

**An examination of the pharmacodynamics
and pharmacokinetics of Levo-alpha-
acetylmethadol (LAAM), compared to
methadone, in opioid maintenance patients**

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Table of Contents

| | |
|---|------------|
| Abstract..... | i |
| Declaration | ii |
| Acknowledgements | iii |
| Publications in support of this thesis | iv |
| Abbreviations, prefixes and symbols | v |
| 1. Introduction and Literature Review..... | 1 |
| 1.1. Overview of opioid dependence and treatment..... | 2 |
| 1.1.1. Consequences of illicit opioid use | 3 |
| 1.1.2. General principles of treatment for opioid dependence..... | 5 |
| 1.1.3. Summary | 7 |
| 1.2. Overview of opioid pharmacology..... | 8 |
| 1.2.1. Opioid receptor pharmacology..... | 8 |
| 1.2.2. General pharmacodynamic effects of opioid drugs | 11 |
| 1.2.2.1. Analgesia..... | 11 |
| 1.2.2.2. Alterations in mood..... | 12 |
| 1.2.2.3. Respiratory depression..... | 12 |
| 1.2.2.4. Constriction of pupil (miosis) | 14 |
| 1.2.2.5. Cardiovascular effects..... | 15 |
| 1.2.2.6. Constipation | 16 |
| 1.2.2.7. Other effects | 17 |
| 1.2.3. The core features of opioid dependence - tolerance and dependence..... | 17 |
| 1.2.3.1. Tolerance..... | 18 |
| 1.2.3.2. Physical dependence | 19 |
| 1.2.3.3. Biological mechanisms underlying tolerance and dependence..... | 22 |
| 1.2.3.4. Summary | 25 |
| 1.3. Maintenance treatment of opioid dependence..... | 25 |

| | | |
|--------------|---|----|
| 1.4. | Methadone maintenance treatment..... | 26 |
| 1.4.1. | Pharmacology of methadone..... | 27 |
| 1.4.1.1. | Receptor target | 27 |
| 1.4.1.2. | Pharmacokinetics | 29 |
| 1.4.1.2.1. | Absorption and distribution..... | 29 |
| 1.4.1.2.2. | Metabolism and excretion | 31 |
| 1.4.1.2.3. | Stereoselectivity in the pharmacokinetics of methadone | 32 |
| 1.4.1.2.4. | The influence of extrinsic factors on methadone pharmacokinetics..... | 33 |
| 1.4.1.3. | Pharmacodynamic effects during repeated dosing of methadone..... | 34 |
| 1.4.2. | Effectiveness of methadone maintenance treatment..... | 37 |
| 1.4.3. | Factors that determine success in MMT | 39 |
| 1.4.4. | Limitations of methadone maintenance treatment | 39 |
| 1.4.4.1. | The relationship between methadone dosage, plasma concentration, and treatment outcome..... | 40 |
| 1.4.4.2. | Symptom complaints during methadone maintenance treatment | 42 |
| 1.4.4.2.1. | The phenomenon of ‘not-holding’ | 43 |
| 1.4.4.2.2. | Affective states | 47 |
| 1.4.5. | Summary | 48 |
| 1.4.6. | Alternatives to methadone..... | 49 |
| 1.4.6.1. | Buprenorphine..... | 50 |
| 1.5. | Levo-Alpha-Acetylmethadol [LAAM] | 52 |
| 1.5.1. | Developmental history and key studies in LAAM maintenance treatment ... | 53 |
| 1.5.1.1. | Relative treatment effectiveness: LAAM versus Methadone maintenance | 60 |
| 1.5.2. | General pharmacology of the acetylmethadol group of drugs..... | 63 |
| 1.5.3. | Pharmacology of LAAM and its demethylated metabolites..... | 64 |
| 1.5.3.1. | Chemistry and structure | 64 |
| 1.5.3.2. | Neuropharmacology..... | 65 |
| 1.5.3.2.1. | Receptor Target. | 65 |
| 1.5.3.2.2. | Animal studies <i>in vitro</i> | 68 |
| 1.5.3.3. | Pharmacokinetics of LAAM, nor-LAAM and dinor-LAAM. | 69 |
| 1.5.3.3.1. | Absorption and bioavailability. | 72 |
| 1.5.3.3.2. | Distribution..... | 73 |
| 1.5.3.3.2.1. | Binding in plasma..... | 75 |

