Concomitant alcohol and alcohol-interactive medication use by older New Zealanders: Investigating the prevalence, and potential associations with health, healthcare utilization, and depression

A thesis presented in partial fulfillment of the requirements for the degree of Doctor of Clinical Psychology

at Massey University, Manawatū

New Zealand

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2021

ABSTRACT

Background: Older adults are more vulnerable to the adverse effects of *alcohol-medication interactions* (AMIs) than younger populations, and are more likely to use medications capable of causing an AMI when used with alcohol (*alcohol-interactive* (AI) medications). Survey findings from the United States (US) and Europe indicate many older adults use alcohol and AI-medications concomitantly. However, the prevalence of this issue in New Zealand is currently unknown, and few observational studies have explored the impact of *concomitant alcohol and AI-medication use* (concomitant alcohol/AI-medication use) on health outcomes in community samples. Research exploring motivating factors underlying alcohol use by AI-medication users indicates having awareness of AMI risks often motivates reduced alcohol consumption. There is also evidence that depression may increase the likelihood of concomitant alcohol/AI-medication use, particularly when alcohol is used to 'self-medicate' depressive symptoms. However, the moderating effects of depression on alcohol use by AI-medication users have not been directly assessed in a large community sample.

Design and Methods: Two studies were conducted, both involved secondary analysis of existing survey data and national pharmaceutical claims data. Samples were drawn from a representative sampling frame of older adults living in New Zealand. The first study (study 1) analysed data from a survey of adults aged 54-70 years, and the second study (study 2) analysed data from an augmented sample aged 49-83 years. The prevalence of concomitant alcohol/AI-medication use was explored in both study samples overall, and in subsamples of participants aged ≥65 years. Study 1 investigated the potential impact of concomitant alcohol/AI-medication use on general physical health and healthcare utilization. Study 2 assessed the potential relationships between alcohol use, AI-medication use, and depression. An evidence-based protocol was developed to inform methods of classifying AI-medications and measuring

AI-medication use among survey participants using pharmaceutical dispensing records. Relationships between variables of interest were assessed using a series of hierarchical regression models and Chi-squared tests.

Results: Alcohol and AI-medications were used concomitantly by approximately one-in-four participants aged 54-70 years, one-in-three participants aged 49-83 years, and two-in-five participants aged 65-83 years. Concomitant alcohol/AI-medication use was not significantly associated with physical health or healthcare utilization, although these non-significant findings may reflect limitations of the outcome measures used in the present research. Alcohol use was negatively associated with AI-medication use, with stronger associations being observed for medications associated with more severe AMIs. These findings are consistent with research and theory indicating AMI awareness may lead to reduced alcohol consumption by AI-medication users. Depression did not influence the relationship between AI-medication use and alcohol use.

Conclusions: The present research findings indicate many New Zealand older adults are at risk of AMI. Providing relevant health warnings may help reduce the potential for AMI-related harm, although additional intervention may be needed for many older adults. Future research in this area should include longitudinal health outcome measures that are specific to the effects of AMI, and measures that assess drinking motives directly. The two studies presented in the present thesis were the first to explore the prevalence of concomitant alcohol/AI-medication use by older adults in New Zealand, which is a major contribution of this project overall. Another important contribution was the development of an evidence-based framework for measuring AI-medication use among survey participants.

ACKNOWLEDGMENTS

I would like to begin my acknowledgments by thanking my three supervisors. To my primary supervisor, Dr Joanne Allen, thank you for guiding me throughout this project. In particular, your patience, knowledge, and attention to detail helped me understand the complexities of this project. Dr Andy Towers, thank you for constantly encouraging me, and for taking the time to help me see the bigger picture when I found myself getting lost in the details of this project. Associate Professor Joanne Taylor, thank you for your thoughtful feedback on every draft I sent you, and for helping me persevere with my doctoral studies whenever I encountered challenges along the way.

I would like to thank others who contributed this project. Professor Janie Sheridan and Dr David Newcombe, thank you for taking the time to review my research protocol. Importantly, I would like to thank the Massey University Health and Aging Research Team for providing the data analysed in this research. I am also grateful for the scholarship I received for this project from the HOPE-Selwyn foundation.

I would also like to thank the people in my life who supported me throughout this journey. My wonderful partner Sarah, you have been through this journey with me, and it has certainly been challenging at times. Your love and support have kept me moving forward. Also, to mum, dad, and Alice, thank you all for your constant support and encouragement throughout my studies. To my friends, I am grateful to have had you all there to talk to and laugh with when I needed to. In particular, I am grateful to Amy for the comradery we shared as we progressed through our research and clinical training together.

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CHAPTER 1: BRIEF INTRODUCTION & THESIS OUTLINE

New Zealand's population is gradually aging due to a decline in both birth rates and death rates per capita (Statistics New Zealand, 2020). Moreover, a large cohort of people born between 1950 and the early 1970s commonly described as the 'baby boomer' generation are reaching older adulthood. New Zealand is therefore experiencing sudden growth in the population aged ≥65 years (Statistics New Zealand, 2020). Research from the United States (US) indicates potentially harmful alcohol consumption patterns are more prevalent among the baby boomers than previous generations (Savage, 2014), and that drinking patterns among this cohort often continue into older adulthood (McEvoy et al., 2013). Nationally representative survey data indicates approximately 40-50% of older adults living in New Zealand engage in potentially harmful alcohol consumption patterns (Stevenson et al., 2015; Towers et al., 2011; Towers, Sheridan et al., 2018). Such high rates of potentially harmful drinking in this rapidly growing population are concerning, given that vulnerability to alcohol related harm increases during older adulthood (Moore et al., 1999). Additionally, older adults are considerably more likely than younger cohorts to use medications that have the potential to interact with alcohol in a way that poses harm (Moore et al., 2007). Research conducted in the US and Europe indicates many older adults use alcohol and alcohol-interactive medications concomitantly (Holton et al., 2017), however the prevalence of this issue in New Zealand's older adult population is currently unknown.

The present thesis explores the prevalence of concomitant alcohol and alcohol-interactive medication use among older adults living in New Zealand, and investigates a variety of potential associations between alcohol use, alcohol-interactive medication use, physical health, healthcare utilization, and depression. Chapters 2-8 provide a broad review of the literature relevant to the thesis topic, highlighting gaps in existing knowledge, and reviewing research and theory that informed hypotheses for the present research. Chapter 9 introduces the present

research, states the research questions and hypotheses investigated in this project, and summarizes the content of subsequent chapters. Methods of previous studies exploring the prevalence of concomitant alcohol and alcohol-interactive medication use are reviewed in chapter 10. Chapter 11 describes the development and implementation of a research protocol for measuring alcohol-interactive medication use among survey participants using national pharmaceutical claims data. Two studies were conducted in the present thesis, which are described in chapters 12 (study 1) and 13 (study 2). Both studies explored the prevalence of concomitant alcohol and alcohol-interactive medication use in large community samples of older adults living in New Zealand. Study 1 explored the potential of impact of concomitant alcohol and alcohol-interactive medication use on health and healthcare utilization. Study 2 explored potential relationships between alcohol use, AI-medication use, and depression. Chapter 14 discusses findings of studies 1 and 2, and draws conclusions.

CHAPTER 2: ALCOHOL USE IN OLDER ADULTHOOD

This chapter reviews relevant research relating to alcohol use by older adults. The definition of older adulthood adopted in the present research is discussed in section 2.1. The next section (2.2) discusses methods of measuring and describing drinking patterns in survey research, and survey studies into the drinking patterns of New Zealand older adults are then reviewed in section 2.3. Common motivating factors underlying alcohol use by older adults are then discussed in section 2.4, and health outcomes associated with alcohol use during older adulthood are described in section 2.5.

2.1: DEFINITION OF OLDER ADULTHOOD

The research conducted in the present thesis uses chronological age as an indicator of older adulthood, with a chronological age threshold of ≥65 years being used to identify subsamples of participants who are considered older adults. The threshold of 65-years was selected because this is the age at which New Zealand citizens reach eligibility for superannuation (New Zealand Government, 2020), and also because this was found to be a useful threshold for comparing the present research findings with previous studies in this area. Participants aged below this threshold are also included in the present research to capture persons who are approaching older adulthood (the study 1 sample was aged 54-70 years, and the study 2 sample was aged 49-83 years). It should be noted that chronological age is an imperfect approach to classifying older adulthood, as the biological and cognitive changes associated older adulthood do not occur at any single chronological age (MacDonald et al., 2011). It should also be noted that studies reviewed throughout the introduction chapters of the present thesis use varying chronological age thresholds to classify older adult populations.

2.2: MEASURING AND DESCRIBING DRINKING PATTERNS

In survey research, patterns of alcohol use are measured primarily based on participant self-report (Dawson, 2003; Dufour, 1999). As self-report methods do not measure alcohol use directly, this approach presents several methodological issues that must be considered when interpreting survey research into drinking patterns. Moreover, several terms describing various patterns of alcohol consumption commonly feature in the literature, although the way in which these terms are operationalized tends to vary from one study to the next. As research into the prevalence and correlates of alcohol use is a key focus of the present thesis, some issues regarding the way drinking patterns are measured and described by researchers are discussed below.

2.2.a: Drinkers and non-drinkers

The most basic classification of alcohol use reported on in survey research is the distinction between people who use alcohol (drinkers) and those who do not (non-drinkers or abstainers). Drinkers are typically defined as those who report using alcohol within a specific timeframe. However, timeframes within which alcohol use is measured may vary, and in some studies may be unspecified. For example, the 2012/13 *New Zealand Health Survey* (*NZHS)* (Ministry of Health, 2015) identified drinkers based on alcohol use during the past year, whereas the *2009-2011 Attitudes and Behaviour towards Alcohol Survey* (*ABAS*) (Research New Zealand, 2013) defined drinkers as those who reported drinking during the past four weeks, or those who said they use alcohol but had not done so in the past four weeks. Therefore, specified timeframes across which alcohol use is measured are a key detail to consider when interpreting research distinguishing drinkers and non-drinkers.

2.2.b: Drinking frequency and drinking quantity

Alcohol use is also often described in the literature based in terms of a) *drinking frequency,* which describes how often an individual consumes alcohol and/or b) *drinking quantity*, which refers to the amount of alcohol one typically consumes (Hodges & Maskill, 2014). Some standardized screening instruments developed for the identification of alcohol problems include measures of drinking quantity/frequency. For example, items from the *Alcohol Use Disorders Identification Test* (AUDIT) (Saunders et al., 1993) or its shorted version (AUDIT-C) (Bush et al., 1998) are included in several New Zealand surveys (e.g., Ministry of Health, 2015; Oakley-Browne et al., 2006; Towers et al., 2011). Alternatively, drinking quantity/frequency may be assessed using 'ad hoc' questionnaire items that are tailored to specific research questions. While ad hoc measures are often necessary, an advantage of standardized measures is that their utility has been empirically tested (Dawson, 2003).

As with research distinguishing drinkers and non-drinkers, an important consideration when interpreting drinking quantity/frequency data is the timeframe within which alcohol use is measured (Dawson, 2003). For example, the 2012/13 NZHS study (Ministry of Health, 2015) assessed drinking frequency by asking participants about the typical frequency at which they consumed alcohol during the past 12-months ('at least 3-4 times weekly'; '1 or 2 times weekly' 'less than 1 or 2 times weekly'). As another example, drinking frequency was measured in the 2009-2011 ABAS study (Research New Zealand, 2013) by asking participants to estimate the number of days they used alcohol during the past month (1 day, 2-4 days, 5-10 days, 11-29 days, or 30+ days). While both of these examples provide useful information, findings of studies reporting on drinking frequency/quantity measured across different timeframes cannot be directly compared for two reasons. Firstly, individual drinking patterns may change over time, and secondly, participants' ability to accurately recall drinking quantity/frequency is likely to decrease with increasing timeframes (Dawson, 2003).

Drinking quantity survey questions are often worded in terms of the 'typical' or 'usual' number of alcoholic drinks consumed per drinking day (Dawson, 2003). However, the amount of alcohol contained in an alcoholic beverage depends on its volume (i.e., serving size) and alcohol concentration (Dawson, 2003; Dufour, 1999). To deal with this issue, drinking quantity is sometimes assessed in terms of *standard drinks* (SDs), with each SD representing a fixed amount of pure alcohol (Dawson, 2003). The specific amount of alcohol contained in a SD varies across countries, and reflects the most commonly used alcohol serving size of the respective population (Kalinowski & Humphreys, 2016). The appeal of drinking quantity measures using SDs is that they attempt to increase measurement accuracy (Dawson, 2003; Dufour, 1999). However, this approach may actually present an additional source of measurement error because many respondents do not attempt to convert their responses into SDs, and some may be incapable of doing so (Dawson, 2003).

2.2.c: Moderate drinking, heavy drinking, binge drinking, and hazardous drinking

Some common descriptors used to report particular drinking patterns include moderate drinking, heavy drinking, binge drinking, and hazardous drinking. *Moderate drinking* and *heavy drinking* are terms researchers often use to categorize various levels of drinking quantity and/or frequency within a sample or population. In this context, heavy drinking typically implies a higher drinking quantity and/or frequency pattern, and may also refer to a drinking pattern that exceeds the recommendation of recognised guidelines for safe alcohol use (Dufour, 1999). *Binge drinking* is another aspect of alcohol consumption that researchers may be interested in, which generally refers to instances when an individual consumes a large quantity alcohol on one occasion. Binge drinking measured by the AUDIT (Saunders et al., 1993) or the AUDIT-C (Bush et al., 1998) is defined as ≥6 drinks consumed in the same day. However, definitions may vary with regards to the amount of consumed alcohol that constitutes a binge drinking episode (Gmel et al., 2003; Herring, Berridge, & 2008), and some studies apply

different thresholds for men and women (e.g., Courtney & Polich, 2009). *Hazardous drinking* (also referred to as 'risky drinking') refers to an alcohol consumption pattern that poses risk of short-term or long-term harm (Hodges & Maskill, 2014). Hazardous drinking is generally determined based on an individual's average drinking frequency, typical drinking quantity, and episodic binge drinking frequency. The AUDIT (Saunders et al., 1993) and the AUDIT-C (Bush et al., 1998) are commonly used measures of hazardous drinking.

2.3: PATTERNS OF ALCOHOL USE BY ADULTS AND OLDER ADULTS IN NEW ZEALAND

This section reviews survey research into the drinking patterns of New Zealanders, with particular attention being paid to New Zealand's older adult population. As discussed in the previous section (2.2), methods of measuring and describing patterns of alcohol use tend to vary. Relevant information about the alcohol use measures and/or descriptors used in each study reviewed in this section is therefore provided throughout this section, either in text or in footnotes. Overall, the studies reviewed below indicate that a) the vast majority of New Zealand adults and older adults drink alcohol at least occasionally; b) when compared with younger cohorts, New Zealand older adults drink more often but consume less alcohol per drinking occasion; c) approximately 40-50% of New Zealand older adults drink hazardously; d) in New Zealand, males tend to drink more often and consume larger amounts of alcohol per occasion than females; and e) older adults living in New Zealand consume alcohol at a higher rate than those living in most other countries.

2.3.a: Drinking prevalence

Results from the *2012/13 NZHS* study (Ministry of Health, 2015) indicate past 12-month drinking prevalence among New Zealanders aged ≥15 years is approximately 79%. Similarly, the *2009-2011 ABAS* study (Research New Zealand, 2013) found that 78% of a sample of New

Zealanders aged ≥18 years self-identified as drinkers[1]. This study also explored drinking prevalence across different age groups, and found that 76% of those aged 45-64 years and 73% of those aged ≥65 years self-identified as drinkers (Research New Zealand, 2013). More recently, the 2016 New Zealand *Health Work and Retirement* (HWR) study, which is a large nationally representative survey of New Zealand older adults, found that 83% of participants aged ≥50 years were identified as current drinkers based on AUDIT-C responses (Towers, Sheridan, et al., 2018). Overall, these findings indicate that the vast majority of New Zealand adults drink alcohol at least occasionally, and that rates of alcohol use remain high in older populations.

2.3.b: Drinking frequency and drinking quantity

The *2012/13 NZHS* (Ministry of Health, 2015) reported that approximately 31% of drinkers aged ≥15 years consume alcohol with 'high frequency' (3 or more times weekly). Drinking frequency in this study was higher among older age groups, with >50% of male drinkers aged ≥75 years and >40% of female drinkers aged 65-74 years being identified as high frequency drinkers. Similar age differences in drinking frequency were also observed in the 2009-2011 ABAS study (Research New Zealand, 2013), with rates of past month daily drinking being 1% among drinkers aged 18-24 compared with 15% among those aged ≥65 years. Both of these studies also found age differences in drinking quantity. The 2012/13 NZHS study (Ministry of Health, 2015) found that approximately 80% of drinkers aged 20-24 years reported drinking to intoxication during the past year, compared to <10% of those aged ≥75 years. Similarly, the 2009-2011 ABAS study, 54% of drinkers aged 18-24 consuming at least 7 drinks on their most recent drinking occasion, compared to 12% of those aged ≥65 years (Research New Zealand,

[1] Drinkers were defined as those who reported past four-week alcohol use, or those who said they use alcohol but had not done so in the past four weeks (Research New Zealand, 2013)

2013). These results therefore indicate older drinkers in New Zealand drink more often but consume less alcohol per drinking occasion when compared with younger cohorts.

2.3.c: Hazardous drinking

Three publications from the HWR survey (Stevenson et al., 2015; Towers el al., 2011; Towers, Sheridan et al.,2018) provide information about the prevalence of hazardous drinking measured using standardized AUDIT-C threshold scores[2] (Bush et al., 1998; Dawson et al., 2005). Findings from the 2006 NZHWR survey indicate a hazardous drinking prevalence of approximately 45% to 50% among New Zealanders aged 55-70 years (Stevenson et al., 2015; Towers et al., 2011), and 2016 NZHRW survey findings indicate approximately 40% of New Zealanders aged 50-89 years drink hazardously (Towers, Sheridan et al., 2018). These findings indicate a substantial portion of New Zealand's older adult population use alcohol in a way that poses risk of serious harm.

2.3.d: Gender differences

New Zealand survey findings show gender differences in drinking patterns in adult and older adult populations. The 2009-2011 ABAS study (Research New Zealand, 2013) found that, in comparison to adult female drinkers (aged ≥18-years), adult male drinkers were more likely to report drinking at least every second day during the past four weeks (19% versus 11%). Males were also more likely to report drinking ≥7 standard drinks on their most recent drinking day (35% versus 26%). Similar gender differences are seen in New Zealand's older adult population. Data from the 2010 HWR survey (Towers, Sheridan et al., 2017) indicates that

[2] AUDIT-C scores are yielded based on participant responses to three items assessing 1) typical drinking frequency (never, monthly or less, 2-4 times monthly, 2-3 times weekly, ≥4 or more times weekly); 2) quantity of drinks consumed on a typical drinking day (1-2, 3-4, 5-6, 7-9, ≥10); and 3) frequency of binge drinking as defined by ≥6 drinks consumed on a single occasion (never, less than monthly, weekly, daily or almost daily). Scores on each item range from 0-4, total scores range from 0-12, and an overall score of ≥4 is indicative of hazardous drinking (Bush et al., 1998; Dawson et al., 2005).

approximately 39% of older male drinkers and 29% of older female drinkers consume alcohol 4 or more times weekly. This study also found that female drinkers were more likely to drink two or less drinks on a typical drinking day (82% versus 46%), and less likely to consume 5 or more drinks per drinking day (6% versus 26%). Overall, these findings indicate New Zealand males tend to drink more often and consume more alcohol per occasion than females, and that these differences continue into older adulthood.

2.3.e: Differences across countries in older adult drinking patterns

Towers, Minicuci et al. (2017) compared survey data on older adult drinking patterns collected in nine countries, including New Zealand, England, the United States (US), China, Ghana, India, Mexico, Russian Federation, and South Africa. Among the countries included in the analyses, New Zealand had the second highest rate of past year drinkers (83%), which was only slightly lower than the rate observed in England (87%). This study also found that rates of heavy drinking[3] among older drinkers living in New Zealand (18%) were comparable to those living in England (17%), and considerably higher than the rates observed in many other countries (except China and South Africa). Moreover, while higher rates of heavy drinking were observed among drinkers living in China (31%) and South Africa (23%), population rates of alcohol use were much lower in both of these countries in comparison to New Zealand. Heavy drinkers therefore made up a larger portion of the older adult population in New Zealand (14%) than in China (11%) and South Africa (6%). Overall, these findings indicate the prevalence of alcohol use and heavy drinking by older adults in New Zealand is similar to England, and higher than most other countries (Towers, Minicuci et al., 2017).

[3] Towers et al. (2017) defined heavy drinking as ≥5 drinks on ≥3 days per week for men, and ≥3 drinks on ≥3 days per week for women.

2.4: DRINKING MOTIVES: WHY DO OLDER ADULTS DRINK?

Research highlights that, in New Zealand, there are concerning levels of alcohol use in older adults (Stevenson et al., 2015; Towers et al., 2011; Towers, Sheridan et al., 2018). In order to develop health or policy responses to change these drinking trends, it is important to understand why such drinking occurs in the first place. A study by Khan et al. (2006) exploring drinking motives in a sample of 100 New Zealand drinkers aged ≤65 years found that the most commonly endorsed reasons for drinking were related to social enhancement (e.g., drinking to be social), mood regulation (e.g., drinking to relax) and eating practices (e.g., drinking before meals). Similarly, a study of older adults living in Finland (Immonen et al., 2011) found that 'having fun or celebrating' and 'social reasons' were the most commonly endorsed drinking motives among participants. This Finnish study also found '*at-risk' drinkers*[4] were more likely to endorse drinking for mood regulation purposes (most commonly to relieve depression, loneliness, or anxiety). The findings of these studies therefore indicate that many older adults drink for social reasons, and that drinking to regulate mood is also common among older adults, particularly those engaging in hazardous (or 'risky') drinking patterns.

2.5: EFFECTS OF ALCOHOL ON OLDER ADULTS' HEALTH AND WELLBEING

One of the factors that is of paramount interest in international research on older adult's alcohol consumption is the effect that alcohol has on the health. This subsection reviews literature into the associations of alcohol use and health outcomes. Research indicating moderate drinking is associated with a variety of desirable health outcomes is discussed first, followed by a summary of the health risks associated with alcohol use during older adulthood.

[4] Immonen et al. (2011) defined 'at-risk' drinkers as those who reported consuming >7 drinks weekly, ≥5 drinks per typical drinking day, or ≥3 drinks on multiple days during a typical week

2.5.a: Relationship between moderate drinking and health

Epidemiological studies consistently show an inverted relationship between alcohol consumption and health, where moderate drinking is associated with better outcomes than abstinence or heavy drinking across a range of dimensions such as cardiovascular health (de Gaetano et al., 2002; Foerster et al., 2009; Matsumoto et al., 2014; Ronksley et al., 2011; Shai et al., 2004), cognitive functioning (Lang et al., 2007), and depressive symptoms (Chan et al., 2009; Coulson et al., 2014; Rodgers et al., 2000). While such findings are often interpreted as evidence for the health benefits of moderate drinking, it is possible that such findings reflect important existing sociodemographic and behavioural differences between moderate drinkers and abstainers (Fekjaer, 2013; Naimi et al., 2005). For example, Scott et al. (2020) found the relationship between moderate drinking and fewer depressive symptoms was explained by increased social interaction among older moderate drinkers. Similarly, Towers, Philipp et al. (2018) found that the relationship between moderate drinking and physical health was substantially reduced among older women and completely eliminated among older men when a control measure of socioeconomic status (SES) was included in their analysis. These results suggest the association between moderate drinking and positive health outcomes is largely the result of confounding variables rather than a causal relationship. In the absence of potential health benefits, it is important to understand whether older drinkers are placing themselves at increased risk of alcohol-related harm due to their patterns of consumption.

2.5.b: Risks associated with drinking in older adults

Physiological changes that occur during later life appear to increase older adult's vulnerability to many adverse health consequences of alcohol consumption. Body water content decreases during older adulthood, leaving a smaller volume of fluid across which consumed alcohol is distributed (Moore et al., 2007). Additionally, production of the enzyme alcohol-dehydrogenase (ADH), which is involved alcohol metabolism, decreases in later life (Moore

et al., 2007). Due to these changes in body-mass and metabolism, older adults generally show higher blood alcohol levels (BALs) in response to consumption relative to younger or middle-aged adults (Davies & Bowen, 1999; Jones & Neri, 1989; Pozzato et al., 1995). Older adults who misuse alcohol have heightened risk of cognitive impairment due to the acceleration of age-related declines in white matter (Sorg et al., 2015; Thomas & Rockwood, 2001). Alcohol misuse among older adults also increases risk of hip fracture due to lowered bone density and increased likelihood of falling because of the effect alcohol has on factors such as reaction time and balance (Yuan et al., 2001). Many chronic conditions that can be caused or exacerbated by alcohol (e.g., cirrhosis, dementia, pancreatitis, and gastritis) are highly prevalent in older populations (Moore et al., 1999). Unsurprisingly, rising alcohol consumption in older adults around the world is correlated with increasing rates of alcohol use disorders in older adults (Han et al., 2017) and alcohol-related hospitalisations of older drinkers (Sacco et al., 2015).

One of the most fundamental risks associated with drinking during older adulthood is the potential for harm associated with concomitant alcohol and medication use. With advancing age and associated onset of health morbidity, older adults are more likely to use one or more medications with the potential to cause an adverse *alcohol-medication interaction* (AMI) when used concomitantly with alcohol (*alcohol-interactive (AI) medications*) (Moore et al., 2007). While rates of AI-medication use in the New Zealand population are currently unknown, the prevalence of AI-medication use in a large US community sample was 43% among adults aged ≥20 years and 78% among those aged ≥65 years (Breslow et al., 2015). Moreover, health risks posed by heightened rates of AI-medication use among older populations are compounded by increased susceptibility to AMI related harm due to age-related physiological changes that typically occur during older adulthood (Moore et al., 2007).

2.6: SUMMARY

Alcohol consumption is highly prevalent among older adults living in New Zealand, with many older New Zealanders engaging in potentially harmful drinking patterns (Stevenson et al., 2015; Towers el al., 2011; Towers, Sheridan et al.,2018). Survey studies conducted in New Zealand and abroad indicate drinking motives relating to both social enhancement and mood regulation are common among older adults (Immonen et al., 2011; Khan et al., 2006), with mood regulation related drinking motives being most common among those engaging in potentially harmful drinking patterns (Immonen et al., 2011). Several studies have found evidence for an association between moderate drinking and desirable health outcomes (Chan et al., 2009; Coulson et al., 2014; de Gaetano et al., 2002; Foerster et al., 2009; Lang et al., 2007; Matsumoto et al., 2014; Rodgers et al., 2000; Ronksley et al., 2011; Shai et al., 2004), however this relationship likely reflects sociodemographic differences between groups who abstain, drink moderately and drink heavily, rather than a causal association (Fekjaer, 2013; Naimi et al., 2005; Scott et al., 2020; Towers, Philipp, et al., 2018). Risks of alcohol-related harm increase with age due to age-related changes in body mass, metabolism and illness susceptibility (Davies & Bowen, 1999; Jones & Neri, 1989; Moore et al., 1999 ; Mukamal et al., 2006; Pozzato et al., 1995; Sorg et al., 2015; Thomas & Rockwood, 2001; Yuan et al., 2001). In particular, the combination of increasing morbidity and ongoing alcohol use places older drinkers at heightened risk of harm due to their increased likelihood of using one or more AI-medications, and increased susceptibility to AMIs (Moore et al., 2007).

CHAPTER 3: ALCOHOL-MEDICATION INTERACTION PROCESSES

An understanding of the harm posed by *concomitant alcohol and AI-medication use* ('concomitant alcohol/AI-medication use' hereafter) among older adults requires consideration of the nature of *alcohol-medication interactions* (AMIs). There are three broad categories of AMI processes. Firstly, alcohol can reduce the therapeutic effectiveness of many medications by exacerbating the condition they are used to treat (Moore et al., 2007). Secondly, alcohol can enhance the effects of many medications directly – these are known as pharmacodynamic interactions. Thirdly, pharmacokinetic interactions can occur between alcohol and certain medications, which involve interferences in normal drug absorption, distribution, and metabolism (Adams, 1995; Moore et al., 2007; Nagaraj et al., 2017; Weatherman & Crabb, 1999).

3.1: ALCOHOL EXACERBATING CONDITIONS

Many conditions known to be exacerbated by alcohol are common in older populations, such as cognitive impairment, depression, diabetes mellitus, gastrointestinal problems, gout, hypertension, and insomnia (Moore et al., 2007). The use of alcohol by older adults with such conditions can have an indirect effect on the effectiveness of medication treatment. Specifically, as medication doses are selected based on the degree of morbidity (i.e., higher doses for more serious conditions), alcohol use may undermine the effectiveness of a prescribed medication dose by exacerbating the seriousness of the condition being treated (Moore et al., 2007).

3.2: PHARMACODYNAMIC INTERACTIONS

Alcohol can have pharmacodynamic interactions with medications that have similar effects to those caused by alcohol. For example, both alcohol and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen can cause gastrointestinal (GI) bleeding independently of one another. As a result, GI-bleeding risk is higher among persons using both alcohol and NSAIDs than those using only alcohol or only NSAIDs (Kaufman et al., 1999). Similarly, sedation and orthostatic hypotension are common effects of alcohol. Drugs that can cause sedation (e.g. benzodiazepines) and hypotension (e.g. barbiturates) can therefore exacerbate these effects of alcohol, and in turn increase the likelihood of alcohol-related falls (Moore, 2007). The risks of pharmacodynamic alcohol medication interactions are particularly relevant to older populations, as susceptibility to GI-bleeding increases with age (Moore, 2007), as does the likelihood of injury due to an alcohol-related fall (Stenbacka et al., 2002).

3.3: PHARMACOKINETIC INTERACTIONS

Pharmacokinetic interactions can occur between alcohol and a range of medications. Such interactions can occur due to interferences in a) the initial metabolism of alcohol in the stomach and liver (first-pass metabolism), b) the concentration of alcohol and/or medication through the body (distribution), and c) the final stage of alcohol and/or medication metabolism in the liver (hepatic metabolism).

3.3.a: First-pass metabolism

First-pass metabolism of alcohol refers to the initial stage at which alcohol is broken down by the body before reaching *systemic circulation* (i.e. the bloodstream) (Sharma et al., 1995). This first-pass metabolism process occurs in the stomach soon after ingestion. While alcohol is being absorbed from the gastrointestinal tract into the bloodstream (a process called gastric emptying), a small amount of alcohol is metabolized in the stomach by the enzyme ADH. The

remaining alcohol is then transported to the liver where it is metabolised further (Moore et al., 2007; Sharma et al., 1995). Some medications interfere with the first-pass metabolism of alcohol by inhibiting ADH activity in the stomach (e.g. acetylsalicylic acid; histamine H_2 receptor antagonists) or by increasing the rate of gastric emptying (e.g. metoclopramide). Such interactions cause increased blood alcohol levels (BALs) relative to alcohol consumption quantity, and are more likely to occur in older persons because ADH levels diminish with age (Moore, et al., 2007).

3.3.b: Distribution

Following first-pass metabolism, alcohol is distributed from the liver throughout the body water. Changes in the ratios of body fat and body water which normally occur with aging have an important impact on the distribution of alcohol (Moore et al., 2007; Weatherman & Crabb, 1999). Specifically, older adults typically have higher body fat ratios and lower body water ratios than younger adults, and therefore tend to have higher BALs relative to alcohol consumption volume (Davies & Bowen, 1999; Jones & Neri, 1989). Additionally, higher body fat ratio can increase the half-life of fat-soluble sedative drugs, such as benzodiazepines. Therefore, older adults who use alcohol and fat-soluble sedatives concomitantly may experience prolonged and increased sedation (Moore et al., 2007; Weatherman & Crabb, 1999).

3.3.c: Hepatic metabolism

Following distribution, alcohol is transported back to the liver and metabolised. This final stage in alcohol metabolism is called *hepatic metabolism*. While there are several pathways through which hepatic metabolism of alcohol may occur, key enzymes implicated in pharmacokinetic AMIs involving hepatic metabolism interference include ADH and *cytochrome P450* (CPY) enzymes (Adams, 1995; Moore et al., 2007; Nagaraj et al, 2017; Weatherman & Crabb, 1999).

For people who drink occasionally, ADH metabolizes most of the alcohol that reaches the liver. When alcohol is metabolized by ADH, it is converted into a chemical that is toxic to the liver called *acetaldehyde*, which is then further metabolized by *aldehyde dehydrogenase* (ALDH). A medication used for alcohol aversion therapy called *disulfiram* (commonly known as 'Antabuse') acts by inhibiting ALDH. Alcohol use during the course of disulfiram treatment elicits highly unpleasant symptoms (e.g. facial flushing, nausea, headache, and dyspnea) resulting from acetaldehyde accumulation (Adams, 1995; Moore et al., 2007; Nagaraj et al, 2017; Weatherman & Crabb, 1999). Disulfiram is not typically prescribed to older adults because the consequences of this type of AMI may be more serious in older adult populations (Adams, 1995). However, *disulfiram-like interactions* can occur between alcohol and other medications that inhibit ALDH activity, such as metronidazole (NZF, 2017).

AMIs involving interferences in CPY activity can occur when alcohol is used with medications that are metabolized by CPY enzymes (e.g. warfarin, benzodiazepines, phenytoin). For people who drink moderately, CPY enzymes metabolize a small fraction of alcohol that reaches the liver. However, regular heavy drinking can increase CPY enzyme activity 10-fold, which can result in a need for higher medication doses to achieve desired therapeutic effects (Moore et al., 2007). Episodic heavy drinking can deplete CPY enzymes, in turn increasing risks of medication overdose and alcohol poisoning (Moore et al., 2007; Weatherman & Crabb, 1999). Older persons may be particularly sensitive to these interactions because hepatic drug metabolism efficiency appears to decrease by up to 30% in older adulthood due to age related CPY enzyme impairment (Heuberger, 2012).

3.4: SUMMARY

In addition to the generally greater risks associated with alcohol use for older adults discussed in the previous chapter, alcohol use poses significant risk for older adults with medicated health

conditions (Moore et al., 2007). Alcohol may interfere with the therapeutic effects of medications by exacerbating the health condition they are used to treat. The harmful effects of alcohol may be exacerbated by medications which have similar effects to those caused by alcohol such as GI-bleeding, sedation, and hypotension. Other alcohol-medication interactions may result from interferences in the metabolism and distribution of alcohol and/or medications. Due to age-related changes in illness susceptibility, body-mass, and metabolism, older adults are particularly susceptible to alcohol-medication interactions (Adams, 1995; Moore et al., 2007; Nagaraj et al, 2017; Weatherman & Crabb, 1999). This places them at considerably higher risk of alcohol-related harm even for levels of drinking that may be considered non-hazardous for other age-groups or for healthier cohorts (Towers, Sheridan et al., 2018). The next chapter reviews research exploring the rate at which older adults may be exposed to AMIs.

CHAPTER 4: PREVALENCE OF AMI EXPOSURE & THE CONCOMITANT USE OF ALCOHOL AND AI-MEDICATION BY OLDER ADULTS

The previous chapter discussed the nature of AMIs, and highlighted that older adults are more vulnerable to AMI related harm relative to younger cohorts due to the physiological changes that occur with aging. To further explore the AMI related harm posed to older adults, this chapter reviews research exploring the prevalence of potential AMI exposure in older adult populations. Research into AMI related healthcare utilization is discussed first, followed by a review of survey research exploring rates of older adults who use of both alcohol and AI-medications.

4.1: AMI-Related Healthcare Utilisation Rates

While published data on the rate of AMI exposure in New Zealand is currently unavailable, hospital records show that the prevalence of AMIs is increasing in the US. The annual rates per capita of emergency department visits resulting from AMIs in the US doubled between 2005 and 2011 (Castle et al., 2016), and an analysis of hospital discharge records in the US state of Kentucky found a 187% increase in AMI-related hospital admissions among adults aged 50+ between 2001 and 2012 (Zanjani et al., 2016). These findings indicate growth in the public health burden resulting from concomitant alcohol/AI-medication use. However, many cases of concomitant alcohol/AI-medication use may not result in ED visits or hospitalisation. Therefore, to get a sense of the prevalence of concomitant alcohol/medication use among older adults, findings from survey studies must also be considered.

4.2: Estimated Prevalence of Concomitant Alcohol/AI-Medication Use Based on Survey Data

A number of survey studies exploring the prevalence of concomitant alcohol/AI-medication use have been conducted in the US (e.g., Breslow et al., 2015), Europe (e.g., Immonen et al., 2013), and Australia (Ilomäki et al., 2008). Data on medication use within community samples can be derived either by self-report measures or administrative data resources such as pharmaceutical dispensing records. However, self-report measures are necessary when assessing the prevalence of concomitant alcohol use by AI-medication users, because information on rates, frequency and quantity of alcohol use are not available via other sources for general community samples. There are also several methodological issues apparent in this field which impact upon the inferences drawn about rates of concomitant alcohol/AI-medication use. It is therefore necessary to briefly highlight these methodological issues before discussing the results of survey studies exploring the prevalence of concomitant alcohol/AI-medication use.

4.2.a: Methodological considerations

Some researchers have examined only a narrow range of medications, such as sedative/hypnotic medications (Bye et al., 2017; Ilomäki et al., 2008) and other classes of psychotropic drugs (Du et al., 2016; Wolf et al., 2017), when providing estimated rates of concomitant use. Consequently, prevalence estimates provided by these studies are limited to AMIs attributable to these classes of medications and the populations who use them. However, studies including a wide variety of medications in their analyses are difficult to compare due to differing populations of interest, and studies variously reporting information relating to a) rates of alcohol use among AI-medication users, b) rates of AI-medication use among drinkers, or c) overall sample rates of individuals identified as both drinkers and AI-medication users (i.e. concomitant users). Moreover, the research designs employed in such studies infer

concomitant use by measuring alcohol use and medication use separately, rather than directly assessing concomitant use with a single measure. For example, Qato et al. (2015) inferred concomitant alcohol/AI-medication based on survey questions regarding drinking frequency (alcohol measure), and by having participants provide containers of any medications they used regularly (medication use measure). Furthermore, any attempts to compare the findings of these studies are complicated by differences in specific measures and measurement thresholds used to identify drinkers and medication users. Consequently, the population prevalence of concomitant alcohol/AI-medication use is likely to be overestimated by studies using highly inclusive measurement thresholds and underestimated by those adopting more stringent thresholds. See chapter 10 for a more comprehensive review of survey research methods used to identify rates of concomitant alcohol/AI-medication use.

4.2.b: Results of survey data analyses

The results of six studies exploring rates of concomitant alcohol/AI-medication use using survey data from older adult samples in the US (Breslow et al., 2015; Pringle et al., 2005; Qato et al., 2015), Finland (Aira et al., 2005; Immonen et al., 2013) and Ireland (Cousins et al., 2014) are reviewed here. These studies are most relevant because they included a wide range of medication classes in their analyses (rather than focusing on a few potentially AI drug classes) and thus provide the best available evidence on the population prevalence of potential AMIs. As these studies have important methodological differences, their respective sample and measurement characteristics are summarized in Table 1, and the implications of their research designs are considered as their findings are discussed. This discussion is structured in terms of the reported rates of 1) alcohol use among study participants who are AI-medication users 2) AI-medication use in study participants who consume alcohol, 3) study participants identified as users of both alcohol and AI-medications (i.e., concomitant alcohol/AI-medication users), and 4) observed relationships between alcohol use and AI-medication use.

