



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.

Table of Contents

Declaration	ii
Acknowledgements	iii
Abstract.....	iv
Table of Contents	vi
List of Tables	xiii
List of Figures.....	xv
List of Abbreviations	xviii
Publications Related to This Thesis	xix
1. INTRODUCTION	1
1.1. General introduction	1
1.2. Background.....	3
1.2.1. Origins and history of opioid use	3
1.2.2. Opioid tolerance and dependence	5
1.2.3. Aetiology of opioid dependence	6
1.2.4. Consequences of opioid use and dependence	7
1.2.5. Summary	9
1.3. Neurobiology of opioid dependence.....	10
1.3.1. Opioid receptors and ligands.....	10
1.3.2. Second messengers and effectors.....	11
1.3.3. Cellular and synaptic adaptations following chronic opioid use	13
1.3.4. Cross-tolerance and -dependence.....	16
1.3.5. Neurobiological basis of maintenance pharmacotherapies	16
1.3.6. Summary	17
1.4. Methadone maintenance treatment.....	17
1.4.1. Origins and history of methadone maintenance.....	18
1.4.2. Pharmacology of methadone.....	20

1.4.3.	Effectiveness of treatment	21
1.4.4.	Shortcomings of methadone maintenance	23
1.4.4.1.	Mechanism of intervention	23
1.4.4.2.	Methadone-related deaths	24
1.4.4.3.	Individual variability in response to methadone	26
1.4.4.4.	Affective responses	29
1.4.4.5.	Hyperalgesia.....	31
1.4.4.6.	Methadone during pregnancy.....	31
1.4.4.7.	Methadone withdrawal syndrome.....	33
1.4.4.8.	The process of treatment delivery	34
1.4.4.9.	Attitudes of intended recipients, patients and providers of treatment.....	35
1.4.5.	Summary	36
1.5.	Alternative maintenance pharmacotherapies for opioid dependence	36
1.5.1.	LAAM.....	37
1.5.2.	Buprenorphine.....	38
1.5.3.	Opioid antagonists: naloxone and naltrexone	40
1.5.4.	Short-acting and injectable opioids.....	41
1.5.4.1.	Heroin.....	42
1.5.4.2.	Morphine.....	43
1.5.5.	Summary	47
1.6.	Slow-release oral morphine (SROM): a new alternative to methadone.....	48
1.6.1.	SROM for maintenance treatment of opioid dependence	49
1.6.1.1.	Anecdotal reports and case studies	50
1.6.1.2.	Clinical trials	50
1.6.1.3.	Summary	55
1.6.2.	Safety and efficacy of Kapanol™	56
1.6.2.1.	Pre-clinical studies	57
1.6.2.2.	Clinical studies.....	60
1.6.2.3.	Summary	63
1.7.	Overview of the present research	64
1.7.1.	Aims	66
1.7.2.	Expected outcomes.....	67
2.	OVERVIEW OF RESEARCH METHODOLOGY AND PARTICIPANTS.....	68
2.1.	Introduction	68
2.2.	General methods	69
2.2.1.	Subjects	69
2.2.2.	Study design	70

2.2.3.	Clinical procedures.....	71
2.2.4.	Research procedures and measures.....	72
2.2.4.1.	Pre-study interview and eligibility assessment.....	72
2.2.4.2.	Transfer between medications.....	73
2.2.4.3.	24-hour inter-dosing interval study.....	74
2.3.	Research participants.....	78
2.3.1.	Subject details.....	78
2.3.1.1.	Methadone treatment and holding status.....	78
2.3.1.2.	Demographics.....	79
2.3.1.3.	Drug use history.....	80
2.3.1.4.	Drug treatment history.....	81
2.3.1.5.	Criminal and legal history.....	82
2.3.1.6.	Attitudes towards methadone maintenance treatment.....	84
2.3.2.	Subject compliance and attrition.....	87
2.3.2.1.	Completion rates.....	87
2.3.2.2.	Assessment order and duration.....	90
2.3.2.3.	Unsanctioned drug use on day of assessments.....	91
2.4.	Discussion.....	93
2.4.1.	Ethical considerations.....	93
2.4.2.	Methods of statistical inference.....	94
2.4.3.	Internal and external validity.....	95
2.4.4.	Characteristics and representativeness of the sample.....	100
2.4.5.	Summary.....	101
3.	PHARMACOKINETICS OF METHADONE AND SROM.....	103
3.1.	Introduction.....	103
3.1.1.	Pharmacokinetic characteristics of maintenance pharmacotherapies.....	104
3.1.2.	Methadone pharmacokinetics.....	105
3.1.3.	Morphine pharmacokinetics.....	111
3.1.4.	The present study.....	117
3.1.4.1.	Aims.....	117
3.1.4.2.	Hypotheses.....	118
3.2.	Methods.....	119
3.2.1.	Subjects and procedures.....	119
3.2.2.	Analysis of plasma samples.....	119
3.2.3.	Pharmacokinetic and statistical analyses.....	119
3.3.	Results.....	121
3.3.1.	Pharmacokinetics of methadone and SROM.....	121

