Medication prescribing in the elderly and the effect on health related outcomes:

An investigation of bias in observational studies using computerised claims databases

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Table of Contents

Table of Contents ..... **II**
List Of Tables ..... **V**
List Of Figures ..... **VII**
ABSTRACT ..... **VIII**
Declaration ..... **X**
Manuscripts Contributing To This Thesis ..... **XI**
Presentations Arising Out Of This Thesis ..... **XII**
Awards Arising Out Of This Thesis ..... **XIII**
Acknowledgements ..... **XIV**
Abbreviations ..... **XVI**
Preface ..... **XVII**
1 Introduction **1**
1.1 Background 1
1.2 Aim 5
2 Current Methods for Dealing with Confounding **6**
2.1 Numerical Adjustment Techniques for Measured Confounders 7
2.1.1 Comorbidity Scores 7
2.1.2 Propensity Scores 8
2.2 Study Designs for Unmeasured Confounders 10
2.2.1 The Self-controlled Case-series Design 11
2.2.2 Instrumental Variable Analysis 15
3 Department of Veterans' Affairs Computerised Claims Database **30**
3.1 Patient Information 30
3.2 Exposure Data 31
3.3 Outcome Data 31
3.4 Utilisation of the DVA Database for Observational Studies 32
4 Antipsychotics in the elderly and the risk of death, stroke, hip fracture and pneumonia: A Review of evidence **34**
4.1 Preface 34
4.2 Antipsychotics in the elderly and the risk of death, stroke, hip fracture and pneumonia: A Review of evidence 35

4.2.1 Background 35
4.2.2 Review Objective 36
4.2.3 Study Design 36
4.2.4 Results 37
4.2.5 Discussion 41
4.2 Additional discussion 55
5 Factors associated with choice of antipsychotic treatment in elderly veterans: potential confounders for observational studies 58
5.1 Preface 58
5.2 Factors associated with choice of antipsychotic treatment in elderly veterans: potential confounders for observational studies 59
5.2.1 Introduction 62
5.2.2 Objective 64
5.2.3 Methods 64
5.2.4 Results 67
5.2.5 Discussion 68
5.3 Additional Discussion 74
6 Antipsychotics and the risk of death in the elderly: An instrumental variable analysis using two preference based instruments 75
6.1 Preface 75
6.2 Antipsychotics and the risk of death in the elderly: An instrumental variable analysis using two preference based instruments 77
6.2.1 Introduction 79
6.2.2 Objective 81
6.2.3 Methods 81
6.2.4 Results 84
6.2.5 Discussion 87
6.3 Additional Discussion 101
7 The risk of hospitalisation for stroke associated with antipsychotic prescribing in the elderly: self-controlled case-series results 104
7.1 Preface 104
7.2 Typical antipsychotics increased the risk of stroke in the first week of treatment in the elderly: self-controlled case-series results 107
7.2.1 Introduction 110

7.2.2 Methods 113
7.2.3 Results 115
7.2.4 Discussion 117
7.2.5 Conclusion 118
7.3 Additional Discussion 126
8 Antipsychotics and the risk of hospitalisation for hip fracture and pneumonia in the elderly: Self-controlled case-series and instrumental variable analysis results 128
8.1 Preface 128
8.2 Antipsychotics and the risk of hospitalisation for hip fracture and pneumonia in the elderly: Self-controlled case-series and instrumental variable analysis results 129
8.2.1 Background 132
8.2.2 Objective 135
8.2.3 Methods 135
8.2.4 Results 139
8.2.5 Discussion 141
8.2.6 Conclusion 145
8.3 Additional Discussion 153
8.4 Is it time to rethink the risk/benefit ratio of antipsychotic use in the elderly? 154
9 Summary and Conclusions 157
9.2 Future Directions 162
9.3 Conclusion 163
References 165
Appendix 1 Derivation of the IV estimate 174

List Of Tables

Table 4.1: Studies on the risk of death associated with antipsychotic medicines 45