Table 1: Methodological Characteristics of Reviewed Survey Studies Reporting on Rates of Concomitant Alcohol/AI-Medication Use

Author	Sample Characteristics	Medication use measure	AI-Medication Identification Resource(s)	Alcohol use measure	Medication user definition	Drinker definition
Aira et al., 2005	523 community dwelling adults aged ≥75 years living in Finland	Prescription sheets for medications in current use were provided by participants	N/A	Interview questions about past year drinking quantity and frequency	Regular medication use at survey completion date (includes AI and non-AI medications)	≥1 drink weekly during past year
Immonen et al., 2013	2,100 community dwelling adults aged >65 years living in Finland	Participants listed medications prescribed by their doctors	SFINX (Böttiger et al., 2009)	Quantity and frequency questionnaire from the AUDIT (Saunders et al., 1993) and NIAAA (2007) guidelines	AI-medication in use at survey completion date	≥ drink monthly
Cousins et al., 2014	3,815 community dwelling adults aged ≥60 years living in Ireland	Participants provided containers for medications they used "on a regular basis, like every day or every week"	Stockley's Drug Interactions (2013); The British National Formulary (Joint formulary committee, 2013); and the Irish Medicines Formulary (2013)	CAGE (Ewing, 1984; Buchsbaum et al., 1992) and questions regarding past 6-month frequency and quantity of consumption	AI-medication use at survey completion date	≥1 drink during past 6 months

Notes: SFINX = The Swedish, Finnish, INteraction X-referencing; NIAAA = National Institute on Alcohol Abuse, & Alcoholism; AUDIT = Alcohol Use Disorders Identification Test; CAGE = Cut-down, Annoyed, Guilty, Eye-opener

Table 1: Continued

Author	Sample Characteristics	Medication use measure	AI-Medication Identification Resource(s)	Alcohol use measure	Medication user definition	Drinker definition
Breslow et al., 2015	26,657 community dwelling adults living in the US aged 20+; includes an older adult subsample (age ≥65 years)	One question about past month medication use, and participants also provided medication containers.	Drugs.com (2013) Caremark.com (2010); Healthline.com (2006); DailyMed (2014); NIAAA, (2014); Weathermon and Crabb, (1999)	Questions about past year drinking quantity and frequency	AI-medication use during past month	≥1 drink during past year and ≥12 drinks during lifetime.
Pringle et al., 2005	83,321 adults aged ≥65 living in the US and receiving medical benefits offered to older adults within a low-moderate income bracket.	Pharmaceutical claims records	First DataBank (2004)	Questions about drinking quantity and frequency, and drinking status (e.g. former drinker)	AI-medication dispensed during past 45 days	≥1 drink monthly
Qato et al., 2015	2,975 community dwelling adults aged ≥57 living in the US	Participants provided containers of medications they used regularly	Thomson Micromedex database (cited in Qato et al., 2015)	Questions about drinking quantity and frequency	Regular AI-medication use at survey completion	≥1 drink weekly during past 3 months

Note: NIAAA = National Institute on Alcohol Abuse, & Alcoholism

Alcohol use among AI-medication users

Reported rates of alcohol use among older AI-medication users range from approximately 20% in the US (Pringle et al., 2005) to approximately 60% in both Ireland (Cousins et al., 2014) and Finland (Immonen et al., 2013). However, these studies have important methodological differences which limit their interpretation and generalisability across countries. With regards to sampling, participants in the US study were substantially older than those participating in the other two studies. In addition, the US sample consisted exclusively of participants receiving pharmaceutical benefits offered to those within a low-income bracket, whereas the other two studies included nationally representative community samples. As both older age and lower SES have been associated with reduced alcohol use (Moos et al., 2005; Moore et al., 2005; Towers, Philipp et al., 2018), the lower rate of drinking in the US sample may reflect these differences. With regards to measurement differences, while the Finnish and US studies used similar thresholds to define participants as drinkers (those drinking at least monthly), the drinking criteria used in the Irish study was much more inclusive in comparison (those drinking during the past six months). Consequently, the results of the latter study may provide an overestimation of concomitant alcohol use among AI-medication users.

AI-medication use among drinkers

Reported rates of AI-medication use among older drinkers range from 77% in the US (Breslow et al., 2015) to 87% in Finland (Aira et al., 2005). However, these findings cannot be seen as indicative of population differences between the US and Finland due to important sampling and measurement differences between the studies (see Table 1). With regards to sampling differences, participants included in the Finish sample were older than those participating in the US study (≥75 years vs. ≥65 years). Given that the likelihood of AI-medication use increases with age (Moore et al., 2007), age differences likely contribute to the differing results between these studies. With regards to measurement differences, the US study only included

medications identified as AI in the analysis, whereas the Finish study did not exclude non-AI-medications. In addition, while participants identified as drinkers in the Finnish study reported using alcohol at least weekly, the inclusion criteria used to identify drinkers in the US sample required participants to report drinking at least once during the past year and at least 12 drinks during their lifetime. To summarize, the findings of these studies are not directly comparable due to age differences between to the two samples, and methodological differences in the identification of both alcohol users and AI-medication users.

Rates of concomitant alcohol/AI-medication use

Two US studies have reported on total sample rates of participants identified as both drinkers and AI-medication users. These studies indicate rates of concomitant alcohol/AI-medication use by older adults range from approximately 20% (Qato et al., 2015) to approximately 35% (Breslow et al., 2015). One important difference between these studies relates to the age of participants (Table 1), as Breslow et al. (2015) had an older sample than Qato et al. (2015). Both studies had similar designs in terms of AI-medication use identification, although a key measurement difference between these studies relates to drinking thresholds used to identify drinkers (Table 1). Qato et al. (2015) defined drinkers as those who reported using alcohol at least weekly, whereas participants identified as drinkers by Breslow et al. (2015) reported drinking during the past year. Therefore, the classification method used by Breslow et al. (2015) likely overestimated concomitant alcohol/AI-medication use, relative to the comparatively stringent classification method employed by Qato et al. (2015).

Relationships between alcohol use and AI-medication use

Five studies reviewed here explored relationships between alcohol use and AI-medication use among participants. Three studies (Breslow et al., 2015; Immonen et al., 2013; Qato et al., 2015) found that AI-medication use was significantly less common among drinkers when compared to non-drinkers, one study (Cousins et al., 2014; Immonen et al., 2013) found that

alcohol use was significantly less common among those using AI-medications, and one study (Pringle et al., 2005) found that individuals using multiple AI-medications were significantly less likely to consume alcohol. To summarize, a negative association between alcohol use and AI-medication use is a consistent finding in survey studies including a wide variety of AI-medications in their analysis.

4.3: SUMMARY

Published data relating to the prevalence of, and potential for, AMI exposure in New Zealand's older adult population is currently unavailable. While US research shows increasing rates of AMI related ED visits and hospital admissions (Castle et al., 2016; Zanjani et al., 2016), estimates of rates of concomitant AI-alcohol use in community samples of older adults vary greatly. Studies conducted in the US and Europe suggest a) 20%-60% of older AI-medication users use alcohol, b) 77%-87% older of drinkers use AI-medications, and c) one-in-five to one-in-three older adults use alcohol and AI-medications concomitantly (Aira et al., 2005; Breslow et al., 2015; Cousins et al., 2014; Immonen et al., 2013; Pringle et al., 2005; Qato et al., 2015). This variation likely reflects differences in methods used across studies, with key issues including the sources of data, the base population of interest, and the measurement and operationalisation of AI medication use, alcohol use, and concomitant alcohol/medication use. One consistent finding across survey studies exploring concomitant alcohol/AI-medication use, is that alcohol use is negatively associated with AI-medication use (Breslow et al, 2015; Cousins et al., 2014; Pringle et al., 2005; Qato et al., 2015). The next chapter reviews research into the motivating factors underlying drinking patterns among older AI-medication users.

CHAPTER 5: MOTIVATING FACTORS UNDERLYING DRINKING BEHAVIOUR AMONG AI-MEDICATION USERS

Research exploring the concomitant use of alcohol with a wide range of AI-medications consistently shows that AI-medication users are less likely to drink than non-users of AI-medications (Breslow et al, 2015; Cousins et al., 2014; Pringle et al., 2005; Qato et al., 2015). This suggests many older adults alter their alcohol intake to accommodate their medication regimes. However, the high rates of concomitant alcohol/AI-medication use reported across survey studies show that many older adults continue to drink despite using AI-medications. This chapter reviews literature exploring the motivating factors underlying drinking behaviour among older AI-medication users, and highlights research suggesting healthy changes in drinking behaviour may be particularly difficult for older AI-medication users with mental health problems such as depression.

5.1: AMI-RELATED KNOWLEDGE

Perhaps unsurprisingly, some research findings suggest knowledge about the potential adverse impact of concomitant alcohol/AI-medication use on health motivates changes in drinking behaviour among many AI-medication users. A qualitative analysis by Gavens et al. (2016) found that older persons who reduced their alcohol intake following chronic illness onset often cited discussions about potential AMIs with health professionals as motivation for drinking behaviour changes. Similarly, a survey study by Zanjani et al. (2013) found that, when compared to non-drinkers, older drinkers identified fewer AI-medications when completing a quiz (i.e., a list containing both AI and non-AI-medications) and had less knowledge of the potential alcohol-interactivity of medications they used personally. Another survey study by Wilkinson et al. (2016) found that older adults were more receptive to information relating to alcohol-medication interactions than other types of alcohol safety information, such as

recommended drinking guidelines and more general health risks of alcohol. Overall, these findings suggest that knowledge of the potential for alcohol to interact with medication is a strong motivator for changes in drinking behaviour for many older adults, perhaps even more so than other forms of alcohol safety information.

If AMI related health knowledge is associated with lower alcohol consumption, one might reasonably assume the provision of AMI related health information would facilitate reductions in alcohol consumption among adults taking potentially AI-medications. Accordingly, interventions aimed at reducing AMI exposure have focused on educating older adults about the risks associated with concomitant alcohol/AI-medication use in pharmacy settings (Benza et al., 2010; Zanjani et al., 2018a, 2018b, 2018c). These interventions have been shown to effectively increase older adults' AMI awareness at immediate post-test (Benza, et al., 2010; Zanjani et al., 2018a, 2018b) and three-month follow-up (Zanjani et al., 2018c). However, despite having positive effects on AMI awareness, educational interventions appear to have little effect on drinking intentions at post-test (Zanjani et al., 2018b) and have actually been associated with decreased intentions to reduce alcohol consumption at three-month follow-up (Zanjani et al., 2018c). In other words, while educational interventions appear to effectively increase older adults' AMI related awareness, simply providing AMI related information does not appear to facilitate desired changes in alcohol consumption and may actually have an adverse effect on drinking behaviour.

5.2: INFORMATION AVOIDANCE

The findings relating to AMI knowledge and drinking behaviour reviewed thus far seem somewhat contradictory. While the likelihood of alcohol use appears to be lower among older AI-medication users who are aware of the potential for AMI related harm, increasing older adults' awareness of AMI risks does not appear to facilitate healthy changes in drinking behaviour. A possible explanation for this discrepancy is that AI-medication users who change

their drinking behaviour in response to health information are more likely to have sought information about AMI risks than those less inclined to respond to such information. For example, Zanjani et al. (2013) found that older drinkers displayed less willingness to discuss the potential for AMI related harm with friends and family. Similarly, Gavens et al. (2016) found that many older chronically ill drinkers avoided discussing alcohol-related harm with health professionals and others rationalised their drinking with selective interpretations of health information, placing greater importance on evidence that health problems are unrelated to alcohol use. Additionally, a qualitative analysis by Zanjani, Allen, Smith et al. (2018) found pharmacy staff often cited denial of personal AMI risk as a key barrier to healthy changes in drinking behaviour among older adults. Overall, these findings highlight the possibility that some AI-medication users who do not alter their alcohol intake may actively avoid and/or dismiss information relating to AMI risks.

According to a review by Sweeny et al. (2010) exploring motivators of information avoidance in multiple contexts, people typically avoid information that challenges cherished beliefs and identifies a need for unwanted action or change. In the context of concomitant alcohol/AI-medication use, such information might be that which challenges beliefs about alcohol-related harm and highlights a need for reduced alcohol consumption. Barriers to changes in drinking behaviour may therefore serve to motivate avoidance of AMI related information for many older adults and may also prevent exposure to AMI information from leading to reduced alcohol consumption.

5.3: MENTAL HEALTH RELATED BARRIERS TO DRINKING BEHAVIOUR CHANGE

There is some evidence indicating barriers to drinking behaviour change may be heightened among older AI-medication users suffering from mental health problems. Firstly, the observed negative association between alcohol use and AI-medication use (Breslow et al, 2015; Cousins et al., 2014; Pringle et al., 2005; Qato et al., 2015) is less evident in studies focusing on

medications commonly used to treat psychiatric difficulties (e.g., Bye & Rossow, 2017; Ilomäki et al., 2008, 2013). For example, research from the US has shown that antidepressants are the most commonly used class of AI-medication among older drinkers (Qato et al., 2015), and are among the more commonly involved drug classes in AMI related emergency department visits (Castle et al., 2016). Secondly, a survey study of mental health service users conducted by Cheng et al. (2018) found that nearly half of the sample reported having used alcohol and psychotropic medications concomitantly despite having considered the risk of AMI prior to alcohol consumption (it is notable that antidepressants were the most commonly used medication class among participants in this study). Finally, qualitative findings suggest alcohol is often used to alleviate negative affect among chronically ill older adults (Gavens et al., 2016) and to 'self-medicate' depressive symptoms among older medication users (Haighton et al., 2018). To summarize, these findings suggest reliance on alcohol as an affect-regulation strategy may prevent changes in drinking behaviour among older adults with mental health problems, particularly those experiencing symptoms of depression.

5.4: SUMMARY

Research into factors motivating concomitant alcohol/medication use suggests older AI-medication users who drink typically have less knowledge of AMI risks than those who abstain from alcohol (Zanjani et al., 2013). However, interventions aim to educate older adults about AMI risks do not appear to motivate healthy changes in alcohol consumption, despite effectively enhancing awareness of AMI related harm (Benza et al., 2010; Zanjani et al., 2018a, 2018b, 2018c). Other research findings suggest this discrepancy may be due to avoidance and/or denial of AMI-related information among older drinkers who are less inclined to change their drinking behaviour in response to health information (Gavens et al., 2016; Zanjani et al., 2012; Zanjani, Allen, Smith et al., 2018). There is therefore a need to identify barriers to drinking behaviour change among AI-medication users.

There is also evidence that mental health factors such as depression may hinder drinking behaviour change among AI-medication users. Alcohol use is common among users of medications used to treat psychiatric conditions such as depression (Bye & Rossow, 2017; Ilomäki et al., 2008, 2013; Qato et al., 2015), and users of mental health services often report using alcohol and medications concomitantly despite being aware of the potential for AMI related harm (Cheng et al., 2018). Additionally, qualitative research indicates older AI-medication users may often use alcohol to regulate emotion and/or 'self-medicate' symptoms of depression (Gavens et al., 2016; Haighton et al., 2018). The next chapter aims to explain these findings using theories of health behaviour and alcohol use.

CHAPTER 6: MOTIVATIONAL THEORIES OF HEALTH BEHAVIOUR AND ALCOHOL USE

The research reviewed in the previous chapter provided a starting point to form hypotheses for the second study conducted in the present thesis. This chapter aims to contextualize these findings using motivational theories of health behaviour and alcohol consumption.

6.1: SOCIAL COGNITIVE THEORIES OF HEALTH BEHAVIOUR: MOTIVATION TO CHANGE

The term *health behaviour* broadly refers to any behaviour performed in the service of preventing adverse health outcomes and/or promoting health and well-being (Norman & Conner, 2005). Altering alcohol consumption to reduce risk of AMI is therefore an example of health behaviour that is highly relevant to the present thesis. Several *social cognitive theories* attempt to explain the way cognitive factors (e.g., thoughts, beliefs, attitudes) influence health behaviour engagement (Norman & Conner, 2005; Sutton, 2000). These theories may therefore provide insight into psychological factors motivating changes in drinking patterns among AI-medication users.

Social cognitive theories of health behaviour can generally be divided into two groups: *Motivational models* focus on identifying predictors of health behaviour at single points in time; and *stage models* focus on identifying the processes through which health behaviours change over time (Sutton, 2000). The appeal of stage models is their consideration of factors determining whether adopted health behaviours are maintained. However, the components of stage models are not easily applied to cross-sectional research (Sutton, 2000). The present subsection therefore focuses on dominant motivational health behaviour models including *Self-Efficacy Theory* (SET) (Bandura, 1982); the *Health Belief Model* (*HBM)* (Janz & Becker, 1984; Rosenstock, 1974; Rosenstock et al., 1988); *Protection Motivation Theory*

(*PMT)* Maddux, & Rogers, 1983; Rogers, 1975); and the *Theory of Planned Behaviour* (TPB) (Ajzen, 1991). The key constructs and general tenets of these theories are summarized in Table 2.

6.1.a: Evaluation of models in relation to AMI related health behaviour

Overall, there is substantial overlap between the theories included in Table 2. Each model assumes that people are future oriented, and that behaviour is influenced by personal evaluations of the pros and cons of possible courses of action (Sutton, 2002). The primary point of difference between these models relates to specific construct definition. Lippke and Ziegelmann (2008) therefore argue that the value of each social cognitive model often depends on the specific health behaviour in question. Therefore, the present subsection seeks to identify which model best provides a parsimonious account of the findings discussed in chapter 5.

Table 2: Motivational Models of Health Behaviour: Key Constructs and General Tenets

Model	Key constructs	General tenet of the model
SET	***Outcome expectancies***: beliefs about the positive and negative consequences of a given behaviour (e.g. physical health outcomes; social and self-evaluative outcomes) ***Self-efficacy:*** an individual's beliefs about their ability to successfully perform a given behaviour	Health behaviour is more likely if one a) expects the resulting positive consequences to outweigh the negative consequences and b) has high self-efficacy beliefs in relation to the health behaviour.
HBM	***Cue of action:*** any stimuli that draws attention to the threat of adverse health outcomes and in turn initiates decision making processes about health behaviour ***Perceived susceptibility:*** beliefs about personal vulnerability to a given adverse health outcome ***Perceived severity***: beliefs about the potential severity of an adverse health outcome ***Perceived benefits:*** beliefs about the effectiveness of health behaviours ***Perceived barriers:*** beliefs about potential downsides of health behaviour engagement ***Self-efficacy:*** an individual's beliefs about their ability to successfully perform a health behaviour	Health behaviour is more likely if one a) perceives the threat of illness/harm to be high, b) believes the resulting positive consequences outweigh the negative consequences, and c) has high self-efficacy beliefs in relation to the behaviour.

Table 2: Continued

Model	Key constructs	General tenet of the model
PMT	***Protection motivation:*** motivation to protect oneself against adverse health outcomes ***Adaptive responses*** (to threat): adopting health behaviour ***Maladaptive responses:*** responding to threat of illness/harm in a way that does not reduce risk (e.g. denial of risk) ***Response costs:*** perceived negative aspects of performing adaptive behaviour ***Rewards***: perceived positive/rewarding aspects of maladaptive behaviour ***Vulnerability appraisal:*** beliefs about personal vulnerability to a given adverse health outcome ***Severity appraisal***: beliefs about the potential severity of an adverse health outcome ***Response efficacy:*** the perceived usefulness/effectiveness of a health behaviour ***Self-efficacy:*** an individual's beliefs about their ability to successfully perform a health behaviour	Health behaviour is more likely if one a) perceives the threat of illness/harm to be high, b) believes the rewarding aspects of maladaptive behaviours to be minimal, c) perceives the costs of health behaviour to be small, d) believes health behaviour will mitigate threat and/or promote health, and e) has high self-efficacy beliefs in relation to the behaviour .
TPB	***Intentions:*** the intention to perform a given behaviour ***Attitudes:*** personal evaluations a given behaviour ***Behavioural beliefs:*** beliefs about the consequences of a given behaviour, which are thought to underpin one's attitude toward that behaviour ***Subjective norms***: perceived expectations of other people regarding the behaviour ***Normative beliefs:*** beliefs about others' expectations, which are thought to underpin one's subjective norm in relation to health behaviour. ***Perceived behavioural control:*** the perceived level of ease/difficulty in performing a health behaviour ***Control beliefs:*** beliefs that formulate one's perceived behavioural control	Health behaviour is more likely if one a) believes the positive consequences outweigh the negative consequences; b) believes the health behaviour is evaluated positively by important others', and c) perceives the behaviour to be relatively easy to perform (similar to self-efficacy beliefs)

Awareness of AMI risk motivates health behaviour change

A key research finding discussed in the previous chapter is that knowledge of potential AMI risks appears to motivate many older adults to reduce their alcohol intake (Gavens et al., 2016; Wilkinson et al., 2016; Zanjani et al., 2013). The idea that awareness of the potential threat of

illness or harm motivates health behaviour is implicit in all of the social cognitive models reviewed (e.g., outcome expectancies in SET; behavioural beliefs in TRA/TPB). However, only two models (HBM; PMT) include specific constructs relating to perceived threat of adverse health outcomes (perceived susceptibility/severity; vulnerability/severity appraisals; see Table 2).

Information avoidance and denial of risk among concomitant AI-medication users

Another key research finding is that alcohol use among AI-medication users is often associated with a range of avoidant coping strategies, such as avoiding AMI related health information (Gavens et al., 2016; Zanjani et al., 2013) and denying personal AMI-risk (Zanjani, Allen, Smith et al., 2018). Among the reviewed social cognitive theories of health behaviour (Table 2), PMT is the only model with a specific construct that accurately captures this behaviour (i.e., maladaptive responses).

Mental health and self-medication as barriers to change

Each model in Table 2 includes constructs that partially explain findings suggesting self-medication is often barrier to drinking behaviour change among AI-medication users with mental health issues such as depression (e.g., Cheng et al., 2018; Gavens et al., 2016; Haighton et al., 2018). For example, self-medication may influence one's expectations about alcohol use (outcome expectancies; rewards; behavioural beliefs) and reduced drinking (outcome expectancies; perceived barriers; response costs; behavioural beliefs). Additionally, reliance on alcohol to regulate affect may influence the extent to which one feels capable of change (self-efficacy; perceived behavioural control). However, health behaviour theories do not directly explain the relationship between depression and self-medication via alcohol use.

6.1.b: Protection Motivation Theory (PMT)

Among the social cognitive health behaviour theories reviewed in this chapter (Table 2), Rogers' (1975) PMT appears to provide the best parsimonious account of the research reviewed in chapter 5. PMT was developed to explain the way people respond to information about health-related threat. The model defines responses to such information as either *adaptive responses* (i.e. adopting a recommended health promoting behaviour) or *maladaptive responses* (e.g. avoidance, wishful thinking, denial). These responses are thought to depend on one's level of protection motivation (the intention to perform a recommended health behaviour), with higher protection motivation increasing the likelihood of adaptive responses. Two independent fear appraisal processes are thought to influence protection motivation, including threat appraisals and coping appraisals. The *threat appraisal* process involves an evaluation of *severity (*of the adverse health outcome) and *vulnerability* (personal susceptibility to the adverse health outcome). Protection motivation is thought to increase when threat is perceived to be high, unless there is some advantage in performing maladaptive behaviour (*rewards*). The coping appraisal process includes *response-efficacy* (the perceived usefulness of a health promoting behaviour) and *self-efficacy* (beliefs about personal ability to successfully perform a given behaviour). Protection motivation is thought to increase when response-efficacy and self-efficacy are perceived to be high, unless the cost of health behaviour engagement (*response cost*) is perceived as being too great (Maddux, & Rogers 1983; Rogers, 1975).

Overall, PMT (Maddux & Rogers, 1983; Rogers, 1975) includes constructs conceptualizing perceived health threat as a motivator for health behaviour change (severity/vulnerability), which supports research indicating awareness of AMI risk is associated with reduced alcohol consumption (Gavens et al., 2016; Wilkinson et al., 2016; Zanjani et al., 2013). The construct of *maladaptive responses* captures the avoidant coping strategies associated with continued

alcohol use among older AI-medication users (Gavens et al., 2016; Zangani et al., 2013, 2018d). Additionally, PMT includes several constructs (rewards, response costs, self-efficacy) which explain how self-medication with alcohol may prevent changes in drinking patterns (Gavens et al., 2016; Haighton et al., 2018). However, none of the health behaviour theories reviewed (including PMT) explains why self-medication with alcohol is commonly reported among AI-medication users with depression (Haighton et al., 2018). The following subsection therefore discusses this relationship in relation to motivational theories of alcohol use.

6.2: THEORIES OF ALCOHOL USE: MOTIVATION TO DRINK

Motivational models of alcohol use conceptualize drinking as a strategic behaviour for regulating affect (Cooper et al., 1995; Cox & Klinger, 1988). The motivational model proposed by Cooper et al. (1995) distinguishes between *coping motives* (drinking to escape, avoid, or alleviate unpleasant emotions) and *enhancing motives* (drinking to increase positive emotional and/or social experiences).

Coping and enhancing motives appear to differ in terms of both antecedents and consequences. Factors which are predictive of enhancing motives include positive alcohol expectancies relating to social/emotional enhancement, sensation seeking tendencies, and positive affect. In contrast, positive expectations about the tension reduction properties of alcohol, avoidant coping tendencies, emotional dysregulation, and higher negative affect appear predictive of coping motives (Cooper et al., 1995). Given that emotional dysregulation and negative affect are core features of most emotional disorders (Hofmann et al., 2012), Cooper's model may help to explain the potential relationship between depression and alcohol/AI-medication use.

With regards to consequences, *coping motives* appear more predictive of alcohol dependence than *enhancing motives* (Cooper et al., 1992; 1995). Cooper et al. (1995) suggest this is because the motivational consequences of negative affect are considerably more powerful than those of

positive affect. Individuals who predominantly use alcohol for *coping motives* may therefore become reliant on alcohol to regulate unpleasant emotions that occur in everyday life. In contrast, individuals who drink for *enhancing motives* are able to exert greater personal control over their alcohol consumption, and choose to drink when they see fit (Cooper et al., 1995). This model therefore provides further support the idea that self-medication (or drinking to cope) may lower alcohol related *self-efficacy* among AI-medication users.

6.3: SUMMARY

The present chapter aimed to identify theories that help explain the motivational factors underlying drinking behaviour among older adults who use AI-medications. Protection motivation theory (Maddux & Rogers, 1983; Rogers, 1975) includes several constructs that help explain research findings implicating AMI related knowledge, avoidant coping strategies, and self-medication with alcohol as common factors influencing drinking behaviour among AI-medication users. Cooper's motivational model of alcohol use (Cooper et al., 1992; 1995) provides further explanation of a potential relationship between self-medication related drinking motives and concomitant alcohol/AI-medication use. Additionally, Cooper's model also helps explain why self-medication with alcohol may be more common among AI-medication users with depression. The next chapter reviews relevant literature relating to the occurrence of depression during older adulthood.

CHAPTER 7: DEPRESSION DURING OLDER ADULTHOOD

As discussed in section 5.3, research findings indicate concomitant alcohol use may be more common among older AI-medication users with depression. The present chapter therefore reviews relevant literature into depression during older adulthood. This includes discussion of a) the term 'late-life depression', b) key symptoms of late-life depression, c) the prevalence of depression among older adults, d) the aetiology of late-life depression, and e) common factors associated with both depression and AI-medication use.

7.1: DEFINING LATE-LIFE DEPRESSION

Generally speaking, the term *late-life depression* refers to depression that is experienced during older adulthood. This includes depression with onset during older adulthood (*late-onset late-life depression*), and depression that persists during older adulthood from earlier life (*early-onset late-life depression*). More specifically, *late-life depression* is often used to refer to the occurrence of depressive syndromes during older adulthood (Alexopulos, 2005), such as those described by the *Diagnostic and Statistical Manual for Mental Disorders* (DSM) (American Psychiatric Association, 2013). When used in this way, the term usually refers to *Major Depressive Disorder* (MDD), but may also describe other unipolar depressive disorders such as *dysthymia*. Additionally, late-life depression may also refer to patterns of depressive symptoms falling below the threshold required for an MDD diagnosis (Fiske et al.,2009; Meeks et al., 2011; Rodda et al., 2011), sometimes referred to as '*sub-threshold depression'* (SubD). While less severe than MDD, SubD greatly reduces health and quality of life among older adults, and is approximately 2-3 times more prevalent than major depression in older adult populations (Meeks et al., 2011).

7.2: Symptoms of Depression in Older Adulthood

Depressed mood and a loss of interest in normally pleasurable activities (anhedonia) are generally considered to be the core features of depression, and the presence of one of these symptoms is required for a diagnosis of MDD (American Psychiatric Association, 2013). Additional depressive symptoms include cognitive disturbances (e.g. difficulty concentrating, negative thoughts, feelings of worthlessness, hopelessness, or suicidal ideation); psychomotor agitation (e.g. irritability, restlessness) or retardation (e.g. flat affect, slowed body movements); vegetative symptoms (e.g. sleep disturbance, eating disturbance, changes in body weight, loss of energy, fatigue, or reduced sexual desire); and anxiety symptoms (Stefanis & Stefanis, 1999).

While the overall symptom presentation of depression can be similar for younger and older adults (Chiu et al., 2003), the likelihood of certain symptoms appears to change during older adulthood. Depressive symptoms that appear more common among older adults include impaired cognitive processing speed, executive dysfunction (Butters et al., 2004), early morning wakening, fatigue, hopelessness (Christensen et al., 1999), anxiety, irritability, and somatic symptoms (Taylor, 2014). Dysphoria and feelings of worthlessness or guilt appear to be less common in older persons (Gallo et al., 1994, 1997).

7.3: Prevalence of Late-Life Depression

While the current prevalence of late-life depression in New Zealand is unclear, data collected from the 2002/3 *New Zealand Mental Health Survey* indicated the past 12-month prevalence of MDD was 5.2% among New Zealanders aged 45-65 and 1.7% among those aged 65+ (Wells et al., 2006). However, according to *The World Health Organisation* (WHO), the global prevalence of depression has risen in recent years, and depression is now the leading global

cause of poor health and disability (WHO, 2017a). Additionally, while rates of depression were once less prevalent in older populations (Byers et al., 2010; Henderson et al., 1998; Wells et al., 2006), recent estimates suggest the prevalence of depression peaks between the ages of 55-74 (WHO, 2017b). This shift may be partially explained by changes in rates of late-life depression risk factors (discussed in the next subsection), given that rates of chronic illness, disability, and poor self-rated health are considerably higher among the baby-boomers than previous generations (King et al., 2013).

7.4: Aetiology of Late-Life Depression

Late-life depression has been described as "the quintessential biopsychosocial disorder" (Aziz & Steffens, 2013, p. 511). In other words, a broad range of biological, psychological, and social variables appear to be involved in the aetiology of late-life depression. Some factors appear associated with increased vulnerability to late-life depression (i.e., risk factors), while others are associated with decreased late-life depression vulnerability (i.e., protective factors). However, the significance of certain risk factors appears to differ depending on the age at which symptoms of depression first appear. Specifically, non-genetic biological factors appear to be the most significant risk factors associated with depression that arises during older adulthood (late-onset late-life depression), whereas psychosocial and genetic factors appear to have greater association with depression arising prior to older adulthood (early-onset late-life depression) (Fiske et al., 2009).

7.4.a: Psychosocial factors

Several psychological factors (e.g., neuroticism, rumination, and avoidant coping styles) appear to increase risk of depression across all stages of the lifespan, including older adulthood (Fiske et al., 2009). There are also a variety of social factors which appear to increase risk of depression across the lifespan, such as stressful events (e.g., bereavement, divorce), lower SES,

and decreased social support (Fiske et al., 2009; Rodda et al., 2011). Interestingly, while the occurrence of many social risk factors for depression increases during later life, the relative impact of these factors on the occurrence of depression appears to be stronger during younger and middle adulthood than during older adulthood (Fiske et al., 2009; Rodda et al., 2011). This may partially be due to the predictability of particular social risk factors during later life (Rodda et al., 2011). For example, adjusting to the death of a spouse can be particularly difficult during midlife, as this is typically an unexpected event at this stage of life. In contrast, older adults who experience spousal bereavement are more likely to have prepared themselves for this event, and may therefore be better able to adjust to life without their spouse (Rodda et al., 2011). There is also some evidence that certain psychological resilience factors increase during older adulthood, and this may reduce the impact of social risk factors on depression (Fiske et al., 2009). In particular, older adults are more likely to utilize the cognitive strategy of 'positive reappraisal' in response to life stressors, and tend to focus more on emotionally meaningful and positive aspects of experience. Therefore, older adults appear more likely to utilize cognitive strategies that foster effective emotional regulation, which may in turn protect against depression in response to social stressors (Fiske et al., 2009).

7.4.b: Genetic factors

Estimates of MDD heritability range from 28% (Fernandez-Pujals et al., 2015) to 38% (Kendler et al., 2006; Sullivan et al., 2000). However, genetic influence on the occurrence of depression appears to be less significant in depression with onset during older adulthood (Fiske et al., 2009). For example, a study by Tozzi et al. (2008) found that age of MDD onset was significantly earlier among those with a family history of depression, and that MDD with onset after age 50 years was not associated with depression among biological relatives. Similarly, a large twin study by Kendler et al. (2005) found that early onset in twins with MDD increased likelihood of MDD occurrence in co-twins. Given that approximately half of late-life

depression cases have a late-onset (Fiske et al., 2009), the influence of genetic vulnerability on rates of depression is likely to be lower in older populations than younger populations.

7.4.c: Non-genetic biological risk-factors

Theoretical models of late-life depression generally stress the importance of non-genetic biological risk factors (see Aziz & Steffens, 2013; Blazer & Hybels, 2005; Fiske et al., 2009). Normal age-related changes in neurotransmitter and endocrine activity may contribute to depressive symptoms (Blazer & Hybels, 2005), and physical conditions that increase vulnerability to depression are common in later life (Alexopolous, 2005; Aziz & Steffans, 2013; Blazer, 2003; Blazer & Hybels, 2005; Fiske et al., 2009). Some of the strongest predictors of late-life depression include poor self-rated health, physical disability or functional impairment, physical pain, sleep disturbance, and the presence of chronic illness (see Chang-Quan et al., 2010; Cole & Dendukri, 2003; Djernes, 2006; Vink et al., 2008). While virtually any serious chronic health condition can contribute to the development of late-life depression (Fiske et al., 2009), specific illnesses identified as risk-factors include hypertension and hypotension (Vink et al., 2008), diabetes, respiratory disease, endocrinological disorders (Djernes, 2006), cardiovascular disease, cerebrovascular disease, Parkinson's disease, and dementia (Djernes, 2006; Vink et al., 2008).

7.5: Prevalence of Late-life Depression Among AI-Medication Users

Research exploring cross-sectional predictors of late-life depression show the prevalence of depression is heightened among older adults who use somatic and/or psychotropic medications (Djernes, 2006; Vink et al., 2008). Moreover, many of the non-genetic biological risk factors for depression described above likely go hand-in-hand with AI-medication use. For example, sedative medications used to treat sleep disturbances interact with alcohol by enhancing the sedating effects of both drugs; many pain killers used to treat physical pain may interact with

alcohol, and medication used to treat many chronic conditions associated with late-life depression (e.g., diabetes, respiratory disease, dementia, Parkinson's disease) may interact with alcohol (Moore et al., 2007). It is therefore likely that the prevalence of depression is heightened among older adults using AI-medications due to heightened prevalence of depression risk factors in this population.

7.6: SUMMARY

Late-life depression refers to experiences of depressive symptoms that occur during older adulthood. Biological factors are of particular significance to the aetiology of late-life depression, many of which are likely to be associated with AI-medication use. Therefore, depression is likely to be common among older adults who use AI-medications. Given the evidence for an association between depression and alcohol use among older AI-medication users (Cheng et al., 2018; Gavens et al., 2016; Haighton et al., 2018), further research exploring the potential moderating effects of depression on the relationship between AI-medication use and alcohol use is warranted.

CHAPTER 8: SUMMARY AND RESEARCH GAPS

Cross-national comparisons of survey data indicate New Zealand has one of the highest rates of alcohol use by older adults globally (Towers et al., 2017). Given that vulnerability to alcohol related harm increases during older adulthood (Davies & Bowen, 1999; Jones & Neri, 1989; Moore et al., 1999 ; Mukamal et al., 2006; Pozzato et al., 1995; Sorg et al., 2015; Thomas & Rockwood, 2001; Yuan et al., 2001), there is a need for research into the prevalence and impact of alcohol related health issues in New Zealand's rapidly growing older adult population. One key issue is the potential harm posed to older adults using both alcohol and AI-medication (Moore et al., 2007). Older adults are more likely to use AI-medications than younger cohorts, and are more susceptible to AMI related harm due to age related changes in body mass and metabolism (Adams, 1995; Moore et al., 2007; Nagaraj et al, 2017; Weatherman & Crabb, 1999). Analyses of survey data indicates a high prevalence of concomitant alcohol/AI-medication use among older adults living in the US (e.g., Breslow et al., 2015; Qato et al., 2015) and Europe (e.g., Cousins et al., 2014). However, the prevalence of AMI risk among New Zealand older adults is currently unknown. There is therefore a need for research exploring the prevalence and associated public health burden of concomitant alcohol/AI-medication use by older adults in New Zealand.

There is also a need to explore motivating factors underlying differences in alcohol use among older AI-medication users, as this may help inform interventions aimed at reducing AMI related harm. Existing research indicates awareness of personal AMI related harm is a key factor associated with reduced alcohol use among older AI-medication users (Gavens et al., 2016; Wilkinson et al., 2016; Zanjani et al., 2013), whereas avoidant coping strategies (such as information avoidance, wishful thinking, and denial) may be associated with unsafe alcohol/AI-medication use (Gavens et al., 2016; Zanjani, Allen, Smith et al., 2018). There is also some evidence suggesting drinking motivated for the purpose of self-medication may

prevent changes in alcohol use among AI-medication users with mental health issues, particularly depression (Cheng et al., 2018; Gavens et al., 2016; Haighton et al., 2018). Moreover, a variety of conditions which are often treated with AI-medications are also associated with late-life depression (Djernes, 2006; Moore et al., 2007; Vink et al., 2008). Therefore, the prevalence of depression may be heightened among older adults who use AI-medications. However, the potential moderating effects of depression on the relationship between alcohol use and AI-medication use have not been explored in a large community sample. Further research is therefore needed into the potential relationships between alcohol use, AI-medication use, and depression among older adults.

CHAPTER 9: THE PRESENT INVESTIGATION

The present research aimed to expand existing knowledge relating to concomitant alcohol/AI-medication use by older adults, while also addressing the research gaps discussed in chapter 8. Two cross-sectional analyses were conducted using survey data collected from the New Zealand Health, Work and Retirement study (Towers & Noone, 2007; Towers & Stevenson, 2014), and linked national pharmaceutical dispensing data accessed from the New Zealand Pharmaceutical Collection (Ministry of Health, 2015). These analyses explored a range of research questions relating to the prevalence and correlates of concomitant alcohol/AI-medication use among New Zealand older adults, and hypotheses were informed by the literature reviewed in the previous chapters of this thesis. These research questions and hypotheses are described below. The contents of subsequent chapters are then summarized.

