Benzodiazepine-related aggression: Consideration of intrapersonal factors

by

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Abstract

**Background:** Benzodiazepines are commonly prescribed for the reduction or management of anxiety and agitation. However, it is becoming increasingly apparent that for some individuals, benzodiazepine use is associated with increased agitation, and at times, aggressive or violent behaviour. The nature of aggressive behaviour, and the potential medico-legal outcomes associated with such behaviour, means that understanding of this response is warranted. Despite a number of studies being conducted on the association between benzodiazepine use and aggression, the response remains poorly understood. This thesis aims to enhance our understanding of this response, specifically by critically reviewing the currently available literature base and by conducting two original cross-sectional studies.

**Methods:** The literature exploring benzodiazepine-related aggression was explored through a systematic review which was conducted in line with PRISMA guidelines. A cross-sectional study of 204 community benzodiazepine users, aged 18-51, applied the Reinforcement Sensitivity Theory to test the predictive nature of motivational tendencies in understanding aggression. Multiple hierarchical regression analyses were conducted on this data. A second, smaller cross-sectional study of 82 community-based violent and non-violent offenders, aged 21-56, examined group differences in relation to benzodiazepine use patterns and intrapersonal characteristics. This data were analysed using independent samples t-tests and non-parametric tests (i.e., when assumptions were violated).

**Results:** The systematic review identified that although a number of studies have been conducted in this area, varying methodologies and the over-arching low quality of studies which have been conducted prompts more questions than clear conclusions. The research does however suggest that benzodiazepine-related
aggressive responses may be linked most closely with alprazolam and diazepam use. The community-based cross-sectional study suggested that benzodiazepine-related aggression was more likely to be experienced by those who used alprazolam and exhibited persistent approach tendencies, or motivational drive. The offender cross-sectional study demonstrated that violent offenders were significantly more likely to present with benzodiazepine dependence, alprazolam use at higher doses, depression and personality diagnoses, sensation seeking, and a history of violent behaviour than non-violent offenders.

**Conclusions:** Taken together, the systematic review and two studies showed alprazolam use to pose a greater risk of subsequent aggression than diazepam use, and demonstrated that intrapersonal factors can further our understanding of benzodiazepine-related aggression. Specifically, the two empirical studies highlighted the role of impulse control and maladaptive coping strategies to manage negative affect in this response. Key implications include recommended changes to benzodiazepine prescribing practices and policy, especially in forensic contexts; the impact of such research on future medico-legal decision making; how these outcomes can inform selection of appropriate treatment targets within addiction and forensic mental health sectors; and future development of the literature base.
Chapter One: Overview of Benzodiazepine Misuse

1.1 Introduction

Recent estimates suggest that between 1-20% of benzodiazepine users experience some form of anger or aggressive response following consumption (Lader, 2011), rather than the expected sedating and calming effects. Concern about this response not only arises because it is paradoxical to the desired indications of benzodiazepines, but because it has the potential for significant health, personal and legal costs. Unfortunately, however, minimal research has explored the underlying mechanisms for why this response occurs. Instead, the majority of related literature merely assess whether or not an association exists between benzodiazepine use and aggressive behaviour. It is argued throughout this thesis that without an understanding of how benzodiazepine-related aggression occurs, or the factors associated with this response, little change can be affected to reduce the likelihood of related harms, or to improve the safety of benzodiazepine consumption.

Benzodiazepines are frequently being noted by users as influencing their criminal and/or violent behaviour. For example, more than a quarter of Australian benzodiazepine-using police detainees (27.1%) attribute their current offence to benzodiazepine use, most commonly due to the psychopharmacological effect (74%; Payne & Gaffney, 2012); benzodiazepine use has been frequently blamed for unspecified crime (14%), unprovoked aggressive behaviour (20%) and fights (13%) by injecting drug users (Smith, Miller, O’Keefe, & Fry, 2007); and incarcerated young male violent offenders most frequently blame diazepam (in combination with alcohol) as a facilitator of violent crime (Forsyth, Khan & McKinlay, 2011). Although these data rest on self-reported (and potentially biased) attributions, they provide an insight into the potentially dangerous effects that benzodiazepines may
have in influencing aggressive behaviour, despite prior findings that benzodiazepines are mostly associated with acquisitive or property crime (e.g., Bradford & Payne, 2012; Darke & Ross, 1994; Darke et al., 2010; Horyniak, Reddel, Quinn, & Dietze, 2012; Payne & Gaffney, 2012). Of note, crimes against the person are the second most commonly reported criminal behaviour in Australia, behind public order offences (Australian Bureau of Statistics [ABS], 2013), and assault offences alone are estimated to cost the nation $3.03b annually (Smith, Jorna, Sweeney, & Fuller, 2014). The potential legal and financial ramifications of this response (in addition to the medical and social costs) highlight the need to further understand benzodiazepine-related aggression.

Further knowledge and understanding about benzodiazepine-related aggression is important in a number of ways. First, as a problematic substance-related outcome, there will be implications for substance use treatment and relapse prevention strategies. Second, risks of violent behaviour could be identified and become violent offender rehabilitation treatment targets. Third, medical prescription and regulation of benzodiazepines in the greater community, addiction medicine, and in justice health (where a higher rate of violent tendencies may naturally be observed) are likely to be impacted. Finally, it is likely that such knowledge will inform future medico-legal decisions regarding an offender’s culpability, and their punishment and rehabilitation needs.

1.1.1 Thesis overview

The current thesis aims to enhance understanding of the relationship between benzodiazepine use and subsequent interpersonal aggression and violence. As will be argued in the following chapters, this seemingly paradoxical response is of particular concern given the frequency of benzodiazepine prescription coupled with the
increasing misuse of benzodiazepines across healthy, clinical, and forensic populations. Within this overarching aim, the following research has three specific directives:

1. To systematically review the benzodiazepine-aggression literature base to specifically identify benzodiazepine type and dose, and individual characteristics associated with benzodiazepine-related aggression.

2. To enhance the theoretical rigour of benzodiazepine-aggression literature.

3. To identify characteristics associated with benzodiazepine-related violence in a benzodiazepine-using, community-based criminal justice sample.

In order to achieve these aims, the thesis is structured as follows. Chapter 1 provides an introduction to benzodiazepine use and misuse, and argues the importance of research exploring problematic, or contra-indicative, outcomes associated with benzodiazepine use. Chapter 2 follows with an introduction to interpersonal aggression, and its links with benzodiazepine use, and argues that intrapersonal factors are an important consideration when investigating aggressive behaviour. This chapter also introduces a well-validated theory of motivational tendencies, the Reinforcement Sensitivity Theory, which is used to enhance the theoretical rigour of the literature base (i.e., Aim 2). An argument is presented regarding how this theory specifically adds to our understanding of benzodiazepine-related aggression. Chapter 3 presents a systematic review of the currently available literature exploring the association between benzodiazepine use and subsequent aggression or violence, providing a critical overview of what is currently understood about this response, and identifying key gaps in the literature base, some of which are then targeted by two original studies (i.e., Aim 1). Chapter 4 presents an original, cross-sectional study of community members which assesses the relative importance
of motivational tendencies (as defined by the Reinforcement Sensitivity Theory), compared to benzodiazepine-related factors (i.e., type, dose), in predicting aggression. Chapter 5 presents a second, smaller cross-sectional study which examines the differences between violent and non-violent offenders’ benzodiazepine use patterns and intrapersonal characteristics (i.e., Aim 3). Chapter 6 combines the findings of Chapters 3-5 with a discussion of how the thesis furthers our understanding of benzodiazepine-related aggression. Implications relating to benzodiazepine prescribing practices and policy, especially in forensic contexts, medico-legal decision making, and selection of appropriate treatment targets within addiction and forensic mental health sectors are discussed. Opportunities for further developing the literature base regarding benzodiazepine-related aggression are also considered.

In order to understand the nature and depth of these implications, however, it is important to first understand the nature of benzodiazepine (mis)use. The following sections provide an overview of benzodiazepine use and misuse, including a discussion of why benzodiazepines are so frequently misused, common side effects, and the occurrence of behavioural disinhibition following benzodiazepines, which includes aggressive behaviour. It is then argued that although informative and necessary, neurological understandings of benzodiazepine-related aggression are currently insufficient and impractical platforms on which to base intervention, policy or management strategies, warranting closer investigation of other contributory and explanatory factors in this response.

1.2 Medical Indications for Benzodiazepine Prescriptions

Benzodiazepines are commonly prescribed to treat symptoms of stress, anxiety, and sleep disorders (Bisaga, 2008), as well as to assist in the management of
symptoms associated with alcohol (Ashton, 2002) and heroin dependence (Fry, Smith, Bruno, O’Keefe, & Miller, 2007). Benzodiazepines are also used for anaesthesia, epilepsy (Drugs and Crime Prevention Committee [DCPC], 2007), and acute psychosis with hyperexcitability and aggressiveness (Ashton, 2002). Despite their wide range of indications, which informs the doses at which they are prescribed, benzodiazepines are generally used for their anxiolytic and sedative properties. Benzodiazepines can be short- (e.g., oxazepam, temazepam, alprazolam) or long-acting (e.g., diazepam), and bind primarily to the GABA_A receptor (Paton, 2002), potentiating the inhibitory action of gamma-aminobutyric acid (GABA; Lader, 2011). This suppresses the central nervous system (CNS), slowing down the messages received and sent from the brain (DCPC, 2007).

Benzodiazepines are widely prescribed. For example, during 2005, benzodiazepines were among the most commonly prescribed pharmaceuticals in Victoria (DCPC, 2007) and across Australia (Nicholas, 2010). Between 2002 and 2007 there was a national increase (from 23.76 to 24.11 defined daily dose/1000 population/day) in the prescription of anxiolytics, sedatives, and hypnotics (Hollingworth & Siskind, 2010). Although it appears that the total amount of benzodiazepines dispensed has since decreased, the quantity of benzodiazepines prescribed per script has increased (Islam, Conigrave, Day, Nguyen, & Haber, 2014). Notably, rates of diazepam prescriptions have remained stable, and alprazolam prescriptions have increased eight-fold between 1992 and 2011 (Islam et al., 2014). A separate examination of prescription data indicated that in 2011, diazepam was the most commonly dispensed anxiolytic, and temazepam was the most commonly dispensed sedative (Stephenson, Karanges, & McGregor, 2013). Although less readily available, international data also indicate a high rate of benzodiazepine
prescription and dispensing. For example, Norwegian rates of benzodiazepine dispensing are increasing (Bjørner, Tvete, Aursnes, & Skomedal, 2013), benzodiazepine prescriptions are written at a rate of 37.6 per 100 persons across America (Paulozzi, Mack, & Hockenberry, 2014), and dispensing of diazepam and lorazepam significantly increased in England between 2011 and 2012 (The Health and Social Care Information Centre [HSCIC], 2013).