Table 4.2: Studies on the risk of cerebrovascular events and stroke associated with antipsychotic medicines 48

Table 4.3: Studies on the risk of hip/femur fracture associated with antipsychotic medicines 51

Table 4.4: Studies on the risk of pneumonia associated with antipsychotic medicines 53

Table 4.5: Summary of studies on the risks associated with antipsychotic medicines 54

Table 4.6: Efficacy of atypical antipsychotics in elderly patients with dementia, Number needed to treat 57

Table 5.1: Characteristics of new users of antipsychotics, for all patients aged over 65 years of age and for patients resident in aged-care facilities 71

Table 5.2: Multivariate model: Significant independent predictors of typical antipsychotic initiation compared to atypical antipsychotic initiation 73

Table 6.1: Demographic characteristics for patients first dispensed antipsychotics between 2003 and 2006 92

Table 6.2: Risk difference for death within one year for typical compared to atypical antipsychotics 93

Table 6.3: *Comparison of the Instruments: Instrument Strength:* Proportion of actual treatment correctly predicted by the instrument 94

Table 6.4: *Comparison of the Instruments: Covariate Balance:* Comparison of patient characteristics between actual treatment prescribed and between doctor preference for treatment for the full cohort 95

Table 6.5: *Comparison of the Instruments: Covariate Balance:* Comparison of patient characteristics between actual treatment prescribed and between nursing home facility preference for treatment for the subset of patients resident in nursing home facilities 98

Table 7.1: Patient characteristics of the study population included in the case-series analysis 120

Table 7.2: Case-series analysis for the association between first hospitalisation for stroke and exposure to typical or atypical antipsychotics 122
Table 7.3: Case-series analysis for the association between first hospitalisation for stroke and exposure to typical or atypical antipsychotics for patients with at least one dispensing of an antipsychotic during the study period… 123
Table 8.1: Patient characteristics of the study population included in the case-series analysis 146
Table 8.2: Demographics of the study population included in the Instrumental Variable Analysis for patients resident in a nursing home facility 147
Table 8.3: Case-series analysis for the association between first hospitalisation for hip fracture and exposure to typical or atypical antipsychotics 150
Table 8.4: Case-series analysis for the association between first hospitalisation for pneumonia and exposure to typical or atypical antipsychotics 151
Table 8.5: Risk differences for hospitalisation for hip fracture or pneumonia per 100 patients treated with typical compared to atypical antipsychotics, unadjusted, covariate adjusted and instrumental variable adjusted results. 152

List Of Figures

Figure 2.1: Representation of the self-controlled case-series analysis 13
Figure 2.2: Representation of a randomised control trial analysis 19
Figure 7.1: Age at first hospitalisation for Stroke for unexposed patients, atypical antipsychotic initiators and typical antipsychotic initiators 121
Figure 7.2: Case-series analysis for the association between first hospitalisation for stroke and exposure to antipsychotics for the period 2003 to 2004 124
Figure 7.3: Case-series analysis for the association between first hospitalisation for stroke and exposure to antipsychotics for the period 2005 to 2006 125

ABSTRACT

Background: This thesis explores the effects of medication prescribing on patient outcomes in an ageing population, specifically, the population of Australian veterans. The primary source of data is the computerised administrative claims database maintained by the Commonwealth Department of Veterans‟ Affairs. This database is a valuable resource yet knowledge about how these data can be analysed and interpreted to study the effects of medicine use in the Australian setting is limited. An important source of bias in observational studies relating medication prescribing to health outcomes arises from confounding by the reason for prescription, or confounding by indication. The extent to which traditional pharmacoepidemiological studies utilising administrative claims databases can deal with confounding is limited as these data sources often lack information on many potentially important confounders, such as clinical information, life style factors and disease severity.

Aim: The aim of this thesis was to investigate the use of two methods, developed to overcome possible bias in observational studies due to unmeasured confounding; instrumental variable analysis and the self-controlled case-series design. To illustrate how these techniques may be used to overcome confounding, I investigate how they apply to the assessment of the adverse effects of antipsychotic prescribing in the elderly.