9.1: RESEARCH QUESTIONS AND HYPOTHESES

9.1.a: Research questions

1. *What is the prevalence of concomitant alcohol/AI-medication use in New Zealand's older adult population? (explored in studies 1 and 2)*
2. *Does concomitant alcohol/AI-medication use impact on physical health and healthcare utilization among older New Zealanders? (study 1)*
3. *Is there a relationship between AI-medication use and alcohol use among New Zealand older adults, and do differences in AMI risks associated with various AI-medications influence the strength of this relationship? (study 2)*
4. *Does depression moderate the potential relationship between AI-medication use and alcohol use? (study 2)*

9.1.b: Hypotheses for research question 2:

In relation to the second research question, as outlined in chapter 3, research shows that vulnerability to AMI related harm increases during older adulthood. This led to hypotheses 1 and 2.

- *Hypothesis 1: concomitant AI-medication use will be negatively associated with self-reported physical health after controlling for associations of alcohol use and AI-medication use individually*
- *Hypothesis 2: after controlling for the individual associations of AI-medication use and alcohol use, concomitant alcohol/AI-medication use will be positively associated with healthcare utilization*

9.1.c: Hypotheses for research question 3:

Hypotheses in relation to the third research question were informed by literature reviewed in chapters 5 and 6, including research findings and theory (PMT). Previous research has consistently shown a negative association between AI-medication use and alcohol use. Awareness of personal AMI risk appears to motivate reduced alcohol consumption for many older AI-medication users, which supports the PMT proposition that appraisals of personal *vulnerability* to health threat often motivates health behaviour. Additionally, PMT would also suggest appraisals of the *severity* of health threat exert influence on health behaviour. This led to hypotheses 3 and 4.

- *Hypothesis 3: AI-medication use will be negatively associated with alcohol use*
- *Hypothesis 4: The strength of the hypothesized negative association between AI-medication use and alcohol use will be strongest for AI-medications associated with higher AMI risks*

9.1.d: Hypothesis for research question 4:

The hypothesis in relation to research question four was informed by research reviewed in chapter 5 and theory reviewed in chapter 6 (PMT; Cooper's drinking model), suggests depression may be associated with alcohol consumption for self-medication purposes (coping motives), which may in turn prevent changes in alcohol consumption by AI-medication users. This led to hypothesis 5:

- *Hypothesis 5: depression will weaken the hypothesized negative association between AI-medication use and alcohol use*

9.2: Summary of Subsequent Chapter Content

9.2.a: Summary of chapter 10

The next chapter of the present thesis reviews the research designs implemented in previous survey studies exploring rates of concomitant alcohol/medication. The purpose of chapter 10 was to identify key strengths and limitations of various methods for measuring and classifying alcohol use, AI-medication use, and concomitant alcohol/AI-medication use. The conclusions drawn from this review were then used to inform the research designs implemented in the present project.

9.2.b: Summary of chapter 11

Chapter 11 is divided into two main sections. The first section (11.1) establishes a research protocol for classifying the alcohol-interactivity potential of medications, and for using participants' pharmaceutical records to measure AI-medication use in survey research. The implementation of this research protocol in the present project is then described in section 11.2.

9.2.c: Summary of chapters 12 and 13

The first study implemented in the present thesis is described in chapter 12, and the second study is described in chapter 13. Both studies explored the prevalence of concomitant alcohol/AI-medication use among participants (research question 1). Study 1 (chapter 12) explored the hypothesized associations of concomitant alcohol/AI-medication use on physical health and healthcare utilization (i.e., hypotheses 1 and 2). Study 2 (chapter 13) explored the hypothesized relationships between alcohol use, AI-medication use, and depression (i.e., hypotheses 3, 4, and 5). Each of these chapters include a discussion section covering topics specific to the research questions addressed in that study. Discussion topics specifically relevant to study 1 are covered in section 12.6, and topics relevant to study 2 are covered in section 13.6. As both studies explored the prevalence of concomitant alcohol/AI-medication use, much of the discussion relating to research question 1 is covered in chapter 14.

9.2.d: Summary of chapter 14

Chapter 14 begins with a general discussion of studies 1 and 2 (section 14.1), both of which explored the prevalence of concomitant alcohol/AI-medication use. The sample characteristics and results of the two studies are compared first. Findings of the present research are then compared with those of other studies exploring the prevalence of concomitant alcohol/AI-medication use in older adult populations, and methodological issues relating to both studies are discussed. The second section of chapter 14 discusses the overall contribution of the present thesis (section 14.2), and the third section (14.3) summarizes key points raised by the project overall.

CHAPTER 10: MEASURING CONCOMITANT ALCOHOL AND AI-MEDICATION USE: A REVIEW OF SURVEY RESEARCH DESIGNS

Approaches to the operationalisation of concomitant alcohol-medication use have varied greatly across previous epidemiological studies. These methodological decisions have significant implications for the precision of related estimates. Evaluation of these research designs and their implications for estimates are an important part of understanding the limitations of the current research and improving estimates in the future. This chapter is a methodological review focusing on approaches to a) measuring and defining AI-medication use, b) measuring and defining alcohol use, and c) operationalizing concomitant alcohol/AI-medication use. Methods of identifying the potential alcohol-interactivity of medications are not discussed in the present chapter and are covered in chapter 11. This review focuses on measures used to identify participants who use both alcohol and medications in a close enough proximity of time for both substances to be present in the body simultaneously. Conclusions drawn from this review informed the methods of estimating concomitant alcohol/AI-medication use utilized in the two studies included in the present thesis.

10.1: STUDIES REVIEWED

Eighteen studies are reviewed in this chapter. These studies were selected for review because they utilised survey data and aimed to estimate sample rates of potential concomitant alcohol/medication use. Seventeen studies (i.e., Aira et al., 2005; Breslow et al., 2015; Bye & Rossow, 2017; Cousins et al., 2014; del Río et al., 1996; del Rio et al., 2002; Du et al., 2016; Forster et al., 1993; Ilomäki et al., 2008; Ilomäki et al., 2013; Immonen et al., 2013; Jalbert et al., 2008; John et al., 2007; Pringle et al., 2005; Qato et al., 2015; Swift et al., 2007; Veldhuizen

et al., 2009; Wolf et al., 2017) employed cross-sectional designs, and one study (i.e., Pringle et al., 2006) conducted a longitudinal analysis.

10.2: MEASUREMENTS OF MEDICATION USE

Appropriate assessment of medication use by participants in survey research projects require consideration of the methods used to collect data on medication use, and the criteria applied to define participants as medication users based on the data collected. Across the studies reviewed, three approaches to collecting data on medication use were utilized and these are presented in Table 3. Some relied solely on self-report survey questions about medication use (e.g., Immonen et al., 2013), while the majority had participants provide some verification of medication use, such as medication containers or prescription sheets for the medications reported (e.g., Breslow et al., 2015). Two studies (Pringle et al., 2005, 2006) identified medication use by accessing participants' prescription medication claims records. Studies that either have participants provide verification of medication use or access prescription claims data are likely to have a lower risk of misclassification bias than those relying solely on self-reports. This is because self-report measures are susceptible to recall issues and biased reporting, both in terms of medications used (Holton et al., 2017) and the timing and duration of their use (which are key factors in the identification of concomitant use, as will be discussed in section 10.4).

Table 3: Methods of Identifying Participant Medication Use Utilized Among The Reviewed Studies

Method of medication use identification	Author(s)/year
Self-report survey questions	Bye, & Rossow (2017); Del Rio et al. (1996); del Río et al.(2002); Immonen et al. (2013); Swift et al. (2007)
Provision of medications, packages, or prescription sheets	Aira et al. (2005); Breslow et al., 2015; Cousins et al., 2014; Du et al. (2016); Forster et al. (1993); Ilomäki et al. (2008) Ilomäki et al., 2013; Jalbert et al., 2008; John et al., 2007; Qato et al., 2015; Veldhuizen et al. (2009); Wolf et al. (2017)
Access to pharmaceutical claims records	Pringle et al. (2005, 2006)

Table 4 details the temporal criteria against which participants were classified as being users/non-users of medications. There was much variation across the reviewed studies regarding these temporal criteria. Some studies explored current medication use, which has typically been defined as any medication use within a specific timeframe (e.g, Breslow et al., 2015). Other studies explored regular medication use and medication use as needed across unspecified timeframes (e.g. Cousins et al., 2014). One study (Bye et al., 2017) explored specific periods of continuous medication use (daily or almost daily use) as well as any medication use during the past year. Given that interactions between alcohol and medications require both substances to be used within a close enough time proximity for an interaction to occur, it is important for studies exploring concomitant alcohol/AI-medication use to carefully specify the timeframe within which medications are used.

Table 4: Criteria Used to Define Participants as Medication Users Among the Reviewed Studies

Definition of medication use	Author(s)/year
Current medication use	
Past 24 hours:	Swift et al., 2007
Past 2- days	Veldhuizen et al., 2009
Past week	Du et al., 2016; John et al., 2007; Wolf et al., 2017
Past 2-weeks	Del Rio et al., 1996, 2002
Past month	Breslow et al., 2015; Jalbert et al., 2008
Past 45-days	Pringle et al., 2005, 2006
Timeframe unspecified	Forester et al., 1993
Regular medication use	
Timeframe unspecified	Aira et al., 2005; Cousins et al., 2014; Qato et al., 2015
Regular or as needed medication use	
Timeframe unspecified	Ilomäki et al., 2008; Ilomäki et al., 2013
As needed medication use	
Timeframe unspecified	Aira et al., 2005
Any medication use	
Past year	Bye et al., 2017
Continuous use (daily or almost daily use)	
1-4 weeks during past year	Bye et al., 2017
>4 weeks during past year	Bye et al., 2017

10.3: MEASUREMENTS OF ALCOHOL USE

As with measures of medication use, the initial consideration for the identification of alcohol use relates to the methods of data-collection. All studies reviewed here relied on self-report methods to determine use of alcohol. Most studies used one of three methods to measure alcohol consumption; 1) non-standardised survey questions about quantity and frequency of alcohol use; 2) standardised alcohol use screening tools; or 3) a combination of standardised screening tools and non-standardized drinking quantity and/or frequency questions (Table 5). While non-standardized measures may provide information relating to alcohol consumption quantity and frequency, it is difficult to determine the accuracy of non-standardised measures as they lack important information such as reliability, validity, sensitivity, and specificity (Kimberlin & Winterstein, 2008). Moreover, the ability to compare findings across studies may be hampered by such ad-hoc measures. Studies using standardised measures to determine

alcohol use among participants therefore have clear advantages over those relying solely on non-standardized survey questions.

Table 5 Alcohol Use Measures Utilized in Previous Studies

Measures	Author(s)/year
Non-standardized quantity/frequency questions	
Past week	John et al., 2007; Veldhuizen et al., 2009
Past two-weeks	Del Rio et al., 1996, 2002
Past year	Aira et al., 2005; Breslow et al., 2015 Ilomäki et al., 2008; Jalbert et al., 2008
Unspecified timeframe	Pringle et al., 2005, 2006; Qato et al., 2015
Other non-standardized measures	
Question about (any) alcohol use (past 24 hours)	Swift et al., 2007
Self-reported qualitative drinking categories (e.g. non-drinker, former-drinker, regular-drinker)	Forester et a., 1993; Pringle et al., 2005, 2006
Standardized measures only	
FFQ	Du et al., 2016; Wolf et al., 2017
AUDIT and NIAAA guidelines	Immonen et al., 2013
Standardized measures and non-standardized measures	
AUDIT and past year frequency questions	Bye et al., 2017
CAGE and past year quantity/frequency questions	Ilomäki et al., 2013
CAGE and past 6-month quantity/frequency questions	Cousins et al., 2014

Measure abbreviations: FFQ = Food Frequency Questionnaire (Haftenberger et al., 2010); AUDIT = Alcohol Use Disorders Identification Test (Saunders et al. 1993); CAGE = Cut-down, Annoyed, Guilty, Eye-opener (Ewing,1984): NIAAA = National Institute for Alcohol Abuse and Alcoholism

In addition to the variability in instruments used to identify alcohol use across the reviewed studies, there is also much variation regarding the criteria used to define participants as alcohol users (Table 6). One study reported on alcohol use in relation to problematic drinking groups such as daily drinkers and binge drinkers (Ilomäki et al., 2013). Conversely, some studies reported on regular drinking (e.g. Bye et al., 2017), and others required participants to report

having used alcohol within a specific period of time prior to survey completion (e.g. Cousins et al., 2014). While the utility of different alcohol use thresholds depends on the specific research question being asked, having clearly defined inclusion criteria helps ensure information gathered is meaningful. As for medication use, the temporal criteria against which participants are classified in terms of alcohol use has similar a methodological impact and is a key consideration when determining concomitant use.

Table 6 Minimum Level of Alcohol Consumption Required to Qualify as a Drinker

Lowest drinking thresholds	Author(s)/year
Problematic drinking groups only	
Daily drinking = alcohol consumed daily (past year)	Ilomäki et al., 2013
Heavy drinking = >2 drinks daily (past year)	
Binge drinking = 5+ drinks at least once monthly (past year)	
Problem drinking = CAGE score of 2 or more	
Regular drinking groups only	
At least two drinking days weekly (past year)	Ilomäki et al., 2008
At least one drinking day weekly (unspecified timeframe)	Qato et al., 2015
At least one drinking day monthly	
Past year	Bye et al., 2017; Immonen et al., 2013
Unspecified timeframe	Pringle et al., 2005, 2006
Any alcohol use within a specific timeframe	
Past week	Veldhuizen et al., 2009
Past 2 weeks	Del Rio et al., 1996, 2002
Past 6-months	Cousins et al., 2014
Past year	Aira et al., 2005; Breslow et al., 2015; Jalbert et al., 2008; Swift et al., 2007

10.4: OPERATIONALIZED MEASURES OF CONCOMITANT ALCOHOL/MEDICATION USE

Key to the operationalization of any epidemiological concept in prevalence studies is the identification of measurement thresholds that are both *sensitive*[5] and *specific*[6] (Loong, 2003). In other words, the quality of an outcome measure depends on its ability to successfully identify true-positive and true-negative cases while avoiding false-negative and false-positive case identification. Therefore, evaluating the sensitivity and specificity of a research design requires a clearly defined outcome or phenomenon of interest.

As studies exploring concomitant alcohol/medication use are primarily concerned with risk of AMI exposure, Breslow et al. (2015) argue that operationalized measures should aim to identify participants who use alcohol and medications either simultaneously or within a close enough time proximity for an AMI to occur. Sensitivity would therefore refer to the extent to which a threshold is maximally able to capture participants who *do use* alcohol and AI-medication within a timeframe that that puts them at risk of AMI exposure. In contrast, specificity would refer to the extent to which a threshold is maximally able to capture participants who *do not* use alcohol and medication within a timeframe that puts them at risk of AMI exposure. In this regard, designs with highly flexible inclusion criteria would likely provide the highly sensitive estimates (i.e., criteria prioritise capture of exposed persons at the risk of capturing non-exposed persons), whereas those using highly stringent inclusion criteria would provide highly specific estimates (i.e., criteria prioritise capture exposed persons at the risk of missing some exposed persons). For example, a measure which defined every participant who had used

[5] *Sensitivity* estimates are concerned with the ability of a given classification measure to accurately identify true positive cases and minimize false negative case identification within a sample or population

[6] *Specificity* refers to the ability of a given classification measure to minimize false positive case identification and maximise the identification of true negative cases.

alcohol at any time in their life and medication at any time in their life as a concomitant user would have perfect sensitivity because every true positive case would be included. However, such a measure would likely falsely identify a large number of participants as concomitant users, and thus would have very poor specificity.

To address this key issue, this section of the present chapter evaluates various operationalised measures of concomitant alcohol/medication use. The aim of this discussion is to identify methods of maximizing both sensitivity and specificity based on the operationalisation of concomitant alcohol/medication use proposed by Breslow et al. (2015), i.e., the use of alcohol and medication within a timeframe that poses risk of AMI exposure. While this task is complicated by differences in half-lives between various medications (which present differing windows of opportunity for AMIs), additional considerations include the time windows within which alcohol and medication use are measured, and the frequency at which alcohol is consumed. The methodological strengths and/or limitations of three studies (Bye et al., 2017; Cousins et al., 2014; Wolf et al., 2017) are outlined below to illustrate both these issues as they appear in the literature and inform the rationale for the definitions adopted in the current research.

10.4.a: Example of a highly sensitive research design

Cousins et al. (2014) estimated the prevalence of concomitant alcohol/AI-medication use by conducting a cross-sectional analysis of a sample of older adults (aged ≥60 years) using data collected by the Irish Longitudinal Study of Aging (TILDA). In this study, concomitant alcohol/AI-medication users were defined as those who a) were identified as regular AI-medication users across an unspecified timeframe, and b) reported using alcohol during the past six-months. As the drinking threshold utilized in this inclusion criteria was relatively low (i.e. any alcohol during the past six months), the operationalisation of concomitant alcohol/AI-

medication use utilized by Cousins et al. (2014) is likely to capture most of the true-positive cases within their sample. This study therefore provides an example of a highly sensitive research design for the identification of concomitant alcohol/AI-medication use. However, this design is also likely to yield a high number of false-positive cases, as many participants identified as at-risk using this design may not use alcohol and AI-medication concomitantly. In other words, the operationalisation of concomitant alcohol/AI-medication use adopted by Cousins et al. (2014) likely achieves high sensitivity at the expense of decreased specificity, by casting a 'wider net', so to speak.

10.4.b: Example of a highly specific research design

Wolf et al. (2017) explored rates of concomitant alcohol/psychotropic-medication use among older adults (aged 60-79 years) using data collected in two German National Health Surveys. The operationalized definition of concomitant alcohol/medication use utilized in this study included a) self-reported daily alcohol use (past year), and b) past 7-day psychotropic drug use. Due to the highly stringent drinking threshold utilized in this study, the likelihood of an individual being incorrectly identified as a concomitant alcohol/medication user based on these criteria is relatively low. However, it is also unlikely that all concomitant users would be identified using such a design, particularly those who do not drink daily. This study therefore provides an example of an operationalized concomitant alcohol/medication use measurement with high specificity and low sensitivity.

10.4.c: Example of a research design providing estimates with both high sensitivity and high specificity

While no study reviewed here provides a single measurement of concomitant alcohol/medication use that can be considered high in both sensitivity and specificity, studies providing multiple measures of concomitant use are able to provide a clearer overall estimate.

For example, Bye et al. (2017) provided the following estimates of concomitant alcohol and sedative/hypnotic drug use: 1) rates of individuals reporting the use of alcohol and the use of sedative hypnotics during the past year; 2) rates of individuals reporting frequent alcohol use (at least once weekly, past year) and short continuous sedative/hypnotic drug use (1-4 consecutive weeks of daily or almost daily use during the past year), or reporting infrequent alcohol use (1–3 times monthly, past year) and long continuous sedative/hypnotic drug use (self-report, at least one month of daily or almost daily use, past year), or engaging in frequent alcohol use and long-continuous sedative/hypnotic drug use. The first estimate utilized in this study is likely to have high sensitivity and low specificity (due to its flexible inclusion criteria), and the second is likely to have high specificity and low sensitivity (due to its stringent inclusion criteria). In doing so, this design is likely to provide an underestimate and an overestimate of concomitant use, and it is therefore reasonable to infer that the actual population prevalence falls somewhere between these two measurements. This approach therefore may have greater utility for public health research and planning than research designs providing a single estimate

10.5: CONCLUSIONS

The present chapter reviewed methods of measuring alcohol use, medication use, and concomitant alcohol/medication use that have been applied in survey studies exploring research questions relating to AMI risk among participants. The purpose of this chapter was to identify key methodological principles to inform the study designs implemented in the present research (see chapters 12-13). Five key points were identified from this discussion, which are listed below (section 10.5.a). The application of these methodological considerations to the present research is then discussed in section 10.5.b.

10.5.a: Key points raised in this chapter

1. Given that self-report measures of medication use may be susceptible to problems such as biased reporting and recall issues, risk of medication use misclassification may be reduced by accessing participants' medication containers, prescription sheets, or pharmaceutical dispensing records
2. Standardized alcohol use questionnaires have clear advantages over ad hoc measures, which lack empirical support for their utility and do not facilitate comparisons across studies
3. As the likelihood of simultaneous alcohol and AI-medication use increases with repeated use of both substances over time, drinking frequency may be a better indicator of concomitant use than drinking quantity
4. Measures of AI-medication use and alcohol use that include appropriate temporal criteria may enhance measurement precision when estimating the potential for AMI, as this helps to infer the likelihood that both substances are taken in a close enough proximity of time for an interaction to occur.
5. It is extremely difficult to provide a single estimate of concomitant alcohol/AI-medication use that has both sensitivity and specificity. As such, studies that provide multiple estimates, based on differing levels of drinking frequency by AI-medication users, may have greater utility for public health research and planning

10.5.b: How this chapter informed the present research

The present research aimed to explore rates of concomitant alcohol/AI-medication use in a large sample of New Zealand older adults, using existing survey data collected by the *Health Work and Retirement* (HWR) Study (Towers & Noone, 2007; Towers & Stevenson, 2014). The methodological considerations listed in the previous subsection (10.5.a) informed the design of the present research in the following ways. In light of the first point listed above, the present

research made use of an HWR project in which consenting participants survey data was linked with their national health records (HWR Data-Linkage Project) (Allen 2014). This enabled medication use to be measured by accessing participants pharmaceutical dispensing records, which is a key strength of the present research. Another strength of the present research, in relation to the second point listed, was the use of the AUDIT-C (Bush et al., 1998), which is a standardized measure of alcohol consumption. In light of the third point listed, the present research utilized a single item from the AUDIT-C, which assesses how often an individual typically consumes alcohol (i.e., drinking frequency). However, in relation to the fourth point listed, a key limitation of the AUDIT-C is that it does not specify a timeframe across which drinking frequency is assessed. To compensate for the potential problems this issue may create in terms of specificity, the present research focused on measuring regular AI-medication use across a specified timeframe, which is a more conservative approach than focusing on current use only. In relation to the fifth point listed, the present research aimed to provide multiple estimates of concomitant alcohol/AI-medication use based on drinking frequency among regular AI-medication users.

CHAPTER 11: IDENTIFYING PARTICPANT AI-MEDICATION USE USING PHARMACUETICAL CLAIMS DATA: PROTOCOL AND METHODOLOGY

The current research required extensive planning, primarily due to the complex procedures required when incorporating research and administrative data sources (i.e., national pharmaceutical record collections). In addition to the methodological considerations reviewed in chapter 10, it was necessary to develop a research protocol providing clear guidelines for a) classifying AI-medications in research, and b) using pharmaceutical claims records to identify medication users among survey participants. Relevant literature was reviewed to ensure methodological decisions were empirically supported and/or carefully modelled on methods adopted by other researchers. The protocol was then developed by the author, submitted for peer review[7], and implemented by the author. This chapter details the research protocol developed for the present thesis, it's rationale, and describes the implementation of procedures used to identify AI-medication use among survey participants using pharmaceutical claims records.

11.1: RESEARCH PROTOCOL

This section of the present chapter establishes a research protocol for determining the potential alcohol-interactivity of medications, and for using pharmaceutical claims data to identify medication use in survey research. The first subsection discusses the classification of AI-medications, and the categorization of AI-medications based on their associated levels of AMI

[7] With thanks to reviewers Professor Janie Sheridan and Dr David Newcombe from the Centre for Addiction Research, University of Auckland

risk. The second subsection discusses methods of identifying current and regular medication use by accessing survey participants pharmaceutical claims records.

11.1.a: Identifying AI-medications to explore concomitant alcohol/AI-medication use

Decisions about AI-medication identification and categorisation implemented in the present research protocol were informed by methods adopted in previous studies exploring concomitant alcohol/AI-medication use. Four studies in this field (namely, Breslow et al., 2015; Cousins et al., 2014; Immonen et al., 2013; Qato et al., 2015) were selected for review because they 1) included a wide variety of medications in their analyses and 2) provided reference to the specific resources they used to identify potentially AI-medications. Key considerations included decisions about how many resources indicating the potential for medications to have an adverse drug-interaction with alcohol should be used to identify AI-medications, and the specific inclusion criteria used for defining and categorizing AI-medications in terms of the risk they present for AMI. Three approaches to AI-medication identification were used across the four studies reviewed.

The simplest method for identifying AI-medications used among the reviewed studies is to utilize a single *drug-interaction identification resource* (i.e., a resource for assessing the clinical effects of drug interactions) (Grannell, 2020). This method, which was adopted by Immonen et al. (2013) and Qato et al. (2015), may have limitations in terms of sensitivity and/or specificity depending on the specific resource utilized. Barrons (2004) compared various drug interaction identification compendia by assessing search outputs of 80 drug pairs, 40 of which represented clinically significant drug interactions. Each resource falsely identified at least one drug pair as a clinically significant drug interaction and/or failed to identify at least one clinically significant drug interaction. These results highlight the possibility that the use of a

single resource could lead to false positive and/or false negative identification of AI-medications.

Another approach, which was adopted by Cousins et al. (2014), is to use multiple drug-interaction identification resources and define drugs as AI when identified as such by *at least one* resource. The benefit of this approach is a reduced likelihood of false negative AI-medication identification, as any AI-medications missed by one resource are likely to be identified by another. However, the shortcoming of this approach is the increased likelihood of false positive AI-medication identification as any medications incorrectly identified as alcohol-interactive in any resource used would be incorrectly be defined as AI in the study. In other words, this method likely to have high sensitivity, but its specificity may be compromised.

A third approach to AI-medication identification, adopted by Breslow et al. (2015), is to use multiple drug-interaction identification resources and define drugs as AI when identified as such by *more than one* resource. The benefit of this method is a reduced likelihood of false positive AI-medication identification, as it is likely that medications incorrectly identified as alcohol-interactive in one resource will not be identified as alcohol-interactive in others. However, the shortcoming of this method is increased the likelihood of false negative AI-medication identification, as AI-medications missed by one resource might be defined as non-AI in the study. In other words, this method is likely to have high specificity, but its sensitivity may be compromised.

Approach to AI-medication identification adopted in the present research

The present research used only one drug-interaction resource to identify AI-medications for three reasons. Firstly, potential limitations of specificity and sensitivity cannot be fully addressed by using multiple resources because inclusion criteria aimed at increasing sensitivity

would likely reduce specificity while criteria aimed at increasing specificity would likely lead to reduced sensitivity. Secondly, as health behaviour models indicate that increased potential for an adverse AMI will have consequences for alcohol use, AI-medications in this project were categorized into ordinal groups of differing levels of alcohol-interactivity. As such, the use of multiple resources could lead to inconsistency in reporting on AI-medication use overall, and AI-medication use by interactivity severity. This is because some medications might be defined as AI based on information gained from one or more resources, yet not identified as AI by the resource used to identify interactivity severity. As a result, the overall total of AI-medications included in the analyses would be greater than the combined total of AI-medications across AI-medication severity categories. Finally, drug interaction notifications to GPs and Pharmacists in New Zealand are generated from one resource (the New Zealand Formulary (NZF)), which takes the form of a coloured sticker placed by pharmacists on the medication packaging. This single resource therefore provides the best indicator of patient behaviours in New Zealand.

Thus, for consistency and comparability with existing literature, inclusion criteria for identifying and categorizing AI-medications in the present research are based on those used by other authors. The inclusion criteria for defining AI-medications adopted in the present research are based on those used by Cousins et al. (2014), who defined AI-medications as those having "specified alcohol interactivity and/or […] a cautionary warning and/or recommendation for advisory labels [related to alcohol use]" (p.1473). These criteria were selected as a model in the present research because they are clearly defined and can easily be applied to a single drug-interaction identification resource. The criteria developed for categorizing AI-medications into multiple levels of alcohol interactivity in the present research were designed to resemble those used by Qato et al. (2015) as this was the only study selected

for review that included such categories. AI-medication severity categories utilized in the Qato et al. (2015) study included the following:

- Contraindicated AI-medications: medications contraindicated for use with alcohol
- Major AI-medications: those capable of causing interactions that are life threatening or that require medical attention
- Moderate AI-medications: medications capable of causing interactions in which the therapeutic effects of the medication are reduced through the exacerbation of the individual's condition
- Mild AI-medications: medications capable of causing alcohol-interactions with limited clinical significance

11.1.b: Using pharmaceutical claims to identify AI-medication users

Another key consideration for the present research relates to methods of identifying medication use among survey participants based on pharmaceutical claims, which enables detailed assessments of the timing and duration of AI-medication use. Specifically, the present research aimed to identify participants who a) were current users of AI-medications at the time they responded to the survey, and b) had used AI-medications regularly for an extended period prior to survey completion. These decisions were informed by literature comparing alternative methods of identifying current medication use based on pharmaceutical claims and previously adopted research designs aimed at identifying regular medication use based on pharmaceutical claims.

Fixed-window and legend-time measures of current medication use

There are two main methods of identifying current medication use based on pharmaceutical claims data. The 'fixed-window method' assumes any medications dispensed within a fixed number of days prior to survey response are in current use. The 'legend-time method' infers

current use when the number of days for which a medication is supplied is greater than or equal to the number of days between dispensing date and response date (Lau et al., 1997). The accuracy of each of these methods appears to vary across certain medication classes. Sensitivity and specificity estimates suggest the fixed-window method is at least as accurate as the legend-time method in identifying current use of most drugs and more accurate in identifying current use of many drugs. However, the legend-time method appears to have higher sensitivity and specificity as a measure of current antibiotic use (Lau et al., 1997; Nielsen et al., 2008). Utilizing the legend-time method for antibiotics and the fixed window method for all other medications may therefore maximize accurate current medication use identification.

Optimal time intervals for fixed-window current medication use identification

A key consideration when using the fixed-window method is the size of the specified time window in which pharmaceutical dispensations are considered to be in current use. Studies comparing fixed-window time intervals suggest a 90-day fixed-window has optimal sensitivity and specificity for identifying current medication use for most drug classes (King et al. 2001; Lau et al., 1997; Pit et al., 2008). However, a 30-day fixed window appears to be the best method (with regards to sensitivity/specificity) for identifying current use of non-steroidal anti-inflammatory drugs (NSAID's) and benzodiazepines (Pit et al., 2008). To achieve the optimum accuracy of current medication use, the present research utilized a) the legend-time method to identify current antibiotic use, b) a 30-day fixed window approach to identify current use of benzodiazepines and NSAIDs, and c) a 90-day fixed window approach to identify the current use of all other medications.

Regular medication use identification

Previous data-linkage studies have defined regular medication use by multiple dispensings within a six-month fixed window. Regular medication use was defined by three dispensings over the past six months in a study of older adults living in Ireland (Richardson et al., 2013).

Another study of older veterans living in Australia defined regular medication use as at least one dispensing in the past 3 months (indicating current use), and at least one other dispensing occurring during the three months preceding the past three months (Roughead et al., 2010).

While the studies just described provide a basic guideline for the identification of regular medication use using data-linkage methods, medications prescribed in Australia and Ireland are usually dispensed in one-month supplies. A six-month time-window would likely be insufficient in the context of New Zealand, where most medicines can be dispensed in 3 month supplies, and may often last slightly longer than 3 months due to issues with compliance (e.g. occasionally forgetting to take medication). The present research therefore defines regular AI-medication use as multiple dispensings within a 244-day (8-months) fixed window, with at least one dispensing occurring within a timeframe indicative of current medication use (i.e. legend time for antibiotics; 30-day fixed window for NSAIDs and benzodiazepines; 90-day fixed window for all other medications) and at least one dispensing that does not indicate current use.

11.2: METHODOLOGY

This section of the present chapter discusses the implementation of the research protocol described above. All of the described procedures were carried out using SPSS software. The first subsection (11.2.a) describes the data sources used in the present research. This includes survey data provided by the Health, Work and Retirement (HWR) Study (Towers & Noone, 2007; Towers & Stevenson, 2014), pharmaceutical claims data provided by the New Zealand Pharmaceutical Collection (PHARMS) (Ministry of Health, 2015), and AI-medication identification data provided by NZF (NZF, 2017). Methods of classifying AI-medications within the NZF data and PHARMS data are discussed in the second subsection (11.2.b), and the third subsection (11.2.c) describes methods used to identify AI-medications within the

PHARMS data. Methods of establishing regular AI-medication use among HRW participants are then described in the fourth subsection (11.2.d).

11.2.a: Data sources

Survey data: The Health Work & Retirement Study (HWR)

Survey data analysed in the present research was gathered from The New Zealand, Health, Work, and Retirement (HWR) Study, which is a large ongoing nationally representative survey of older adults living in New Zealand. Data from the 2006 HWR survey (Towers & Noone, 2007) was analysed in study 1, and study 2 analysed the data from the 2010 HWR survey (Towers & Stevenson, 2014). Both studies included a subset of participants who consented to have their survey data linked with their national health records as part of the *HWR Data-Linkage Project* (Allen, 2016). This enabled participant medication use to be ascertained by accessing their pharmaceutical claims records. Details regarding HWR participant recruitment, data-linkage recruitment, and the characteristics of the final study samples are described in chapters 12 (study 1) and 13 (study 2).

Pharmaceutical claims data: The New Zealand Pharmaceutical Collection (PHARMS)

Pharmaceutical data obtained in the HWR data-linkage project is collected via the *New Zealand Pharmaceutical collection* (PHARMS), a data collection system run by the New Zealand Ministry of Health and the Pharmaceutical Management Agency (PHARMAC) that compiles information regarding claims of subsidized pharmaceutical dispensings in New Zealand (Ministry of Health, 2015). This includes records of a) prescribed community pharmaceuticals by a retail pharmacy or to an outpatient by a hospital pharmacy b) prescribed hospital pharmacy pharmaceuticals distributed by retail pharmacies, and c) prescribed community pharmaceuticals used for non-subsidized purposes distributed under Special Authority Application. The PHARMS data does not capture information relating to medication used by

inpatients within hospitals, medications used for non-subsidized purposes without Special Authority Application, or medications distributed at costs below the minimum price eligible for PHARMAC subsidization[8] (Horsburgh et al., 2009).

Drug-interaction identification resource: The New Zealand Formulary (NZF)

Data on AI-medications were provided by the NZF. This resource is commonly used among New Zealand healthcare professionals and was selected to increase relevance of results in the context of New Zealand. The NZF is an online resource designed to provide New Zealand healthcare professionals with medication information and practice guidance that is clinically validated, with the aim of aiding in safe and effective medication selection for individual patients (NZF, 2017). The drug interaction information provided by NZF is derived from Stockley's Interaction Alerts, a computerised version of Stockley's Drug Interactions, which is the most comprehensive and complete drug interaction index available (Stockley's Drug Interactions, 2017). The NZF provides two categorical variables relating to potential interactions between drugs: 1) the *'severity key'*, which relates to the severity of a potential drug interaction (see Table 7); and 2) the *'action key'*, which provides practice guidelines based largely on the likelihood of a potential drug interaction (see Table 8).

Table 7: NZF Severity Key Ordinal Categories

Output	Indication
Nothing expected	For interactions that are unlikely to result in an effect, or for drugs pairs where no interaction occurs.
Mild	For interactions that could result in an effect that is mild and unlikely to unduly concern or incapacitate the majority of patients.
Moderate	For interactions that could result in an effect that may either cause considerable distress or partially incapacitate a patient. These interactions are unlikely to be life-threatening or result in long-term effects.
Severe	For interactions that could totally incapacitate a patient or result in either a permanent detrimental effect or a life-threatening event.

[8] Dispensings are not eligible for subsidization when the cost of the medicine is lower than that of the patient contribution (Horsburgh et al., 2009). For most subsidized medications, the prescription charge to the patient is $5 (Ministry of Health, 2018)

Table 8: NZF Action Key Ordinal Categories

Output	Indication
No action	For interactions where close follow up or monitoring are probably not automatically warranted due to the low probability of an interaction, but where more information is given in the event of a problem
Information	For interactions where close follow up or monitoring are probably not automatically warranted due to the low probability of an interaction, but where more information is given in the event of a problem
Monitor	For interactions where the drug pair is valuable and no compensatory action is possible, but the patient needs to be monitored to assess the outcome. For interactions where biochemical or therapeutic drug monitoring is recommended and further action may be needed based on the results
Adjust	For interactions where the interaction can be accommodated, but where it is recommended that either one of the drugs is changed, or the dose is altered on initiating the combination.
Avoid	For interactions where a drug combination is best avoided. This will mainly be used to highlight contraindicated drug pairs.

11.2.b: Classifying AI-medications within the NZF data

NZF was used to identify AI-medications with inclusion criteria based on those used previously by Cousins et al. (2014). Specifically, AI-medications were defined as *those referred to as having potential alcohol-interactivity, those including a cautionary warning against alcohol use, and/or those including some sort of recommendation regarding alcohol consumption*. The NZF *severity key* variable was used to identify medications with specified alcohol interactivity (i.e., severity key = 'mild', 'moderate', or 'severe'), and the *action key* variable was used to identify medications with an alcohol-related warning or recommendation (i.e. action key = 'information', 'monitor', 'adjust', or 'avoid'). Medications with a 'nothing expected' *severity key* output and a 'no action' *action key* output were therefore flagged as *non-AI-medications.* The methods of AI-medication and non-AI-medication identification based on NZF variable outputs used in the present research are summarised in Table 9.

Table 9: AI-Medication and Non-AI-medication NZF Severity and Action Key Outputs

NZF Severity key		NZF Action key		AI Classification
Mild, moderate, or severe	+	No action, information, monitor, adjust, or avoid	=	AI-medication
Nothing expected	+	Information, monitor, adjust, or avoid	=	AI-medication
Nothing expected	+	No action	=	Non-AI-medication

NZF severity and action key variables were used to assign AI-medications to ordinal categories of varying alcohol-interactivity levels. These categories included *contraindicated* (medications contraindicated for use with alcohol); *major* (interactions with detrimental effects that may be permanent or life-threatening; or interactions that may result in significant distress or incapacitation, and the likelihood of interaction is high enough to warrant close monitoring or dosage adjustment); *moderate* (interactions that may result in significant distress or incapacitation, but the likelihood of interaction is not high enough to warrant close monitoring or dosage adjustment); and *mild AI-medications* (potential interactions are of little clinical significance). The NZF severity key and action key outputs used to identify medications within each of these categories are shown in Table 10.

Table 10: Categorisation of AI-medications Levels of Alcohol-Interactivity Potential Based on NZF Severity and Action Key Variables

NZF Severity key		NZF Action key		Severity Categorisation
Nothing expected, mild, moderate, or severe	+	Avoid	=	Contraindicated AI-medication
Severe, or moderate	+	Monitor, or adjust	=	Major AI-medication
Moderate	+	No action, information	=	Moderate AI-medication
Mild	+	No action, information	=	Mild AI-medication
Nothing expected	+	Information	=	Mild AI-medication

11.2.c: Matching NZF data with PHARMS data

Identification of medications listed in the PHARMS data indicated as being AI by the NZF was carried out using SPSS software. Medications identified as being AI in the NZF data were matched with medications listed in the PHARMS data through string variables containing the chemical names of medications generally used by both datasets. Specific differences in the way medication chemical names were documented in each of these data sources were addressed during data cleaning procedures. This subsection describes the differences between chemical medication name entries within the PHARMS and NZF datasets, the data-cleaning procedures used to address these differences, and the methods used to match these datasets. All PHARMS medications that were identified as being AI by the NZF are listed in Appendix-A. This includes information relating to PHARMS chemical names, medication ids, brand names, and brand codes; AI-severity classification; and where applicable, medications classified as benzodiazepines, NSAIDs, or antibiotics.

