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

An investigation of bias in observational studies using computerised claims databases

Nicole Pratt BSc (Hons)

Discipline of Public Health

School of Population Health and Clinical Practice

Faculty of Health Sciences

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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

Signed: _____

Nicole Pratt (Candidate)

Date: _____

Manuscripts Contributing To This Thesis

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- 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

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- 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

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- 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

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- 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

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"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.

1 Introduction

1.1 Background

Appropriate prescribing in the elderly is an important public health issue as this population is at greater risk of experiencing medicine related adverse events,[4] more likely to be on poly-therapy and have higher rates of chronic illness.[5] Inappropriate prescribing is a major cause of adverse drug reactions.[6] [7] The rate of adverse drug reactions in Australia increased from 2.5 per 1000 person years in 1981 to 12.9 per 1000 person years in 2002 with male patients over 80 years experiencing the largest increase.[8] Consequently, the identification of the adverse effects of drugs and more appropriate use of medicines has the potential to prevent hospital admissions and improve patient outcomes.

Computerised claims databases are convenient sources of information to evaluate the effects of medicines at the population level.[9] Pharmacoepidemiological studies have become increasingly feasible in the Australian environment due to the availability of computerised administrative claims databases. These studies are required to inform policy makers and clinicians about the „real world" safety and effectiveness of medicines that are widely available on the market. A valuable source of linked data in Australia is the Department of Veterans" Affairs (DVA) health information data source. The veteran population consists of veterans who have served in Australia"s armed forces and their eligible spouses or dependants. This data source contains information collected for administrative and billing purposes but is a valuable source of data for post-marketing observational studies as it contains comprehensive information about

exposures (pharmaceutical products) and outcomes (health care encounters) in the veteran population. These data include claims recorded by Medicare Australia, for the Medicare Benefits Scheme (MBS) and Pharmaceutical Benefits Scheme (PBS) as well as public and private hospital claims. Data are collected longitudinally and linked at the individual patient level. These data are complete and reliable and have undergone validity checks at the point of inclusion into the DVA system. The veteran population consists of approximately 310,000 persons, with a median age of 80 years.

In 2004 the Department of Veterans‟ Affairs commissioned a project, Veterans‟ MATES (Veterans‟ Medicines And Therapeutics Education Services), that would provide information to veterans and general practitioners to reduce the potential harm and improve patient outcomes associated with the use of medicines. The implementation of the Veterans‟ MATES project has necessitated the construction of a unique data source in Australia that provides us with many opportunities for monitoring of medicine and health service utilisation, and the evaluation of health outcomes linked to specific exposures. In this thesis I look specifically at the use of these data for assessing the adverse effects of medicines, however, these data sources have the potential to aid in the evaluation of health service provision and to evaluate pharmaceutical policy. The techniques that are explored in this thesis focus on veterans‟ health but the fundamentals regarding the use of these data are directly applicable to the wider health system which is important given the current environment of building and accessing linked data at the state level in Australia.

One of the advantages of data sources, such as the DVA database, is that they already exist. This means that this database may be exploited to answer questions about patient outcomes in a large population without the need for costly patient recruitment and data collection. This database provides a large population from which to draw

subjects, and as a result, studies will often have the advantage of large sample sizes and therefore increased statistical power to detect rare events. Additionally, because the data are collected longitudinally, studies will have extended follow-up which means that the long-term safety of therapy for chronic conditions can be measured. These data are also useful for exploring the effects of medicines in subsets of the population typically excluded from experimental trials, such as the elderly and patients with multiple co-morbid conditions, or when experimental trials cannot be performed.[10]

While there are many advantages, both practically and economically, to using computerised claims databases for observational studies of medicine effects there are also some disadvantages. This is because subjects in observational studies are not randomised to treatment but are prescribed medications based on both patient and doctor characteristics. When the underlying factors associated with the probability of exposure to a medicine are also independently associated with the outcome of interest then the association between the exposure and outcome is likely to be biased due to „confounding by indication".[1 11] In this situation treatment groups are not comparable and measured differences in outcomes between the groups may not be attributable to the effects of treatment alone.[12]

Confounding is not a new concept in statistics and many methods exist to adjust for imbalances between treatment groups.[1] These methods are often numerical and therefore rely on the confounders being measured. Because the purpose of claims data is primarily financial, clinical information is rarely collected. Consequently, many potentially important confounders such as smoking, body mass index (BMI), disease severity and diagnosis are not recorded and therefore cannot be adjusted for using traditional statistical methods. Unfortunately in the study of medicines it is this clinical

information that is crucial in order to separate out the effects of the medicine and the effects due to other patient characteristics.

Much work has been done in the area of pharmacoepidemiology on techniques and study designs to control for unmeasured confounding. In 2008, the United States (US) Food and Drug Administration (FDA) prepared guidelines on best practices for conducting scientifically Sound Pharmacoepidemiologic Safety Studies using Large Electronic Healthcare Datasets.[13] Guidelines in this document came under two broad topics. The first concerned the validity of data held within databases; the representativeness of the populations contained in these databases, and whether other non-US electronic data sources could be considered by the FDA. The second topic pertained to the utilisation of the data held within these sources and the extent to which study designs and methods to control for confounding influence the reliability of the results of studies utilising these data. In particular, the FDA sought to determine "what are the effective strategies to address confounding by indication and the effect of measured and unmeasured confounders?" This thesis attempts to answer this question both by determining which study designs are available for the purpose of confounding control and to compare and contrast them using the specific example of the risks of antipsychotic medication prescribing in the elderly using an Australian data source.

There has been much debate about the most appropriate method for dealing with the problem of confounding, particularly in the context of computerised claims databases when studying the effects of medicines yet few studies have been published that have investigated appropriate study designs in the Australian setting. In this thesis, I will demonstrate that there are ways of handling unmeasured confounding either by the use of novel study designs or by utilising the information that can be measured, but in a novel way.

1.2 Aim

The aim of this thesis is to investigate the use of two methods, developed to overcome possible bias in observational studies due to unmeasured confounding; the self-controlled case-series design and instrumental variable analysis. The self-controlled case-series design attempts to control for unmeasured confounding by using the patient as their own control, thereby implicitly controlling for constant patient specific confounders. Instrumental variable analysis aims to control for unmeasured confounding by attempting to mimic the process of random assignment in an RCT. 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.

2 Current Methods for Dealing with Confounding

Observational studies are often required to complete the investigation of the effects of prescription medicines once medicines are on the market. Randomised controlled trials, completed prior to marketing, generally only provide evidence of the short-term efficacy and safety of medicines compared to placebo. Additionally, once medicines become available on the market they may be used in populations untested in clinical trials and little may be known about the effects of treatment in these populations. Observational studies using computerised claims databases can help to fill this gap in knowledge, however, they may be criticised because they often provide inconsistent results.[14] The main issues leading to these discrepancies relate to the validity of the study design used and the potential for bias due to unmeasured confounding.[14] Unmeasured confounding arises in studies utilising computerised claims databases as these data sources often lack complete information on many important clinical confounders.

A confounder is defined statistically as a variable that is associated with the exposure that is also independently associated with the event of interest.[11] For a confounder to cause a bias in the exposure outcome association, this confounder needs to be distributed disproportionately between the levels of exposure. In a randomised experiment treatment groups may be directly compared, as the process of randomisation will most often distribute covariates evenly among the treatment groups. In a non-randomised experiment, such as an observational study, a direct comparison of treatment groups may produce a biased estimate of treatment effect as subjects exposed to treatment may differ systematically from subjects in the comparison group.[15] Approaches to combat confounding are dependent on the type of confounders likely to

influence an association and whether variables can be measured in the available data to adjust for them. There are various strategies that can be employed to control for confounding, either numerical adjustment techniques if confounders are measurable, or if confounders are unmeasured, special study designs may be employed. These methods are explored in the following sections.

2.1 Numerical Adjustment Techniques for Measured Confounders

Computerised claims databases contain information that may be used to help control for confounding. These include demographic variables, such as age and gender, health service encounters, such as general practitioner visits and hospital admissions, and prescribed medication. Information contained in computerised claims data bases is often extensive and may require synthesis to be of use in adjusting for confounding. Summary scores such as comorbidity scores[16-18] and propensity scores[15] have been utilised in pharmacoepidemiological studies of drug effects and are useful because they summarise information into a single score which is associated with the health status of the patient or their probability of exposure. Comorbidity scores may then be used to numerically to adjust for confounding due to health status while propensity scores may be used to adjust for confounding due to likelihood of treatment.

2.1.1 Comorbidity Scores

Many confounders in pharmacoepidemiologic studies are related to the health status of a patient.[18] A patient‟s health status can be estimated by determining how many conditions they have using data on prescriptions and clinical conditions. These

measures are referred to as comorbidity scores.[16-18] The score is used to numerically adjust for confounding under the assumption that true comorbidity is correlated with worse health outcomes and comorbidity is associated with the probability of exposure.

Comorbidity tends to increase with age so one simple strategy to control for confounding in observational studies is to adjust an association by age. When more complex information is available, other validated comorbidity scores may be constructed. These scores vary depending upon the type of information they utilise. The Charlson Index[19] uses diagnostic information from International Classification of Disease Version 9 (ICD-9) coded primary and secondary diagnoses of hospital separations. Other scores, such as the Chronic Disease Scores[20] and RxRisk,[21] use information on medications dispensed as indicators of chronic co-morbid conditions. The RxRisk score is particularly useful in the pharmaceutical claims databases as it only uses information on medications prescribed and has been validated in the Australian setting.[22]

2.1.2 Propensity Scores

Confounders may also be related to the probability of prescription, that is, particular subgroups of patients may be more likely to receive treatment. This selective prescribing results in an imbalanced distribution of patient characteristics between the exposed and unexposed groups and a biased estimate of effect if not adequately controlled.[11] The likelihood of a patient being prescribed a medicine can be estimated by calculating the conditional probability that a patient is exposed to treatment, given their characteristics at the time of prescription.[15] This probability is referred to as a propensity score. The propensity score once estimated can then be used in various

techniques to control for confounding including regression adjustment, stratification or matching. Stratifying patients into groups with similar propensity for treatment may lead to a less biased estimate of effect,[23] as treated and untreated patients with the same propensity will have similar distributions of confounders[24] with the only difference being the actual treatment received. Another advantage of using the propensity score in model adjustment is that it reduces many confounders into a single score, which may overcome model convergence problems when outcomes are rare or data within levels of the individual covariates are sparse.

Simulation studies suggest that the propensity score is effective in reducing bias in observational studies when covariates are included in the model that predict the outcome of interest regardless of their association with exposure, while the inclusion of covariates that are strongly associated with exposure only will lead to an increase in variance but no decrease in bias.[25] In computerised claims databases there are many potential covariates. To assist in determining which covariates to include a high-order propensity-score algorithm has been proposed which systematically determines possible covariates for inclusion into the model based on both the covariate‟s association with outcome and its prevalence in the population.[26]

2.2 Study Designs for Unmeasured Confounders

In general, a patient‟s overall level of illness is an important confounder and may influence prescribing. The propensity score and comorbidity score may be used as a proxy measurement of overall patient illness and presence of disease, however, they cannot completely measure severity of disease. Effect measures derived from analyses adjusted for comorbidity and propensity scores may still be subject to residual confounding. Since the propensity score relies on the measurement of covariates at the time of the medication dispensing the ability of the score to deal with confounding may be limited as other potentially important confounders that influence the doctor‟s decision to prescribe may be unmeasured in administrative data, including smoking, weight and frailty. Hence bias due to unmeasured confounding may still be present except to the extent that unmeasured confounders are correlated with those measured confounders used to compute the score.[27]

In this situation special study designs and analytical approaches are required to attempt to combat the problem of unmeasured confounding. Study designs that have been developed for this purpose include the self-controlled case-series design[28 29] and instrumental variable analysis.[30] The next section explores each of these designs in more detail.

2.2.1 The Self-controlled Case-series Design

In a traditional cohort study, exposed and unexposed patients are recruited, or constructed in the case of claims databases, and followed up to compare the incidence rates of outcome events. In pharmacoepidemiology, exposed subjects may be very different to unexposed patients in unmeasurable ways. One way to overcome this problem is to use the patient as the unit of analysis and compare exposed periods with unexposed periods within the same individual. The case-series design uses this within person design but uses only those subjects with events (cases) and compares the incidence of events occurring during pre-defined periods after an exposure with the incidence of events at other periods of time within the same individual.[31]

The main advantage of the self-controlled case-series design is that fixed and sometimes unknown patient specific confounders that may vary between individuals are controlled for due to the within person design. This design is of particular advantage in studies in which the aim is to compare the risk of medicine exposure compared to non-use. The analogous design in experimental trials is the comparison of exposure to a medicine compared to placebo. Randomised controlled trials are robust towards confounding as the process of randomisation helps to ensure that the only difference between the exposed and placebo groups is the exposure. In observational studies those subjects who receive medicines may be very different to those that do not in ways that are likely to be associated with the outcome. The within person subject design controls implicitly for factors that may be constant within patient, such as sex, smoking and weight.

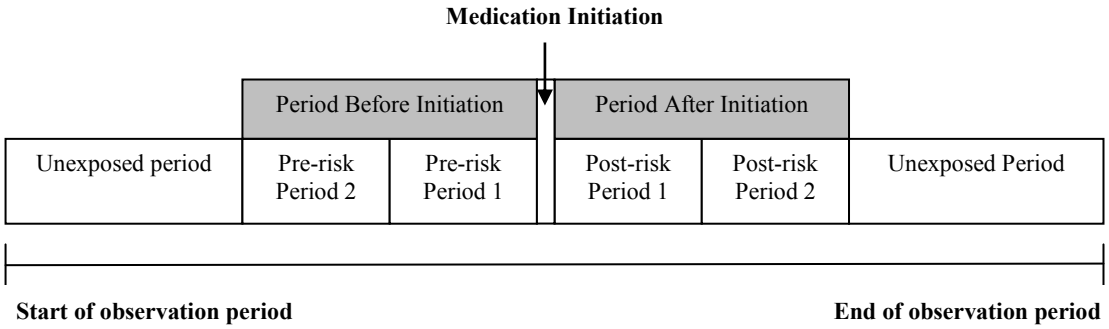
The self-controlled case-series design was initially developed to investigate the acute adverse events associated with vaccinations[32] and has been used widely in this

area[32-36]. The method has also been applied to the investigation of other pharmaceuticals, for example, exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture[31] and acute myocardial infarction,[37] concurrent exposure to selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs and the risk of upper gastrointestinal bleeding,[38] bupropion and the risk of sudden death,[39] oral bisphosphonates and the risk of atrial fibrillation,[40] thiazolidinediones and the risk of fractures,[41] antipsychotics and the risk of stroke in the elderly,[42] and inhaled tiotropium bromide and the risk of stroke.[43] One further study investigated the safety of strontium ranelate for osteoporosis in postmenopausal women[44] with the aim of assessing how the self-controlled case-series design may be used to detect adverse events of medicines using routinely collected administrative claims data. This study identified that the self-controlled case-series design provided an efficient and versatile method for the assessment of medication safety.[44]

2.2.1.1 Derivation

The self-controlled case-series design uses cases only and each individual‟s observation period is partitioned by age group and exposure status.[28 29] Risk periods relative to medication exposure are constructed based on each individual‟s exposure history. Periods of time before and after exposure initiation are defined and all other observation time considered unexposed time (Figure 2.1). The incidence of outcomes in each of these exposure risk periods are compared to the incidence of outcomes in unexposed time using a poisson model. Due to the within person study design only age and other possible time-dependent variables need to be modeled explicitly.

Figure 2.1: Representation of the self-controlled case-series analysis



The self-controlled case-series design also extends to the inclusion of patients who have experienced the event of interest but were not exposed. These patients will contribute information on the impact of other confounders, such as age and frailty, on the risk of the outcome.[28 29] This may be particularly important for studies in the elderly as many outcomes, such as hospitalisations are age dependent and the likelihood of certain medicine exposures increases with increased age.

2.2.1.2 Assumptions

While the self-controlled case-series methodology appears to be advantageous the method has strong assumptions which may limit its applicability in certain situations. These assumptions are that events must be independent and recurrent, the occurrence of an event must not alter the probability of subsequent exposure, and the occurrence of the event must not censor or affect the observation period.[28]

Assumption 1: Events must be independent and recurrent

The first assumption states that outcome events must be independent and recurrent. This means that the occurrence of one event must not affect the probability of subsequent events,[28] that is, events must rise from a non-homogenous poisson process.[29] When analysing outcomes such as hospitalisation this assumption is unlikely to hold, as patients who experience a hospitalisation may be more likely to be hospitalised again. It has been shown, however, that provided the outcome is rare, the analysis will be valid if only the first hospitalisation is used and subsequent hospitalisations igonored.[28]

Assumption 2: The occurrence of an event must not alter the probability of subsequent exposure

The second assumption states that events must be independent of exposure, that is, the occurrence of a hospitalisation must not alter the probability of subsequent medicine initiation. This assumption is likely to be invalid for hospitalisation outcomes where medicines are commonly initiated during hospital stay. When hospitalisations are likely to increase the probability of medicine initiation, the high incidence of hospitalisation in the non-exposed risk period will lead to under estimated relative incidence in the post-exposure risk periods or a bias towards the null. Alternatively, if hospitalisations are likely to preclude particular medicines from being initiated an under estimated relative incidence is likely in the non-exposed risk periods or a bias away from the null. One way to overcome this problem is to include pre-exposure risks periods[28] which are then considered seperately from the non-exposed reference period.

Assumption 3: The occurrence of the event must not censor or affect the observation period

The last assumption states that the occurrence of the event must not censor or affect the observation period. This means that hospital events must not increase the probability of death which may be an unreasonable assumption for some hospitalisation events but not others. Farrington et al.[45] has shown, however, that the case-series method may be robust to failure of this assumption.

In Chapter 7, I apply the self-controlled case-series design to the investigation of the risks of antipsychotic treatment in elderly veterans and explore the validity of the assumptions. The self-controlled case-series design is particularly useful in this example as typical antipsychotics have not been widely tested in RCTs against placebo controls and little is known about the safety of these medicines. In Chapter 7, I also explore the use of the self-controlled case-series design to highlight the presence of confounding by indication and the ability of the design to adjust for confounding by including pre-exposure risk periods.

2.2.2 Instrumental Variable Analysis

Often the objective of pharmacoepidemiological studies is to compare the safety or efficacy of two medicines of the same class for the same indication. In this situation there may be concern about the effects of confounding when patients are selectively prescribed one medicine over the other for reasons that may be related to the outcomes of interest.

Recently, much work has been done investigating a method which attempts to adjust the results of more traditional observational study designs, such as cohort studies, for unmeasured confounding.[46] This method, the instrumental variable analysis, attempts to mimic randomisation in a randomised controlled trial (RCT) by distributing both measured and unmeasured characteristics equally between the treatment groups. This method exploits the existence of another variable (the instrument) that can be measured in the database, which acts as a surrogate for randomisation. A valid instrument has the property that it influences the exposure decision but has no direct effect on the health outcome under study,[47] except through its association with treatment.

With the increased popularity of and access to large computerised administrative claims databases, the methods developed in the economics area have also become relevant in the evaluation of the effects of pharmaceuticals as many clinically important confounders are not contained in these data sources.[48] Instrumental variable analysis has been used in the economic literature since the 1920s[30] as a way of handling selection bias. More recently these methods have gained in popularity in the medical literature. The method has been used to evaluate the effects of medical services,[49 50] pharmaceuticals,[51-53] interventions[54] and changes in policy.[55]

The advantage of an instrumental variable analysis is that it is not necessary to identify confounders, either measured or unmeasured, if an appropriate instrument exists.[48] Assignment to treatment group via the instrument is used as a surrogate for the actual treatment received[52] and should be independent of patient characteristics, therefore, the estimate of the effect of treatment will be less prone to bias. Potential instruments are variables that can be measured in the available data that are correlated with prescribing but are not directly associated with patient specific characteristics which in turn may be related to the outcome of interest. Provided that a valid

instrument exists, the distribution of unmeasured and unknown covariates will be balanced between comparison groups in a similar way to an intention to treat analysis in a randomised controlled trial.[56]

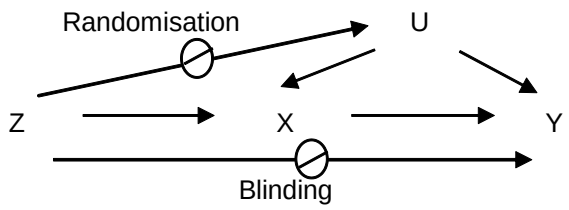
Instruments that have been identified thus far in the medical literature for use with claims databases include doctor specific variables, such as prescribing[51-53] or surgery technique preference,[57] geographical variables, such as distance to hospital,[50] regional cardiac catheterisation rates,[27] day of the week[58] and calendar period.[59] Doctor prescribing preference has been used widely to examine the effects of medication prescribing[51-53]. Doctor prescribing preference was proposed as a suitable instrument under the assumption that doctors preference to prescribe a medicine is correlated with the actual treatment received by the patient but not associated with the event of interest either directly or through other confounding variables.[60] Prescribing preference has been used as an instrument in studies comparing the risk of gastrointestinal toxicity and myocardial infarction[52] with conventional NSAIDs compared to Cox-II inhibitors. It has also been used to compare the risk of death[51 53] and cerebrovascular events[61] between typical and atypical antipsychotics.

The issue of unmeasured confounding is of particular importance when utilising claims data for observational studies as potentially important information on clinical confounders are not collected. Instrumental variable analysis is also useful for evaluating the effect of treatments or interventions at the population level, because instruments may be more valid at this level, and is therefore valuable for policy evaluation. It may be less useful when the aim is to assess effectiveness of treatment at the individual level.[27] This means that the estimates from the instrumental variable analysis are specific to population effects rather than individual effects.

2.2.2.1 Derivation

The instrumental variable analysis considers an alternative variable which may act as a surrogate for treatment in a way that is similar to random treatment assignment. The process of randomisation in an RCT (Figure 2.2) should distribute patient characteristics evenly between treatment arms. However, if a patient is entered into a trial and is assigned to a particular treatment (Z) this is no guarantee that the patient will actually receive the assigned treatment (X). The probability that a patient will actually receive the assigned treatment is higher than if they were not randomised to it. Those who actually take the assigned treatment are termed compliers while those who do not are termed non-compliers. If compliance to treatment is affected by factors that are associated with the outcome of interest (Y) then the estimate of treatment effect based on actual treatment received will be biased. This is why the analysis of treatment effect in randomised controlled trials is often carried out based on the treatment assigned rather that actual treatment received. This is called an intention to treat analysis and attempts to conserve the original balance in patient covariates assured by the randomisation process. The instrumental variable analysis can be shown to be derived from an RCT in which the level of non-compliance is related to unmeasured confounders (U)[56]. In this situation assignment to treatment is unconfounded, but actual treatment receipt, or compliance, is confounded.[56] Randomised controlled trials are often blinded, meaning that the treatment the patient is randomised to remains concealed from the patient and the investigators. Blinding ensures that treatment assignment has no systematic influence on the outcome.

Figure 2.2: Representation of a Randomised Control Trial Analysis



The intention to treat (ITT) estimate is calculated as the difference in outcome rates between the treatment arms as follows,

$$ITT = P[Y|Z=1] - P[Y|Z=0] \quad (1)$$

If treatment is truly efficacious then the ITT will tend to be biased towards the null with increasing levels of non-compliance. The instrumental variable estimate rescales the ITT estimate by the amount of compliance. This is achieved by dividing the ITT estimate by the level of compliance. As compliance decreases (or non-compliance increases) the ITT estimate is biased towards the null but by dividing the ITT estimate by a smaller number we inflate the instrumental variable estimate (see Appendix I).

If we consider an observational study in which two treatments are to be compared, X is the actual treatment received which may be related to factors U. Rather than Z being randomised as in an RCT we consider Z to be a doctors preference for treatment, that is, some doctors prefer treatment A while others prefer treatment B. A doctor who prefers treatment A tends to prescribe treatment A to most of his or her patients while the doctor who prefers treatment B will prescribe treatment B to most of his or her patients. The choice of treatment then will be made based on their preference rather than the characteristics of the patient presenting. If doctors who prefer treatment A do

not systematically differ from doctors who prefer treatment B then differences in treatment based on preference should not be affected by confounding. In this way doctor preference is called an instrument. The instrumental variable estimator is the difference in effect under the instrument divided by the level of association between the instrument and receiving treatment as follows,

$$IV = P[Y|Z=1] - P[Y|Z=0] \ / \ P[X|Z=1] - P[X|Z=0] \quad (2)$$

If the probability of treatment given the instrument is high and the probability of treatment when not on the instrument is low the denominator will approach 1 and the instrumental variable estimator will be similar to the intention to treat estimator. In the case of poor compliance, that is, where the instrument is not associated with actual treatment the denominator will approach zero so any change in the numerator will be inflated resulting in an overestimate of treatment effect. This relationship between instrument strength and bias suggests that there is a critical balance between instrument strength and confounding control that must be explored when conducting instrumental variable analyses.

