Heroin-assisted treatment: from efficacy to effectiveness and long-term outcome
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Appendix 1

Poster calling for a conference on heroin-assisted treatment (Rotterdam, 1981).
Appendix 2

BMJ Letters in reaction to: Medical prescription of heroin to treatment resistant heroin addicts: Two randomised controlled trials.

Prescription of heroin to treatment resistant heroin addicts: Double blinding is not possible

Editor — As mentioned in the discussion of the paper by van den Brink et al. (Van den Brink et al., 2003) experiments with heroin maintenance cannot be double blind. This problem is much more serious than the authors acknowledge, particularly because considerable sanctions were connected to the participants’ responses.

The participants in the control groups knew that the promise of heroin maintenance later on could be withdrawn if they improved during the control period without heroin on prescription. Moreover, the participants in the experimental groups knew that they could be expelled from the experiment if they deteriorated while receiving heroin. Finally, the participants who improved while receiving heroin were aware that they would have a fair chance of continued heroin on prescription provided that they deteriorated in an interim period without heroin provision. Even if improvement could have been measured fully unobtrusively rather than with self reports, this would have created serious problems.

However, it is not certain that the results are positively biased because of this. It means that heroin experiments are tests in the sense of examinations rather than scientific experiments. If much is at stake in examinations people might fail not because they lack skills but because the tests are too nerve racking. This may have suppressed the results.

Europe is currently flooded by a tidal wave of expensive and demanding heroin maintenance experiments. Even if these experiments could be conducted as double blind trials there are other reasons why experimental studies are inappropriate in such cases (Dehue, 2002a, b).

Trudy Dehue
Replacement therapies need to be tested on a level playing field

Editor — The study of medical prescription of heroin by van den Brink et al should be interpreted with caution (Van den Brink et al., 2003).

Firstly, the selection of opiate dependent patients with at least four weeks of continuous treatment in the past five years does not define resistance to treatment with methadone treatment, but rather, early treatment intervention. This may explain the substantial treatment response to longer term methadone in the control group, where the only intervention is randomisation into a controlled trial.

Secondly, in such a study taking methadone and heroin dosage levels into account is crucial when evaluating clinical outcome; adequate doses of opiate replacement are critical to treatment success (Dole et al., 1968). Actual doses are reported only in the electronic version of the paper and show that doses of combined heroin and methadone in the heroin treatment groups are about 20% higher in terms of methadone equivalents compared with the control methadone only treatment group. Furthermore, this latter group received a mean methadone dose of about 75 mg/day, which may be suboptimal. The discrepancy in methadone dosage equivalents between the two groups may account for the apparently favourable effects of additional heroin.

Lastly, the deterioration after discontinuing heroin at the end of the study may simply reflect a transition from adequate to inadequate amounts of prescribed opiate replacement therapy.

Heroin treatment needs robust evaluation as it is intensive and expensive compared with other opiate replacement drugs, including methadone and buprenorphine (Ferri et al., 2003). Clinical studies comparing heroin with other opiate replacement therapies need to be conducted on a level playing field.

Laurence J Reed, Cornelis de Wet, Jennifer Bearn
Treatment needs to be multifaceted

Editor — That 45-88% of the participants in the study of van den Brink et al did not respond to the co-prescription of heroin is disappointing (Van den Brink et al., 2003).

As a general practitioner I see daily the interaction between patients’ well-being and their social circumstances. Poor housing, unemployment, and chronic relationship difficulties are well recognised contributors to the illness behaviour. In the treatment of heroin addicts we need to take a multifaceted approach to their treatment. My anecdotal experience has been that those addicts who are either in employment or who are able to find employment while in treatment fare better than those who remain unemployed.

I long to see the day when we are able to provide a community based drug treatment programme that offers the provision of housing, sheltered employment, drug treatment, and psychological support together. If rehabilitation is our serious aim we need to provide a much more coordinated treatment programme or we will be forever disappointed with the long term results.

Iain B Craighead
Dutch heroin trials show retention is better with methadone alone

Editor — The conclusion by van den Brink et al that medical co-prescription of heroin to treatment resistant heroin addicts was more effective than methadone alone is not supported by all of their data (Van den Brink et al., 2003). Rather, the better quality retention data significantly favour the methadone only group.

The trialists’ claim that heroin co-prescription is superior to routine methadone maintenance is based on a higher proportion of subjects showing overall improvement on a dichotomous, multidomain outcome index. However, the measures making up the index were based on self reports and likely to be biased in favour of the heroin groups because the study was not blinded and subjects given heroin were transferred to special, new clinics. The performance ratings are more a measure of the heroin subjects’ enthusiasm for the new treatment centres and the legal use of heroin.