NZF and PHARMS differences in medication chemical name documentation

Initially, medication chemical names within the NZF and PHARMS datasets were not compatible due to differences in documentation between the two data sources. The differences were that:

- All chemical names listed in the NZF data referred to a single substance (e.g. aspirin), whereas some chemical name entries in the PHARMS data referred to multiple substances (e.g. aspirin with paracetamol and codeine),
- Chemical names included in the NZF data typically contained only the active ingredient of each drug (e.g. abacavir), whereas the PHARMS data often included documentation of specific preparation salts (e.g. abacavir sulphate),

- Chemical names were documented using lowercase letters only within the NZF data (e.g. aspirin), whereas entries in the PHARMS data began with capital letters (e.g. Aspirin), and
- The NZF chemical medication name entries included an indication of whether the medication is for topical or systemic use - e.g. “suvorexant (systemic)” or “tacrolimus (topical)”.

Data cleaning procedures were developed to address these issues so that automated scripts could be used to match chemical medication names between the two data sources.

Data cleaning

SPSS string variable functions were used to manipulate chemical medication names within the NZF and PHARMS datasets. Topical/systemic use indications were removed from the NZF data, and rare cases of chemical entries containing multiple substrings (e.g. isosorbide mononitrate) were flagged. The second substring of these cases were then removed so that each chemical name within the NZF data contained only a single word (e.g. isosorbide). All NZF cases containing multiple substrings were manually checked following automated data cleaning processes and corrections were made where necessary.

Cleaning of the chemical names documented in the PHARMS data involved removal of all capital letters (because the NZF entries contained only lowercase letters). The following preparation salts were identified within the PHARMS data using two resources (drugs.com, 2018; Wiedmann & Naqwi; 2016) and deleted*: acetate; bromide; calcium; carbonate; citrate; decanoate; estolate; fumarate; hydrochloride; maleate; mesylate; pamoate; phosphate; potassium; sodium; succinate; sulfate; sulphate;* and *tartrate*. Two new variables were then created for cases containing multiple chemical ingredients. The substrings ‘and’ ‘with’ and ‘,’

(which had separated substrings representing different active ingredient within a single medication) were then removed.

Data Matching

Automated scripts were generated to match drugs identified within the NZF and PHARMS datasets. Matches were considered finalized when strings within the cleaned datasets matched exactly. In some cases, strings within the NZF data matched with single substrings in PHARMS data entries containing multiple substrings. In such cases, these matches were checked manually and corrected accordingly. See Appendix B for a list of automatically and manually corrected matches of chemical medication names between the NZF and PHARMS datasets.

11.2.d: Using PHARMS data to identify AI-medication users within the HWR samples

Once AI-medications were identified within the PHARMS data, the final task was to identify AI-medication users within the HWR samples. This process involved three key steps: 1) identifying current AI-medication users; 2) identifying which current AI-medication users could also be defined as regular AI-medication users; 3) assigning regular AI-medication users into groups based on the AI-medication severity categories described previously.

Identifying current AI-medication users

As discussed in section 11.1.b, the definition of current medication use adopted in the present research varied for specific medication classes (benzodiazepines, NSAIDs, and antibiotics). The PHARMS data included a drug classification system adapted from the Anatomical Therapeutic Chemical (ATC) medicines (World Health Organization, n.d.). This enabled for antibiotic and NSAIDs to be identified easily within the PHARMS data, as there were specific categories corresponding to these drug classes. However, the modified version of ATC used in the PHARMS data did not include a category that directly captured the class of benzodiazepines. This issue was resolved by comparing benzodiazepines listed in the standard

ATC system[9] against the chemical names of medications included in the PHARMS data. The following medications were then defined as benzodiazepines: *alprazolam; bromazepam; chlordiazepoxide hydrochloride; clobazam; clonazepam; diazepam; flunitrazepam; loprazolam mesylate; lorazepam; lormetazepam; midazolam; nitrazepam; oxazepam; temazepam; triazolam; zopiclone*. Once benzodiazepines, NSAIDs, and antibiotic drugs were identified, an overall categorisation of current AI-medication use was calculated using the *legend-time*[10] method for antibiotics; a *30-day fixed-window*[11] method for NSAIDs and benzodiazepines; and a *90-day fixed-window*[12] for method for all other medications.

Identifying regular AI-medication users

As discussed in section 11.1.b, the present research defined regular AI-medication use as a) at least one medication dispensing indicative of current AI-medication use, and b) at least one other AI-medication dispensing within an 8-month fixed window. However, the research questions for this project related to AI-medication use in general, rather than specific classes of AI-medications. A decision therefore needed to be made about whether each dispensing must reflect a single medication (e.g., 2 dispensing of lorazepam), or whether multiple dispensings of different AI-medications could also constitute regular AI-medication use (e.g., 1 lorazepam dispensing and 1 codeine dispensing). The latter option was selected for the following reasons. The present research is based on the assumption that risk of AMI increases with frequency of AI-medication use over time (see Chapter 10). As such, AMI risk among

[9] https://www.whocc.no/atc_ddd_index/

[10] Legend-time method: data-linkage method of identifying current medication use. Infers current use when the number of days for which the medication is supplied is greater than or equal to the number of days between medication dispensing date and survey response date

[11] 30-day fixed window: data-linkage method of identifying current medication use. Infers current use when a medication is dispensed during the past 30 days prior to survey response date

[12] 90-day fixed window: data-linkage method of identifying current medication use. Infers current use when a medication is dispensed during the past 90 days prior to survey response date

current AI-medication users is considered higher for those who used AI-medications in the recent past, even if the specific medications used were different. Moreover, by focusing on regular AI-medication use rather than current use, the present research already adopted a conservative approach to estimating the prevalence of concomitant alcohol/AI-medication use. Excluding cases of regular use on such a technicality would therefore unnecessarily reduce measurement sensitivity.

Categorizing regular AI-medication users

Another decision then needed to be made about how to apply the AI-medication severity categories (i.e., mild, moderate, major/contraindicated) when regular use is identified based on multiple dispensings of different medications. This issue was resolved by using medications in current use to assign AI-medication users into their respective AI-medication severity groups. The classification of regular AI-medication use across severity categories adopted in the present research is shown in Table 11.

Table 11: Dispensing Records of AI-Medication User Groups

AI-Medication User Groups	Pharmaceutical Dispensings Received by Participants	
	Current use*****	Past 244 days (not in current use)
Contraindicated AI-medication users	At least one contraindicated AI-medication	At least one AI-medication (mild, moderate, major, or contraindicated)
Major AI-medication users	At least one major AI-medication, and no contraindicated AI-medications	At least one AI-medication
Moderate AI-medication users	At least one moderate AI-medication, and no major or contraindicated AI-medications	At least one AI-medication
Mild AI-medication users	At least one mild AI-medication, and no moderate, major, or contraindicated AI-medications	At least one AI-medication

Note: *****current use = legend time for antibiotics; 30-day fixed-window for benzodiazepines & NSAIDs; 90-day fixed-window for all other drugs.

CHAPTER 12: CONCOMITANT ALCOHOL & ALCOHOL-INTERACTIVE MEDICATION USE BY OLDER NEW ZEALANDERS: EXPLORING THE IMPACT ON HEALTH AND HEALTHCARE UTILISATION (STUDY 1)

12.1: ABSTRACT

Background: Vulnerability to alcohol-medication interactions (AMIs) increases during older adulthood due to age related changes in body mass, metabolism, and illness susceptibility. High rates of concomitant alcohol and alcohol-interactive (AI) medication use have been observed among older adults living in the United States and Europe, however the prevalence of this issue in New Zealand's older adult population is currently unknown. Additionally, only a small number of observational studies have explored the public health impact of AMIs. **Objectives**: This study explored the prevalence of concomitant alcohol/AI-medication use among older New Zealanders, and the impact of concomitant alcohol/AI-medication use on self-rated physical health and healthcare utilisation. **Design and Methods:** This study included a large community sample of New Zealand older adults, and involved secondary analysis of survey data and pharmaceutical claims records. Sample weights were applied to survey data to increase representativeness to New Zealand's older adult population. Associations between variables of interest were explored using one hierarchical multiple regression model and two hierarchical logistic regression models. **Results:** One-in-four participants used alcohol and AI-medications concomitantly. Concomitant alcohol/AI-medication use was not significantly associated with self-rated health or healthcare utilisation. **Discussion:** The results of the present study indicate a substantial portion of New Zealand's older adult population are at risk of AMI. Non-significant findings of the present study likely reflect measurement issues, and should therefore be interpreted with caution. Future research exploring the public health burden of concomitant alcohol/AI-medication use should include longitudinal outcome measures that are specific to the effects of AMI.

12.2: INTRODUCTION

As discussed in chapter 3, interactions between alcohol and medications can increase risks of overdosing, cause a number of serious side effects such as gastrointestinal bleeding and psychomotor impairment, and interfere with the therapeutic effects of medication treatment regimens (Adams, 1995; Moore, Whiteman, & Ward, 2007; Weathermon & Crabb, 1999). These risks are of particular concern for older adults, as this population are more likely to be using medications with the potential to interact negatively with alcohol, and are particularly sensitive to the effects of alcohol-medication interactions (AMIs) due to age-related changes in body mass and metabolism (Moore et al., 2007).

Cross-sectional survey findings suggest concomitant alcohol/AI-medication use is common among community dwelling older adults living in the United States (US) and Europe (Aira et al., 2005; Breslow et al., 2015; Cousins et al., 2014; Immonen et al., 2013; Qato et al., 2015). For example, Qato et al. (2015) found that approximately one-in-five participants from their sample of United States older adults reported using alcohol and AI-medications regularly. While equivalent data directly identifying the rate of AMIs in New Zealand's older adult population is currently unavailable, findings from recent research suggests that older adult potential exposure to AMIs may be a significant issue in New Zealand. For example, cross national comparisons of survey findings indicate that older adults living in New Zealander tend to drink more often and in greater quantity per occasion than those living in other countries such as the US, China, and Russia (Towers et al., 2017). Moreover, research by the Health Quality and Safety Commission (2018) suggests approximately 35% of New Zealander's aged ≥65 years use 5 or more long-term medications for their health conditions. As such, the prevalence of concomitant alcohol/AI-medication use by older New Zealanders is an issue that warrants investigation.

There is also need for survey research identifying potential relationships between concomitant alcohol/AI-medication use and adverse health outcomes. A recent systemic review of 20 studies reporting on concomitant alcohol/AI-medication use found that only four studies reviewed included information about potential AMI related adverse health outcomes (Holton et al., 2017). This included three studies reporting on associations between alcohol/AI-medication use and falls (Immonen et al.,2013; Sheahan et al., 1995; Wong et al., 2016), and one study reporting on AMI related hospital admissions (Onder et al., 2002). Overall, the range of potential concomitant alcohol/AI-medication use health associations explored to date is low, and there is a need for further research investigating other ways alcohol/AI-medication use may affect public health.

12.3: THE PRESENT STUDY

12.3.a: Aims

The present study aimed to address the gaps in the literature outlined above by a) exploring the prevalence of concomitant alcohol/AI-medication use in a community sample of New Zealand older adults, and b) investigating the potential impact of concomitant alcohol/AI-medication use on self-rated physical health and healthcare utilization.

12.3.b: Hypotheses

Given that vulnerability to AMI-related harm appears to increase during older adulthood, the present study had the following hypotheses.

1. After controlling for relevant demographic variables (i.e. SES[13]) and the individual effects of alcohol use and AI-medication use, concomitant alcohol/AI-medication use will be negatively associated with self-rated physical health
2. Concomitant alcohol/AI-medication use will be positively associated with healthcare utilization, after controlling for SES and the individual effects of alcohol use and AI-medication use

12.4: METHODS

12.4.a: Participants

Health, Work & Retirement Survey: 2006 data wave

Survey data analysed in the present study was collected in the initial 2006 data wave of New Zealand Health Work, and Retirement (HWR) study, which is a large ongoing longitudinal survey of older adults living in New Zealand. HWR participants were recruited through random selection from the New Zealand electoral roll. To ensure New Zealand's Māori population were adequately represented in the survey, an oversample of persons indicated as being of Māori decent on the electoral role was undertaken. Surveys were posted to 13,045 New Zealanders aged 55-70 years, with 5,264 surveys being posted to individuals from the general population, and 7,781 being posted to individuals of Māori descent. The response rate in the initial data wave was 51.1%, with surveys returned by 6,662 individuals. This included 3,108 individuals from the general sample (59% response rate), and 3554 individuals (46% response rate) from the Māori sub-sample (Towers & Noone, 2007). The present study sample

[13] Towers, Philipp, Dulin, and Allen (2016) found that the relationship between moderate drinking and physical health was substantially reduced among older women and completely eliminated among older men when a control measure of SES was included in their analysis.

included a subset of the 2006 HWR cohort who consented for their survey data to be linked with their national health records as part of the HWR data linkage project (Allen, 2016).

HWR Data-Linkage Project

In 2014, written informed consent to data-linkage was sought from participants recruited in the initial 2006 data wave and remained in the longitudinal study. A second approach to data-linkage consent occurred in 2015 and included those who did not respond in the 2014 approach, yet were active participants in the 2014 survey (i.e., they responded to the survey, had not withdrawn from the study, and were not indicated as being deceased by national mortality records or other notification to the study). Consent was sought from 2,158 participants across the two approaches – 1,403 participants consented to data-linkage, 188 declined, and 567 did not respond. Minimum identifiers of consenting participants (name, gender, and date of birth) were provided to the Ministry of Health Analytic Services (formerly New Zealand Health Information Service) and a direct-match strategy was implemented to link to participants' National Health Index (NHI) number. Data were then matched by the Ministry of Health Analytic Services to health records based on NHI number, before all identifying information were removed and records assigned a new identification number for the purposes of linkage to HWR study survey data (Allen, 2016). Of the 1,403 participants who consented to data-linkage, 1,324 were matched successfully to an NHI number.

Final unweighted and weighted samples

The present study sample included 1,319 participants from the 2006 HWR study (Towers & Noone, 2007), who participated in the HWR data-linkage project (Allen, 2016), and responded to a survey item assessing drinking frequency (19.8% of the original random sample). This included 629 male participants (47.7%) and 690 female participants (52.3%). Ages ranged from 54-70 years, and the mean age of the sample was 61.1 years (SD= 4.5 years). A total of 344 participants (26.1%) were aged ≥65 years. For analyses addressing research questions

about the prevalence of concomitant alcohol/AI-medication use, the sample was weighted (by ethnicity, gender, and age) to adjust for oversampling and ensure representativeness to the population of New Zealanders aged 55-70 (see Stevenson, 2015). The weighted sample consisted of 1,720 participants, 860 of whom were male (50.0%) and 860 were female (50.0%). Ages in the weighted sample ranged from 54-70 years, and the mean age was 61.6 years (SD= 4.5 years). A total of 507 participants (29.4%) in the weighted sample were aged ≥65 years.

12.4.b: Measures

AI-medication use

Participants' pharmaceutical claims records were used to determine AI-medication use within the sample. This data was derived from the New Zealand Pharmaceutical Collection (PHARMS). The New Zealand Formulary (NZF) was used to identify *AI-medications*[14] within the PHARMS data and categorize them into ordinal groups of varying alcohol-interactivity levels (*mild*[15], *moderate*[16], *major*[17], and *contraindicated*[18]). The specific methods of identifying and categorizing AI-medications within the PHARMS data based on information provided by the NZF are detailed in the Chapter 11.2.

Participants were identified as AI-medication users if their pharmaceutical claims records indicated they a) were currently using AI-medication(s) at the time of survey completion, and b) had used AI-medication(s) on a regular basis prior to survey completion. The research

[14] AI-medications: those referred to as having potential alcohol-interactivity, those including a cautionary warning against alcohol use, and/or those including some sort of recommendation regarding alcohol consumption.

[15] Mild AI-medications: potential interactions are of little clinical significance.

[16] Moderate AI-medications: interactions may result in significant distress or incapacitation, but the likelihood of interaction is not high enough to warrant close monitoring or dosage adjustment.

[17] Major AI-medications: for interactions with detrimental effects that may be permanent or life-threatening OR interactions that may result in significant distress or incapacitation and the likelihood of interaction is high enough to warrant close monitoring or dosage adjustment.

[18] Contraindicated AI-medications: medications contraindicated for use with alcohol.

protocol developed for this project informed the specific methods used to determine which participants could be defined as AI-medication users based on this definition (see chapter 11.1 and 11.2). Briefly, current use of antibiotics was determined using the legend-time method; current use of NSAIDs and benzodiazepines was determined using a 30-day fixed-window; and current use of all other medications (excluding antibiotics, NSAIDs, and benzodiazepines) was determined using a 90-day fixed-window. Participants were defined as current regular AI-medication users if they were (1) identified as currently using AI-medications based on the criteria just described, and 2) dispensed at least one other AI-medication supply during the past 244 days (prior to survey completion) that was not in current use at the time of survey completion. AI-medication users were then assigned to one of three groups (mild, moderate, and major/contraindicated AI-medication users) based on the highest alcohol-interactivity level of medications in current use (see Table 12). For some analyses, moderate and major/contraindicated AI-medication use categories were also combined to identify participants using AI-medications with the potential to cause a clinically significant AMI (clinically significant AI-medication users).

Table 12: Pharmaceutical Dispensing Records of Participants Defined as Mild, Moderate, or Major/Contraindicated AI-Medication Users

AI-Medication User Groups	Pharmaceutical dispensing by participant	
	Current use	Past 244 days (not in current use)
Major/Contraindicated AI-medication users*	At least one major or contraindicated AI-medication	At least one AI-medication (mild, moderate, major, or contraindicated)
Moderate AI-medication users*	At least one moderate AI-medication, and no major or contraindicated AI-medications	At least one AI-medication
Mild AI-medication users	At least one mild AI-medication, and no moderate, major, or contraindicated AI-medications	At least one AI-medication

Note: Current use = Legend time for antibiotics; 30-day fixed-window for benzodiazepines & NSAIDs; 90-day fixed-window for all other drugs.
Note: *clinically significant AI-medication users

Alcohol use

The HWR survey includes the Alcohol Use Disorders Identification Test – C (AUDIT-C, Bush et al., 1998), which consists of three items assessing alcohol consumption patterns; specifically, the quantity and frequency of alcohol use, as well as binge drinking frequency. The present study used the AUDIT-C frequency item to measure alcohol use among participants. Those who reported using alcohol 'never' or 'monthly or less' were defined as *minimal/non-drinkers*, and *regular drinkers* were defined as those who reported drinking at least twice monthly. Responses on the AUDIT-C frequency item were then used to categorize regular drinkers as either *light/moderate-drinkers* (those who reported using alcohol '2-4 times monthly' or '2-3 times weekly') or *heavy-drinkers* (those who reported using alcohol '4 or more times weekly').

Physical health

The 2006 HWR survey included items of the SF12v2 (Ware et al., 2000), a self-report questionnaire that assesses a range of specific physical and mental health dimensions represented in separate subscales. The SF12v2 also produces two overall subscale scores relating to general physical and mental health dimensions. Subscale scores range from 0-100 (M=50, SD=10). The present study used the general physical health SF12v2 subscale to measure HWR participants' physical health. Scoring of the SF12v2 was based on normative data gathered in a New Zealand population derived from the 2008 New Zealand General Social Survey and factor score coefficients derived from the 2006-07 New Zealand Health Survey (Frieling et al., 2013). The SF12v2 physical health scale has shown good internal consistency ($\alpha > .80$) in large samples of US adults aged ≥18 years (Cheak-Zamora et al., 2009) and older adults aged ≥65 years (Shah & Brown, 2020).

Healthcare utilisation

The 2006 HWR survey included healthcare utilisation items originally developed for the New Zealand *Taking The Pulse* (TTP) survey, a nationally representative survey run by the New

Zealand *Ministry of Health* (1999) for population health monitoring. The present study utilized TTP questions to measure past 12-month GP visits (≤2 to ≥3), and past 12-month emergency department (ED) visits and/or overnight hospital admissions (0 to ≥1). The higher threshold of ≥3 GP visits was selected because subsidised medications used among participants are likely to have been prescribed by GPs. Past 12-month ED-visits and overnight hospital admissions (ED-visits/OHAs hereafter) were combined into a single dichotomous variable because it was impossible to determine whether reported ED visits and overnight hospital admissions resulted from separate or single events (i.e. ED visits that also result in overnight admission to hospital).

Demographic variables

In light of the association of SES with alcohol use, participant SES was measured using the economic living standard index short-form (ELSI-sf): a 25-item self-report measure of consumption capacity, economic social restrictions, and material wealth in New Zealand (Jensen et al.,2005). The ELSI-sf authors reported high internal consistency (α <.80) for this measure in a large New Zealand community sample (Jensen et al., 2005). Raw scores on the ELSI-sf range from 0-31, with higher scores indicating higher SES. ELSI-sf scores were also categorised into three levels of living standards including 'hardship' (score of ≤16) 'comfortable' (scores from 17-24) and 'good' (score of ≥25). Other demographic variables included ethnicity, age, marital status, and education level. Ethnicity was defined as 'New Zealand European' (NZE), 'Māori', or 'Other'. Age groups included '54-59 years', '60-64 years', and '65-70 years'. Marital status groups included 'Married, Civil Union, or De Facto', and 'Other'. Education level was defined as 'Tertiary Education' or 'No Tertiary Education'.

12.4.c: Analyses

All analyses were conducted using SPSS software. Descriptive statistics were used to describe sample rates and frequency of alcohol use, and characterise the demographic composition of the sample by alcohol use frequency category.

To explore the prevalence of concomitant alcohol/AI-medication use, descriptive statistics were used to describe sample rates of AI-medication use, rates of alcohol use among AI-medication users, and overall sample rates of concomitant AI-medication use. These analyses were applied to the unweighted and weighted samples. Additionally, to enhance comparability of the present study with other studies exploring rates of concomitant alcohol/AI-medication use by older adults, these analyses were also applied to unweighted and weighted subsamples of participants aged ≥65 years.

Hierarchical multiple regression was used to test the association of concomitant alcohol/AI-medication and physical health. The SF12v2 physical component scale was entered as an outcome variable. ELSI-SF raw scores were entered at step 1 to control for the effect of living standards. Binary variables were entered at step 2 to control for the effects of alcohol use ('minimal/non-drinkers' versus 'regular drinkers') and AI-medication use ('non-users' and 'mild AI-medication users' versus 'clinically significant AI-medication users'[19]). These two variables were then entered as an interaction term variable ('AI-medication use*alcohol use') at step 3, to assess whether the association of AI-medication use with physical health differed with concomitant alcohol use. Missing cases were deleted pairwise to maximize statistical power of the available data. R squared (R^2) was used to assess the level of variance in physical health explained by predictor variables at each step in the model. Additional variance in

[19] Clinically significant AI-medications include moderate and major/contraindicated AI-medications.

physical health explained by predictors introduced at steps 2 and 3 was assessed using R squared change (ΔR^2). Standardized beta values (β) were used to assess the direction and statistical significance (alpha level = <.05) of relationships between predictor variables and physical health.

Two hierarchical logistic regression models were constructed to assess the main effects and interaction effects of alcohol use and AI-Medication use on the likelihood of past 12-month healthcare utilization. The outcome variable in the first of these models was past 12-month ED-visits/OHAs (0 versus ≥1), and the outcome variable in the second model was past 12-month GP visits (≤2 versus ≥3). As with the multiple regression model described in the previous paragraph, the ELSI-SF scale was entered at step 1 to control for the effect of living standards, binary variables were entered at step 2 to control the effects of AI-medication use and of alcohol use, and an 'AI-medication use*alcohol use' interaction term was entered at step 3 to assess whether the association of AI-medication use with health service use differed with concomitant alcohol use. The goodness of fit both logistic regression models was assessed using Hosmer and Lemeshow Chi-squared tests (HLT). At each step of both logistic regression models, the variance in healthcare utilization explained by predictor variables was assessed using Cox and Snell R squared, and Nagelkerke R squared. Beta values (*B*) were used to assess whether relationships between predictor variables and healthcare utilization outcome variables reached statistical significance (alpha level = <.05), and odds ratios (*OR*) were used to assess the extent to which predictor variables influenced the likelihood of past 12-month healthcare utilization.

12.5: RESULTS

12.5.a: Characteristics of drinkers

Table 13 shows the demographic characteristics of the weighted sample (*N* = 1,720) overall and by drinking frequency category.

Table 13: Weighted Sample Characteristics by Drinking Frequency (N = 1,720)

Demographic variable	Total % of Sample	Drinking Frequency (AUDIT-C)		
		Minimal/ non-drinker	Light/ moderate-drinker	Heavy-drinker
Total sample	100% (1720.1)	461.9 (26.9%)	673.1 (39.1%)	585.1 (34.0%)
Gender				
Male	50.0% (860.3)	173.4 (20.2%)	304.8 (35.4%)	382.1 (44.4%)
Female	50.0% (859.8)	288.4 (33.5%)	368.4 (42.8%)	203 (23.6%)
Age				
54-59	37.4% (643.3)	170.5 (26.5%)	264.6 (41.1%)	208.2 (32.4%)
60-64	33.2% (570.4)	142.1 (24.9%)	211.9 (37.1%)	216.4 (37.9%)
65-70	29.4% (506.4)	149.2 (29.5%)	196.7 (38.8%)	160.5 (31.7%)
Ethnicity				
NZE	87.6% (1506.5)	391.3 (26.0%)	603.6 (40.1%)	511.6 (34.0%)
Māori	3.7% (63.8)	27.3 (42.8%)	24.1 (37.8%)	12.4 (19.4%)
Other	8.7% (149.6)	43.1 (28.8%)	45.4 (30.3%)	61.1 (40.8%)
Education level				
Tertiary education	15.2% (261.3)	43.5 (16.6%)	91.5 (35.0%)	126.3 (48.3%)
No tertiary education	83.3% (1433.3)	408.3 (28.5%)	572 (39.9%)	453 (31.6%)
Missing (n = 25.5)	1.5%			
Marital Status				
Married, civil union, or de facto	77.7% (1335.8)	325.5 (24.4%)	526.8 (39.4%)	483.5 (36.2%)
Other	21.4% (368.5)	134 (36.4%)	137.7 (37.4%)	96.8 (26.3%)
Missing (n = 15.8)	0.9%			
Living Standards				
Hardship	10.2% (175)	97 (55.4%)	45 (25.7%)	33 (18.9%)
Comfortable	31.5% (541)	144 (26.6%)	241.6 (44.7%)	155.4 (28.7%)
Good	56.7% (975.3)	208.7 (21.4%)	374.6 (38.4%)	392 (40.2%)
Missing (n = 28.8)	1.7%			

Overall, 73.1% of the weighted sample (*n* = 1,258) reported using alcohol at least twice monthly (i.e., regular drinkers). Regular drinking was most common among participants who were male (79.8%), aged 60-64 years (75.1%), NZ European (74.1%), those with good economic living standards (78.6%), those with tertiary level education (83.3%), and those of married, civil union, or de facto marital status (75.6%). The weighted sample rate of heavy

drinking (alcohol use 4 or more times weekly) was 34% (*n* = 585). Heavy drinking was more common among those who were male (44.4%), aged 60-64 (37.9%), of other ethnicity (40.8%), those with good living standards (40.2%), those with tertiary level education (48.3%), and those of married, civil union, or de facto marital status (36.2%). The unweighted sample characteristics by drinking frequency is shown in Appendix-C (Table 30).

12.5.b: Prevalence of concomitant alcohol/AI-medication use

Table 14 presents the unweighted and weighted sample rates of concomitant alcohol/AI-medication use. These results reflect a breakdown of the alcohol use patterns by a) the total sample; b) dichotomous samples reflecting 'non-users of AI-medications' and 'AI-medication users'; and c) a breakdown of the sub-samples within the 'AI-medication' use group based on AI-medication severity categories. Percentages are provided for overall sample rates of concomitant alcohol/AI-medication use, and for rates of alcohol use within AI-medication use samples and subsamples. The present study did not assess the statistical significance of the variation in alcohol use between AI-medication user groups, however this is explored in study 2 (chapter 13).

Rates of AI-medication use

The unweighted and weighted sample rates of participants identified as current regular users of at least one AI-medication were 35.9% (*n* = 473), and 34.4% (*n* = 591.2) respectively. Within the unweighted sample, 146 (11.1%) participants were mild AI-medication users, 151 (11.4%) were moderate AI-medication users, and 176 (13.3%) were major/contraindicated AI-medication users. Weighted sample rates of mild, moderate, and major/contraindicated AI-medication use were 11.9%, 11.7%, and 10.7% respectively (Table 14).

Table 14: Unweighted and Weighted Sample Rates of Alcohol Use, AI-Medication Use, and Cncomitant Alcohol/AI-Medication Use

Alcohol Use	Unweighted sample (*N* = 1,319)						Weighted sample (*N* = 1,720.1)					
	Total Sample	No AI-Medication Sample	AI-Medication sample	AI-medication sample by potential interaction severity			Total Sample	No AI-Medication Sample	AI-Medication sample	AI-medication sample by potential interaction severity		
				Mild	Moderate	Maj/Con*				Mild	Moderate	Maj/Con*
Minimal/non-drinkers	416	236	180	40	61	79	461.9	282.4	179.5	43.2	67.4	68.9
%Sample	31.5%	17.9%	13.6%	3.0%	4.6%	6.0%	26.9%	16.4%	10.4%	2.5%	3.9%	4.0%
%AI-Medication		27.9%	38.1%	27.4%	40.4%	44.9%		25.0%	30.4%	21.0%	33.4%	37.4%
Regular drinkers	903	610	293	106	90	97	1258.2	846.6	411.7	162.0	134.4	115.2
%Sample	68.5%	46.2%	22.2%	8.0%	6.8%	7.4%	73.1%	49.2%	23.9%	9.4%	7.8%	6.7%
%AI-Medication		72.1%	61.9%	72.6%	59.6%	55.1%		75.0%	69.6%	79.0%	66.6%	62.6%
Light/moderate	509	342	167	50	55	62	673.2	453.5	29.7	64.4	81.7	73.6
%Sample	56.4%	25.9%	12.7%	8.0%	6.8%	7.4%	39.1%	26.4%	12.8%	3.7%	4.8%	4.3%
%AI-Medication		40.4%	35.3%	34.2%	36.4%	35.2%		40.2%	37.2%	31.4%	40.5%	40.0%
Heavy	394	268	126	56	35	35	585.1	393.1	192.0	97.7	52.7	41.6
%Sample	43.6%	20.3%	9.6%	4.2%	2.7%	2.7%	34.0%	22.9%	11.2%	5.7%	3.1%	2.4%
%AI-Medication		31.7%	26.6%	38.4%	23.2%	19.9%		34.8%	32.5%	47.6%	26.2%	22.7%
Total Sample	1,319	846	473	146	151	176	1,720.1	1,128.9	591.2	205.2	201.8	184.1
%Sample	100.0%	64.1%	35.9%	11.1%	11.4%	13.3%	100.0%	65.6%	34.4%	11.9%	11.7%	10.7%

Notes: *****This severity category includes major AI-medications, and contraindicated AI-medications (i.e., major/contraindicated AI-medications)

Rates of concomitant alcohol use among AI-medication users

Of the 473 participants identified as current regular AI-medication users in the unweighted sample, 293 (61.9%) were identified as regular drinkers, and 126 (26.6%) were heavy drinkers. Among those identified as AI-medication users in the weighted sample, 69.6% were regular drinkers, with 32.5% being heavy drinkers (Table 14).

Sample rates of concomitant alcohol.AI-medication use

Unweighted and weighted sample rates of participants identified as both regular-drinkers and current regular AI-medication users (i.e., concomitant alcohol/AI-medication users) were 22.2% and 23.9% respectively (Table 14). A total of 187 participants in the unweighted sample (14.2%) were concomitant users of alcohol and AI-medications with the potential to cause a clinically significant AMI (i.e., moderate AI-medications, or major/contraindicated AI-medications). The weighted sample rate of participants identified as being at risk of a clinically significant AMI was 15.5% (*n* = 249.6).

Concomitant alcohol/AI-medication use among participants aged ≥65 years

A total of 344 participants within the unweighted sample were aged ≥65 years, 156 of whom (45.2%) were identified as current regular users of one or more AI-medications. Within the weighted sample, 506.5 participants were aged ≥65 years, 43.3% of whom (*n* = 219.1) were AI-medication users. The unweighted and weighted rates of regular drinking among AI-medication users aged ≥65 years were 63.5% (*n* = 99) and 66.1% (*n* = 144.9) respectively. The overall prevalence of concomitant alcohol/AI-medication use among participants aged ≥65 years was 28.8% in the unweighted sample, and 28.6% in the weighted sample. Among participants aged ≥65 years in the unweighted sample, 19.5% (*n* = 67) used alcohol concomitantly with AI-medications with the potential to cause a clinically significant AMI

(i.e., moderate, or major/contraindicated AI-medications). The rate of clinically significant AMI risk among those aged ≥65 years in the weighted sample was 18.3% (*n* = 92.5).

12.5.c: Alcohol, AI-medication, and physical health

Hierarchical multiple regression was used to assess a) the main effects of alcohol use and AI-medication use on physical health (assessed by SF12-v2) after controlling for living standards (ELSI-sf scores), and b) the interaction of alcohol and AI-medication use on the prediction of health after controlling for living standards and the main effects of alcohol and AI-medication use. All participants (*n* = 1,319) had data available for alcohol use and AI-medication use; SF12-v2 data was available for 1,228 participants; ELSI-sf data was available for 1,291 participants; and 1,204 participants had data for both the SF12-v2 and the ELSI-sf. Preliminary analyses showed the assumptions of normality, linearity, and homoscedasticity were not violated. Assessment of multicollinearity showed no correlations between independent variables exceeding .70 (excluding those between the interaction term and main effects variables). A summary of the results from the hierarchical regression is presented in Table 15.

Table 15: Multiple Regression Predicting Variance in Physical Health

	Step 1			**Step 2**			**Step 3**		
	β	R^2	ΔR^2	*B*	R^2	ΔR^2	*β*	R^2	ΔR^2
Model Predictors									
Living Standards	.33***			.28***			.28***		
Alcohol use				.06*			.06*		
AI-medication use				-.29***			-.27***		
Alcohol use x AI-medication use							-.02		
Model Summary		.111	.111***		.199	.088***		.199	.000

Note: * $p < .05$; ** $p < .01$; *** $p < .001$
Note: Living standards were determined based on continuous ELSI-sf scores
Note: Alcohol use was coded as 0 for those using alcohol monthly or less (minimal/non-drinkers) and 1 for those using alcohol at least twice monthly (regular drinkers)
Note: AI-Medication use was coded as 0 for non-users and Mild-AI-medication users and 1 for those using moderate or major/contraindicated AI-medications

Living standards was entered at step 1 and explained 11.1% of the variance in physical health. After entry of alcohol use and AI-medication use variables at step 2, the variance of the model was 19.9%, F (3, 1200) = 99.30, $p < .001$. The two variables explained an additional 8.8% of the variance in physical health after controlling for living standards, R squared change = .09, F change (2, 1200) = 65.75, $p < .001$. After entry of an interaction term variable at step 3 (alcohol use * AI-medication use), the total variance of the model as a whole remained at 19.9% F (3, 1199) = 74.47, $p < .001$. The addition of the interaction term explained 0.00% of the variance in physical health after controlling for living standards and the main effects of alcohol use and AI-medication use, R squared change = .00, F change (1, 1199) = .187, p .665.

In the final model, statistically significant predictors of physical health included living standards, alcohol use, and AI-medication use, with living standards recording a higher beta value (beta = .28, $p <.001$) than AI-medication use (beta = -.27, $p < .001$), and alcohol use (beta = .06, $p = .04$). The variance in physical health explained by living standards, alcohol use, AI-medication use, and the interaction term was 7.2%, 0.3%, 2.8%, and 0.0% respectively. Figure 1 displays the mean SF12-v2 scores for drinkers and non-drinkers across AI-medication user vs. non-user categories after controlling for the effects of variables entered in the model.

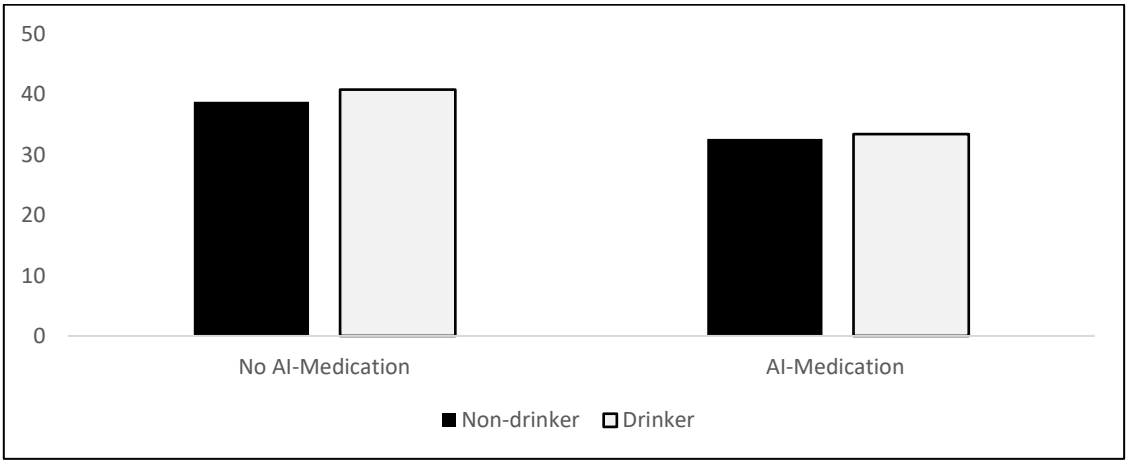

Figure 1: Mean SF12-v2 Physical Component Scores Cross Alcohol Use and AI-Medication Use Categories

12.5.d: Alcohol, AI-medication, and healthcare utilisation

Two hierarchical logistic regression models assessed the main effects and interaction effects of alcohol use and AI-Medication use on the likelihood of past 12-month ED-visits/OHAs (≥1) and GP-visits (≥3). In both models, the living standards were entered as a control variable at step 1, Alcohol Use and AI-Medication Use were entered at step 2, and an interaction term (Alcohol Use * AI-medication Use) was entered at step 3. Summaries of the logistic regression models for ED-visits/OHAs and GP-visits are presented in Table 16 and Table 17 respectively.