Poor adherence to prescribing guidelines and protocols partially explains the high rate of benzodiazepine prescriptions. For example, an examination of Tasmanian nursing home residents’ medication \((n = 2345)\) identified that benzodiazepines were among the most frequently inappropriately prescribed medications (Stafford, Alswayan, & Tenni, 2011). Prescribing guidelines suggest that benzodiazepines should only be used for short-term treatment, and that careful dose titration is necessary when coming off benzodiazepines, due to their dependence potential (e.g., Jones, Nielsen, Bruno, Frei, & Lubman, 2011; Nicholas, Lee, & Roche, 2011). Alprazolam is widely considered to have the most abuse and harm potential of the benzodiazepines, due to its short-acting effects, and has therefore been recently up-scheduled in Australia to a controlled substance (Schedule 8). The only other benzodiazepine to fall under Schedule 8 restrictions is flunitrazepam. Australia’s rescheduling of alprazolam is despite unchanged classification of alprazolam as a drug of moderate risk of harm or dependence (i.e., Class C) in other countries (United Kingdom: Misuse of Drugs Act 1971 UK; New Zealand: Misuse of Drugs Act 1975 NZ). Such rescheduling attempts to reduce the accessibility of alprazolam, and therein reduce the associated harmful sequelae. However, as discussed by Islam and colleagues (2014), such rescheduling often leads to compensatory increased (mis)use of a substitute benzodiazepine, and a broader
policy regarding the prescribing and regulation of benzodiazepines as a psychotropic
drug class is required.

1.3 Prevalence of Non-Medical Use of Benzodiazepines

The following sections outline the widespread misuse of benzodiazepines in
Australia and internationally. Importantly, the Australian rates below were recorded
prior to the recent rescheduling of alprazolam, and therefore it is as yet unclear how
benzodiazepine use patterns have been impacted.

1.3.1 Defining non-medical use.

The terms ‘misuse’ and ‘non-medically prescribed use’ are used
interchangeably within this thesis to refer to benzodiazepine use which is not within
the explicit boundaries of a prescription from an appropriately qualified prescriber
(except where otherwise stated). This may include using a higher dose than detailed
on the prescription, extending use past the period (or the reason) for which
benzodiazepines were indicated, or using non-prescribed (i.e., black market)
benzodiazepines.

1.3.2 Australian data.

1.3.2.1 General community. The Australian Institute of Health and Welfare’s
(AIHW) National Drug Strategy Household Survey (NDSHS) is conducted on a
regular basis to explore the nature of substance use by Australian individuals aged 14
years and over. They define non-medical use of a substance as use to enhance or
induce a drug experience, enhance performance, or for cosmetic reasons (AIHW,
2011). Unfortunately, this survey does not explicitly report on benzodiazepine use,
but instead describes pharmaceutical medication misuse, which includes pain killers,
tranquillisers, steroids, methadone and buprenorphine, and other medical opiates.
Therefore, both the specificity and the scope of the findings is greatly reduced, and the following rates are commented on with caution.

The rate of pharmaceutical misuse in the general community has been steadily and significantly increasing over the past decade. In 2010, 7.4% of the general Australian population reported ever having misused pharmaceutical medications, with 4.2% reporting such use in the 12 months prior to the survey (AIHW, 2011). By 2013, 4.7% reported misusing pharmaceuticals in the past 12 months, representing a 1% increase since 2007 (AIHW, 2014). Use of tranquilisers specifically displayed a non-significant increasing trend, though they were the second most frequently misused pharmaceutical drug following pain-killers/analgesics, with 1.6% of people aged 14 years or older reporting their misuse (AIHW, 2014). Inspection of age and gender indicates that tranquilisers were predominantly misused by females aged 20-29 years, and males aged 30-39 years (AIHW, 2014). Compared to the 2010 data (AIHW, 2011), a new cohort of older males appear to be reporting tranquiliser misuse, potentially warranting targeted attention in community prevention strategies. Recent estimates however, indicate that benzodiazepine misuse occurs at a considerably greater rate in both clinical and forensic populations.

1.3.2.2 Clinical samples. National figures demonstrate high use of benzodiazepines in illicit drug-using populations, as 83% of Australian people who inject drugs (PWID) have used benzodiazepines (Stafford & Burns, 2012). Within Victoria alone, the majority of PWID interviewed between 2008 and 2010 for the Illicit Drug Reporting System (IDRS) reported recent benzodiazepine use (74%), with 6% injecting benzodiazepines (Horyniak et al., 2012). Moreover, interviews with drug treatment clients have demonstrated that only 14% are using
benzodiazepines as prescribed, and that whilst only 7% present solely for benzodiazepine-related treatment, an additional 37% report benzodiazepine use to also cause concern (Nielsen et al., 2008). More recent national figures suggest that benzodiazepines are commonly used in the context of other substance use, as 85% of those who seek treatment primarily for benzodiazepine use report additional drugs of concern (mostly alcohol and cannabis; AIHW, 2013a). It is noted, however, that the number of people presenting for treatment for benzodiazepine misuse has reduced, with only 2% of national drug and alcohol treatment episodes targeting benzodiazepines as the principal drug of concern, and a further 7% of episodes targeting benzodiazepines as an additional drug of concern (AIHW, 2013a). Historical data suggests that females were more likely to report difficulties with benzodiazepines (DCPC, 2007), however recent figures are suggesting males are now reporting slightly higher rates of benzodiazepine-related problems than females (AIHW, 2013a). Alprazolam and diazepam appear to be the favoured benzodiazepines in clinical drug-using populations (Nielsen et al., 2008; Stafford & Burns, 2012).

1.3.2.3 Forensic samples. The Drug Use Monitoring in Australia (DUMA) program, an initiative of the Australian Institute of Criminology, reviews the substance use and crime patterns of police detainees on a quarterly basis. Compared to 2007, when 15% of police detainees reported having used illegal (i.e., non-prescribed) benzodiazepines in the previous 12 months (Loxley, 2007), recent figures indicate that 25% of adult police detainees now report non-medical benzodiazepine use (Ng & Macgregor, 2012). This rate is also higher than that pertaining to tranquiliser or sleeping pills misuse reported by new prison entrants (16%; AIHW, 2013b). Importantly, benzodiazepines are the most commonly used type of
pharmaceutical among police detainees, often used in combination with other drugs (McGregor, Gately & Fleming, 2011; Ng & Macgregor, 2012). Specifically, alprazolam and diazepam are preferred (McGregor et al., 2011; Sweeney & Payne, 2012).

The recent inclusion of urinalysis into the DUMA program provides corroboration of self-reported substance use. Consistent with self-reported rates, nearly one in five (23%) detainees tested positive for benzodiazepines between 2009 and 2010 (Sweeney & Payne, 2012). During this period, benzodiazepines were the second most commonly detected drug (following cannabis), and were most commonly detected among females (36%), detainees aged 31-35 years old (32%), and property offenders (31%; Sweeney & Payne, 2012). Of note, 20% of violent detainees tested positive for benzodiazepines (Sweeney & Payne, 2012), highlighting the importance of elucidating the link between benzodiazepine use and violent behaviour.

1.3.3 International data.

Similar to Australia, benzodiazepines are among the most commonly misused pharmaceuticals in New Zealand (Sheridan, Jones, & Aspden, 2012), England (Home Office Statistics, 2012; HSCIC, 2011), America (Substance Abuse and Mental Health Services Administration [SAMHSA], 2011), and Thailand (Kerr et al., 2010; Puangkot, Laohasiriwong, Saenqsuwan, & Chiawiriyabunya, 2011). Furthermore, illicit benzodiazepines are being seized at increasing rates in European countries, and benzodiazepine trafficking and abuse across the Middle East is also rising (International Narcotics Control Board, 2014). Given such international use of benzodiazepines, enhanced understanding of benzodiazepine-related aggression is likely to have wide-reaching implications.
1.4 Motivations to Misuse Benzodiazepines

Despite their widespread misuse, few studies have assessed why people use benzodiazepines for non-medical reasons. There is some indication that benzodiazepines are used as relief from negative emotions and life experiences, predominantly by individuals with low levels of novelty seeking (Adams et al., 2003). However, studies of clinical and forensic populations suggest that benzodiazepine use may be more complex, as findings indicate that benzodiazepines are used for multiple reasons. Non-medical use of benzodiazepines has been primarily attributed to the reduction of anxiety and stress by American street-based illicit drug users, methadone maintenance patients, and residential drug treatment clients (Rigg & Ibañez, 2010), and Australian adult police detainees (n = 986; McGregor et al., 2011) and injecting drug users (n = 102; Best, Wilson, Reed, & Harney, 2012). Subsidiary reasons for non-medical use of benzodiazepines include pain relief, drug substitution, to get high (Rigg & Ibañez, 2010; Nielsen et al., 2013), and managing alcohol and drug withdrawal (Best et al., 2012; McGregor et al., 2011; Nielsen et al., 2008; Nielsen et al., 2013). At other times, benzodiazepines are used merely due to availability and curiosity (McGregor et al., 2011), and specifically to improve the effects of heroin (Best et al., 2012). As such, opioid users may be more likely to use benzodiazepines for recreational reasons (i.e., enhance their opioid intoxication; Jones, Mogali, & Comer, 2012), although one French study of opiate-dependent individuals (n = 92) suggested that benzodiazepines were most commonly used for a combination of self-therapeutic and hedonistic motivations over time (Fatséas, Lavie, Denis, & Auriacombe, 2009). This deviation may reflect cultural differences, or be an effect of self-report data where recall bias may have impacted the various outcomes. The literature, however, does paint a concerning picture of
benzodiazepines which are inappropriately prescribed and then used to excess for both self-medication and to enhance other substance use. As discussed by Bennett, Holloway, Brookman, Parry, and Gorden (2014), users may apply ‘techniques of neutralization’ to justify their misuse of prescription medication. Introduced as a method to explain away delinquent criminal behaviour (Sykes & Matza, 1957), techniques of neutralization enable the individual to dismiss any social or legal constraints on their behaviour (Bennett et al., 2014). Initially, these included denial of responsibility, denial of injury, denial of victim, condemnation of condemners, and appeals to higher loyalties (Sykes & Matza, 1957). Application of the concept to cannabis use has resulted in substance use specific ‘risk denial techniques’ (e.g., scapegoating, comparing risk, emphasising personal control; Peretti-Watel, 2003; Sandberg, 2012). Indeed, to justify prescription medication misuse, university students most commonly referenced biological need (i.e., desperate for medication), legitimacy (i.e., person had superior knowledge or experience of the drug), or denial of choice (i.e., GP unavailability, cost of prescription; Bennett et al., 2014). Unfortunately, however, although sedatives and tranquillisers were misused by this sample, the results are not medication type specific. Regarding benzodiazepines specifically, some Australian drug users perceive them to be an “entitlement” as they are legally available (Nielsen et al., 2008). This sentiment is likely to impact the effectiveness of public health promotion and awareness strategies regarding benzodiazepine-related aggression.

