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

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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.*

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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)

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Dedication

…To my mother

Berney Dassanayake…

List of publications included as part of the thesis

Paper 1 (Chapter 3): Dassanayake TL, Michie P, Carter G, Jones A. Effects of benzodiazepines, Antidepressants and opioids on driving: a systematic review of epidemiological and experimental evidence. *Drug Safety* 2011, 34 (2): 125-156.doi:10.2165/11539050-000000000-00000

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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.

- Dassanayake TL, Michie P, Carter G, Jones A. Effects of benzodiazepines, Antidepressants and opioids on driving: a systematic review of epidemiological and experimental evidence. *Drug Safety* 2011, 34 (2): 125-156.

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.

- Dassanayake TL, Michie PT, Jones AL, Carter GL, Mallard T, Whyte IM. Cognitive impairment in patients clinically recovered from central nervous system depressant dru overdose. *Journal Clinical Psychopharmacology*. In press
- Dassanayake TL, Michie PT, Jones AL, Carter GL, Mallard T, Whyte IM. 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 all authors.

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

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- Dassanayake TL, Jones AL, Michie PT, Carter GL, McElduff P, Stokes BJ, Whyte IM. Risk of Road Traffic Accidents in Patients Discharged Following Treatment for Psychotropic Drug Overdose: a Self-Controlled Case Series Study in Australia. *CNS Drugs*. 26 (3): 1-8

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.

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- Dassanayake TL, Michie PT, Jones AL, Carter GL, Mallard T, Whyte IM. Cognitive impairment in patients clinically recovered from central nervous system depressant drug overdose. *Journal Clinical Psychopharmacology.*
- Dassanayake TL, Michie PT, Jones AL, Carter GL, Mallard T, Whyte IM. 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.

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- Dassanayake TL, Jones AL, Michie PT, Carter GL, McElduff P, Stokes BJ, Whyte IM. Risk of Road Traffic Accidents in Patients Discharged Following Treatment for Psychotropic Drug Overdose: a Self-Controlled Case Series Study in Australia. *CNS Drugs*. In press

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List of additional publications

Journal abstracts:

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- Cognitive impairment in patients discharged following CNS-depressant drug overdose, and its implications in driving. *Australasian Society of Psychiatric Research Conference.* 5-8 December 2011, Dunedin, New Zealand

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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 ($\leq 10^{th}$ 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 carryout during the post-discharge period, and discuss the clinical implications in post-discharge management of patients treated for CNS-D overdose.