Emergency department visits and overnight hospital admissions (ED-visits/OHAs)

Step 1 of the model for ED-visits/OHAs was statistically significant (X^2 (1, N = 1,287) = 23.30, p <.001) indicating higher living standards were associated with a reduced risk of past year ED visits/OHAs. The ELSI-sf scale explained between 1.8% (Cox and Snell R2 square) and 3.0% (Nagelkerke R squared) of the variance in ED-visits/OHAs. The model was significantly improved by the addition of step 2 (block X^2 (2, N = 1,287) = 26.27, p <.001; full model X^2 (3, N = 1,287) = 49.47, p <.001), with the overall model at step 2 explaining between 3.8% (Cox and Snell R square) and 6.3% (Nagelkerke R squared) of the variance in ED-visits/OHAs (the additional variables therefore explained between 2.0% and 3.3% of the variance in ED-visits/OHAs). The model was not significantly improved by the addition of step 3 (block X^2 (1, N = 1,287) = 0.19, p =.658; full model X^2 (4, N = 1,287) = 49.77, p <.001).

The final model explained between 3.8% (Cox and Snell R square) and 6.4% (Nagelkerke R squared) of the variance in ED-visits/OHAs, correctly classified 83.2% of cases, and had adequate fit as indicated by non-significant HLT (X^2 (8, N = 1,287) = 6.70, p =.570). Significant predictors of ED-visits/OHAs in the final model (see Table 16) included living standards and AI-Medication use (p =<.001). The OR for AI-Medication use was 2.50, indicating AI-Medication users were 2.5 times more likely to report past year of ED-visits/OHAs than non-users.

Table 16: Hierarchical Logistic Regression Model Predicting ≥1 Emergency Department Visits and/or Overnight Hospital Admissions During the Past Year (n = 1,287)

Predictors	Step 1		Step 2		Step 3	
	B	OR (95% CI)	*B*	OR (95% CI)	*B*	OR (95% CI)
Living standards	-.23***	0.79 (0.72, 0.87)	-.19***	0.82 (0.75, 0.91)	-.19***	0.82 (0.75, 0.91)
Alcohol use			-.06	0.94 (0.68, 1.31)	.00	1.00 (0.66, 1.52)
AI-medication Use			.83***	2.29 (1.67, 3.13)	.92***	2.50 (1.51, 4.15)
Alcohol use*AI-medication use					-.15	0.86 (0.45, 1.65)

Note: * p < .05; ** p < .01; *** p < .001
Note: Living standards were determined based on ELSI-sf scores
Note: Alcohol use was coded as 0 for those using alcohol monthly or less and 1 for those using alcohol at least twice monthly
Note: AI-Medication use was coded as 0 for non-users and mild-AI-medication users and 1 for those using moderate or major/contraindicated AI-medications

GP-visits

Step 1 of the model for GP-visits was statistically significant (X^2 (1, N = 1,287) = 15.66, p <.001), with the ELSI-sf scale explaining between 1.2% (Cox and Snell R square) and 1.6% (Nagelkerke R squared) of the variance in GP-visits. The model was significantly improved by the addition of step 2 (block X^2 (2, N = 1,287) = 153.69, p <.001; full model X^2 (3, N = 1,287) = 169.35, p <.001), with the overall model at step 2 explaining between 12.3% (Cox and Snell R squared) and 16.4% (Nagelkerke R squared) of the variance in GP-visits (the additional variables therefore explained between 11.1% and 14.8% of the variance in GP-visits). The model was not significantly improved by the addition of step 3 (block X^2 (1, N = 1,287) = 0.22, p =.639; full model X^2 (4, N = 1,287) = 169.57, p <.001).

The final model explained between 12.3% (Cox and Snell R square) and 16.5% (Nagelkerke R squared) of the variance in GP-visits, correctly classified 65.3% of cases, and had adequate fit as indicated by non-significant HLT (X^2 (7, N = 1,287) = 4.66, p =.701). Significant predictors of GP visits in the final model (see Table 17) included living standards (p < .05) and

AI-medication use (p <.001). The OR for AI-Medication use was 5.27, indicating AI-medication users were more than 5 times more likely to report ≥3 past year GP-visits than non-users.

Table 17: Hierarchical Logistic Regression Model Predicting ≥3 Past Year GP visits (n = 1,287)

Predictors	Step 1		Step 2		Step 3	
	B	OR (95% CI)	*B*	OR (95% CI)	*B*	OR (95% CI)
Living standards	-.15***	0.86 (0.80, 0.93)	-.09*	0.91 (0.84, 0.99)	-.09*	0.91 (0.84, 0.99)
Alcohol use			-.04	0.96 (0.74, 1.25)	-.07	.93 (0.69, 1.25)
AI-medication Use			1.75***	5.77 (4.25, 7.82)	1.66***	5.26 (3.25, 8.54)
Alcohol use*AI-medication use					-.15	1.16 (0.62, 2.16)

Note: * p < .05; ** p < .01; *** p < .001
Note: Living standards were determined based on ELSI-sf scores
Note: Alcohol use was coded as 0 for those using alcohol monthly or less and 1 for those using alcohol at least twice monthly
Note: AI-Medication use was coded as 0 for non-users and mild-AI-medication users and 1 for those using moderate or major/contraindicated AI-medications

12.6: DISCUSSION

This section discusses topics of particular relevance to study 1, as points of discussion that apply to both studies implemented in the present thesis are covered in chapter 14. The results of the present study are summarized first. The findings and methods of the present study are then compared to those of previous observational studies exploring similar research questions. Strengths and limitations specific to study 1 are then discussed, and conclusions are provided.

12.6.a: Summary of results

The present study explored the prevalence of concomitant alcohol/AI-medication use, and the impact of concomitant alcohol/AI-medication use on health and healthcare utilisation, in a sample of New Zealand older adults. Almost a quarter of participants aged 54-70 years were identified as being at risk of AMI, and approximately one-in-six were at risk of exposure to an

AMI of clinical significance. Over one quarter of those aged 65-70 years were at risk of AMI, and approximately one-in-five were at risk of clinically significant AMI. The hypothesized associations of concomitant alcohol/AI-medication use with health and health care utilization were not supported by the results. After controlling for living standards, AI-medication use, and alcohol use, concomitant alcohol/AI-medication use was not a significant predictor of self-rated physical health or past 12-month healthcare utilization.

12.6.b: The present study in the context of existing observational research into concomitant alcohol/AI-medication use health outcomes

Previous research findings

To the authors knowledge, four other observational studies have explored associations of concomitant alcohol/AI-medication use on health outcomes in large older adult samples. Consistent with the present study, non-significant findings were reported in two studies examining the potential association between concomitant alcohol/AI-medication use and falls (Sheahan et al., 1995; Wong et al., 2016). In contrast, Immonen et al. (2013) found that 'at risk drinkers' who used AI-medications were significantly more likely to report having fallen when intoxicated than those using non-AI-medications (13.8% vs 4.1%). Similarly, Onder et al. (2002) found that recent alcohol consumption increased the odds of suffering an adverse drug reaction by 24% in a sample of older adults attending EDs across 81 hospitals in Italy.

Differences in outcome measures

The mixed findings described above may reflect differences in the outcome measures used between studies. Specifically, the studies that found significant associations of concomitant alcohol/AI-medication use (Immonen et al., 2013; Onder et al., 2002) included specific outcome variables that were potentially more relevant to the effects of AMIs. Immonen et al. (2013) used an outcome measure of alcohol-related falls, whereas Sheahan et al. (1995) and

Wong et al. (2016) included general measures of falls, and the health outcome measure used in the present study was even more broad (i.e., self-rated physical health). Moreover, Onder et al. (2002) reported on adverse drug reaction related ED visits, whereas the healthcare utilization measures included in present study were much more general in comparison (i.e., past 12-month GP visits, ED-visits, and OHAs). It is therefore possible that the health and healthcare utilization measures included in the present study were too broad to capture specific effects of concomitant alcohol/AI-medication use.

Differences in drinking measures

Alcohol use measurement differences may also contribute to the mixed results of observational studies reporting on concomitant alcohol/AI-medication related health outcomes. The two studies reporting significant findings included alcohol measures that considered both drinking quantity and drinking frequency. Immonen et al. (2013) defined 'risky drinkers' as those consuming >7 drinks weekly, ≥5 drinks per typical drinking day, and/or ≥3 drinks at least twice weekly, and recent drinkers were defined as those consuming an average of ≥40g of alcohol per day prior to hospital admission in the study by Onder et al. (2002). In contrast, the present study and the study by Sheahan et al. (1995) assessed drinking frequency only, and the drinking measure Wong et al. (2002) utilized (total drinks per month) was unable to specify typical drinking quantity or frequency with any level of accuracy (e.g., 30 drinks per month could reflect a variety of drinking quantity/frequency patterns).

The present study focused on drinking frequency over drinking quantity because this was seen as being a more reliable predictor of simultaneous exposure to alcohol and AI-medications (Breslow et al., 2015). However, the likelihood of simultaneous exposure causing an AMI is also depends on the amount of alcohol consumed and the class of AI-medication used (Moore et al., 2007). Given that drinking quantity was considered in both studies finding adverse health associations of concomitant alcohol/AI-medication use (Immonen et al., 2013; Onder et al.,

2002), a focus on drinking frequency over drinking quantity might partially explain the non-significant findings of the present study.

12.6.c: Strengths and limitations[20]

A key strength of the present study was the nationally representative sample, which increased the generalizability of the study findings to the population of New Zealanders aged 54-70 years. However, due to the age distribution of the study sample, the results are not easily generalized to the population of New Zealanders aged ≥65 years, which is generally considered the definition of older adulthood (Cannon, 2015). The age of the study sample was therefore a key limitation of the present study. The cross-sectional research design of the present study was also a potential limitation, given the nature of the research questions addressed. Health behaviour theorists (e.g., Maddux & Rogers, 1983; Janz & Becker, 1984; Rogers, 1975; Rosenstock et al., 1988) argue that perceived personal vulnerability to a given adverse health outcome is often a strong motivator for health behaviour change. It would therefore be reasonable to assume that having significant alcohol related health problems, and/or experiencing an acute AMI requiring medical attention, would be sufficient motivation for many older adults to stop drinking. Such cases would not be identified in the present study, as alcohol consumption was assessed at the time of survey completion, and the outcome variables were not measured longitudinally. Finally, the use of broad outcome variables that are non-specific to the effects of AMIs, and the overemphasis on drinking frequency over drinking quantity, were also potential limitations of the present study (as discussed previously in section 12.6.b).

[20] Several methodological strengths and limitations relating to measures of AI-medication use and alcohol use are discussed in Chapter 14, as these points also apply to study 2

12.6.d: Summary and conclusions

A substantial portion of the present study sample were identified as users of both alcohol and AI-medications. Concomitant alcohol/AI-medication use was not associated with self-rated health, past-12-month GP visits, or past month ED-visits and/or OHAs. However, these findings should be interpreted with caution, given that the heightened risks of AMI related harm for older adults are well documented in the pharmacological literature (Moore et al., 2002). As discussed, the non-significant findings of the present study likely reflect methodological issues. Future observational research into the health outcomes of concomitant alcohol/AI-medication use should include longitudinal outcome measures that are specific to the effects of AMI.

CHAPTER 13: RISK OF ALCOHOL-MEDICATION INTERACTIONS AMONG OLDER NEW ZEALANDERS: EXPLORING ASSOCIATIONS BETWEEN ALCOHOL USE, MEDICATION USE, AND DEPRESSION (STUDY 2)

13.1: ABSTRACT

Background: Vulnerability to adverse alcohol-medication interactions (AMIs) increases during older adulthood. Existing research findings indicate awareness of AMI risks is associated with reduced alcohol consumption among AI-medication users, and mental health factors such as depression may be associated with concomitant use of alcohol and AI-medication. **Objectives:** This study explored associations between AI-medication use, alcohol use, concomitant alcohol/AI-medication use, and depression among older adults. **Design and Methods**: This study included a large community sample of New Zealand older adults, and involved secondary analysis of survey data and pharmaceutical claims records. Sample weights were applied to survey data to increase representativeness to New Zealand's older adult population. Associations between variables of interest were explored using Chi-squared tests and hierarchical logistic regression. **Results:** More than one-in-three participants were at risk of AMI. AI-medication use was associated with less alcohol use, with lower rates of alcohol use being seen among those using AI-medications associated with higher AMI-severity. Depression did not influence the association between AI-medication use and alcohol use. **Discussion:** Many New Zealand older adults are at risk of AMI exposure. These risks may be mitigated by alerting older adults to their risk of AMI related harm.

13.2: INTRODUCTION

Interactions between alcohol and medications can increase risks of overdosing, cause a number of serious side effects such as gastrointestinal bleeding and psychomotor impairment, and may interfere with the therapeutic effects of medication treatment regimens (Adams, 1995; Moore, Whiteman, & Ward, 2007; Weathermon & Crabb, 1999). These risks are of particular concern for older adults, as this population is more likely to be using medications with the potential to interact negatively with alcohol, and are particularly sensitive to the effects of alcohol-medication interactions (AMI's) due to age-related changes in body mass and metabolism (Moore et al., 2007). Survey research exploring rates of alcohol and alcohol-interactive (AI) medication use among older adults has shown that, while AI-medication use is negatively associated with alcohol use, concomitant alcohol and AI-medication use is common among community dwelling older adults (Cousins et al., 2014; Breslow et al., 2015; Pringle et al., 2005; Qato et al., 2015).

Given the potential for alcohol related harm in older people, there is a need to identify factors underlying drinking behaviour among older AI-medication users that may inform intervention strategies aimed at reducing alcohol AMI exposure. Existing research findings show that having knowledge about AMI risk is negatively associated with alcohol use by AI-medication users (Gavens et al., 2016; Zanjani et al., 2013). These findings support motivational theories of health behaviour that propose perceived health threat often facilitates healthy behaviour change (e.g. Rogers, 1983; Rosenstock, 1974).

Conversely, avoidant coping strategies, such as avoidance of AMI related health information or denial of personal risk, appear to be associated with concomitant alcohol/AI-medication use (Gavens et al., 2016; Zanjani et al., 2013; Zanjani, Allen, Smith et al., 2018). There is also evidence indicating alcohol use for self-medicating purposes may prevent healthy changes in drinking behaviour by AI-medication users with mental health problems, particularly those

with symptoms of depression (Gavens et al., 2016; Haighton et a., 2018). These findings support motivational models of alcohol use proposing that people with higher negative affect and avoidant coping styles often use alcohol to self-medicate, and that self-medication in turn reduces volitional control over alcohol consumption (Cooper et al., 1995).

13.3: THE PRESENT STUDY

13.3.a: Aims

The present study analysed data from a nationwide survey of community dwelling older adults living in New Zealand. The aims of this study were to assess sample rates of concomitant alcohol/AI-medication use, and to explore the potential relationships between AI-medication use, alcohol use, and depression.

13.3.b: Theoretical framework

The theoretical framework adopted in the present study was based on health behaviour principles detailed in the *Protection Motivation Theory (PMT)* (Maddux & Rogers, 1983; Rogers, 1975) and Cooper's two-factor motivational model of alcohol use (Cooper et al., 1995). These theories were selected because they provide a parsimonious account regarding factors underlying drinking behaviour among AI-medication users (see chapter 6).

13.3.c: Hypotheses

The study had three hypotheses

- Firstly, based on previous epidemiological research showing a negative association between AI-medication use and alcohol use (Cousins et al., 2014; Breslow et al., 2015; Pringle et al., 2005; Qato et al., 2015), it was hypothesised that alcohol use would be less prevalent among AI-medication users than non-users of AI-medications.

- Secondly, it was hypothesised that alcohol use would be less common among participants using medications with higher levels of alcohol-interactivity than those using forms of AI-medication associated with milder AMIs. This hypothesis was based on the PMT principles of *vulnerability* and *severity* (Maddux & Rogers, 1983; Rogers, 1975), as well as research findings suggesting older AI-medication users who stop drinking may do so in response to knowledge of AMI risks (Gavens et al., 2016; Zanjani et al., 2013).

- Thirdly, it was hypothesized that depression would weaken the negative association between AI-medication use and alcohol use. This hypothesis was based on research suggesting some AI-medication users with depression may drink for self-medication purposes (Cheng et al., 2018; Gavens et al., 2016; Haighton, et al., 2018), PMT principles of *self-efficacy* and *response costs*, and the principle of '*drinking to cope'* from Cooper's motivational model of alcohol use (Cooper et al., 1995).

13.4: METHOD

13.4.a: Participants

Health, Work and Retirement study (HWR) 2010

The present study is a secondary analysis of data from the 2010 wave of the *Health, Work and Retirement (HWR) study*, which is a large ongoing nationally representative survey of older adults living in New Zealand that started in 2005. The 2010 data-wave was used in the present study because this was the first HWR survey to include a measure of depressive symptoms. The cohort consists of participants recruited across two waves occurring in 2006 and 2010. Participants were randomly selected from the New Zealand electoral roll, and over sampling of those indicated as having Māori descent was undertaken to ensure adequate representation of New Zealand's Māori (indigenous) population. Participants recruited in 2006 participated

in the initial HWR study, which originally consisted of 6,662 participants aged 55-70 years. The 2010 HWR recruitment wave aimed to increase representation of younger (aged 50-84 years) and older (70-84) age groups within the sample. The 2010 HWR sample consisted of 3,305 New Zealand adults aged ≥48 years, 1,981 of whom were recruited in 2006 and 1,324 were recruited in 2010 (Towers & Stevenson, 2014). The present study includes a subsample of the 2010 HWR cohort who consented to having their survey data linked with their national health records as part of the HWR data-linkage project.

Data-linkage

The HWR data linkage project links consenting participants' survey data with their national health records. In 2014, written informed consent was sought among participants of the 2010 HWR study. A second approach to data linkage consent occurred in 2015 and included those who did not respond in the 2014 approach, yet were active participants in the 2014 HWR survey. Consent was sought from 2,475 participants across the two approaches, 1,727 of whom consented to data linkage. Minimum identifiers of consenting participants (name, gender, and date of birth) were provided to the Ministry of Health Analytic Services (formerly New Zealand Health Information Service) and a direct-match strategy was implemented to link to participants' National Health Index (NHI) number (Allen, 2016). Data were then matched by the Ministry of Health Analytic Services to health records based on NHI number, before all identifying information were removed and records assigned a new identification number for the purposes of linkage to HWR study research data. Of the 1,727 participants who consented to data-linkage, 1,625 were matched successfully to their NHI (and were therefore able to participate in the data-linkage project). Among those successfully matched to their NHI, 1,191 (73.3%) were recruited in 2006, and 434 (26.7%) were recruited in 2010. Table 18 shows the number of 2010 HWR participants who were approached for and consented to data linkage, and were successfully matched to their NHI number across both waves of recruitment.

Table 18: Process of Data-Linkage Recruitment Among 2010 HWR Participants

	Wave of recruitment		Total
	2006	2010	
Total HWR 2010 sample	1,981	1,324	3,305
Approached for data linkage	1,783	692	2,475
Consented to data linkage	1,257	470	1,727
Matched to NHI (final sample)	1,191	434	1,625

Final unweighted and weighted samples

The present study sample included 1,621 participants from the 2010 HWR study (Towers & Stevenson, 2014), who participated in the HWR data-linkage project (Allen, 2016), and responded to a survey item assessing drinking frequency (49.0% of the original random sample). This included 765 male participants (47.2%) and 856 female participants (52.8%). Ages ranged from 49-83 years, and the mean age of the sample was 63.4 years (SD= 6.1 years). A total of 710 participants (43.8%) were aged ≥65 years. For analyses addressing research questions about the prevalence of concomitant alcohol/AI-medication use, the sample was weighted (by ethnicity, gender, and age) to adjust for oversampling and ensure representativeness to the population of New Zealand's older adult population (see Stevenson, 2015). The weighted sample consisted of 1,736 participants, 870 of whom were male (50.1%) and 866 were female (49.9%). Ages in the weighted sample ranged from 49-83 years, and the mean age was 63.5 years (SD= 6.0 years). A total of 771 participants (44.4%) in the weighted sample were aged ≥65 years.

13.4.b: Measures

AI-medication use

Participants' pharmaceutical claims records were used to determine AI-medication use within the sample. This data was derived from the New Zealand Pharmaceutical Collection

(PHARMS). The New Zealand Formulary (NZF) was used to identify *AI-medications*[21] within the PHARMS data and categorize them into ordinal groups of varying alcohol-interactivity levels (*mild*[22], *moderate*[23], *major*[24], and *contraindicated*[25]). The specific methods of identifying and categorizing AI-medications within the PHARMS data based on information provided by the NZF are detailed in the Chapter 11.2.

Participants were identified as AI-medication users if their pharmaceutical claims records indicated they a) were currently using AI-medication(s) at the time of survey completion, and b) had used AI-medication(s) on a regular basis prior to survey completion. The research protocol developed for this project informed the specific methods used to determine which participants could be defined as AI-medication users based on this definition (see Chapter 11.1 and 11.2). Briefly, current use of antibiotics was determined using the legend-time method; current use of NSAIDs and benzodiazepines was determined using a 30-day fixed-window; and current use of all other medications (excluding antibiotics, NSAIDs, and benzodiazepines) was determined using a 90-day fixed-window. Participants were defined as current regular AI-medication users if they were (1) identified as currently using AI-medications based on the criteria just described, and 2) dispensed at least one other AI-medication supply during the past 244 days (prior to survey completion) that was not in current use at the time of survey completion. AI-medication users were then assigned to one of three groups (mild, moderate, and major/contraindicated AI-medication users) based on the highest alcohol-interactivity level

[21] AI-medications: those referred to as having potential alcohol-interactivity, those including a cautionary warning against alcohol use, and/or those including some sort of recommendation regarding alcohol consumption.

[22] Mild AI-medications: potential interactions are of little clinical significance.

[23] Moderate AI-medications: interactions may result in significant distress or incapacitation, but the likelihood of interaction is not high enough to warrant close monitoring or dosage adjustment.

[24] Major AI-medications: for interactions with detrimental effects that may be permanent or life-threatening OR interactions that may result in significant distress or incapacitation and the likelihood of interaction is high enough to warrant close monitoring or dosage adjustment.

[25] Contraindicated AI-medications: medications contraindicated for use with alcohol.

of medications in current use (Table 19). For some analyses, moderate and major/contraindicated AI-medication use categories were also combined to identify participants using AI-medications with the potential to cause a clinically significant AMI (clinically significant AI-medication users).

Table 19: Pharmaceutical Dispensing Records of Participants Defined as Mild, Moderate, or Major/Contraindicated AI-Medication Users

AI-Medication User Groups	Pharmaceutical dispensing by participant	
	Current use	Past 244 days (not in current use)
Major/Contraindicated AI-medication users*	At least one major or contraindicated AI-medication	At least one AI-medication (mild, moderate, major, or contraindicated)
Moderate AI-medication users*	At least one moderate AI-medication, and no major or contraindicated AI-medications	At least one AI-medication
Mild AI-medication users	At least one mild AI-medication, and no moderate, major, or contraindicated AI-medications	At least one AI-medication

Note: Current use = Legend time for antibiotics; 30-day fixed-window for benzodiazepines & NSAIDs; 90-day fixed-window for all other drugs.
Note: *clinically significant AI-medication users

Alcohol use

The HWR survey includes the Alcohol Use Disorders Identification Test – C (AUDIT-C, Bush et al., 1998), which consists of three items assessing alcohol consumption patterns; specifically, the quantity and frequency of alcohol use, as well as binge drinking frequency. The present study used the AUDIT-C frequency item to measure alcohol use among participants. Those who reported using alcohol 'never' or 'monthly or less' were defined as *minimal/non-drinkers*, and *regular drinkers* were defined as those who reported drinking at least twice monthly. Responses on the AUDIT-C frequency item were then used to categorize regular drinkers as either *light/moderate-drinkers* (those who reported using alcohol '2-4 times monthly' or '2-3 times weekly') or *heavy-drinkers* (those who reported using alcohol '4 or more times weekly').

Depression

Depression was measured with a shortened version of the *Centre for Epidemiologic Studies Depression Scale* (CES-D; Radloff, 1977), which includes 10 items selected for the assessment of depression in older people (CES-D-10) (Andersen et al., 1994). Raw scores on the CES-D-10 range from 0 – 30. The present study adopted a dichotomous scoring threshold of 10, which is recommended by Anderson et al. (1994), so that participants scoring below 10 were categorized as 'not depressed' and those scoring ≥10 were categorized as 'depressed'. The chronbach's alpha coefficient for this measure was $\alpha = .82$ in the present study sample.

Demographic variables

Participant SES was measured using the Economic Living Standard Index short form (ELSI-sf), a 25-item self-report measure of consumption capacity, economic social restrictions, and material wealth (Jensen et al., 2005). This measure was included to control for the association between SES and alcohol consumption (see Scott et al., 2018; Towers, Philipp et al., 2018), when assessing relationships between alcohol use, AI-medication use, and depression. Raw scores on the ELSI-sf range from 0-31, with higher scores indicating higher SES. ELSI-sf raw scores were also categorised into three levels of living standards ('hardship'; 'comfortable'; 'good'). Other demographic variables of interest included age, ethnicity, marital status, and education level. Age groups included '48-54 years', '55-64 years', '65-74 years', and ' ≥75 years'. Ethnicity was defined as 'New Zealand European' (NZE), 'Māori', or 'Other'. Marital status groups included 'Married, Civil Union, or De Facto', and 'Other'. Education level was defined as 'Tertiary Education' or 'No Tertiary Education'.

13.4.a: Analysis

All analyses were conducted using SPSS software. Descriptive statistics were used to describe unweighted sample rates and frequency of alcohol use, and characterise the demographic composition of the unweighted sample by alcohol use frequency category.

To explore the prevalence of concomitant alcohol/AI-medication use, descriptive statistics were used to describe sample rates of AI-medication use, rates of alcohol use among AI-medication users, and overall sample rates of concomitant AI-medication use. These analyses were applied to the total weighed sample, and to unweighted and weighted subsamples of participants aged ≥65 years. The prevalence of concomitant alcohol/AI-medication use across the total unweighted sample was also explored when assessing the association between AI-medication use and alcohol use, as discussed in the following two paragraphs.

Hypothesized associations between AI-medication use and alcohol use were explored in the unweighted sample. To test the hypothesis that alcohol use would be less common among those using AI-medications, 2x2 chi-square test of independence was used to compare rates of minimal/non-drinker status versus light-moderate/heavy drinker status among users and non-users of AI-medications. The effect size of the 2x2 chi-squared test was assessed using the Phi coefficient. A 3x2 chi-square test of independence was used to further explore this hypothesis across 3 drinking frequency categories. Cramer's V was used to measure effect size of the 3x2 Chi-squared test. Standardized residuals were analysed to determine whether cells deviated from expected frequencies at <.05 (critical value of ±1.96) or <.01 (critical value of ±2.58) levels of significance.

To test the hypothesis that alcohol use would be less common among those using AI-medications with higher alcohol interactivity, a 4x2 chi-squared test of independence was used to compare rates of minimal/non-drinker status versus light-moderate/heavy drinker status

across AI-medication user severity categories. This was then further explored across the extended drinking frequency categories using a 4x3 chi-squared test of independence. Effect sizes were measured using Cramer's V, and standardized residuals were used to determine whether cells deviated from expected frequencies at <.05 or <.01 levels of significance.

A hierarchical logistic regression model was used to test the hypothesis that the predicted negative relationship between AI-medication use and alcohol use would be moderated by depression. In this model, alcohol use was entered as binary outcome variable (regular drinkers versus minimal/non-drinkers). ELSI-SF raw scores were entered at step 1 to a control for the effect of living standards. Binary variables were entered at step 2 to control for the main effects of AI-medication use ('non-users' and 'mild AI-medication users' versus 'clinically significant AI-medication users'), and depression (CES-D-10 cut-off score of ≥10). These two variables were then entered as an interaction term variable ('AI-medication use*depression') at step 3, to whether the association of AI-medication use with alcohol use differed with the presence of depression. A Hosmer and Lemeshow Chi-squared test (HLT) was used to assess the regression model's goodness of fit. The variance in alcohol use explained by predictors at each step of the model was assessed using Cox and Snell R squared, and Nagelkerke R squared. Beta values (*B*) were examined to assess whether relationships between predictor variables and alcohol use reached statistical significance (alpha level = <.05), and odds ratios (OR) were used to assess the extent to which predictor variables influenced the likelihood of alcohol use.

13.5: RESULTS

13.5.a: Characteristics of drinkers

Table 20 shows the demographic characteristics of the weighted sample overall (*N*= 1,736), and by drinking frequency. The unweighted sample demographics by drinking frequency are shown in Appendix C (Table 31).

Table 20: Demographic Weighted Sample Characteristics Across Drinking Frequency Groups

Demographic variable	Total % of Sample	Drinking Frequency (AUDIT-C)		
		Minimal/non-drinker	Light/moderate-drinker	Heavy-drinker
Total sample	100% (1735.7)	525.7 (30.3%)	680.3 (39.2%)	529.7 (30.5%)
Gender				
Male	50.1% (870)	204.5 (23.5%)	343.2 (39.4%)	322.4 (37.1%)
Female	49.9% (865.7)	321.2 (37.1%)	337.1 (38.9%)	207.3 (23.9)
Age				
48-54	8.9% (155.7)	50.1 (32.4%)	67.9 (43.9%)	36.6 (23.7%)
55-64	46.6% (809.6)	224.2 (27.7%)	330.4 (40.8%)	255.1 (31.5%)
65-74	43.7% (758.1)	247.2 (32.6%)	277.1 (36.6%)	233.7 (30.8%)
75+	0.8% (13.4)	4.2 (31.3%)	4.9 (36.7%)	4.3 (32.1%)
Ethnicity				
NZE	88.6% (1509.8)	434.7 (28.8%)	590.6 (39.1%)	484.5 (32.1%)
Māori	6.3% (108.2)	54.5 (50.4%)	37.6 (34.8%)	16.2 (15%)
Other	5.1% (86.2)	28.3 (32.8%)	34.7 (40.3%)	23.2 (26.9%)
Education level				
Tertiary education	32.1% (554.4)	135.3 (24.4%)	212.9 (38.4%)	206.2 (37.2%)
No tertiary education	67.9% (1175)	388.1 (33.0%)	464.3 (39.5%)	322.6 (27.5%)
Marital Status				
Married, civil union, de facto	78.8% (1362.8)	361.7 (26.5%)	555.1 (40.7%)	446.0 (32.7%)
Other	21.2% (366.2)	161.7 (44.2%)	122.3 (33.4%)	82.2 (22.4%)
Living Standards				
Hardship	11.9% (201.6)	114.9 (57.0%)	62.0 (30.8%)	24.7 (12.3%)
Comfortable	26.9% (455.6)	163.5 (35.9%)	193.8 (42.5%)	98.3 (21.6%)
Good	61.2% (1037.9)	234.0 (22.5%)	405.8 (39.1%)	398.0 (38.3%)

A total of 1,210 participants (69.7%) were identified as regular drinkers (light/moderate and heavy), and 530 (30.5%) were heavy drinkers (alcohol use four or more times weekly). Regular drinking was most common among those who were male (86.5%), aged 55-64 (82.3%), NZ European (71.2%), educated at tertiary level (75.6%), those with good living standards (77.5%), and those who were of married, civil union, or de facto marital status (73.4%). Rates of heavy drinking were highest among those who were male (37.1%), aged ≥75 years (32.1%), NZ European (32.1%), educated at tertiary level (37.2%), with good living standards (38.2%), and of married, civil union, or de facto marital status (32.7%).

13.5.b: Weighted prevalence of concomitant alcohol/AI-medication use

Table 21 presents the weighted sample rates of concomitant alcohol/AI-medication use. These results reflect a breakdown of the alcohol use patterns by a) the total sample; b) dichotomous samples reflecting 'non-users of AI-medications' and 'AI-medication users'; and c) a breakdown of the sub-samples within the 'AI-medication' use group based on AI-medication severity categories. Percentages are provided for overall sample rates of concomitant alcohol/AI-medication use, and for rates of alcohol use within AI-medication use samples/subsamples.

Overall, 939 participants (54.1%) in the weighted sample were current regular users of at least one AI-medication, 66.3% of whom (n = 623) were regular drinkers. The rate of heavy drinking among AI-medication users in the weighted sample was 27.9% (n = 262). Across the total weighted sample, 623 participants (35.9%) were identified as being regular drinkers and current regular AI-medication users (Table 21). A total of 439 participants in the weighted sample (25.3%) used alcohol concomitantly with AI-medications that pose risk of clinically significant AMI (i.e., moderate AI-medications, or major/contraindicated AI-medications).

Table 21: Weighted Sample Rates of Alcohol Use, AI-Medication Use, and Concomitant Alcohol/AI-Medication Use

Alcohol Use	Total Sample	No AI-Medication Sample	AI-Medication sample	AI-medication sample by potential interaction severity		
				Mild	Moderate	Maj/Con*
Minimal/non-drinkers	525.7	209.7	316.0	65.9	101.0	149.1
%Sample	30.3%	12.1%	18.2%	3.8%	5.8%	8.6%
%AI-Medication		26.3%	33.7%	26.5%	31.6%	40.3%
Regular drinkers	1210.0	587.3	622.7	183.2	218.8	220.7
%Sample	69.7%	33.8%	35.9%	10.6%	12.6%	12.7%
%AI-Medication		73.7%	66.3%	73.5%	68.4%	59.7%
Light/moderate	680.3	319.6	360.7	93.4	130.5	136.9
%Sample	39.2%	18.4%	20.8%	5.4%	7.5%	7.9%
%AI-Medication		40.1%	38.4%	37.5%	40.8%	37.0%
Heavy	529.7	267.7	262.0	89.9	88.4	83.8
%Sample	30.5%	15.4%	15.1%	5.2%	5.1%	4.8%
%AI-Medication		33.6%	27.9%	36.1%	27.6%	22.7%
Total Sample	1735.7	797.0	938.7	249.1	319.8	369.8
%Sample	100.0%	45.9%	54.1%	14.4%	18.4%	21.3%

Notes: *This severity category includes major AI-medications, and contraindicated AI-medications (i.e., major/contraindicated AI-medications)

13.5.c: Concomitant alcohol/AI-medication Use among those aged ≥65 years in the Unweighted and Weighted samples

A total of 710 participants within the unweighted sample were aged ≥65 years, 465 of whom (65.5%) were identified as current regular users of one or more AI-medications. Within the weighted sample, 771 participants were aged ≥65 years, 63.6% of whom (*n* = 490) were AI-medication users. The unweighted and weighted rates of regular drinking among AI-medication users aged ≥65 years were 62.4% (*n* = 290) and 67.3% (*n* = 330) respectively. The overall prevalence of concomitant alcohol/AI-medication use among participants aged ≥65 years was 40.8% in the unweighted sample, and 42.8% in the weighted sample. Among participants aged ≥65 years in the unweighted sample, 28.3% (*n* = 201) used alcohol concomitantly with AI-medications with the potential to cause a clinically significant AMI

(i.e., moderate, or major/contraindicated AI-medications). The rate of clinically significant AMI risk among those aged ≥65 years in the weighted sample was 30.4% (*n* = 234).

13.5.d: Unweighted prevalence of concomitant alcohol/AI-medication use: exploring the hypothesized associations between AI-medication use and alcohol use

Rates of AI-medication use

Across the total unweighted sample, 897 participants (55.3%) used at least one AI-medication regularly, with the remaining 724 participants (44.7%) identified as non-users. The unweighted sample rates of *mild*, *moderate*, and *major/contraindicated* AI-medication use were 14.6% (n = 237), 17.5% (n = 283), and 23.2% (n = 377), respectively.

Alcohol consumption by users vs. non-users (binary AI-medication use)

The unweighted sample rate of participants identified as both drinkers and AI-medication users was 34.0% (551 participants). A chi-square test of independence showed the rate of alcohol use was significantly lower among AI-medication users (61.4%) than non-users of AI-medications (72.4%), X^2 (1, N = 1,621) = 21.50, p <.001, *phi* = 0.11. When this relationship was explored by drinking frequency category (Table 22), comparison of standardized residuals indicated rates of minimal/non-drinker status were significantly lower than expected among non-users of AI-medications (p < .01) and significantly higher than expected among AI-medication users (p < .05); X^2 (2, N = 1,621) = 21.82, p <.001, *Cramer's V* = .12. However, no significant deviations from expected frequencies were observed across light/moderate and heavy drinking categories.

Table 22: Binary AI-medication by Drinking Frequency: Chi-Squared Test

Binary AI-Medication Use Categories	Drinking Frequency (AUDIT-C)		
	Minimal/non-drinker	Light/moderate-drinker	Heavy-drinker
No AI-Medication Use	27.6% (-2.8)**	41.9% (1.3)	30.5% (1.6)
AI-Medication Use	38.6% (2.5)*	36.6% (-1.1)	24.9% (-1.4)

Note: Values in parentheses represent standardized residuals; * p <.05; ** p <.01

Alcohol consumption by mild, moderate, and major/contraindicated AI-medication users

The sample rates of participants identified as both regular drinkers (*light/moderate* or *heavy*) and users of *mild*, *moderate*, and *major/contraindicated* AI-medications were 10.5%, 11.3%, and 12.2% respectively. The respective sample rates of participants identified as both light/moderate drinkers and users of mild, moderate, or major/contraindicated AI-medications were 5.6%, 6.9%, and 7.8%. The sample rates of participants identified as both heavy-drinkers and users of mild, moderate, major/contraindicated AI-medications were 4.9%, 4.4%, and 4.4% respectively.

A chi-square test of independence showed significant differences in alcohol use across AI-medication user severity categories (Table 23), X^2 (3, N = 1,621) = 47.48, p <.001, *Cramer's* V = 0.17. Standardized residuals showed rates of non-drinker status were significantly lower than expected among those not using AI-medications and significantly higher than expected among major/contraindicated AI-medication users (p < .01), while rates of drinker status were significantly higher than expected among those not using AI-medications (p <.05) and significantly lower than expected among those using major/contraindicated AI-medications. When this relationship was further explored across drinking frequency categories (X^2 (6, N = 1,621) = 52.21, p <.001, *Cramer's* V = 0.13), the rate of heavy drinking was significantly lower than expected among major/contraindicated AI-medication users only (p <.01), and rates of light/moderate drinking did not deviate significantly from expected frequencies across AI-medication use categories (see Table 24).

Table 23: AI-Medication Severity by Binary Drinking: Chi-Squared Test

AI-Medication Use	Non-drinkers	Drinkers
Non-use	27.6% (-2.8)**	72.4% (2.0)*
Mild	28.3% (-1.4)	71.7% (1.0)
Moderate	35.3% (.5)	64.7% (-.3)
Major/Contraindicated	47.5% (4.6)**	52.5% (-3.3)**

Note: values in parenthesis represent standardized residuals; * <.05; **<.01
Note: X^2 (3, N = 1,621) = 47.48, p <.001, *phi* = .17.

Table 24: AI-Medication Severity by Drinking Frequency: Chi-Squared Test

AI-Medication User Severity Categories	Drinking Frequency (AUDIT-C)		
	Minimal/non-drinker	Light/moderate-drinker	Heavy-drinker
N/A	27.6% (-2.8)**	41.9% (1.3)	30.5% (1.6)
Mild	28.3% (-1.4)	38.0% (-.2)	33.8% (1.9)
Moderate	35.3% (.5)	39.6% (.2)	25.1% (-.7)
Major/Contraindicated	47.5% (4.6)**	33.4% (-1.7)	19.1% (-3.1)**

Notes: values in parenthesis represent standardized residuals; * <.05; **<.01
Note: X^2 (6, N = 1,621) = 52.21, p <.001, *phi* = .179.