1.4.1 Benzodiazepine sources.

Not only are benzodiazepines inappropriately prescribed and misused, but so too are they acquired from a number of sources. Consequently, there is concern about a large hidden population of pharmaceutical misusers who may be unable to be
accessed through regular health care streams. Analysis of drug trends in Melbourne, Hobart, and Darwin demonstrate that benzodiazepines are often diverted through the black market, commonly through forged prescriptions or doctor shopping (Fry et al., 2007). Indeed, although reflecting a reduction since the 2011-2012 period, benzodiazepines were the most commonly detected pharmaceuticals on the Australian border during 2012-2013 (Australian Crime Commission [ACC], 2014). It appears, however, that substance users are using a combination of legitimate prescriptions and illegitimate methods (i.e., street dealers, theft, from friends, as a gift) to source benzodiazepines (Best et al., 2013; Havens, Walker, & Leukefeld, 2010; Nielsen et al., 2013). Poor adherence to prescribing protocols appears to be inadvertently supporting benzodiazepine diversion onto the black market. For example, Ibañez, Levi-Minzi, Rigg, and Mooss (2013) recently identified that diversion of benzodiazepines from healthcare providers is resulting in the provision of more benzodiazepine pills (on average) than street dealers. Their survey of various drug users ($n = 1207$) indicated that although patients were accessing healthcare providers at a lesser frequency than non-healthcare sources, they were receiving greater quantities of benzodiazepines per visit. In addition, healthcare providers were more likely to be accessed by higher income participants (Ibañez et al., 2013), again highlighting the likelihood of a hidden population of benzodiazepine users who are unlikely to be accessed through health care streams. Combined, the findings demonstrated that benzodiazepines are easily accessible, and such ease appears to be resulting in increasing incidence of benzodiazepine-related harms.

1.5 Benzodiazepine-related Harms

Benzodiazepines are being increasingly linked with medical emergencies and harm. Worryingly, between 2000 and 2009, benzodiazepine-related cases made up
the highest proportion of pharmaceutical drug-related ambulance attendances in Melbourne, and there was a significant increase in the proportion of benzodiazepine-related cases requiring transport to hospital (Lloyd & McElwee, 2011). These rates continue to rise across Victoria, with benzodiazepines becoming the second most common drug category overall (after alcohol) involved in attendances (Lloyd, Matthews, & Gao, 2014). Worse, coronial data from 2011 indicates that half (50.3%) of Victorian drug-related deaths involve benzodiazepines; a figure second only to opioid analgesics (51.4%; Coroners Court of Victoria, 2013). Benzodiazepines are similarly reported at high, and increasing, rates in hospitalisation and/or mortality data in America (SAMHSA, 2012), England and Wales (Office for National Statistics, 2014), and Scotland (Zador et al., 2007). International findings demonstrate benzodiazepine use is common in non-fatally injured emergency room patients (e.g., Rockett, Putnam, Jia, & Smith, 2006), especially those with violent injuries (e.g., Kurzthaler et al., 2005) and overdose (Hamad, Al-Ghadban, Carvounis, Soliman, & Coritsidis, 2000). Injection of benzodiazepines can also lead to a number of intravenous-related health complications (Breen, Degenhardt, Roxburgh, Bruno, & Jenkinson, 2004). In addition, benzodiazepines increase the risk of being involved in a traffic accident by 60-80%, with a 40% increase in responsibility (Dassanayake, Michie, Carter, & Jones, 2011). Indeed, benzodiazepines are the second most prevalent form of drug found in the blood of Victorian drivers injured in motor vehicle collisions, following cannabis (Ch’ng et al., 2007). Of note, benzodiazepine-related harm data appears to suggest that females may be more likely than males to require ambulance or medical attention following benzodiazepine use (Longo, Hunter, Lokan, White, & White, 2000; Lloyd & McElwee, 2011; Lloyd et al., 2014). This gender inequality reflects a population experiencing drug-related harm which is
not reflected in the illicit drug research. Consideration of specific benzodiazepines has suggested that alprazolam may be the most toxic benzodiazepine (Isbister, O’Regan, Sibbritt, & Whyte, 2004). Indeed, since 2005, and the rise of alprazolam prescribing, alprazolam has been increasingly associated with heroin-related deaths in Victoria (Rintoul, Dobbin, Nielsen, Degenhardt, & Drummer, 2010). However, recent coronial data from Australia and England indicate diazepam to be the most commonly identified benzodiazepine in drug-related deaths (Coroners Court of Victoria, 2013; Office for National Statistics, 2014). Through reviewing such national and international data on benzodiazepine-related harms, a number of improvements to benzodiazepine prescribing protocols have been suggested.

Where benzodiazepines are prescribed, Dobbin (2014) suggests that benzodiazepine-related harms can be reduced via thorough assessments of patient needs and drug risk, as well as a comprehensive management plan involving pharmaceutical medication not subject to abuse and non-medicinal approaches. Lader (2014) further argues that a combined pharmaceutical and psychological strategy is most appropriate, and that benzodiazepine prescription should only follow the exhaustion of alternative options. Such recommendations are made not only in response to the concerning harms identified above, but also the more common side effects associated with benzodiazepine use.

1.5.1 Medical effects of benzodiazepine use.

Benzodiazepines can produce multiple short- and long-term side effects. Other than the intended anxiolytic and sedative effects, short term effects can include drowsiness, vertigo, motor incoordination, mild impairments in memory and concentration, and emotional depression (Longo & Johnson, 2000). Aggravation or production of depressive symptoms may be due to serotonin and norepinephrine
inhibition, whilst blunted pleasure and pain may be due to the inhibition of the emotional centers in the brain (Ashton, 2002). At very high doses the depressing effects of benzodiazepines can induce unconsciousness, coma, and even death when used in combination with other drugs (DCPC, 2007). Furthermore, benzodiazepines can induce neurological changes leading to tolerance, withdrawal, and dependence (DCPC, 2007). Withdrawal symptoms can include anxiety, insomnia, autonomic hyperactivity, and seizures (Longo & Johnson, 2000).

Continued use of benzodiazepines can result in effects such as avolition, memory loss, personality change, anxiety, irritability, sleep problems, somatic problems, and increased aggressiveness (DCPC, 2007). Moreover, benzodiazepine-induced impaired concentration and attention can negatively affect memory, especially episodic memory, which may influence uncharacteristic behaviours (Ashton, 2002). As such, benzodiazepine use has been frequently associated with increased paradoxical behaviour.

1.5.2 Paradoxical effects of benzodiazepines.

Benzodiazepines have been associated with paradoxical effects, such as excitement, irritability, aggression, hostility, and impulsivity (Longo & Johnson, 2000). Such disinhibition, or the loss of restraint over behaviour, is often socially inappropriate, unpredictable, and uncharacteristic of the individual (Bond, 1998). Whilst only in a minority of cases (Paton, 2002), disinhibitory reactions (e.g., aggression, hyperactivity, inappropriate sexual behaviour) have been observed during benzodiazepine use and withdrawal (Bond, 1998), and may lead to involvement with the criminal justice system (Redman, 1994). This so called ‘Rambo effect’ can occur at both therapeutic and higher doses (DCPC, 2007), and has been suggested to be more common following intravenous administration (Ashton, 2002).
Two main physiological mechanisms have been hypothesised to explain such disinhibition. In some cases, benzodiazepines can stimulate the CNS, leading to increased talkativeness, mania, anxiety, restlessness, sleep disturbances, acute rage, and extreme aggression (DCPC, 2007). This can also include nightmares, hallucinations, exacerbated seizures, and hyperactive behaviour (Ashton, 2002). Individuals report feeling invisible and invincible, and are sometimes unaware of committing a crime (Fry et al., 2007). Conversely, the Rambo effect may result from CNS depression which reduces inhibitions, leading to impaired judgement (DCPC, 2007) and the suppression of external social cues which would normally guide behaviour (Longo & Johnson, 2000). By decreasing the restraining influence of the cortex, such depression can provoke increased excitement, psychosis, anxiety, hostility, rage, and alcohol use (Paton, 2002). It is unclear what influences these two seemingly opposite effects.

Additional neurological theories specifically attempting to account for aggressive behaviour post-benzodiazepine consumption include discussion of genetic factors, GABA-related inhibition of neurotransmission, and disruption of the endogenous anxiety/threat-detection system (for reviews, see Essman, 1978; Hoaken & Stewart, 2003; Paton, 2002; van der Bijl & Roelofse, 1991). The majority of related research has been conducted on animals, and therefore has limited generalizability to humans. These studies have noted, however, that certain subunits on the GABA<sub>A</sub> receptors (γ, α) may be implicated in aggression mediation (e.g., Lee & Gammie, 2010; Miczek, Fish, & DeBold, 2003), with one study suggesting low doses of the receptor agonists (i.e., midazolam, triazolam) can significantly increase aggression duration and frequency (i.e., biting; Gourley, DeBold, Yin, Cook, & Mizek, 2005). Combining benzodiazepines with alcohol has also been demonstrated
to enhance aggressive responding in rodents (de Almeida, Saft, Rosa, & Miczek, 2010; Miczek, Weerts, & DeBold, 1993), and some evidence suggests a history of (Ferrari, Parmigiani, Rodgers, & Palanza, 1997), or predisposition towards (Weerts, Miller, Hood, & Miczek, 2010), aggressive behaviour enhances benzodiazepine-related aggression. As informative as such findings are, however, the majority of such research provide little options in the way of realistic screening or intervention targets for benzodiazepine-related aggression in humans, or have yet to be replicated in human research (i.e., role of pre-existing aggressive tendencies). Dose seems equally unable to assist our understanding, as both high (Paton, 2002) and low doses (Hoaken & Stewart, 2003) of benzodiazepines have been implicated in subsequent aggressive responding. It is therefore important to extend beyond neurological reasoning to explore more easily measurable, and potentially changeable, factors, such as situational and intrapersonal elements which are associated with this response, and base such research on examination of human participants. It is precisely these factors that have been argued to be more important in understanding the benzodiazepine-aggression relationship (Hoaken & Stewart, 2003; Lion, Azcarate, & Koepke, 1975), but which have failed to attract much investigation.

1.6 Summary

Benzodiazepines are frequently prescribed and misused, often in an attempt to secure a physiological high and/or reduce negative affective experiences. However, benzodiazepines have increasingly become associated with medical and psychosocial harm on a global level, with ambulance and morbidity data reflecting a rise in benzodiazepine use in their patients. Of note, approximately one fifth of users experience increased aggressive behaviour following benzodiazepine use, and such incidents are as yet poorly understood. Animal data suggests that those who
experience an aggressive response may be physiologically vulnerable; however the applicability of such findings to human screening and prescribing policies is limited. This thesis aims to improve our understanding of benzodiazepine-related aggression by exploring the role of contributory factors (such as personality or intrapersonal characteristics), in an effort to provide risk indicators more amenable to rapid screening (for prescribers) and intervention. The following chapter begins by defining the concept of aggression in general in an attempt to provide a broader context, before presenting an argument that intrapersonal factors are a highly relevant and important concept to explore in order to more fully understand benzodiazepine-related aggression. A well-validated theory of personality and motivational tendencies which will be used to explore the role of such factors in benzodiazepine-related aggression is then introduced. The chapter concludes with a more in-depth discussion of the aims of the thesis and how three unique studies (a systematic review and two cross-sectional studies) were developed to attend to these aims.
Chapter Two: Aggression, Intrapersonal factors and Rationale for Thesis

2.1 Understanding Aggression

Like all behaviour, aggression cannot be explained through recourse to one explanatory factor. Instead, it is multiply-determined, influenced by a complex interplay of internal (i.e., beliefs, neurobiology, personality, intoxication) and external (i.e., environment, opportunity, frustration) factors. The general aggression model (GAM; Anderson & Bushman, 2002), for example, proposes that situational (e.g., aggression cues, drugs, frustration, incentives, pain) and person inputs (e.g., traits, beliefs, values, attitudes, goals) inform behavioural outcomes (i.e., an aggressive episode) through the internal states that they create. Such internal states may include cognitions such as hostile thoughts or aggressive scripts, feelings such as anger or hostility, and heightened physiological arousal (Anderson & Bushman, 2002). Factors which have been empirically linked with aggressive behaviour include certain neurotransmitters and brain structures (i.e., serotonin, GABA, frontal lobe, limbic system), mental health diagnoses and distress, sociological factors (i.e., peer pressure, social information processing), personality predispositions (i.e., impulsivity, hostility, antisociality, anger), and criminal history (for reviews, see Anderson & Bokor, 2012; Chereji, Pintea, & David, 2012; Schenk & Fremouw, 2012). Notably, associations between illicit drugs and violent crime have been well established in the literature (Friedman, 1998), with particular reference to alcohol (e.g., Lennings, Copeland, & Howard, 2003), methamphetamines (e.g., McKetin et al., 2014), and anabolic steroids (e.g., Klötz, Petersson, Isaacson, & Thiblin, 2007; Lundolm, Kall, Wallin, & Thiblin, 2010). Surprisingly, however, examinations of benzodiazepine-related aggression or violence have rarely included exploration of potential contributory factors such as those listed above (i.e., mental health,
sociological factors, intrapersonal differences). By improving our understanding of benzodiazepine-related aggression, we can hope to affect change in reducing the frequency of this response, reducing health care costs (financial and personal), and reducing forensic spending for judiciary, incarceration, and rehabilitation phases.