3.3.1.1.	Comparisons for all subjects	121
3.3.1.2.	Comparisons for methadone holders and non-holders	125
3.4.	Discussion.....	129
4.	OPIOID WITHDRAWAL, PHYSIOLOGICAL RESPONSES, AND SYMPTOM COMPLAINTS DURING A 24-HOUR INTER-DOSING INTERVAL FOR METHADONE AND SRM.....	137
4.1.	Introduction	137
4.1.1.	Prevalence, causes and patterns of methadone symptom complaints	137
4.1.2.	Methadone dose, plasma concentrations and treatment outcomes.....	139
4.1.3.	Temporal changes in opioid effects and plasma drug concentrations.....	141
4.1.4.	The present study	145
4.1.4.1.	Aims	147
4.1.4.2.	Hypotheses	148
4.2.	Methods	149
4.2.1.	Subjects and procedures	149
4.2.2.	Measures	149
4.2.3.	Statistical analyses	150
4.3.	Results	151
4.3.1.	Indices of opioid effect during the inter-dosing interval	151
4.3.1.1.	Comparisons for all subjects.....	151
4.3.1.2.	Comparisons for methadone holders and non-holders.....	155
4.3.2.	Frequency of symptoms complaints.....	160
4.4.	Discussion.....	163
5.	MOOD STATES DURING A 24-HOUR INTER-DOSING INTERVAL FOR METHADONE AND SRM.....	167
5.1.	Introduction	167
5.1.1.	Effects of methadone and other opioids on mood state	168
5.1.2.	Short-term mood effects associated with methadone administration	169
5.1.3.	Long-term mood effects associated with methadone administration.....	171
5.1.4.	Mood effects associated with non-opioid mechanisms of methadone action.....	174
5.1.5.	Mood effects associated with variability in plasma concentrations of (R)- and (S)-methadone	175
5.1.6.	Summary	176
5.1.7.	The present study	178
5.1.7.1.	Aims	178
5.1.7.2.	Hypotheses	178
5.2.	Methods	180

5.2.1.	Subjects and procedures	180
5.2.2.	Measures	180
5.2.3.	Statistical analyses	181
5.3.	Results	182
5.3.1.	Mood states during the inter-dosing interval	182
5.3.1.1.	Comparisons for all subjects	182
5.3.1.2.	Comparisons for methadone holders and non-holders.....	185
5.3.2.	Determinants of mood responses	187
5.3.2.1.	Dose, plasma drug concentrations and opioid withdrawal	187
5.3.2.2.	Ratio of (S)- to (R)-methadone	190
5.3.3.	Reliability of the Profile of Mood States	193
5.4.	Discussion.....	194
6.	SENSITIVITY TO PAIN DURING A 24-HOUR INTER-DOSING INTERVAL FOR METHADONE AND SROM.....	199
6.1.	Introduction	199
6.1.1.	Relationship between sensitivity to pain and chronic exposure to opioids..	199
6.1.2.	Clinical implications of opioid-induced hyperalgesia.....	206
6.1.3.	Mechanisms of pain, nociception and hyperalgesia.....	207
6.1.4.	The present study	211
6.1.4.1.	Aims	212
6.1.4.2.	Hypotheses.....	212
6.2.	Methods	213
6.2.1.	Subjects and procedures	213
6.2.2.	Measures	213
6.2.3.	Statistical analyses	214
6.3.	Results	216
6.3.1.	Electrical stimulation	216
6.3.2.	Cold pressor test.....	219
6.3.3.	Relatedness of pain induction methods.....	221
6.4.	Discussion.....	222
7.	CLINICAL EFFICACY AND ACCEPTABILITY OF METHADONE AND SROM.....	229
7.1.	Introduction	229
7.1.1.	Limitations of the existing evidence-base.....	230
7.1.2.	Selecting appropriate outcome indicators	232
7.1.3.	The present study	233