13.5.e: Interaction of AI-medication use and depression in the prediction of alcohol use

A hierarchical logistic regression model assessed the main effects and interaction effects of AI-medication use and depression on the likelihood of alcohol use. Living standards was entered as a control variable at step 1, AI-medication use and depression were entered at step 2, and the interaction term (AI-medication use*depression) entered at step 3. The results of this model are summarized in Table 25.

Table 25: Hierarchical Logistic Regression Model Assessing Interaction Effects of AI-Medication Use and Depression on Alcohol Use

Predictor and Step	*B*	S.E	Wald	df	*P*	OR	95 % CI for OR Lower	Upper	*p* X^2 Block (N = 1,488)
Step 1									
Living Standards	.33	.04	78.35	1	<.001	1.39	1.30	1.50	p <.001
Step 2									
Living Standards	.30	.04	52.83	1	<.001	1.35	1.25	1.47	p <.001
AI-Medication	-.46	.12	15.30	1	<.001	.63	.50	.79	
Depression	-.03	.15	.03	1	.86	.97	.72	1.32	
Step 3									
Living Standards	.30	.04	52.92	1	<.001	1.35	1.25	1.47	p =.638
AI-Medication	-.43	.13	10.67	1	<.01	.65	.50	.84	
Depression	.05	.23	.05	1	.82	1.06	.67	1.67	
AI-Medication * Depression	-.14	.29	.22	1	.64	.87	.49	1.54	

As shown in Table 25, step 1 of the model was statistically significant (χ^2 (1, N = 1,488) = 82.12, p = <.001), with ELSI-sf scores explaining between 5.4% (Cox and Snell R square) and 7.5% (Nagelkerke R square) of the variance in alcohol use. The model of alcohol use was significantly improved with the addition of step 2 (block: X^2 (2, N = 1,488) = 15.83, p <.001; full model: X^2 (3, N = 1,488) = 97.95, p <.001), with the overall model at step 2 explaining between 6.4% (Cox and Snell R square) and 8.8% (Nagelkerke R square) of the variance in alcohol use (the additional variables therefore explained between 1% and 1.3% of the variance in alcohol use). The model was not significantly improved with the addition of step 3 (block X^2 (1, N = 1,488) = 0.22, p =.638; full model X^2 (4, N = 1,488) = 98.12, p <.001). The final model explained between 6.4% (Cox and Snell R Square) and 8.9% (Nagelkerke R Square) of the variance in alcohol use, and had adequate fit as indicated by non-significant HLT (X^2 (7, N = 1,488) = 4.18, p = .758). The only significant predictors of alcohol use in the final model were living standards and AI-medication use.

13.6: DISCUSSION

This section discusses topics of particular relevance to study 2, and points of discussion that apply to both studies implemented in the present thesis are covered in chapter 14. The present study explored the prevalence of concomitant alcohol/AI-medication use in a sample of New Zealand older adults, and assessed the potential relationships between AI-medication use, alcohol use, and depression. Approximately two thirds of the sample reported using alcohol at least two days monthly, and just over half of the sample used at least one AI-medication regularly. More than one third of participants aged 49-83 years were at risk of AMI exposure, and approximately one quarter were at risk of suffering an adverse AMI of clinical significance. Among those aged ≥65 years, approximately two-in-five participants were at risk of AMI, and more than one-in-four were at risk of a clinically significant AMI.

13.6.a: Hypothesized relationships between alcohol use and AI-medication use

The hypothesis that alcohol use would be less common among those using AI-medications was supported, as participants identified as AI-medication users were significantly less likely than non-users of AI-medications to report using alcohol two or more times monthly. This finding is consistent with previous studies exploring rates of concomitant alcohol/AI-medication use among older adults in the US and Ireland (Cousins et al., 2014; Breslow et al., 2015; Pringle et al., 2005; Qato et al., 2015).

The hypothesis that AI-medications with higher levels of alcohol-interactivity would be associated with less alcohol use was generally supported by the results. Rates of self-reported alcohol use (at least twice monthly) were significantly lower among those using AI-medications identified as having the highest level of alcohol-interactivity (i.e. major/contraindicated AI-medications). When this association was explored across drinking frequency groups, the data showed that those using medications identified as highly alcohol-

interactive were significantly less likely to report heavy drinking (four days weekly), but rates of light-moderate drinking (two days monthly to three days weekly) did not differ significantly across AI-medication severity groups.

Given that the AI-medication severity categories utilized in this study were identified using the same drug-interaction identification system used by New Zealand prescribers and pharmacists, it is likely that some of the participants identified major/contraindicated AI-medication users in this study would have been advised about AMI risks from their prescribers. As such, the observed negative association between alcohol use and major/contraindicated AI-medication use is consistent with previous studies indicating AMI related knowledge leads to reduced alcohol use (Gavens et al., 2016; Zanjani et al., 2013), as well as the principles of severity and vulnerability described by PMT (Maddux & Rogers, 1983; Rogers, 1975).

13.6.b: Hypothesized moderator role of depression

The hypothesis that depression would moderate the hypothesized negative association between AI-medication use and alcohol use was not supported by the results. After controlling for living standards, depression was not a significant predictor of concomitant alcohol use by AI-medication users. While these results do not support findings of previous studies implicating self-medication as a motivator for alcohol use among AI-medication users (e.g., Gavens et al., 2016; Haighton, et al., 2018), it should be noted that drinking motives were not directly measured in the present study. Although drinking to alleviate distress is common among people with depression (Bolton et al., 2009; Boschloo et al., 2012 Brown & Stewart, 2008), it cannot be assumed that all people with depression self-medicate with alcohol, or that drinking to cope occurs exclusively in the context of depression. As such, the non-significant findings of the present study should not be interpreted as evidence against the role of self-medication in concomitant alcohol/AI-medication use.

13.6.c: Strengths and limitations

A key strength of the present study was the nationally representative sample, which increases the generalizability of the findings to the population of New Zealanders aged 48-83 years. Additionally, in comparison to the sample included in study 1 (see sections 12.4.c and 12.6.c), the present study sample was more representative of the population of New Zealanders aged ≥65 years, which is generally considered the definition of older adulthood. The age distribution of the sample was therefore a key strength of the present study. As stated previously, a potential limitation of the present study was that a measure of drinking motives was not included in the analysis.

13.6.d: Summary and conclusions

The results of this study indicate that many New Zealand older adults are at risk of AMI related harm. Providing older adults with information about the risks of combined alcohol/AI-medication use may help mitigate their risk of AMI exposure. Such interventions should emphasize information about heightened susceptibility to AMIs during older adulthood, and the severity of AMI related harm. However, previous research indicates the effectiveness of educational interventions aimed at reducing AMI risk are often limited (Zanjani et al., 2018a, 2018b, 2018c). Therefore, after providing AI-medication users with appropriate AMI-related health warnings, clinicians should continue screening for alcohol use at follow-up appointments and provide further intervention when needed. Future survey research exploring factors underlying concomitant alcohol/AI-medication use should utilize measures that directly assess participants' reasons for drinking, such as the older adult version of *The Drinking Motives Questionnaire* (Gilson et al., 2013).

CHAPTER 14: GENERAL DISCUSSION

The present chapter consist of three sections. The first section (14.1) includes a general discussion of topics relevant to both studies included in the present thesis. Discussion topics of particular relevance to study 1 were covered in chapter 12 (section 12.6), and topics particularly relevant to study 2 were discussed in chapter 13 (section 13.6). Section 14.1 therefore focuses on the prevalence of concomitant alcohol/AI-medication use, as this issue was explored in both studies. The second section of this chapter (14.2) summarizes the main contributions of the present thesis, and conclusions relating the project overall are then summarized in the final section (14.3).

14.1: DISCUSSION OF STUDIES 1 & 2

The first research question of the present project - "What is the prevalence of concomitant alcohol/AI-medication use in New Zealand's older adult population?" - was explored in both study 1 and study 2. Both studies utilized the same methods of answering this question, and there were notable differences in the results of the two studies. Before making inferences about the meaning of these differing results, it is important to consider potential demographic differences between the two samples. Therefore, the characteristics of the two study samples are discussed, followed by a comparison of the findings (14.1.a). The results of the present research are then compared with those of other studies exploring the prevalence of concomitant alcohol/AI-medication use (14.1.b), and methodological strengths and limitations of studies 1 and 2 are discussed (14.1.c).

14.1.a: Summary and comparison of study 1 & study 2

Sample characteristics

As discussed in chapters 12 and 13, both studies included in the present thesis involved secondary analysis of data collected from the NZHWR study (Towers & Noone, 2007; Towers

& Stevenson, 2014). The study 1 sample (see section 12.4.a) included participants from the 2006 HWR study (Towers & Noone, 2007), and the study 2 sample (see section 13.4.a) included participants from the 2010 HWR study (Towers & Stevenson, 2014). Overall, the demographic characteristics of the two study samples were very similar, which is unsurprising given that 73% of the study 2 sample were recruited from the study 1 sample (see section 13.4.a). However, age distribution was an important point of difference between the two samples, as discussed below.

Differences in age distribution between the two study samples were partly due to data collection occurring four years earlier for study 1 than study 2. Those who participated in both studies were therefore older at the time of data collection for study 2 (2010) than they were for study 1 (2006). Additionally, participants newly recruited into the HWR study during the 2010 data-wave were selected to increase the representation of both younger and older age groups (Towers & Stevenson, 2014), as discussed in section 13.4.a. Consequently, there were two notable differences in age distribution across the two samples. Firstly, the 2010 sample (study 2) was older overall, with a higher portion of participants being aged ≥65-years (44% vs 29%). Secondly, the 2010 sample captured a wider age bracket (48-83 years) than the 2006 sample (54-70 years). As mentioned in section 12.6.c, the results of study 2 therefore have more generalizability to the population of New Zealanders aged ≥65 years than the results of study 1.

Observed rates of concomitant alcohol/AI-medication use

Overall, the present research observed higher rates concomitant alcohol/AI-medication use in older study samples and subsamples. The prevalence concomitant of alcohol/AI-medication use were higher in the study 2 sample (36%) than the comparatively younger study 1 sample (24%). Similarly, sample rates of clinically significant AMI risk were also higher in study 2 (25%) than study 1 (15%). These differences likely reflect rates of AI-medication use across

the two samples, as rates of alcohol use were similar in both studies (approximately 70%), whereas the prevalence of AI-medication use was lower in study 1 (34%) than the comparatively older study 2 sample (54%). Additionally, rates of concomitant alcohol/AI-medication use were higher in subsamples aged ≥65 years relative to the total samples in both studies (29% among those aged 65-70 in study 1, and 43% among those aged 65-83 in study 2). The variation in results observed between samples and subsamples in the present research therefore provides further evidence that concomitant alcohol/AI-medication use increases with age (Breslow et al., 2015; Moore et al., 2002).

14.1.b: Comparing the results of Study 1 and Study 2 with those of other studies exploring the prevalence of alcohol/AI-medication use

The results of survey studies exploring the prevalence of concomitant alcohol/AI-medication use in older adult populations were reviewed in chapter 4 (section 4.2). As discussed in previous chapters (section 4.2.a; chapter 10), cross-study comparisons of reported rates of concomitant alcohol/AI-medication use are complicated due to methodological differences between studies. This subsection compares the present research findings to those of three studies reviewed in chapter 4 (Breslow et al., 2015; Cousins et al., 2014; Qato et al., 2015). These studies were selected for comparison because they had community older adult samples, included a wide variety of medications in their analyses, and utilized methods of AI-medication measurement and classification[26] of comparable quality to those adopted in the present research. There were however important differences between these studies and the present research with regards to alcohol use classification and the age distribution of study samples.

[26] Breslow et al. (2015), Cousins et al. (2015) and Qato et al. (2015) measured medication use by having participants provide medication containers and or prescription sheets. Each of these studies also utilized drug-interaction identification resources to classify medications as AI

The potential impact of these methodological differences is therefore considered when comparing the study findings.

Sample rates of AI-medication use

All three studies reviewed (Breslow et al., 2015; Cousins et al., 2014; Qato et al., 2015) reported higher overall sample rates of AI-medication use than observed in the present research[27], although the rate observed by Qato et al. (2015) was very similar to that of study 2. Specifically, sample rates of AI-medication use observed by Qato et al. (2015), Cousins et al. (2014), and Breslow et al. (2015) were 57%, 72%, and 78% respectively. Much of this variation may be accounted for by age differences between samples, as rates of AI-medication use were higher in samples with a larger portion of participants aged ≥65 years[28] (see figure 2). However, rates of AI-medication use among those aged 65-83 years in study 2 (67%) were still lower than observed in Cousins et al.'s (2014) sample of older adults living in Ireland and Breslow et al.'s (2015) US older adult sample. These findings may therefore indicate that older adults living in New Zealand are less likely to use AI-medications than those living in Ireland or the US.

[27] Sample rates of AI-medication use were 34% in study 1 and 54% in study 2

[28] Sample rates or participants aged ≥65-years in the studies by Qato et al. (2015), Cousins et al. (2014), and Breslow et al. (2015) were 58%, 72%, and 100% respectively.

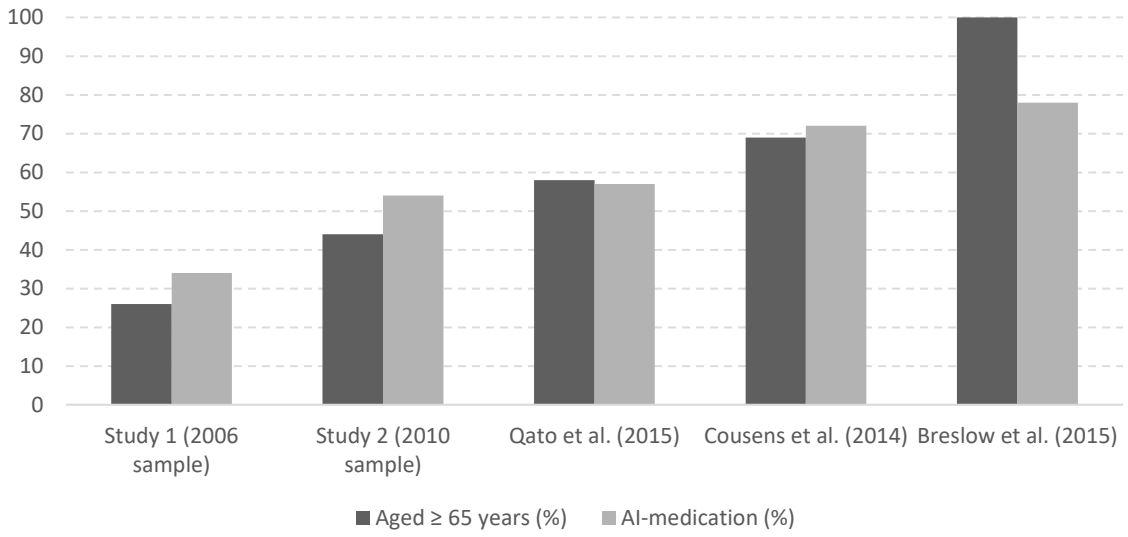

Figure 2: Sample Rates of AI-medication Use and Participants Aged ≥65 Years in the Present Research and Previous Research

Concomitant alcohol use among AI-medication users

Rates of alcohol use among AI-medication users in Cousins et al.'s (2014) sample of older adults living in Ireland (60%) were lower than observed in the present research (69% in study 1, and 66% in study 2). This difference is not fully explained by Cousins et al.'s (2014) study sample being comparatively older to those of the present research (see Figure 2), given that higher rates of alcohol use were also observed among subsamples of AI-medication users aged ≥65 years in study 2 (67%). It is noteworthy that the threshold Cousins et al. (2014) used to identify drinkers (past 6-month drinking) was considerably more inclusive than the threshold used in the present research (alcohol use at least twice monthly). As discussed in chapter 10, more inclusive thresholds have higher risk of false positive case identification, whereas more conservative thresholds have higher risk of false negative cases. These results therefore indicate that alcohol use may be more common among older AI-medication users living in New Zealand than those living in Ireland.

Sample rates of concomitant alcohol/AI-medication use

Two studies selected for comparison with the present research reported on overall sample rates of concomitant alcohol/AI-medication use (Breslow et al., 2015; Qato et al., 2015), both of which were conducted in the US. The rate of concomitant alcohol/AI-medication use observed by Breslow et al. (2015) in their sample of adults aged ≥65 years (35%) was considerably lower than observed among the study 2 subsample of participants aged 65-83 years (43%). Additionally, Breslow et al. (2015) used a drinker classification threshold (past year drinking) that was considerably more inclusive (and therefore likely yielded more false positive cases), than the threshold used in the present research. This would suggest the prevalence of concomitant alcohol/AI-medication use among adults aged ≥65 years is higher in New Zealand than in the US.

The rate of concomitant alcohol/AI-medication use observed by Qato et al. (2015) in their sample of US adults aged 57-84 years (20%) was notably lower than the rate observed among New Zealanders aged 48-83 years in study 2 (36%). Both of these study samples were generally comparable in terms of age distribution and observed rates of AI-medication use (see Figure 2). The threshold Qato et al. (2015) used to identify drinkers (weekly drinking) was slightly more conservative, yet comparable to the threshold used in the present research (drinking at least twice monthly). Overall, when taking sample differences and alcohol use classification methods into consideration, the results described above indicate rates of concomitant alcohol/AI-medication use are likely higher among older adults living in NZ than those living in the US.

14.1.c: Strengths and limitations of studies 1 and 2

The present research had several methodological strengths. As discussed in section 10.5, the operationalization of concomitant alcohol/AI-medication use adopted in the present research

was carefully considered and aimed to achieve an optimal balance between sensitivity and specificity. Methods used to classify AI-medications and identify participant AI-medication use by accessing their pharmaceutical claims records were informed by an evidence-based protocol (section 11.1). The AI-medication measurement methods utilized in the present research were therefore a key strength of both studies. Additionally, the present research utilized a widely used measure of alcohol consumption (the AUDIT-C (Bush et al., 1998)), which may help the research design to be replicated more easily.

There were some important limitations regarding the alcohol consumption measure used in study 1 and study 2. The present research did not measure drinking quantity or episodic binge drinking among participants. As discussed in section 10.4, this decision was based on the assumption that drinking frequency is the most reliable indication of simultaneous alcohol/AI-medication exposure (Breslow et al., 2015). However, this approach did not allow for a standardized threshold score to be applied to the AUDIT-C (Bush et al., 1998), which also requires consideration of average drinking quantity and binge drinking frequency. Additionally, as mentioned in chapter 12, while drinking frequency may be the best indicator of simultaneous alcohol/medication use, the specific type of medication and the amount of alcohol consumed also contribute to the likelihood of AMI (see sections 12.6.b, and 12.6.c). Future studies may therefore enhance concomitant alcohol/AI-medication use measurement precision by establishing appropriate drinking quantity thresholds to be applied to specific AI-medication classes.

There was also a key limitation regarding the categorization of AI-medications in the present research. Specifically, the likelihood and clinical relevance of particular AMIs often depends on the health status of the patient medications are prescribed to. For example, interactions between alcohol and paracetamol (which was classified as a ‘major AI-medication in the present research) are only relevant to a small group of alcoholics who use high doses of

paracetamol on a long-term basis (NZF, 2017). In such cases permanent liver damage may occur, which may be fatal, however for most people no interaction will not occur (NZF, 2017). Therefore, the extent to which the present research was able to provide information about the clinical relevance of concomitant alcohol/AI-medication use was limited.

14.2: CONTRIBUTIONS OF THE PRESENT THESIS

There were two major contributions of this project overall. Firstly, rates of concomitant alcohol/AI-medication use by older adults living in New Zealand had not been explored previously. The present research therefore provides much needed information about the prevalence of a potentially serious public health issue in New Zealand's rapidly growing older adult population. Secondly, an important issue highlighted throughout the present thesis is that there are many methodological challenges apparent when assessing concomitant alcohol/AI-medication use among survey participants. The research protocol described in chapter 11 is therefore an important contribution of this project, as this provides an evidence-based framework for measuring AI-medication use in survey research by accessing pharmaceutical dispensing records. Moreover, by implementing this protocol using data from an ongoing nationally representative survey of older adults (Towers & Noone, 2007; Towers & Stevenson, 2014), this project could help facilitate further research into concomitant alcohol/AI-medication use in New Zealand's older adult population.

14.3: CONCLUSIONS

There are many issues apparent when assessing the prevalence and correlates of concomitant alcohol/AI-medication use in community samples. In addition to the challenges of measuring concomitant alcohol/AI-medication use, many health-related outcome measures may not capture the specific harms associated with AMIs, and the utility of cross-sectional research designs may be limited given that drinking patterns may change in response to AMI-related

harm. Overall, the findings of the present research suggest many older adults living in New Zealand are at risk of AMI exposure, and the prevalence of this issue may be higher in New Zealand than many other countries. Importantly, the present research findings indicate rates of AMI risk are particularly high among New Zealanders aged ≥65 years, a rapidly growing population of people (Statistics New Zealand, 2020) who are highly vulnerable to alcohol-related harm (Moore et al., 2007). There is therefore a need for further research into the predictors and outcomes of concomitant alcohol/AI-medication use in this population.

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APPENDIX A: LIST OF AI-MEDICATIONS WITHIN THE PHARMS DATA

Information pertaining to medications within the PHARMS data identified as AI-medications by NZF is provided in Tables 26 and 27. Both Tables are organized according to unique chemical names of AI-medications listed in the PHARMS data, which are listed in the left column of each table. PHARMS chemical ids and AI-medication severity categorizations are provided for each unique chemical name. Any medications that were classified as benzodiazepines, NSAIDs, or antibiotics are identified, and where applicable, associated medication brand names and brand codes are provided. Table 26 includes all unique chemical names with multiple associated brand names, and Table 27 includes those with one or less associated brand names.

Table 26: Relevant Information About PHARMS Medications Identified as AI By NZF: Chemical Names with Multiple Associated Brand Names

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Acarbose	1247	Moderate		Accarb	12470225
				Glucobay	12470201
Acebutolol	1001	Mild		ACB	10010302
				Sectral	10010101
Acitretin	2363	Moderate		Neotigason	23630201
				Novatretin	23630225

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Alprazolam	2632	Moderate	Benzodiazepines	Arrow-Alprazolam	26320325
				Xanax	26320301
Amitriptyline	1059	Moderate		Amirol	10590125
				Amitrip	10590301
				Arrow-Amitriptyline	10590126
				Tryptanol	10590303
Amlodipine	2793	Moderate		Apo-Amlodipine	27930226
				Calvasc	27930225
				Norvasc	27930101
Apomorphine hydrochloride	1024	Moderate		APO-go	10242525
				Apomine	10242526
				Mayne	10240101
				Movapo	10242527

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Aspirin	1087	Mild		Aspec 300	10870501
				Aspro Clear	10870102
				Cartia	10872526
				Disprin	10870103
				Ecotrin	10870601
				Ethics Aspirin	10870125
				Ethics Aspirin EC	10872525
				HMG	10870201
				Solprin	10870101
				SRA	10870701
Atenolol	1094	Mild		Anselol	10940101
				Apo-Atenolol	10940103
				Atenolol AFT	10942525
				Atenolol Tablet USP	10940226
				Global Atenolol	10940105
				Loten	10940202
				Mylan Atenolol	10940225
				Noten	10940126
				Tenormin	10940104

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Atenolol with chlorthalidone	1095	Mild		Loten-C	10950102
				Tenoret 50	10950201
				Tenoretic	10950101
Atropine sulphate	1097	Major		AstraZeneca	10970401
				Atropt	10970601
				Baxter	10970302
				Fawns and McAllan	10970101
Azathioprine	1100	Major		Azamun	11000102
				Imuprine	11000125
				Imuran	11000201
				Thioprine	11000103
Baclofen	2364	Moderate		Alpha-Baclofen	23640104
				Lioresal	23640102
				Lioresal Intrathecal	23642525
				Pacifen	23640101
Betaxolol	1149	Mild		Apo-Betaxolol	11490225
				Betoptic	11490201
				Betoptic S	11490101

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Brimonidine tartrate	3713	Mild		AFT	37132526
				Alphagan	37132525
				Arrow-Brimonidine	37132527
Bromocriptine mesylate	1167	Moderate		Alpha-Bromocriptine	11670103
				Apo-Bromcriptine	11670301
				Apo-Bromocriptine	11670102
				Parlodel	11670101
Bupivacaine hydrochloride	2855	Moderate		Marcain Heavy	28550101
				Marcain Isobaric	28550201
Buspirone hydrochloride	6006	Moderate		Biron	60060201
				Buspar	60060202
				Orion	60060226
				Pacific Buspirone	60060225
Candesartan cilexetil	1254	Mild		Atacand	12542525
				Candestar	12542526
Captopril	2841	Mild		Apo-Captopril	28410326
				Capoten	28410601
				Captohexal	28410125
				m-Captopril	28410327

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Carbamazepine	1217	Moderate		Tegretol	12170301
				Tegretol CR	12170701
				Teril	12170401
Carvedilol	3772	Mild		Dicarz	37722726
				Dilatrend	37722525
Cefamandole nafate	1230	Moderate	Antibiotics	Baxter	12300203
				Mandol	12300202
Celiprolol	2514	Mild		Celol	25140102
				Selectol	25140101
Cetirizine hydrochloride	2833	Mild		Allerid C	28332525
				Cetirizine - AFT	28332526
				Histaclear	28332527
				Razene	28330125
				Zetop	28330126
				Zyrtec	28330101
Chlorpromazine hydrochloride	1283	Moderate		Largactil	12830401
				Largactil Forte	12830501

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Ciclosporin	2421	Mild		Neoral	24210302
				Sandimmun	24210101
Cilazapril	2770	Mild		Inhibace	27700101
				Zapril	27700125
Cilazapril with hydrochlorothiazide	1127	Mild		Apo-Cilazapril/Hydrochlorothiazide	11270125
				Inhibace Plus	11270101
Cimetidine	1297	Mild		Apo-Cimetidine	12970204
				Cytine	12970103
				Duomet	12970201
				Tagamet	12970401
Ciprofloxacin	2819	Moderate	Antibiotics	Ciloxan	28190401
				Cipflox	28190325
				Ciprofloxacin Rex	28190326
				Ciproxin	28190301
				Rex Medical	28190226
Citalopram hydrobromide	1193	Moderate		Arrow-Citalopram	11930126
				Cipramil	11930101
				Citalopram - Rex	11930127
				PSM Citalopram	11930128

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Clomipramine hydrochloride	1315	Moderate		Anafranil	13150101
				Apo-Clomipramine	13150225
				Clopress	13150202
Clonazepam	1316	Moderate	Benzodiazepines	Paxam	13160225
				Rivotril	13160201
Clonidine	1317	Moderate		Catapres-TTS-1	13170201
				Catapres-TTS-2	13170301
				Catapres-TTS-3	13170401
Clonidine hydrochloride	1318	Moderate		Catapres	13180501
				Clonidine BNM	13180825
				Dixarit	13180801
Clozapine	1078	Moderate		Clopine	10782725
				Clozaril	10780201
Codeine phosphate	1332	Moderate		Alpha-codeine phosphate	13320203
				Douglas	13320501
				PSM	13320302
Cyclizine hydrochloride	6010	Moderate		Marzine	60100101
				Nausicalm	60100125
				Nauzene	60100126

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Cyclizine lactate	6011	Moderate		Nausicalm	60110126
				Valoid	60110101
				Valoid (AFT)	60110125
Cyproterone acetate	2707	Moderate		Androcur	27070101
				Androcur Depot	27070201
				Pacific Cyproterone	27070126
				Procur	27070127
				Siterone	27072525
Cyproterone acetate with ethinyloestradiol	2706	Moderate		Diane-35	27060101
				Diane-35 ED	27060201
				Estelle 35-ED	27060225
				Ginet	27060227
				Ginet 84	27060226
Dextropropoxyphene with paracetamol	1392	Major		Apo-Paradex	13920201
				Capadex	13920101
				Di-Gesic	13920202
				Paradex	13920203

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Diazepam	1397	Moderate	Benzodiazepines	Arrow-Diazepam	13970225
				D-Pam	13970203
				Diazemuls	13970602
				Hospira	13970601
				Pro-Pam	13970303
				Stesolid	13970501
Diclofenac sodium	1401	Major	NSAIDs	Anfenax SR	14011301
				Apo-Diclo	14010103
				Apo-Diclo SR	14011203
				Diclax	14010202
				Diclax SR	14011201
				Diclofenac Sandoz	14010226
				Diclohexal	14010225
				Flameril	14010204
				Flameril Retard	14011204
				Voltaren	14010901
				Voltaren D	14011101
				Voltaren Ophtha	14011001
				Voltaren SR	14010302

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Diflunisal	1411	Major	NSAIDs	Ansal	14110202
				Dolobid	14110201
Diltiazem hydrochloride	2528	Moderate		Apo-Diltiazem	25280205
				Apo-Diltiazem CD	25280625
				Cardizem	25280201
				Cardizem CD	25280403
				Dilacor XR	25280902
				Dilcard 30	25280102
				Dilcard 60	25280202
				Dilzem	25280203
				Dilzem LA	25280701
				Dilzem SR	25280901
Diphenoxylate hydrochloride with atropine sulphate	1424	Major		Diastop	14240102
				Lomotil	14240101
Dorzolamide with timolol	3781	Mild		Arrow-Dortim	37812526
				Cosopt	37812525
Doxazosin	2515	Mild		Apo-Doxazosin	25150326
				Cardoxan	25150302
				Dosan	25150225

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Doxepin hydrochloride	1438	Moderate		Anten	14380101
				Sinequan	14380402
Doxycycline	2529	Mild	Antibiotics	Doryx	25290301
				Doxine	25290401
				Doxy	25290303
				Doxy-100	25290402
				Doxy-50	25290102
				Vibra-Tab	25290101
Enalapril maleate	2711	Mild		Acetec	27110228
				Arrow-Enalapril	27110327
				Enahexal	27110325
				Ethics Enalapril	27110329
				m-Enalapril	27110126
				Renitec	27110201
Ergotamine tartrate with caffeine	1462	Mild			
				Cafergot	14620301
				Cafergot S29	14620325
Erythromycin	1465	Moderate	Antibiotics	Emu-V	14650401
				Eryc	14650501
				Stiemycin	14650301

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Erythromycin ethyl succinate	6026	Moderate	Antibiotics	E-Mycin	60260502
				EES	60260101
				ERA	60260601
Erythromycin lactobionate	6028	Moderate	Antibiotics	Baxter	60280201
				ERA	60280202
				Erythrocin IV	60280225
				Mayne	60280101
Escitalopram	3926	Moderate		Air Flow Products	39262626
				Loxalate	39262625
Famotidine	2373	Mild		Apo-Famotidine	23730104
				Famox	23730103
				Pepcidine	23730101
				Pepzan	23730102
Felodipine	2398	Moderate		Agon SR	23980202
				Felo 10 ER	23980225
				Felo 2.5 ER	23980325
				Felo 5 ER	23980125
				Plendil ER	23980301

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Fentanyl	3801	Moderate		Boucher and Muir	38011526
				Durogesic	38012925
				Fentanyl Sandoz	38013726
				Hospira	38011625
				Mylan Fentanyl Patch	38013725
Fluoxetine hydrochloride	2636	Moderate		Arrow-Fluoxetine	26360226
				Fluox	26360103
				Lovan	26360202
				Plinzene	26360104
				Prozac 20	26360201
Fluphenazine decanoate	1533	Moderate		Baxter	15330102
				Mayne	15330301
				Modecate	15330325
Flurbiprofen	1536	Major	NSAIDs	Froben	15360101
				Froben SR	15360301
Gabapentin	1062	Moderate		Arrow-Gabapentin	10620226
				Neurontin	10622528
				Nupentin	10620225

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Glibenclamide	1567	Major		Apo-Glibenclamide	15670204
				Daonil	15670202
				Gliben	15670104
				Semi-Daonil	15670101
Gliclazide	1568	Major		Apo-Gliclazide	15680125
				Diamicron	15680101
				Glizide	15680127
				Nidem	15680126
Glipizide	1569	Major		Glipid	15690101
				Minidiab	15690102

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Glyceryl trinitrate	1577	Moderate		Anginine	15770201
				Glytrin	15772525
				Lycinate	15770225
				Minitran	15770105
				Nitro-Dur	15770104
				Nitrobid	15770301
				Nitrocor	15770102
				Nitroderm TTS	15770103
				Nitrolingual	15770401
				Nitrolingual Pump Spray	15770601
				Rectogesic	15772625
Griseofulvin	1579	Moderate		Griseostatin	15790201
				Grisovin 500	15790301
Haloperidol	1583	Moderate		Haloperidol - MercuryPharma	15830625
				Serenace	15830301
Haloperidol decanoate	2530	Moderate		Haldol	25300101
				Haldol Concentrate	25300301

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Hyoscine hydrobromide	1629	Moderate		Hospira	16290301
				Isopto Hyoscine	16290201
				Martindale	16290325
				Scopoderm TTS	16290101
Hyoscine N-butylbromide	1631	Moderate		Buscopan	16310201
				Gastrosoothe	16310125
Ibuprofen	2798	Major	NSAIDs	Anafen	27980301
				Arrowcare	27980127
				Brufen	27980202
				Brufen SR	27980401
				Ethics Ibuprofen	27980126
				Fenpaed	27980525
				I-Profen	27980125
				Ibugesic	27980128
				Panafen	27980103
Imipramine hydrochloride	1642	Moderate		Imipramin	16420101
				Tofranil	16420125
				Tofranil s29	16420126

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Insulin aspart	3783	Moderate		NovoRapid	37832625
				NovoRapid FlexPen	37832725
				NovoRapid Penfill	37832525
Insulin glargine	3857	Moderate		Lantus	38572525
				Lantus SoloStar	38572725
Insulin glulisine	3908	Moderate		Apidra	39082525
				Apidra SoloStar	39082625
Insulin isophane	1649	Moderate		Humulin N	16490201
				Humulin NPH	16490325
				Insulatard	16492501
				Protaphane	16490402
				Protaphane Penfill	16490301

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Insulin isophane with insulin neutral	6300	Moderate		Humulin 30/70	63000225
				Humulin 50/50	63000301
				Humulin 60/40	63000302
				Humulin 70/30	63000102
				Humulin 80/20	63000103
				Humulin 90/10	63000305
				Mixtard 15	63000306
				Mixtard 30	63000307
				Mixtard 50	63000308
				Penmix 10	63000106
				PenMix 10	63000201
				PenMix 20	63000202
				PenMix 30	63000203
				PenMix 40	63000204
				PenMix 50	63000205
Insulin lispro with insulin lispro protamine	3882	Moderate		Humalog Mix 25	38822525
				Humalog Mix 50	38822625

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Insulin neutral	1648	Moderate		Actrapid	16480101
				Actrapid Penfill	16480301
				Humulin R	16480202
				Velosulin	16482501
Insulin zinc suspension	1655	Moderate		Humulin L	16550101
				Humulin U	16550201
				Monotard	16550102
				Ultratard	16550202
Interferon alpha-2a with ribavirin	3823	Moderate		Roferon RBV Combination Pack	38232525
				Roferon RBV Combination Pack Starter Kit	38232625
Interferon beta-1-alpha	1248	Moderate		Avonex	12480101
				Avonex Pen	12482625
Isoniazid	1679	Moderate		PSM	16790101
				Rifinah	16790301

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Isosorbide dinitrate	2377	Moderate		Carvasin	23770203
				Coronex	23770201
Isosorbide mononitrate	2836	Moderate		Corangin	28360201
				Duride	28360304
				Imdur	28360302
				Imtrate	28360303
				Ismo 20	28360101
				Ismo 40 Retard	28360225
Isotretinoin	1688	Moderate		Isotane 10	16880126
				Isotane 20	16880225
				Oratane	16880125
				Roaccutane	16880101
Isradipine	2771	Mild		Dynacirc	27710301
				Dynacirc-SRO	27710201
Ketoconazole	1696	Major		Ketopine	16960325
				Link Healthcare	16960125
				Nizoral	16960201
				Sebizole	16960302

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Codes
Ketoprofen	1697	Major	NSAIDs	Kefen SR	16970302
				Orudis	16970701
				Oruvail	16970505
				Oruvail EC	16970601
				Oruvail SR	16970303
Ketotifen	1698	Moderate		Asmafen	16980202
				Zasten	16980101
Labetalol	1699	Mild		Albetol	16990302
				Hybloc	16990102
				Trandate	16992525
Leflunomide	3763	Major		AFT-Leflunomide	37632626
				Arava	37632525
Lisinopril	2797	Mild		Arrow-Lisinopril	27970325
				Ethics Lisinopril	27970326
				Prinivil	27970301
				Zestril	27970202
Lisinopril with hydrochlorothiazide	2795	Mild		Prinzide	27950101
				Zestoretic	27950102

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Lithium carbonate	2466	Moderate		Douglas	24660401
				Lithicarb FC	24660201
				Priadel	24660301
Loratadine	2831	Mild		Apo-Loratadine	28310126
				Claratyne	28310101
				Lora-tabs	28310125
				Loraclear Hayfever Relief	28310127
				Lorafix	28310128
				LoraPaed	28310225
Lorazepam	1730	Moderate	Benzodiazepines	Ativan	17300403
				Lorapam	17300401
				Lorzem	17300402
Losartan potassium	1061	Mild		Cozaar	10610201
				Losartan Actavis	10612527
				Lostaar	10612526
Losartan potassium with hydrochlorothiazide	1068	Mild		Arrow-Losartan & Hydrochlorothiazide	10680526
				Hyzaar	10680525

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Mefenamic acid	1769	Major	NSAIDs	Mefic	17690102
				Ponstan	17690101
Metformin hydrochloride	1794	Moderate		3M	17940106
				Apo-Metformin	17940205
				Apotex	17940227
				Arrow-Metformin	17940226
				Diabex	17940225
				Glucomet	17940104
				Glucophage	17940201
				Metchek	17940127
				Metformin Mylan	17940228
				Metomin	17940103

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Methadone hydrochloride	1795	Moderate		AFT	17950425
				Biodone	17950501
				Biodone Extra Forte	17950701
				Biodone Forte	17950602
				Douglas	17950402
				GlaxoWellcome	17950601
				Martindale	17950225
				Methaforte	17950502
				Methatabs	17950101
				Pallidone	17950102
				PSM	17950301
				PSM Methaforte	17950525
Methotrexate	1797	Major		Baxter	17972525
				Biomed	17972626
				DBL Methotrexate	17972825
				Hospira	17971001
				Ledertrexate	17970101
				Mayne	17971201
				Methoblastin	17970201
				Methotrexate Ebewe	17971125
				Methotrexate Sandoz	17973425
				Pharmacia	17971202
				Trexate	17970225

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Methyldopa	1806	Mild		Aldomet	18060202
				Douglas	18060301
				Prodopa	18060201
Methylphenidate hydrochloride	1809	Major		Ritalin	18090101
				Ritalin SR	18092525
				Rubifen	18090125
				Rubifen SR	18092526
Methylphenidate hydrochloride extended-release	3880	Major		Concerta	38802725
				Ritalin LA	38803225
Metoclopramide hydrochloride	1814	Moderate		AstraZeneca	18140325
				Maxolon	18140101
				Metamide	18140102
				Pfizer	18140302
Metoprolol succinate	1817	Mild		Betaloc CR	18170301
				Metoprolol - AFT CR	18170325
				Myloc CR	18170326
Metoprolol tartrate	1818	Mild		Betaloc	18180401
				Lopresor	18180201
				Mycol	18180202
				Slow-Lopresor	18180301