| | | |
|--------------|--|------------|
| 1.5.3.3.3. | Metabolism and excretion. | 75 |
| 1.5.3.3.3.1. | Drug-drug interactions <i>in vivo</i> | 78 |
| 1.5.3.3.4. | Half-life. | 79 |
| 1.5.3.3.5. | Clearance | 80 |
| 1.5.3.3.6. | Summary | 81 |
| 1.5.3.4. | Pharmacodynamics of LAAM. | 82 |
| 1.5.3.4.1. | Animal studies. | 82 |
| 1.5.3.4.1.1. | In vivo antinociceptive activity. | 82 |
| 1.5.3.4.1.2. | Other pharmacological effects. | 83 |
| 1.5.3.4.2. | Human studies. | 85 |
| 1.5.3.4.2.1. | Acute dosing. | 85 |
| 1.5.3.4.2.2. | Chronic dosing. | 89 |
| 1.5.3.4.3. | Symptom complaints during LAAM maintenance treatment. | 93 |
| 1.5.3.4.4. | Cognitive functioning. | 95 |
| 1.5.3.5. | Toxicity. | 96 |
| 1.5.3.6. | Summary. | 100 |
| 1.6. | The present study - experimental rationale and aims. | 101 |
| 1.6.1. | Aims | 103 |
| 2. | General Methods | 105 |
| 2.1. | Overview. | 105 |
| 2.2. | The South Australian Methadone Program. | 105 |
| 2.3. | Study design. | 105 |
| 2.4. | Participants. | 106 |
| 2.4.1. | Maintenance patients. | 106 |
| 2.4.1.1. | Patient attrition and representativeness of sample. | 107 |
| 2.4.2. | Drug free control subjects. | 109 |
| 2.5. | Drugs and drug administration. | 109 |
| 2.6. | Procedures and measures. | 110 |
| 2.6.1. | Clinical procedures. | 110 |
| 2.6.1.1. | Transfer between methadone and LAAM. | 110 |
| 2.6.1.2. | Transfer between LAAM and methadone. | 111 |
| 2.6.2. | Inter-dosing interval studies. | 111 |
| 2.6.3. | Measures. | 114 |

| | | |
|------------|---|-----|
| 2.6.3.1. | Physiological measures..... | 114 |
| 2.6.3.1.1. | Blood pressure, heart rate and respiratory rate..... | 114 |
| 2.6.3.1.2. | Pupil diameter..... | 114 |
| 2.6.3.2. | Subjective measures..... | 114 |
| 2.6.3.2.1. | Pain detection and threshold..... | 114 |
| 2.6.3.2.2. | Measures of subjective positive opioid effect and symptom complaints..... | 115 |
| 2.6.3.2.3. | Measures of psychological health status..... | 116 |
| 2.6.3.2.4. | Cognitive psychomotor performance..... | 116 |
| 2.6.3.2.5. | Neurocognitive function..... | 116 |
| 2.6.4. | Plasma and urinary drug concentration analysis..... | 117 |
| 2.6.4.1. | Blood collection..... | 117 |
| 2.6.4.2. | Plasma LAAM, norLAAM, dinorLAAM and (R)-(-) and (S)-(+) methadone..... | 117 |
| 2.6.4.3. | Plasma benzodiazepine and morphine concentrations..... | 118 |
| 2.6.4.4. | Urinary LAAM, nor-LAAM, and dinor-LAAM concentrations..... | 119 |
| 2.6.5. | Order of testing and duration on maintenance treatment prior to inter-dosing studies..... | 119 |

3. Steady State Pharmacodynamics and Pharmacokinetics of (R)-(-) Methadone in Methadone Maintenance Patients..... 121

| | | |
|----------|--|-----|
| 3.1. | Introduction..... | 121 |
| 3.2. | Hypotheses..... | 122 |
| 3.3. | Methods..... | 123 |
| 3.3.1. | Analyses..... | 123 |
| 3.3.1.1. | Pharmacokinetic analyses..... | 123 |
| 3.3.1.2. | Statistical and other analyses..... | 124 |
| 3.4. | Results..... | 125 |
| 3.4.1. | Participant details..... | 125 |
| 3.4.2. | Pharmacodynamic responses for all patients..... | 127 |
| 3.4.2.1. | Physiological responses..... | 127 |
| 3.4.2.2. | Subjective Responses..... | 132 |
| 3.4.3. | Steady state pharmacokinetics of (R)-(-) methadone – all patients..... | 136 |
| 3.4.4. | Comparison for holder and non-holder groups..... | 137 |

| | | |
|-----------|--|------------|
| 3.4.4.1. | Demographic details. | 137 |
| 3.4.4.2. | Pharmacodynamic responses. | 138 |
| 3.4.4.3. | Pharmacokinetic parameters. | 142 |
| 3.5. | Discussion. | 145 |
| 3.5.1. | Pharmacodynamic responses. | 145 |
| 3.5.2. | Steady State Pharmacokinetics of (R)–(-) methadone. | 149 |
| 3.5.3. | Holder versus non-holder comparisons..... | 151 |
| 3.5.4. | Conclusions and clinical implications..... | 153 |
| 4. | Steady State Pharmacodynamics and Pharmacokinetics of LAAM, Nor-LAAM and Dinor-LAAM in Maintenance Patients..... | 154 |
| 4.1. | Introduction. | 154 |
| 4.2. | Hypotheses. | 155 |
| 4.3. | Methods..... | 156 |
| 4.3.1. | Analyses. | 156 |
| 4.3.2. | Pharmacokinetic analyses. | 156 |
| 4.3.3. | Statistical analyses. | 157 |
| 4.4. | Results. | 158 |
| 4.4.1. | Patient details. | 158 |
| 4.4.2. | Pharmacodynamic responses – comparison for all subjects. | 160 |
| 4.4.2.1. | Physiological responses. | 160 |
| 4.4.2.2. | Subjective responses. | 163 |
| 4.4.3. | Steady state pharmacokinetics of LAAM, nor-LAAM and dinor-LAAM – all patients | 169 |
| 4.4.4. | Pharmacokinetic and pharmacodynamic comparisons for self reported methadone non-holders and holders while on LAAM..... | 174 |
| 4.4.4.1. | Demographic details. | 174 |
| 4.4.4.2. | Pharmacodynamic responses. | 175 |
| 4.4.4.3. | Pharmacokinetic parameters. | 177 |
| 4.5. | Discussion. | 181 |
| 4.5.1. | Pharmacodynamic responses. | 181 |
| 4.5.2. | Steady State Pharmacokinetics of LAAM, nor-LAAM and dinor-LAAM.. | 186 |
| 4.5.3. | Relationship between plasma concentrations of LAAM and nor-metabolites and physiological indices of opioid effect and withdrawal suppression..... | 190 |