The trialists present separate sets of retention data for subjects who injected and inhaled heroin. When these are combined in fixed effects meta-analyses they show that subjects receiving methadone only were 23% more likely to be in treatment at the end of 12 months (relative risk, 95% confidence interval 11% to 37%, \( p = 0.0001 \)). It is necessary to give only seven methadone patients access to heroin to cause one premature loss in the first 12 months of methadone maintenance treatment (number needed to treat to harm, 4.2 to 12.0).

The results of the Dutch trials show that patients on methadone maintenance attending a clinic an average two times a day to use heroin are significantly more likely to be lost to treatment than other patients receiving methadone. This finding highlights the need to evaluate programmes that provide maintenance patients with heroin for use at a time and in a place of their choosing.

John Caplehorn
**Heroin handouts are flawed policy**

Editor — We question the conclusions of van den Brink et al, who say that the use of heroin is comparable or perhaps better than methadone for resistant addicts (Van den Brink et al., 2003). Their measures of efficacy should raise serious questions as to the validity of the study. Deterioration of up to 40% in performance measure, or increases of cocaine or amphetamine of up to 20%, were deemed successes as long as at least one of three measures improved by at least 40%.

To consider deterioration of performance measures of up to 40% as acceptable smacks of manipulating measures of success to fit the data. A 40% deterioration is staggering and should be considered a clear failure.

Finally, even the authors concede that 45-88% of the participants did not respond to the heroin handout, yet they consider it a success. We are also not presented with the hard data on HIV or hepatitis conversion rates during the heroin handout. We are not given data on criminality or breadth of illegal drugs used.

Fundamentally, the medical world needs to understand that heroin handouts are simply keeping addicts addicted. As seen in Switzerland, heroin handouts simply further the addiction and enslavement of suffering addicts (Satel and Aeschbach, 1999). Creative approaches such as those used in Sweden should be examined and implemented to press users more rigorously towards abstinence (Sullivan, 1999).

Eric A Voth, Ernst Aeschbach
Authors’ reply

Editor — Dehue thinks that our study was a nerve racking test for the patients because considerable sanctions were connected with participants’ treatment responses. This is based on the false assumptions that patients would be expelled from the experiment if they deteriorated while receiving heroin and that patients in the control condition would lose their opportunity to enter heroin assisted treatment if they improved during the treatment with methadone alone. Measures on illicit drug use and criminal activities showed excellent agreement with urine analysis and police register data, indicating that patients in the trial were accurate and reliable in their reporting.

Reed et al assume that patients were required to be in continuous methadone maintenance treatment for only four weeks in the previous five years. Study participants were in methadone treatment for around 12 years on average and were using methadone 28 days in the month before the start of the trial. At the end of the trial the methadone dosage in the experimental groups was on average about 10 mg lower than in the control groups, but this difference was neither significant nor clinically relevant. Therefore a difference in methadone dosage between the treatment conditions is unlikely to have accounted for the observed efficacy of medically prescribed heroin.

Craighead finds it disappointing that 45-88% (actual data 45-78) of the participants did not respond to co-prescribed heroin. We believe that 22-55% response in a chronic, treatment resistant population of heroin addicts with very few assets, serious health problems, and massive social impairments is a substantial effect.

We disagree with Caplehorn’s conclusion that the study data favour continuation of methadone treatment in this population. Although treatment retention is often a prerequisite for treatment effectiveness, retention can never replace effectiveness data (response) in establishing efficacy. Additional analyses show that the observed efficacy of heroin prescription is not due to some Hawthorn or Honeymoon effect (www.ccbh.nl).

Voth and Aeschbach question the validity and clinical relevance of the primary outcome variable of the study. In the trial, similar results in favour of the heroin assisted treatment were obtained with various other response definitions,
including definitions that did not allow any deterioration or increase in cocaine use. Heroin prescription resulted in modest reductions in cocaine use and large reductions in criminality.

With regard to their final statement, we refer to Rehm et al, who showed that after five years only 34% of the patients were still in heroin assisted treatment and that most of the patients who left the heroin programme started another treatment, generally methadone maintenance or abstinence treatment (Rehm et al., 2001).

The view that heroin assisted treatment furthers the addiction and enslavement of suffering addicts is therefore not supported by the data. In contrast, the findings indicate that heroin assisted treatment can be a useful addition to the treatment armature available for these suffering, chronically impaired patients.

Wim van den Brink, Peter Blanken, Vincent M Hendriks, Maarten W J Koeter, Barbara J van Zwieten, Jan M van Ree.