2.2.2.2 The Instrumental Variable model and its estimator

When there are potential measured covariates to be included in the model the instrumental variable estimator can also be calculated using a regression model [46]. In a conventional model the estimate of treatment effect (X) on an outcome (Y) can be calculated using standard ordinary least squares equation as follows

$$Y = \alpha + \beta X + E \quad (3)$$

This model assumes that there exists no correlation between treatment and the errors (E). In an observational study, where exposure to treatment is associated with patient characteristics that are also correlated with the outcome, the estimate of effect β will be biased as there is residual correlation between treatment and the errors. In general, the addition of other variables, or confounders (C), into the model will reduce the level of bias, however, many unmeasured confounders may exist in computerised claims databases and numerical adjustments cannot be made for them.

The instrumental variable analysis addresses the problem of unmeasured confounding by partitioning the error term into two parts; that which can be explained by another variable (Z), or the instrument, and a random error F.[60] The ordinary least squares equation can now be specified in terms of a system of linear equations.

First the treatment is predicted by the instrument and confounders:

$$X = \gamma + \delta_1 Z + \delta_2 C + F \quad (4)$$

In the second stage, the outcome is predicted by replacing treatment X by the predicted probabilities of treatment (X*) from the first stage model:[60]

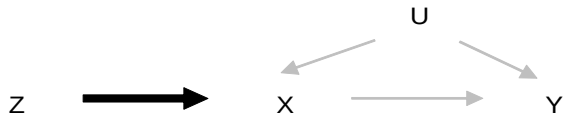
$$Y = \alpha + \beta X^* + E \quad (5)$$

2.2.2.3 Assumptions

Like other statistical approaches, the validity of the instrumental variable estimation relies on assumptions.[52] There are four assumptions that must be met in order for the instrumental variable analysis to result in an unbiased estimate of effect.[46] These assumptions state that the instrument should be 1: independent of confounders, 2:

associated with treatment, 3: independent of the outcome, except through its association with treatment and 4: treatment effects are homogenous amongst subgroups of the population. These assumptions will be explored using the example of doctor prescribing preference which has been proposed as a suitable instrument under the assumption that doctors preference is correlated with the actual treatment received by the patient, is not associated with the event of interest either directly or through other confounding variables.[60] To illustrate these assumptions I will explore how they apply to the doctor preference instrument which will be defined as the treatment, either typical or atypical antipsychotic, prescribed to the last patient seen by that doctor who was initiated on antipsychotic treatment.[51]

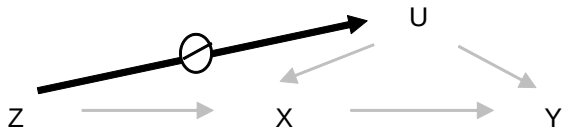
Assumption 1: (Z→X relationship) An instrument should be associated with treatment



The first assumption states that the instrument (Z) must be associated with exposure (X). In the example of doctor prescribing preference this assumption means that the prescribing preference must be strongly correlated with the actual medication prescribed. That is, that a doctor who last prescribed an typical antipsychotic is more likely to prescribe a typical antipsychotic to the current patient and similarly a doctor who last prescribed an atypical antipsychotic is more likely to prescribe an atypical antipsychotics to the current patient. This assumption can be tested by examining the association between the instrument and the actual treatment prescribed from the first stage of the two-stage least squares regression model.

This assumption ensures that equation (1) can be estimated and the denominator of equation (2) is not zero.[46] If this assumption does not hold then the random error term will mask the effect of the treatment variable and the instrumental variable analysis will produce results similar to the ordinary least squares model.[10] This is similar to a randomised controlled trial that has high levels of non-compliance. In this case where treatment is truly efficacious, the treatment effect will be biased towards the null. In the observational study failure to meet this assumption will lead to studies that are underpowered, even in very large studies as treatment effects will be small.[62]

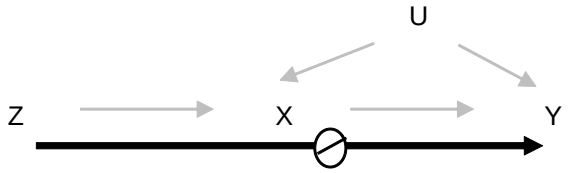
Assumption 2: (Z→U relationship): An instrument must be unrelated to patient characteristics



The second assumption states that the relationship between the instrument (Z) and the exposure (X) must not be confounded by other variables (U). The absence of a Z→U relationship is similar to randomisation in a randomised controlled trial. This means that equation (4) can be estimated without bias, such that, there is no correlation between the instrument and other factors explaining treatment receipt.[46] This assumption is referred to as the independence assumption and can be tested by examining whether observed patient-level characteristics differ between the levels of the instrument.[63] The ability of the instrument to balance measured characteristics over its levels provides some assurance about its ability to also distribute those that are unmeasured.

In the example of prescribing preference as the instrument, the preference of the prescribing doctor, that is the medication last prescribed to another of his or her patients, should not be related to the patient characteristics of the present patient.[63] This assumption may be violated if doctors who more frequently prescribe typical antipsychotics see patients with a different prognosis than those who frequently prescribe atypical antipsychotics.

Assumption 3: Exclusion Restriction (Z→Y relationship): An instrument should be related to the outcome only through its association with treatment



The third assumption states that there should be no correlation between the instrument (Z) and other factors explaining the outcome (Y). This means that the instrument should influence the outcome neither directly nor through its relationship with other variables.[46] The absence of a Z→Y relationship is similar to blinding in an RCT.

The assumption that doctor prescribing preference is not correlated with the outcome may not be easily fulfilled in practice. To assess this assumption, other factors that may influence the outcome can be measured over the levels of the instrument. If we expect that doctor preference changes over time due to increased awareness of potential adverse events or marketing influences then we might expect some level of correlation with outcome, particularly if the doctor is more likely to see particular subgroups of patients, as is the case with specialist doctors.[46] This assumption may be

tested by examining whether the instrument is related to other characteristics of the doctor that may potentially influence the outcome of interest.

Assumption 4: Monotonicity: Treatment effects should be homogenous

The monotonicity assumption states that the effects of treatment should be homogenous among subgroups of the population.[46] This means that the strength of the instrument should not vary over subgroups of the population. When treatment effects are heterogeneous the average treatment effects may be biased. This is because the instrumental variable estimator relies on the fact that the proportion of non-compliers in each assignment arm is the same so that, by taking differences of treatment effects weighted by the proportions of patients in each of the groups, these effects cancel out (Appendix A).

Treatment effect heterogeneity will be violated if the influence of the instrument on the probability of treatment differs in subgroups of the population. For example, when the instrument is strongly associated with treatment in high risk subgroups but weakly associated with treatment in low risk subgroups or when sicker patients benefit more from treatment than healthier patients.[46] This assumption may be tested by determining whether the strength of the instrument varies over subgroups of the population.[63]

2.2.2.5 Interpretation

The interpretation of the instrumental variable estimator is based not only on the ability of the instrument to meet the assumptions but it is also only generalisable to a subgroup of the population. The instrumental variable estimator is calculated as the

difference in average outcome among patients between levels of the instrument, scaled by the difference in treatment status induced by the instrument, or the strength of the instrument.[56] This means that the instrumental variable estimator can be interpreted as the average treatment effect in compliers,[56] where compliers are the marginal subgroup of patients whose treatment status was determined by the value of the instrument.[49] This „marginal" population excludes those patients who would always receive treatment or would never receive treatment and consists of patients whose likelihood of being treated depends only on the doctor"s preference.

Validation studies of the doctor preference instrument have found that this instrument is valid and generally stronger when the study population is restricted to primary care doctors.[63 64] This restriction helps to satisfy the exclusion restriction assumption that treatment effects should be homogenous amongst subgroups. The restriction of the analysis to specific groups of patients for whom the instrument is valid also restricts the representativeness of the results generated from instrumental variable analyses.

2.2.2.6 Limitations

The application of the instrumental variable analysis may be limited in practice as it may be difficult to find valid instruments, the assumptions of the method are easily violated and not all assumptions can be tested directly.[46] The failure to meet the assumptions of the analysis may lead to a greater bias than that it was designed to reduce; bias due to confounding.[65]

A potential limitation of the instrumental variable analysis is that it relies on large sample sizes to produce precise estimates. When instrumental variable analyses are

conducted in computerised claims databases this is rarely a restriction as most studies have the possibility of very large sample sizes. Statistical inefficiency is another limitation of instrumental variable analysis,[52] particularly those based on weak instruments, or instruments that are not strongly associated with actual treatment received. This is because the instrumental variable analysis yields estimates with large standard errors, due to its two-stage estimation approach. Consequently, there appears to be a critical trade-off between bias and variance[66] in instrumental variable analyses. While instrumental variable estimates may be less biased they have a higher variance and a simulation study[66] has found that the bias-variance trade-off may favor the instrumental variable estimate only when the instrument is strong.

Another limitation of the instrumental variable analysis is that it is generally only valid only for comparisons within class,[47] that is, between the choice of treatment rather than the decision itself to treat. This is because of the inability to identify the moment when a doctor decides not to assign treatment to a patient who might be a candidate for treatment.[47]

2.2.2.8 Doctor Prescribing Preference as an Instrument

Doctor prescribing preference has been used extensively as an instrument in pharmacoepidemiological studies. This instrument has been used to investigate the comparative safety of non-steroidal anti-inflammatory drugs (NSAIDs) and Cox-II inhibitors for pain due to osteoartihrtitis[52] and to compare the risk of death between typical and atypical antipsychotics.[51 53] Initially the doctor prescribing preference was determined as the most recent prescription written by the same doctor to another of his or her patients[51] but has been extended to include other definitions of preference.[64]

Randomised controlled trial evidence showed that Cox-II inhibitors were no more efficacious than the non-selective NSAIDs but Cox-II inhibitors were marketed as having the advantage of increased gastro-intestinal safety.[67] Observational studies, however, failed to show an improvement in gastrointestinal risk with Cox-II inhibitors[68-72] as expected from RCT evidence.[73 74] One of these reasons for this may be the selective prescribing of the Cox-II inhibitors to patients at higher risk of gastrointestinal events resulting in an estimate of risk biased towards the null. A study[52] investigating the risk of gastrointestinal events and acute myocardial infarct within 6 months of initiating an NSAID used an instrumental variable analysis to adjust for unmeasured confounding. The results of this study suggested that the risk estimates of the gastrointestinal benefits of the Cox-IIs were underestimated using a conventional regression analysis while the instrumental variable estimate was similar to the estimate from the RCTs.[52] The association between NSAID use and acute myocardial infarct, however, was unchanged using the instrumental variable approach. The authors of this study suggested that doctors may have been more aware of the gastrointestinal risk, which then influenced their prescribing of NSAIDs in these patients.[52] Acute myocardial infarcts, however, were unexpected outcomes so cardiovascular risk factors may not have influenced the doctors prescribing decision, resulting in analyses less biased by confounding.

Doctor prescribing preference has also been used as an instrument to compare the safety of the two classes of antipsychotics, typical and atypical antipsychotics.[51 53 61 64] One study[51] in the US found a significantly increased risk of death with typical compared to atypical antipsychotics (Risk difference 7.3 per 100 patients (95% CI 2.0 to 12.6) within 180 days) using doctor prescribing preference as the instrument. Another study[53] in the Canadian population, also found a significantly increased risk of death

with typical antipsychotics, however, the effect estimate was smaller (Risk difference 4.2 per 100 patients (95% CI 1.2 to 7.3) within 180 days). A study investigated the validity of the instrument and found that the doctor preference instrument satisfied the assumption that it was not related to patient characteristics, that is, preference was not related to important risk factors for death.[63] However, this study also found that the analysis needed to be restricted to primary care doctors in order for the exclusion restriction assumption to be more plausible.[63] The authors of the study concluded that doctor prescribing preference appeared to be a potentially valid instrument, however, further work should focus on standard methods to test the assumption of the analysis. Subsequently, Rassen et al[64] investigated the use of various other definitions of prescribing preference in the same US and Canadian populations. This study found that doctor prescribing preference was generally a strong instrument and reduced covariate balance.[64]

The identification of an appropriate instrument, that is, one that meets the assumptions, is crucial for instrumental variable analyses to be used in practice. In Chapter 6, I investigate the use of the doctor prescribing preference as an instrument to compare the risk of death between the classes of antipsychotics to investigate further the assumptions of this instrument in the Australian population. In this chapter, I also propose a new instrument, nursing home prescribing preference.

3 Department of Veterans' Affairs Computerised Claims Database

The source of data for the studies in this thesis is the administrative claims database maintained by the Department of Veterans‟ Affairs (DVA). This dataset includes all claims data processed by the DVA and has information relating to medicines dispensed under the Australian Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS), hospital admissions and allied health services for which DVA pay a benefit. These data are collected for veterans of Australia‟s defence force and their eligible family members

The treatment population has approximately 310,000 live members with a median age of 80 years. The data file contains over 80 million pharmacy records, 200 million medical and allied health service records and over six million hospital records. Data contained in these databases will now be briefly discussed.

3.1 Patient Information

Patient specific demographic data are contained in the DVA client database, including, date of birth, date of death, sex, level of entitlement and residential status in aged care facilities.

3.2 Exposure Data

Pharmaceutical supply information is contained in the DVA pharmacy database. Medicines are coded according to the World Health Organization anatomical and therapeutic chemical (ATC) classification[75] and the Schedule of Pharmaceutical Benefits item codes.[76] The data elements recorded include pharmaceutical benefits scheme item code, supply date and prescription date, type of prescription, number of repeats ordered, dispensed price, pack size, and formulation strength. The Anatomical Therapeutic Chemical (ATC) Drug Classification can be linked to the pharmaceutical benefits scheme item code. The ATC classification codes pharmaceutical products into groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.[77]

Prescription supply information in the pharmacy database does not contain information relating to the underlying diagnosis nor the prescribed dose. Algorithms have been devised to predict likely dosing information based on the frequency of repeat supply of the medicine and the time between multiple supplies of the medicine in the entire population. These algorithms usually define duration as the period within which 75% of veterans returned for a repeat dispensing of the medicine of interest.

3.3 Outcome Data

For pharmacopeidemiology research, outcomes are usually defined as health service utilisation or hospital admissions. Health service claims are available in the medical and allied health databases including specialist visits and general practitioner attendances. The data elements contained in these records include date of service, item

number, and service costs. Admissions claimed in private and public hospitals are also available in the hospital database. The data elements contained in these records include date of hospital admission and separation, primary and secondary diagnosis codes, procedure codes and health region of providers and clients. Hospitalisations are coded according to the WHO International classification of diseases, 10th revision, Australian modification (ICD-10-AM).[78]

3.4 Utilisation of the DVA Database for Observational Studies

A quality use of medicines initiative currently underway, the Veterans‟ Medicines Advice and Therapeutics Education Services (Veterans‟ MATES) project, aims to provide information to veterans and general practitioners to improve the use of medicines in the veteran community. Veterans‟ MATES uses data from the DVA claims database to identify members of the veteran community who may be at risk of medication misadventure and provides information which may assist in improving the management of their medicines.

The Veterans‟ MATES projects has undertaken drug utilisation studies investigating trends in cardiovascular medicines[79] and non-steroidal anti-inflammatory drugs,[80] and the effect of the increased utilisation of NSAIDs in high risk subgroups on adverse patient outcomes.[81] The influence of the Veterans‟ MATES program on the rate of home medicine reviews performed by Australian general practitioners was explored in another study[82] and the extent to which the increased rate of home medicine reviews translated into better health outcomes for patients.[83] The risk of antibiotic use and hospitalisation for pneumonia associated with proton-pump inhibitors has also been investigated.[84]

This thesis builds upon the work currently undertaken in the Veterans‟ MATES projects, to further explore the use of this dataset for conducting outcome studies of medicines in the elderly. Specifically, I address the way in which observational studies relying on administrative data are able to address the problem of unmeasured confounding.

4 Antipsychotics in the elderly and the risk of death, stroke, hip fracture and pneumonia: A Review of evidence

4.1 Preface

This thesis comprises a series of four articles investigating the safety of antipsychotic prescribing in elderly patients to treat the behavioral disturbances of dementia. Antipsychotics were chosen as a case study to explore the use of novel techniques and methods to adjust for unmeasured confounding as these medicines are understudied in randomised controlled trials in the elderly and we must rely on observational studies to monitor their safety in this population.

In the following section, I review the current evidence of the safety of antipsychotics in the elderly. I have focused on four main outcomes: death, stroke, hip fracture and pneumonia. Each of these outcomes has been investigated to varying degrees in the literature and are outcomes that are readily available in the DVA dataset. I provide a comparison of the methods used to investigate each outcome in the published literature and highlight the consequences of confounding by comparing the results of the various study designs with those obtained from randomised controlled trials, where available.

4.2 Antipsychotics in the elderly and the risk of death, stroke, hip fracture and pneumonia: A Review of evidence

4.2.1 Background

Dementia is a growing public health concern with the number of new cases expected to rise with Australia"s ageing population.[85] Antipsychotics are frequently, and increasingly, prescribed to treat the behavioural symptoms associated with dementia despite their modest efficacy and potential for serious side effects.[2 86] There are two main classes of antipsychotics, the older typical antipsychotics and the newer atypical antispychotics. Examples of typical antipsychotics include haloperidol, periciazine and chlorpromazine. Examples of atypical antipsychotics include risperidone, olanzapine and quetiapine. A Cochrane review[86] failed to find any evidence of benefit with haloperidol treatment in patients with agitated dementia and recommended that it should not be used routinely. Another Cochrane review[2] found that atypical antipsychotics may help to improve symptoms of dementia such as aggression, psychosis and agitation[87-91], however, improvements were often limited to patients with more severe dementia.[89] One study[3] found that risperidone may be more effective in reducing aggressiveness than haloperidol. It has been suggested that the number of patients needed to treat for 12 weeks with atypical antipsychotics to achieve a clinically significant improvement in one patient is in the range of 4 to 12[92].

Side effects such as extra-pyramidal symptoms[87-91] and somnolence,[88-90] are common with both classes of antipsychotics. These effects, however, may be less frequent[93] and less severe[3] with risperidone compared to haloperidol, but only at lower doses.[93] Evidence regarding the more serious adverse events of antipsychotics is

limited to atypical antipsychotics and little is known about the safety of typical antipsychotics in the elderly. Furthermore, most randomised controlled trials have limited follow-up of up to 12 weeks and the safety of both antipsychotic classes with long-term treatment remains unclear.

4.2.2 Review Objective

The aim of this review was to synthesise the current evidence regarding the serious adverse events of antipsychotics in elderly patients. The endpoints of interest were death, cerebrovascular events, hip fracture and pneumonia. Where possible we compared the results of randomised controlled trial studies or meta-analyses with evidence from observational studies.

4.2.3 Study Design

We searched the PUBMED database and the Cochrane controlled trials register for all English-language articles published up to September 2009. We also conducted a manual search of bibliographies for other relevant articles. We included double-blind randomised controlled trials (RCTs), meta-analyses and published observational studies that evaluated adverse events of either typical or atypical antipsychotic medications in elderly populations. All studies were included if they reported on at least one of the adverse events of interest; death, cerebrovascular events, hip fracture or pneumonia. Studies specifically investigating the use of antipsychotics in schizophrenic patients were not included. In PUBMED we combined the results of 2 domains: Dementia (MESH terms Dementia OR Dementia, Vascular NOT Schizophrenia), and drug therapy (Antipsychotic Agents) with each of the following searches for the outcomes of

interest; death (Death OR Death, Sudden, Cardiac OR Death, Sudden OR Mortality), cerebrovascular events (Stroke), hip fracture (Hip Fractures) and pneumonia (Pneumonia OR Pneumonia, Bacterial OR Pneumonia, Aspiration).

Studies were grouped by outcome type and categorised according to the primary study medication comparison. Studies were rated according to a hierarchy of evidence of study designs[94] with meta analyses considered as the highest level of evidence. Observational cohort studies were considered stronger evidence than case-control designs. Studies employing the self-controlled case-series design or instrumental variable analysis were also included. These studies are not formally recognised in the hierarchy of evidence, however, we have considered these studies as they attempt to account for the common problem of unmeasured confounding in observational studies. The probable place of instrumental variable analysis in the hierarchy is either equivalent or better than cohort studies. The place of the self-controlled case-series is as yet unclear.

4.2.4 Results

This review included 38 studies, 15 evaluated the risk of death, 17 evaluated cerebrovascular events, 8 evaluated the risk of hip fracture and 3 evaluated the risk of pneumonia associated with antipsychotic prescribing. Details of the studies meeting our search criteria are presented in Tables 4.1, Table 4.2, Table 4.3 and Table 4.4. A summary of evidence is presented in Table 4.5.

Risk of death associated with antipsychotic medicines

One meta analysis involving 15 RCTs of atypical antipsychotics compared to placebo found a 50% relative increase in risk of death or an absolute increase of 1 extra

death per 100 with atypical antipsychotics compared to non-use.[92] Meta-analyses of risperidone compared to placebo showed a non-significant 20% to 30% relative increased risk of death with short-term treatment (<12 weeks).[89 92 95] One additional RCT, not included in the meta-analyses, found a 42% relative increased risk of death with atypical antipsychotics with extended duration of treatment.[96] No RCT evidence was available for the risk of death associated with typical antipsychotics. Only one RCT comparing the risk of death between the classes was found.[3] This study, limited to 12 weeks duration, found a non-significant 70% relative increased risk of death or 2 extra deaths per 100 patients treated with haloperidol compared to risperidone,[3] however, this may be due to insufficient statistical power as the number of patients in this study was small.

Observational evidence for atypical antipsychotics compared to non-use from a cohort study was consistent with the longer duration RCT results[97] while a case-control study gave a much higher estimate.[98] In contrast, a cross-sectional study found a protective effect of atypical antipsychotic use in hospitalised dementia patients.[99] Three observational studies suggest that typical antipsychotics are associated with an increased risk of death compared to non-use[98 100 101] while a cross-sectional study found no increased risk.[99]

Observational cohort studies comparing the risk of death between the classes consistently found an increased risk of death with typical compared to atypical antispychotics,[51 53 97 102 103] however, the size of this excess differed between studies. Conventional statistical methods adjusting for measured confounders suggested an increased risk over 6 months of between 2 and 3 deaths per 100 patients treated with typical compared to atypical antipsychotics[97 102 103] while those that used an instrumental variable analysis, to adjust for unmeasured confounding, found an increased risk of between 4 and 7 deaths per 100 patients treated.[51 53] One observational

cohort study[100] and one case-control study[98] did not identify a significant difference between the classes.

Risk of cerebrovascular events associated with antipsychotic medicines

Five meta-analyses reported a significantly increased risk of cerebrovascular events with atypical antipsychotics compared to placebo.[2 88-90 104] When the outcome was limited to cerebrovascular events requiring hospitalisation no increased risk was observed,[88 104] suggesting that the majority of strokes were mild. No RCT evidence was located for the risk of cerebrovascular events with typical antipsychotics.

Observational cohort studies found similar results to the meta-analyses. One observational cohort study found no increased risk of hospital admissions for cerebrovascular events with atypical antipsychotics compared to non-use.[105] One cohort study that included all diagnoses of stroke from general practitioner notes found a significantly increased risk.[106] Two case-control studies failed to find any association between atypical antipsychotics and cerebrovascular events compared to non-use.[107 108] One further study used a self-controlled case-series design to control for unmeasured confounding, found an increased risk of stroke as diagnosed through general practitioner notes for up to 70 days after initiation.[42]

The strongest evidence available for the risk of cerebrovascular events with typical antipsychotics was from observational cohort studies. One study found no increased risk of hospital admissions for cerebrovascular events[105] while the other found a significantly increased risk of stroke as diagnosed in GP notes.[106] Two case-control studies failed to find any association between typical antipsychotics and cerebrovascular events.[107 108] A self-controlled case-series study found an increased risk of stroke with

typical antipsychotic initiation compared to non-use which persisted up to 140 days after treatment initiation.[42]

A temporal association between antipsychotics and stroke was also identified. Three studies, all using different study designs, found and increased risk of stroke with antipsychotics.[42 109 110] This risk was highest immediately following treatment initiation but returned to base-line with longer term treatment.[42 109 110]

Six cohort studies compared the risk of stroke between the classes with conflicting results. Three studies found equivalent risk,[110-113] one found a reduced risk[114] while two found an increased risk[61 106] with typical compared to atypical antipsychotics.

Risk of hip fracture associated with antipsychotic medicines

No RCT evidence for the risk of hip fracture associated with either typical or atypical antipsychotics was located. One observational cohort study[115] and one case-control study[116] found an increased risk of hip fracture with atypical antipsychotics compared to non-use, while two case-control studies found no increased risk.[107 117] Typical antipsychotics were consistently associated with a significantly increased risk of hip fracture in three case-control studies compared to non-use.[107 116 117] An association between duration of therapy and hip fracture was also found in two case-control studies.[117 118] One study found that the risk increased with increased duration of exposure,[118] while another case-control study found that the risk was highest after six months continuous duration but then declined to base line with longer-term exposures.[117] Hip fracture risk was associated with dose in one case-control study[119] but not another.[117]

Only one cohort study[115] was identified that directly compared the risk of hip fracture between the classes of antipsychotics. This study found a significantly increased risk of hip fracture with typical antipsychotics compared to atypical antipsychotics.[115] Of the three case-control studies, two found a greater risk of hip fracture with typical antipsychotics compared to atypical,[107 117] while one found similar risks between the classes,[116] however, no formal statistical tests were performed for these comparisons.