| | | |
|-----------|---|------------|
| 4.5.4. | Holder versus non-holder comparisons..... | 191 |
| 4.5.5. | Conclusions and clinical implications..... | 191 |
| 5. | Evaluation of LAAM as an Alternative Substitution Treatment for MMT patients: Part one - Comparative Pharmacodynamics of Methadone and LAAM | 193 |
| 5.1. | Introduction..... | 193 |
| 5.2. | Hypotheses | 194 |
| 5.3. | Methods..... | 194 |
| 5.3.1. | Analyses | 195 |
| 5.4. | Results | 196 |
| 5.4.1. | General | 196 |
| 5.4.2. | Drug use | 197 |
| 5.4.3. | Pharmacodynamic measures | 198 |
| 5.4.3.1. | Physiological responses | 198 |
| 5.4.3.2. | Subjective responses | 201 |
| 5.4.3.3. | Comparison for holder and non-holder groups - self-reported withdrawal..... | 205 |
| 5.4.3.4. | Symptom complaints..... | 207 |
| 5.5. | Discussion..... | 213 |
| 6. | Evaluation of LAAM as an Alternative Substitution Treatment for Methadone Maintenance Patients: Part two - Comparison of Affective States During the Inter-dosing Interval for Methadone and LAAM..... | 219 |
| 6.1. | Introduction..... | 219 |
| 6.1.1. | Methadone maintenance treatment and affective states..... | 219 |
| 6.1.2. | Pharmacodynamic mechanisms – influence on affective states. | 221 |
| 6.1.3. | Mood state changes following administration of methadone. | 222 |
| 6.1.4. | Fluctuations in mood states in response to changes in plasma methadone concentration..... | 222 |
| 6.1.5. | The present study..... | 224 |
| 6.1.6. | Hypotheses..... | 225 |
| 6.2. | Methods..... | 225 |
| 6.2.1. | Measures..... | 226 |
| 6.2.2. | Statistical Analyses..... | 227 |

| | | |
|-----------|---|------------|
| 6.3. | Results..... | 228 |
| 6.3.1. | Depression and Anxiety..... | 228 |
| 6.3.2. | Mood states across the inter-dosing interval for all patients..... | 230 |
| 6.3.3. | Fluctuations in mood across the inter-dosing interval–Holders vs non-holders..... | 236 |
| 6.4. | Discussion..... | 246 |
| 7. | Evaluation of LAAM as an Alternative Substitution Treatment for Methadone Maintenance Patients: Part three - the Comparative Effect of Methadone and LAAM on Psychomotor and Neurocognitive Functioning..... | 249 |
| 7.1. | Introduction..... | 249 |
| 7.1.1. | Cognitive and psychomotor functioning in LAAM and methadone maintained patients..... | 249 |
| 7.1.1.1. | Simple motor performance and reaction time..... | 250 |
| 7.1.1.2. | Information processing and psychomotor speed..... | 251 |
| 7.1.1.3. | Sustained attention (vigilance)..... | 252 |
| 7.1.1.4. | Immediate memory..... | 253 |
| 7.1.1.5. | Learning/memory and comprehension, and executive functioning..... | 253 |
| 7.1.1.6. | Complex psychomotor/cognitive performance..... | 256 |
| 7.1.1.7. | Summary..... | 258 |
| 7.1.1.8. | The present study..... | 258 |
| 7.2. | Hypotheses..... | 259 |
| 7.3. | Methods..... | 259 |
| 7.3.1. | Unpredictable tracking..... | 260 |
| 7.3.1.1. | OSPAT Pilot Study..... | 260 |
| 7.3.2. | Neurocognitive function..... | 261 |
| 7.3.2.1. | Materials..... | 263 |
| 7.3.2.2. | Summary of dependent variables derived from neuropsychological tests..... | 268 |
| 7.3.3. | Statistical Analyses..... | 269 |
| 7.4. | Results..... | 271 |
| 7.4.1. | General..... | 271 |
| 7.4.2. | Psychomotor Performance..... | 272 |
| 7.4.3. | Neurocognitive functioning for all patients..... | 273 |