Methods: The instrumental variable analysis was used to compare the risk of death, hip fracture and pneumonia between the antipsychotic classes. The instrumental variable analysis aims to control for unmeasured confounding by attempting to mimic the process of random assignment in a randomised controlled trial. The self-controlled case-series design was used to investigate the risk of hospitalisation for stroke, hip fracture and pneumonia associated with antipsychotic initiation. The self-controlled case-series design uses a patient as their own control, thereby implicitly controlling for constant patient specific confounders, even those that are unmeasured.

Results: Using a cohort of 20,205 elderly patients aged over 65 years of age, I have shown that the profiles of patients receiving antipsychotic medicines vary between the class of antipsychotic initiated and those variables that differ are likely to be associated with the reported adverse events of these medicines. This indicates the potential for confounding in observational studies of antipsychotics and suggests that appropriate study designs are required to minimise the effect of confounding in order to get a clear understanding of the potential adverse events of these medicines.

The instrumental variable analysis suggested that typical antipsychotics were associated with an extra 24 (95% confidence interval (CI) 18-30) deaths per 100 patients per year compared to atypical antipsychotics, and an extra 10 (95% CI 7-14) deaths per 100 patients per year among nursing home residents. In this analysis I proposed a new instrument, facility prescribing preference, as an alternative to the doctor prescribing preference instrument; the latter which has been used extensively in the pharmacoepidemiological literature. I was able to show that facility preference may be a valid instrument for further work in this area as it was highly correlated with actual

treatment (Odds Ratio 19.2; 95% CI 17.1-21.6), provided a good balance of measured patient characteristics and was consistently strong over time.

While the instrumental variable analysis can provide information regarding the comparative risk of antipsychotics between the classes it cannot inform about the individual risk of these medicines compared to no treatment. To answer this question I used the self-controlled case-series design to estimate the excess risk of hospitalisation for stroke, hip fracture and pneumonia after initiation of an antipsychotic. Atypical antipsychotics were not associated with an increased risk of stroke, which is consistent with randomised controlled trial evidence. No such evidence is available for typical antipsychotics in the elderly, however, the case-series analysis suggests that there is a small but significantly increased risk of hospitalisation for stroke in the first week after initiation (Incidence Rate Ratio (IRR); 2.1, 95% CI 1.1-4.2). For pneumonia the risk was raised in all periods after antipsychotic initiation. This risk was highest in the first week after initiation and remained significantly raised by 50% with more than 12 weeks of treatment (Typical antipsychotics IRR; 1.5, 95% CI 1.2-1.9, Atypical antipsychotics IRR; 1.5, 95% CI 1.3-1.7). The risk of hip fracture was significantly increased for both classes but this risk was sustained only with long-term typical antispychotic use (IRR; 1.3, 95% CI 1.1-1.6).

The self-controlled case-series design has been used extensively in the investigation of vaccine safety. I have found, however, that the application of this design to the study of the effects of medicine prescribing in the elderly may require the addition of an unexposed group to control for the increasing incidence of hospitalisation with age in this population. I also explored the use of risk periods prior to initiating therapy with antipsychotics. Patients were more likely to have had a hospitalisation for stroke in the week prior to initiating typical antipsychotics (IRR; 6.9, 95% CI 4.7-10.0) while atypical antipsychotic initiators had no excess risk in the same period (IRR; 1.2, 95% CI 0.5-2.6). These results suggest that the use of pre-exposure risk periods may be required in medicine outcome studies when the outcome of interest is a hospitalisation event that leads to an increased likelihood of initiating treatment.