7.1.3.1.	Aims	234
7.1.3.2.	Hypotheses	234
7.2.	Methods	235
7.2.1.	Subjects and procedures	235
7.2.2.	Measures	235
7.2.3.	Analysis of hair samples	239
7.2.4.	Statistical analyses	239
7.3.	Results	241
7.3.1.	Drug use	241
7.3.2.	Health and social functioning.....	243
7.3.3.	Depression and self-esteem.....	247
7.3.4.	Sleep patterns	249
7.3.5.	Treatment satisfaction and preference	252
7.4.	Discussion.....	261
8.	OPIOID WITHDRAWAL AND DOSING SCHEDULES DURING THE TRANSFER BETWEEN METHADONE AND SROM.....	269
8.1.	Introduction	269
8.1.1.	Optimising patient outcomes during the transfer between methadone and SROM	269
8.1.2.	The present study	275
8.1.2.1.	Aims	276
8.1.2.2.	Hypotheses	276
8.2.	Methods	277
8.2.1.	Subjects, procedures, and measures	277
8.2.2.	Statistical analyses	277
8.3.	Results	278
8.3.1.	Transfer from methadone to SROM	278
8.3.1.1.	Comparisons for all subjects	278
8.3.1.2.	Comparisons for methadone holders and non-holders.....	282
8.3.1.3.	Comparisons of withdrawal during stabilisation and at steady-state....	285
8.3.2.	Transfer from SROM back to methadone.....	286
8.3.2.1.	Comparisons for all subjects	286
8.3.2.2.	Comparisons for methadone holders and non-holders.....	288
8.3.2.3.	Comparisons of withdrawal during stabilisation and at steady-state....	290
8.3.3.	Comparisons of transfer from methadone to SROM and vice versa	291
8.4.	Discussion.....	293

9. GENERAL SUMMARY AND DISCUSSION.....	302
9.1. Introduction	302
9.2. Summary of major findings	303
9.2.1. Pharmacokinetics and pharmacodynamics.....	303
9.2.2. Clinical efficacy and acceptability	308
9.2.3. Transfer between medications.....	310
9.3. Clinical implications of research findings	312
9.4. Directions for further research.....	316
9.5. Summary.....	321
References.....	324