| | | |
|----------|---|-----|
| 7.4.4. | Neurocognitive functioning – Comparisons for holders and non-holder groups..... | 277 |
| 7.4.5. | Exploratory analyses..... | 279 |
| 7.5. | Discussion..... | 279 |
| 7.5.1. | Unpredictable tracking performance..... | 280 |
| 7.5.2. | Neuropsychological performance..... | 281 |
| 7.5.2.1. | Methadone vs LAAM..... | 281 |
| 7.5.2.2. | Maintenance patients vs control subjects..... | 283 |
| 7.5.3. | Holder vs non-holders comparisons..... | 287 |
| 7.5.4. | Limitations..... | 287 |
| 7.6. | Conclusions and clinical implications..... | 287 |

| | | |
|-----------|---|------------|
| 8. | Characterisation of the Relative <i>in vitro</i> Potencies of LAAM, Nor- and Dinor-LAAM..... | 289 |
| 8.1. | Introduction..... | 289 |
| 8.2. | Materials and Methods..... | 290 |
| 8.2.1. | General..... | 290 |
| 8.2.2. | Animal Housing and maintenance..... | 290 |
| 8.2.3. | Guinea pig ileum assay..... | 291 |
| 8.2.3.1. | Drugs and solutions..... | 291 |
| 8.2.3.2. | Tissue Preparation..... | 291 |
| 8.2.3.3. | Experimental procedure..... | 291 |
| 8.2.3.4. | Data analysis..... | 292 |
| 8.2.4. | Receptor Binding studies..... | 293 |
| 8.2.4.1. | Drugs..... | 293 |
| 8.2.4.2. | Tissue preparation..... | 293 |
| 8.2.4.3. | Receptor Binding experimental procedure..... | 293 |
| 8.2.4.4. | Data analysis..... | 294 |
| 8.3. | Results..... | 295 |
| 8.3.1. | Guinea pig isolated ileum assay..... | 295 |
| 8.3.2. | Receptor binding..... | 296 |
| 8.4. | Discussion..... | 297 |

| | |
|---|----------------|
| 9. General Summary and Discussion..... | 302 |
| 9.1. Summary of major findings..... | 302 |
| 9.2. Limitations | 308 |
| 9.3. Future directions..... | 309 |
| 9.4. Conclusions. | 311 |
| Appendices..... | 312 |
| References..... | 343 |

List of Tables

| | |
|---|-----|
| Table 1-1: Summary of binding affinities of LAAM, nor-LAAM, and dinor-LAAM for opioid receptors..... | 67 |
| Table 2-1: Demographic details of methadone maintenance patients (n=19) at time of entry to study..... | 108 |
| Table 3-1: Demographic details of 18 patients who participated in the 24-hour methadone inter-dosing interval study. | 126 |
| Table 3-2: Drug use for each individual patient that participated in the methadone inter-dosing interval study | 127 |
| Table 3-3: One-Way repeated measures analysis of variance for physiological indices of opioid effect for all methadone patients (n=18) and control subjects (n=10)... | 131 |
| Table 3-4: One way repeated measures analysis of variance for subjective measures of opioid effect for all methadone patients (n=18) and control subjects (n=10)... | 135 |
| Table 3-5: Pharmacokinetic parameters for (R)-(-) methadone following dosing of between 30 – 150 mg daily racemic methadone in 18 patients who underwent the 24-hour methadone inter-dosing interval study. | 137 |
| Table 3-6: Demographic details of methadone patients who completed the methadone interdosing interval study divided into those who reported that they were holders (n=8) or non-holders (n=8). | 138 |
| Table 3-7: Repeated measures analyses of variance for all pharmacodynamic responses, according to holding status: holders (n=8) and non-holders (n=8)..... | 139 |
| Table 3-8: Area under the curve for all pharmacodynamic responses according to holding status: holders (n=8) and non-holders (n=8)..... | 141 |
| Table 3-9: Disposition of (R)-(-) methadone for 16 patients following dosing of between 30– 150 mg racemic methadone in patients who were studied during the 24-hour methadone inter-dosing interval study.. | 144 |
| Table 4-1: Details of LAAM dosage, plasma screening results, and self reported drug use of 17 patients that participated in the LAAM inter-dosing interval study..... | 159 |
| Table 4-2: Repeated measures analyses of variance for physiological and subjective indices of opioid effect for all LAAM patients (n=17) and control subjects (n=10)..... | 168 |