Risk of Pneumonia associated with antipsychotic medicines

Observational evidence for the risk of pneumonia compared to non-use was limited to two case-control studies.[120 121] One study found that both atypical and typical antipsychotics were associated with increased risk of hospitalisation for pneumonia and this risk was highest in the first week of treatment.[120] Another case-control study found that any antipsychotic use was a significant risk factor for pneumonia.[121]

Only one study could be located comparing the risk of pneumonia between the classes.[61] This cohort study used an instrumental variable analysis and found no difference in the risk of pneumonia between the classes.[61]

4.2.5 Discussion

This review included 38 studies that evaluated the risk of either death, cerebrovascular events, hip fracture or pneumonia associated with antipsychotic prescribing in the elderly. We found that RCT evidence regarding the risk of death with antipsychotics in the elderly was limited to atypical antipsychotics and the majority of these RCTs had a maximum of 12 weeks follow-up. RCT evidence shows an absolute

increase of 1 extra death per 100 treated with atypical antipsychotics compared to non-use. Observational studies have also identified an increased risk of death with both typical and atypical antipsychotics compared to non-use. The collective evidence shows that typical antipsychotics are associated with a greater risk of death than the atypical antipsychotics, however, the estimates of risk differ between studies. Conventional observational cohort studies estimated between 2 and 3 extra deaths per 100 patients treated with typical compared to atypical antipsychotics over 6 months or between 4 and 7 deaths per 100 patients using instrumental variable analyses. These discrepancies suggest that unmeasured confounding may have contributed to an underestimate of risk in the traditional cohort study. No RCT evidence comparing the risks between the classes was available to confirm these analyses, however one RCT found that haloperidol was associated with 2 extra deaths per 100 patients treated compared to risperidone within 12 weeks, which if extrapolated to 6 months gives similar estimates to instrumental variable analyses.

RCT evidence of the risk of cerebrovascular events was limited to the atypical antipsychotics and demonstratesd that atypical antipsychotics were associated with an increased risk of all cerebrovascular events[2] but not serious strokes requiring hospitalisation.[88 104] Cerebrovascular events appear to be the most studied and reported adverse event associated with antipsychotics in observational studies, however, the definition of this outcome was not consistent between studies. In studies of antipsychotics compared to non-use there appeared to be two definitions of outcome, cerebrovascular hospitalisation events including transient ischaemic attacks and diagnosis of stroke from general practitioner notes. In general, cohort studies reported negative associations when investigating cerebrovascular hospitalisation events and positive associations when investigating outcomes defined as a diagnosis of stroke from

general practitioner notes which supports the findings from available RCTs. In contrast, case-control studies failed to find statistically significant results for either outcome definition. Case-control studies often employ techniques to minimise possible bias, such as matching or numerical adjustment for potential confounders, however, studies of this type may still be subject to unmeasured confounding[122] and while relatively easy to conduct the results of such studies may not be reliable.

Studies have also identified that the increased risk of stroke may be time dependent, with the risk increased immediately following treatment initiation and returning to base-line after one to 3 months.[123 109] Observational cohort studies comparing the classes have used consistent definitions of outcome, specifically, hospitalisation for stroke, however, results vary. Three studies found no difference in risk[111-113] between the classes, one found a reduced risk[114], while two found an increased risk[61 106] with typical compared to atypical antispychotics. One study,[61] using the instrumental variable method to adjust for unmeasured confounding, found a 10% increased risk of stroke with typical compared to atypical antipsychotics but only after 60 days treatment. The result of this study may not be reliable, however, as the prevalence of cerebrovascular disease at baseline in the studied population was high.[51]

While no RCT data for the risk of hospitalisation for hip fracture could be located, a Cochrane review[2] found that risperidone may be associated with an increased risk of falls in the elderly which suggests that an increased risk of fracture may also be likely. Observational studies reported an increased risk of hip fracture with both classes compared to non-use and this risk may increase with increasing duration of therapy. Each of these studies, however, was performed in different target populations and results may not be generalisable to the elderly. Additionally, bias due to unmeasured confounding may be present in all studies as analyses were adjusted for measured

confounders only and all but one study used a case-control design. It is unclear whether the risk of hip fracture differs between the classes. Only one cohort study formally tested the comparative risk of hip fracture between the classes finding an increased risk with typical antipsychotics.

A Cochrane review[2] also identified that risperidone may be associated with an increased risk of upper respiratory tract infections in the elderly and a meta-analysis[124] found that one of the major causes of death associated with atypical antipsychotics was pneumonia. Few observational studies have investigated the risk of pneumonia associated with antipsychotics in elderly patients, however, available studies report an increased risk associated with treatment. This risk appeared to be highest in the first week of treatment but returned to baseline after 90 days.[120] The only study to compare the risk of pneumonia between the classes,[61] used an instrumental variable analysis and concluded that there was no difference between typical and atypical antipsychotics.

In summary, we have identified that the harms associated with antipsychotics in the elderly are under reported in published RCTs and the risks of treatment may not be limited to death and cerebrovascular events. Observational cohort evidence appears to support the findings from RCTs, where available but estimates of risk differed according to the method of analysis employed to control for confounding. Case-control studies often provided contrasting results to those from the cohort studies and from available RCTs, suggesting that it may be a less reliable study design. Observational evidence has highlighted the potential for these medicines to be associated with other serious adverse events that were not reported in RCTs including hip fracture and pneumonia, however, these studies have mostly used a case-control design. In the absence of RCT data, good quality observational studies will be required to clarify these risks.

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

Author (year)	Study Design	Outcome	Sample Population	Follow-up	Drug/Comparison	Result
LEVEL I Evidence: Meta-Analyses						
Studies that compared atypical antipsychotic treatment to placebo						
Katz 2007 [89] (Australia, New Zealand, Canada, Europe, US)	Meta-analysis (3 RCTs, 1 prospective study)	Death	Institutionalised dementia patients Aged >=55 N=895	12 weeks	Risperidone /Placebo	3.1% v 1.8% HR=1.26 (0.53-2.99)
Schneider 2005 [92]	Meta-analysis (15 RCTs)	Death	Institutionalised and Non-Institutionalised dementia patients Aged >55(?) N=5204	6-26 weeks	Atypical/Placebo	3.5% v 2.3% OR=1.54 (1.06-2.23) RD=0.01 (0.004-0.02) ~1 per 100
					Risperidone/Placebo	OR=1.30 (0.76-2.23)
Haupt 2006 [95]	Meta-analysis (6 RCTs)	Death	Alzheimers Patients Mean age 82.3 N=1721	4-12	Risperidone/Placebo	4.0% V 3.1% RR=1.21 (0.71-2.06)
LEVEL II Evidence: Randomised Controlled Trial						
Studies that compared atypical antipsychotic treatment to placebo						
Ballard 2009 [96] (UK)	Randomised. Placebo-controlled, parallel, two group treatment discontinuation trial	Death	Institutionalised dementia patients N=165	12 months	Risperidone/Placebo	47% v 33% HR=0.58 (0.36-0.92)
Studies that compared typical and atypical antipsychotic treatment						
DeDeyn [3] (Europe)	Randomised, Placebo-controlled trial	Death	Dementia patients N=344	12 weeks	haloperidol/risperidone	6.2% v 3.8% OR=1.68 (0.72-3.92) [92]

Author (year)	Study Design	Outcome	Sample Population	Follow-up	Drug/Comparison	Result
LEVEL III Evidence: Observational Studies						
Studies that compared atypical antipsychotic treatment to no treatment						
Gill 2007 (Canada) [97]	Cohort	Death	Non-institutionalised dementia patients Aged >=65 N=9100 matched pairs	180 days	Atypical/Non-use	**Adjusted HR=1.32 (1.12-1.54)** RD=1.1 per 100 (0.1-2.1)
Gill 2007 (Canada) [97]	Cohort	Death	Institutionalised, dementia patients Age >=65 N=4036 matched pairs	180 days	Atypical/Non-use	**Adjusted HR=1.23 (1.05-1.45)** RD=1.5 per 100 (-0.5-3.4)
Trifiro2007 (Netherlands) [98]	Case-control (Matched)	Death	Dementia Patients Age >85 N=398 cases, 4023 controls	Not reported	Atypical/Non-use	**OR=2.2 (1.2-3.9)**
Raivio 2007 (Finland)[99]	Cross-sectional	Death	Hospitalised Dementia Patients Age > 70 N=254 (N=28 Atypical)	2 years	Atypical/Non-use	**HR=0.49 (0.24-0.99)**
Studies that compared typical antipsychotic treatment to no treatment						
Ray2001 (US) [101]	Cohort	Sudden Cardiac Death	Non-institutionalised Aged 15-84 N=1282995	12 months	Typical/non-use	**RR=2.39 (1.77-3.22)**
Kales 2007 (US) [100]	Cohort	Death	Veteran, Dementia Patients Age >65 N=10,615	12 months	Non-use/Typical	**Adjusted RR=0.66 (0.53-0.82)**
Trifiro2007 [98] (Netherlands)	Case-control (Matched)	Death	Dementia Patients Age >85 N=398 cases, 4023 controls	Not reported	Typical/Non-use	**OR=1.8 (1.4-2.3)**
Raivio 2007 (Finland) [99]	Cross-sectional	Death	Hospitalised Dementia Patients Age > 70 N=254 (N=95 Typical)	2 years	Typical/Non-use	**HR=0.68 (0.46-1.03)**

Author (year)	Study Design	Outcome	Sample Population	Follow-up	Drug/Comparison	Result
LEVEL II Evidence: Observational Studies (continued)						
Studies that compared typical and atypical antipsychotic treatment						
Gill 2007 (Canada) [97]	Cohort	Death	Non-institutionalised dementia patients Aged >=65 N=9100 matched pairs	180 days	Typical/Atypical	Adjusted HR=1.23 (1.00-1.50) RD=2.6 per 100 (0.5-4.5)
Gill 2007 (Canada) [97]	Cohort	Death	Institutionalised, dementia patients Age >=65 N=4036 matched pairs	180 days	Typical/Atypical	Adjusted HR=1.27 (1.09-1.48) RD=2.2 per 100 (0.0-4.4)
Hollis 2007 (Australia) [103]	Cohort	Death	Veterans/Spouses Age >=65 N=16634	60 days	Typical/Atypical	haloperidol (T) v olanzapine(AT) HR=2.22 (2.04-2.42) risperidone (AT) v olanzapine (AT) HR=1.23 (1.07-1.40) chlorpromazine (T) v Olanzapine (AT) HR=1.31 (1.09-1.57)
Hollis 2007 (Australia) [102]	Cohort	Death	Institutionalised Veterans/ spouses Age >=65 N=6602	60 days	Typical/Atypical	haloperidol (T) v Olanzapine (AT) HR=2.17 (1.86-2.53) chlorpromazine (T) v Olanzapine (AT) HR=2.72 (1.84-4.01)
Kales 2007 (US) [100]	Cohort	Death	Veteran, Dementia Patients Age >65 N=10,615	12 months	Typical/Typical	Adjusted RR=0.93 (0.75-1.16)
Schneeweiss 2007 (Canada) [53]	Cohort (Propensity score adjusted and IV analysis)	Death	All patients Age >=65 N=37241	180 days	Typical/Atypical	HR= 1.32 (1.23-1.42) RD=4.2 (1.2-7.3) per 100
Wang 2005 (US)[51]	Cohort (Propensity score adjusted and IV analysis)	Death	All patients Age >=65 N=22890	180 days	Typical/Atypical	HR=1.37 (1.27-1.49) IV RD=7.3 (2-12.6) per 100
Trifiro2007 (Netherlands)[98]	Case-control (Matched)	Death	Dementia Patients Age >85 N=398 cases, 4023 controls	Not reported	Typical/Atypical	OR=1.3 (0.7-2.4)

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

Study Design	Study Design	Outcome	Sample Population	Follow-up	Drug/Comparison	Result
LEVEL I Evidence: Meta-Analyses						
Studies that compared atypical antipsychotic treatment to placebo						
Ballard 2008 (Europe, US, Australia) [2]	Cochrane review Meta-Analysis (16 studies, 5 risperidone, 3 olanzapine, 3 quetiapine, 3 aripiprazole)	CV Events	Dementia patients N=1954	10-13 weeks	Risperidone/Placebo	RR=3.6 (1.7,7.7)
Schneider 2006 [90]	Meta-analysis (15 studies, 5 risperidone, 5 olanzapine, 3 quetiapine, 3 aripiprazole)	CV Events	Dementia patients N=5110	6-26 weeks	Atypical/Placebo	OR=2.13 (1.20-3.75) 1.9% v 0.9% OR(Risperidone)=3.43 (1.60-7.32) 3.1% v 1.0%
DeDeyn 2005 (Australia, New Zealand, Canada, Europe, US) [88]	Pooled Analysis of 3 RCTs	CV Events	Institutionalised patients Age >= 55 N=1155	12 weeks	Risperidone/Placebo	3.9% v 1.6% (avg 30.7 days after tmt)
Hermann 2005 (Australia, Int, USA BEL) [104]	Pooled Analysis 6 RCTs	CV Events	Dementia Patients N=1721	Not reported	Atypical/Placebo	3.3% v 1.1% RR=3.2 (1.4-7.2)
Katz 2007 (Australia, New Zealand, Canada, Europe, US) [89]	Meta-analysis (3 RCTs, 1 prospective study)	CV Events	Institutionalised dementia patients Age >= 55 N=895	12 weeks	Risperidone/Placebo	1.6% v 0.8% P>0.01
DeDeyn 2005 (Australia, New Zealand, Canada, Europe, US) [88]	Pooled Analysis of 3 RCTs	Stroke – Serious CV Event requiring Hospitalisation	Institutionalised patients Age >= 55 N=1155	12 weeks	Risperidone/Placebo	1.6% v 0.7%
Hermann 2005 (Australia, Int, USA BEL) [104]	Pooled Analysis 6 RCTs	Stroke – Serious CV Event requiring Hospitalisation	Dementia Patients N=1721	Not reported	Atypical/Placebo	1.5% v 0.6% RR=2.3 (0.5-10.7)

Study Design	Study Design	Outcome	Sample Population	Follow-up	Drug/Comparison	Result
LEVEL III Evidence: Observational Studies						
Studies that compared atypical antipsychotic treatment to no treatment						
Barnett 2007 (US)[105]	Cohort	Hospital Admission for CV event (inc TIA)	Dementia patients, veterans Age >=65 years N=14029 (Atypical N=1585)	18 months	Atypical/non-use	HR=1.2 (0.8-1.7)
Sacchetti 2008 (Italy)[106]	Cohort	Diagnosis of stroke (GP Notes)	Patients Age >64 N=74162	3.5 months maximum	Atypical/ Unexposed	RR=2.46 (1.07-5.65)
Liperoti 2005 (US)[108]	Case-control (matched)	Hospital Admission for CV event (inc TIA)	Institutionalised patients with dementia 1130 cases, 3658 controls	NR	Atypical/non-use	Risperidone OR=0.87 (0.67-1.12) Olanzapine OR=1.32 (0.83-2.11) Other atypical OR=1.57 (0.65-3.82)
Kolanowski 2006 (US)[107]	Case-Control (Unmatched)	Diagnosis of Stroke	Patients Age >45 N=959	45 days	Atypical/non-use	OR=0.98 (0.64-1.52)
Douglas 2008 (UK)[42]	Case-series	Diagnosis of stroke (GP Notes – excluding TIA)	N=6790	Not reported	Atypical Exposed/ Unexposed	Overall (all exposed periods) IRR=2.32 (1.73-3.10) Significant up to 70 days atypical
Studies that compared typical antipsychotic treatment to no treatment						
Barnett 2007 (US) [105]	Cohort	Hospital Admission for CV event (inc TIA)	Dementia patients, veterans Age >=65 years N=14029	18 months	Typical/non-use	HR=1.3 (0.5-3.5)
Sacchetti 2008 (Italy))[106]	Cohort	Diagnosis of stroke (GP Notes)	Patients Age >64 N=74162	3.5 months maximum	Typical/ Unexposed	(butyrophenones v no-use) RR=3.55 (1.56-8.07) (phenothiazines v no-use) RR=5.79 (3.07-10.9)
Liperoti 2005 (US) [108]	Case-control (matched)	Hospital Admission for CV event (inc TIA)	Institutionalised patients with dementia Age > 65 1130 cases, 3658 controls	Not reported	Typical/non-use	OR=1.24 (0.95-1.63)
Kolanowski 2006 (US) [107]	Case-Control (Unmatched)	Diagnosis of Stroke (no further information)	Patients Age > 45 N=959	45 days	Typical/non-use	OR=1.18 (0.63-2.24)
Douglas 2008 (UK) [42]	Case-series	Diagnosis of stroke (GP Notes – ex TIA)	N=6790	Not reported	Typical Exposed/ Unexposed	Overall (all exposed periods) IRR=1.6 (1.55-1.84) Significant up to 140 days typical

Study Design	Study Design	Outcome	Sample Population	Follow-up	Drug/Comparison	Result
Studies that compared all antipsychotic treatment to no treatment						
Percudani 2005 (Italy) [114]	Cohort	Hospital Admission for cerebrovascular-related outcome	Patients Age >=65 N=1645978	<2 years	Antipsychotic/non-use	OR= 1.24 (1.16-1.32)
Sacchetti 2009 (Italy) [109]	Cohort	Diagnosis of stroke (GP Notes)	Patients Age > 64 N=128308+6180	3.5 months maximum	Antipsychotic/non-use	1st month 12.4 (8.4-18.1) Not Sig subsequent months
Kleijer 2008 (Netherlands) [123]	Case-Control (Matched)	Hospital Admission for stroke (inc TIA)	Patients Age > 50 N=2448	1 year	Antipsychotic/non-use	Current use OR=1.6 (1.3-2.0) Past 8-30 days OR=2.0 (1.3-3.3) Past >30 OR=1.2 (0.9-1.6) 0-7 days OR=9.9 (5.7-17.2) 8-14 days OR=2.6 (1.3-5.3) 15-30 days OR=2.1 (1.0-4.5) 31-90 days OR=1.5 (1.0-2.2) >90 days OR= 1.0 (0.7-1.3)
Studies that compared typical and atypical antipsychotic treatment						
Hermann 2004 (Canada) [113]	Cohort	Hospital Admission for stroke	Patients Age > 65 N=11400	Max 5 years	Risperidone/Typical Olanzapine/Typical	RR=1.4 (0.7-2.8) RR=1.1 (0.5-2.3)
Gill 2005 (Canada) [112]	Cohort	Hospital Admission for stroke	Dementia patients Age >= 65 N=32710	Avg 220 days	Atypical/Typical	HR=1.01 (0.8-1.3)
Finkel 2005 (US) [111]	Cohort	Hospital Admission for stroke	Dementia patients >60 years N=18477	3 months	Olanzapine/ Risperidone Quetiapine/ Risperidone Haloperidol/ Risperidone	OR=1.1 (0.6-1.7) OR=0.78 (0.2-1.9) OR=1.9 (1.0-3.6)
Percudani 2005 (Italy) [114]	Cohort	Hospital Admission for cerebrovascular-related outcome	Patients >=65 N=1645978	<2 years	Atypical/Typical	OR= 1.42 (1.24-1.64)
Wang 2007 (US) [61]	Cohort Propensity Score, IV Analysis (*Doctor Preference*)	Hospital Admission for stroke	Patients >=65 N=22890	180 days	Typical/Atypical	30 days HR=1.08 (0.99-1.18) 60 days HR=1.10 (1.02-1.19) 180 days HR=1.09 (1.02-1.16) IV analyses not reported
Sacchetti 2008 (Italy) [106]	Cohort	Diagnosis of stroke (GP Notes)	Patients >64 N=74162	3.5 months maximum	Typical/ Atypical	(butyrophenones v Atypical) RR=1.44 (0.55-3.76) (phenothiazines v Atypical) RR=2.34 (1.01-5.41)

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

Author	Study Design	Outcome	Sample Population	Follow-up	Drug/Comparison	Result
LEVEL III Evidence: Observational Studies						
Studies that compared atypical antipsychotic treatment to no treatment						
Normand 2005 (Canada) [115]	Cohort	Hip fracture	Dementia Patients Age > 65 N=1286395	Not reported	Atypical/non-use	OR=2.2 (2.1-2.4)
Liperoti 2007 (US) [116]	Case-control (Matched to hospitalised controls, septicemia, GI bleed, MI within facility)	Hospitalisation for hip fracture	Nursing Home Patients Age >= 65 N=1787 cases, 5606 controls	Not reported	Atypical v non-use	OR=1.37 (1.11-1.69)
Kolanowski 2006 (US) [107]	Case-Control (Unmatched)	Diagnosis of hip Fracture (no further information given)	Community Dwelling Dementia Patients Age > 45 N=959	45 days	Atypical/non-use	OR=1.47 (0.82-2.65)
Pouwels 2009 (Netherlands) [117]	Case-control (Matched)	Hospitalisation for Hip fracture	Patients Age>18 N=6763 cases, 26341 controls	Up to 12 years	Atypical/no-use	OR=0.83 (0.42, 1.65)
Studies that compared typical antipsychotic treatment to no treatment						
Liperoti 2007 (US) [116]	Case-control (Matched to hospitalised controls, septicemia, gi bleed, mi within facility)	Hospitalisation for hip fracture	Nursing Home Patients Age >= 65 N=1787 cases, 5606 controls	Not reported	Typical v non-use	OR=1.35 (1.06-1.71)
Kolanowski 2006 (US) [107]	Case-Control (Unmatched)	Diagnosis of hip Fracture (no further information given)	Community Dwelling Dementia Patients Age > 45 N=959	45 days	Typical/non-use	OR=2.33 (1.08-5.03)
Pouwels 2009 (Netherlands) [117]	Case-control (Matched)	Hospitalisation for Hip fracture	Patients Age>18 N=6763 cases, 26341 controls	Up to 12 years	Typical/no-use	OR=1.76 (1.48, 2.08)

Author	Study Design	Outcome	Sample Population	Follow-up	Drug/Comparison	Result
Studies that compared all antipsychotic treatment to no treatment						
Hugenholz 2005 (UK)[118]	Case-Control (Matched Birth-year, sex, medical practice)	Hospitalisation for hip fracture	All Patients with a hip fracture N=22250 matched pairs Age >=18	3 years	Antipsychotics/non-use	Current user v no-use OR=1.3 (1.1-1.5) Recent starter v no-use OR=1.2 (0.92-1.6) Non-recent starter v no-use OR=1.3 (1.1-1.5) Prior user OR=1.3 (1.2-1.5) Increasing risk with increasing duration of exposure
Vestergaard 2006 (Denmark) [119]	Case-control (Matched)	Hospitalisation for Hip Fracture	All Patients Age > 0 N=10530 cases, 31535 controls	Up to 5 years	Antipsychotics/no-use	<0.05 DDD/day: OR=1.2 (1.1-1.4) 0.05-0.099 DDD/day: OR=1.8 (1.5-2.0) >=0.1 DDD/day: OR=1.8 (1.6-2.0)
Pouwels 2009 (Netherlands) [117]	Case-control (Matched)	Hospitalisation for Hip fracture	Patients Age>18 N=6763 cases, 26341 controls	Up to 12 years	Antipsychotics/no-use	Current Use: OR=1.7 (1.4-2.0) Recent Use: OR=1.4 (1.2-1.7) Past Use: OR=1.3 (1.1-1.6) Increasing risk in first 6 months, then decrease then increasing risk with duration of exposure
Studies that compared typical and atypical antipsychotic treatment						
Normand 2005 (Canada) [115]	Cohort	Hip fracture	Dementia Patients Age > 65 N=54690	Not reported	Atypical v typical	OR=0.5 (0.4-0.5)

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

Author	Study Design	Outcome	Sample Population	Follow-up	Drug/Comparison	Result
LEVEL III Evidence: Observational Studies						
Studies that compared atypical antipsychotic treatment to no treatment						
Knol 2008 (Netherlands) [120]	Case-control (controls matched by source population)	hospital diagnosis of pneumonia	Patients >=65 patients with no prior pneumonia N=884	6 months	Atypical v Non-use	OR=3.1 (1.9-5.1)
Studies that compared typical antipsychotic treatment to no treatment						
Knol 2008 (Netherlands) [120]	Case-control (controls matched by source population)	Hospitalisation for pneumonia	Patients >=65 patients with no prior pneumonia N=884	6 months	Typical v Non-use	OR=1.5 (1.2-1.9)
Studies that compared all antipsychotic treatment to no treatment						
Knol 2008 (Netherlands) [120]	Case-control (controls matched by source population)	Hospitalisation for pneumonia	Patients >=65 patients with no prior pneumonia N=884	6 months	Antipsychotics v Non-use	Duration of treatment 0-8 days OR=4.4 (2.9-7.2) 8-14 days OR=2.3 (1.1-4.9) 15-30 days OR=1.9 (1.0-3.1) 31-90 days OR=2.0 (1.1-3.0) >90 days OR=1.1 (0.9-0.6)
Wada 2001 (Japan) [121]	Case-Control (unmatched)	Pneumonia	Alzheimers patients treated in psychiatric hospitals N=121	Not reported	Antipsychotics v non use	OR=3.13 (1.46-6.69)
Studies that compared typical and atypical antipsychotic treatment						
Wang 2007 (US) [61]	Cohort (Propensity Score, IV Analysis (*Doctor Preference*))	Diagnosis of Pneumonia	All patients N=22890	180 days	Typical v Atypical	30 days HR=1.11 (0.76-1.63) 60 days HR=1.03 (0.76-1.38) 180 days HR=0.84 (0.66-1.05) IV analyses not reported

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

Outcome	Drug	Comparison	Experimental	Cohort	Case-control	Propensity	Case-series	IV
Death	Atypical	Non-use	+/=	+	+			
	Typical	Non-use		+	+			
	Both*	Non-use						
	Typical	*Atypical*	+	+/=	=	+		+
CV Event	Atypical	Non-use	+	+	=		+	
	Typical	Non-use		+	=		+	
	Both*	Non-use		+				
	Typical	*Atypical*		=/+				
Hospitalisation for Stroke	Atypical	Non-use	=					
	Typical	Non-use		=				
	Both*	Non-use			+			
	Typical	*Atypical*		=/+/-		+		+
Hip Fracture	Atypical	Non-use		+	+/=			
	Typical	Non-use			+			
	Both*	Non-use			+			
	Typical	*Atypical*		+				
Pneumonia	Atypical	Non-use			+			
	Typical	Non-use			+			
	Both*	Non-use			+			
	Typical	*Atypical*						=

* All antipsychotics combined

4.2 Additional discussion

The review of the literature revealed that randomised controlled trial evidence, for the safety of antipsychotics in the elderly, is limited to the atypical antipsychotics, in particular risperidone. Collectively, evidence suggests that atypical antipsychotics are associated with an increased risk of death and cerebrovascular events. Based on RCT evidence the number needed to treat with risperidone to show clinical benefit ranges from 3 to 13 patients over a 12 week period (Table 4.6). This means that for every 100 patients treated with risperidone we would expect between 8 and 33 patients to receive any clinical improvement in symptoms of aggression or psychosis while there would be one extra death and 1.7 extra cerebrovascular events than would have otherwise occurred over the same period. Population harm estimates for the additional risks of hip fracture and pneumonia associated with antipsychotics could not be calculated as the case-control design is unable to provide estimates of underlying risks of treatment.