List of Tables

Table 2-1. Subject demographics (n=18).....	80
Table 2-2. Frequency of life-time and month-prior-to-treatment drug use (n=18).....	81
Table 2-3. Drug treatment history (n=18).....	82
Table 2-4. Criminal and legal history (n=18).....	84
Table 2-5. Attitudes towards methadone maintenance for all subjects (n=18) and the methadone holder (n=9) and non-holder (n=9) subgroups.....	86
Table 2-6. Frequency of additional drug detection in urine and plasma samples taken immediately prior to 24-hour inter-dosing assessments for methadone and SR0M (n=14).....	92
Table 3-1. Summary of previous pharmacokinetic evaluations of morphine as Kapanol™.....	115
Table 3-2. Pharmacokinetic parameters for (R)- and (S)-methadone and morphine during a 24-hour inter-dosing interval for methadone and SR0M (n=14).....	123
Table 3-3. Pharmacokinetics of (R)- and (S)-methadone and morphine in methadone holders (n=7) and non-holders (n=7).....	128
Table 4-1. Repeated-measures ANOVA for subjective and physiological indices of opioid effects (n=14).....	152
Table 4-2. Repeated-measures ANOVA for subjective and physiological indices of opioid effects according to methadone holding status (n=14).....	158
Table 4-3. Frequency of symptom complaints during a 24-hour inter-dosing interval for methadone and SR0M: comparisons for all subjects (n=14) and the methadone holder (n=7) and non-holder (n=7) subgroups.....	162
Table 5-1. Repeated-measures ANOVA for the Profile of Mood States (n=14).....	183
Table 5-2. Repeated-measures ANOVA for the Profile of Mood States according to methadone holding status (n=14).....	187
Table 5-3. Correlation coefficients for relationships between Profile of Mood States scores and dose, plasma drug concentrations, and the severity of opioid withdrawal (n=14).....	188
Table 7-1. Frequency of diacetylmorphine and 6-mono-acetylmorphine detection in hair samples for methadone and SR0M: comparison for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.....	241
Table 7-2. Proportion of subjects self-reporting use of additional drugs in the previous month for methadone and SR0M: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.....	243
Table 7-3. Responses to social functioning items from the Opiate Treatment Index for methadone and SR0M (n=15).....	246
Table 7-4. Self-esteem responses for methadone and SR0M (n=15).....	249
Table 7-5. Sleep latency, duration and awakenings for methadone and SR0M for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.....	250
Table 7-6. Sleep satisfaction, waking behaviour and dreaming patterns for methadone and SR0M (n=15).....	251

Table 7-7. Leeds Sleep Evaluation Questionnaire: assessments of sleep whilst maintained on SROM in comparison to sleep whilst maintained on methadone for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.....	252
Table 7-8. Relationship between VAS-rated preference for methadone or SROM and outcomes for the SF-36 Health Survey and VAS-rated treatment satisfaction (n=15).....	256
Table 7-9. Reasons for preferring methadone or SROM: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups.	258
Table 8-1. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days of SROM maintenance (n=16).....	281
Table 8-2. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days of SROM maintenance according to methadone holding status (n=16).....	284
Table 8-3. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days following transfer from SROM back to methadone (n=11).....	288
Table 8-4. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days of SROM maintenance according to methadone holding status (n=16).....	290
Table 8-5. Repeated-measures ANOVA for the number and intensity of withdrawal symptoms during the first five days following transfer from methadone to SROM and vice versa (n=11).....	292

List of Figures

Figure 2-1. Plasma morphine concentrations during a 24-hour inter-dosing interval for SROM in a single subject suspected of additional heroin use prior to testing.....	88
Figure 2-2. Flow chart of subject recruitment, randomisation and sample sizes (n) for data presented in Chapters 3-8.....	89
Figure 3-1. Plasma concentrations of (R)- and (S)-methadone and morphine during a 24-hour inter-dosing interval for methadone and SROM (n=14). Concentrations have been normalised to 70 mg and 300 mg doses for racemic methadone and SROM, respectively. Data are presented as mean \pm SE.....	121
Figure 3-2. Relationship between maintenance dose for methadone and SROM and area under the plasma concentration-time curve for (R)-methadone and morphine.	124
Figure 3-3. Plasma (S)-/(R)- methadone ratio during a 24-hour inter-dosing interval for methadone (n=14). Data are presented as mean \pm SE.	125
Figure 3-4. Observed and dose normalised (70 mg racemic methadone) plasma concentrations for (R)- and (S)-methadone during a 24-hour inter-dosing interval for methadone: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. Error bars for (S)-methadone are excluded for clarity in data presentation. * $p < 0.05$ (holders vs. non-holders for (R)-methadone).....	126
Figure 3-5. Observed and dose normalised (300 mg SROM) plasma morphine concentrations during a 24-hour inter-dosing interval for SROM: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. * $p < 0.05$ (holders vs. non-holders).	127
Figure 4-1. Opioid withdrawal during a 24-hour inter-dosing interval for methadone and SROM (n=14). Data are presented as mean \pm SE. * $p < 0.05$ (methadone vs. SROM).....	151
Figure 4-2. Physiological indices of opioid effects and safety during a 24-hour inter-dosing interval for methadone and SROM: pupil diameter, respiration rate, heart rate, systolic (S) and diastolic (D) blood pressure (n=14). Data are presented as mean \pm SE. $p > 0.05$ for all differences (methadone vs. SROM).	155
Figure 4-3. Opioid withdrawal during a 24-hour inter-dosing interval for methadone and SROM: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. * $p < 0.05$ (methadone vs. SROM).	157
Figure 4-4. Pupil diameter and respiration rate during a 24-hour inter-dosing interval for methadone and SROM: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. $p > 0.05$ for all differences (methadone vs. SROM).....	160
Figure 5-1. Total Mood Disturbance scores for the Profile of Mood States during a 24-hour inter-dosing interval for methadone and SROM (n=14). Data are presented as mean \pm SE. $p > 0.05$ for all differences (methadone vs. SROM).	182
Figure 5-2. Profile of Mood States scores during a 24-hour inter-dosing interval for methadone and SROM (n=14). Data are presented as mean \pm SE. $p > 0.05$ for all differences (methadone vs. SROM).....	184
Figure 5-3. Morphine Benzidine Group and Morphine Group scale scores from the Addiction Research Centre Inventory during a 24-hour inter-dosing interval for	