| | |
|--|-----|
| Table 4-3: Pharmacokinetic parameters for LAAM, nor-LAAM and dinor-LAAM following dosing of between 30 – 150 mg LAAM alternate daily in 17 patients who underwent the 48 hour inter-dosing interval study. | 172 |
| Table 4-4: Urinary recovery of LAAM, nor-LAAM and dinor-LAAM following chronic dosing of between 30 to 150 mg LAAM alternate daily in 16 patients enrolled in a maintenance program. | 173 |
| Table 4-5: Demographic details of patients participating in the LAAM interdosing study divided into those who reported that they were methadone holders (n=8) or methadone non-holders (n=8). | 174 |
| Table 4-6: LAAM inter-dosing study: Repeated measures analyses of variance for all pharmacodynamic responses, according to holding status [holders (n=8) and non-holders (n=8)]. | 176 |
| Table 4-7: Disposition of LAAM, nor- and dinor-LAAM for 16 patients following dosing of between 30 – 150 mg LAAM in patients who were studied during the 48-hour LAAM inter-dosing interval study, according to holding status [Holders (n=8) and non-holders (n=8)]. | 180 |
| Table 5-1: Frequency of drug detection in urine and plasma samples taken immediately prior to both the methadone and LAAM inter-dosing studies (n=16), and according to holding status [holders (n=8) and non-holders (n=8)]. | 198 |
| Table 5-2: Comparison of area under the effect versus time curve for each pharmacodynamic parameter for patients (n=16) who underwent one 24-h inter-dosing interval study when taking methadone and one 48-h inter-dosing interval study when taking LAAM. | 207 |
| Table 5-3: Number of patients (n=16) and control subjects (n=10) reporting specific symptom complaints at least once during the inter-dosing study period for methadone and LAAM, and during the study period for control subjects; comparisons for all patients (n=16) and methadone holder(n=8) and non-holder(n=8) groups. | 210 |
| Table 5-4: Comparison of area under the effect versus time curve for severity of specific symptom complaints reported by patients (n=16) during the inter-dosing study period for methadone and LAAM. | 212 |

| | |
|---|-----|
| Table 6-1: Beck Depression Inventory (BDI)-II scores (possible range 0-63) for methadone and LAAM for all patients (n=16) who participated in the methadone and the LAAM interdosing intervals studies ((holders (n=8) and non-holders (n=8)), and for control subjects (n=10)..... | 229 |
| Table 6-2: STAI trait anxiety scores (possible range 20 – 80) for methadone and LAAM for all patients (n=16) who participated in the methadone and the LAAM interdosing intervals studies ((holders (n=8) and non-holders (n=8)), and for control subjects (n=10). | 230 |
| Table 6-3: One way repeated measures analysis of variance for each POMS subscale for patients participating in the methadone interdosing study, and the LAAM interdosing study (n=16) and control subjects (n=10)..... | 232 |
| Table 6-4: Comparison of area under the effect versus time curve for each POMS scale for patients (n=16) who underwent one 24-h inter-dosing interval study when taking methadone and one 48-h inter-dosing interval study when taking LAAM, and for control subjects (n=10). | 235 |
| Table 6-5: Repeated measures analysis of variance for all POMS scales, for patients (n=16) participating in the Methadone inter-dosing study according to holding status [holders (n=8) and non-holders (n=8)]. | 237 |
| Table 6-6: Repeated measures analysis of variance for all POMS scales, for patients (n=16) participating in the LAAM inter-dosing study according to holding status [holders (n=8) and non-holders (n=8)]. | 238 |
| Table 6-7: Comparison of area under the effect versus time curve for TMD, confusion, fatigue and tension scales for self-reported methadone holders (n=8), and self reported methadone non-holders (n=8) who underwent one 24-h inter-dosing interval study when taking methadone and one 48-h inter-dosing interval study when taking LAAM. | 245 |
| Table 7-1: List of neuropsychological tests used in neurocognitive assessment of maintenance patients and control subjects..... | 263 |
| Table 7-2: Summary of demographic details of maintenance patients (n=16) and drug free control subjects (n=10). | 271 |
| Table 7-3: Summary of self reported drug use (% used in last month) in maintenance patients (n=16) for both the methadone and LAAM inter-dosing studies and for drug free control subjects (n=10)..... | 272 |

| | |
|---|-----|
| Table 7-4: Mean±sd for neuropsychological measures for maintenance patients (n=16) undergoing the methadone and LAAM interdosing studies, and for control subjects (n=10)..... | 275 |
| Table 7-5: Mean±sd for all neurocognitive measures, according to holding status (holders =8, non-holders=8), for patients participating in the methadone inter-dosing study..... | 278 |
| Table 7-6: Mean±sd for all neurocognitive measures, according to holding status (holders =8, non-holders=8), for patients participating in the LAAM inter-dosing study..... | 278 |
| Table 8-1: Descriptive statistics for the inhibitory effects (IC ₅₀) of racemic-methadone, nor-LAAM, dinor-LAAM, and LAAM on the electrically induced twitch of the isolated guinea pig ileum. | 296 |
| Table 8-2: Binding affinities of LAAM, nor-LAAM, dinor-LAAM, racemic-methadone, (R)-(-) and (S)-(+)-methadone for μ opioid receptors in rat brain homogenates. IC ₅₀ and Ki values are mean±sd | 297 |

