Effects of Central Nervous System Depressant Drug Overdose on Cognitive Functions and Driving

Waidyaratne Dassanayake Mudiyanselage Tharaka Lagath Dassanayake
MBBS, MPhil

This thesis is submitted for the degree of Doctor of Philosophy,
The University of Newcastle, Australia

Submitted: March 2012
Declarations

_statement of originality_

This thesis 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 made
available for loan and photocopying subject to the provisions of the Copyright Act
1968.

**Unless an Embargo has been approved for a determined period.

_Thesis by Publication_

I hereby certify that this thesis is in the form of a series of published papers of which I
am a joint author. I have included as part of the thesis a written statement from each
co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to
my contribution to the joint publications.

Tharaka Dassanayake (Date)
Acknowledgements

First I wish to thank the people and the institutions that helped me to get this PhD position at the University of Newcastle. The Department of Physiology at the Faculty of Medicine, University of Peradeniya granted me a generous 4-year leave. Thanks you to my work colleagues back in Sri Lanka for encouraging me in many ways to pursue this PhD and sharing the departmental workload in my absence. I am grateful to the Department of Education, Employment and Workplace Relations of the Australian Government for supporting my PhD with an Endeavour Postgraduate Scholarship.

I cannot express enough of my gratitude to my supervisors Emeritus Professor Patricia Michie, Professor Alison Jones and Professor Gregory Carter. Pat had always been an exemplary figure of academic rigor and integrity that I could look up to. Pat, thanks for your guidance throughout the progress of this work, and many more thanks for backing me up when things were not progressing. Alison played a pivotal role in inception of this research, and continued to drive from Sydney for our fortnightly research meetings for more than two years despite all her commitments. Greg had been constantly tracking and supporting my work: countless ad hoc meetings and discussions that I had with him proved extremely fruitful.

This thesis would not have become a reality without support of many other people. My co-authors Professor Ian Whyte, Dr. Trevor Mallard, Dr. Patrick McElduff and Mr. Barrie Stokes helped me at different stages of study design, data collection and analysis, and manuscript preparation. Dr. Colin Page, Dr. Michael Downes, Dr. Geoff Isbister and all members of the Clinical Toxicology Team and the Consultation-Liaison Psychiatry Team at Calvary Mater Newcastle helped in participant recruitment. Special thanks to Dr. Jane Robertson, Professor Catherine D'Este, Mr. Phil Sparks and Ms Kerry Rogers who helped in the epidemiological study and NSW Roads and Traffic authority and Centre for Health Record Linkage who undertook data-linkage in that study. To Members of the Department of Clinical Pharmacology and Toxicology and my lab-mates at School of Psychology: thank you for your comments, suggestions and friendship. I greatly appreciate the goodwill of the patients who participated in my research at a turbulent time of their lives.

Finally, thanks to my wife Deva, for her love, friendship and commitment during the four long years of my PhD research.
Dedication

...To my mother

Berney Dassanayake...
List of publications included as part of the thesis


Statement of contribution of others

Co-author statement

We, Patricia Therese Michie, Alison Linda Jones and Gregory Leigh Carter attest that Research Higher Degree candidate Tharaka Dassanayake contributed to the following papers/publications of which we are co-authors.


All authors designed the study. Tharaka did the literature search, evaluated the papers, performed meta-analyses and wrote the initial manuscript. All authors revised the paper.


Tharaka took the leading role in designing this project, collected all data and performed the statistical analyses. He wrote the two manuscripts that were revised by the all authors.


This study was jointly developed by Tharaka and other co-authors. Tharaka handled data acquisition. Tharaka and Patrick McEllduff performed data analysis and interpretation.

Tharaka wrote the first manuscript which was revised by all authors.
Co-author statement

I, Ian Macgregor Whyte, attest that Research Higher Degree candidate Tharaka Dissanayake contributed to the following papers/publications of which I am a co-author.