Conclusion: This thesis has illustrated that identifying and reducing confounding will enhance the validity of observational studies investigating the safety of medicines using computerised claims databases. By employing methods that help to overcome the problem of confounding I was able to demonstrate that antipsychotic use in the elderly is associated with significant harm and the increasing use of these medicines in Australia poses a major public health concern. Randomised controlled trial evidence suggests that for every 100 patients treated with atypical antipsychotics over 12 weeks, only 8 to 33 would show any benefit, however, there would be 1 additional death and 2 additional cerebrovascular events. Using the self-controlled case-series design I estimated that there would be 8 additional pneumonias, and 2.5 additional hip fractures for every 100 patients treated with atypical antipsychotics over 12 weeks. In addition, typical antispychotics were found to be associated with at least equivalent, if not more, harm. The knowledge obtained in this thesis will help to inform how Australian computerised claims databases may be interrogated to examine the safety of medicines that are under investigated in randomised controlled trials. This information will allow prescribers and policy makers to make more informed decisions about the risks of medicines.

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.

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> Pratt N.L., Roughead E.E., Salter A., Ryan P., Antipsychotics and the risk of death in the elderly: An instrumental variable analysis using two preference based instruments. Pharmacoepidemiology and Drug Safety

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Manuscripts Contributing To This Thesis

- Pratt N.L., Roughead E.E., Salter A., Ryan P., Antipsychotics and the risk of death in the elderly: An instrumental variable analysis using two preference based instruments. Pharmacoepidemiology and Drug Safety, Accepted 3 February 2010. Published online: Apr 16 2010

- Pratt N.L., Roughead E.E., Salter A., Ryan P., Factors associated with choice of antipsychotic treatment in elderly veterans: potential confounders for observational studies. ANZJPH, Accepted April 2010

- Pratt N.L., Roughead E.E., Salter A., Ryan P., The risk of hospitalisation for stroke associated with antipsychotic prescribing in the elderly: Self-controlled case-series results. Resubmitted to Drugs & Aging, May 2010

- Pratt N.L., Roughead E.E., Salter A., Ryan P., Antipsychotics and the risk of hospitalisation for hip fracture and pneumonia in the elderly: Self-controlled case-series and instrumental variable analysis results. Submitted to Drug Safety, February 2010

To be submitted for publication:

- Pratt N.L., Roughead E.E., Antipsychotics in the elderly and the risk of death, stroke, hip fracture and pneumonia: A Review of evidence.

Presentations Arising Out Of This Thesis

- Pratt N. Using an Australian administrative data set for post-marketing surveillance of antipsychotics in elderly veterans: The challenge of unmeasured confounding. (Invited Presentation). Joint meeting of the Australian Statistical Society and Australian Epidemiological Society, Adelaide, June 2010

- Pratt N. Are antipsychotics safe in the elderly? National Prescribing Service, National Medicines Symposium. Melbourne, May 2010

- Pratt N. Measuring the impact of Medicines Policy and Practice on Drug Utilisation, Costs and Health (Expert Panel Member) National Prescribing Service, Data workshop. Sydney, May 2010

- Pratt N. Risks associated with the use of Antipsychotics in the elderly: Results of an Instrumental Variable analysis to control for unmeasured confounding. State Population Health Conference. Adelaide, October 2009

- Pratt N, Roughead E. Ryan P, Peck R, Gilbert A. Antipsychotics and the risk of hip fracture, pneumonia and stroke: Self-controlled case-series and instrumental variable analysis results. 25th International Conference on Pharmaco-epidemiology & Therapeutic Risk Management. Pharmacoepidemiology Drug Safety 2009; 18: Suppl 1, S29, Providence, Rhode Island, August 2009

- Pratt N, Roughead E. Using Australian administrative data sets for post-marketing surveillance. (Invited Presentation). Therapeutic Goods Administration. Canberra, June 2009

- Pratt N. Analysis techniques for PBS data (Expert Panel Member) National Prescribing Service, Working with PBS Data workshop. Sydney, November 2008

- Pratt N. Veterans‟ MATES: Reducing Harm and Improving Patient Outcomes (Keynote Speaker). National Data Linkage Symposium. Adelaide, October 2008