### 2.1.1 A note on definitions.

There is contention within the literature regarding the definitions of ‘aggression’ and ‘violence’. This includes various definitions of aggression as involving anger, verbal, psychological, indirect (or social), and physical aspects (e.g., Björkqvist, 1994; Buss & Perry, 1992); instrumental or reactive motives (Buss, 1961); and highly specific types of violence (i.e., intimate partner violence; e.g., Straus & Mickey, 2012; Grych & Swan, 2012). Violence has been described as a more severe type of aggression (DeWall, Anderson & Bushman, 2011), and is therefore more frequently used in forensic contexts than research arenas (which favour the term ‘aggression’), although the two terms have and can be used interchangeably (e.g., Anderson & Bokor, 2012).

The current thesis adopts the definition of ‘aggression’ proposed by Baron and Richardson (1994), which is commonly referenced in aggression and violence literature (e.g., Anderson & Bokor, 2012; Hoaken & Stewart, 2003). However, as physical aggression is the topic of interest, some modifications to the definition have been made, in order to exclude instances and discussion of verbal or psychological aggression, as it is considered that they reflect very different types of aggression, and likely include different psychological barriers and different consequences. For the purposes of this thesis, aggression is therefore defined as *physical* force directed towards a person motivated to avoid such force (i.e., psychological or verbal aggression/violence was excluded). The current thesis also uses ‘violence’ to refer to
more severe or officially documented acts of aggression (i.e., resulting in conviction). To not include ‘violence’ within our definition would exclude the forensic studies which explored ‘violent behaviour’ or ‘violent crime’, and to exclude studies exploring ‘aggression’ would exclude a wealth of data from clinical and healthy populations (including the experimental data), involving a somewhat lower severity of violent behaviour.

2.1.2 Importance of intrapersonal factors.

Personality traits and motivational tendencies provide indicators of a person’s characteristic manner of interacting with the world. They are pervasive and endure across time and situations, and can inform the likelihood of engagement in certain behaviours. Research in the addiction field has demonstrated the applicability of an individual’s personality traits to problematic substance use, related problems, and treatment (e.g., Staiger Kambouroglou, & Dawe, 2007). Similar findings have also been demonstrated in the aggression and violence literature (e.g., Hosie, Gilbert, Simpson, & Daffern, 2014; Jones, Miller, & Lynam, 2011; Miller, Lynam, & Leukefeld, 2003). Not surprisingly, such intrinsic person characteristics have been argued to be highly influential in the benzodiazepine-violence relationship (Hoaken & Stewart, 2002; Lion et al., 1975). Interestingly, however, little research has been conducted into these potential explanatory factors.

Investigation of the benzodiazepine-aggression relationship has tended to focus on establishing and replicating associative findings. As will be discussed in greater depth in Chapter 3, cross-sectional and laboratory studies have found positive findings between certain benzodiazepines, such as diazepam and alprazolam, and self-reported aggression or behavioural proxies of aggressive behaviour. However, only cursory investigation of contributory or explanatory factors has occurred.
Notably, only a handful of cross-sectional and experimental studies have assessed the potential role of intrapersonal characteristics, including psychiatric vulnerability or personality traits, when examining benzodiazepine-related aggression. For example, Dåderman and colleagues explored the case histories of Swedish male forensic populations (via file review and semi-structured interviews) to identify whether there was a link between flunitrazepam use, personality and violent offending. Although in one study they found no personality differences between flunitrazepam users and non-users (Dåderman & Edman, 2001), they suggested that certain personality traits (i.e., boredom susceptibility, verbal aggression, Dåderman & Lidberg, 1999; anxiety, low self-esteem, Dåderman, Fredriksson, Kristiansson, Nilsson, & Lidberg, 2002; psychopathy characteristics, Dåderman, Edman, Meurling, Levander, & Kristiansson, 2012) may influence an aggressive response to flunitrazepam. However, their conclusions relied on targeted examination of flunitrazepam-using violent offenders (Dåderman & Lidberg, 1999; Dåderman et al., 2002) or violent offenders without non-violent control groups (Dåderman & Edman, 2001; Dåderman et al., 2012), failed to statistically account for poly-substance use, have limited generality, and cannot suggest temporal causality between flunitrazepam use and violent offending. However, the use of more stringent, controlled designs has provided little further explanation of the role of intrapersonal factors in this response. To date, only two experimental studies have explicitly examined the role of personality in benzodiazepine-related aggression (Ben-Porath & Taylor, 2002; Wilkinson, 1985), though an additional early study did identify interesting personality-related results post-hoc (Cherek, Steinberg, Kelly, Robinson, & Spiga, 1990). Wilkinson (1985), using double-blind and placebo-controlled methods, and a competitive reaction time task, identified that diazepam-related aggression may be
mediated by trait anxiety. In her study, undergraduates who were less cautious of their environment (i.e., low trait-anxious) displayed the greatest enhancement in responding indicative of aggression following diazepam consumption, compared to high trait-anxious undergraduates. In a similarly designed study, Ben-Porath and Taylor (2002) suggested that diazepam-related aggression may be related to hostility, as undergraduates who exhibited higher scores on a standardised hostility measure displayed greater increases in aggression following diazepam use than those with lower hostility scores. This group difference, however, failed to reach significance. Cherek and colleagues (1990) also highlighted the role of hostility, as increased aggressive responding following diazepam use was only observed in participants with high hostility scores. However, the sample on which this conclusion is based was very small \((n = 9)\), making overall conclusions regarding the role of hostility in this response tentative at best. Unfortunately, additional laboratory studies which reported to measure personality characteristics failed to analyse or discuss whether individual differences affected aggressive responding (Bond, Curran, Bruce, O’Sullivan, & Shine, 1995; Bond & Lader, 1988; Bond & Silveira, 1993; Pietras et al., 2005).

Research into benzodiazepine-related aggression has rarely explored the role of contributory factors, such as intrapersonal characteristics. As noted above, the handful of studies which have included such analysis examined various characteristics, often with minimal (if any) theoretical reasoning as to the relevance or importance of the characteristic(s) selected. The current thesis aims to build on this research, by taking a theory-driven approach to understanding the personality and motivational factors associated with benzodiazepine-related aggression. Such an approach can provide treatment and risk management outcomes which are based
upon a strong theoretical basis, are testable, and can inform the development of further research. As will be demonstrated in Chapter 4, a large community-based study will use a well-validated theory of approach and avoidance motivation, the Reinforcement Sensitivity Theory (RST), to measure the role of motivational tendencies in benzodiazepine-related aggression. The main assumptions of this theory are presented below, with commentary on how this theory may be valuable in furthering our understanding of benzodiazepine-related aggression.

### 2.1.2.1 Gray’s (revised) Reinforcement Sensitivity Theory

The RST is a neuropsychological theory of emotion, motivation, learning processes, and personality (Corr, 2009). The theory has undergone substantial revisions since its original conceptualisation (Gray, 1982), and the current thesis applies the Gray and McNaughton (2003) revision (rRST). The theory postulates that individual sensitivities to punishment and reward lead to motivations to engage in approach or avoidance behaviour. An individual’s tendency to engage in approach or avoidance behaviour provides an indication of their underlying personality (i.e., trait impulsivity or anxiety, respectively; Corr, 2009). This theory was purposefully selected due to its strong validation across research of problematic substance use and related outcomes (e.g., Booth & Hasking, 2009; Dissabandara, Loxton, Dias, Daglish, & Stadlin, 2012; Loxton et al., 2008), its biological underpinnings which specifically account for the impact of benzodiazepines on the functioning of certain motivational tendencies (see discussion below; Gray & McNaughton, 2003), and its conceptually sound nature. In addition, the current application of the rRST not only enhances our understanding of benzodiazepine-related aggression and theoretical rigour of related research, but it also expands the rRST literature to include benzodiazepine use, providing precedence for future comparative studies. The theory
proposes three separate but interacting motivational systems which make up personality (Corr, 2004), and influence approach, avoidant, and cautious behaviour (Corr, 2008).

**Approach tendencies.** The behavioural approach system (BAS) mediates reactions to appetitive stimuli (Corr, 2004), and is thought to be primarily modulated by dopamine (Pickering & Corr, 2008). Approach motivation promotes anticipatory pleasure, and is associated with the personality traits of optimism, hope, reward orientation, and impulsivity (Corr & Perkins, 2006). However, it has been suggested that impulsivity does not explain the full range of processes involved in this system, such as restraint and planning (Corr, 2009), and that extraversion (Pickering & Corr, 2008) or reward learning (Berkman, Lieberman, & Gable, 2009) may mediate activation of the system instead. This contention is reflected in the two main measures of the BAS, where Torrubia, Ávila, Moltó, and Caseras (2001) conceptualise the system as primarily involving sensitivity to reward cues in their Sensitivity to Punishment Sensitivity to Reward Questionnaire (SPSRQ), whilst Carver and White’s (1994) BIS/BAS scales include three components which seem to involve the processes mentioned above – drive (i.e., goal pursuit, functional impulsivity), fun seeking (i.e., dysfunctional impulsivity, minimal thought to consequences), and reward responsiveness (i.e., positive energy and affect in response to reward cues; Tull, Gratz, Latzman, Kimbre, & Lejuez, 2010). Clinically, approach motivation has been associated with addictive behaviours, high-risk impulsive behaviours, and some aspects of mania (Corr & Perkins, 2006). It has been suggested that impulsivity, more than reward responsiveness, underlies the approach motivation and substance use relationship (Corr, 2008). Of note, and as will be discussed in Chapter 4, approach motivations have been consistently associated with
aggressive behaviour, most notably the BAS characteristic Drive. Reflecting a tendency to be persistent in the pursuit of desired goals, Drive has been positively associated with anger (Smits & Kuppens, 2005), the tendency to not suppress anger or its expression (Cooper, Gomez, & Buck, 2008), and aggressive behaviour (Harmon-Jones, 2003; Seibert, Miller, Pryor, Reidy, & Zeichner, 2010), and appears to operate along similar neural structures and pathways as does aggressive behaviour (Beaver, Lawrence, Passamonti, & Calder, 2008). Due to its strong association with aggressive tendencies, particular attention is paid to whether Drive can contribute to our understanding of benzodiazepine-related aggression.