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Metronidazole	1820	Contraindicated		Flagyl	18200203
				Flagyl-S	18200301
				Trichozole	18200202
Midazolam	2539	Moderate	Benzodiazepines	Baxter	25390225
				Hypnovel	25390101
				Pfizer	25390226
Mirtazapine	3901	Major		Apo-Mirtazapine	39012626
				Avanza	39012625
Morphine hydrochloride	1830	Major		Douglas	18300502
				PSM	18300501
				RA-Morph	18300401

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Morphine sulphate	1831	Major		Arrow-Morphine LA	18310125
				AstraZeneca	18311102
				Baxter	18310901
				DBL Morphine Sulphate	18310801
				Douglas	18311601
				Kapanol	18311801
				LA-Morph	18310402
				m-Eslon	18312225
				Martindale	18311425
				MST Continus	18310401
				RMS	18311401
				Sevredol	18312101
Nadolol	1838	Mild		Apo-Nadolol	18380202
				Corgard	18380101
Naproxen	2782	Major	NSAIDs	Naprosyn	27820901
				Naprosyn Enteric	27821201
				Naprosyn SR 1000	27820601
				Naprosyn SR 750	27820501
				Naxen	27821102
				Noflam 250	27820904
				Noflam 500	27821103
				Noflam EC	27821202

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Naproxen sodium	2783	Major	NSAIDs	Naxen Sodium	27830103
				Noflam-N	27830201
				Sonaflam	27830125
				Synflex	27830202
Nicotine	3722	Mild		Habitrol	37223626
				Nicabate	37222525
				Nicotinell	37222925
				Nicotrol	37223225
Nicotinic acid	1861	Major		Apo-Nicotinic Acid	18610402
				Niacin-Odan	18610425
				PSM	18610401

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Nifedipine	1863	Moderate		Adalat	18630501
				Adalat 10	18630125
				Adalat Oros	18630401
				Adalat Retard	18630201
				Adefin XL	18630326
				Alpha-Nifedipine	18630204
				Apo-Nifedipine Retard	18630202
				Arrow-Nifedipine XR	18630425
				Nical	18630602
				Nyefax	18630603
				Nyefax Retard	18630203
Nitrazepam	1865	Moderate	Benzodiazepines	Insoma	18650102
				Nitrados	18650104
Nortriptyline hydrochloride	1876	Moderate		Allegron	18760101
				Norpress	18760125

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Olanzapine	1140	Moderate		Dr Reddy's Olanzapine	11402825
				Olanzine	11400226
				Olanzine-D	11402826
				Zypine	11400227
				Zypine ODT	11402827
				Zyprexa	11400201
				Zyprexa Relprevv	11401725
				Zyprexa Zydis	11402728
Ondansetron	2710	Moderate		Dr Reddy's Ondansetron	27100125
				Ondansetron ODT-DRLA	27102826
				Onrex	27100326
				Zofran	27100302
				Zofran Zydis	27102725
Ornidazole	1906	Moderate		Arrow-Ornidazole	19060125
				Tiberal	19060101
Oxazepam	1911	Moderate	Benzodiazepines	Benzotran	19110103
				Ox-Pam	19110202
				Serepax	19110203

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Oxprenolol	1912	Mild		Captol 40	19120101
				Captol 80	19120201
				Captol SR	19120401
				Slow Trasicor	19120402
				Trasicor	19120102
Oxybutynin	1914	Moderate		Apo-Oxybutynin	19140102
				Ditropan	19140101
Oxycodone hydrochloride	3822	Moderate		Oxycodone Controlled Release Tablets(BNM)	38223127
				Oxycodone Orion	38223526
				OxyContin	38223125
				Oxydone BNM	38223126
				OxyNorm	38223625

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Paracetamol	1929	Major		Apo-Paracetamol	19290803
				Disprol	19290805
				Douglas	19290205
				Ethics Paracetamol	19290226
				Gacet	19290525
				HMG	19290601
				Junior Parapaed	19290225
				Pacimol	19290825
				Pamol	19290301
				Panadol	19290501
				Panadol Colourfree	19290204
				Paracare	19290625
				Paracare Double Strength	19290305
				Parafast	19290827
				Pharmacare	19290826
				PSM	19290701
				PSM Paracetamol Double Strength	19290303
				PSM Paracetamol Elixir Paediatric	19290202
				PSM Paracetamol Junior Suspension	19290206
				Six Plus Parapaed	19290325

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Paracetamol with codeine	1931	Major		Apo-Paracodeine	19310102
				Codalgin	19310125
				Codral Pain	19310105
				Pamol Plus	19310103
				Panadeine	19310101
				Paracetamol + Codeine (Relieve)	19310127
				ParaCode	19310126
Paroxetine hydrochloride	6009	Moderate		Aropax	60090101
				Loxamine	60090125
Perindopril	2806	Mild		Apo-Perindopril	28060125
				Coversyl	28060101
Pethidine hydrochloride	1953	Moderate		AstraZeneca	19530502
				DBL Pethidine Hydrochloride	19530301
				Douglas	19530202
				Mayne	19530401
				PSM	19530201

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Phenytoin sodium	1978	Moderate		Dilantin	19780401
				Dilantin Forte	19780501
				Dilantin Infatab	19780101
				Hospira	19780625
Pimozide	1990	Moderate		Orap	19900101
				Orap Forte	19902525
Pindolol	1991	Mild		Apo-Pindolol	19910601
				Pindol	19910603
				Visken	19910504
				Vypen	19910404
Pioglitazone	3800	Moderate		Actos	38002725
				Pizaccord	38002726
				Vexazone	38002727
Piroxicam	1996	Major	NSAIDs	Candyl D	19960401
				Douglas	19960701
				Feldene	19960702
				Piram-D	19960402

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Prazosin	2031	Mild		Apo-Prazo	20310225
				Apo-Prazosin	20310426
				Hyprosin	20310101
				Minipress	20310402
				Pratsiol	20310301
Primidone	2041	Moderate		Apo-Primidone	20410125
				Mysoline	20410101
Prochlorperazine	6012	Moderate		Antinaus	60120201
				Buccastem	60120101
				Stemetil	60120501
				Stemetil EFF	60120701
Promethazine hydrochloride	2478	Moderate		Allersoothe	24780225
				Hospira	24780502
				Phenergan	24780301
				Promethazine Winthrop Elixir	24780325

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Propranolol	2060	Mild		Angilol	20600102
				Angilol LA	20600601
				Apo-Propranolol	20600203
				Cardinol	20600103
				Cardinol 160	20600502
				Cardinol LA	20600602
				Inderal	20600101
				Inderal LA	20600603
				Roxane	20602525
Quetiapine	1183	Moderate		Dr Reddy's Quetiapine	11832527
				Quetapel	11832526
				Seroquel	11832525
Quinapril	2772	Mild		Accupril	27720301
				Accupro	27720102
				Arrow-Quinapril 10	27720225
				Arrow-Quinapril 20	27720325
				Arrow-Quinapril 5	27720125
Quinapril with hydrochlorothiazide	3749	Mild		Accuretic 10	37492525
				Accuretic 20	37492625

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Ranitidine	2080	Mild		Apo-Ranitidine	20800602
				Arrow-Ranitidine	20800625
				Douglas	20802602
				Peptisoothe	20800325
				Ranitidine Relief	20800626
				Zanidin	20800503
				Zantac	20800601
				Zantac-C	20802601
Risperidone	1011	Moderate		Actavis	10110428
				Apo-Risperidone	10110526
				Dr Reddy's Risperidone	10112528
				Ridal	10110425
				Risperdal	10110401
				Risperdal Consta	10112825
				Risperdal Quicklet	10113125
				Risperon	10110525

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Salbutamol	2096	Major		Airomir	20961601
				Asmol	20960602
				Asthalin	20961526
				Broncolin	20960326
				Pharmacia	20961425
				Respax	20961501
				Respigen	20961627
				Respolin	20960604
				Respolin Autohaler	20961101
				SalAir	20961628
				Salamol	20961626
				Salapin	20960325
				Salbutamol Turbuhaler	20961701
				Salbuvent	20960603
				Salbuvent Forte	20960902
				Ventodisk	20961302
				Ventolin	20960301
				Ventolin Forte	20960901
				Ventolin Nebules	20961402
				Volmax	20960201

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Salbutamol with ipratropium bromide	6311	Major		Combivent	63110101
				Duolin	63110225
				Duolin HFA	63112525
Selegiline hydrochloride	2642	Major		Apo-Selegiline	26420102
				Apo-Selegiline S29	26420125
				Eldepryl	26420201
				Selgene	26420103
Sertraline	3927	Moderate		Arrow-Sertraline	39272525
				Sertraline Actavis	39272527
				Zoloft	39272526
Sildenafil	3890	Moderate		Silagra	38902626
				Vedafil	38902727
				Viagra	38902725
Sotalol	2169	Mild		Apo-Sotalol	21690225
				Mylan	21690102
				Sotacor	21690301

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Sulindac	2193	Major	NSAIDs	Aclin	21930225
				Clinoril	21930202
				Daclin	21930201
				Saldac	21930203
Tacrolimus	1088	Major		Prograf	10880201
				Tacrolimus Sandoz	10880225
Temazepam	2224	Moderate	Benzodiazepines	Euhypnos	22240102
				Normison	22242525
				Somapam	22240103
Tenoxicam	2536	Major	NSAIDs	AFT	25362625
				Reutenox	25360125
				Tilcotil	25360101
Terazosin	2543	Mild		Apo-Terazosin	25432525
				Arrow	25430326
				Hytrin	25430701
				Hytrin BPH	25430302
				Hytrin BPH Starter Pack	25430501
				Hytrin Starter Pack	25430502

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Thalidomide	3845	Major		Thalidomide Pharmion	38452525
				Thalomid	38452625
Thioridazine hydrochloride	2255	Moderate		Aldazine	22550302
				Melleril	22550201
				Melleril Retard	22550501
Tiaprofenic acid	2537	Major	NSAIDs	Surgam	25370201
				Surgam SA	25370301
Timolol	2266	Mild		Apo-Timol	22660104
				Apo-Timop	22660425
				Arrow-Timolol	22660226
				Blocadren	22660105
				Gen-Timolol	22660204
				Hypermol	22660102
				Tilmat	22660101
				Timoptol	22660402
				Timoptol XE	22660501
Timolol maleate with pilocarpine	2268	Mild		Timpilo 2	22680101
				Timpilo 4	22680201

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Tinidazole	2269	Contraindicated		Dyzole	22690102
				Fasigyn	22690101
Topiramate	1133	Moderate		Arrow-Topiramate	11330425
				Topamax	11332525
				Topiramate Actavis	11330426
Tramadol hydrochloride	3906	Moderate		Arrow-Tramadol	39062525
				Tramal SR 100	39062625
				Tramal SR 150	39062725
				Tramal SR 200	39062825
Trandolapril	1031	Mild		Gopten	10310301
				Odrik	10310102
Triazolam	2295	Moderate	Benzodiazepines	Halcion	22950101
				Hypam	22950104
				Pharmacia	22950102
				Trycam	22950103
Trifluoperazine hydrochloride	2298	Moderate		Stelazine	22980101
				Stelazine Section 29	22980325
				Stelazine Spansules	22980401

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Trimethoprim	2300	Moderate	Antibiotics	TMP	23000202
				Triprim	23000201
Trimipramine maleate	2301	Moderate		Surmontil	23010501
				Tripress	23010302
Venlafaxine	3785	Moderate		Arrow-Venlafaxine XR	37853025
				Efexor XR	37852725
Verapamil hydrochloride	2317	Moderate		Civicor	23170102
				Civicor Retard	23170801
				Isoptin	23170101
				Isoptin SR	23170901
				Verpamil	23170104
				Verpamil SR	23170902
Warfarin sodium	2331	Mild		Coumadin	23310401
				Marevan	23310602
Ziprasidone	3873	Moderate		Zeldox	38732825
				Zusdone	38732826

Table 26: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Zopiclone	2484	Moderate	Benzodiazepines	Apo-Zopiclone	24840125
				Imovane	24840101
				Zo-Tab	24840102
				Zopiclone Actavis	24840126

Table 27: Relevant Information About PHARMS Medications Identified as AI By NZF: Chemical Names with One or Less Associated Brand Names

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Acebutolol with hydrochlorothiazide	1005	Mild		Secadrex	10050101
Amantadine hydrochloride	1048	Moderate		Symmetrel	10480101
Amisulpride	3884	Moderate		Solian	38842825
Aripiprazole	3878	Moderate		Abilify	38782925
Aspirin with Chloroform	3216	Mild			
Aspirin with Codeine	1093	Moderate			

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Aspirin with paracetamol and codeine	1092	Major		Codcomol	10920101
Benazepril	2794	Mild		Cibacen	27940301
Bismuth subcitrate, metronidazole and tetracycline	1122	Contraindicated		Helidac	11220101
Bisoprolol fumarate	3949	Mild		Bosvate	39492725
Brimonidine tartrate with timolol maleate	3839	Mild		Combigan	38392525
Bromazepam	1166	Moderate	Benzodiazepines	Lexotan	11660201
Bupivacaine Hydrochloride	2855	Moderate			
Buprenorphine hydrochloride	2521	Moderate		Temgesic	25210101
Buprenorphine Hydrochloride	2521	Moderate			
Buprenorphine with naloxone	3950	Moderate		Suboxone	39502625
Bupropion hydrochloride	3892	Major		Zyban	38922525
Caffeine	3740	Mild			
Caffeine citrate	3933	Mild		Biomed	39332525

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Captopril with hydrochlorothiazide	2840	Mild		Capozide	28400201
Celecoxib	1271	Major	NSAIDs		
Chlordiazepoxide hydrochloride	6007	Moderate	Benzodiazepines	Nova-Pam	60070201
Cisapride	2781	Moderate		Prepulsid	27810201
Citalopram hydrobromide (Celapram)	1190	Moderate		Celapram	11902525
Clobazam	1308	Moderate	Benzodiazepines	Frisium	13080101
Clonidine Hydrochloride	1317	Moderate			
Codeine	3267	Moderate			
Cycloserine	3994	Contraindicated		King	39942525
Cyproheptadine hydrochloride	2470	Moderate		Periactin	24700101
Dantrolene	1373	Moderate		Dantrium	13730201
Desipramine hydrochloride	1379	Moderate		Pertofran	13790101
Dexamfetamine sulfate	1389	Major		PSM	13890101

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Dextromethorphan	1256	Moderate			
Dextropropoxyphene	1391	Major		Doloxene	13910101
Dihydrocodeine tartrate	2427	Moderate		DHC Continus	24270101
Dimenhydrinate	1418	Moderate		Dramamine	14180101
Dimethyl fumarate	4053	Moderate		Tecfidera	40532625
Dimethyl sulphoxide	3277	Moderate		Douglas	32770101
Diphenhydramine hydrochloride	2472	Moderate		Benadryl	24720101
Disulfiram	1432	Contraindicated		Antabuse	14320101
Droperidol	8792	Moderate		Droleptan	87920101
Enalapril maleate with hydrochlorothiazide	2708	Mild		Co-Renitec	27080401
Ergotamine tartrate with cyclizine	1459	Moderate		Migril	14590101
Ergotamine tartrate with diphenhydramine	1460	Moderate		Ergodryl	14600101
Erythromycin estolate	1466	Moderate	Antibiotics	Eromycin	14660201

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Erythromycin stearate	6027	Moderate	Antibiotics	ERA	60270401
Ethionamide	2858	Mild			
Ethosuximide	1481	Moderate		Zarontin	14810201
Fenbufen	1489	Major	NSAIDs		
Fenoprofen Calcium	1490	Major	NSAIDs		
Fentanyl citrate	3896	Moderate			
Fentanyl Citrate	1274	Moderate			
Fexofenadine hydrochloride	1194	Mild		Telfast	11940301
Flunarizine	1049	Moderate			
Flunitrazepam	2436	Moderate	Benzodiazepines	Rohypnol	24360101
Fluoxetine Hydrochloride	2636	Moderate			
Fluphenazine hydrochloride	1535	Moderate		Anatensol	15350201
Gabapentin (Neurontin)	1060	Moderate		Neurontin	10602625

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Glycopyrronium	4043	Major		Seebri Breezhaler	40432525
Glycopyrronium bromide	4047	Major		Max Health	40472525
Glycopyrronium Bromide	1578	Major			
Glycopyrronium with indacaterol	4058	Major		Ultibro Breezhaler	40582525
Haloperidol Decanoate	2530	Moderate			
Hydroxyzine Hydrochloride	1627	Moderate			
Idoxuridine with dimethyl sulphoxide	3307	Moderate		Douglas	33070101
Insulin aspart with insulin aspart protamine	3982	Moderate		NovoMix 30 FlexPen	39822725
Insulin lispro	1192	Moderate		Humalog	11920101
Insulin Neutral	1648	Moderate			
Interferon alfa-2a	2845	Moderate		Roferon-A	28451501
Interferon alfa-2b	2445	Moderate		Intron-A	24451601

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Interferon Alpha-2B	2445	Moderate			
Interferon alpha-n	6023	Moderate		Wellferon	60230101
Interferon beta-1-beta	3707	Moderate		Betaferon	37072525
Isosorbide Dinitrate	2377	Moderate			
Ivermectin	3964	Mild		Stromectol	39642525
Levamisole	1186	Moderate			
Levomepromazine maleate	1799	Moderate		Nozinan	17990101
Loprazolam mesylate	1729	Moderate	Benzodiazepines	Dormonoct	17290101
Lormetazepam	1731	Moderate	Benzodiazepines	Noctamid	17310101
Losartan	1061	Mild			
Losartan with hydrochlorothiazide	3788	Mild			
Loxapine succinate	1732	Moderate		Loxapac	17320101

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Maprotiline hydrochloride	1760	Moderate		Ludiomil	17600201
Meloxicam	3912	Major	NSAIDs	Arrow-Meloxicam	39122525
Meprobamate	1780	Major		Equanil	17800101
Methyldopa with hydrochlorothiazide	1805	Mild		Hydromet	18050101
Metoclopramide Hydrochloride	1814	Moderate			
Metoclopramide hydrochloride with paracetamol	1815	Major		Paramax	18150101
Mianserin hydrochloride	1824	Moderate		Tolvon	18240101
Morphine tartrate	2383	Major		Hospira	23830101
Niclosamide	1859	Major		Yomesan	18590101
Nicorandil	3975	Moderate		Ikorel	39752625
Nimorazole	1864	Moderate		Naxogin	18640101
Nizatidine	2490	Mild		Axid	24900101

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Nortriptyline Hydrochloride	1876	Moderate			
Olanzapine pamoate monohydrate	3940	Moderate			
Omeprazole, amoxycillin and metronidazole	1177	Contraindicated		Helicosec	11770101
Papaveretum	1927	Moderate		Baxter	19270101
Paracetamol with Codeine	1931	Major			
Paraldehyde	2059	Major		AFT	20590101
Pentazocine	1944	Moderate		Fortral	19440301
Pericyazine	1950	Moderate		Neulactil	19500201
Phenelzine sulphate	1955	Contraindicated		Nardil	19550101
Phenylbutazone	2494	Major	NSAIDs	Butazolidin	24940101
Pindolol with clopamide	1989	Mild		Viskaldix	19890101
Pizotifen	2000	Moderate		Sandomigran	20000101

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Procainamide hydrochloride	2044	Mild		Procainamide Durules	20440101
Procarbazine hydrochloride	2047	Moderate		Natulan	20470101
Promethazine theoclate	2054	Moderate		Avomine	20540101
Quetiapine Fumarate	1183	Moderate			
Rosiglitazone	3739	Moderate			
Sertraline Hydrochloride	1030	Moderate			
Sulpiride	1007	Moderate			
Tamsulosin hydrochloride	3910	Mild		Tamsulosin-Rex	39102525
Terazosin Hydrochloride	2543	Mild			
Teriflunomide	4054	Moderate		Aubagio	40542525
Timolol Maleate	2266	Mild			
Tolbutamide	2277	Major		Diatol	22770101

Table 27: Continued

Chemical Names	ID	AI-Classification	Drug Class (where relevant)	Brand Names	Brand Code
Tramadol	1229	Moderate			
Tranylcypromine sulphate	2285	Contraindicated		Parnate	22850101
Varenicline tartrate	3920	Major		Champix	39202525
Verapamil Hydrochloride	2317	Moderate			
Zuclopenthixol decanoate	3803	Moderate		Clopixol	38032525
Zuclopenthixol dihydrochloride	1226	Moderate			
Zuclopenthixol hydrochloride	3898	Moderate		Clopixol	38982525

APPENDIX B: LIST OF AI-MEDICATION MATCHES BETWEEN THE PHARMS AND NZF DATA-SETS

Chapter 11 described the data-matching process that were applied to identify medications within the PHARMS data that were classified as AI-medications by NZF (see section 11.2.c). As discussed, SPSS syntax scripts were generated to prepare the two datasets for matching. The following preparation salts were removed from medication chemical names within the PHARMS data using automated processes: *acetate; bromide; calcium; carbonate; citrate; decanoate; estolate; fumarate; hydrochloride; maleate; mesylate; pamoate; phosphate; potassium; sodium; succinate; sulfate; sulphate;* and *tartrate*. Some medications within the PHARMS data contained multiple active ingredients. In such cases, a new variable was created for each chemical, and matching processes were applied to these individually. Matches were considered finalized when strings within the cleaned datasets matched exactly. In some cases, strings within the NZF data matched with single substrings in PHARMS data entries containing multiple substrings. These matches were checked manually and corrected accordingly.

Matches between the PHARMS data and NZF data are listed in Tables 28 and 29. PHARMS medications containing a single active ingredient are listed in Table 28, and those containing multiple active ingredients are listed in Table 29. In both tables, the alcohol-interactivity classification of matched medications are listed in the right hand column, and matches that required manual checking are listed in **bold** font. In Table 29, the alcohol interactivity of the individual active ingredients of matched medications are identified where applicable (*mild; **moderate; ***major; ****contraindicated).

Table 28: NZF/PHARMS Matches: Medications Containing One Active Ingredient

PHARMS Chemical Name	NZF Match	AI-Classification
Acarbose	Acarbose	Moderate
Acebutolol	Acebutolol	Mild
Acitretin	Acitretin	Moderate
Alprazolam	alprazolam	Moderate
Amantadine hydrochloride	amantadine	Moderate
Amisulpride	amisulpride	Moderate
Amitriptyline	amitriptyline	Moderate
Amlodipine	amlodipine	Moderate
Apomorphine hydrochloride	apomorphine	Moderate
Aripiprazole	aripiprazole	Moderate
Aspirin	aspirin	Mild
Atenolol	atenolol	Mild
Atropine sulphate	atropine	Major
Azathioprine	azathioprine	Major
Baclofen	baclofen	Moderate
Benazepril	benazepril	Mild
Betaxolol	betaxolol	Mild
Bisoprolol fumarate	bisoprolol	Mild
Brimonidine tartrate	brimonidine	Mild
Bromazepam	bromazepam	Moderate
Bromocriptine mesylate	bromocriptine	Moderate
Bupivacaine hydrochloride	bupivacaine	Moderate
Bupivacaine Hydrochloride	bupivacaine	Moderate
Buprenorphine hydrochloride	buprenorphine	Moderate
Buprenorphine Hydrochloride	buprenorphine	Moderate
Bupropion hydrochloride	bupropion	Major
Buspirone hydrochloride	buspirone	Moderate
Caffeine	caffeine	Mild
Caffeine citrate	caffeine	Mild
Candesartan cilexetil	**candesartan**	Mild
Captopril	captopril	Mild
Carbamazepine	carbamazepine	Moderate
Carvedilol	carvedilol	Mild
Cefamandole nafate	**cefamandole**	Moderate
Celecoxib	celecoxib	Major
Celiprolol	celiprolol	Mild
Cetirizine hydrochloride	cetirizine	Mild
Chlordiazepoxide hydrochloride	chlordiazepoxide	Moderate
Chlorpromazine hydrochloride	chlorpromazine	Moderate
Chlorpropamide	chlorpropamide	Major
Ciclosporin	ciclosporin	Mild
Cilazapril	cilazapril	Mild

Note: Items in bold font required manual correction

Table 28: Continued

PHARMS Chemical Name	NZF Match	AI-Classification
Cimetidine	cimetidine	Mild
Ciprofloxacin	ciprofloxacin	Moderate
Cisapride	cisapride	Moderate
Citalopram hydrobromide	**citalopram**	Moderate
Citalopram hydrobromide (Celapram)	**citalopram**	Moderate
Clobazam	clobazam	Moderate
Clomipramine hydrochloride	clomipramine	Moderate
Clonazepam	clonazepam	Moderate
Clonidine	clonidine	Moderate
Clonidine hydrochloride	clonidine	Moderate
Clonidine Hydrochloride	clonidine	Moderate
Clozapine	clozapine	Moderate
Codeine	codeine	Moderate
Codeine phosphate	codeine	Moderate
Cyclizine hydrochloride	cyclizine	Moderate
Cyclizine lactate	**cyclizine**	Moderate
Cycloserine	cycloserine	Contraindicated
Cyproheptadine hydrochloride	cyproheptadine	Moderate
Cyproterone acetate	cyproterone	Moderate
Dantrolene	dantrolene	Moderate
Desipramine hydrochloride	desipramine	Moderate
Dexamfetamine sulfate	dexamfetamine	Major
Dextromethorphan	dextromethorphan	Moderate
Dextropropoxyphene	dextropropoxyphene	Major
Diazepam	diazepam	Moderate
Diclofenac sodium	diclofenac	Major
Diflunisal	diflunisal	Major
Dihydrocodeine tartrate	dihydrocodeine	Moderate
Diltiazem hydrochloride	diltiazem	Moderate
Dimenhydrinate	dimenhydrinate	Moderate
Dimethyl fumarate	**dimethyl fumarate**	Moderate
Dimethyl sulphoxide	**dimethyl sulfoxide**	Moderate
Diphenhydramine hydrochloride	diphenhydramine	Moderate
Disulfiram	disulfiram	Contraindicated
Doxazosin	doxazosin	Mild
Doxepin hydrochloride	doxepin	Moderate
Doxycycline	doxycycline	Mild
Droperidol	droperidol	Moderate
Enalapril maleate	enalapril	Mild
Erythromycin	erythromycin	Moderate
Erythromycin estolate	erythromycin	Moderate

Note: items in bold font required manual correction

Table 28: Continued

PHARMS Chemical Name	NZF Match	AI-Classification
Erythromycin ethyl succinate	**erythromycin**	Moderate
Erythromycin lactobionate	**erythromycin**	Moderate
Erythromycin stearate	**erythromycin**	Moderate
Escitalopram	escitalopram	Moderate
Ethionamide	ethionamide	Mild
Ethosuximide	ethosuximide	Moderate
Famotidine	famotidine	Mild
Felodipine	felodipine	Moderate
Fenbufen	fenbufen	Major
Fenoprofen Calcium	fenoprofen	Major
Fentanyl	fentanyl	Moderate
Fentanyl citrate	fentanyl	Moderate
Fentanyl Citrate	fentanyl	Moderate
Fexofenadine hydrochloride	fexofenadine	Mild
Flunarizine	flunarizine	Moderate
Flunitrazepam	flunitrazepam	Moderate
Fluoxetine hydrochloride	fluoxetine	Moderate
Fluoxetine Hydrochloride	fluoxetine	Moderate
Fluphenazine decanoate	fluphenazine	Moderate
Fluphenazine hydrochloride	fluphenazine	Moderate
Flurbiprofen	flurbiprofen	Major
Gabapentin	gabapentin	Moderate
Gabapentin (Neurontin)	**gabapentin**	Moderate
Glibenclamide	glibenclamide	Major
Gliclazide	gliclazide	Major
Glipizide	glipizide	Major
Glyceryl trinitrate	**glyceryl**	Moderate
Glycopyrronium	glycopyrronium	Major
Glycopyrronium bromide	glycopyrronium	Major
Glycopyrronium Bromide	glycopyrronium	Major
Griseofulvin	griseofulvin	Moderate
Haloperidol	haloperidol	Moderate
Haloperidol decanoate	haloperidol	Moderate
Haloperidol Decanoate	haloperidol	Moderate
Hydroxyzine Hydrochloride	hydroxyzine	Moderate
Hyoscine hydrobromide	**hyoscine**	Moderate
Hyoscine N-butylbromide	**hyoscine**	Moderate
Ibuprofen	ibuprofen	Major
Imipramine hydrochloride	imipramine	Moderate
Insulin aspart	**insulin**	Moderate
Insulin glargine	**insulin**	Moderate

Note: items in bold font required manual correction

Table 28: Continued

PHARMS Chemical Name	NZF Match	AI-Classification
Insulin glulisine	**insulin**	Moderate
Insulin isophane	**insulin**	Moderate
Insulin lispro	**insulin**	Moderate
Insulin neutral	**insulin**	Moderate
Insulin Neutral	**insulin**	Moderate
Insulin zinc suspension	**insulin**	Moderate
Interferon alfa-2a	**interferon**	Moderate
Interferon alfa-2b	**interferon**	Moderate
Interferon Alpha-2B	**interferon**	Moderate
Interferon alpha-n	**interferon**	Moderate
Interferon beta-1-alpha	**interferon**	Moderate
Interferon beta-1-beta	**interferon**	Moderate
Isoniazid	isoniazid	Moderate
Isosorbide dinitrate	**isosorbide**	Moderate
Isosorbide Dinitrate	**isosorbide**	Moderate
Isosorbide mononitrate	**isosorbide**	Moderate
Isotretinoin	isotretinoin	Moderate
Isradipine	isradipine	Mild
Ivermectin	ivermectin	Mild
Ketoconazole	ketoconazole	Major
Ketoprofen	ketoprofen	Major
Ketotifen	ketotifen	Moderate
Labetalol	labetalol	Mild
Leflunomide	leflunomide	Major
Levamisole	levamisole	Moderate
Levomepromazine maleate	levomepromazine	Moderate
Lisinopril	lisinopril	Mild
Lithium carbonate	lithium	Moderate
Loprazolam mesylate	loprazolam	Moderate
Loratadine	loratadine	Mild
Lorazepam	lorazepam	Moderate
Lormetazepam	lormetazepam	Moderate
Losartan	losartan	Mild
Losartan potassium	losartan	Mild
Loxapine succinate	loxapine	Moderate
Maprotiline hydrochloride	maprotiline	Moderate
Mefenamic acid	mefenamic-acid	Major
Meloxicam	meloxicam	Major
Meprobamate	meprobamate	Major
Metformin hydrochloride	metformin	Moderate
Methadone hydrochloride	methadone	Moderate

Note: Items in bold font required manual correction

Table 28: Continued

PHARMS Chemical Name	NZF Match	AI-Classification
Methotrexate	methotrexate	Major
Methyldopa	methyldopa	Mild
Methylphenidate hydrochloride	methylphenidate	Major
Methylphenidate hydrochloride extended-release	**methylphenidate**	Major
Metoclopramide hydrochloride	metoclopramide	Moderate
Metoclopramide Hydrochloride	metoclopramide	Moderate
Metoprolol succinate	metoprolol	Mild
PHARMS Chemical Name	NZF Match	AI-Classification
Metoprolol tartrate	metoprolol	Mild
Metronidazole	metronidazole	Contraindicated
Mianserin hydrochloride	mianserin	Moderate
Midazolam	midazolam	Moderate
Mirtazapine	mirtazapine	Major
Morphine hydrochloride	morphine	Major
Morphine sulphate	morphine	Major
Morphine tartrate	morphine	Major
Nadolol	nadolol	Mild
Naproxen	naproxen	Major
Naproxen sodium	naproxen	Major
Niclosamide	niclosamide	Major
Nicorandil	nicorandil	Moderate
Nicotine	nicotine	Mild
Nicotinic acid	nicotinic-acid	Major
Nifedipine	nifedipine	Moderate
Nimorazole	nimorazole	Moderate
Nitrazepam	nitrazepam	Moderate
Nizatidine	nizatidine	Mild
Nortriptyline hydrochloride	nortriptyline	Moderate
Nortriptyline Hydrochloride	nortriptyline	Moderate
Olanzapine	olanzapine	Moderate
Olanzapine pamoate monohydrate	**olanzapine**	Moderate
Ondansetron	ondansetron	Moderate
Ornidazole	ornidazole	Moderate
Oxazepam	oxazepam	Moderate
Oxprenolol	oxprenolol	Mild
Oxybutynin	oxybutynin	Moderate
Oxycodone hydrochloride	oxycodone	Moderate
Papaveretum	papaveretum	Moderate
Paracetamol	paracetamol	Major
Paraldehyde	paraldehyde	Major
Paroxetine hydrochloride	paroxetine	Moderate

Note: Items in bold font required manual correction

Table 28: Continued

PHARMS Chemical Name	NZF Match	AI-Classification
Pentazocine	pentazocine	Moderate
Pericyazine	periciazine	Moderate
Perindopril	perindopril	Mild
Pethidine hydrochloride	pethidine	Moderate
Phenelzine sulphate	phenelzine	Contraindicated
Phenylbutazone	phenylbutazone	Major
Phenytoin sodium	phenytoin	Moderate
Pimozide	pimozide	Moderate
Pindolol	pindolol	Mild
Pioglitazone	pioglitazone	Moderate
Piroxicam	piroxicam	Major
Pizotifen	pizotifen	Moderate
Prazosin	prazosin	Mild
Primidone	primidone	Moderate
Procainamide hydrochloride	procainamide	Mild
Procarbazine hydrochloride	procarbazine	Moderate
Prochlorperazine	prochlorperazine	Moderate
Promethazine hydrochloride	promethazine	Moderate
Promethazine theoclate	**promethazine**	Moderate
Propranolol	propranolol	Mild
Quetiapine	quetiapine	Moderate
Quetiapine Fumarate	quetiapine	Moderate
Quinapril	quinapril	Mild
Ranitidine	ranitidine	Mild
Risperidone	risperidone	Moderate
Rosiglitazone	rosiglitazone	Moderate
Salbutamol	salbutamol	Major
Selegiline hydrochloride	selegiline	Major
Sertraline	sertraline	Moderate
Sertraline Hydrochloride	sertraline	Moderate
Sildenafil	sildenafil	Moderate
Sotalol	sotalol	Mild
Sulindac	sulindac	Major
Sulpiride	sulpiride	Moderate
Tacrolimus	tacrolimus	Major
Tamsulosin hydrochloride	tamsulosin	Mild
Temazepam	temazepam	Moderate
Tenoxicam	tenoxicam	Major
Terazosin	terazosin	Mild
Terazosin Hydrochloride	terazosin	Mild
Teriflunomide	teriflunomide	Moderate

Note: Items in bold font required manual correction

Table 28: Continued

PHARMS Chemical Name	NZF Match	AI-Classification
Thalidomide	thalidomide	Major
Thioridazine hydrochloride	thioridazine	Moderate
Tiaprofenic acid	tiaprofenic-acid	Major
Timolol	timolol	Mild
Timolol Maleate	timolol	Mild
Tinidazole	tinidazole	Contraindicated
Tolbutamide	tolbutamide	Major
Topiramate	topiramate	Moderate
Tramadol	tramadol	Moderate
Tramadol hydrochloride	tramadol	Moderate
Trandolapril	trandolapril	Mild
Tranylcypromine sulphate	tranylcypromine	Contraindicated
Triazolam	triazolam	Moderate
Trifluoperazine hydrochloride	trifluoperazine	Moderate
Trimethoprim	trimethoprim	Moderate
Trimipramine maleate	trimipramine	Moderate
Varenicline tartrate	varenicline	Major
Venlafaxine	venlafaxine	Moderate
Verapamil hydrochloride	verapamil	Moderate
Verapamil Hydrochloride	verapamil	Moderate
Warfarin sodium	warfarin	Mild
Ziprasidone	ziprasidone	Moderate
Zopiclone	zopiclone	Moderate
Zuclopenthixol decanoate	zuclopenthixol	Moderate
Zuclopenthixol dihydrochloride	**zuclopenthixol**	Moderate
Zuclopenthixol hydrochloride	zuclopenthixol	Moderate

Note: Items in bold font required manual correction

Table 29: NZF/PHARMS Matches: Medications Containing Multiple Active Ingredients

PHARMS Chemical Name	Active Ingredients			NZF AI-Classification
	Chemical 1	Chemical 2	Chemical 3	
Diphenoxylate hydrochloride with atropine sulphate	diphenoxylate	**atropine*** **		Major
Ergotamine tartrate with caffeine	ergotamine	caffeine*		Mild
Ergotamine Tartrate with Caffeine	ergotamine	caffeine*		Mild
Aspirin with Chloroform	aspirin*	chloroform		Mild
Atenolol with chlorthalidone	atenolol*	chlorthalidone		Mild
Pindolol with clopamide	pindolol*	clopamide		Mild
Aspirin with Codeine	aspirin*	codeine**		Moderate
Paracetamol with codeine	paracetamol***	codeine**		Major
Paracetamol with Codeine	paracetamol***	codeine**		Major
Ergotamine tartrate with cyclizine	ergotamine	cyclizine		Moderate
Idoxuridine with dimethyl sulphoxide	idoxuridine	**dimethyl sulfoxide****		Moderate
Ergotamine tartrate with diphenhydramine	ergotamine	diphenhydramine**		Moderate
Cyproterone acetate with ethinyloestradiol	cyproterone**	ethinyloestradiol		Moderate
Acebutolol with hydrochlorothiazide	acebutolol*	hydrochlorothiazide		Mild
Captopril with hydrochlorothiazide	captopril*	hydrochlorothiazide		Mild
Cilazapril with hydrochlorothiazide	cilazapril*	hydrochlorothiazide		Mild
Enalapril maleate with hydrochlorothiazide	enalapril*	hydrochlorothiazide		Mild
Lisinopril with hydrochlorothiazide	lisinopril*	hydrochlorothiazide		Mild
Losartan potassium with hydrochlorothiazide	losartan*	hydrochlorothiazide		Mild
Losartan with hydrochlorothiazide	losartan*	hydrochlorothiazide		Mild
Losartan with Hydrochlorothiazide	losartan*	hydrochlorothiazide		Mild
Methyldopa with hydrochlorothiazide	methyldopa*	hydrochlorothiazide		Mild
Quinapril with hydrochlorothiazide	quinapril*	hydrochlorothiazide		Mild
Glycopyrronium with indacaterol	glycopyrronium***	indacaterol		Major

Note: Items in bold font required manual correction
Note: Single chemical alcohol interactivity level indicators = *mild; **moderate; ***major; ****contraindicated

Table 29: Continued

PHARMS Chemical Name	Active Ingredients			NZF AI-Classification
	Chemical 1	Chemical 2	Chemical 3	
Insulin aspart with insulin aspart protamine	**insulin****	**insulin****		Moderate
Insulin isophane with insulin neutral	**insulin****	**insulin****		Moderate
Insulin lispro with insulin lispro protamine	**insulin****	**insulin****		Moderate
Salbutamol with ipratropium bromide	salbutamol***	ipratropium		Major
Buprenorphine with naloxone	buprenorphine**	naloxone		Moderate
Dextropropoxyphene with paracetamol	dextropropoxyphene***	paracetamol***		Major
Metoclopramide hydrochloride with paracetamol	metoclopramide**	paracetamol***		Major
Timolol maleate with pilocarpine	timolol*	pilocarpine		Mild
Interferon alpha-2a with ribavirin	interferon**	ribavirin		Moderate
Brimonidine tartrate with timolol maleate	brimonidine*	timolol*		Mild
Dorzolamide with timolol	dorzolamide	timolol*		Mild
Aspirin with paracetamol and codeine	aspirin*	paracetamol***	codeine**	Major
Omeprazole, amoxycillin and metronidazole	omeprazole	amoxycillin	metronidazole****	Contraindicated
Bismuth subcitrate, metronidazole and tetracycline	bismuth subcitrate	metronidazole****	tetracycline	Contraindicated

Note: Items in bold font required manual correction
Note: Single chemical alcohol interactivity level indicators = *mild; **moderate; ***major; ****contraindicated

APPENDIX C: STUDY 1 AND STUDY 2 UNWEIGHTED SAMPLE CHARACTERISTICS BY DRINKING FREQUENCY

Table 30: Study 1 Unweighted Sample Characteristics by Drinking Frequency

Demographic variable	Total % of Sample	Drinking Frequency (AUDIT-C)		
		Minimal/ non-drinker	Light/ moderate-drinker	Heavy-drinker
Total sample				
	100% (1319)	426 (31.5%)	509 (38.6%)	394 (29.9%)
Gender				
Male	47.7% (629)	142 (22.6%)	244 (38.8%)	243 (38.6%)
Female	52.3% (690)	274 (39.7%)	265 (38.4%)	151 (21.9%)
Age				
54-59	41.6% (549)	172 (31.3%)	229 (41.7%)	148 (27.0%)
60-64	32.3% (426)	127 (29.8%)	154 (36.2%)	145 (34.0%)
65-70	26.1% (344)	117 (34.0%)	126 (36.6%)	101 (29.4%)
Ethnicity				
NZE	61.1% (806)	207 (25.7%)	331 (41.1%)	268 (33.3%)
Māori	31.2% (411)	173 (42.1%)	147 (35.8%)	91 (22.1%)
Other	7.7% (102)	36 (35.3%)	31 (30.4%)	35 (34.3%)
Education level				
Tertiary education	14.1% (182)	39 (21.4%)	61 (33.5%)	82 (45.1%)
No tertiary education	85.9% (1111)	365 (32.9%)	437 (39.3%)	309 (27.8%)
Missing (n = 26)	2.0%			
Marital Status				
Married, civil union, or de facto	75.8% (1000)	283 (28.3%)	398 (39.8%)	319 (31.9%)
Other	23.2% (306)	130 (42.5%)	106 (34.6%)	70 (22.9%)
Missing (n = 13)	1.0%			
Living Standards				
Hardship	12.8% (165)	99 (60.0%)	44 (26.7%)	22 (13.3%)
Comfortable	32.9% (425)	137 (32.2%)	178 (41.9%)	110 (25.9%)
Good	54.3% (701)	165 (23.5%)	276 (39.4%)	260 (37.1%)
Missing (n = 28)	2.1%			

Table 31: Study 2 Unweighted Sample Characteristics by Drinking Frequency

Demographic variable	Total % of Sample	Drinking Frequency (AUDIT-C)		
		Minimal/non-drinker	Light/moderate-drinker	Heavy-drinker
Total sample	100% (1,621)	546 (33.7%)	631 (38.9%)	444 (27.4%)
Gender				
Male	47.2% (765)	191 (25.0%)	325 (42.5%)	249 (32.5%)
Female	52.8% (856)	355 (41.5%)	306 (35.7%)	195 (22.8%)
Age				
48-54	9.1% (147)	48 (32.7%)	66 (44.9%)	33 (22.4%)
55-64	47.1% (764)	239 (31.3%)	310 (40.6%)	215 (28.1%)
65-74	43.0% (697)	255 (36.6%)	250 (35.9%)	192 (27.5%)
75+	0.8% (13)	4 (30.8%)	5 (38.5%)	4 (30.8%)
Ethnicity				
NZ European	68.8% (1098)	308 (28.1%)	446 (40.6%)	344 (31.3%)
Māori	27.4% (438)	209 (47.7%)	149 (34.0%)	80 (18.3%)
Other	3.8% (61)	22 (36.1%)	24 (39.3%)	15 (24.6%)
Education level				
Tertiary education	30.2% (488)	127 (26.0%)	195 (40.0%)	166 (34.0%)
No tertiary education	69.8% (1126)	417 (37.0%)	432 (38.4%)	277 (24.6%)
Marital Status				
Married, civil union, de facto	77.6% (1254)	370 (29.5%)	511 (40.7%)	373 (29.7%)
Other	22.4% (361)	174 (48.2%)	117 (32.4%)	70 (19.4%)
Living Standards				
Hardship	12.4% (196)	113 (57.7%)	61 (31.1%)	22 (11.2%)
Comfortable	29.1% (461)	184 (39.9%)	187 (40.6%)	90 (19.5%)
Good	58.5% (927)	234 (25.2%)	369 (39.8%)	324 (35.0%)

APPENDIX D: CASE STUDY

Case Study 5: Research

Alcohol and Alcohol-Interactive Medication Use During Older Adulthood

This case study was completed during the period of an internship as part of a Doctor of Clinical Psychology, and represents the work of Eddie Barnard under the supervision of Dr Joanne Taylor.