methadone and SROM (n=14). Data are presented as mean \pm SE. $p > 0.05$ for all differences (methadone vs. SROM).....	185
Figure 5-4. Total Mood Disturbance and Tension scores from the Profile of Mood States during a 24-hour inter-dosing interval for methadone and SROM: comparisons for the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. $p > 0.05$ for all differences (methadone vs. SROM).....	186
Figure 5-5. Relationship between changes in the average number of self-reported withdrawal symptoms and peak to trough variation in Total Mood Disturbance for SROM compared to methadone (n=14). Positive scores for X and Y axes indicate reduced withdrawal severity and mood change for SROM compared to methadone. ...	189
Figure 5-6. Change in Total Mood Disturbance and Morphine Benzodrine Group scale scores between assessments prior to dosing and at the time of peak plasma (R)-methadone and morphine concentrations for methadone and SROM (n=14). Data are presented as mean \pm SE. * $p < 0.05$ (prior to dosing vs. time of peak concentration).	190
Figure 5-7. Relationship between the ratio of the area under the plasma-concentration time curves for (S)- compared to (R)-methadone and average Profile of Mood States scores during a 24-hour inter-dosing interval for methadone (n=13).....	192
Figure 6-1. Stimulus detection and pain detection thresholds following electrical stimulation of the earlobe during a 24-hour inter-dosing interval for methadone and SROM (n=14). Data are presented as mean \pm SE. * $p < 0.05$ (methadone vs. SROM).217	
Figure 6-2. Scatterplot of average electrical stimulation pain detection scores obtained approximately 6 weeks apart for methadone and SROM (n=14).	219
Figure 6-3. Pain detection and tolerance for the cold pressor test prior to dosing for methadone and SROM (n=14). Data are presented as mean \pm SE. $p > 0.05$ for all differences (methadone vs. SROM).....	220
Figure 6-4. Scatterplot of cold pressor pain tolerance scores obtained approximately 6 weeks apart for methadone and SROM (n=14).	221
Figure 7-1. SF-36 Health Survey scores for methadone and SROM: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups. Dotted lines show normative means for (A) South Australia population norms and (B) a sample of heroin users upon entry to methadone maintenance. Data are presented as mean \pm SE.* $p < 0.05$, ** $p < 0.01$ (methadone vs. SROM).....	244
Figure 7-2. Beck Depression Inventory scores for methadone and SROM: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. $p > 0.05$ for all differences (methadone vs. SROM).	248
Figure 7-3. VAS (0-100mm) ratings of treatment satisfaction for methadone and SROM: comparisons for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. $p < 0.05$ methadone vs. SROM. * $p < 0.05$ (methadone vs. SROM).....	254
Figure 7-4. VAS (0-100mm) preference for methadone or SROM for all subjects (n=15) and the methadone holder (n=8) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. P values denote significance of difference between the mean for each group and the 'no preference' scale midpoint (50mm).	255
Figure 8-1. Relationship between original methadone doses and SROM doses at the end of the SROM stabilisation period (n=18).....	278