Aversive (inhibitory) tendencies. The fight-flight-freeze system (FFFS) mediates reactions to both conditioned and unconditioned aversive stimuli, and produces escape or avoidance behaviours (Corr, 2004). This system is associated with the emotion of fear (Corr, 2004), and fearful and avoidant personality traits (Corr & Perkins, 2006). When threat is distal, this system produces flight or freezing, whilst in the face of proximal danger, it produces a fight reaction (Jackson, 2009). Empirical research has demonstrated that individuals highly sensitive to fear are more likely to engage in threat magnification, perceiving threats as especially close and intense (Perkins, Cooper, Abdelall, Smilie, & Corr, 2010). Clinically, a strong fear system is associated with phobia and panic (Corr & Perkins, 2006).

The behavioural inhibition system (BIS) aims to resolve goal conflict which generates anxiety (Corr, 2004). Thought to be distributed over a number of neural structures (Pickering & Corr, 2008), this system assesses risk and works to increase risk aversion (Corr, 2008). Conflicts are usually approach-avoidance, but can also be approach-approach, or avoidance-avoidance (Corr & Perkins, 2006). Simultaneous and similar activation of the above two systems stimulates this conflict resolution
system (Pickering & Corr, 2008). The system increases arousal (Tull et al., 2010), initiates risk assessment, scans memory (Corr, 2004), and increases the negative valence of stimuli in order to resolve the goal conflict (Corr & Perkins, 2006). Subjectively, the process presents as rumination and worry, with a sense of possible danger or loss (Corr, 2004), and is predominantly associated with trait anxiety (Corr, 2002). Clinically, inadequate goal resolution presents as generalised anxiety and obsessive-compulsive disorder (Corr & Perkins, 2006). An important distinction between the BIS and FFFS is that in situations of threat which do not need to be faced, fear mediates avoidant behaviour (Perkins, Kemp, & Corr, 2007), yet when threatening stimuli must be faced, the BIS is activated, producing anxiety-mediated risk assessment, cautious approach behaviour, or withheld entrance (Perkins et al., 2007). Anxiolytics (i.e., benzodiazepines) have been demonstrated to selectively impact the BIS, and reduce the salience of threats of punishment, failure, or the uncertainties of novel situations, reducing inhibited behaviour and promoting a more care-free attitude (Gray & McNaughton, 2003).

Collectively, the approach and avoidance motivations driven mediated by the BIS and FFFS in response to aversive stimuli are referred to as punishment sensitivity. Individuals who display strong punishment sensitivity only are argued to be least likely to engage in aggressive behaviour following benzodiazepine consumption. Although benzodiazepines may induce a change from threat-reactive behaviour to neutral, pre-threat behaviour, it is suggested that in most individuals this does not extend to violent behaviour. These individuals are not sensitive to reward cues or impulsive by nature, and therefore would be less likely to act with minimal thought to consequences, such as responding aggressively to slights or frustration. It is acknowledged that some trait-fearful individuals may engage in aggressive
behaviour when they perceive a threat to be especially close or intense (Jackson, 2009), though this behaviour presents only in a minority of cases. However, as outlined below, if a punishment sensitive individual also exhibits strong approach motivation, benzodiazepine-related aggression is argued to be increasingly likely.

*System interactions and frustrative non-reward.* Initially, the RST conceived reward and punishment sensitivity as separate motivational systems (Kambouropoulos & Staiger, 2004). However, inconsistent findings in the literature regarding individual responses to reward and punishment prompted a different conceptualisation (Corr, 2004). The Joint Systems Hypothesis (JSH) proposes that under certain conditions, reward and punishment can exert interdependent effects, as the related sensitivities are both facilitative and antagonistic (Corr, 2004). This hypothesis describes the ability of aversive stimuli to facilitate fear and anxiety whilst antagonising approach motivation, and of appetitive stimuli to facilitate approach behaviour whilst inhibiting avoidance (Corr, 2004). Specifically, individuals with high levels of impulsivity (or approach motivation) and low levels of trait anxiety will demonstrate the strongest reactions to appetitive stimuli, and vice versa for aversive stimuli (Kambouropoulos & Staiger, 2004).

However, the systems do not always interact in such an antagonistic fashion. Whilst it has been suggested that a personality characterised by both high trait anxiety and high impulsivity is unlikely (Pickering & Corr, 2008), individuals with such a trait pattern have been found to demonstrate the greatest level of behavioural inhibition (Kambouropoulos & Staiger, 2004), neuroticism (Perkins et al., 2007), and quick response times during goal pursuit (Berkman et al., 2009). Moreover, such an interaction between appetitive and aversive motivations is evident in frustrative non-reward (FN), experienced when the expected reward is higher than the actual
reward (Corr, 2002). FN is a signal of non-reward (i.e., punishment) which implicates aversive motivation, and also reflects a sensitivity to reward cues and expectancies, implicating appetitive motivation; an individual with high appetitive motivation (i.e., BAS) would be the first to detect non-reward and experience FN (Corr, 2002). This suggests that FN may be caused by reward sensitivity and mediated by punishment sensitivity, and therefore levels of FN should be greatest in individuals with both high approach and avoidance motivation (Corr, 2002). It is these individuals who we would expect to be most likely to experience aggressive responses in the face of frustration or goal blocking.

Such interactive effects have yet to be explored in relation to substance-related aggression, much less benzodiazepine-related aggression. The complexity of the antagonistic and facilitative interactions between human motivational systems demonstrates why it is essential to more deeply explore the intrapersonal characteristics of those who experience benzodiazepine-related aggressive behaviour, in order to provide more educated treatment and pharmaceutical management options. The original study presented in Chapter 4 was specifically designed in order to elucidate such deeper understanding of this response.

2.2 Summary and Thesis Rationale

A number of serious medical and forensic outcomes are associated with benzodiazepine use. Most notably, benzodiazepine-related disinhibition is a cause for concern, due to its association with motor vehicle accidents, risk taking, aggressive incidents, and subsequent memory deficits, which can have implications in both medical and forensic arenas. In particular, benzodiazepine-related aggression is poorly understood, despite the high rate of benzodiazepine misuse in criminal justice samples (including violent offenders), in countries where violent crime remains
among the most commonly recorded types of crime. The potential legal, medical and social ramifications of violent behaviour, and the increasing diversion of benzodiazepines onto the black market and subsequent increases in misuse, indicates a need to further understand the relationship between benzodiazepine use and violence. The complexity likely involved in this response has impacted the literature base, as there are a number of explanatory gaps and flaws in what we understand about benzodiazepine-related aggressive behaviour. One core gap in the literature is the identification of clear, consistent risk indicators for this response.

It has been suggested that a drug can alter the occurrence of aggressive behaviour in an individual, depending on the individual’s underlying personality (Paton, 2002). This premise is supported by laboratory findings demonstrating individuals with certain underlying characteristics (i.e., hostility, low trait anxiety) to be more likely to experience significant increases in aggressive behaviour following benzodiazepine consumption (e.g., Cherek et al., 1990; Wilkinson, 1985). However, despite such early theorizing (Lion et al., 1975), surprisingly little empirical literature has been conducted into contributory factors such as personality or motivational states. Without clear understanding of such contributory mechanisms, efforts cannot be made to curtail benzodiazepine-related violence and its harmful medical and legal sequelae. Furthermore, prescribing policy cannot be informed about potential risks and contraindications for the prescription of benzodiazepines. This thesis will therefore investigate the premise that intrapersonal factors (i.e., personality, motivational factors, mental health) provide strong indicators of whether aggressive behaviour is experienced post benzodiazepine consumption. Examining such individual differences provides clear, easily identifiable risk factors to be considered when prescribing benzodiazepines.
2.2.1 Thesis aims, hypotheses and chapters.

The overall aim of the following research is to further understand the relationship between benzodiazepine use and subsequent interpersonal aggression and violence. This seemingly paradoxical response is of concern given the reasons that benzodiazepines are generally prescribed, the context in which they are prescribed, and the increasing misuse of benzodiazepines in healthy, clinical, and forensic populations. Within this overarching aim, the following research has three specific directives:

1. To systematically review the benzodiazepine-aggression literature base to specifically identify benzodiazepine type and dose, and individual characteristics associated with benzodiazepine-related aggression.
2. To enhance the theoretical rigour of benzodiazepine-aggression literature.
3. To identify characteristics associated with benzodiazepine-related violence in a benzodiazepine-using, community-based criminal justice sample.

Attending to Aim 1, Chapter 3 presents a systematic review of the currently available literature exploring benzodiazepine-related aggression. Particular attention is paid to the role of different benzodiazepine types and dose, as well as participant characteristics, in understanding this response. As will be discussed, the current literature base, whilst informative, is flawed and often inconsistent, and highlights the need for further systematic research of the various types of benzodiazepines and greater statistical and measurement control.

Attending to Aim 2, Chapter 4 presents an original, cross-sectional study of community members which tests a well-validated theory of motivational tendencies against benzodiazepine-related aggression, and assesses the relative importance of such tendencies, compared to benzodiazepine-related factors (i.e., type, dose), in
predicting general aggression (i.e., including anger, verbal aggression) and physical aggression specifically. Participants are community members over the age of 18 years, who report having used benzodiazepines at some point during the past year. Through the use of hierarchical multiple regression, the study tests the hypotheses that:

1. Motivational factors will significantly predict engagement in benzodiazepine-related aggressive behaviour over and above benzodiazepine type or use;
2. BAS-Drive will significantly predict general aggression and physical aggression; and
3. BAS-Drive will moderate the relationship between BIS and aggressive outcomes. Specifically, it is predicted that the relationship between BIS and aggressive behaviour will be stronger for individuals with high levels of BAS-Drive.

Attending to the final aim, Chapter 5 presents a second, smaller cross-sectional study which examines the differences between violent and non-violent offenders’ benzodiazepine use patterns and intrapersonal characteristics (i.e., mental health, personality). Participants are community-based offenders who committed a crime in the six months prior to data collection, and who report using benzodiazepines on a regular (at least monthly) basis. The study predicts that:

1. Individuals engaged in violent crime will report greater benzodiazepine use, and higher doses, than non-violent offenders; and
2. Violent offenders will display a more complex psychiatric and social history than non-violent offenders.
The findings of Chapters 3-5 will be combined in Chapter 6 in a discussion of how the thesis furthers our understanding of benzodiazepine-related aggression. Based on the combined research, the chapter will discuss the implications for benzodiazepine prescribing practices and policy, provide commentary on the recent rescheduling of alprazolam to a controlled substance (Schedule 8), discuss access to benzodiazepines in forensic contexts, and indicate treatment targets both within the addiction and forensic mental health sectors. It is hoped that this research will also inform legal decision making about the potential culpability of an offender, and the use of (in)appropriate legal defences.
Chapter Three: Benzodiazepine Use and Aggressive Behaviour: A Systematic Review

Please note, this chapter presents an expanded version of a systematic review published in the Australian and New Zealand Journal of Psychiatry (2014), due to copyright reasons. A link to the original article has been appended for your consideration (Appendix A).