- Dissanayake TL, Michie PT, Jones AL, Mallard T, Whyte IM, Carter GL. Cognitive skills underlying driving in patients discharged following self-poisoning with central nervous system depressant drugs. *Traffic Injury Prevention*. Tharaka took the leading role in designing this project, collected all data and performed the statistical analyses. He wrote the two manuscripts that were revised by the co-authors.


This study was jointly developed by Tharaka and other co-authors. Tharaka handled data acquisition. Tharaka and Patrick McElduff performed data analysis. Tharaka wrote the manuscript and which was revised by all co-authors.
Co-author statement

I, Trevor A. Mallard, attest that Research Higher Degree candidate Tharaka Dassanayake contributed to the following publications of which I am a co-author.


Tharaka took the leading role in designing this project, collected all data and performed the statistical analyses. He wrote the two manuscripts that were revised by the co-authors.
Co-author statement

I, Patrick McElduff, attest that Research Higher Degree candidate Tharaka Dassanayake contributed to the following publication of which I am a co-author.


This study was jointly developed by Tharaka and other co-authors. Tharaka acquired data from primary sources. Tharaka and I performed data analysis. Tharaka wrote the initial manuscript which was reviewed by all co-authors.
Co-author statement

I, Barrie James Stokes, attest that Research Higher Degree candidate Tharaka Dassanayake contributed to the following publication of which I am a co-author.


This study was jointly developed by Tharaka and other co-authors. Tharaka made the main contribution to data acquisition and analysis and wrote the manuscript which was revised by all authors.
List of additional publications

Journal abstracts:


Conference presentations:

• Cognitive function in patients with sedative psychotropic drug overdose. *Centre for Brain and Mental Health Research Postgraduate and Postdoctoral Conference*. October 2009, University of Newcastle, Australia


• Incomplete recovery of cognitive functions at discharge in patients with CNS depressant drug overdose. *North American Congress of Clinical Toxicology*. 7-12 October 2010. Denver, Colorado USA.

• Increased risk of road traffic accidents in patients discharged following treatment for psychotropic drug overdose. *Priority Research Centre for Brain and Mental Health Fourth Annual Postgraduate and Postdoctoral Conference*. 30 November 2011, Newcastle

Table of Contents

Synopsis ........................................................................................................... 1

CHAPTER 1: Introduction ............................................................................. 3

1. Epidemiology of CNS-D overdose ..................................................... 4
2. Effects of CNS-D overdose ................................................................. 5
3. Effects of CNS-D overdose on cognitive functions and driving .......... 7
   3.1. Empirical evidence ........................................................................ 8
References .................................................................................................... 10

CHAPTER 2: Literature Review on Cognitive Effects of Central Nervous
System Depressant Drugs ......................................................................... 14

2.1. Cognitive functions underlying everyday activities ......................... 14
2.1.1. Cognitive functions underlying activities of daily living ............... 17
2.1.2. Cognitive framework of automobile driving: theoretical approaches.. 18
   2.1.3. Neurocognitive correlates of automobile driving: behavioural
evidence ................................................................................................. 20
   2.1.3.1. Visual attention and visuomotor skills .................................. 20
   2.1.3.2. Working memory and executive functions ........................... 22
2.1.4. Role of neuropsychological tests in predicting driving performance .. 23

2.2. Acute neurocognitive effects of CNS-Ds ........................................... 26
2.2.1. Benzodiazepines ........................................................................ 26
   2.2.1.1. Attention, perceptual and psychomotor functions ........... 27
   2.2.1.2. Memory ........................................................................... 28
   2.2.1.3. Executive functions and working memory ...................... 29
2.2.2. Antidepressants .......................................................................... 31
   2.2.2.1. Attention, perceptual and psychomotor functions .......... 31
CHAPTER 3 (PAPER 1): Effects of Benzodiazepines, Antidepressants and Opioids on Driving: A Systematic Review of Epidemiological and Experimental Evidence ................................................. 57

ABSTRACT ................................................................................. 58

BACKGROUND ........................................................................... 60

Objectives ................................................................................. 62

METHODOLOGY ................................................................. 63

Literature search strategy ....................................................... 63

Inclusion criteria ....................................................................... 64