In general this review found that cohort and instrumental variable analyses gave more consistent results to RCTs for mortality outcomes as have self-controlled case-series for the risk of cerebrovascular events. Observational evidence has highlighted the potential for these medicines to be associated with other serious adverse events that were not reported in RCTs including hip fracture and pneumonia, however, these studies have mostly used a case-control design. In the absence of RCT data, good quality observational studies will be required to clarify these risks.

This thesis explores the use of instrumental variable analysis and self-controlled case-series to investigate the risk of hip fracture and pneumonia associated with antispychotics for which limited evidence exists. However, the first step is to determine whether confounding is likely to be an issue in the assessment of the risks of

antipsychotics. Investigating whether the characteristics of patients prescribed typical and atypical antipsychotics differ in ways that are likely to be associated with reported adverse events of these medicines will help to determine the extent to which confounding by indication may influence the results of an outcome study.[125] In Chapter 5, I compare the characteristics of new users of antipsychotics measured at initiation of treatment. One of the limitations of computerised claims databases is that many factors that influence prescribing cannot be measured and investigators have no way of determining the reasons why doctors prescribed the medicine or their choice of medicines. Knowledge about how treatment groups differ based on measured characteristics is likely to inform whether unmeasured confounding is also present.

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

Study	*Study Design*	*Follow-up*	*Risperidone n/N (%)*	*Placebo n/N (%)*	*RD[1]*	*NNT[2]*
Clinical End Point						
>50% Improvement in Behave-AD[3] total score						
Katz 1999 [126]	Double-blind placebo controlled RCT (n=625)	12 weeks	(45%)	(33%)	12%	8
Schneider 2006[90]	Meta Analysis of 3 studies (n=1001)	12 weeks	266/574 (46%)	139/427 (33%)	14%	7.4
>30% Improvement in Behave-AD[3] total score						
DeDeyn 1999[3]	Double-blind placebo controlled RCT (n=344)	12 weeks	(72%)	(61%)	11%	9
Schneider 2006[90]	Double-blind placebo controlled RCT (n=290)	10 weeks	125/196 (64%)	62/94 (66%)	-2%	
CGI-C[4] (much/very much improved)						
Brodaty 2005[127]	Double-blind placebo controlled RCT (n=93)	12 weeks	27/46 (59%)	12/47 (26%)	33%	3.3
Schneider 2006[90]	Meta Analysis of 2 studies (n=717)	8-12 weeks	227/351 (65%)	175/366 (48%)	17%	6
Katz 2007[89]	Meta Analysis of 4 studies (n=889)	End point	(28%)	(17%)	11%	9
Sultzer 2008[128]	Double-blind placebo controlled RCT (n=421)	12 weeks	(61%)	(40%)	21%	5
CGI-C[4] (at least minimal improvement)						
Schneider 2006[91]	Double-blind placebo controlled RCT (n=421)	12 weeks	24/84 (29%)	29/139 (21%)	8%	12.5

[1] RD: Risk Difference
[2] NNT: Number Needed to Treat
[3] BEHAVE-AD: Behaviour Pathology in Alzheimer‟s Disease Rating Scale
[4] CGI-C: Clinical Global Impression of Change

5 Factors associated with choice of antipsychotic treatment in elderly veterans: potential confounders for observational studies

5.1 Preface

This chapter contains the first of four articles submitted for publication in peer reviewed journals. This article investigates whether confounding by indication can be detected and quantified in observational studies. The aim of this study was to describe the characteristics of new users of atypical and typical antipsychotics between 2003 and 2006 in the Australian DVA population, including patient characteristics, prescribing doctor characteristics and nursing home characteristics. This study was performed to demonstrate the existence of confounding by assessing the distribution of known risk factors for documented adverse events of these medicines between the two classes of antipsychotics.[129] I also investigated whether these characteristics changed over time, in particular, before and after the listing of risperidone on the Australian Pharmaceutical Benefits Scheme in 2005.

5.2 Factors associated with choice of antipsychotic treatment in elderly veterans: potential confounders for observational studies

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STATEMENT OF AUTHORSHIP

Nicole Pratt (Candidate)

Corresponding author, designed the study, extracted the data, performed all the analyses, interpreted data, drafted the manuscript.

Signed……..Date……

Libby Roughead

Contributed to the design and interpretation of the study, and reviewed the manuscript. I give consent for Nicole Pratt to present this paper for examination towards the Doctor of Philosophy.

Signed……..Date……

Amy Salter

Contributed to the design and interpretation of the study, and reviewed the manuscript. I give consent for Nicole Pratt to present this paper for examination towards the Doctor of Philosophy.

Signed……..Date……

Philip Ryan

Contributed to the design and interpretation of the study, and reviewed the manuscript. I give consent for Nicole Pratt to present this paper for examination towards the Doctor of Philosophy.

Signed……..Date……

ABSTRACT

Background: Antipsychotics are commonly used in the elderly despite limited efficacy and potential for serious adverse events. A lack of safety data from randomised controlled trials means that observational studies are required to investigate the comparative safety of antipsychotics. Observational study results, however, have varied, which may be due to lack of control for unmeasured confounding. An understanding of the factors that influence prescribing is important in determining to what extent confounding is likely to impact on the assessment of the risks between these medicines.

Objective: To compare the characteristics of new users of atypical and typical antipsychotics in order to determine the extent of confounding that would be likely to be present in observational studies. We compared the distribution of patient characteristics, prescribing doctor characteristics, nursing home characteristics and known risk factors for documented adverse events of these medicines between typical and atypical antipsychotic initiators.

Methods: Using the Australian Government Department of Veterans‟ Affairs administrative claims dataset, patient characteristics, prescribing doctor characteristics and health care utilisation were compared between atypical and typical antipsychotic initiators. Significant independent predictors of use were calculated using a multivariate log-binomial model.

Results: Compared to patients on typical antipsychotics (N=10,966), patients prescribed atypical antipsychotics (N=9,239) were more likely to be resident in an aged care facility (Relative Risk (RR)=1.08, 95% CI 1.05-1.12), previously prescribed lipids

lowering therapy (RR=1.09 95% CI 1.05-1.13), taking anticholinesterases (RR=1.19, 95% CI 1.15-1.23), antidepressants (RR=1.18 95% CI 1.15-1.22) or anti-parkinson medications (RR=1.30, 95% CI 1.25-1.36) and atypical antipsychotics were more likely to be prescribed by the patient‟s usual doctor (RR=1.12, 95% CI 1.09-1.16). Patients prescribed atypical antipsychotics were less likely to be male (RR=0.91, 95% CI 0.89-0.94), dispensed morphine (RR=0.53, 95% CI 0.49-0.57) or oral corticosteroids (RR=0.86, 95% CI 0.81-0.91), less likely to be dispensed more than 5 unique medicines (RR=0.88, 95% CI 0.83-0.93), and less likely to have been hospitalised for myocardial infarction or pneumonia in the previous 12 months.

Conclusions: The differences in measured characteristics between atypical and typical antipsychotic initiators indicate that there is potential for confounding to be present in observational studies. Future pharmacoepidemiogical research in Australia, investigating the potential adverse events of antipsychotics, should consider the variables identified in this study to control for confounding.

5.2.1 Introduction

Antipsychotics are commonly prescribed to treat the behavioural symptoms of dementia. There are two broad classes of antipsychotics, the older typical antipsychotics and the newer atypical antipsychotics. Antipsychotics were only subsidised on the Pharmaceutical Benefits Scheme (PBS) for the treatment of patients with schizophrenia until July 2005, at this time the atypical antipsychotic, risperidone, was listed for the treatment of the behavioural symptoms of dementia. This listing was made after evidence from placebo controlled randomised clinical trials (RCTs) found a significant improvement in aggression,[2] psychosis,[2 88] and agitation[88] with risperidone. These trials also identified an increased risk of death and cerebrovascular events[2] associated with antipsychotics and subsequent observational studies have identified associations with hip fracture[107 115 116 118] and pneumonia.[120 121]

Antipsychotic use has increased in Australia,[130] yet little is known about the factors that influence prescribing between the classes. An Australian study[103] in the veteran population aged over 65, investigated the risk of death associated with antipsychotic medicines during the period 2003 to 2004, prior to the listing of risperidone on the PBS. The characteristics of the study population indicated that atypical antipsychotic initiators were younger, more likely to be female, more likely to be in a nursing home, dispensed cholinesterase inhibitors, but less likely to have been dispensed medicines for Parkinson‟s disease or morphine. No published data exist on the characteristics of patients prescribed these medicines after the listing of risperidone in 2005.

Studies in the United States[51] and Canada[53] have also identified that differences exist in the characteristics of older patients who initiate typical compared to atypical

antipsychotics. Atypical users were more likely to be older, female, to have a history of dementia, delirium, mood disorders and psychotic disorders, and to be using antidepressants.[51 53] They were also less likely to have been prescribed anticholinesterases and fewer had a history of cerebrovascular disease, congestive heart failure, other ischaemic heart disease or diabetes.[51 53]

The apparent selective prescribing of antipsychotics in the elderly may be attributable to many factors including prescribers‟ perception of comparative safety of typical and atypical antipsychotics and the issuing of safety messages. Atypical antipsychotics are thought to be less sedating and less likely to cause extra-pyramidal symptoms and somnolence[2 3] compared to the typical antipsychotics. They are more likely, however, to be associated with published warnings of serious adverse events (www.pbs.gov.au accessed 11/03/2010) due to the availability of placebo controlled trial data on atypical antipsychotics. Risperidone was listed for the behavioural symptoms of dementia on the PBS with a caution that in placebo controlled-trials, in elderly patients with dementia, there were significantly higher rates of cerebrovascular events, including stroke.

Due to limited clinical trial data, little is known about the risk of typical antipsychotics. Convenient sources of information to fill this gap are computerised claims databases linking pharmaceutical dispensing with outcomes such as hospitalisations. 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 will be measured as they are used in routine clinical practice. Such studies, however, may be biased due to confounding if antipsychotics are selectively prescribed based on factors associated

with the adverse events of these medicines. With the increasing availability of computerised claims databases there is a great opportunity to perform observational studies to investigate the safety of medicines in the Australian population, however, an understanding of the factors that influence prescribing is crucial in determining to what extent confounding is likely to impact on the assessment of the risks between these medicines.

5.2.2 Objective

We aimed to compare the characteristics of new users of atypical and typical antipsychotics. We assessed the distribution of patient characteristics, prescribing doctor characteristics, nursing home characteristics and known risk factors for documented adverse events of these medicines between typical and atypical antipsychotic initiators.[129] Additionally we aimed to investigate whether these characteristics changed after the listing of risperidone on the Australian Pharmaceutical Benefits Scheme in 2005.

5.2.3 Methods

The source of data for this study was the administrative claims database maintained by the Department of Veterans‟ Affairs (DVA). DVA clients include veteran‟s who served in the Australian defence force and their spouses or dependents. Clients eligible for a „Gold card‟ are entitled to all health care services including pharmaceuticals, general practitioner and specialist services and all public and private hospital care subsidised by DVA. The DVA dataset includes all claims data processed by DVA for

medical and allied health visits and hospital admissions and has information relating to medicines dispensed under the Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme. Data capture for pharmaceuticals and public and private hospital admissions is complete for the population as all medicines and services are above the concessional co-payment for veterans.

The data file contains 200-million medical and allied health service records, over six million hospital records and 80-million pharmacy records for a treatment population of 310,000 veterans. The DVA maintains a client file, which includes data on sex, date of birth, date of death and family status. Medicines are coded according to the World Health Organization anatomical and therapeutic chemical (ATC) classification[75] and the Schedule of Pharmaceutical Benefits item codes.[76] Hospitalisations are coded according to the WHO International classification of diseases, 10th revision (ICD-10).[78]

For each patient we identified the first antipsychotic dispensed in each year of the study between 1st January 2003 and 31st December 2006. The date of dispensing of the antipsychotic was then classified as the index date. Patients were included if no other antipsychotic had been dispensed in the previous 12 months, they were aged over 65 years of age, and had been gold card holders for at least 12 months prior to the index date. Typical antipsychotics included chlorpromazine, trifluoperazine, periciazine, thioridazine, haloperidol, ziprasidone. Atypical antipsychotics included clozapine, olanzapine, quetiapine, amisulpride, risperidone, aripiprazole.

At the index date we defined the following patient characteristics: age, gender, residential aged care status, veteran status, conflict fought, previous classes of medications, number of unique medicines dispensed in the previous 12 months, and comorbidity score as measured by RxRiskV.[22] Prior hospitalisations for primary

diagnoses of stroke (ICD10 codes I60-I64), hip/femur fracture (ICD10 codes: S720 & S721), myocardial infarction (ICD10 codes: I21), chronic heart failure (ICD10 codes: I500, I501 & I509), pneumonia (ICD10 codes: J12-J18), and dementia (ICD10 codes: F00-F03) were also identified in the 12 months prior to the index date. These hospitalisations have been identified in the literature as having possible associations with antipsychotics.[2 107 115 116 118 120 121] The doctor who prescribed the index antipsychotic was determined and classified as the usual doctor if this doctor prescribed the majority of the patients" scripts in the previous 12 months.

We also compared these characteristics in the subset of patients resident in an aged care facility at the index date. For these subjects, we also compared their type of care (respite or continuous) and level of care (high or low).

The relationships between the characteristics and the type of incident antipsychotic were measured using log binomial regression models. Variables significant in the univariate analyses at the 0.2 level were included in the multivariate models to identify the significant (alpha<0.05) independent predictors of first time antipsychotic prescribing.

To test whether there was a change over time in the characteristics of patients initiated on a typical or atypical antipsychotic, an interaction term was entered into the model between each variable and an indicator variable for year of prescription.

5.2.4 Results

There were 20,205 subjects included in the study: 9,239 new users of atypical antipsychotics and 10,966 new users of typical antipsychotics. The univariate associations are presented in Table 5.1. When all variables were entered into the model, patients dispensed atypical antipsychotics were more likely to be resident in an aged care facility (Relative Risk (RR)=1.08 95% CI 1.05-1.12), previously dispensed lipid lowering therapy (RR=1.09 95% CI 1.05-1.13), anticholinesterases (RR=1.19 95% CI 1.15-1.23), antidepressants (RR=1.18 95% CI 1.15-1.22) or anti-parkinson medications (RR=1.30 95% CI 1.25-1.36) than patients dispensed typical antipsychotics. Atypical antipsychotics were also more likely to be prescribed by the patient‟s usual doctor (RR=1.12 95% CI 1.09-1.16). Additionally, patients prescribed atypical antipsychotics were less likely to be male (RR=0.91 95% CI 0.89-0.94), less likely to be dispensed more than 5 unique medicines (RR=0.88 95% CI 0.83-0.93), less likely to be dispensed morphine (RR=0.53 95% CI 0.49-0.57) or oral corticosteroids (RR=0.86 95% CI 0.81-0.91) and less likely to have been hospitalised for myocardial infarction or pneumonia in the previous 12 months (Table 5.2).

When analysed over time the only significant changes in the characteristics between the classes were for gender, anti-parkinsons medication and prior hospitalisations for pneumonia. Prior to the listing of risperidone on the Australian pharmaceutical benefits scheme, atypical antispychotics were more likely to be dispensed to patients with prior anti-parkinsons medications compared to after the listing. Additionally, atypical antipsychotics were less likely to be dispensed to patients with a prior hospitalisation for pneumonia, compared to after the listing of risperidone.

In the subset analysis of patients resident in aged care facilities, the predictors of atypical antipsychotic use were similar to those of the main analysis (Table 2). Atypical antipsychotics were more likely to be prescribed to patients in respite compared to continuing care (RR=1.15 95% CI 1.04-1.27) and to patients in high care compared to low care (RR=1.10 95% CI 1.07-1.13) (Table 5.2).

5.2.5 Discussion

In this study we have found that characteristics such as gender, concomitant prescribing and prior hospitalisations are unevenly distributed between new users of atypical and typical antipsychotics. Atypical antipsychotics were less likely to be dispensed to patients with pre-existing comorbidity and those with prior dispensings of morphine but were more likely to be dispensed to women and patients with prior dispensings of lipids lowering therapy or anticholinergic medicines. Atypical antipsychotics were also less likely to be dispensed to patients previously hospitalised for myocardial infarction or pneumonia, indicating that typical antipsychotics may be selectively prescribed to patients with serious prior adverse events.

Our results are similar to those of other studies conducted in the US and Canada,[51] [53] which also identified potentially important differences in the characteristics of patients between the classes. The consequence of this selective prescribing in these studies appeared to be an overestimate of the risk of death associated with typical compared to atypical antipsychotics. Unadjusted relative mortality risk estimates suggested a 50% increased risk of death with typical antipsychotics compared to atypical antipsychotics while adjusted estimates ranged from 32% to 37%.[51] [53]

The DVA computerised claims database does not contain information on other possible clinical confounders such as frailty, disease severity and lifestyle factors including smoking and alcohol consumption. While adjustments for measured confounders can be made in conventional statistical models, unmeasured confounders will only be accounted for to the extent that they are correlated with those that are measured.[27] Many methods are currently being developed to control for unmeasured confounding. These include novel study designs, such as the self-controlled case-series design[28] and prescription sequence event analysis.[131] Additionally, methods may be employed that utilise the information that can be measured in administrative claims data but in novel ways, such as the use of instrumental variables.[56 62] These studies have found an increased risk of between 4 and 7 extra deaths per 100 patients treated with typical antipsychotics instead of atypical antipsychotics after 6 months.[51 53] These estimates compare to conventional adjusted estimates of between 2 and 3 extra deaths per 100 patients treated for 6 months with typical compared to atypical antispychotics.[97 102 103] We have also performed an instrumental variable analysis in the DVA cohort.[132] We estimated that, among elderly patients resident in nursing home facilities, there would be an additional 10 deaths for every 100 patients treated with typical antipsychotics after one year.[132] [Chapter 6.2] No randomised controlled trial evidence comparing the risks between the classes was available to confirm these analyses, however, one study found that haloperidol was associated with 2 extra death per 100 patients treated compared to risperidone within 12 weeks,[3] which if extrapolated to 6 months and one year gives similar estimates to instrumental variable analyses. These results suggest that an understanding of the determinants of prescribing is essential when conducting observational studies in computerised claims databases and

appropriate study designs are required to exclude the possibility of unmeasured confounding.

One of the limitations of this study is our inability to determine the indication for antipsychotics use. We limited our study to those veterans aged over 65 years for whom the majority of prescribing is likely to be for dementia, however, it is possible that some use in this population is for other indications. The variables examined in this study are limited to those that were available in the DVA data source and were similar to those that have been used by previous researchers.[51 53] Additionally, our study was performed in the Australian veteran population and our results may not be generalisable to other health care settings.

This study has identified that the profiles of patients receiving antipsychotic medicines vary between the class of antipsychotic initiated and those variables that differ between exposure groups are likely to be associated with the reported adverse events of these medicines. The differences in measured characteristics between atypical and typical antipsychotic initiators indicate that there is potential for confounding to be present in observational studies. Future pharmacoepidemiogical research in Australia, investigating the potential adverse events of antipsychotics, should consider the variables identified in this study to control for confounding.

