Letters to the Editor

COMMENTS ON MATTICK ET AL.: THE NEED FOR INDEPENDENT DATA RE-ANALYSES

Sir—Mattick et al.’s (2003) recent article presents the results of the world’s largest comparative trial of buprenorphine and methadone maintenance [1]. However, the report is disappointing. There are problems with the analyses and their presentation and, most importantly, the discussion appears to undermine the finding that retention was significantly better in methadone maintenance.

Multiple analyses and statistical significance

In the abstract, Mattick et al. (2003) conclude retention was 10% worse in buprenorphine maintenance over the 13-week trial period. They used a Cox regression analysis which showed a statistically significant difference in retention in the methadone and buprenorphine groups ($P = 0.037$). However, in the discussion they conclude the association between treatment group and retention may be spurious. They do this after dividing the cut-off for statistical significance by four, reducing it from 0.05 to 0.0125. In this way, they conclude a $P$-value of 0.037 was statistically non-significant.

The authors explain that the adjustment in the cut-off was required because they had made four analyses of the association of treatment group with retention. However, they have confused multiple comparisons with multiple analyses. Adjustments are made when performing multiple comparisons because multiple hypotheses are tested. Mattick et al. (2003) made multiple tests of the one hypothesis, that retention was the same in the two treatment groups. It was not only unnecessary but also misleading to adjust the cut-off point for statistical significance.

Moreover, the less powerful comparisons of the proportions still in treatment at the end of the study period and retention in the first 6 weeks of treatment were of borderline significance ($P = 0.061$, $P = 0.053$, Cox regression, respectively) and both favoured methadone. A Cox regression would be expected to provide a more precise and statistically significant estimate of effect than univariate analyses because it uses the subjects’ time treatment information as well as the retention rates [2, 3]. Similarly, a Cox regression using all the data from the 13-week study would be expected to be more powerful than a similar analysis of retention in the first 6 weeks.

The authors should have reported their most powerful analysis and used the discussion to explore their finding that retention was significantly better in methadone maintenance.

Exclusions

Eight buprenorphine and three methadone maintenance patients who were randomized but who never received their first dose were excluded [1]. While including these subjects in a study of retention may seem to disadvantage buprenorphine unnecessarily, excluding them is even more problematic [4]. It would have been better to present two sets of results: one including the 11 subjects and the other excluding them. If the 11 subjects are included, even the crude difference in the percentages retained in treatment, 58.5% (120/205) for methadone and 48.0% (96/200) for buprenorphine, becomes statistically significant, $P = 0.034$. A buprenorphine subject’s risk of leaving treatment prematurely was 25% higher than a methadone subject’s (95% CI, RR 1.02–1.55, $P = 0.018$). The risk of a methadone subject leaving treatment prematurely was 10.5% less (95% CI, ARD 0.9% to 20.3%). It is only necessary to treat 10 individuals for 13 weeks with methadone, rather than buprenorphine, to avoid one premature loss to treatment (95% CI, NNT 4.9–111.1).

Urinalysis analyses

Unfortunately, Mattick et al. [1] provide neither power estimates nor confidence intervals to help readers interpret the apparent lack of a significant difference between the treatment groups’ urinalysis results. Indeed, their analysis of covariance (ANCOVA) had less power than a simple comparison of the mean numbers of morphine-positive urine specimens. The $P$-values for the two analyses (ANCOVA, difference in means) of the TEP data are 0.30 and 0.051, while for the PUC data they are 0.67 and 0.088, respectively. All analyses favour buprenorphine over methadone.

These results suggest that a more powerful test and better modelling may show that buprenorphine is significantly more effective than methadone at reducing in-treatment heroin use [5].

Independent re-analysis

While there are problems with the current report [1], the trial is a major administrative achievement. Its results
provide good evidence that methadone is better at retaining patients in short-term maintenance where clinicians can adjust daily doses. The results may also show buprenorphine is significantly better than methadone at reducing in-treatment heroin use. Happily, the uncertainty over the trial’s results and the problems with their reporting can be resolved by independent re-analyses of the individual patient data.

JOHN CAPLEHORN  
School of Public Health  
A27, University of Sydney  
Sydney  
NSW 2006  
Australia  
Fax: 61.2.9351.5049  
E-mail: johnc@health.usyd.edu.au

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HEROIN ADDICTS AND CONSENT TO HEROIN THERAPY: A COMMENT ON HALL ET AL. (2003)

Sir—In their editorial, Hall, Carter & Morley [1] present an incorrect interpretation of my central argument. The point of my paper [2] is that there are solid reasons to suspect that the capacity of heroin addicts to consent to heroin therapy is compromised because of their addiction. As one medical commentator on my paper states, if active heroin addicts can give voluntary and competent consent to heroin therapy without any problems, then we need a new conceptualization of addiction: they are not addicted, almost by definition [3]. Yet obviously there are problems and grey zones. The solution is to investigate the issue empirically in order to determine the extent of the problem. (As we have done for consent to research on depression and other mental illnesses.) Ultimately, the question can only be solved on a case by case basis, using standardized assessment tools adapted for this purpose. The MacArthur Competence Assessment Tool (MacCAT-T) is the particular assessment tool I chose to discuss. [4] It is the most promising candidate available, and it has proved its merits in the areas of depression and schizophrenia.

