony of clinical trial reporting that overdoses on street heroin in the methadone group were not counted as SAEs caused by methadone (one could argue they were actually caused by its failure). We leave it to the reader to decide which is safer: sterile, pharmaceutical-quality heroin of a precise, prescribed dose administered in a safe, medically-supervised environment; or street heroin of unknown purity and dose, cut with unknown additives, and injected in back alleys.

The authors refer to NAOMI subjects as “early non-responders rather than refractory to MMT since they were eligible for NAOMI if they had previously received a methadone dose of only 60 mg for four weeks”. Here again the authors confuse a minimum requirement with an average. In fact, NAOMI participants had tried opioid addiction treatment an average of 11 times prior to the study. More than 90% of participants had tried methadone two or more times, and half had tried it three or more times.

The authors complain about the cost of the trial, which was approximately \$10 million. Clinical trials are indeed expensive, especially with the added costs of Good Clinical Practices and in this instance, additional measures mandated by Health Canada. But when compared to the costs in Canada of heroin addiction in the neighbourhood of \$5 billion each and every year, this seems a bargain if it helps to identify an important cost-effective treatment alternative.

Speaking of which, the authors state that methadone is more cost-effective than heroin therapy. This is absolutely false. The published economic analysis of the Dutch heroin trial found heroin therapy provided greater benefit and at the same time, resulted in incremental cost savings of more than 12,000 euros per patient per year over methadone alone.⁸ The NAOMI study will be publishing a similar article showing heroin therapy to be incrementally cost-effective compared to methadone in the Canadian context. The question therefore is not whether we can afford to offer heroin-assisted therapy, but whether we can afford not to.

As stated in the NAOMI report, we believe that methadone, provided according to best-practice guidelines, should remain the treatment of choice for the majority of patients and should be readily accessible. Heroin-assisted therapy should be offered as second-line treatment for those who do not benefit from methadone. Regrettably, the authors of the commentary appear to have closed their minds to the possibility of second-line alternatives. Imagine where we would be if early cancer researchers had refused to search for alternative chemotherapy regimens because they had a first line regimen that was moderately effective.

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RÉSUMÉ

La prescription de diacétylmorphine (l'ingrédient actif de l'héroïne) sous supervision médicale aux personnes ayant une opiomanie réfractaire aux traitements est un sujet controversé et souvent politisé. Tout comme le traitement de maintien à la méthadone qui, dans les années 1960, avait été contesté par certains thérapeutes qui lui préféraient les traitements fondés sur l'abstinence, le traitement assisté par héroïne est aujourd'hui

contesté par certains fournisseurs de traitements à la méthadone – et ce, malgré l'efficacité prouvée du traitement à l'héroïne dans non moins de six essais aléatoires menés en Suisse, aux Pays-Bas, en Espagne, en Allemagne, au Canada et au Royaume-Uni. Au Canada, l'Initiative nord-américaine sur les médicaments opiacés (NAOMI) a clairement montré que le traitement assisté par héroïne est supérieur à la méthadone chez les sujets qui présentent une héroïnomanie chronique et réfractaire aux traitements, tant sur le plan de la rétention en traitement que des résultats cliniques. Un groupe international d'examen interne, trois comités d'éthique pour la recherche, le Comité ECR des IRSC, la Direction des produits thérapeutiques de Santé Canada et plusieurs évaluateurs d'articles scientifiques ont examiné l'essai NAOMI. Néanmoins, les auteurs d'un commentaire publié dans ce numéro de la RCSP réproouvent, dans cet essai, le mode de prescription de la méthadone, l'utilisation d'une analyse en intention de traiter, ainsi que la sécurité et le coût de l'essai. Nous profitons de la tribune qui nous est donnée pour réagir aux nombreuses erreurs et idées fausses dans leur commentaire.

Mots clés : dépendance à l'héroïne; héroïne; méthadone; essai clinique contrôlé randomisé

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