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

	All Patients					Residential Aged Care				
	Typical (n=9239)		Atypical (n=10966)		P-value	Typical (n=4582)		Atypical (n=4566)		P-value
	N	*%*	*N*	*%*		*N*	*%*	*N*	*%*	
Patient Characteristics										
Age (mean, SD)	83.7	5.2	83.7	5.1	0.79	85.2	5.0	84.8	4.9	<.0001
Male	6646	60.6%	5040	54.6%	<.0001	2376	52.0%	2276	49.7%	0.02
Veteran	6819	62.2%	5235	56.7%	<.0001	2453	53.7%	2386	52.1%	0.11
RxRisk (mean, SD)	5.4	3	4.9	2.8	<.0001	4.8	2.9	4.6	2.7	<.0001
Vietnam Conflict	162	1.5%	126	1.4%	0.49	22	0.5%	28	0.6%	0.43
Residential Aged Care	4566	41.6%	4582	49.6%	<.0001					
Care Type (respite)						119	2.6%	148	3.2%	0.09
Care Level (high)						3686	80.7%	3794	82.8%	0.01
Doctor Characteristics										
Usual Doctor	5161	47.1%	5067	54.8%	<.0001	2600	56.9%	2717	59.3%	0.02
Medications Last 12 months										
>=5 Unique Medicines	10318	94.1%	8514	92.2%	<.0001	4256	93.2%	4209	91.9%	0.02
Anticholinesterase	1180	10.8%	1550	16.8%	<.0001	592	13.0%	720	15.7%	<.001
Antidepressants	4496	41.0%	4448	48.1%	<.0001	1998	43.8%	2170	47.4%	<.001
Antiepileptic	1048	9.6%	929	10.1%	0.24	441	9.7%	502	11.0%	0.05
Antiparkinsons	484	4.4%	759	8.2%	<.0001	258	5.7%	389	8.5%	<.0001
Asprin	3506	32.0%	2972	32.2%	0.77	1458	31.9%	1510	33.0%	0.30
Bisphosphonates	1380	12.6%	1215	13.2%	0.24	574	12.6%	619	13.5%	0.19
ACE/A2RB	4920	44.9%	4081	44.2%	0.32	1911	41.9%	1866	40.7%	0.27

	All Patients					Residential Aged Care				
	Typical (n=9239)		**Atypical** (n=10966)		**P-value**	**Typical** (n=4582)		**Atypical** (n=4566)		**P-value**
	N	***%***	***N***	***%***		***N***	***%***	***N***	***%***	
Antihypertensive	528	4.8%	333	3.6%	<.0001	175	3.8%	119	2.6%	<.001
Beta Blocking Agents	2751	25.1%	2201	23.8%	0.04	976	21.4%	980	21.4%	0.99
Cardiac	3804	34.7%	2798	30.3%	<.0001	1523	33.4%	1345	29.4%	<.0001
Calcium Channel Blockers	2717	24.8%	2086	22.6%	<.001	896	19.6%	867	18.9%	0.39
Diuretics	4219	38.5%	3075	33.3%	<.0001	1787	39.1%	1595	34.8%	.
Lipids	2897	26.4%	2496	27.0%	0.34	872	19.1%	956	20.9%	0.04
Vasoprotectives	297	2.7%	190	2.1%	0.001	95	2.1%	67	1.5%	0.01
Diabetes	1254	11.4%	908	9.8%	<.001	513	11.2%	466	10.2%	0.09
HRT	290	2.6%	284	3.1%	0.08	102	2.2%	115	2.5%	0.40
Inhaled corticosteroids	2145	19.6%	1586	17.2%	<.0001	723	15.8%	709	15.5%	0.63
Morphine	1687	15.4%	499	5.4%	<.0001	636	13.9%	312	6.8%	<.0001
Oral NSAIDs	3519	32.1%	2606	28.2%	<.0001	1195	26.2%	1108	24.2%	0.03
Oral corticosteroids	1603	14.6%	811	8.8%	<.0001	469	10.3%	365	8.0%	<.0001
Sedative Hypnotics	4033	36.8%	3202	34.7%	0.002	1731	37.9%	1685	36.8%	0.26
Warfarin	1222	11.1%	865	9.4%	<.0001	427	9.4%	366	8.0%	0.02
Hospitalisation in last 12 months										
Chronic Heart Failure	434	4.0%	273	3.0%	<.0001	174	3.8%	151	3.3%	0.17
Dementia	433	3.9%	461	5.0%	<.001	224	4.9%	276	6.0%	0.02
Hip/femur Fracture	417	3.8%	324	3.5%	0.25	255	5.6%	239	5.2%	0.43
Myocardial Infarction	217	2.0%	126	1.4%	<.001	82	1.8%	65	1.4%	0.13
Pneumonia	537	4.9%	292	3.2%	<.0001	232	5.1%	172	3.8%	<.001
Stroke	482	4.4%	362	3.9%	0.08	230	5.0%	201	4.4%	0.13

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

	All Patients			Residential Aged Care		
	RR	***95% CI***	***P-value***	***RR***	***95% CI***	***P-value***
Patient Characteristics						
Age				1.00	(0.99- 1.00)	0.01
Male	0.91	(0.89- 0.94)	<.0001	0.92	(0.89- 0.94)	<.0001
RxRisk (mean, SD)	0.95	(0.94- 0.97)	<.0001			
Residential Aged Care (6 months)	1.08	(1.05- 1.12)	<.0001			
RAC Characteristics						
Care Type (respite)				1.15	(1.04- 1.27)	0.01
Care Level (high)				1.10	(1.07- 1.13)	<.0001
Doctor Characteristics						
Usual Doctor	1.12	(1.09- 1.16)	<.0001	1.13	(1.10- 1.16)	<.0001
Medications Last 12 months						
>=5 Unique Medicines	0.88	(0.83- 0.93)	<.0001	0.88	(0.83- 0.93)	<.0001
Antihypertensives				0.91	(0.84- 0.99)	0.03
Cardiac				0.96	(0.93- 0.99)	0.01
Diuretic				0.96	(0.93- 1.00)	0.03
Anticholinesterase	1.19	(1.15- 1.23)	<.0001	1.17	(1.13- 1.21)	<.0001
Antidepressants	1.18	(1.15- 1.22)	<.0001	1.15	(1.12- 1.19)	<.0001
Antiparkinsons	1.30	(1.25- 1.36)	<.0001	1.28	(1.22- 1.33)	<.0001
Lipids	1.09	(1.05- 1.13)	<.0001	1.05	(1.01- 1.08)	0.01
Bisphosphonates				1.06	(1.02- 1.10)	0.01
Morphine	0.53	(0.49- 0.57)	<.0001	0.51	(0.47- 0.56)	<.0001
Oral corticosteroids	0.86	(0.81- 0.91)	<.0001	0.83	(0.79- 0.88)	<.0001
Oral NSAIDs				0.96	(0.93- 0.99)	0.02
Hospitalisation in last 12 months						
Myocardial Infarction	0.86	(0.75- 0.98)	0.03	0.86	(0.75- 0.99)	0.03
Pneumonia	0.85	(0.77- 0.93)	<0.001	0.85	(0.77- 0.93)	<0.001

5.3 Additional Discussion

In the previous paper we identified that confounding is likely to be present in the assessment of the risks of antipsychotics as patient characteristics that are likely to be related to documented adverse outcomes of antipsychotics are disproportionally distributed amongst exposure groups.[133] The association between characteristics, such as increased comorbidity and prior dispensing of morphine, and an outcome such as death is plausible and therefore there is the potential for confounding when comparing outcomes associated with these medicines. Confounding is also likely when assessing the risk of outcomes such as pneumonia as we found that prior pneumonia is a predictor of antipsychotic class prescribed and the strength of this association changed over time.

Other studies have found similar results[51 53]. These studies found that typical antipsychotic initiators were more likely to be male, to have chronic heart failure, other ischemic heart disease and cardiovascular disease[51 53]. Utilisation of other medicines and health care services, however, differed between the previous studies and the study presented in this chapter. This suggests that some variation in prescribing is likely due to underlying differences in the health care settings under study.

In the following Chapter I investigate the comparative risk of death between the antipsychotic classes, both by adjusting the conventional statistical analysis using the measured confounders identified in the study presented in this chapter and by investigating the use of the instrumental variable analysis to further adjust for possible unmeasured confounders.

6 Antipsychotics and the risk of death in the elderly: An instrumental variable analysis using two preference based instruments

6.1 Preface

In Chapter 5, I identified that patients who received typical antipsychotics differed from those who received atypical antipsychotics. Patients treated with typical antipsychotics were generally sicker, had more comorbidity, were more likely to be on morphine and more likely to be male, which are all potential risk factors for death. Typical antipsychotics were also selectively prescribed to patients with prior hospitalisations for myocardial infarction and pneumonia. These variables are likely to be related to potential adverse events of treatment and suggest that confounding will be present when comparing the risks between the antipsychotic classes.

While we are able to adjust for measured confounders in observational studies, such as those identified in the study presented in Chapter 5, unmeasured confounders will only be accounted for to the extent that they are correlated with those that are measured.[27] Observational study designs employing numerical adjustment for measured confounders may be subject to residual confounding. Instrumental variables analysis has been suggested as a possible alternative to traditional observational studies comparing the risk of outcomes between two classes of medicines when there is concern about the effects of unmeasured confounding. An instrumental variable analysis exploits the existence of another variable that is available in the data set that may be used as a proxy for actual treatment received. This variable should be unrelated to

factors that influence prescribing and should produce a treatment effect estimate less prone to bias. The ability of the instrumental variable analysis to adjust for unmeasured confounding, however, is reliant on the availability of an instrument and its validity; that is, how well it meets the assumptions of the method.

Instrumental variable analyses are useful for studying the comparative effectiveness and safety of medicines, however, their application may be sensitive to violations of assumptions and not all valid instruments may be valid in all situations. In the following study, I show how the choice of instrument is critical in the interpretation and generalisability of instrumental variable analyses, by utilising two different instruments in the comparison of the risk of death between typical and atypical antipsychotics. I show that while instruments may appear to be valid in one population, these instruments may not be directly translatable to the Australian environment, particularly when the underlying market conditions of the medicines change dramatically over the study period.

The comparison of the risk of death between the typical and atypical antipsychotic medicines was chosen as a case study for the use of instrumental variable analyses as there are randomised controlled trial data available from which to benchmark our results and other similar instrumental variable analyses have been performed in other populations[51 53] to allow comparison between studies. This information about the validity of instruments using examples where we have the ability to compare results to RCT evidence will inform about how these instruments may be applied to other outcomes of these medicines, such as hip fracture and pneumonia, for which no RCT evidence exists (Chapter 8).

6.2 Antipsychotics and the risk of death in the elderly: An instrumental variable analysis using two preference based instruments

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STATEMENT OF AUTHORSHIP

Nicole Pratt (Candidate)

Corresponding author, designed the study, extracted the data, performed all the analyses, interpreted data, drafted the manuscript.

Signed……..Date……

Libby Roughead

Contributed to the design and interpretation of the study, and reviewed the manuscript. I give consent for Nicole Pratt to present this paper for examination towards the Doctor of Philosophy.

Signed……..Date……

Amy Salter

Contributed to the design and interpretation of the study, and reviewed the manuscript. I give consent for Nicole Pratt to present this paper for examination towards the Doctor of Philosophy.

Signed……..Date……

Philip Ryan

Contributed to the design and interpretation of the study, and reviewed the manuscript. I give consent for Nicole Pratt to present this paper for examination towards the Doctor of Philosophy.

Signed……..Date……

ABSTRACT

Purpose: Observational studies have investigated the comparative safety of antipsychotics with varying results. Instrumental variable analysis has been suggested as a possible alternative to conventional analyses when there is concern about the effect of unmeasured confounding in observational studies. Using the example of the risk of death with typical compared to atypical antipsychotics, we aimed to explore the performance of two different instruments. We used the doctor prescribing preference instrument, which has been used in previous studies, to investigate further the assumptions of this instrument in the Australian population. We also propose an alternative instrument, nursing home facility preference.

Methods: With the Australian Department of Veterans' Affairs administrative claims database, we used an instrumental variable analysis to compare the risk of death after 12 months between the two antipsychotic classes.

Results: Using the doctor prescribing preference instrument we estimated 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. Facility prescribing preference was a stronger instrument (OR=19.2 95% CI 17.1-21.6) and provided a better balance of covariates than doctor prescribing preference.

Conclusions: Our study has shown that valid instruments in one population may not be directly applicable to other health care settings and testing of assumptions is crucial when performing instrumental variable analyses. Facility prescribing preference appears to be a potentially valid instrument for further work in this area.

6.2.1 Introduction

Antipsychotics are frequently prescribed to treat the behavioural symptoms of dementia[130] despite their limited efficacy[2 86] and effectiveness[91]. There are questions concerning the potential risks of antipsychotics as they have been associated with death[92 96 97 134] and morbidity including stroke,[2] hip fracture[107 115 116 118] and pneumonia.[120 121]

Antipsychotics are available in two broad classes, typical and atypical antipsychotics. Randomised controlled trial (RCT) evidence suggests that atypical antipsychotics are associated with an increased risk of death in elderly patients with dementia.[92 96] One study estimated one extra death for every 100 people treated for 12 weeks with atypical antipsychotics compared to placebo,[92] while another estimated seven extra deaths for every 100 people treated for 12 months.[96] RCT evidence for typical antipsychotics is limited, however, one study suggests that there may be two extra deaths for every 100 people treated with haloperidol compared to placebo after 12 weeks.[92]

Observational cohort studies have found an increased risk of death with typical antipsychotics compared to atypical antipsychotics,[51 53 97 102 103 134] however, risk estimates vary. Hazard ratios range from 1.2 to 2.7,[51 53 97 102 103 134] while risk difference estimates range from 2 up to 7 extra deaths per 100 patients after 6 months.[51 53 97 134] These discrepancies may be due to confounding as studies have shown that differences exist in the characteristics of patients who receive atypical compared to typical antipsychotics[51 53] and these characteristics are likely to be associated with death. While observational studies are able to adjust for measured confounders using conventional

adjustment techniques, unmeasured confounders will only be accounted for to the extent that they are correlated with those that are measured[27] and failure to adjust for unmeasured confounding is likely to bias comparative safety studies of antipsychotics.

The use of instrumental variables has been suggested as a possible alternative to conventional analyses when there is concern about the effect of unmeasured confounding.[47 56] Instrumental variable (IV) analysis attempts to mimic the process of randomisation in an RCT by exploiting the existence of another variable (the instrument) which can be measured in the available data, which is highly correlated with the probability of exposure but unrelated to the outcome of interest except through its association with treatment.[46] The instrument is similar to random arm assignment in that it should distribute both measured and unmeasured patient characteristics evenly between exposure groups resulting in an estimate less affected by confounding.

In practice, instruments may be difficult to find and many of the assumptions of the method are not testable explicitly.[65] Two observational studies of death with antipsychotics employed the IV technique using a measure of doctor prescribing preference as the instrument[51 53] finding a significantly increased risk with typical antipsychotics. A subsequent study[64] investigated various definitions of doctor prescribing preference and found that the choice and validity of the instrument is crucial to the interpretability of the results of IV analyses.

In this study, we investigate the applicability of the doctor prescribing preference instrument in the Australian population. We also explore the use of an alternative instrument, nursing home facility prescribing preference which may be a potentially valid instrument as a study[135] found that among nursing home residents, doctors choice of antipsychotic appeared to depend more upon facility factors and economic forces

rather than patient characteristics[135] and therefore, may be unrelated to the risk of death in these patients.

6.2.2 Objective

Using the example of the risk of death with typical compared to atypical antipsychotics in elderly veterans, we aimed to investigate the performance of two different instruments: doctor prescribing preference and nursing home facility preference.

6.2.3 Methods

The source of data for this study was an administrative claims database maintained by the Department of Veterans‟ Affairs (DVA). This dataset includes all claims data processed by DVA including medicines dispensed under the Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS), hospital admissions and medical and allied health visits. The treatment population has approximately 310,000 live members with a median age of 80 years. The DVA maintains a client file, which includes data on sex, date of birth, date of death and family status. Medicines are coded according to the World Health Organization anatomical and therapeutic chemical (ATC) classification[75] and the Schedule of Pharmaceutical Benefits item codes.[76] Hospitalisations are coded according to the WHO International classification of diseases, 10th revision, Australian modification (ICD-10).[78]

Conventional Cohort Analysis

A cohort of all incident users of antipsychotics between 1st January 2003 and 31st December 2006 was selected and the risk of death within 12 months was compared between typical and atypical antipsychotic initiators. Typical antipsychotics included chlorpromazine, trifluoperazine, periciazine, thioridazine, haloperidol, ziprasidone. Atypical antipsychotics included clozapine, olanzapine, quetiapine, amisulpride, risperidone, aripiprazole. The incident antipsychotic script was determined as the first script dispensed to a patient within the study period. Patients were included if they had no other antipsychotic script dispensed in the previous 12 months, had been full entitlement card holders for at least 12 months and were aged over 65 years at study entry (1st January 2003).

Risk differences were calculated for the risk of death within 12 months using linear regression models with robust variance to account for clustering within doctors.[136] We controlled for the following patient characteristics: age, gender, residential aged care status, dispensing of morphine, anti-epilepsy medicines, inhaled corticosteroids, oral corticosteroids, oral non-steroidal anti-inflammatory drugs (NSAIDs), sedative hypnotics, cardiac medicines, lipid-lowering therapy, calcium channel blockers, anticholinsesterases, antidepressants and medications for diabetes. Hospitalisations for the primary diagnoses of stroke (ICD-10 codes; I60-I64), hip fracture (ICD-10 codes; S720, S721), pneumonia (ICD-10 codes; J12-J18), myocardial infarction (ICD-10 code; I21) and chronic heart failure (ICD-10 codes; I500, I5001-I509) occurring in the 12 months prior to the index date, were also included in the adjusted models. These hospitalisations have been identified in the literature as having possible associations with antipsychotics.[2 107 115 116 118 120 121] In the subset analysis of patient‟s resident in nursing home facilities we also adjusted for care type: high or low care, and admission

type: continuing or respite. All analyses were adjusted for individual covariates (Covariate Adjusted models). We also calculated, for each individual, a propensity score,[15] that is, the predicted probability of the use of atypical compared to typical antipsychotics given the measured covariates at the time of the prescription. All covariates were included in the propensity score model if they were predictive of death, regardless of their association with exposure.[25] All analyses were then adjusted by quintiles of the propensity score (Propensity Score Adjusted models). All analyses were performed using SAS version 9.12 (SAS Institute, Cary, NC).

Instrumental Variable Analysis

For the instrumental variable analysis[47 56] we used a 2-stage least squares regression model to estimate the mortality risk differences over one year between typical and atypical antipsychotics. For the full cohort we used a measure of doctor prescribing preference for atypical or typical antipsychotics as the instrument.[51 53 61 63] Doctor preference (IV1) was calculated as the most recent new prescription written for an antipsychotic medicine for another of the prescribing doctors‟ patients. For the subset of patients resident in nursing home facilities we used the facilities‟ preference (IV2) for atypical or typical antipsychotics as the instrument. Facility preference was calculated as the antipsychotic prescribed most frequently to other initiated patients over a 12 month period in the same nursing home.

We tested the strength and performance of each of the instruments by investigating the following assumptions: 1) the instrument should be associated with treatment; 2) be unrelated to patient characteristics; and 3) be related to the outcome only through its association with treatment.[46]

To measure the strength of each instrument we calculated the percentage of patients whose actual treatment prescribed was correctly predicted by the instrument using a logistic regression model. The resulting odds ratios and c-statistics were calculated to test the association of the instrument with actual treatment.

To test the assumption that the instruments were unrelated to patient characteristics we compared the distribution of patient-specific covariates between the typical and atypical antipsychotics based on actual treatment received and between levels of the instruments.

The assumption that the instrument be related to the outcome only through its association with treatment is not directly testable. As a proxy, we determined whether other factors that may be associated with death, such as doctor or facility characteristics, differed over levels of the instrument. For the overall analysis we determined whether type of care, as measured by whether the prescribing doctor was the patient‟s usual doctor, was related to the doctor‟s antipsychotic preference. For patients resident in aged care facilities we determined whether level of care; high or low care, or admission type; continuing or respite, was related to the facility‟s antipsychotic preference.

6.2.4 Results

Demographic characteristics of the cohorts are presented in Table 6.1. There were 9,312 patients initiated on typical antipsychotics and 7,227 patients initiated on atypical antipsychotics in the full cohort. Of these, 46.8% and 29.5% of patient‟s first prescribed typical and atypical antipsychotic respectively had died within 12 months of initiation. Haloperidol was the most frequently prescribed typical antipsychotic (74%

haloperidol, 14% periciazine and 12% other typical antipsychotics). Risperidone and olanzapine accounted for the majority of all atypical antipsychotic dispensing (49% risperidone, 41% olanzapine and 10% other atypical antipsychotics). In the subset of patients resident in nursing home facilities, 3,805 patients were initiated on typical antipsychotics and 3,506 patients were initiated on atypical antipsychotics.

Conventional Analysis

In the conventional analysis (Covariate Adjusted model) the risk of death was significantly increased with typical antipsychotics compared to atypical antipsychotics (Table 6.2). This indicates that for every 100 patients treated with typical antipsychotics we would expect 10.6 extra deaths (95% CI 9.2-12.1) than if they were treated with atypical antipsychotics for 12 months. Propensity score adjusted models produced similar results (Table 6.2). When restricted to patients in nursing home facilities, typical antipsychotics were associated with an extra 9 deaths per 100 patients per year (95% CI 6-11) compared to atypical antipsychotics (Table 6.2).

Instrumental Variable Analysis

An instrumental variable analysis in the full cohort (Covariate Adjusted model), using doctor preference as the instrument, estimated that typical antipsychotics increased the risk of death by 23.8 per 100 patients per year (95% CI 17.6-30.0) compared to atypical antipsychotics (Table 6.2). The risk difference estimated by the propensity score adjusted IV model was smaller with an estimated 20.5 extra deaths per 100 patients per year treated with typical compared to atypical antipsychotics (Table 6.2). In the subset of patients resident in nursing home facilities and using facility

preference as the instrument, there were 10.1 extra deaths per 100 patients per year (95% CI 6.6-13.7) treated with typical compared to atypical antipsychotics (Table 6.2). Propensity Score Adjusted models produced similar results (Table 6.2).

Comparison of the Instruments: Instrument Strength

Facility preference showed a stronger correlation with the actual treatment prescribed (Odds Ratio (OR) = 19.2; 95% CI 17.1-21.6, C-statistic 81%) than doctor preference (OR = 3.5; 95% CI 3.2-3.8, C-statistic 65%) (Table 6.3). While both preference instruments were highly associated with the actual treatment received; the facility preference instrument has a higher proportion correctly predicted overall and shows greater consistency over the study period than the doctor preference instrument (Table 6.3).

Comparison of the Instruments: Covariate Balance

Table 6.4 presents the difference in the prevalence of each measured covariate between patients‟ dispensed typical and atypical antispychotics in the full cohort and between patients prescribed antipsychotics by doctors who prefer typical antipsychotics compared to those doctors who preferred atypical antipsychotics. Positive values indicate a higher prevalence of that characteristic in patients dispensed typical antipsychotics, while negative values indicate a lower prevalence. Values further from zero indicate a greater difference in the prevalence of that characteristic between the classes. Table 6.5 shows the difference in the prevalence of each measured covariate for patient‟s resident in nursing home facilities based on actual treatment dispensed and nursing home preference. While both preference instruments appear to balance out the

patient characteristics, the instrument based on facility preference produced more comparable groups than did the instrument based on doctor preference.

Comparison of the Instruments: relationship with outcome

To test the assumption that the instrument is unrelated to the risk of death we determined whether other doctor or facility characteristics, that may influence mortality, were associated with antipsychotic preference. In the full cohort, we found that doctors who last prescribed atypical antipsychotics were more likely to be the patient‟s usual doctor (Table 6.4). In the subset of patients resident in nursing home facilities we found that the facility preference was associated with level of care but not admission type (Table 6.5).

6.2.5 Discussion

In this study we have explored the use of two preference-based instruments. We used doctor prescribing preference, which has been used in previous studies[51 53] comparing the risk of death between the classes, to investigate further the assumptions of this instrument in the Australian population. We also investigated the use of a new instrument, nursing home facility preference. Facility preference appears to be a valid instrument as it is both highly correlated with actual treatment, provides good balance of measured patient characteristics and is consistently strong over the entire study period. Doctor prescribing preference, however, was a weaker instrument and more variable over time. The atypical antipsychotic, risperidone, was introduced onto the Australian market in 2005 and our results show that the proportion of patients who

received atypical antipsychotics by doctors who last prescribed an atypical antipsychotic increased over the study period. This variability over time lead to a weaker instrument overall and suggests that this instrument may not be good surrogate for „preference" particularly in the presence of strong changes in the markets of the two opposing therapies.

We found that while the overall interpretation of the IV analyses did not differ to the conventional cohort analysis, there were differences in the validity of the instruments used and therefore, in the magnitude of the estimates of risk. Using the doctor prescribing preference instrument, we estimated that there would be 24 additional deaths within 12 months with typical compared to atypical antipsychotics. Using the nursing home facility preference instrument we estimated that there would be an additional 10 deaths for every 100 patients treated with typical antipsychotics. These latter results are similar to other comparative safety studies[51 53] of antipsychotics that also used an IV approach but higher than another study that used a conventional cohort approach.[97] This is most likely due to the methodology as the instrumental variable analysis helps to account for unmeasured confounding. The excess deaths in our study obtained using the doctor prescribing preference instrument, however, are likely to be an overestimate of the true risk difference as a consequence of a applying a weaker instrument. Additionally, the IV estimate based on doctor preference has a much wider confidence interval compared to the IV estimate based on facility preference. This effect was also seen in a simulation study[66] that found that the use of a weak doctor preference instrument resulted in larger variance estimates, outweighing the benefit of the bias reduction.

The ability of our preference instruments to balance measured characteristics also differed. Many of the patient characteristics were more evenly distributed over the levels of both instruments, however, fewer covariates were significantly associated with facility preference. This suggests that our IV analysis may not have completely eliminated residual confounding, however, because we also adjusted our analysis by measured covariates this bias would be minimised.

We were not able to directly test the assumption that our instruments were unrelated to the risk of death, however, we did examine whether other doctor or facility characteristics that may influence mortality were associated with antipsychotic preference. Doctor preference was associated with the prescribing doctor being the patients‟ usual doctor, indicating that doctors who last prescribed atypical antipsychotics were more likely to be the current patients‟ usual doctor. If being prescribed antipsychotics by your usual doctor also meant that the patient was under better care and at lower risk of death, then the estimate of risk difference may be biased away from the null. Alternatively, if being prescribed antipsychotics by your usual doctor meant you were under less appropriate care and at higher risk of death then the estimate of risk difference may be biased towards the null. Facility preference was associated with level of care, indicating that facilities that most often prescribed atypical antipsychotics were more likely to be high care facilities. If being in high care facilities is associated with an increased risk of death then the estimate of risk difference may be biased towards the null.

One of the limitations of this study is our inability to control for possible clinical confounders such as frailty, disease severity and lifestyle factors, such as smoking and alcohol consumption. The utilisation of an appropriate instrument should help to

account for any bias caused by this omission and a previous study[137] suggests that failure to adjust for these factors would result in an underestimate of the difference in risk of death between typical and atypical antispychotics, hence a bias towards the null in our study. Another limitation of our study is that all typical and atypical antipsychotics were analysed together and all medicines in these broad classes may not all have the same risk of death. While the reasons why typical antipsychotics may be associated with an increased risk of death over atypical antipsychotics remains unclear, a study[138] found that patients initiated on typical antipsychotics were more likely than those initiated on atypical antipsychotics to have a higher risk of death due to cardiovascular, infectious (including pneumonia) and respiratory causes. Additionally, we have examined all cause mortality and the utility of the IV analysis may be different for specific causes of death. Finally, our study was performed in the Australian health care setting and our results may not be generalisable to other health care settings and the applicability of the nursing home preference instrument in this situation is unknown.

Despite these limitations, this study adds to the growing body of evidence that suggests that typical antipsychotics are no safer than the atypical antipsychotics, however, it is important to note that atypical antipsychotics are not risk free. A meta-analysis [92] has identified that for every 100 patients treated with atypical antipsychotics for 12 weeks there would be 1 death that may not have otherwise occurred over the same period. The number needed to treat to show clinical benefit with atypical antipsychotics ranged from 3 to 13 patients over a 12 week period [3 89-91 126-128]. This suggests that there will be 1 death for every 8 to 33 person helped with these medicines.