List of Figures

| | |
|---|-----|
| Figure 1-1: Chemical structure of methadone.. | 27 |
| Figure 1-2: Metabolic pathways for LAAM and structural formulas for LAAM, nor-LAAM and nor-LAAM. | 65 |
| Figure 3-1: Mean (\pm SEM) heart rate (beats per minute) (upper panel); systolic (S) blood pressure and diastolic (D) blood pressure (lower panel) of methadone patients (closed squares: n=18) who underwent the methadone inter-dosing interval study and for control subjects (open squares: n=10) for the period 0-24 hours. | 129 |
| Figure 3-2: Mean (\pm SEM) respiratory rate (breaths per minute) of methadone patients (closed squares: n=18) who underwent the 24 hour methadone interdosing interval study and of control subjects (open squares: n=10) for the period 0-24 hours..... | 130 |
| Figure 3-3: Mean (\pm SEM) pupil diameter (mm) for methadone patients (closed square: n=18) who underwent the 24 hour methadone interdosing interval study and for control subjects (open squares: n=10) for the period 0-24 hours..... | 131 |
| Figure 3-4: Mean (\pm SEM) Morphine Benzedrine Group Scale scores (upper panel: maximum possible score =16) and Morphine Group scores (lower panel; maximum possible score = 8) for methadone patients (n=18) who underwent the 24-hour methadone interdosing interval study and for control subjects (n=10) for the period 0 to 24 hours..... | 133 |
| Figure 3-5: Mean (\pm SEM) pain detection (D) and pain threshold scores (T) (volts) for methadone patients (closed squares: n=18) who participated in the 24 hour methadone inter-dosing interval study and for control subjects (open squares: n=10) for the period 0 to 24 hour..... | 134 |
| Figure 3-6: Mean (\pm SEM) withdrawal scores (maximum possible score=16) for methadone patients (closed squares: n=18) who participated in the 24-hour methadone inter-dosing interval study and for control subjects (open squares: n=10) for the period 0 to 24 hours.. | 135 |
| Figure 3-7: Mean (\pm SEM) plasma (R)-(-) methadone concentration-time profile for 18 maintenance patients during a 24-hour inter-dosing interval. | 136 |
| Figure 3-8: Mean (\pm SEM) withdrawal scores (maximum possible score = 16) for holders (closed circles: n=8) and non-holders (open circles: n=8) who participated in the 24-hour methadone inter-dosing interval study.. | 140 |

| | |
|---|-----|
| Figure 3-9: Mean (\pm SEM) plasma (R)-(-) methadone concentration-time profiles for holders (closed circles: n=8) and non-holders (open circles: n=8) during one 24-hour inter-dosing interval. | 142 |
| Figure 4-1: Mean (\pm SEM) heart rate (beats per minute) (upper panel); systolic (S) blood pressure and diastolic (D) blood pressure (lower panel) of LAAM patients (closed triangles: n=17) who underwent the LAAM inter-dosing interval study and for control subjects (open squares: n=10) for the period 0-48 hours..... | 161 |
| Figure 4-2: Mean (\pm SEM) respiratory rate (breaths per minute) of LAAM patients (closed triangles: n=17) who underwent the 48-hour LAAM interdosing interval study and of control subjects (open squares: n=10) for the period 0-48 hours.. | 162 |
| Figure 4-3: Mean (\pm SEM) pupil diameter (mm) for LAAM patients (closed triangles: n=17) who underwent the 48 hour LAAM interdosing interval study and for control subjects (open squares: n=10) for the period 0-48 hours.. | 163 |
| Figure 4-4: Mean (\pm SEM) Morphine Benzadrine Group Scale scores (upper panel: maximum possible score =16) and Morphine Group Scale scores (lower panel; maximum possible score = 8) for LAAM patients (n=17) who underwent the 48-hour LAAM interdosing interval study and for control subjects (n=10) for the period 0 to 48 hours.. | 165 |
| Figure 4-5: Mean (\pm SEM) pain detection (D) and pain threshold (T) scores (volts) for LAAM patients (closed triangles: n=17) who participated in the 48-hour LAAM inter-dosing interval study and for control subjects (open squares: n = 10) for the period 0 to 48 hour..... | 166 |
| Figure 4-6: Mean (\pm SEM) withdrawal scores (maximum possible score = 16) for LAAM patients (closed triangles: n=17) who participated in the 48 hour LAAM inter-dosing interval study and for control subjects (open squares: n=10) for the period 0 to 48 hours. | 167 |
| Figure 4-7: Mean (\pm SEM) plasma LAAM, nor-LAAM and dinor-LAAM concentration-time profiles for 17 LAAM maintenance patients during one 48-h inter-dosing interval at steady state..... | 169 |
| Figure 4-8: Mean (\pm SEM) plasma LAAM concentrations-time profile for holders (n=8) and non-holders (n=8) during one 48-hour inter-dosing interval. | 177 |
| Figure 4-9: Mean (\pm SEM) plasma nor-LAAM concentrations-time profile for holders (n=8) and non-holders (n=8) during one 48 hour inter-dosing interval..... | 178 |