Figure 8-2. Changes in SROM dose as a function of the original methadone dose and the previous day's dose for the first 10 days of SROM maintenance (n=18). Data are presented as mean \pm SE.	279
Figure 8-3. Opioid withdrawal as a function of the time since dosing for the first five days following transfer from methadone to SROM (n=16). Data are presented as mean \pm SE. * $p < 0.05$ (3, 6 and 12 h compared to 0 h each day).	280
Figure 8-4. Relationship between initial SROM:methadone dose ratio and the (A) time to achieve a stable SROM dose (n=18) and (B) average withdrawal prior to dosing for days 2-5 of SROM maintenance (n=16).	282
Figure 8-5. Changes in SROM dose as a function of the original methadone dose and the previous day's dose for the first 10 days of SROM maintenance: comparisons for the methadone holder (n=9) and non-holder (n=9) subgroups. Data are presented as mean \pm SE. $p > 0.05$ for all differences (holders vs. non-holders).	283
Figure 8-6. Opioid withdrawal as a function of the time since dosing for the first five days following transfer from methadone to SROM: comparisons for the methadone holder (n=9) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. $\dagger p < 0.05$ (0 h days 2-5 compared to 0 h day 1), * $p < 0.05$ (3, 6 and 12 h compared to 0 h each day).	284
Figure 8-7. Pre-dose opioid withdrawal during stabilisation (averaged days 2 to 5) on SROM and at steady-state after at least 4 weeks on a stable dose of methadone and SROM: comparisons for all subjects (n=14) and the methadone holder (n=7) and non-holder (n=7) subgroups. Data are presented as mean \pm SE. * $p < 0.05$ (steady-state vs. stabilisation).	285
Figure 8-8. Opioid withdrawal as a function of the time since dosing for the first five days following transfer from SROM back to methadone (n=11). Data are presented as mean \pm SE. $\dagger p < 0.05$ (0 h days 2-5 compared to 0 h day 1), * $p < 0.05$ (3, 6 and 12 h compared to 0 h each day).	287
Figure 8-9. Opioid withdrawal as a function of the time since dosing for the first five days following transfer from SROM back to methadone: comparisons for the methadone holder (n=7) and non-holder (n=4) subgroups. Data are presented as mean \pm SE. $\dagger p < 0.05$ (0 h days 2-5 compared to 0 h day 1), * $p < 0.05$ (3, 6 and 12 h compared to 0 h each day).	289
Figure 8-10. Pre-dose opioid withdrawal during re-stabilisation (averaged days 2 to 5) on methadone and at steady-state after at least 4 weeks on a stable dose of methadone and SROM: comparisons for all subjects (n=10) and the methadone holder (n=6) and non-holder (n=4) subgroups. Data are presented as mean \pm SE. * $p < 0.05$ (steady-state vs. stabilisation).	291
Figure 8-11. Withdrawal prior to dosing (averaged days 2 to 5) for the first 5 days following transfer from methadone to SROM (SROM stabilisation) and vice versa (methadone re-stabilisation): comparisons for all subjects (n=11) and the methadone holder (n=7) and non-holder (n=4) subgroups. Data are presented as mean \pm SE. $p > 0.05$ for all differences (methadone re-stabilisation vs. SROM stabilisation).	292

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.

Mitchell, T.B., White, J.M., Somogyi, A.A., and Bochner, F. (2002). Slow-release oral morphine as a maintenance pharmacotherapy for opioid dependence. *Drug and Alcohol Dependence*, 66 (supp 1), 120.

Mitchell, T.B., White, J.M., Somogyi, A.A., and Bochner, F. (2001). The steady-state pharmacokinetics and pharmacodynamics of slow-release oral morphine (Kapanol®) in the treatment of opioid dependence. Prepared for the Victorian State Government Department of Health, Australia.

Conference papers

Mitchell, T.B., White, J.M., Somogyi, A.A., and Bochner, F. (2002). Slow-release oral morphine as a maintenance pharmacotherapy for opioid dependence. Annual meeting of the College on Problems of Drug Dependence, Quebec City, Canada.

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