Observational studies investigating the comparative safety of antipsychotics are important as there are few „head-to-head" RCTs in the elderly, however, observational

studies are often criticised due to their potential for bias due to unmeasured confounding.[14] IV analysis may be a useful approach for observational studies where there is concern about the effects of unmeasured confounding, however, instruments are hard to find and the assumptions are difficult to check. Our study has shown that valid instruments in one population may not be directly applicable to other health care settings and testing of assumptions is crucial when performing IV analyses. Facility prescribing preference appears to be a potentially valid instrument for further work in this area.

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

	All Patients	
	Typical Antipsychotics (n = 9,312)	***Atypical Antipsychotics (n = 7,227)***
Age (median (range))	83 (80-87)	83 (80-87)
Male (N (%))	5665 (60.8)	3990 (55.2)
Nursing Home resident (N (%))	3805 (40.9)	3506 (48.5)
Deaths within 12 months (N (%))	4354 (46.8)	2132 (29.5)
	Nursing Home Residents	
	Typical Antipsychotics (n = 3,805)	***Atypical Antipsychotics (n = 3,506)***
Age (median (range))	85 (82-89)	85 (81-88)
Male (N (%))	1982 (52.1)	1759 (50.2)
Deaths within 12 months (N (%))	1916 (50.4)	1311 (37.4)

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

	All Patients	
	Estimate	***95 % CI***
Unadjusted RD	17.3	(15.8, 18.7)
Covariate Adjusted RD	10.6	(9.2, 12.1)
PS Adjusted RD	11.5	(10.0, 13.0)
Doctor Preference Instrument		
Covariate Adjusted IV RD	23.8	(17.6, 30.0)
PS Adjusted IV RD	20.5	(13.7, 27.2)
	Nursing Home Residents	
	Estimate	***95% CI***
Unadjusted RD	13.0	(10.7, 15.3)
Covariate Adjusted RD	8.5	(6.2, 10.7)
PS Adjusted RD	9.1	(6.9, 11.4)
Facility Preference Instrument		
Covariate Adjusted IV RD	10.1	(6.6, 13.7)
PS Adjusted IV RD	10.5	(6.9, 14.2)

PS: Propensity Score, HR: Hazard Rate, RD: Risk Difference, IV:Instrumental Variable

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

% actual treatment predicted by the instrument							
	Year						
Instrument	***2003***	***2004***	***2005***	***2006***	***Overall***	***OR (95% CI)***	***C-statistic***
Doctor Preference							
Typical	76.1	75.4	62.8	59.4	68.9	3.5 (3.2-3.8)	65%
Atypical	58.0	55.9	61.0	70.3	61.1	1.0	
Facility Preference							
Typical	85.5	86.0	83.4	74.2	83.9	19.2 (17.1-21.6)	81%
Atypical	77.8	78.8	77.8	81.5	78.7	1.0	

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**

	Actual Treatment			Doctor Preference		
	Prevalence Difference ***(Typical-Atypical)***	***95% CI***	***P-value***	***Prevalence Difference*** ***(Typical-Atypical)***	***95% CI***	***P-value***
Patient Characteristics						
Age (>85)	-0.3%	(-1.8, 1.1)	0.66	-0.6%	(-2.5, 1.3)	0.55
Male	5.6%	(4.1, 7.2)	<0.01	1.1%	(-0.9, 3.1)	0.30
Veteran	5.1%	(3.6, 6.6)	<0.01	0.8%	(-1.2, 2.8)	0.42
Vietnam Conflict	0.2%	(-0.1, 0.6)	0.23	-0.2%	(-0.6, 0.3)	0.52
Nursing Home resident (6 months)	-7.7%	(-9.2, -6.1)	<0.01	-6.3%	(-8.4, -4.3)	<0.01
Antipsychotic prescribed by patients‟ usual Doctor	-9.4%	(-11.1, -7.7)	<0.01	-7.0%	(-9.2, -4.8)	<0.01
Prior Medicines in last 12 months						
>=5 Unique Medicines	0.9%	(0.3, 1.6)	0.01	0.3%	(-0.5, 1.2)	0.43
ACE/A2RB C09	-0.0%	(-1.5, 1.5)	1.00	1.6%	(-0.4, 3.7)	0.12
Anticholinesterase	-6.1%	(-7.2, -5.0)	<0.01	-4.0%	(-5.4, -2.5)	<0.01
Antidepressants	-7.9%	(-9.4, -6.4)	<0.01	-3.2%	(-5.2, -1.2)	<0.01
Antiepileptic	-0.5%	(-1.4, 0.4)	0.29	-0.1%	(-1.4, 1.1)	0.83
Antihypertensive	0.9%	(0.3, 1.6)	<0.01	0.2%	(-0.6, 1.0)	0.55

	Actual Treatment			Doctor Preference		
	Prevalence Difference ***(Typical-Atypical)***	***95% CI***	***P-value***	***Prevalence Difference*** ***(Typical-Atypical)***	***95% CI***	***P-value***
Antiparkinsons	-4.1%	(-4.8, -3.3)	<0.01	-2.0%	(-3.0, -1.1)	<0.01
Asprin	-0.9%	(-2.3, 0.5)	0.23	-0.8%	(-2.7, 1.1)	0.39
Beta Blocking Agents	1.2%	(-0.2, 2.5)	0.08	2.1%	(0.4, 3.9)	0.02
Bisphosphonates	-0.5%	(-1.5, 0.6)	0.37	-1.2%	(-2.6, 0.2)	0.08
Calcium Channel Blockers	1.7%	(0.4, 3.0)	0.01	0.6%	(-1.2, 2.3)	0.53
Cardiac	4.0%	(2.5, 5.4)	<0.01	4.7%	(2.8, 6.6)	<0.01
Diabetes	1.2%	(0.2, 2.2)	0.02	0.7%	(-0.5, 2.0)	0.26
Diuretics	4.6%	(3.1, 6.1)	<0.01	2.9%	(1.0, 4.8)	<0.01
HRT	-0.6%	(-1.2, -0.1)	0.02	-0.3%	(-0.9, 0.3)	0.38
Inhaled corticosteroids	2.5%	(1.3, 3.7)	<0.01	1.0%	(-0.5, 2.6)	0.19
Lipids	-0.8%	(-2.1, 0.6)	0.27	-1.5%	(-3.2, 0.3)	0.11
Morphine	10.1%	(9.2, 11.1)	<0.01	4.3%	(3.0, 5.6)	<0.01
Oral NSAIDs	3.1%	(1.7, 4.5)	<0.01	1.4%	(-0.5, 3.3)	0.14
Oral corticosteroids	5.7%	(4.7, 6.6)	<0.01	3.9%	(2.6, 5.3)	<0.01
Sedative Hypnotics	1.3%	(-0.2, 2.7)	0.09	1.5%	(-0.5, 3.4)	0.13
Vasoprotectives	0.5%	(0.1, 1.0)	0.02	0.1%	(-0.5, 0.8)	0.71
Warfarin	1.4%	(0.5, 2.4)	<0.01	1.5%	(0.2, 2.7)	0.02

	Actual Treatment			Doctor Preference		
	Prevalence Difference ***(Typical-Atypical)***	***95% CI***	***P-value***	***Prevalence Difference*** ***(Typical-Atypical)***	***95% CI***	***P-value***
Prior Hospitalisations last 12 month						
Chronic Heart Failure	1.0%	(0.5, 1.6)	<0.01	0.8%	(0.1, 1.5)	0.04
Dementia	-1.0%	(-1.7, -0.4)	<0.01	-0.9%	(-1.8, -0.1)	0.04
Hip/femur Fracture	0.3%	(-0.3, 0.9)	0.33	0.1%	(-0.6, 0.9)	0.74
Myocardial Infarction	0.7%	(0.3, 1.1)	<0.01	0.0%	(-0.5, 0.6)	0.90
Pneumonia	1.9%	(1.3, 2.5)	<0.01	0.9%	(0.1, 1.7)	0.02
Stroke	0.4%	(-0.2, 1.0)	0.22	0.2%	(-0.6, 1.1)	0.58

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**

	Actual Treatment			Nursing Home Preference		
	Prevalence Difference ***(Typical-Atypical)***	***95% CI***	***P-value***	***Prevalence Difference*** ***(Typical-Atypical)***	***95% CI***	***P-value***
Patient Characteristics						
Age (>85)	4.0%	(1.7, 6.2)	<0.01	2.5%	(0.2, 4.8)	0.03
Male	1.9%	(-0.4, 4.2)	0.10	1.2%	(-1.1, 3.5)	0.30
Veteran	1.1%	(-1.2, 3.4)	0.36	0.9%	(-1.4, 3.1)	0.46
Vietnam Conflict	-0.0%	(-0.4, 0.3)	0.80	-0.0%	(-0.4, 0.3)	0.82
Antipsychotic prescribed by patients‟ usual Doctor	-4.5%	(-6.9, -2.1)	<0.01	-2.9%	(-5.2, -0.5)	0.02
Nursing Home Characteristics						
Level of care (high/low)	-2.3%	(-4.2,0.5)	0.01	-3.0%	(-4.9,-1.1)	<0.01
Admission type (continuing/respite)	-0.3%	(-1.1,0.4)	0.42	0.3%	(-0.5,1.0)	0.46
Prior Medicines in last 12 months						
>=5 Unique Medicines	-0.1%	(-1.2, 0.9)	0.78	0.4%	(-0.6, 1.4)	0.46
ACE/A2RB C09	0.2%	(-2.0, 2.4)	0.87	-0.3%	(-2.6, 1.9)	0.78
Prior Medicines in last 12 months (continued)						

	Actual Treatment			Nursing Home Preference		
	Prevalence Difference ***(Typical-Atypical)***	***95% CI***	***P-value***	***Prevalence Difference*** ***(Typical-Atypical)***	***95% CI***	***P-value***
Anticholinesterase	-2.9%	(-4.6, -1.2)	<0.01	-2.6%	(-4.3, -0.9)	<0.01
Antidepressants	-4.4%	(-6.7, -2.1)	<0.01	-3.0%	(-5.3, -0.6)	0.01
Antiepileptic	-1.2%	(-2.6, 0.2)	0.10	-1.6%	(-3.1, -0.2)	0.02
Antihypertensive	1.0%	(0.2, 1.8)	0.02	1.4%	(0.5, 2.2)	<0.01
Antiparkinsons	-3.2%	(-4.4, -2.0)	<0.01	-0.8%	(-2.0, 0.4)	0.21
Asprin	-1.9%	(-4.0, 0.3)	0.08	-1.3%	(-3.5, 0.8)	0.23
Beta Blocking Agents	-0.4%	(-2.3, 1.5)	0.68	-0.1%	(-2.0, 1.7)	0.88
Bisphosphonates	-1.0%	(-2.5, 0.5)	0.18	-1.3%	(-2.8, 0.2)	0.10
Calcium Channel Blockers	0.2%	(-1.6, 2.0)	0.81	-0.0%	(-1.9, 1.8)	0.97
Cardiac	3.5%	(1.4, 5.6)	<0.01	2.2%	(0.0, 4.3)	0.05
Diabetes	0.6%	(-0.9, 2.1)	0.42	-0.1%	(-1.6, 1.4)	0.88
Diuretics	3.4%	(1.3, 5.6)	<0.01	1.1%	(-1.1, 3.3)	0.32
Hormone Replacement Therapy	-0.4%	(-1.1, 0.3)	0.31	-0.0%	(-0.7, 0.7)	0.94
Inhaled corticosteroids	0.2%	(-1.5, 1.9)	0.78	-0.1%	(-1.8, 1.5)	0.87
Lipids	-2.3%	(-4.1, -0.4)	0.02	-1.9%	(-3.8, -0.1)	0.04
Morphine	7.2%	(5.8, 8.6)	<0.01	4.9%	(3.5, 6.4)	<0.01
Oral NSAIDs	1.2%	(-0.8, 3.2)	0.25	1.8%	(-0.2, 3.9)	0.08
Oral corticosteroids	1.9%	(0.6, 3.2)	<0.01	1.0%	(-0.3, 2.4)	0.12
Prior Medicines in last 12 months (continued)						

	Actual Treatment			Nursing Home Preference		
	Prevalence Difference ***(Typical-Atypical)***	***95% CI***	***P-value***	***Prevalence Difference*** ***(Typical-Atypical)***	***95% CI***	***P-value***
Sedative Hypnotics	0.3%	(-1.9, 2.5)	0.81	0.6%	(-1.7, 2.8)	0.63
Vasoprotectives	0.5%	(-0.2, 1.1)	0.14	0.5%	(-0.1, 1.1)	0.12
Warfarin	0.8%	(-0.5, 2.1)	0.22	0.4%	(-1.0, 1.7)	0.57
Prior Hospitalisations in last 12 months						
Chronic Heart Failure	0.5%	(-0.3, 1.4)	0.24	0.0%	(-0.9, 0.9)	0.97
Dementia	-1.0%	(-2.0, 0.0)	0.06	-0.6%	(-1.7, 0.4)	0.22
Hip/femur Fracture	0.3%	(-0.7, 1.4)	0.51	1.1%	(0.1, 2.1)	0.04
Myocardial Infarction	0.5%	(-0.1, 1.1)	0.09	0.1%	(-0.5, 0.7)	0.78
Pneumonia	1.2%	(0.3, 2.1)	0.01	0.9%	(0.0, 1.9)	0.05
Stroke	0.5%	(-0.5, 1.5)	0.33	0.2%	(-0.8, 1.2)	0.70

6.3 Additional Discussion

Instrumental variable (IV) analysis may be a useful approach for observational studies where there is concern about the effects of unmeasured confounding. The approach, however, has limitations including that it may only be relevant for comparative studies of drug effectiveness or safety and studies have shown that while the instrumental variable estimate may be less biased it may also be less precise.[66] Additionally, instruments may be hard to find and assumptions are difficult to check. The study presented in Chapter 6 has shown that valid instruments in one setting may not be directly applicable to other populations. The instrumental variable analysis using doctor prescribing preference may only be useful when there are no other factors that might influence prescribing preference such as marketing of new classes of medicines in the group of interest. Instrumental variable estimates may be adversely affected when the preference for medicines within a class changes dramatically or when new medicines emerge on the market. This is important, as it suggests that instruments found to be valid in one setting may not be directly applicable to other settings which may limit the use of instrumental variable analysis in practice. Instrumental variable analyses are none-the-less a potential tool for pharmacoepidemiological studies and further work is required to explore the validity of new instruments. This may be achieved by the use of simulation studies to test the ability of the analysis to control for unmeasured confounding under various conditions.

Other studies have used doctor prescribing preference as an instrument[51 53] and subsequent studies have explored the validity of this instrument[63] and other definitions of the instrument.[64] These studies found that doctor prescribing preference was

generally strong and reduced covariate imbalance, however, the utilisation of different instruments resulted in varying conclusions.[64] In one study[64] authors investigated definitions of doctor prescribing preference for antipsychotics in two different populations of patients to compare the risk of death, within 180 days of initiation, between typical and atypical antipsychotic initiators. The conventional analysis in the British Columbia cohort estimated 3.6 extra deaths per 100 patients (95% CI 2.7, 4.4) initiated on typical compared to atypical antipsychotics[64], while for the Pennsylvania cohort the estimate was 3.9 per 100 patients (95% CI 2.7,5.1).[64] The instrumental variable analysis estimate using the standard doctor preference instrument found a marginal increase in the estimate of risk in the British Columbia cohort but almost a doubling of the estimate in the Pennsylvania cohort to 7.7 extra deaths per 100 patients (95% CI 1.3, 14.1). The authors then restricted the cohorts to patients who were prescribed their medicine by their primary care doctor. The rationale for this restriction was that the exclusion restriction assumption was more likely satisfied.[63] The instrument in the restricted cohort was weaker, thus produced a better balance of covariates, however, the instrumental variable estimate in this restricted cohort was decreased and no longer significant.[64] The application of a seemingly better instrument, based on its ability to fulfill the assumptions of the approach, resulted in a very different conclusion. These results make the interpretation of instrumental variable analyses difficult and suggest that there is a critical balance between instrument strength and covariate balance. The results from my study presented in Chapter 6 highlight that the testing of assumptions is crucial when performing instrumental variable analyses, even when applying instruments shown to be valid in other settings.

Additionally, the study presented in Chapter 6, employed the use of propensity scores to adjust for confounding. The propensity score adjustment appeared to provide

no additional confounding control over the standard numerical adjustment using the individual covariates. This relationship is useful in the context of administrative claims databases as the propensity score reduces many confounders into a single score, which may over-come model convergence problems when outcomes are rare or data within levels of the individual covariates are sparse. This becomes particularly important with the advent of higher-order propensity score adjustment models[26] which attempt to identify and prioritise covariates systematically through the use of an automated algorithm. Such high-order propensity score algorithms may provide improved effect estimates than when restricted to pre-defined covariates and have the advantage of exploiting the entire administrative claims databases to control for confounding.

Clinically, the results of the study presented in this chapter add to the growing evidence that typical antipsychotics are not safer than the atypical antipsychotics but have a higher mortality risk. While the typical antipsychotic, haloperidol, is not currently approved in Australia for the indication of dementia, it is an accepted indication.[139] The product information for this medicine suggests that an increased risk of mortality with typical antispychotics found in observational studies may be due to confounding: "*Observational studies suggest that, similar to atypical drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the finding of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some other characteristic(s) of the patient is not clear*".[140] Our study has shown that the risk of death with typical antipsychotics is greater than with atypical antipsychotics and this is unlikely to be due to confounding. Prescribers should be aware that there is a risk of death with both classes of antipsychotics, however, where the medicine is deemed appropriate, it appears that typical antipsychotics may be a less favorable choice.

7 The risk of hospitalisation for stroke associated with antipsychotic prescribing in the elderly: self-controlled case-series results

7.1 Preface

In Chapter 5 of this thesis, evidence of measured confounding was identified, indicating the likelihood for bias due to unmeasured confounding when comparing adverse events between the classes of antipsychotics. In Chapter 6 I compared the risk of death between the antipsychotic classes using an instrumental variable analysis to adjust for both measured and unmeasured confounding. While the instrumental variable analysis provides information regarding the comparative risk between the classes it cannot inform us about the individual risk of these medicines compared to no treatment.[47]

The results of the instrumental variable analysis suggested that the risk of death was greater with typical compared to atypical antipsychotics, however, it is important to note that the results of randomised controlled trials suggest that atypical antipsychotics are not risk free.[2] A long term randomised controlled trial found that the risk of death was higher with atypical antipsychotics compared to placebo[96] estimated at one extra death per 100 patients treated over 12 weeks.

Traditional study designs such as cohort and case-control studies have been used in pharmacoepidemiology to answer the question about the excess risk of an outcome in exposed compared to unexposed groups. The idea behind employing an unexposed

group is to provide a baseline risk, that is, what would have happened to the exposed group had they not been exposed. In order to do this comparison, the unexposed patient needs to be as similar as possible to the exposed patient so that any difference in outcome can be attributed to the only difference between the groups; the exposure. To achieve balance between treatment groups we may numerically adjust for confounders, or those variables that are unevenly distributed between the exposed and unexposed groups that are also associated with the outcome of interest. However, when utilising computerised claims databases we may not always be able to adjust for these differences between groups as the reasons why doctors decide to prescribe a medicine to one patient and not another are not recorded.

Techniques such as the propensity score and comorbidity scores attempt to rectify the disparity between the exposed and unexposed groups by identifying which patients are more similar to each other, then performing the analysis within these groups. The idea here is that those patients with similar „likelihood" for treatment should be more similar to each other with the only difference being that some were treated and some were not. The problem with propensity scores is that they may only be as good as the data used in their construction and will only be useful to the extent that measured covariates are correlated with those that are unmeasured.[27]

Within-patient study designs provide an alternative to traditional cohort and case-control designs by utilising the fact that a patient is more similar to him or herself over short periods of time than they are to other patients. In this way, comparing the risk of an outcome in unexposed time compared to exposed time within an individual patient's history should not require adjustment for confounders. This method may be of much

value in the computerised claims database when many confounders may be unmeasured.

In the following paper, I investigate a within-person study design; the self-controlled case-series design, to investigate the risk of hospitalisation for stroke with typical and atypical antipsychotics. Randomised controlled trial evidence suggests that the risk of cerebrovascular events with the atypical antipsychotic, risperidone, is nearly four times greater than with placebo.[2] When the events were limited to cerebrovascular events requiring hospitalisation no increased risk was observed.[88 104] No randomised controlled trial data are available for the risk of stroke with typical antipsychotics.

In the following paper, I investigate the risk of stroke with atypical antipsychotics using the self-controlled case-series design as we are able to bench-mark results with evidence from randomised controlled trials. This information is then used to apply the method to the risk of stroke with typical antipsychotics for which no RCT evidence exists. The ability of self-controlled case-series design to replicate RCT evidence would allow us to use the method to investigate the risk of other reported adverse events of these medicines identified in observational studies, including hip fracture and pneumonia (Chapter 8).

7.2 The risk of hospitalisation for stroke associated with antipsychotic prescribing in the elderly: self-controlled case-series results

Resubmitted

Drugs & Aging

STATEMENT OF AUTHORSHIP

Nicole Pratt (Candidate)

Corresponding author, designed the study, extracted the data, performed all the analyses, interpreted data, drafted the manuscript.

Signed……..Date……

Libby Roughead

Contributed to the design and interpretation of the study, and reviewed the manuscript. I give consent for Nicole Pratt to present this paper for examination towards the Doctor of Philosophy.

Signed……..Date……

Amy Salter

Contributed to the design and interpretation of the study, and reviewed the manuscript. I give consent for Nicole Pratt to present this paper for examination towards the Doctor of Philosophy.

Signed……..Date……

Philip Ryan

Contributed to the design and interpretation of the study, and reviewed the manuscript. I give consent for Nicole Pratt to present this paper for examination towards the Doctor of Philosophy.

Signed……..Date……

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8 Antipsychotics and the risk of hospitalisation for hip fracture and pneumonia in the elderly: Self-controlled case-series and instrumental variable analysis results

8.1 Preface

In Chapter 6 and Chapter 7 of this thesis, I identified the conditions under which instrumental variable analyses and the self-controlled case-series design may be applicable to explore adverse events of medicine prescribing in the elderly. The results of these studies were confirmed against RCT evidence where available. This information regarding the ability of self-controlled case-series and instrumental variable analysis to replicate RCT evidence also allows us to apply the method to the investigation of the risk of other reported adverse events of these medicines, including hip fracture and pneumonia. These outcomes are both common in the elderly and are highly correlated with patient characteristics such as age and frailty. Since factors that influence these outcomes are also those likely to influence the choice of antipsychotic (Chapter 5) and are related to ageing there is the potential for confounding in observational outcome studies of these medicines.

The following paper (Chapter 8.2) investigates the risk of hospitalisation for hip fracture and pneumonia both between typical and atypical antipsychotics, using an instrumental variable analysis, and between exposed and non-exposed periods within the same patient, using the self-controlled case-series design.

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

Submitted

Drug Safety

STATEMENT OF AUTHORSHIP

Nicole Pratt (Candidate)

Corresponding author, designed the study, extracted the data, performed all the analyses, interpreted data, drafted the manuscript.

Signed……..Date……

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Signed……..Date……

ABSTRACT

Background: Antipsychotics are commonly used in the elderly to treat the behavioural symptoms of dementia. Randomised control trial data on the safety of antipsychotics is limited and little is known about the long-term effects of these medicines. Observational studies have investigated the risk of hip fracture and pneumonia with antipsychotics but varying results may due to lack of control for unmeasured confounding.

Objective: To investigate the risk of hospitalisation for hip fracture and pneumonia in the elderly exposed to antipsychotic medication using two techniques to control for unmeasured confounding.

Methods: A self-controlled case-series design was used to measure the excess risk of hospitalisation for hip fracture and pneumonia after antipsychotic exposure compared to no-exposure over four years from 2002 to 2006. We compared the risk of hospitalisation for each outcome between the classes using an instrumental variable analysis using doctor prescribing preference as the instrument. For those patients resident in nursing home facilities we used the facility prescribing preference as the instrument.

Results: There was a significantly increased risk of hip fracture one week after exposure to typical antipsychotics and the risk remained significantly raised with more than 12 weeks continuous exposure (Incidence rate ratio (IRR) 1.34, 95% Confidence interval (CI) 1.14-1.59). For the atypical antipsychotics, there was a significantly increased risk of hip fracture in the first week after initiation (IRR=2.09, 95% CI 1.19-3.67) and up to 8 weeks after exposure. The risk of hospitalisation for pneumonia was

highest in the first week of treatment with typical (IRR=4.01, 95% CI 2.57-6.26) and atypical antipsychotics (IRR=3.19, 95% CI 2.02-5.06) and the risk remained significantly raised by 50% with long-term exposures. Instrumental variable analysis showed no difference in the risk of hip fracture or pneumonia between the classes.