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Supervisor: Dr Joanne Taylor, Clinical Psychologist (Massey University)

Abstract

Background: Vulnerability to adverse alcohol-medication interactions (AMIs) increases during older adulthood. Existing research findings indicate differences in awareness of AMI risks and mental health factors such as depression influence alcohol use among older alcohol interactive (AI)-medication users. **Objectives:** This study explored associations between AI-medication use, alcohol use, and depression among older adults. **Design and Methods**: This study included a large community sample of New Zealand older adults, and involved secondary analysis of survey data and pharmaceutical claims records. Associations between variables of interest were explored using Chi-squared tests and hierarchical binary logistic regression. **Results:** One-in-three participants were at risk of AMI. AI-medication use was associated with less alcohol use, with lower rates of alcohol use being seen among those using AI-medications associated with higher AMI-severity. Depression did not influence the association between AI-medication use and alcohol use. **Discussion:** Many New Zealand older adults are at risk of AMI exposure. These risks may be mitigated by alerting older adults to their risk of AMI related harm.

Introduction

Interactions between alcohol and medications can increase risks of overdosing, cause a number of serious side effects such as gastrointestinal bleeding and psychomotor impairment, and interfere with the therapeutic effects of medication treatment regimens (Adams, 1995; Moore, Whiteman, & Ward, 2007; Weathermon & Crabb, 1999). These risks are of particular concern for older adults, as this population is more likely to be using medications with the potential to interact negatively with alcohol, and are particularly sensitive to the effects of alcohol-medication interactions (AMI's) due to age-related changes in body mass and metabolism (Moore et al., 2007). Survey research exploring rates of alcohol and alcohol-interactive (AI) medication use among older adults has shown that, while AI-medication use is negatively associated with alcohol use, concurrent alcohol and AI-medication use is common among community dwelling older adults (Cousins et al., 2014; Breslow et al., 2015; Pringle et al., 2005; Qato et al., 2015). Given the potential for alcohol related harm in older people, there is a need to identify factors underlying drinking behaviour among older AI-medication users that may inform intervention strategies aimed at reducing alcohol AMI exposure.

One factor which appears to differ between older AI-medication users who use alcohol and those who abstain from alcohol is knowledge about the risks of AMIs. Survey findings have shown that, compared with non-drinkers, older drinkers are able to identify fewer AI-medications from a medication list (containing both AI and non-AI medications) and are less knowledgeable about the potential alcohol-interactivity of medications they use (Zanjani et al., 2013). Similarly, qualitative findings indicate reduced alcohol intake following chronic illness onset during older adulthood is often motivated by discussions with health providers about potential AMIs (Gavens et al., 2016). These findings suggest decisions to reduce alcohol consumption among older AI-medication users are often motivated by awareness about the risks of AMI.

Given the evidence that relevant health knowledge motivates changes in alcohol consumption among many AI-medication users, it would be reasonable to assume that providing information about AMI risks would lead to reduced alcohol consumption among older AI-medication users. However, a health education intervention developed by Zanjani et al. (2018a, 2018b, 2018c) successfully enhanced older adults' AMI awareness, yet had little effect on drinking intentions in the short term, and actually appeared to significantly decrease intentions to reduce alcohol consumption in the long term (Zanjani et al., 2018a, 2018b, 2018c). While the likelihood of alcohol use is lower among AI-medication users who are aware of the potential for AMI related harm, Zanjani et al.'s results show that simply providing information about AMI risks does not necessarily facilitate healthy changes in drinking behaviour.

A possible explanation is that AI-medication users who change their drinking behaviour in response to health information are more likely to have sought information about AMI risks than those less receptive to educational interventions. Zanjani et al. (2013) found that older drinkers displayed less willingness to discuss the potential for AMI related harm with friends and family. Similarly, Gavens et al. (2016) found that older adults who did not reduce their alcohol intake following chronic illness onset reported avoiding discussions with health professionals about alcohol-related harm as a means of avoiding encouragement to alter drinking patterns. Gavens et al. also found that continued drinking was often rationalised through selective interpretations of health information that placed greater importance on evidence that health problems are unrelated to alcohol use. It is therefore likely that many AI-medication users who continue to drink actively avoid exposure to information about AMI risks, and may selectively focus on evidence supporting their decision to continue drinking.

According to a review by Sweeny, Melnyk, Miller, and Shepperd (2010) exploring motivators of information avoidance in multiple contexts, people typically avoid information that challenges cherished beliefs and identifies a need for unwanted action or change. In the

context of combined alcohol/AI-medication use, such information might be that which challenges beliefs about alcohol related harm and highlights a need for reduced alcohol consumption. Perceived barriers to changes in drinking behaviour may therefore serve to motivate avoidance of AMI related information for many older adults and may also prevent exposure to AMI information from leading to reduced alcohol consumption.

One factor which may be perceived as a barrier to drinking behaviour change for many older AI-medication users is mental health. A recent study of Canadian mental health service users found that nearly half of the sample reported having used alcohol and psychotropic medications concurrently despite having considered the risk of AMI prior to alcohol consumption (Cheng, Mithoowani, Ungar, & Lee, 2018). Findings from qualitative studies conducted in the UK suggest alcohol is often used to regulate emotion among chronically ill older adults (Gavens et al., 2016) and older AI-medication users often self-medicate with alcohol to manage mental health problems, most commonly depression (Haighton, O'Donnell, Wilson, McCabe, & Ling, 2018). These findings are in line with research into self-medication behaviour suggesting alcohol use is often used to regulate emotion among people with depression (Bolton, Robinson, & Sareen, 2009; Boschloo et al., 2012 Brown & Stewart, 2008). As such, mental health factors such as depression may therefore moderate changes in alcohol consumption among older AI-medication users.

The theoretical framework adopted in the present study was based on health behaviour principles detailed in the *Health Belief Model (HBM)* (Janz & Becker, 1984; Rosenstock, 1974) and the principle of co-existing mental health and substance use difficulties known as the *Self-Medication Hypothesis* (Khantzian 1987; 1997). These theories of factors influencing health related behaviours were selected because they provide a parsimonious account regarding factors underlying drinking behaviour among AI-medication users.

The HBM conceptualises health promoting information as a *cue of action* which leads to behaviour change by increasing one's *perceived susceptibility* to harm and eliciting the belief that behaviour change will have positive health consequences (*perceived benefits*). The likelihood of behaviour change is thought to increase with the *perceived severity* of the related health consequence (Janz & Becker, 1984; Rosenstock, 1974). Research supports this relationship between information and healthy behaviour, showing a negative association between AI-medication use and alcohol use (Cousins et al., 2014; Breslow et al., 2015; Pringle et al., 2005; Qato et al., 2015), and differences in AMI related knowledge between AI-medication users who are drinkers and those who are non-drinkers (Zanjani et al., 2013).

The HBM also proposes health behaviour change is dependent on the individual's beliefs about their ability to successfully change behaviour (*self-efficacy*) and potential negative consequences of behaviour change (*perceived barriers*). In other words, healthy behaviour change will not occur when perceived barriers outweigh the perceived benefits, and/or the individual does not believe they are capable of successfully changing their behaviour (Rosenstock, Strecher, & Becker 1988). Therefore, people who self-medicate with alcohol to alleviate emotional distress would be less likely to give up alcohol when prescribed AI-medications due to a) the perceived barrier of increased emotional distress, and b) low feelings of self-efficacy due to reliance on alcohol to regulate emotion. This view is supported by the high rates of concurrent alcohol/AI-medication use observed among mental health service users (Cheng et al., 2018) as well as qualitative findings implicating self-medication as a motivator for alcohol use among AI-medication users (Gavens et al., 2016; Haighton et al., 2018).

Aims and Hypothesis

The present study analysed data from a nationwide survey of community dwelling older adults living in New Zealand to explore the potential relationships between AI-medication use, alcohol use, and depression. The study had three hypotheses. Firstly, based on previous epidemiological research showing a negative association between AI-medication use and alcohol use (Cousins et al., 2014; Breslow et al., 2015; Pringle et al., 2005; Qato et al., 2015)., it was hypothesised that alcohol use would be less prevalent among AI-medication users than non-users of AI-medications. Secondly, it was hypothesised that alcohol use would be less common among participants using medications with higher levels of alcohol-interactivity than those using forms of AI-medication associated with milder AMIs. This hypothesis was based on the HBM principles of perceived severity and perceived susceptibility (Janz & Becker, 1984; Rosenstock, 1974), as well as research findings suggesting older AI-medication users who stop drinking often do so in response to knowledge of AMI risks (Gavens et al., 2016; Zanjani et al., 2013). The third hypothesis was that depression would weaken the negative association between AI-medication use and alcohol use. This hypothesis was based on the HBM principles of self-efficacy and perceived barriers (Rosenstock et al., 1988), the self-medication hypothesis (Khantzian 1987; 1997), and research suggesting alcohol is often used to alleviate emotional distress among AI-medication users with symptoms of depression (Cheng et al., 2018; Gavens et al., 2016; Haighton, et al., 2018).

Method

Participants

Health, Work and Retirement study (HWR) 2010

The present study is a secondary analysis of data from the 2010 wave of the *Health, Work and Retirement (HWR) study*, which is a large ongoing nationally representative survey of older

adults living in New Zealand that started in 2005. The cohort consists of participants recruited across two waves occurring in 2006 and 2010. Participants were randomly selected from the New Zealand electoral roll, and over sampling of those indicated as having Māori descent was undertaken to ensure adequate representation of New Zealand's Māori (indigenous) population. Participants recruited in 2006 participated in the initial HWR study, which originally consisted of 6,662 participants aged 55-70 years. The 2010 HWR recruitment wave aimed to increase representation of younger (aged 50-84 years) and older (70-84) age groups within the sample. The 2010 HWR sample consisted of 3,305 New Zealand adults aged ≥48 years, 1,981 of whom were recruited in 2006 and 1,324 were recruited in 2010 (Towers & Stevenson, 2014). The present study includes a subsample of the 2010 HWR cohort who consented to having their survey data linked with their national health records as part of the HWR data-linkage project.

Data-linkage

The HWR data linkage project links consenting participants' survey data with their national health records. In 2014, written informed consent was sought among participants of the 2010 HWR study. A second approach to data linkage consent occurred in 2015 and included those who did not respond in the 2014 approach, yet were active participants in the 2014 HWR survey. Consent was sought from 2,475 participants across the two approaches, 1,727 of whom consented to data linkage. Minimum identifiers of consenting participants (name, gender, and date of birth) were provided to the Ministry of Health Analytic Services (formerly New Zealand Health Information Service) and a direct-match strategy was implemented to link to participants' National Health Index (NHI) number (Allen, 2016). Data were then matched by the Ministry of Health Analytic Services to health records based on NHI number, before all identifying information were removed and records assigned a new identification number for the purposes of linkage to HWR study research data. Of the 1,727 participants who consented

to data-linkage, 1,625 were matched successfully to their NHI number and included in the present study sample (49.2% of the original sample). For the purposes of this study, participants' pharmaceutical dispensing data from their national health records were used to facilitate identification of their prescription medication use. Table 1 shows the number of 2010 HWR participants who were approached for and consented to data linkage, and were successfully matched to their NHI number across both waves of recruitment.

Table 1: Process of data-linkage recruitment among 2010 HWR participants

	Wave of recruitment		Total
	2006	2010	
Total HWR 2010 sample	1,981	1,324	3,305
Approached for data linkage	1,783	692	2,475
Consented to data linkage	1,257	470	1,727
Matched to NHI (final sample)	1,191	434	1,625

Measures

AI-Medication Use

Participants' pharmaceutical claims data was provided by the New Zealand Pharmaceutical Collection (PHARMS). The New Zealand Formulary (NZF; 2017) was used to identify *AI-medications*[29] within the PHARMS data and categorize them into ordinal groups of varying alcohol interactivity levels (*mild*[30], *moderate*[31], *major*[32], and *contraindicated*[33]).

[29] AI-medications: those referred to as having potential alcohol-interactivity, those including a cautionary warning against alcohol use, and/or those including some sort of recommendation regarding alcohol consumption

[30] Mild AI-medications: potential interactions are of little clinical significance

[31] Moderate AI-medications: interactions may result in significant distress or incapacitation, but the likelihood of interaction is not high enough to warrant close monitoring or dosage adjustment

[32] Major AI-medications: for interactions with detrimental effects that may be permanent or life-threatening OR interactions that may result in significant distress or incapacitation and the likelihood of interaction is high enough to warrant close monitoring or dosage adjustment

[33] Contraindicated AI-medications: medications contraindicated for use with alcohol

Participants were identified as AI-medication users if their pharmaceutical dispensing records indicated they (a) were currently using AI-medication at the time of survey completion, and (b) had used AI-medication on a regular basis prior to survey completion. The research protocol developed for this project informed the specific methods used to determine which participants could be defined as AI-medication users based on this definition (see Appendix A). Briefly, current use of antibiotics was determined using the *legend-time method*[34]; current use of nonsteroidal anti-inflammatory drugs (NSAIDs) and benzodiazepines was determined using a *30-day fixed-window*[35]; and current use of all other medications (i.e. excluding antibiotics, NSAIDs, and benzodiazepines) was determined using a *90-day fixed-window*[36]. Participants were defined as regular AI-medication users if they were (1) identified as currently using AI-medications based on the criteria just described, and 2) dispensed at least one other AI-medication supply during the past 244 days (prior to survey completion) that was not in current use at the time of survey completion. AI-medication users were then assigned to one of three groups based on the highest alcohol-interactivity level of medications in current use (see Table 2).

[34] Legend-time method: data-linkage method of identifying current medication use. Infers current use when the number of days for which the medication is supplied is greater than or equal to the number of days between medication dispensing date and survey response date

[35] 30-day fixed window: data-linkage method of identifying current medication use. Infers current use when a medication is dispensed during the past 30 days prior to survey response date

[36] 90-day fixed window: data-linkage method of identifying current medication use. Infers current use when a medication is dispensed during the past 90 days prior to survey response date

Table 2: Dispensing Records of AI-Medication User Groups

AI-Medication User Groups	Pharmaceutical Dispensing's Received by Group Members	
	Current use	Past 244 days (not in current use)
Contraindicated AI-medication users	At least one contraindicated AI-medication	At least one AI-medication (mild, moderate, major, or contraindicated)
Major AI-medication users	At least one major AI-medication, and no contraindicated AI-medications	At least one AI-medication
Moderate AI-medication users	At least one moderate AI-medication, and no major or contraindicated AI-medications	At least one AI-medication
Mild AI-medication users	At least one mild AI-medication, and no moderate, major, or contraindicated AI-medications	At least one AI-medication

Note: Current use = Legend time for antibiotics; 30-day fixed-window for benzodiazepines & NSAIDs; 90-day fixed-window for all other drugs.

Alcohol Use

The HWR survey included the Alcohol Use Disorders Identification Test – C (AUDIT-C, Bush et al., 1998), which consists of three items assessing the quantity and frequency of alcohol use, and binge drinking frequency. The present study used the AUDIT-C frequency item to categorize participants into one of three drinking groups:

- *Minimal/non-drinkers* (those who reported using alcohol 'never' or 'monthly or less')
- *Light/moderate-drinkers* (those who reported using alcohol '2-4 times monthly' or '2-3 times weekly'
- *Heavy-drinkers* (those who reported using alcohol '4 or more times weekly')

Depression

Depression was measured with a shortened version of the *Centre for Epidemiologic Studies Depression Scale* (CES-D; Radolff, 1977), which includes 10 items selected for the assessment of depression in older people (CES-D-10; Irwin, Artin, & Oxman, 1999). The CES-D-10 had high sensitivity (97%), specificity (84%) and positive predictive value (85%) in the identification of major depression in a sample of the U.S. older population, and the Cronbach's alpha was .92 for the CES-D-10 in a sample of middle-aged U.S. adults (Irwin et al., 1999). Raw scores on the CES-D-10 range from 0 – 30. The present study adopted this dichotomous

scoring, with participants scoring below 10 categorized as ‘not depressed’ and those scoring ≥10 categorized as ‘depressed’.

Demographic variables

In light of the association of SES with alcohol use (Scott, Wiener, & Paulson, 2018; Towers, Philipp, Dulin, & Allen, 2016), participant SES was measured using the Economic Living Standard Index short form (ELSI-sf), a 25-item self-report measure of consumption capacity, economic social restrictions, and material wealth (Jensen, Spittal, & Krishnan, 2005). Raw scores on the ELSI-sf range from 0-31, with higher scores indicating higher SES. ELSI-sf raw scores are then converted into seven levels of living standards ranging from ‘severe hardship’ to ‘very good’. Other demographic variables of interest included ethnicity, age, marital status, and education level. Ethnicity was defined as ‘New Zealand European’ (NZE), ‘Māori’, or ‘Other’. Age groups included '48-54 years', '55-64 years', '65-74 years', and ' ≥75 years'. Marital status groups included ‘Married, Civil Union, or De Facto’, and ‘Other’. Education level was defined as ‘Tertiary Education’ or ‘No Tertiary Education’.

Analysis

All analyses were conducted using SPSS software. Descriptive statistics were used to explore the demographic characteristics of the sample, and chi-square tests of independence were used to explore variation in drinking frequency across demographic variables.

To test the hypothesis that alcohol use would be less common among those using AI-medications, 2x2 chi-square test of independence was used to compare rates of minimal/non-drinker status versus light-moderate/heavy drinker status among users and non-users of AI-medications. A 2x3 chi-square test of independence was used to further explore this hypothesis across drinking frequency categories, and standardized residuals were analysed to determine whether cells deviated from expected frequencies at <.05 or <.01 levels of significance.

To test the hypothesis that alcohol use would be less common among those using AI-medications with higher alcohol interactivity, a 4x2 chi-squared test of independence was used to compare rates of minimal/non-drinker status versus light-moderate/heavy drinker status across AI-medication user severity categories. This was then further explored across drinking frequency categories using a 4x3 chi-squared test of independence. Standardized residuals were used to determine whether cells deviated from expected frequencies at <.05 or <.01 levels of significance.

A binary hierarchical logistic regression model was used to test the hypothesis that the predicted negative relationship between AI-medication use and alcohol use would be moderated by depression. In this model, alcohol use was entered as binary outcome variable (drinkers versus non-drinkers). ELSI-sf scores were used control for the effects of living standards on alcohol use. AI-medication use was entered as a binary variable (non-users and mild AI-medication users versus moderate and major/contraindicated AI-medication users). A binary depression variable was entered using a CES-D-10 cut-off score of ≥10. The interaction term variable was then entered as AI-medication*depression.

Results

Alcohol Consumption Rates Across the Sample

A total of 1075 participants (66.3%) were identified as drinkers (light/moderate and heavy), and 546 (33.7%) were identified as minimal/non-drinkers. The sample rates of light/moderate and heavy drinking were 38.9% and 27.4%, respectively. Table 3 shows the demographic characteristics of the sample across drinking frequency groups.

Table 3: Demographic Sample Characteristics across Drinking Frequency Groups

Demographic variable	Total % of Sample	Drinking Frequency (AUDIT-C)			Chi square	φ_c
		Minimal/non-drinker	Light/moderate-drinker	Heavy-drinker		
Total sample						
Gender						
Male	47.2% (765)	191 (25.0%)	325 (42.5%)	249 (32.5%)	X^2 (2, N = 1,621) = 51.45, p <.001	.18
Female	52.8% (856)	355 (41.5%)	306 (35.7%)	195 (22.8%)		
Age						
48-54	9.1% (147)	48 (32.7%)	66 (44.9%)	33 (22.4%)	X^2 (6, N = 1,621) = 8.21, p =.223	.05
55-64	47.1% (764)	239 (31.3%)	310 (40.6%)	215 (28.1%)		
65-74	43.0% (697)	255 (36.6%)	250 (35.9%)	192 (27.5%)		
75+	0.8% (13)	4 (30.8%)	5 (38.5%)	4 (30.8%)		
Ethnicity						
NZ European	68.8% (1098)	308 (28.1%)	446 (40.6%)	344 (31.3%)	X^2 (4, N = 1,597) = 59.14, p <.001	.14
Māori	27.4% (438)	209 (47.7%)	149 (34.0%)	80 (18.3%)		
Other	3.8% (61)	22 (36.1%)	24 (39.3%)	15 (24.6%)		
Education level						
Tertiary education	30.2% (488)	127 (26.0%)	195 (40.0%)	166 (34.0%)	X^2 (2, N = 1,614) = 23.46, p <.001	.12
No tertiary education	69.8% (1126)	417 (37.0%)	432 (38.4%)	277 (24.6%)		
Marital Status						
Married, civil union, de facto	77.6% (1254)	370 (29.5%)	511 (40.7%)	373 (29.7%)	X^2 (2, N = 1,615) = 45.05, p <.001	.17
Other	22.4% (361)	174 (48.2%)	117 (32.4%)	70 (19.4%)		
Living Standards						
Hardship	12.4% (196)	113 (57.7%)	61 (31.1%)	22 (11.2%)	X^2 (4, N = 1,584) = 110.40, p <001	.19
Comfortable	29.1% (461)	184 (39.9%)	187 (40.6%)	90 (19.5%)		
Good	58.5% (927)	234 (25.2%)	369 (39.8%)	324 (35.0%)		

Note: φ_c = Cramér's V

Chi-square tests of independence indicated significant differences in drinking frequency by gender, ethnicity, education level, marital status, and living standards (p < .001) but not age (see Table 3). Minimal/non-drinker status was most common among women, those of Māori ethnicity, those without tertiary education, those living in hardship, and those of 'other' marital

status. In contrast, rates of minimal/non-drinker status were lowest among those who were male, NZ European, educated at tertiary level, those with good living standards, and those who were of married, civil union, or de facto marital status. Light/moderate drinking was most common among participants who were male, NZ European, educated at tertiary level, with comfortable standards of living, and of married, civil union, or de facto marital status. Conversely, light/moderate drinking was less common among those who were female, Māori, those without tertiary education, those living in hardship and those of other marital status. Rates of heavy drinking were highest among those who were male, NZ European, educated at tertiary level, with good living standards, and of married, civil union, or de facto marital status. Heavy drinking rates were lowest among those who were female, Māori, those without tertiary education, those living in hardship, and of other marital status.

Rates of AI-Medication Use

Across the sample, 879 participants (55.3%) used at least one AI-medication regularly, with the remaining 724 participants (44.7%) identified as non-users. The sample rates of *mild*, *moderate*, and *major/contraindicated* AI-medication use were 14.6%, 17.5%, and 23.2%, respectively.

Alcohol Use Among AI-medication Users

Users vs. Non-users (Binary AI-Medication Use)

The sample rate of participants identified as both drinkers and AI-medication users was 34.0% (551 participants). A chi-square test of independence showed the rate of alcohol use was significantly lower among AI-medication users (61.4%) than non-users of AI-medications (72.4%), X^2 (1, N = 1,621) = 21.50, p <.001, *phi* = 0.11. When this relationship was explored across drinking frequency categories (see Table 4), standardized residuals showed rates of minimal/non-drinker status were significantly lower than expected among non-users of AI-medications (p <.01) and significantly higher than expected among AI-medication users (p

<.05), X^2 (2, N = 1,621) = 21.82, p <.001, *Cramer's V* = .12. However, no significant deviations from expected frequencies were observed across light/moderate and heavy drinking categories.

Table 4: Observed Drinking Frequency within binary AI-medication use groups

Binary AI-Medication Use Categories	Drinking Frequency (AUDIT-C)		
	Minimal/non-drinker	Light/moderate-drinker	Heavy-drinker
No AI-Medication Use	27.6% (-2.8)**	41.9% (1.3)	30.5% (1.6)
AI-Medication Use	38.6% (2.5)*	36.6% (-1.1)	24.9% (-1.4)

Note: Values in parentheses represent standardized residuals; * p <.05; ** p <.01

Mild, Moderate, and Major/Contraindicated AI-Medication Users

The sample rates of participants identified as both drinkers (*light/moderate* or *heavy*) and users of *mild, moderate,* and *major/contraindicated* AI-medications were 10.5%, 11.3%, and 12.2% respectively. The respective sample rates of participants identified as both light/moderate drinkers and users of mild, moderate, or major/contraindicated AI-medications were 5.6%, 6.9%, and 7.8%. The sample rates of participants identified as both heavy-drinkers and users of mild, moderate, major/contraindicated AI-medications were 4.9%, 4.4%, and 4.4% respectively.

A chi-square test of independence showed significant differences in alcohol use across AI-medication user categories (see Table 5), X^2 (3, N = 1,621) = 47.48, p <.001, *Cramer's V* = 0.17. Standardized residuals showed rates of non-drinker status were significantly lower than expected among those not using AI-medications and significantly higher than expected among major/contraindicated AI-medication users (p < .01), while rates of drinker status were significantly higher than expected among those not using AI-medications (p <.05) and significantly lower than expected among those using major/contraindicated AI-medications. When this relationship was further explored across drinking frequency categories (X^2 (6, N = 1,621) = 52.21, p <.001, *Cramer's V* = 0.13), the rate of heavy drinking was significantly lower than expected among major/contraindicated AI-medication users only (p <.01), and rates of

light/moderate drinking did not deviate significantly from expected frequencies across AI-medication use categories (see Table 6).

Table 5: AI-Medication Severety across Binary Drinking: Chi-Squared Test

AI-Medication Use	Non-drinkers	Drinkers
Non-use	27.6% (-2.8)**	72.4% (2.0)*
Mild	28.3% (-1.4)	71.7% (1.0)
Moderate	35.3% (.5)	64.7% (-.3)
Major/Contraindicated	47.5% (4.6)**	52.5% (-3.3)**

Note: values in parenthesis represent standardized residuals; * <.05; **<.01
Note: X^2 (3, N = 1,621) = 47.48, p <.001, *phi* = .17.

Table 6: AI-Medication Severity Across Drinking Frequency: Chi-Squared Test

AI-Medication User Severity Categories	Drinking Frequency (AUDIT-C)		
	Minimal/non-drinker	Light/moderate-drinker	Heavy-drinker
N/A	27.6% (-2.8)**	41.9% (1.3)	30.5% (1.6)
Mild	28.3% (-1.4)	38.0% (-.2)	33.8% (1.9)
Moderate	35.3% (.5)	39.6% (.2)	25.1% (-.7)
Major/Contraindicated	47.5% (4.6)**	33.4% (-1.7)	19.1% (-3.1)**

Notes: values in parenthesis represent standardized residuals; * <.05; **<.01
Note: X^2 (6, N = 1,621) = 52.21, p <.001, *phi* = .179.

AI-Medication use, Depression, and Alcohol Use

A hierarchical binary logistic regression model was used to explore the interaction effects of AI-medication use (moderate or major/contraindicated AI-medication use vs no use or mild-AI-medication use) and depression (CES-D-10 score of ≤10) on the likelihood of alcohol use (drinkers vs. non-drinkers) after controlling for living standards (ELSI-sf scores) and the main effects of depression and AI-medication use. The ELSI-sf scale was entered at step 1, AI-medication use and depression were entered at step 2, and the interaction term (AI-

medication*depression) entered at step 3. As shown in Table 7, step 1 of the model was statistically significant (X2 (1, N = 1,488) = 82.12, p = <.001), indicating ELSI-sf scores accurately distinguished drinkers from non-drinkers. ELSI-sf scores explained between 5.4% (Cox and Snell R square) and 7.5% (Nagelkerke R square) of the variance in alcohol use. The model was significantly improved with the addition of step 2 (block: X2 (2, N = 1,488) = 15.83, p <.001; full model: X2 (3, N = 1,488) = 97.95, p <.001), with the overall model at step 2 explaining between 6.4% (Cox and Snell R square) and 8.8% (Nagelkerke R square) of the variance in alcohol use (the additional variables therefore explained between 1% and 1.3% of the variance in alcohol use). The model was not significantly improved with the addition of step 3 (block X^2 (1, N = 1,488) = 0.22, p =.638; full model X^2 (4, N = 1,488) = 98.12, p <.001). The final model explained between 6.4% (Cox and Snell R Square) and 8.9% (Nagelkerke R Square) of the variance in alcohol use, and had adequate fit as indicated by non-significant HLT (X^2 (7, N = 1,488) = 4.18, p = .758). The only significant predictors of alcohol use in the final model were living standards and AI-medication use.

Table 7: Hierarchical Binary Logistic Regression Model

Predictor and Step	B	S.E	Wald	Df	P	OR	95 % CI for OR Lower	Upper	X^2 Block (N = 1,488)
Step 1									
Living Standards	.333	.038	78.347	1	.000	1.395	1.296	1.502	X2 (1) = 82.12, p <.001
Step 2									
Living Standards	.301	.041	52.826	1	.000	1.351	1.246	1.466	X2 (2) = 15.83, p <.001
AI-Medication	-.463	.118	15.301	1	.000	.629	.499	.794	
Depression	-.028	.154	.032	1	.858	.973	.719	1.316	
Step 3									
Living Standards	.301	.041	52.921	1	.000	1.352	1.246	1.466	X2 (1) = 0.22, p =.638
AI-Medication	-.434	.133	10.671	1	.001	.648	.499	.840	
Depression	.054	.233	.054	1	.817	1.056	.668	1.668	
AI-Medication * Depression	-.137	.292	.220	1	.639	.872	.492	1.545	

Discussion

The aims of the present study were to explore the potential relationships between AI-medication use, alcohol use, and depression in a sample of New Zealand older adults. Most participants (approximately 60%) reported using alcohol at least two days monthly, and just over half of the sample regularly used at least one AI-medication. Approximately one-in-three participants in this study sample were at risk of AMI exposure, and one-in-four were at risk of suffering an adverse AMI of clinical significance.

The hypothesis that alcohol use would be less common among those using AI-medications was supported, as participants identified as AI-medication users were significantly less likely than non-users of AI-medications to report using alcohol two or more times monthly. This finding is consistent with previous studies exploring rates of concurrent alcohol/AI-medication use among older adults in the United States and Ireland (Cousins et al., 2014; Breslow et al., 2015; Pringle et al., 2005; Qato et al., 2015).

The hypothesis that AI-medications with higher levels of alcohol-interactivity would be associated with less alcohol use was generally supported by the results. Rates of self-reported alcohol use (at least twice monthly) were significantly lower among those using AI-medications identified as having the highest level of alcohol-interactivity (i.e. major/contraindicated AI-medications). When this association was explored across drinking frequency groups, the data showed that those using medications identified as highly alcohol were significantly less likely to report heavy drinking (four days weekly), but rates of light-moderate drinking (two days monthly to three days weekly) did not differ significantly across AI-medication severity groups.

Given that the AI-medication severity categories utilized in this study were identified using the same drug-interaction identification system used by New Zealand prescribers and pharmacists, participants most likely to have been advised about AMI risks are those identified

as major/contraindicated AI-medication users. As such, the observed negative association between alcohol use and major/contraindicated AI-medication use is consistent with previous studies indicating AMI related knowledge leads to reduced alcohol use (Gavens et al., 2016; Zanjani et al., 2013)). This finding also supported the principles of perceived severity and perceived susceptibility, described in the HBM (Janz & Becker, 1984; Rosenstock, 1974).

The hypothesis that depression would moderate the negative association between AI-medication use and alcohol use was not supported by the results. Among variables entered into the hierarchical regression model, only living standards and AI-medication use significantly accounted for variance in alcohol use within the sample. While these results do not support findings of previous studies implicating self-medication as a motivator for alcohol use among AI-medication users (Gavens et al., 2016 Haighton, et al., 2018), it should be noted that drinking motives were not directly measured in the present study. Although drinking to alleviate distress is common among people with depression (Bolton et al., 2009; Boschloo et al., 2012 Brown & Stewart, 2008), it cannot be assumed that all people with depression self-medicate with alcohol, or that self-medication motivated alcohol use occurs exclusively in the context of depression. As such, the negative findings should not be interpreted as evidence against the potential role of self-medication in concurrent alcohol/AI-medication use.

The present study had several methodological limitations. Due to the oversampling of Māori participants in the HWR recruitment process, there was an overrepresentation of Māori participants and an underrepresentation of NZE participants within the sample relative to the New Zealand older adult population. Given that Māori participants in this study reported using significantly less alcohol than NZE participants, the results likely underestimate actual population rates of alcohol use and risk of AMI exposure among older adults living in New Zealand. In addition, as stated previously, drinking motives were not directly measured in the present study. Future survey research exploring factors motivating alcohol use among AI-

medication users could address this issue by utilizing measures that directly assess participants reasons for drinking, such as the older adult version of The Drinking Motives Questionnaire (Gilson et al., 2013).

Overall, the results of this study indicate that many New Zealand older adults are at risk of AMI related harm. Providing older adults with information about the risks of combined alcohol/AI-medication use may help mitigate their risk of AMI exposure. Such interventions should emphasize information about heightened susceptibility to AMIs during older adulthood, and the severity of AMI related harm.

Research Contribution to Clinical Training

Given that my internship was based in an Alcohol and Other Drug (AOD) service, the research questions explored in this study were highly relevant to my clinical practice. Reviewing relevant literature regarding the consequences of alcohol-medication interactions provided me with knowledge about alcohol and drug metabolism processes, drug interaction processes, and age-related changes in alcohol sensitivity. I was therefore acutely aware of the physical health risks posed to many clients within the AOD service setting. For example, when discussing older clients during MDT meetings I would ensure their risk of alcohol related harm was considered in light of other factors such as age, medication use, mobility, and health conditions. This knowledge base therefore furthered my ability to advocate for client's safety, and to think more broadly about risk by considering longer-term physical health factors.

The theoretical framework of this study was also highly relevant to my practice. Motivational factors underlying health related behaviour are always an important consideration when working with people with substance use problems. Having reflected on the theoretical constructs explored in this study, I began my internship with awareness that many people may underestimate the potential harm their use of substance poses. I also understood that providing information about these risks, enhancing self-efficacy, and addressing perceived barriers could

facilitate positive changes. Additionally, this project required me consider the impact mental health problems might have on clients' motivation to use substances. This knowledge base was highly beneficial during my internship, and my understanding of these concepts deepened throughout the year as I applied them in a clinical setting. For example, highlighting problem severity and increasing self-efficacy in order to enhance motivation is an important first step toward positive change when treating substance use problems.