- Pratt N. Antipsychotic Prescribing in Elderly Veterans. (Invited Presentation). University of Adelaide, Faculty of Health Sciences Research Expo. Adelaide, July 2008

- Pratt N. QUM: measuring the impacts of policy and practice, outcomes analysis. (Invited Workshop Presentation). National Medicines Symposium. Canberra, May 2008

Awards Arising Out Of This Thesis

- Third Prize Student Abstract at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management 2009

- Scholarship to attend the International Conference on Pharmacoepidemiology & Therapeutic Risk Management awarded by the International Society for Pharmacoepidemiology 2009

- University of Adelaide Faculty of Health Science Postgraduate Travelling Fellowship 2009

- Shultz Travel Scholarship 2008

- Runner-up Presentation Prize at the University of Adelaide, Faculty of Health Sciences Research Expo 2008

- Scholarship to attend the International Conference on Pharmacoepidemiology & Therapeutic Risk Management awarded by the International Society for Pharmacoepidemiology 2007

Acknowledgements

I would like to sincerely thank the Australian Government Department of Veterans‟ Affairs for funding this work. I thank Bob Peck for reviewing the manuscripts and presentations arising out of this thesis.

I would also like to thank my friends and colleagues at the Quality Use of Medicines and Pharmacy Research Centre, University of South Australia and the Data Management and Analysis Centre, University of Adelaide. I would especially like to thank Emmae Ramsay for all her help and advice.

I am also thankful for the advice given to me by Professor Paddy Farrington and Dr Jeremy Rassen.

This thesis is dedicated to many people,

To Libby, thank you for believing in me and for constantly pushing me to achieve. I could not publish this research without your support, threats(!), focus, and those few words “Nicole, what is your question?”.

To Phil, thank you for your constant support and encouragement throughout the years. This would not have been possible without you.

To Amy, whose single lecture way back when, set me on the path to the discovery of the wonderful world of medical statistics. I thank you for your inspiration and reassurance.

To my family and friends who put up with my absences over the last three years but were there for me every step of the way. A special thank you to my mother for her care and loving support, and for all her baby sitting!

To my special little man Oscar, and my wonderful nieces and nephews Bailey, Ethan, Lucy, Jackson and Maddison, thank you for the distraction!. I hope this thesis teaches you that it is never too late to change what you want to be when you grow up.

To Grant, who shares my shadow.

To MY Aaron, as a statistician I like to quantify things, but how do I measure my gratitude and my love for you? Impossible, yet I am safe in the knowledge that there simply aren‟t enough days left in my life to exhaust it. I thank you for everything.

Finally, this thesis is dedicated to my daughter Emma who taught me about strength, courage, resilience and that life must go on.

This is for you …

"You have brains in your head. You have feet in your shoes. You can steer yourself in any direction you choose. You're on your own. And you know what you know. You are the one who'll decide where to go."

"Oh! The Places You'll Go!" Dr Seuss

Abbreviations

ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDS	Chronic Disease Score
DVA	Department of Veterans‟ Affairs
FDA	Food and Drug Administration
ICD-9	International Classification of Disease Version 9
ICD-10	International Classification of Disease Version 10
ICD-10-Aus	International Classification of Disease Version 10 – Australian Version
IV	Instrumental Variable
ITT	Intention To Treat
NSAID	Non-steroidal Anti-Inflammatory Drug
MBS	Medicare Benefits Scheme
PBS	Pharmaceutical Benefits Scheme
PS	Propensity Score
RCT	Randomised Controlled Trial
PPBS	Repatriation Pharmaceutical Benefits Scheme
Veterans‟ MATES	Veterans‟ Medicines Advice Therapeutic Education Service

Preface

This thesis explores the effects of medication prescribing on patient outcomes in an ageing population using data contained in an administrative claims database. The primary source of data is the existing administrative computerised claims database maintained by the Commonwealth Department of Veterans‟ Affairs. This database provides us with a valuable resource yet knowledge about how information in this database can be analysed and interpreted to study the effects of medicine use in the Australian setting is limited. An important source of bias in studies relating medication prescribing to health outcomes arises from confounding by the reason for prescription, or confounding by indication.[1] This thesis will focus on the use of appropriate observational study designs that attempt to address the problem of unmeasured confounding when studying the effects of medicines utilising data contained in administrative claims databases.