| | |
|--|-----|
| Figure 4-10: Mean (\pm SEM) plasma dinor-LAAM concentrations-time profile for holders (n=8) and non-holders (n=8) during one 48 hour inter-dosing interval..... | 179 |
| Figure 5-1: Mean (\pm SEM) heart rate (beats per minute) (upper panel) and systolic (S) blood pressure and diastolic (D) blood pressure (lower panel) in patients (n=16) who underwent one 24-h inter-dosing interval when taking methadone (closed circles) and one 48-h inter-dosing interval when taking LAAM (open squares).. | 199 |
| Figure 5-2: Mean (\pm SEM) respiratory rate (breaths per minute) (upper panel) and pupil diameter (millimeters) (lower panel) in patients (n=16) who underwent one 24-h inter-dosing interval when taking methadone (closed circles) and one 48-h inter-dosing interval when taking LAAM (open squares) and in 10 drug-free control subjects (Closed triangles)..... | 200 |
| Figure 5-3: Mean (\pm SEM) Morphine Benzadrine Group Scores (upper panel: maximum possible score =16) and Morphine Group Scale scores (lower panel: maximum possible score =8) in patients (n=16) who underwent one 24-h inter-dosing interval when taking methadone (closed circles) and one 48-h inter-dosing interval when taking LAAM (open squares) and in 10 drug-free control subjects (closed triangles)..... | 202 |
| Figure 5-4: Mean (\pm SEM) pain detection (D) and pain threshold scores (T) (volts) for patients (n=16) who underwent one 24-h inter-dosing interval when taking methadone (closed circles) and one 48-h inter-dosing interval when taking LAAM (open squares). | 203 |
| Figure 5-5: Mean (\pm SEM) withdrawal scores (maximum possible score = 16) in patients (n=16) who underwent one 24-h inter-dosing interval study when taking methadone (closed circles) and one 48-h inter-dosing interval when taking LAAM (open squares) and in 10 drug-free control subjects (closed triangles). | 204 |
| Figure 5-6: Mean withdrawal scores (maximum possible score =16) of eight self reported holders (upper panel) when taking methadone (closed circles) or LAAM (open squares), and 8 self reported non-holders (lower panel) when taking methadone or LAAM.al study when on LAAM. | 206 |

| | |
|--|-----|
| Figure 6-1 :Mean±SEM Total Mood Disturbance scores for the Profile of Mood States (range of possible scores -32 to 200) in patients (n=16) who underwent one 24-h inter-dosing interval study when taking methadone (closed circles) and one 48-h inter-dosing interval study when taking LAAM (open squares) and in 10 drug free control subjects (closed triangles)..... | 231 |
| Figure 6-2: Profile of Mood States (POMS) scores during a 24 hour interdosing interval for methadone, and a 48 hour interdosing interval for LAAM (n=16), and for drug-free control subjects (n=10). | 233 |
| Figure 6-3: Mean TMD scores of eight self reported methadone holders (upper panel) when taking methadone (closed circles) or LAAM (open squares), and 8 self reported methadone non-holders (lower panel) when taking methadone or LAAM..... | 240 |
| Figure 6-4: Mean Confusion scores of eight self reported methadone holders (upper panel) when taking methadone (closed circles) or LAAM (open squares), and 8 self reported methadone non-holders (lower panel) when taking methadone or LAAM..... | 241 |
| Figure 6-5: Mean Fatigue scores of eight self reported methadone holders (upper panel) when taking methadone (closed circles) or LAAM (open squares), and 8 self reported methadone non-holders (lower panel) when taking methadone or LAAM..... | 242 |
| Figure 6-6: Mean Tension scores of eight self reported methadone holders (upper panel) when taking methadone (closed circles) or LAAM (open squares), and 8 self reported methadone non-holders (lower panel) when taking methadone or LAAM..... | 243 |
| Figure 7-1: Mean OSPAT performance score of ten subjects participating in the pilot study. All subjects performed 12 trials... .. | 261 |
| Figure 7-2: Order of presentation of the neurocognitive tests administered to maintenance patients and control subjects | 268 |
| Figure 7-3: Performance (OSPAT) expressed as mean±SEM relative performance to baseline in 15 patients who underwent one 24-h inter-dosing interval study when taking methadone (closed circles) and one 48-h inter-dosing interval study when taking LAAM and in 10 drug-free control subjects (closed triangles). | 273 |

| | |
|---|-----|
| Figure 8-1: Mean percent depression of twitch height as a function of drug concentration for racemic-methadone, LAAM, nor-LAAM and dinor-LAAM..... | 295 |
| Figure 8-2: Competition displacement curves of [³ H]-DAMGO by LAAM, nor-LAAM, dinor-LAAM, and racemic-methadone..... | 296 |

List of Appendices

| | |
|---|-----|
| Appendix 1: Randomised control trials and open label trials of LAAM..... | 312 |
| Appendix 2: Summary of previous pharmacokinetic evaluations of LAAM..... | 320 |
| Appendix 3: Summary of urinary excretion of LAAM and metabolites as a percent of dose administered in the available literature | 325 |
| Appendix 4: Repeated measures analysis of variance for pharmacodynamics effects to determine if order of testing (LAAM: Methadone, Methadone: LAAM) systematically affected results. | 328 |
| Appendix 5: Summary of the studies of the effects of methadone and LAAM on cognitive and psychomotor performance..... | 330 |
| Appendix 6: Publication in support of this thesis..... | 337 |

