



A comparison of methadone and slow-release oral morphine as maintenance pharmacotherapies for opioid dependence

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Declaration

I hereby declare that this thesis is my own work and contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution and to the best of my knowledge and belief contains no material that has been previously published or written by another person, except where due reference has been made in the text. Any contribution made to the research by others is explicitly acknowledged in the thesis.

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Tim Mitchell

November 6th, 2003

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Abstract

Methadone is highly effective as a maintenance pharmacotherapy for opioid dependence but also exhibits several shortcomings. Of particular concern is the frequency with which patients report inadequate suppression of withdrawal symptoms or adverse effects despite seemingly adequate doses and the application of an individualised approach to dosing. The principal aim of this thesis was to evaluate slow-release oral morphine (SROM) as an alternative maintenance pharmacotherapy to methadone for the treatment of opioid dependence. Eighteen methadone maintenance patients reporting adequate (holders) or inadequate (non-holders) withdrawal suppression between doses were recruited to participate in an open-label, randomly-ordered crossover clinical trial of methadone and SROM. The study featured the concurrent measurement of plasma drug concentrations and both subjective and physiological indices of opioid effect throughout a 24-hour inter-dosing interval on one occasion for methadone and SROM after at least 4 weeks on a stable dose of each drug. Other foci included comparisons of clinical efficacy and acceptability and assessments of opioid withdrawal during the transition between medications. Compared to methadone, SROM was at least as effective overall in suppressing opioid withdrawal between doses and was associated with improved social functioning, fewer and less severe side effects, greater drug liking, reduced heroin cravings, and an enhanced sense of feeling 'normal', and yielded similar outcomes for measures of drug use, depression and health. The majority of patients stated a preference for SROM (78%) over methadone (22%), including 89% of the non-holders and 69% of the holders. The most frequently cited reasons for preferring SROM included fewer side effects, better withdrawal suppression, improved sleep, feeling more normal, improved health, and improved energy. Transfer from methadone to SROM was not associated with a prohibitive degree of opioid withdrawal, providing that an appropriate dose conversion ratio was applied. These findings suggest that SROM is a safe and efficacious maintenance pharmacotherapy for opioid dependence that may be particularly advantageous as an alternative for patients responding poorly to methadone. Further large-scale clinical

trials using double-blind methodologies and standard treatment outcome indicators are warranted.

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List of Abbreviations

| | |
|-------------------------------------|--|
| 6MAM | 6-mono-acetylmorphine |
| AAG | Alpha-acid-glycoprotein |
| AIDS | Acquired immune deficiency syndrome |
| ANOVA | Analysis of variance |
| AUC | Area under the plasma concentration-time curve |
| AUD | Australian dollar |
| BDI | Beck Depression Inventory |
| C _{max} | Maximum plasma concentration |
| C _{min} | Minimum plasma concentration |
| C _{ss} | Average steady-state plasma concentration |
| DAM | Diacetylmorphine |
| DASC | Drug and Alcohol Services Council |
| Df | Degrees of freedom |
| ECG | Electrocardiogram |
| EDDP | 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine |
| HIV | Human immunodeficiency virus |
| HPLC | High performance liquid chromatography |
| Id. no. | Identification number |
| IMOR | Immediate-release oral morphine |
| LAAM | Levo-alpha-acetylmethadol |
| LSEQ | Leeds Sleep Evaluation Questionnaire |
| M3G | Morphine-3-glucuronide |
| M6G | Morphine-6-glucuronide |
| MBG | Morphine Benzedrine Group scale |
| MG | Morphine Group scale |
| MSC | Methadone Symptoms Checklist |
| NAS | Neonatal abstinence syndrome |
| NMDA | N-methyl-D-aspartate |
| OTI | Opiate Treatment Index |
| P/T | Peak to trough plasma concentration ratio |
| POMS | Profile of Mood States |
| RAH | Royal Adelaide Hospital |
| RR | Relative risk ratio |
| SD | Standard deviation |
| SE | Standard error of the mean |
| SROM | Slow-release oral morphine |
| T _{>75%C_{max}} | Time plasma concentration exceeded 75% of C _{max} |
| T _{1/2} | Half-life |
| T _{max} | Time to reach maximum plasma concentration |
| TMD | Total mood disturbance |
| VAS | Visual analogue scale |
| V _d | Volume of distribution |

Publications Related to This Thesis

Journal articles and reports

Mitchell, T.B., White, J.M., Somogyi, A.A., and Bochner, F. (2003). Comparative pharmacodynamics and pharmacokinetics of methadone and slow-release oral morphine as maintenance pharmacotherapies for opioid dependence. *Drug and Alcohol Dependence*, 72, 85-94.

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