To illustrate how study designs may be used to account for confounding, I will apply the designs to the investigation of the adverse effects of antipsychotic prescribing in the elderly. Antipsychotics are often prescribed to treat the symptoms associated with dementia, yet little is known about their long-term safety and efficacy. Randomised controlled trials (RCT) of antipsychotics have been conducted but sample sizes were small and these studies may not have the statistical power to detect rare but serious adverse events nor were they designed to determine longer term effects. Antipsychotics have two main classes, typical and atypical antipsychotics, however, much of the published RCT data in the elderly are limited to the atypical antipsychotics and little is known about the risk of typical antipsychotics in this population.

Convenient sources of information to fill this gap are computerised claims databases linking pharmaceutical dispensings with health outcomes such as hospitalisations and death. The advantages of using computerised claims data are that information is available on large populations with extended follow-up, which means that there is increased statistical power to detect rare events, and exposures to the medicines are measured as they are used in routine clinical practice. Also, the safety of treatment in patient populations typically excluded from randomised controlled trials can be investigated. Despite these advantages, observational studies utilising data contained in computerised claims databases to study the effects of medicines may be criticised because these data sources lack clinical information. Consequently, many potentially important confounders such as disease severity, diagnosis or patient lifestyle factors will be unmeasured and therefore cannot be adjusted for in traditional statistical models.

The investigation of the adverse events associated with antipsychotics is potentially prone to bias due to confounding as those prescribed these medicines are often elderly patients with multiple co-morbid conditions. Atypical antipsychotics may be selectively prescribed in the elderly as these drugs are associated with fewer and less severe side effects than the typical antipsychotics[2 3]. Atypical antipsychotics, however, are more likely to be associated with published warnings of serious adverse events due to the availability of placebo controlled trial data. This selective prescribing based on the different side effect profile suggests that confounding is likely in the assessment of the comparative safety of these medicines and appropriate observational study designs are required to investigate these medicines.

This thesis consists of nine chapters. Chapter 1 explores the advantages and disadvantages of observational studies of medicine effects and the rationale for this thesis. Chapter 2 investigates conventional statistical methods and study designs often

used in observational studies to control for measured confounding. This chapter also explores some new methods and designs that have been developed to overcome bias due to unmeasured confounding in observational studies; the self-controlled case-series design and instrumental variable analysis. The details of the Department of Veterans‟ Affairs claims database that has been utilised for the studies included in this thesis are provided in Chapter 3. In Chapter 4, I present a review of current evidence regarding the risks of antipsychotic prescribing in the elderly. This chapter provides insight into how observational studies may be required to investigate the safety of antipsychotics in populations untested in experimental studies and demonstrates that the design of such studies is crucial to their interpretation. In Chapter 5, I highlight the potential for confounding in the assessment of the risks of antipsychotics, as the profiles of patients who receive typical compared to atypical antipsychotics differ in ways that are likely to be associated with the potential adverse events of these medicines. The following chapter (Chapter 6) explores the use of instrumental variable analyses to compare the risk of death between typical and atypical antipsychotics. Chapter 7 explores the use of the self-controlled case-series design to measure the risk of hospitalisation for stroke associated with antipsychotic initiation. The results of the studies presented in Chapter 6 and 7 are compared to those obtained in randomised controlled trials where available. In Chapter 8, I use the instrumental variable analysis and the self-controlled case-series design to investigate the risk of hip fracture and pneumonia associated with antipsychotic medicines. In Chapter 9, I present an overall summary of these studies, including an analysis of the risk/benefit ratio of antipsychotics. Finally, I make some conclusions regarding the utility of these designs for further work in this area.