3.1 Rationale

Benzodiazepines are one of the most commonly prescribed pharmaceuticals in developed countries (AIHW, 2011; Home Office Statistics, 2012; HSCIC, 2011; Stephenson, Karanges, & McGregor, 2013; SAMHSA, 2011). They are commonly prescribed for the management of anxiety, sleep disorders, agitation and alcohol withdrawal (Ashton, 2002). Although the most common effects of benzodiazepines include sedation and reduced anxiety, there have been reports of some users experiencing behavioural disinhibition following consumption, which includes aggressive behaviour (Bond, 1998; Fry, Smith, Bruno, O’Keefe, & Miller, 2007; Paton, 2002). In fact, it is estimated that anywhere between 1-20% of benzodiazepine users experience some form of increased anger or express aggression (Lader, 2011). Furthermore, a number of clinical case studies report that individuals experience aggressive responding following administration of a range of benzodiazepines including diazepam (Gardos, 1980; Lion, Azcarate, & Koepke, 1975; Zisook and DeVaul, 1977), clorazepate (Karch, 1979), alprazolam (Rosenbaum, Woods, Groves, & Klerman, 1984), clonazepam (Binder, 1987; Kalachnik, Hanzel, Sevenich, & Harder, 2003), and flunitrazepam (Dåderman, Stridlund, Wiklund, Fredriksen, & Lidberg, 2003). Such incidents occurred at both high and low doses (approximate diazepam equivalent doses (DZM) ranging between 5-240mg), and by individuals
with (Kalachnik et al., 2003; Lion et al., 1975) and without (Karch, 1979) histories of aggressive behaviour. Despite this accumulating clinical evidence, there has been no systematic review of the existing literature to inform policy or practice.

A complicating factor is the variable definitions of aggression used within the literature. For the purposes of this report, aggressive behaviour is defined as physical behaviour directed toward another person with the goal of harming or injuring that person, who is motivated to avoid such behaviour (Baron & Richardson, 1994). The term ‘violence’ is often used interchangeably with ‘aggression’, although commonly reflects more serious harm (Anderson & Bushman, 2002) and forensic contexts (Anderson & Bokor, 2012). Our deliberate and sole focus on physical aggression directed toward another person is due to the potential severe medical and legal consequences of such responses (i.e., hospitalisation and mortality; legal responsibility, sentencing, and rehabilitation considerations).

Of note, this issue has significant implications for judicial decision-making pertaining to violent offending behaviour. For example, a study of 102 injecting drug users (with a range of criminal histories) reported that benzodiazepine use was associated with unprovoked aggressive behaviour (20%), fights (13%) and crime (14%; Smith, Miller, O’Keefe, & Fry, 2007). Furthermore, self-reported substance use in adult police detainees (n = 1884) indicated that 27% of users attributed their current offence to benzodiazepine use (Payne & Gaffney, 2012). Although limited by the use of retrospective self-attributions of behaviour and the lack of control for concurrent substance use, these findings do highlight that disentangling these issues via a systematic and critical analysis of the literature is timely.

In terms of how benzodiazepines increase aggressive responding, Lion and colleagues (1975) suggest an interaction between drug use, personality, and
environmental factors, with more recent research highlighting that personality may be as, or more, important than pharmacological factors (Ben-Porath & Taylor, 2002; Hoaken & Stewart, 2003; Paton, 2002; Wilkinson, 1985). The latter premise is highlighted by research implicating both high (Paton, 2002) and low doses (Hoaken & Stewart, 2003) of benzodiazepines in subsequent aggressive responding. The circumstances under which aggressive behaviour is likely to result following benzodiazepine consumption are poorly understood and the literature lacks a systematic review of the empirical research investigating the relationship between benzodiazepine consumption and subsequent aggressive or violent behaviour. This relationship needs to be understood when considering prescribing protocols, and the potential clinical and legal implications of aggressive responses. This chapter therefore reports on a systematic review addressing the question: Does benzodiazepine consumption increase aggressive behaviour in adult humans?

3.2 Methods

A systematic review was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009; Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). The Maryland Scale of Scientific Rigor (Sherman et al., 1998) was applied to assess each study’s internal validity. According to this scale, studies are ranked from 1 (weakest) to 5 (strongest), with the main considerations pertaining to control of extraneous variables, minimisation of error variance, and sufficient power for meaningful statistical differences. Randomised clinical trials (RCT) and well controlled experimental studies provide the strongest level of scientific rigor (Sherman et al., 1998). Although experimental studies can inform the impact of acute doses, they provide limited information on chronic use, and the findings are based on
highly contrived circumstances. Therefore, less rigorous designs (i.e., cross-sectional, prospective) were also included in this review in order to enhance the ecological and clinical validity of the findings. However, at the lowest level of evidence (Merlin, Weston, & Tooher, 2009), case studies were excluded from consideration due to their poor generalizability (Evans, 2003).

3.2.1 Eligibility criteria.

Studies investigating the relationship between benzodiazepines and aggression in adult human populations were located. Inclusion criteria included English language and peer-reviewed journal articles. Studies examining self-reported, observed, and behavioural analogues of other-directed aggression, defined as physical behaviour directed towards another person with the goal of harming or injuring that person who is motivated to avoid such behaviour, were included. Exclusion criteria included animal studies, unrelated neurobiological studies, case studies, and clinical trials which did not explicitly measure aggression. Articles were excluded if they only investigated hostility, anger, self-directed aggression (e.g., self-harming behaviours), the intent to act aggressively, or verbal or psychological aggression. Articles were also excluded if they investigated non-benzodiazepine sedatives, hypnotics, or anxiolytics. Synthesis articles (i.e., reviews, meta-analyses) were excluded following examination of their reference lists for original articles meeting the above criteria.

3.2.2 Information sources.

The search was applied to Medline Complete, PsycARTICLES, PsycINFO, Academic Search Complete, and the Psychology and Behavioural Sciences Collection electronic databases. Search terms used were: benzo*, BZD, sedative, hypnotic, anxiolytic, anti-anxiety medication, anti-anxiety drug, tranquilisers,
tranquilizers, diazepam, lorazepam, temazepam, alprazolam, flunitrazepam, oxazepam, clonazepam, nitrazepam, aggress*, and violen*. The limiter ‘English language’ was used for PsycINFO, Academic Search Complete, and Medline Complete. The limiter ‘peer reviewed’ or ‘scholarly (peer reviewed) journals’ was used for all databases except Medline as this was not available. The limiter of ‘human’ or ‘human population’ was used for PsycARTICLES, PsycINFO, and Medline. The final search was run on 7 December, 2012.

3.2.3 Study selection.

Two authors (BA and PS) independently screened the titles and abstracts of all publications obtained by the search strategy (2492), and assessed the full text of selected articles (64) for inclusion. In questionable cases, the authors discussed the inclusion and exclusion requirements and came to a consensus.

3.2.4 Data extraction.

Information was extracted from each study on: (1) participant characteristics (including gender, age, clinical diagnosis, behavioural history if reported); (2) study design and method (including benzodiazepine type, dose, frequency; versus placebo; corroboration of self-reported information; single- or double-blinded techniques); and (3) type of outcome measure (including behavioural rating scale, behavioural analogues, self-report).

3.3 Results

3.3.1 Study selection.

The initial database search revealed a total of 2492 articles. Of these, 2428 studies were discarded as duplicates or because they did not meet the criteria (see Fig. 1). The full text of the remaining 64 citations was examined in more detail. An additional 15 articles were identified by examining the reference lists of these
citations and through previous literature searches. Thirty articles did not meet the inclusion criteria as described, including 19 non-systematic reviews, and a review investigating the behavioural side effects of benzodiazepines in individuals with an intellectual disability (Kalachnik, Hanzel, Sevenich, & Harder, 2002). Upon detailed study, two studies were excluded (Cherek, Steinberg, & Kelly, 1987; Cowdry & Gardner, 1988) because they reported the same data as a further two (Cherek, Steinberg, Kelly, Robinson, & Spiga, 1990; Gardner & Cowdry, 1985, respectively); the latter two contained more methodological and statistical detail. One experimental study (Brown, 1978) was excluded as it failed to report methodological or statistical outcome detail. Hence, 46 studies met the inclusion criteria.

3.3.2 Study characteristics.

The 46 studies varied considerably in terms of study design, type of samples, the range of benzodiazepines examined and doses considered. Due to the heterogeneity of study design and benzodiazepine type and dose, it was not possible to conduct a meta-analysis on the reviewed data. **Design:** The association between benzodiazepine consumption and subsequent aggressive behaviour had been explicitly investigated in two prospective studies, 25 cross-sectional studies, six clinical studies, and 13 experimental studies. **Sample:** The studies investigated clinical ($n = 15$), forensic ($n = 12$), and healthy community ($n = 19$) samples. **Drug Type:** Benzodiazepines investigated across the studies included diazepam, alprazolam, flunitrazepam, triazolam, temazepam, clonazepam, oxazepam, lorazepam, and clorazepate. Diazepam and alprazolam received the most attention (9 and 6 studies, respectively), and 43.5% ($n = 20$) studies explored non-specific benzodiazepine use. **Dose:** The included studies investigated both therapeutic and higher doses; approximate DZM equivalent doses for the clinical and experimental
Figure 1. PRISMA Flow Diagram depicting the flow of information through the stages of the systematic review.
studies ranged between 3.3-100mg and 2-20mg, respectively. The experimental studies examined acute benzodiazepine administration, whilst the clinical studies explored chronic administration ranging from four days to three months. Cross-sectional and prospective studies did not specify dose. Table 1 and 2 detail the characteristics of the included studies.

3.3.3 Risk of bias within studies.

There were multiple risks of bias in each article reviewed, ranging from limited generalizability to potential confounding by drug interactions, as detailed in the tables. Application of the Maryland Scale of Scientific Rigor (Sherman et al., 1998) demonstrated that overall, 56.5% (n = 26) of the included studies are of a Level 1 standard, and only 6.5% (n = 3) are of a Level 5 standard, indicating that the quality of the evidence base surrounding the benzodiazepine-aggression relationship is poor.

3.4 Synthesis of Results

Does benzodiazepine consumption increase aggressive behaviour in adult humans?

The reviewed literature demonstrated a moderate relationship (with some inconsistency) between benzodiazepine consumption and subsequent aggression. Diazepam demonstrated the greatest association with increased aggression (n = 6 studies), and has been examined in more high level (Levels 4 and 5; n = 3) studies than any other benzodiazepine.