Abstract

Methadone is currently the most widely used agent to manage opioid dependence, but clinical experience has highlighted some limitations with its use. In particular, a relatively high proportion of patients complain of breakthrough withdrawal symptoms (non-holding) at apparently adequate methadone doses. Levo-alpha-acetylmethadol (LAAM) is a long acting opioid that is likely to benefit methadone non-holders; however, relatively little is known about its pharmacology at steady state. The primary aim of this thesis was to evaluate LAAM as an alternative maintenance pharmacotherapy to methadone for the treatment of non-holders; subsidiary aims were to elucidate the pharmacodynamics and pharmacokinetics of LAAM and its active metabolites (nor- and dinor-LAAM), and to examine the *in vitro* activity of LAAM, nor- and dinor-LAAM. Sixteen methadone maintenance patients (non-holders=8) were recruited to participate in a randomised, crossover trial of LAAM and methadone. At steady state there were two testing sessions (24 h for methadone and 48 h for LAAM) that featured the concurrent measurement of plasma drug concentrations and both subjective and physiological indices of opioid effect. Cognitive and psychomotor functions were also assessed once during each inter-dosing interval study. Ten age- and gender-matched controls were also tested. The peak magnitude of methadone's and LAAM's effects were similar. Compared to methadone, LAAM was associated with more stable and less severe withdrawal and mood disturbance. The general pattern of symptom complaints and cognitive function was similar for both drugs. Severity of mood disturbance and withdrawal was similar in holders on methadone and LAAM, but was greater in non-holders when they were taking methadone than LAAM. In comparison to plasma (R)-(-) methadone, plasma nor- and dinor-LAAM concentrations fluctuated little over the dosing interval. Furthermore, nor- and dinor-LAAM were both more potent in the guinea-pig ileum bioassay, and had greater affinity for mu opioid receptors in receptor binding studies, than LAAM. In conclusion, LAAM converted methadone non-holders into LAAM holders. It is proposed that it is the relatively flat plasma concentration-time profile for nor- and dinor-LAAM that confer stability of opioid effect, minimising withdrawal. Therefore, LAAM may have a role in selected patients, whose response to methadone is suboptimal.

Declaration

This work contains no material which 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 previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

David A.L.Newcombe, 31 July, 2006

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Abbreviations, prefixes and symbols

| | |
|-----------------------|---|
| AAG | α_1 acid glycoprotein |
| ANOVA | Analysis of variance |
| AUC | Area under the plasma concentration-time curve (AUC) / area under the effect versus time curve during the dosing interval |
| ARCI | Addiction Research Centre Inventory |
| B.D | Administered twice daily |
| BDI | Beck Depression Inventory |
| C_{\max} | Maximum plasma concentration |
| C_{\min} (first) | Minimum plasma concentration pre-dose |
| C_{\min} (last) | Minimum plasma concentration post dose |
| CL | Total systemic plasma clearance |
| CL/F | Apparent plasma clearance at steady state |
| CL_R | Renal clearance |
| CI | Confidence interval(s) |
| C_{ss} | Steady state plasma concentration |
| CV | Coefficient of variation (%) |
| dinor-LAAM | dinoracetylmethadol |
| EC ₅₀ | Concentration eliciting 50% of effect |
| FDA | Food and Drug Administration |
| HPLC | High performance liquid chromatography |
| IC ₅₀ | Concentration inhibiting 50% of ligand binding |
| <i>i.m</i> | Intramuscular administration |
| <i>i.v</i> | Intravenous administration |
| <i>K_i</i> | Inhibition constant |
| LAAM | Levo-alpha-acetylmethadol |
| LMP | LAAM maintenance patients |
| MBG | Morphine Bazedrine Group scale of the ARCI |
| MG | Morphine Group scale of the ARCI |
| MMP | Methadone maintenance patients |
| MMT | Methadone maintenance treatment |
| MSC | Methadone symptom checklist |
| NMDA | N-methyl-D-aspartate |
| nor-LAAM | noracetylmethadol |
| <i>P</i> | Statistical significance |
| <i>pK_a</i> | Ionisation constant |
| <i>p.o</i> | Oral administration |

| | |
|------------------|--|
| POMS | Profile of Mood States |
| P/T | Peak to trough plasma concentration ratio |
| r | Correlation coefficient |
| r ² | Coefficient of determination |
| s.c | Subcutaneous administration |
| sd | Standard deviation |
| SEM | Standard error of the mean |
| SOWS | Short Opiate Withdrawal Scale |
| STAI | State Trait Anxiety Inventory |
| t ^{1/2} | Half life (distribution phase=t ^{1/2} α: terminal elimination phase=t ^{1/2} β) |
| t _{max} | Time to reach maximum plasma concentration |
| Vd | Volume of distribution |
| q.i.d | Administered four times a day |