At no point do I condemn heroin therapy and endorse an abstinence model of treatment, as the authors state. On the contrary, I note the success of heroin therapy and make suggestions about how to facilitate the consent process. Ironically, it may be Hall et al. who have oversimplified the issues. What we need here are empirical studies on the decisional capacity of heroin addicts to consent to heroin therapy. Only then will we be able to refute the naive view they have no ‘free will’, or say how much they have; but really my paper is not about ‘free will’ at all. This is a philosophical concept. The topic I chose to discuss is ‘decisional capacity’, also called ‘mental competence’. This is a clinical concept with complex legal and ethical associations that often vary across jurisdictions. My point was that although the Swiss Heroin Trials were approved in Europe, they probably would not be approved in Canada or the United States under existing regulations. Interested readers might want to consider the wide variety of reactions to my paper, published in the same issue [5]. Unfortunately, the editorial by Hall et al. does little to advance this debate.

LOUIS C. CHARLAND  
Department of Philosophy and Faculty of Health Sciences  
University of Western Ontario  
London  
Ontario  
Canada N6H 1E2  
E-mail: charland@uwo.ca

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MEGADOSE LORAZEPAM DEPENDENCE

Sir—High dose-dependence on lorazepam has been documented in the literature, with one study indicating an average dose of 26 mg of lorazepam (Martinez-Cano et al. 1996). Although there is no absolute pharmacological reason why lorazepam should be viewed as carrying greater dependence risks than other benzodiazepines, the high potency and relatively short elimination half-life of lorazepam may encourage megadose dependence. Such megadose dependence is likely to occur in certain vulnerable populations. High dose-dependence is associated with increased risks of both physical and psychological complications, including seizure and death on withdrawal (Martinez-Cano et al. 1996). Such a situation is more likely in conditions where there is greater accessibility and lower monitoring of prescriptions for benzodiazepine (Ray 1999).

Mr G, a 39-year-old married male with no significant family history, with a past history of alcohol dependence, abstinent for the last 7 years, presented to the psychiatry services with complaints of excess consumption of lorazepam for the last 5 years.

Five years previously he had undergone internal fixation for fracture of the tibia, during which he was prescribed lorazepam 2 mg by the surgeon for 1 week, probably for sleep disturbance. He enjoyed its pleasurable relaxing effect apart from its allowing him to sleep well. After using lorazepam regularly for 3–4 weeks he developed tolerance. He increased the amount and used his old prescription to purchase the lorazepam, obtained easily from the local chemist. Over the next 4 months the amount increased to 20 mg/day and by the end of 1 year it had risen to 40 mg/day. Until this point he was working regularly and would take the drug as soon as he returned from work. Gradually the amount increased to 150 mg/day towards the second year of regular use. His wife observed him to be drowsy most of the time and at 2–3-hour intervals he was taking 10 tablets (lorazepam 2 mg/tablets). Even during the night he would get up three to four times to take the tablets. He had irritability, restlessness and sleep disturbance on not taking the tablets. For the last year, he had been consuming 300 mg of lorazepam per day. He would take 20 mg every 2–3 hours and drink hot coffee immediately, smoking two cigarettes to enhance the euphoric and relaxing effects of lorazepam. Although on occasion the chemist had advised him not to continue, the chemist dispensed medication upon his daily request. After realization of its adverse social and occupational consequences, and under family pressure, he stopped abruptly. He had a generalized tonic-clonic seizure 14 hours after the last dose.

He was admitted to an intensive care unit and detoxification was accomplished with cross-tapering of diazepam. He recovered without any complications during the next 3 weeks. His initial withdrawal score, CIWA-B (Busto et al. 1989), was 60 and at the end of the third week there were no withdrawal symptoms apart from mild irritability.

A Medline search revealed two studies addressing the issue of high dose benzodiazepine dependence. In the first study, by Martinez-Cano et al. (1996), lorazepam above 10 mg/day, and in the second study (Hallstrom & Lader 1981) above 27 mg/day (equivalent of diazepam 135 mg/day) was considered as high dose-dependence. The maximum dose of lorazepam in the first study was 95 mg/day in high dose-dependent patients. It has been well documented that patients with a past history of alcoholism (Wolf et al. 1989) tend to use higher doses of benzodiazepine (Ciraulo et al. 1988).

The index case highlights some important issues with regard to benzodiazepine use and its complications. Use that began for the purpose of pain relief and insomnia following fracture increased gradually to a megadose over time (tolerance) and was used later for recreational purposes, almost equal to the lethal dose of lorazepam (approximately 200 times the therapeutic dose).

The case also highlights undesirable dispensing practices in developing countries. Poor regulation in developing countries results in indiscriminate dispensing by physicians and pharmacists. It is highly desirable that this unsatisfactory situation should be corrected.

PRABHAT K. CHAND & PRATIMA MURTHY
National Institute of Mental Health and Neurosciences (NIMHANS)
Bangalore 560029
India
Tel: 080 6995274
E-mail: pmurthy@nimbhs.karnic.in

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