3.4.1 Experimental studies.

The 13 experimental studies utilised either the Taylor Aggression Paradigm (TAP; n = 10) or the point subtraction aggression paradigm (PSAP; n = 3), with the majority utilising placebo-controlled (n = 11) and double-blind (n = 9) methods. The
<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Participant Data</th>
<th>Aggression Measure</th>
<th>Limitations</th>
<th>Outcomes</th>
<th>Q.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haller &amp; Deluty, 1990</td>
<td>Cross-sectional</td>
<td>100 cases (80 clients; 49% F)</td>
<td>Severely assaultive psychiatric patients</td>
<td>File examination</td>
<td>Specificity – “anxiolytics” No temporal causality</td>
<td>Anxiolytic prescription positively related to assault severity</td>
</tr>
<tr>
<td>Dawson, 1997</td>
<td>Cross-sectional</td>
<td>18352 18 or older Current drinkers</td>
<td>Self-report questionnaire</td>
<td>Specificity – “sedatives”, “tranquilisers” Reliance on self-report Exclusion of licit use of substances</td>
<td>0.4% used sed/tranq only Sed/tranq use not predictive of past-year alcohol or drug-related fighting</td>
<td>1</td>
</tr>
<tr>
<td>Ryden et al., 1999</td>
<td>Cross-sectional</td>
<td>116 (73% F)</td>
<td>Cognitively impaired, consistently</td>
<td>File examination</td>
<td>Sampling bias No control group (i.e., non-agg sample)</td>
<td>41.4% received anxiolytics (most common L &amp; A) Receiving anxiolytics more</td>
</tr>
<tr>
<td>Source</td>
<td>Design</td>
<td>No.</td>
<td>Mean age (SD)</td>
<td>Details</td>
<td>Aggression Measure</td>
<td>Limitations</td>
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<tr>
<td>Shah et al., 2000</td>
<td>Prospective (6 months)</td>
<td>412</td>
<td>82.3 (9.5)</td>
<td>Melbourne nursing home residents</td>
<td>SOAS</td>
<td>Measurement variability (sensitivity)</td>
</tr>
<tr>
<td>Friedman et al., 2003</td>
<td>Cross-sectional</td>
<td>612</td>
<td>26.23 (1.52)</td>
<td>African-American, low socio-economic status, young adults</td>
<td>Database analysis</td>
<td>Specificity – “seds/tranqs” Cultural and SES generality/confounds</td>
</tr>
<tr>
<td>Voyer et al.</td>
<td>Cross-section</td>
<td>2633</td>
<td>65 or older</td>
<td>Patients of long-term care</td>
<td>Structured</td>
<td>Limited generality</td>
</tr>
<tr>
<td>Source</td>
<td>Design</td>
<td>No.</td>
<td>Mean age (SD)</td>
<td>Details</td>
<td>Aggression Measure</td>
<td>Limitations</td>
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<tr>
<td>al., 2005</td>
<td>sectional</td>
<td></td>
<td></td>
<td>term care facilities (Quebec)</td>
<td>interview</td>
<td>Contextual factors not assessed/controlled</td>
</tr>
<tr>
<td>Giancola &amp; Parrott, 2005</td>
<td>Experiment (PC)</td>
<td>330</td>
<td>23.04 (2.85)</td>
<td>Healthy social drinkers</td>
<td>TAP</td>
<td>Specificity – “sedatives”</td>
</tr>
<tr>
<td></td>
<td>Mixed design</td>
<td></td>
<td></td>
<td></td>
<td>Self-report questionnaires</td>
<td>Reliance on self-report</td>
</tr>
<tr>
<td>Haggård-Grann et al., 2006</td>
<td>Cross-sectional</td>
<td>133 M</td>
<td>35.3 (12.0)</td>
<td>Convicted violent offenders &amp; offenders undergoing forensic psychiatric evaluation</td>
<td>Structured interviews</td>
<td>Recall bias</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Case-crossover design</td>
<td>No corroboration via blood/urine tests</td>
</tr>
<tr>
<td>Whitty &amp; Cross-</td>
<td>Cross-sectional</td>
<td>295</td>
<td>-</td>
<td>Incident reports</td>
<td>Retrospective</td>
<td>Limited generality</td>
</tr>
<tr>
<td>Source</td>
<td>Design</td>
<td>Participant Data</td>
<td>Aggression Measure</td>
<td>Limitations</td>
<td>Outcomes</td>
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<tr>
<td>O'Connor, 2006</td>
<td>sectional cases</td>
<td>(157 clients)</td>
<td>for out-patient methadone stabilisation &amp; detox program</td>
<td>Small sample - only 20 clients provided urine sample 24hrs prior to incident No control group</td>
<td>agg, 80% of those tested were positive for BZD</td>
<td></td>
</tr>
<tr>
<td>Feingold et al., 2008</td>
<td>Cross-sectional</td>
<td>150 M (28 (0.5))</td>
<td>At least 1 long-term relationship (1 year)</td>
<td>Database analysis Limited generality Low statistical power Specificity – “sedatives”</td>
<td>Sedative problems not predictive of IPV</td>
<td>1</td>
</tr>
<tr>
<td>Stalans &amp; Ritchie, 2008</td>
<td>Cross-sectional</td>
<td>19338 cases (54.7F )</td>
<td>Living with intimate partners No treatment for substance use in past year</td>
<td>Database analysis Specificity – “sedatives/pain relievers” Reliance on self-report Limited measure of IPV perpetration (1 item)</td>
<td>Use of sedatives independently and sig increased likelihood of perpetrating IPV after controlling demographic/social factors</td>
<td>1</td>
</tr>
<tr>
<td>Moore et al., 2010</td>
<td>Cross-sectional</td>
<td>1937 cases</td>
<td>Violence report</td>
<td>Database analysis Reliance on adverse incidence database – confounding factors, TZ, D, A, C disproportionately associated with violence (4/31 drugs)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Source</td>
<td>Design</td>
<td>No.</td>
<td>Mean age (SD)</td>
<td>Details</td>
<td>Aggression Measure</td>
<td>Limitations</td>
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<tr>
<td>Nabors, 2010</td>
<td>Cross-sectional</td>
<td>1635</td>
<td>19</td>
<td>Undergraduates</td>
<td>Self-report questionnaire</td>
<td>Specificity – “depressants”</td>
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<td></td>
<td></td>
<td>Limited generality</td>
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<td></td>
<td></td>
<td></td>
<td>No temporal causality</td>
</tr>
<tr>
<td>Rouve et al., 2011</td>
<td>Cross-sectional</td>
<td>56</td>
<td>46</td>
<td>Physical aggressiveness against others</td>
<td>Database analysis</td>
<td>Reliance on adverse incidence database – confounding factors, unreported events</td>
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<tr>
<td>Hakansson et al., 2011</td>
<td>Cross-sectional</td>
<td>5659</td>
<td>29.7-34.8</td>
<td>Swedish CJS clients</td>
<td>Database analysis</td>
<td>Specificity – “tranquilizers”</td>
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<td></td>
<td>Limited generality</td>
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<td>No temporal causality</td>
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<td></td>
<td></td>
<td>Lack of sample</td>
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<tr>
<td>Source</td>
<td>Design</td>
<td>No.</td>
<td>Mean age (SD)</td>
<td>Details</td>
<td>Aggression Measure</td>
<td>Limitations</td>
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<tr>
<td>Shin et al., 2012</td>
<td>Prospective (5-12 month)</td>
<td>376</td>
<td>41.15 (13.33)</td>
<td>Help-seeking US veterans with PTSD</td>
<td>Self-report questionnaire</td>
<td>Small subsample with BZD prescription (23%)</td>
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<td>No temporal causality</td>
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<td></td>
<td></td>
<td>Reliance on self-report</td>
</tr>
<tr>
<td>Lundholm et al., 2012</td>
<td>Cross-sectional</td>
<td>194</td>
<td>30.68 (9.64)</td>
<td>Remand prisoners suspected of violent crime</td>
<td>Structured interviews</td>
<td>Recall bias</td>
</tr>
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<td></td>
<td></td>
<td>No corroboration with blood/urine records</td>
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<td></td>
<td></td>
<td>Case-crossover</td>
</tr>
</tbody>
</table>

Limitations: homogeneity, Recall bias – interviews between 6mth-2years after intake into CJS.
<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>No.</th>
<th>Mean age (SD)</th>
<th>Details</th>
<th>Aggression Measure</th>
<th>Limitations</th>
<th>Outcomes</th>
<th>Q.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afifi et al., 2012</td>
<td>Cross-sectional</td>
<td>25778</td>
<td>20 and above</td>
<td>12 month romantic relationship</td>
<td>Database analysis</td>
<td>Low prevalence &amp; specificity (‘sedatives’, ‘tranquilisers’)</td>
<td>Sed/tranq use increased odds of IPV perpetration than non-users – however n.s. in fully adjusted model</td>
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<td>Underpowered model</td>
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<td></td>
<td></td>
<td>No temporal causality</td>
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<td></td>
<td></td>
<td>Covariates – only select mental dx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mattson et al., 2012</td>
<td>Cross-sectional</td>
<td>181</td>
<td>F: 39.9 (9.3)</td>
<td>Married/cohabiting couples</td>
<td>Individual interview; self-and reported aggression</td>
<td>Gender bias in model</td>
<td>No direct association between sedative use &amp; physical agg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M: 42.7 (8.9)</td>
<td>Substance abuse treatment M: alcohol dependence</td>
<td>Use of highest agg value – overestimate agg?</td>
<td>Specificity of “sedatives”</td>
<td></td>
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<td></td>
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<td></td>
<td>M: alcohol dependence</td>
<td></td>
<td>No temporal causality</td>
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<td></td>
<td>F: sed use indirectly increased minor physical agg</td>
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<td>F: sed use indirectly predicted decreased severe physical agg</td>
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<td>Effects of F sed use eliminated when agg levels combined</td>
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</tbody>
</table>
Notes. Q.I. = quality indicator; A = alprazolam; D = diazepam; C = clonazepam; TZ = triazolam; L = lorazepam; P = participants; DB = double-blind; PC = placebo-controlled; SOAS = Staff Observation Aggression Scale; RAGE = Rating Scale for Aggressive Behavior in the Elderly; agg = aggression; F = female, M = male; IPV = intimate partner violence; CJS = criminal justice system; n.s. = non-significant; B/subjects = between-subjects design; W/subjects = within subjects design.
Table 2

*Characteristics of included studies assessing benzodiazepine-related aggressive behaviour, ordered by benzodiazepine type and year of publication.*