Conclusions: Antipsychotic use in the elderly is associated with an increased risk of hospitalisation for hip fracture, however, the risk is sustained with long-term treatment with typical antipsychotics only. Typical and atypical antipsychotics are both associated with an increased risk of hospitalisation for pneumonia compared to non-use and this increased risk is equivalent for both classes. Given the increased risks of morbidity and mortality associated with these outcomes, practitioners should consider these additional risks when prescribing antipsychotics to treat behavioral symptoms of dementia in the elderly.

8.2.1 Background

Antipsychotics are frequently prescribed in the elderly to treat the behavioural symptoms of dementia. Despite their widespread use, evidence from randomised controlled trials (RCTs)[87-91] of the efficacy and safety of antipsychotics in patients with dementia has been limited to the study of atypical antipsychotics, in particular risperidone. Few clinical trials exist describing the effects of typical antipsychotics in elderly patients.

Atypical antipsychotics have been associated with an improvement in symptoms such as aggression, psychosis and agitation in patients with dementia.[2] These improvements, however, were limited to patients with more severe disease and offset by side effects such as extra-pyramidal symptoms, somnolence and more serious adverse events including stroke[2] and death.[92] A meta-analysis of 6 trials found that the most common adverse event associated with death within 30 days after starting treatment with risperidone was pneumonia.[95] Data also suggest that atypical antipsychotics are associated with falls and upper respiratory tract infections.[2]

Due to the limited long-term adverse event data from RCTs concerning atypical antipsychotics and the lack of RCT data on typical antipsychotics, observational studies have been conducted to investigate the safety of these medicines. Observational studies have identified an increased risk of hip fracture[107 115-118] with antipsychotics compared to non-use. One case-control study found that the risk of hip fracture increased with increased duration of exposure,[118] while another case-control study found that the risk was highest after six months continuous duration but then declined to base-line levels with longer-term exposure.[117] The association between falls or fractures and

antipsychotics may be due to the sedating effects of antipsychotics.[118 143] and a reduction in bone mineral density due to hyperprolactinemia.[118 144 145] An association has also been identified in observational studies between antipsychotics and pneumonia[120 121] with the highest risk identified in the first week of treatment.[120] Antipsychotic medicines may impair swallowing function resulting in the development of aspiration pneumonia.[121] There may be alternative explanations, other than a medication effect, for the finding of an increased risk of hospitalisation for pneumonia immediately after initiating treatment with antipsychotics. Protopathic bias[146] may account for some of the association found, as infections may cause increased confusion[147] or delirium[148] leading to the dispensing of antipsychotics. The existence of protopathic bias has been suggested in other studies investigating the association between antipsychotics and pneumonia[120] and antipsychotics and stroke.[123]

Studies vary in their assessment of hip fracture with atypical antipsychotics with two studies finding no increased risk[107 117] while one study found a significantly increased risk.[116] Typical antipsychotics were consistently associated with a increased risk of hip fracture[107 116 117] and a cohort study found that typical antipsychotics were associated with a significantly increased risk compared to atypical antipsychotics.[115] The risk of pneumonia associated with typical compared to atypical antipsychotics is less well studied. A case-control study found that current users of atypical antipsychotics were at higher risk of pneumonia than users of typical antipsychotics[120] while a cohort study, using an instrumental variable analysis to adjust for unmeasured confounding, found no difference in risk of pneumonia between the classes.[61]

The conflicting results of observational studies comparing the classes of antipsychotics may be due to a lack of control for unmeasured confounding. Atypical

antipsychotics may be selectively prescribed in the elderly as these drugs are thought to be less sedating and less likely to cause other serious side effects than typical antipsychotics.[2] When the reasons for prescribing are also associated with reported adverse events of the medicines, this leads to the problem of confounding. The ability of conventional observational studies to control for such confounding may be limited, particularly when utilising administrative claims data, as these datasets often lack information on potentially important clinical confounders such as frailty, disease severity and lifestyle factors, such as smoking and alcohol consumption.

We used a large administrative claims database to investigate the association between antipsychotic exposure and hospitalisation for hip fracture or pneumonia using two methods to control for unmeasured confounding; the self-controlled case-series design[28] and an instrumental variable analysis.[46 62] The self-controlled case-series design compares the risk of hospitalisation in periods of exposure compared to non-exposure within the same person. This design is likely to exclude the effects of major unmeasured confounders as the within-person study design controls implicitly for confounders that do not vary over time.[28] In the instrumental variable analysis we compared the risk of hospitalisation between the atypical and typical antipsychotics. An instrumental variable analysis exploits the existence of another variable, which can be measured in the available dataset, that is then used as a proxy for actual treatment received.[62] This variable (the instrument) attempts to mimic randomisation in an RCT thereby adjusting for unmeasured confounding.[46]

8.2.2 Objective

The objective of this study was to investigate the risk of hospitalisation for hip fracture and pneumonia in elderly users of antipsychotics using the self-controlled case-series design. We also aimed to compare the difference in risk of hospitalisation for these events between typical and atypical antipsychotics using an instrumental variable analysis.

8.2.3 Methods

The source of data for this study was the administrative claims database maintained by the Department of Veterans‟ Affairs (DVA). This dataset includes all claims data processed by DVA and has information relating to medicines dispensed under the Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme, hospital admissions and medical and allied health visits. The data file contains 120-million pharmacy records, 200-million medical and allied health service records and over six million hospital records for a treatment population of 310,000 veterans. The DVA maintain a client file, which includes data on sex, date of birth, date of death and family status. Medicines are coded according to the World Health Organization anatomical and therapeutic chemical (ATC) classification[75] and the Schedule of Pharmaceutical Benefits item codes.[76] Hospitalisations are coded according to the WHO International classification of diseases, 10th revision, Australian modification (ICD-10).[78]

Self-controlled Case-series Analysis

We used the self-controlled case-series design[28] [29] to compare the rate of hospitalisation for hip fracture and pneumonia in periods of exposure to antipsychotics compared to unexposed periods within the same individual. All patients with a hospitalisation for a primary diagnosis of hip fracture (ICD10 codes: S720, S721) or pneumonia (ICD10 codes: J12-J18) between 1st January 2003 and 31st December 2006 were selected. Patients were included if they were 65 years or older as at 1st January 2003 and had been full entitlement holders (eligible for all health services) for at least 12 months at this time. Medication records were searched for all antipsychotics dispensed during the study period. The first antipsychotic dispensed was obtained and included if no other antipsychotic had been dispensed in the previous 12 months. Typical antipsychotics included chlorpromazine, trifluoperazine, periciazine, thioridazine, haloperidol, ziprasidone. Atypical antipsychotics included clozapine, olanzapine, quetiapine, amisulpride, risperidone, aripiprazole. Patients who were initiated on both atypical and typical antipsychotics at any time during the study period were excluded. Patients exposed to injectable forms of antipsychotics were also excluded as durations of use were unable to be determined.

Dosage information is not available in the data set so duration of antipsychotic use was defined as the period within which 75% of veterans returned for a repeat dispensing of the medicine. These duration periods were calculated at the individual product level. The end of the exposure risk period was defined as one duration period after the last dispensing of an antipsychotic if there were no further dispensing during this time. All prescriptions of antipsychotics after the first dispensing were included and person-time was divided into risk periods; 1week, 2-8 weeks, 8-12 weeks and all remaining

exposure time post antipsychotic initiation (>12 weeks). We also included risk periods; 1week, 2-4 weeks, 5-8 weeks, 9-12 weeks, 13-16 weeks, and 17-20 weeks prior to initiating treatment with an antipsychotic. We included these pre-exposure risk periods to account for the possibility of an increased likelihood of an initiation of an antipsychotic after a hospitalisation event. The actual day of prescription was excluded from this analysis as we were unable to define the temporal association between the exposure and a hospitalisation if they occurred on the same day. All other person-time not exposed to antipsychotics was included in the base-line (unexposed) comparison period. Patients who were not exposed to antipsychotics during the study period were also included in the unexposed period to adjust for the increasing incidence of hospitalisation with age and the possible effects of calendar year.[28]

Incidence rate ratios were calculated using Poisson regression adjusting for age and calendar year. All analyses were performed using SAS version 9.12 (SAS Institute, Cary, NC). To adjust for possible protopathic bias we also performed the self-controlled case-series analysis adjusting for antibiotics commonly prescribed for respiratory tract infections; amoxicillin, amoxicillin/clavulanic acid, cefaclor, cefuroxime, erythromycin, roxithromycin, doxycycline, ciprofloxacin, oral moxifloxacin and oral gatifloxacin (ATC codes: J01CA04, J01CR02, J01DC04, J01DC02, J01FA01, J01FA06, J01AA02, J01MA02 or pharmacy item codes: 08636M, 04329W, 04297E).

Instrumental Variable Analysis

An instrumental variable analysis was performed to compare the risk of hospitalisation for hip fracture or pneumonia between typical and atypical

antipsychotics. All patients‟ dispensed antipsychotics between 1st January 2003 and 31st December 2006 were selected. The index antipsychotic script was determined as the first script dispensed to a patient within the study period. Patients were included if they had no other antipsychotic script dispensed in the previous 12 months, were full entitlement card holders for at least 12 months prior to the index script and were aged over 65 years.

Risk differences were calculated for the risk of hospitalisation for hip fracture or pneumonia within 12 months using linear regression models with robust variance to account for clustering within doctors.[136] In the hip fracture antipsychotic association we controlled for the following patient characteristics; age, gender, number of unique medicines in the last 12 months, nursing home facilities status, dispensing of antidepressants, morphine, oral NSAIDs, oral corticosteroids, sedative hypnotics and cardiovascular medicines; antihypertensives, betablockers, calcium channel blockers, lipids and vasoprotectives in the 12 months before the index date. We also adjusted for prior hospitalisations for the primary diagnoses of hip fracture and dementia occurring in the 12 months before the index date. In the subset analysis of patient‟s resident in a nursing home facility we also adjusted for care type: high or low care, and admission type: continuing or respite. In the pneumonia antipsychotic association we controlled for the following patient characteristics; age, gender, nursing home facilities status, dispensing of medicines for diabetes, inhaled corticosteroids, morphine, sedative hypnotics and cardiac medicines in the 12 months before the index date. We also adjusted for prior hospitalisations for the primary diagnoses of pneumonia occurring in the 12 months before the index date. In the subset analysis of patient‟s resident in a nursing home facility we adjusted for care type: high or low care, and admission type: continuing or respite.

An instrumental variable analysis, using a 2-stage ordinary least squares (OLS) regression was also performed to estimate the difference in risk of hospitalisation for hip fracture and pneumonia between typical and atypical antipsychotics after 12 months. For the full cohort we used a measure of doctor prescribing preference for atypical or typical antipsychotics as the instrument.[51 53 61 63] Doctor preference (IV1) was calculated as the most recent new prescription written for an antipsychotic medicine for another of the prescribing doctors‟ patients. For the subset of patients resident in a nursing home facility we used facility preference (IV2) for atypical or typical antipsychotics as the instrument. Facility preference was calculated as the antipsychotic prescribed most frequently to other initiated patients over a 12 month period in the same nursing home.

8.2.4 Results

The characteristics of the population used in the self-controlled case-series analysis are shown in Table 8.1. There were 8,285 patients with at least one hospitalisation for hip fracture identified in the four year study period. Of these, 610 patients were initiated on typical antipsychotics and 632 patients initiated on atypical antipsychotics. There were 13,932 patients with at least one hospitalisation for pneumonia identified in the four year study period. Of these, 679 patients were initiated on typical antipsychotics and 661 patients initiated on atypical antipsychotics.

Patient characteristics of the nursing home facilities study population used in the instrumental variable analysis are presented in Table 8.2. Typical antipsychotics were more likely to be dispensed to older patients, patients with prior dispensing of

antihypertensives, cardiac medicines, diuretics, morphine and oral corticosteroids, and patients previously hospitalised for pneumonia compared to patients dispensed atypical antipsychotics. Patient‟s dispensed typical antipsychotics were also less likely to have been prescribed the antipsychotic by their usual doctor, less likely to be in high care facilities and less likely to have been previously dispensed anti-cholinesterases, antidepressants, anti-parkinson medicines and lipid lowering therapy. Differences in the distribution of patient characteristics were largely reduced or removed when comparing treatment groups based on the facility prescribing preference instrument.

Self-controlled Case-series Results

The risk of hip fracture was significantly raised in all post-initiation risk periods after one week of exposure to typical antispychotics (Table 3). The risk of hip fracture, was also significantly raised up to 12 weeks prior to initiating a typical antipsychotic (Table 8.3), with the risk increasing steadily in the weeks leading up to first time dispensing of a typical antipsychotic.

For the atypical antipsychotics, there was a significantly increased risk in the first week after initiation and up to 4 weeks after exposure with the risk returning to baseline with longer-term treatment (Table 8.3). There was a significantly increased risk of hospitalisation for hip fracture up to 16 weeks prior to initiating atypical antipsychotics (Table 8.3).

The risk of hospitalisation for pneumonia was significantly increased in all post typical and atypical antipsychotic exposure periods (Table 8.4). The risk was highest in the first week after initiation of antipsychotics, the risk then declining with increasing duration of exposure but remained significantly raised with long-term exposures (Table

8.4). There was a significantly increased risk of hospitalisation for pneumonia in most pre typical antipsychotic initiation risk periods, however, this risk was highest in the 1 to 4 weeks prior to initiation of typical antipsychotics. The risk of pneumonia was raised only in the 2-4 week and 9-12 week pre atypical antipsychotic initiation risk periods (Table 8.4). After adjusting for the use of antibiotics, the incidence rate ratios estimates were reduced marginally in the post initiation risk periods for both typical and atypical antipsychotics but remained significantly raised (Table 8.4).

Instrumental Variable Results

In the instrumental variable analysis, using doctor prescribing preference as the instrument, there was no significant difference in the risk of hip fracture or pneumonia between the classes (Table 8.5). Restricted to nursing home residents and using nursing home preference as the instrument there was no difference in the risk of hip fracture between the classes (Table 8.5).

8.2.5 Discussion

In this study we have used two different methods of analysis to minimise possible bias created by unmeasured confounding in observational studies. Using the self-controlled case-series design we found an increased risk of hospitalisation for hip fracture and pneumonia associated with antipsychotic exposure compared to no exposure. The risk of hip fracture was increased one week after initiation of typical antipsychotics and persisted with longer-term exposures. The risk of hip fracture with atypical antipsychotics was significantly increased for up to 8 weeks after initiation but

declined to baseline levels with longer term exposures. The risk of pneumonia was significantly increased in all post typical and atypical antipsychotic initiation risk periods, however, the risk was highest in the week after initiation and declined with increased duration of exposure. There was a 50% increased risk of pneumonia with more than 12 weeks of treatment with either class of antipsychotic. Instrumental variable analyses suggest no difference in the risk of hospitalisation for hip fracture or pneumonia between the antipsychotic classes for all patients, nor for those patients in nursing home facilities.

The results of the self-controlled case-series analyses highlight the potential for confounding by indication in observational studies of antipsychotics. The risk of hospitalisation for both hip fracture and pneumonia was higher in the weeks leading up to initiation of typical antipsychotics compared to the same periods prior to initiating atypical antipsychotics. This suggests that doctors who prescribe antipsychotics to patients with a recent significant hospitalisation may be more likely to prescribe typical antipsychotics rather than atypical antipsychotics. The apparent selective prescribing of typical antipsychotics following a serious adverse event is likely to bias any association of the risk of hospitalisation with these medicines if not adequately controlled. By partitioning the pre initiation risk periods we have likely excluded the effects of confounding from our estimates in the post initiation risk period. The inclusion of separate pre initiation risk periods is necessary in the situation where hospitalisations are likely to lead to a prescription of an antipsychotic which would lead to an inflation of risk in the pre initiation periods and consequently an underestimate of the incidence risk ratios in the post initiation risk periods.[29]

To account for possible protopathic bias in the antipsychotic-pneumonia association we adjusted for antibiotic dispensing in the self-controlled case-series analysis. This adjustment reduced the estimate of risk marginally in the post initiation risk periods for both typical and atypical antipsychotics, however, the risk remained significantly raised.

One of the limitations of this study was the reliance on hospital data only for outcome events. This approach may have missed less severe outcomes not requiring hospitalisation. This omission would only lead to an underestimate of the risk associated with these medicines. One of the advantages of the self-controlled case-series design is that is controls implicitly for patient specific confounders that do not vary over time, this means that it is not necessary to adjust for variables such as frailty or other risk factors for hip fracture or pneumonia that are constant over time. A limitation of this approach, however, is that it is unable to adjust for changes in prescribing due to rapid changes in underlying disease severity[29] For example, other medications that increase the risk of hip fracture or pneumonia may occur more frequently around the time of antipsychotic initiation. Our analysis, adjusting for antibiotic prescribing, shows that the case-series design may be robust towards this possible bias as our adjusted results differed only slightly from the main analysis.

Previous studies have demonstrated an increased risk of hip fracture for both typical antipsychotics[107 116 117] and atypical antipsychotics[115 116] and others have demonstrated that this risk may be time dependent.[117 118] In our study, we found that both classes were associated with increased risk of hip fracture immediately following initiation but this risk persists with long-term typical antipsychotic treatment only. A previous case-control study[120] found that the risk of pneumonia was highest in the first week of treatment with antipsychotics (OR=4.4, 95% CI 2.9-7.2)[120] but the risk returned

to base-line levels after 90 days treatment.[120] A limitation of this study, however, was the inability to adjust for unmeasured confounding. Our approach using the self-controlled case-series design largely overcomes this problem and we have found similar risk estimates for pneumonia in the weeks immediately following initiation of antipsychotics but we have found that this risk may indeed persist with longer-term treatment with both classes.

The validity of our instrumental variable analysis results rely on the assumptions that; 1) the instrument is associated with treatment; 2) the instrument is unrelated to patient characteristics; and 3) the instrument is related to the outcome only through its association with treatment.[46] We found that both preference instruments were highly correlated with the actual treatment received. The doctor preference instrument correctly predicted the actual treatment prescribed in 65% of cases (Odds Ratio (OR) = 3.5; 95% CI 3.2-3.8), while the facility prescribing preference predicted actual treatment in 81% of cases (OR = 19.2; 95% CI 17.1-21.6). For the second assumption, we found that many of the patient characteristics were more evenly distributed over the levels of the instrument compared to actual treatment prescribed. To examine the third assumption, that a nursing home policy of antipsychotic preference is unrelated to the risk of hospitalisation, we determined whether preference was associated with other facility factors that may influence our outcomes of interest. We found that facility preference for antipsychotics was associated with level of care but not admission type. This means that facilities that most often prescribed atypical antipsychotics were more likely to be high care facilities. Therefore, if being in high care facilities is associated with an increased risk of hospitalisation then the estimate of risk difference between the classes may be biased towards the null.

8.2.6 Conclusion

This study found that typical antispychotics were associated with an increased risk of hospitalisation for hip fracture in all post exposure risk periods after 1 week of treatment, while this risk was increased in the first 8 weeks of treatment only with atypical antipsychotics. Instrumental variable analysis, however, found no difference in the risk of hip fracture between the classes. Typical and atypical antipsychotics are both associated with an increased risk of hospitalisation for pneumonia and this increased risk is equivalent for both classes. These results highlight the importance of considering not only the difference in risk between antipsychotics but also the risk of these medicines compared to no treatment. Given the increased risks of morbidity and mortality associated with hip fracture and pneumonia, practitioners should consider these additional risks when prescribing antipsychotics to treat behavioral symptoms of dementia in the elderly.

Table 8.1: Patient Characteristics of the study population included in the case-series analysis

	N	Follow-up years	Duration of Exposure	Age at first event	Age at first Exposure
Patients with a Hospitalisation for Hip Fracture					
Typical	610	3.7	0.32	85.5	85.0
Atypical	632	4.0	0.63	85.0	85.0
Unexposed	7043	4.0	-	84.0	-
Patients with a Hospitalisation for Pneumonia					
Typical	679	3.3	0.22	84.0	84.0
Atypical	661	3.8	0.53	84.0	84.0
Unexposed	12592	4.0	-	83.0	-

Table 8.2: Demographics of the study population included in the Instrumental Variable Analysis for patients resident in a nursing home facility

	Actual Treatment			Nursing Home Preference		
	Prevalence Difference ***(Typical-Atypical)***	***95% CI***	***P-value***	***Prevalence Difference*** ***(Typical-Atypical)***	***95% CI***	***P-value***
Patient Characteristics						
Age (>85)	4.0%	(1.7, 6.2)	<0.01	2.5%	(0.2, 4.8)	0.03
Male	1.9%	(-0.4, 4.2)	0.10	1.2%	(-1.1, 3.5)	0.30
Veteran	1.1%	(-1.2, 3.4)	0.36	0.9%	(-1.4, 3.1)	0.46
Vietnam Conflict	-0.0%	(-0.4, 0.3)	0.80	-0.0%	(-0.4, 0.3)	0.82
Antipsychotic prescribed by patients usual Doctor	-4.5%	(-6.9, -2.1)	<0.01	-2.9%	(-5.2, -0.5)	0.02
Nursing Home Characteristics						
Level of care (high)	-2.3%	(-4.2,0.5)	0.01	-3.0%	(-4.9,-1.1)	<0.01
Admission type (respite)	-0.3%	(-1.1,0.4)	0.42	0.3%	(-0.5,1.0)	0.46

	Actual Treatment			Nursing Home Preference		
	Prevalence Difference ***(Typical-Atypical)***	***95% CI***	***P-value***	***Prevalence Difference*** ***(Typical-Atypical)***	***95% CI***	***P-value***
Prior Medicines in last 12 months						
>=5 Unique Medicines	-0.1%	(-1.2, 0.9)	0.78	0.4%	(-0.6, 1.4)	0.46
ACE/A2RB C09	0.2%	(-2.0, 2.4)	0.87	-0.3%	(-2.6, 1.9)	0.78
Anticholinesterase	-2.9%	(-4.6, -1.2)	<0.01	-2.6%	(-4.3, -0.9)	<0.01
Antidepressants	-4.4%	(-6.7, -2.1)	<0.01	-3.0%	(-5.3, -0.6)	0.01
Antiepileptic	-1.2%	(-2.6, 0.2)	0.10	-1.6%	(-3.1, -0.2)	0.02
Antihypertensive	1.0%	(0.2, 1.8)	0.02	1.4%	(0.5, 2.2)	<0.01
Antiparkinsons	-3.2%	(-4.4, -2.0)	<0.01	-0.8%	(-2.0, 0.4)	0.21
Asprin	-1.9%	(-4.0, 0.3)	0.08	-1.3%	(-3.5, 0.8)	0.23
Beta Blocking Agents	-0.4%	(-2.3, 1.5)	0.68	-0.1%	(-2.0, 1.7)	0.88
Bisphosphonates	-1.0%	(-2.5, 0.5)	0.18	-1.3%	(-2.8, 0.2)	0.10
Calcium Channel Blockers	0.2%	(-1.6, 2.0)	0.81	-0.0%	(-1.9, 1.8)	0.97
Cardiac	3.5%	(1.4, 5.6)	<0.01	2.2%	(0.0, 4.3)	0.05
Diabetes	0.6%	(-0.9, 2.1)	0.42	-0.1%	(-1.6, 1.4)	0.88
Diuretics	3.4%	(1.3, 5.6)	<0.01	1.1%	(-1.1, 3.3)	0.32
Hormone Replacement Therapy	-0.4%	(-1.1, 0.3)	0.31	-0.0%	(-0.7, 0.7)	0.94
Inhaled corticosteroids	0.2%	(-1.5, 1.9)	0.78	-0.1%	(-1.8, 1.5)	0.87

	Actual Treatment			Nursing Home Preference		
	Prevalence Difference ***(Typical-Atypical)***	***95% CI***	***P-value***	***Prevalence Difference*** ***(Typical-Atypical)***	***95% CI***	***P-value***
Lipids	-2.3%	(-4.1, -0.4)	0.02	-1.9%	(-3.8, -0.1)	0.04
Morphine	7.2%	(5.8, 8.6)	<0.01	4.9%	(3.5, 6.4)	<0.01
Oral NSAIDs	1.2%	(-0.8, 3.2)	0.25	1.8%	(-0.2, 3.9)	0.08
Oral corticosteroids	1.9%	(0.6, 3.2)	<0.01	1.0%	(-0.3, 2.4)	0.12
Sedative Hypnotics	0.3%	(-1.9, 2.5)	0.81	0.6%	(-1.7, 2.8)	0.63
Vasoprotectives	0.5%	(-0.2, 1.1)	0.14	0.5%	(-0.1, 1.1)	0.12
Warfarin	0.8%	(-0.5, 2.1)	0.22	0.4%	(-1.0, 1.7)	0.57
Prior Hospitalisations in last 12 months						
Chronic Heart Failure	0.5%	(-0.3, 1.4)	0.24	0.0%	(-0.9, 0.9)	0.97
Dementia	-1.0%	(-2.0, 0.0)	0.06	-0.6%	(-1.7, 0.4)	0.22
Hip/femur Fracture	0.3%	(-0.7, 1.4)	0.51	1.1%	(0.1, 2.1)	0.04
Myocardial Infarction	0.5%	(-0.1, 1.1)	0.09	0.1%	(-0.5, 0.7)	0.78
Pneumonia	1.2%	(0.3, 2.1)	0.01	0.9%	(0.0, 1.9)	0.05
Stroke	0.5%	(-0.5, 1.5)	0.33	0.2%	(-0.8, 1.2)	0.70