Meta-analysis ........................................................................... 76

RESULTS .................................................................................. 76

Epidemiological studies: risk of traffic accidents and use of benzodiazepines, antidepressants and opioids ............................ 76

Benzodiazepines and ‘z drugs’ .............................................. 78

Antidepressants ...................................................................... 88

Opioids .................................................................................. 89

Drug-alcohol interactions and drug interactions ...................... 89

Experimental studies: effects of benzodiazepines, antidepressants and opioids on driving performance ................................. 92
CHAPTER 6 (PAPER 3): Cognitive Skills Underlying Driving in Patients Discharged Following Self-Poisoning with Central Nervous System Depressant Drugs

ABSTRACT

INTRODUCTION

METHODS

Neuropsychological assessment ............................................. 152
Demographic and clinical data ............................................. 156
Data analysis ................................................................. 157
  Planned intergroup comparisons ......................................... 157
  Unplanned within-group comparisons .................................. 158

RESULTS ................................................................. 159
  Sample characteristics .................................................... 159
  Group comparisons of neurocognitive measures .................... 161
    Visual attention and visuomotor skills ............................ 161
    Executive functions and working memory ......................... 163
    Impulsivity and decision-making (IST) ........................... 164
  Unplanned comparisons ............................................... 165
    Subgroup comparisons ............................................... 165
    Intra-Group analysis for CNS-D overdose ......................... 166

DISCUSSION ........................................................ 166

References ............................................................... 169
CHAPTER 8: Conclusions ................................................................. 216

Cognitive impairment and its impact on daily activities ...................... 218
CNS-D overdose and driving .......................................................... 219
Implications for management of patients during the post-discharge period ... 220
Future directions ........................................................................ 222
References .................................................................................. 224

Appendix ....................................................................................... 226

Appendix 1: Detailed description of data linkage process and explanatory notes
on self-controlled case series analysis .............................................. 227
Synopsis

Self-poisoning with pharmaceutical agents is very common across the world. Central nervous system depressant drugs (CNS-Ds) are among the most common substances taken in overdose in hospital-treated episodes of self-poisoning in Australia, the UK and the US. The majority of the patients with CNS-D overdose treated in hospitals in Australia and the UK are discharged within 24-48 hours of their admission, when they still could potentially have subclinical effects of those drugs.

This thesis systematically reviews published evidence on the effects of CNS-Ds on cognitive functions (Chapter 2), automobile driving and traffic accidents (Chapter 3, Paper 1), and presents original research conducted to examine the effects of CNS-D overdose on cognitive functions underpinning daily activities (Chapter 5, Paper 2), surrogate bedside tests of driving skills (Chapter 6, Paper 3) and risk of traffic accidents (Chapter 7, Paper 4) of patients discharged from hospital following treatment.

Comprehensive neuropsychological assessment shows that patients discharged after treatment for CNS-D overdose have significant residual impairments in multiple cognitive functions including visual attention and visuomotor skills, decision-making, and executive functions and working memory (Chapter 5). The impairments, as estimated by regression models, were equivalent to a ‘cognitive ageing’ of 10-20 years depending on the domain tested. Furthermore, executive dysfunction of the patients tends to worsen with increasing task demands.

Converging evidence from the neuropsychological assessment and epidemiological approach indicates that CNS-D overdose has deleterious effects on driving. In particular, the performance of Trail-Making Test B, when interpreted with
respect to its correlation with driving performance and traffic accident risk, suggests that nearly two-thirds of the patients with CNS-D overdose may be grossly impaired (≤10th percentile) at the time of discharge from hospital (Chapter 6, Paper 3). The epidemiological evidence (Chapter 7, Paper 4) shows that the traffic accident risk of these individuals increases by 3-4 times in the immediate post-discharge period, and remains nearly twice their baseline risk after one week following overdose.

In the concluding chapter (Chapter 8), we examine the impact of these impairments on daily activities that the discharged patients are expected and likely to carry out during the post-discharge period, and discuss the clinical implications in post-discharge management of patients treated for CNS-D overdose.