Table 8.3: Case-series analysis for the association between first hospitalisation for hip fracture and exposure to typical or atypical antipsychotics

Typical Antipsychotic Exposure				
Risk Period	***N***	***N Hospitalisations***	***Person-Years***	***Rate Ratio (95% CI)***
Unexposed	7633	7284	24109	1.00
Pre Typical Antipsychotic initiation				
17-20 weeks	576	20	48	1.38 (0.90 - 2.12)
13-16 weeks	589	15	51	0.98 (0.60 - 1.61)
9-12 weeks	595	26	53	1.61 (1.11 - 2.35)
5-8 weeks	603	39	54	2.35 (1.73 - 3.19)
2-4 weeks	608	51	41	4.02 (3.09 - 5.24)
1 week	610	40	14	9.32 (6.90 - 12.59)
Post Typical Antipsychotic initiation				
1week	608	7	14	1.65 (0.79 - 3.44)
2-4 weeks	594	44	90	1.59 (1.19 - 2.11)
5-8 weeks	506	27	42	2.06 (1.42 - 2.98)
9-12 weeks	328	100	229	1.34 (1.14 - 1.59)
Atypical Antipsychotic Exposure				
Risk Period	***N***	***N Hospitalisations***	***Person-Years***	***Rate Ratio (95% CI)***
Unexposed	7659	7302	24121	1.0
Pre Atypical Antipsychotic initiation				
17-20 weeks	594	21	52	1.33 (0.87 - 2.02)
13-16 weeks	606	26	55	1.54 (1.06 - 2.25)
9-12 weeks	611	40	59	2.17 (1.61 - 2.93)
5-8 weeks	623	46	66	2.24 (1.69 - 2.95)
2-4 weeks	630	29	53	1.74 (1.23 - 2.48)
1 week	632	14	18	2.43 (1.45 - 4.09)
Post Atypical Antipsychotic initiation				
1week	632	12	18	2.09 (1.19 - 3.67)
2-4 weeks	621	50	113	1.38 (1.06 - 1.81)
5-8 weeks	506	15	48	0.97 (0.59 - 1.60)
>8 weeks	424	119	324	1.11 (0.96 - 1.29)

Table 8.4: Case-series analysis for the association between first hospitalisation for pneumonia and exposure to typical or atypical antipsychotics

Typical Antipsychotic Exposure					
Risk Period	***N***	***N Hospitalisations***	***Person-Years***	***Incidence Rate Ratio (95% CI)***	***Incidence Rate Ratio[a] (95% CI)***
Unexposed	13258	12900	41304	1.00	1.00
Pre Typical Antipsychotic initiation					
17-20 weeks	648	25	53	1.49 (1.01 - 2.19)	1.48 (1.01 - 2.18)
13-16 weeks	653	20	54	1.16 (0.75 - 1.79)	1.14 (0.75 - 1.75)
9-12 weeks	666	27	57	1.49 (1.03 - 2.15)	1.51 (1.04 - 2.17)
5-8 weeks	674	33	58	1.77 (1.27 - 2.47)	1.69 (1.22 - 2.35)
2-4 weeks	678	48	45	3.36 (2.55 - 4.43)	3.19 (2.43 - 4.21)
1 week	679	28	15	5.80 (4.03 - 8.36)	5.05 (3.54 - 7.19)
Post Typical Antipsychotic initiation					
1week	677	19	15	4.01 (2.57 - 6.26)	3.08 (1.97 - 4.82)
2-4 weeks	646	77	89	2.67 (2.16 - 3.31)	2.51 (2.04 - 3.09)
5-8 weeks	506	21	39	1.65 (1.08 - 2.51)	1.64 (1.08 - 2.48)
9-12 weeks	284	69	138	1.50 (1.20 - 1.88)	1.52 (1.22 - 1.89)
Atypical Antipsychotic Exposure					
Risk Period	***N***	***N Hospitalisations***	***Person - Years***	***Incidence Rate Ratio (95% CI)***	***Incidence Rate Ratio[a] (95% CI)***
Unexposed	13237	12879	41271	1.0	1.0
Pre Atypical Antipsychotic initiation					
17-20 weeks	626	17	53	1.01 (0.63 - 1.62)	1.02 (0.64 - 1.63)
13-16 weeks	637	14	55	0.80 (0.47 - 1.34)	0.81 (0.48 - 1.35)
9-12 weeks	647	28	58	1.49 (1.04 - 2.15)	1.44 (1.01 - 2.07)
5-8 weeks	658	26	64	1.25 (0.86 - 1.82)	1.24 (0.85 - 1.81)
2-4 weeks	660	27	51	1.63 (1.12 - 2.36)	1.63 (1.13 - 2.35)
1 week	661	9	17	1.58 (0.82 - 3.03)	1.49 (0.78 - 2.85)
Post Atypical Antipsychotic initiation					
1week	659	18	17	3.19 (2.02 - 5.06)	2.95 (1.87 - 4.68)
2-4 weeks	641	69	108	1.94 (1.56 - 2.42)	1.86 (1.50 - 2.31)
5-8 weeks	529	23	46	1.52 (1.01 - 2.28)	1.39 (0.93 - 2.08)
>8 weeks	421	140	284	1.47 (1.28 - 1.69)	1.41 (1.23 - 1.63)

[a] Adjusted for antibiotic dispensing

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

	All Patients	
	Hip Fracture	**Pneumonia**
	Risk Difference (95% CI)	***Risk Difference (95% CI)***
Unadjusted	1.3 (0.6, 2.0)	0.7 (-0.1, 1.5)
Covariate adjusted	0.5 (-0.1, 1.1)	0.3 (-0.4, 0.9)
IV adjusted (IV1)	0.5 (-2.5, 3.4)	1.1 (-1.6, 3.7)
	Nursing home facilities	
	Hip Fracture	**Pneumonia**
	Risk Difference (95% CI)	***Risk Difference (95% CI)***
Unadjusted	2.3 (1.0, 3.6)	-0.4 (-1.2, 0.4)
Covariate adjusted	1.4 (0.2, 2.7)	0.7 (-0.4, 1.9)
IV adjusted (IV2)	1.1 (-0.8, 3.0)	1.5 (-0.3, 3.3)

RD=Risk difference, **IV1=** Instrumental variable – Doctor preference, **IV2=**Instrumental variable – Nursing home facility preference

8.3 Additional Discussion

The study presented in this chapter used a self-controlled case-series design to investigate the risk of hip fracture and pneumonia associated with antipsychotics in the elderly. An increased risk of hip fracture with typical antipsychotics was found which persisted with long-term treatment, while an increased risk of hip fracture with atypical antipsychotics was present for up to 12 weeks after initiation. The risk of pneumonia was raised in all periods after treatment initiation, but was highest in the first week of treatment. As with the analysis of the risk of stroke with antipsychotics (Chapter 7) the risk of both hip fracture and pneumonia hospitalisation was significantly increased in the weeks leading up to antipsychotic initiation. This suggests that patients are likely to be initiated on therapy during their admission or upon discharge. In this situation the self-controlled case-series design may be susceptible to bias particularly when the adverse event of interest is a hospitalisation event that leads to an increased likelihood of initiating treatment. This effect is evident in the association between hip fracture and antipsychotics where delirium is a common complication of hospitalisation for hip fracture for which antipsychotics may be prescribed.[149] I have identified that the exclusion of the period prior to initiating antispychotics from the non-exposed reference period may be required to overcome this bias. The length of these pre-exposure risk periods may not be intuitive and the minimum period should be at least as long as an average length of stay of the hospitalisation of interest. Failure to remove these pre exposure risk periods from the overall „non-exposed" period, may result in an underestimation of the incidence rate ratio and a biased result, if in fact a true association exists.[29]

The next section provides a brief summary of the risks and benefits of antipsychotics in the elderly including the additional evidence found in our study of the risk of hip fracture and pneumonia. I present the number needed to treat and harm with these medicines to show how these results may help to inform clinicians and policy makers about the real world safety of antipsychotics in the elderly.

8.4 Is it time to rethink the risk/benefit ratio of antipsychotic use in the elderly?

Treatment harms are under investigated in randomised controlled trials of antipsychotics in the elderly.[150] Not only are trials limited to the study of the newer class of antipsychotics, the atypical antipsychotics, they often only investigate their short term safety. A Cochrane Review[2] found that risperidone, an atypical antipsychotic, was associated with an improvement in the behavioural symptoms of dementia[2] but the benefits were limited to those with more severe disease.[90] The number needed to treat to show benefit with atypical antipsychotics ranged from 3 to 13 patients over a 12 week period.[3 89-91 126-128] A meta-analysis[92] identified that for every 100 patients treated with risperidone for 12 weeks there would be 1 death that may not have otherwise occurred over the same period. The risk-benefit ratio suggests that there will be 1 death for every 8 to 33 person helped with these medicines.[92] The risk of cerebrovascular events was also significantly higher with risperidone[2] It has been suggested that for every 60 patients with dementia treated with atypical antipsychotics there would be one additional cerebrovascular event over a 6 to 12 week treatment period. The majority of these cerebrovascular events were defined as non-serious and did not require hospitalisation.[104]

Observational studies have identified additional risks associated with antipsychotics including hip fracture[107 115-118] and pneumonia[120 121] which were not detected in the randomised controlled trials. This may be due to the limited follow-up time of the studies or insufficient sample size to detect these rare events. All but one of the observational studies used a case-control study design which means that there are no data available on the absolute rate of these adverse events in the elderly and hence the calculation of a risk benefit ratio is difficult. The potential for antipsychotics to be associated with adverse events such as hip fracture and pneumonia was highlighted in a Cochrane Review which found significantly increased risks of upper respiratory tract infections and falls with risperidone. Additionally, a meta-analysis[95] found that the most common adverse event associated with death within 30 days after starting treatment with risperidone was pneumonia.

A self-controlled case-series analysis was employed in Chapter 7 to attempt to determine the risk of hip fracture and pneumonia associated with antipsychotics. This design has the advantage of controlling for unmeasured confounding due to its within-subject design. Based on the estimates from the case-series analysis, I estimated that there would be one additional hospitalisation for pneumonia for every 13 patients treated with atypical antipsychotics for 12 weeks, and one additional hospitalisation for hip fracture for every 40 patients treated. These numbers suggest that for every 1 to 4 persons helped with atypical antipsychotics, one will be hospitalised for pneumonia and for every 4 to 14 persons helped with these medicines one patient will be hospitalised for hip fracture over the same period. Given the increased risk of mortality associated with hip fracture and pneumonia these medicines pose a significant public health burden.

Overall, for every 100 patients treated with atypical antipsychotics for 12 weeks, 8 to 33 would show benefit, however, there would be 1 additional death, 1.7 additional cerebrovascular events, 8 additional pneumonias and 2.5 additional hip fractures. Considering the modest improvement in terms of efficacy, the risk of these medicines may now outweigh their benefit. There is limited RCT evidence for typical antipsychotics,[86] however, if we consider that they are less efficacious than atypical antispychotics and as observational studies suggest, that they may be associated with more harm, the risk benefit ratio for typical antipsychotics looks even more bleak.

9 Summary and Conclusions

This thesis has explored the use of techniques and study designs to investigate the adverse events of medicines in elderly patients using only those data that are available in administrative computerised claims databases. In Australia, data of this type are becoming increasing available yet knowledge on how to utilise this information is limited. Prior to the work in this thesis there were no published studies that utilised either the self-controlled case-series design or the instrumental variable analysis to investigate the adverse effects of medicines in the Australian setting. The results obtained in this thesis indicate that with due consideration to the issue of unmeasured confounding, computerised claims databases have the ability to provide information to help inform clinicians and policy makers about the safety of widely used medicines. This information is crucial to reduce the reliance on results generated in studies performed internationally in, often, dissimilar health care settings.

Clinically, the results obtained in this thesis are important as the use of antipsychotics is increasing[130] despite the lack of comprehensive information from randomised controlled trials about their efficacy and safety in this population (Chapter 4). Observational studies are required to complete the evaluation of these medicines, however, as discussed in Chapter 4 the results of such studies have differed which may be due to the methods used to control for unmeasured confounding.

The goal of this thesis was to explore the consequences of confounding and to investigate current techniques available in pharmacoepidemiology to deal with the problem. Firstly, a systematic review of literature identified that the safety of

antipsychotics were under investigated in randomised controlled trials, and the results of subsequent observational studies varied in their assessment of risk with these medicines. One of the possible reasons for these discrepancies was bias due to the lack of control of unmeasured confounding when utilising data contained in computerised claims databases.

Confounding was identified as a potential issue in the assessment of the risks of adverse outcomes associated with antipsychotic use in the elderly veteran population (Chapter 5). Using a cohort of 20,205 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 outcomes of these medicines. This selective prescribing may threaten the validity of observational studies comparing the risks of these medicines both compared to no treatment and between the classes. While adjustments for measured confounders can be made, such as those identified in Chapter 5, unmeasured confounders will only be accounted for to the extent that they are correlated with those that are measured. Study designs that minimise unmeasured confounding are required to evaluate the safety of antipsychotic medicines.

This thesis has focused on two different techniques to tackle the problem of unmeasured confounding. The first is the instrumental variable technique, which was used to compare the risk of death between the classes of antipsychotics. The instrumental variable technique attempts to adjust for unmeasured confounding by mimicking randomisation in an RCT. This approach is useful for providing „head" to „head" comparisons of medicines within a class which are often unavailable in randomised controlled trials.[151] Using an instrumental variable analysis I found 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 (Chapter 6). The performance of two preference based instruments: doctor prescribing preference and nursing home facility preference was explored. Nursing home facility was proposed for the first time in this thesis as an alternative to the doctor prescribing preference instrument which has been used extensively in the pharmacoepidemiological literature. I was able to show that facility preference may be a valid instrument 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. I also identified that instruments validated in one population may not be directly applicable to other populations and that the assumptions of the instrumental variable analysis need to be examined with consideration to the specific health care setting to assist interpretation of the study results.

While the instrumental variable analysis can provide information regarding the comparative risk of antipsychotics between the classes it cannot inform the question of individual risk of 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 associated with antipsychotic initiation. The self-controlled case-series design exploits the fact that a patient is more similar to him or herself over short periods of time than they are to other patients. This similarity then implicitly adjusts for constant patient specific confounders, even those that are unmeasured. This design is a potential choice for pharmacoepidemiology studies because of its ease of application. The self-controlled case-series analysis identified that atypical antipsychotics were not associated with an increased risk of hospitalisation for stroke in the elderly which is consistent

with RCT results (Chapter 7). No randomised controlled trial evidence was available for typical antipsychotics in the elderly, however, the case-series analysis suggested that there was 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). The self-controlled case-series design has been used extensively in the investigation of vaccine safety. I have found, however, that the use of this design to study the adverse events of medicines in the elderly may require the inclusion of an unexposed group to control for the increasing incidence of hospitalisation outcomes with increasing age. Additionally, this is the first study to explore the use of risk periods prior to initiating therapy with antipsychotics in a self-controlled case-series design. These pre-exposure risk periods were included to look for evidence of confounding by indication. Patients initiating typical antipsychotics were 7 times more likely to have had a hospitalisation for stroke in the week prior to initiating typical antipsychotics while atypical antipsychotic initiators had no excess risk in the same period. By partitioning the pre-exposure risk periods and excluding the weeks prior to initiating an antipsychotic from the „unexposed" reference period I have aimed to exclude the effects of confounding by indication in the assessment of risk in the post exposure risk periods. The use of pre exposure risk periods may be required in medicine outcome studies when the outcome of interest is likely to influence the probability of exposure.

Using the knowledge gained about the use of each method after benchmarking to available RCT evidence the methods were then used to investigate the risk of hospitalisation for hip fracture and pneumonia (Chapter 8) which are adverse events not previously identified in RCTs but have been detected in observational studies. The risk of hip fracture was significantly increased for both classes but this risk was sustained only with long-term (more than 12 weeks) typical antipsychotic use (IRR 1.3, 95% CI

1.1-1.6). For pneumonia the risk was significantly raised in all post-exposure risk periods, however, the highest risk was in the week after initiation. This risk declined with increased duration of exposure for both typical and atypical antipsychotics but remained significantly raised by 50% with long-term treatment (Typical antipsychotics IRR; 1.5, 95% CI 1.2-1.9, Atypical antipsychotics IRR; 1.5, 95% CI 1.3-1.7). Additionally, using an instrumental variable analysis, typical antipsychotics appear to be no safer than atypical antipsychotics with respect to these outcomes.

Finally, we performed a risk/benefit analysis of antipsychotics which thus far has only been possible for death and cerebrovascular events. Observational studies of hip fracture and pneumonia generally used a case-control design and very few cohort studies were available from which to calculate incidence rates. Randomised controlled trial evidence suggests that that for every 100 patients treated with atypical antipsychotics over 12 weeks, between 8 to 33 patients would be expected to show any clinical benefit from treatment, while there would be 1 additional death and 1.7 additional cerebrovascular events. Using a self-controlled case-series design I estimated that there would be 2.5 additional hip fractures and 8 additional hospitalisations for pneumonia for every 100 patients treated with atypical antipsychotics for 12 weeks (Chapter 8). In addition, typical antispychotics were found to be associated with at least equivalent, if not more, harm.

While unmeasured confounding is a threat to the validity of all observational studies utilising claims data, the extent to which it impacts on the measure of risk is often related to the purpose of the study. This thesis has explored how to deal with the problem of unmeasured confounding when investigating the adverse events of treatment, however, unmeasured confounding may be a more difficult problem to

overcome when investigating the effectiveness of treatments, or the intended effects of treatment. This is because doctors may prescribe particular medicines with greater perceived "efficacy" to sicker patients there by inducing a correlation between treatment choice and disease risk.[11] More work is required to investigate the ability of observational study designs to overcome confounding when investigating the effectiveness or intended effects of treatment.

9.2 Future Directions

Prior to this thesis there had been no published observational studies in Australia that have used either the self-controlled case-series design or the instrumental variable analysis to investigate the outcomes of medicine use. Instrumental variable analysis has been used widely in pharmacoepidemiology, however, much work has focused on the use of the doctor preference instrument. It will be important to investigate new instruments that are potentially valid and are generalisable to wider populations. A potential instrument that may be relevant in Australia is General Practice Clinic preference. This instrument may benefit from an increased generalisability of results over those obtained in nursing homes.

The self-controlled case-series design is a potential choice of study design in pharmacoepidemiology as it aims to control implicitly for fixed and unmeasured patient specific confounders. This is advantageous when many clinical confounders are unavailable. In this thesis, I have identified that the application of the self-controlled case-series design in the elderly may require a control group of patients who have experienced the event of interest but who were not exposed the treatment (Chapter 7).

More work, however, is required to determine for which outcomes this inclusion will be necessary and whether there are circumstances where it may introduce more bias. Studies have highlighted the potential of the self-controlled case-series design for the purpose of post-marketing surveillance and monitoring of adverse events,[44] however, this thesis has identified that the inclusion of pre-exposure risk periods may be necessary when the method is applied to hospitalisation outcomes that are likely to increase the probability of medicine initiation. Failure to account for this will tend to bias associations towards the null and consequently the method will have low sensitivity for detecting adverse events of treatment. Further work in this area should focus on methods to determine the required length of these pre-exposure risk periods.

9.3 Conclusion

In conclusion, this thesis has illustrated that identifying and reducing confounding can 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.

This thesis has demonstrated that administrative claims databases have the potential to provide reliable information on the effects of medication prescribing in the elderly provided that due consideration is given to the problem of unmeasured confounding. Observational studies using data drawn from administrative claims databases must address specific problems inherent in the data sources; the first from bias due to

confounding and secondly the ability to adjust for confounding when not all important confounders are measurable. The knowledge obtained in this thesis will help to inform how Australian 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.

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Appendix 1 Derivation of the IV estimate

The instrumental variable (IV) estimate can be derived by examining the similarity of the method with an RCT that has non-compliance and in which the level of non-compliance is associated with confounders that affect the outcome. [30] Random treatment assignment provides the perfect instrument for confounding control. In observational studies an instrument is a variable Z that mimics random treatment assignment by satisfying the following conditions; Z is independent of U, Z is associated with X and Z is independent of Y given X and U.

Instrumental variable analyses will be of use when the observed X-Y association is confounded by unmeasured covariates but Z-X and Z-Y associations are not confounded. In the case of an RCT, Z is treatment assignment which will balance the distribution of measured and unmeasured covariates. X is actual treatment received which is affected by but not fully determined by Z. In an RCT bias by unmeasured confounding is a threat whenever people fail to comply with their assignment for reasons related to their outcome. This is why RCTs are analysed on intention to treat, which means that the estimate of effect is derived as the difference in outcomes between treatment arms rather than actual treatment received.

The instrumental variable estimate is determined in terms of an intention to treat analysis, however it is also weighted by the strength of the instrument. There are 2 groups of patients in an RCT, compliers who receive the treatment they are randomised to (Z=1 and X=1, Z=0 and X=0) and deifiers who do not receive the treatment they

were randomised to (Z=1 and X=0, Z=0 and X=1). The proportion of patients who are compliers is then $P_c = P(X=1|Z=1) – P(X=1|Z=0)$.

The effect that assignment to treatment 1 rather than treatment 0 would have on the average outcome is validly estimated by the observed difference in average outcome for the group assigned to treatment 1 compared to the group assigned to treatment 0 (the intention to treat estimate of treatment effect, Y(Z=1)-Y(Z=0).

If a patient is assigned to treatment arm (Z=1), there are three types of patients. Those who receive treatment because they were randomised to it (p_c), those who received treatment because they were always going to receive the treatment regardless of whether or not they were randomised to it (p_o) and those who did not receive treatment even though they were randomiased to it ($1-p_1$).

Table A1: Representation of expected data from randomised experiment (Z) with non-compliance [30]

	Randomisation					
	Z=1			Z=0		
	Actual Treatment			***Actual Treatment***		
	X=1		X=0	X=1	X=0	
	Co-operator C=1	Non-co-operator N=1	Non-coperator N=0	Non-co-operator N=1	Non-coperator N=0	Co-operator C=1
Average Y	m_{1c}	m_{1n}	m_{0n}	m_{1n}	m_{0n}	m_{0c}
Proportion	p_c	p_0	$1-p_1$	p_0	$1-p_1$	p_c
	Marginal Treated "Complier"	Always Treated	Never Treated	Always Treated	Never Treated	Marginal Not Treated "Complier"
	$m_{.1} = p_c m_{1c} + p_0 m_{1n} + (1-p_1)m_{0n}$			$m_{.0} = p_0 m_{1n} + (1-p_1)m_{0n} + p_c m_{0c}$		
	$m_{.1} - m_{.0} = p_c(m_{1c} – m_{0c})$ $m_{.1} - m_{.0} = (p_1-p_0)(m_{1c} – m_{0c})$ Effect of treatment X among co-operative people $m_{1c} – m_{0c} = (m_{.1} - m_{.0}) / (p_1-p_0)$					

$\hat{p}_c = \hat{p}_1 - \hat{p}_0$ is the proportion of patients who get treatment (X=1) given they were randomised to it minus the proportion who get treatment (X=1) given they were not randomised to it. This is the proportion of patients who are compliers, that is, those for whom assignment to treatment influenced their actual treatment.

Note that p_1 is made up of two groups of people, those for whom assignment to treatment influenced their treatment decision but also a subgroup p_0 who would always receive treatment regardless of treatment assignment (ie $P(X=1|Z=1)=P(X=1|Z=0)=p_0$). We want $\hat{p}_c$ to be high so that we have a large marginal subgroup, that is a large group for whom treatment was determined by the instrument, and this is the group for whom the instrumental variable effect estimate is generalisable to.

To get an estimate of treatment effect we really want an estimate of effect in the compliers, that is m_{1c}-m_{0c} but we do not know who these people are so we estimate the treatment effect in Z=1 compared to Z=0 and weight by the proportions in each of these categories

The effect of treatment for Z=1 is:

$$m_{\bullet 1} = p_c m_{1c} + p_0 m_{1n} + (1 - p_1) m_{0n}$$

The effect of treatment for Z=0 is:

$$m_{\bullet 0} = p_0 m_{1n} + (1 - p_1) m_{0n} + p_c m_{on}$$

The estimated treatment difference is:

$$m_{\bullet 1} - m_{\bullet 0} = p_c (m_{1c} - m_{0c})$$

$$m_{\bullet 1} - m_{\bullet 0} = (p_1 - p_0)(m_{1c} - m_{0c})$$

This equation exhibits the dilution of the Z effect produced by non-compliance, from 0 (no Z effect if no compliance), to 1 (Z effect equals X effect if full compliance).

The effect of treatment among co-operative people is then

$$m_{1c} - m_{0c} = \frac{m_{\bullet 1} - m_{\bullet 0}}{(p_1 - p_0)}$$

This is the instrumental variable estimator which can be evaluated in terms of a system of structural equations. That is the ordinary least squares estimator of the effect of Z on Y divided by the ordinary least squares estimator of the effect of Z on X (adjusted for other covariates U).