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Participant Data</th>
<th>BZD</th>
<th>Aggression Measure</th>
<th>Limitations</th>
<th>Outcomes</th>
<th>Q.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldman, 1962</td>
<td>Clinical B/subjects</td>
<td>87 (31F) Patients with hypoactive syndrome</td>
<td>Diazepam – dose unclear</td>
<td>Evaluator assessment</td>
<td>Potential drug interactions, Limited information re control, dose, responses, inter-rater reliability, No comparison group, blinding methods</td>
<td>Progressive development of “hatefulness” which led to violence</td>
<td>1</td>
</tr>
<tr>
<td>Wilkinson, 1985</td>
<td>Experiment (DB, PC) W/subjects</td>
<td>60 M 18-24 Undergraduates</td>
<td>Diazepam – 10mg</td>
<td>TAP</td>
<td>Limited generality, Ecological validity</td>
<td>D increased agg over placebo ($p &lt; .01$), D-related agg enhanced in low-anxious Ps ($p &lt; .05$)</td>
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<tr>
<td>Gantner &amp; Taylor, 2003</td>
<td>Experiment (PC, 50% over) Undergraduates</td>
<td>36 (50%) 19 or over Undergraduates</td>
<td>Diazepam – 10mg</td>
<td>TAP</td>
<td>Not double-blind – expectancy bias?</td>
<td>D increased agg behaviour ($p &lt; .01$)</td>
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<tr>
<td>Source</td>
<td>Design</td>
<td>Participant Data</td>
<td>BZD</td>
<td>Aggression Measure</td>
<td>Limitations</td>
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<td>1988</td>
<td>random allocation</td>
<td>F) B/subjects</td>
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<td>60-min between D &amp; task</td>
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<tr>
<td>Cherek et al., 1990</td>
<td>Experiment (DB, PC) W/subjects</td>
<td>9 M Healthy volunteers</td>
<td>Diazepam – 2, 5, 10mg/70kg</td>
<td>PSAP Successive drug doses separated by 96hrs Small sample Self-selection (response bias) Ecological validity</td>
<td>D decreased agg ($p &lt; .025$) 2P increased agg responding (5mg, 10mg/70kg) - high hostility</td>
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<tr>
<td>Ben-Porath &amp; Taylor, 2002</td>
<td>Experiment (DB, PC) random allocation</td>
<td>60 M Undergraduates</td>
<td>Diazepam – 10mg</td>
<td>TAP Limited generality Reliance on self-reported hostility Ecological validity</td>
<td>D increased agg compared to placebo ($p = .05$) - influence of hostility (n.s.)</td>
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<td>Wallace &amp; Taylor, 2002</td>
<td>Experiment (DB, PC)</td>
<td>30 M Undergraduates</td>
<td>Diazepam – 10mg</td>
<td>TAP Limited generality Self-selection (response bias)</td>
<td>D significantly increased agg compared to placebo</td>
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<tr>
<th>Source</th>
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<th>Outcomes</th>
<th>Q.I.</th>
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<td>Forsyth et al., 2011</td>
<td>Cross-sectional</td>
<td>202</td>
<td>16-20</td>
<td>Young serious offenders</td>
<td>Diazepam</td>
<td>Qualitative interviews</td>
<td>Reliance on self-report, Limited generality</td>
<td>D drug most often blamed for crime</td>
<td>D more likely to facilitate violence when with alcohol</td>
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<td>W/subjects</td>
<td>M</td>
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<td>Self-report questionnaire</td>
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<td>(p &lt; .05)</td>
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<td>Dåderma &amp; Lidberg,</td>
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<td>19 M</td>
<td>14-20</td>
<td>Juvenile offenders</td>
<td>Fl</td>
<td>Structured interviews</td>
<td>Questionable temporal causality</td>
<td>All Fl-abusers committed violent offences</td>
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<td>14-20</td>
<td>Juvenile offenders</td>
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<td>Questionable temporal causality</td>
<td>All Fl-abusers committed violent offences</td>
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**Flunitrazepam**

**Participant Data**

- **Source**: Forsyth et al., 2011
- **Design**: Cross-sectional
- **N**: 202
- **Age**: 16-20
- **Details**: Young serious offenders
- **BZD**: Diazepam
- **Aggression Measure**: Qualitative interviews, Self-report questionnaire
- **Limitations**: Reliance on self-report, Limited generality
- **Outcomes**: D drug most often blamed for crime
- **Q.I.**: D more likely to facilitate violence when with alcohol

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>N</th>
<th>Age</th>
<th>Details</th>
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<td>Dåderma &amp; Edman, 2001</td>
<td>Cross-sectional</td>
<td>60 M</td>
<td>27 (5.7)</td>
<td>Non-psychotic forensic psychiatric patients</td>
<td>Fl</td>
<td>Structured &amp; open-ended interviews File examination</td>
<td>Limited generality Reliance on self-report Low statistical power</td>
<td>No personality difference between Fl non/abusers Fl abusers more likely to commit robbery, weapon, theft crimes No sig difference re violent crime</td>
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<td>Dåderman et al., 2002</td>
<td>Cross-sectional</td>
<td>5 M</td>
<td>23-26</td>
<td>Swedish offenders who had used Fl</td>
<td>Fl</td>
<td>File examination</td>
<td>Confounded – concurrent drug use No controls (i.e., non-anxious Fl users) Limited generality Small, targeted sample</td>
<td>Violence promoted in individuals with psychiatric vulnerability (i.e., anxiety)</td>
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<tr>
<td>Bramness et al., 2006</td>
<td>Cross-sectional</td>
<td>415 cases</td>
<td>30 (9.3) (16%)</td>
<td>DUI under Fl only</td>
<td>Fl</td>
<td>Database analysis</td>
<td>Social/environment/personal factors not available Reliance on adverse</td>
<td>Fl not significantly different between violent &amp; non-violent cases</td>
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<td>F)</td>
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<td>7</td>
<td>21.9</td>
<td>Violent</td>
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<td>incidence database – confounding factors, unreported events</td>
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<td>where Fl only drug</td>
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<td>Dåderma n et al., 2012</td>
<td>Cross-sectional</td>
<td>114</td>
<td>22.5</td>
<td>Non-psychotic</td>
<td>Interviews</td>
<td>34% used Fl</td>
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<td>M</td>
<td>(6.6)</td>
<td>offenders &amp; juvenile delinquents</td>
<td>File examination</td>
<td>Failure associated with: Facet 4 psychopathy (poor behavioural control, early behavioural problems, criminal versatility)</td>
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<tr>
<td>Clonazepam</td>
<td></td>
<td>13</td>
<td>21-45</td>
<td>Inpatients -chronic schizophrenia</td>
<td>C 1mg/o.d. (gradually increased, Staff behavioural ratings)</td>
<td>4 patients had agg behaviour during study (only 1 other agg during</td>
<td>2</td>
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<tr>
<td>A-B-A</td>
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<td>38</td>
<td>13-41</td>
<td>tapered) 28 days tx</td>
<td>Limited generality</td>
<td>C tx, at 4mg)</td>
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<td>Rosenberg et al., 1987</td>
<td>Cross-sectional</td>
<td>38 (18F)</td>
<td>Intractable seizure disorder</td>
<td>Clonazepam File examination</td>
<td>Drug interaction? Variations in testing – prior to or during C tx Limited generality</td>
<td>1P displayed “marked agg” Sig diff in VIQ-PIQ discrepancy compared to non-side effect patients (not specific to behavioural side effect) No personality differences</td>
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<td>Alprazolam</td>
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<td>16 F</td>
<td>24-42</td>
<td>Outpatients Borderline personality disorder</td>
<td>Alprazolam – FDS (1-6mg; M = 4.7mg o.d.)</td>
<td>Self-report Behavioural observation</td>
<td>Histories of dyscontrol 1wk washout – carry over effects? Limited generality</td>
<td>A increased severe dyscontrol over placebo 1P displayed other-directed agg</td>
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<td>Source</td>
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<td>Noyes et al., 1988</td>
<td>RCT (DB, PC, random allocation)</td>
<td>525</td>
<td>M: Panic disorder, agoraphobia, anxiety attacks</td>
<td>Alprazolam – FDS (1-10mg)</td>
<td>1wk medication washout – sufficient?</td>
<td>Limited generality</td>
<td>Aggressive/violent behaviour reported by 1P (4mg o.d.)</td>
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<td>Bond &amp; Silveira, 1993</td>
<td>Experiment (DB, PC, random allocation)</td>
<td>48</td>
<td>- Moderate social drinkers</td>
<td>Alprazolam – 1mg (with &amp; without alcohol)</td>
<td>Modified TAP</td>
<td>Ecological validity</td>
<td>A did not increase agg compared to placebo</td>
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<td>O'Sullivan et al., 1994</td>
<td>RCT (DB, PC, random allocation)</td>
<td>154</td>
<td>35 Inpatients with Panic disorder</td>
<td>Alprazolam – FDS (1-10mg)</td>
<td>Structured interview</td>
<td>Limited generality</td>
<td>A increased agg in 2Ps</td>
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<td>Bond et al., 1995</td>
<td>Experiment (PC, random allocation)</td>
<td>B/subjects 23 (17F) A: 40.8 Patients Panic disorder with agoraphobia</td>
<td>Alprazolam (post 8wks treatment; O’Sullivan et al)</td>
<td>Modified TAP</td>
<td>Limited generality</td>
<td>A increased agg following provocation (p&lt;.01) Decrease in hostility</td>
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<td>Cherek et al., 1991</td>
<td>Experiment (DB, PC)</td>
<td>W/subjects 5M 25-36 Healthy volunteers</td>
<td>Triazolam – 0.125, 0.25, 0.5mg/70kg</td>
<td>PSAP</td>
<td>Limited generality</td>
<td>T decreased agg in 2Ps at 2 lower doses increased agg in 1P</td>
<td>3</td>
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<td>Berman</td>
<td>Experiment</td>
<td>46 M 18-30 Undergrad</td>
<td>Triazolam TAP</td>
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<td>T increased agg</td>
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<tr>
<td>&amp; Taylor, 1995</td>
<td>B/subjects</td>
<td>uates</td>
<td>0.25mg</td>
<td>Self-selection (response bias)</td>
<td>No examination of T dose-response curve</td>
<td>Self-selection (response bias) responding ($p &lt; .01$) &amp; increased no. of Level 10 shocks ($p &lt; .01$) compared to placebo Threat did not influence T-related agg responding</td>
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<td>Burgio et al., 1992</td>
<td>Clinical (SB)</td>
<td>Gero-psychiatry inpatients</td>
<td>Oxazepam FDS (10-30mg o.d.) 4-26 days</td>
<td>Single-blind method – observer bias?</td>
<td>No non-treatment comparison group Treatment effects collapsed over O &amp; Haloperidol groups</td>
<td>No significant change between baseline agg &amp; agg during treatment Physical agg least frequent of targets</td>
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<td>Temazepam</td>
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<td>Limited generality</td>
<td>T unique contributor to</td>
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<td>ley &amp; Pearl, 1997</td>
<td>sectional</td>
<td>(44% F) Homeless</td>
<td>m</td>
<td>structured interviews</td>
<td>No control for polydrug use</td>
<td>Reliance on self-report</td>
<td>No temporal causality</td>
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<td>Pietras et al., 2005</td>
<td>Experiment (PC)</td>
<td>8 M 20-37(30.4) Parolees</td>
<td>Lorazepam</td>
<td>PSAP</td>
<td>Self-selection (response bias)</td>
<td>Blinding method unclear</td>
<td>1P displayed increased agg (by 400%) compared to placebo</td>
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<td>Bond &amp; Lader, 1988</td>
<td>Experiment (DB, PC, random)</td>
<td>45 19-46 Healthy volunteers</td>
<td>Oxazepam</td>
<td>Modified TAP</td>
<td>Self-selection (response bias)</td>
<td>Ecological validity</td>
<td>L &amp; O increased agg compared to placebo</td>
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<td>allocation)</td>
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<td>– 1.0, 2.0mg</td>
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<td>L greater increase in aggression than O ($p &lt; .05$)</td>
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<td>Weisman et al., 1998</td>
<td>Ex periment (DB, PC)</td>
<td>44 M, 18-24 Undergraduates</td>
<td>Diazepam O, TAP</td>
<td>Limited generality</td>
<td>O &amp; CL no effect</td>
<td>D increased agg at low provocation compared to placebo ($p &lt; .05$)</td>
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<td>B/subjects</td>
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<td>– 10mg, O – 50mg, CL – 15mg</td>
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<td>Rothschild et al., 2000</td>
<td>Cross-sectional</td>
<td>323, 18-82 Hospital Inpatients</td>
<td>Alprazolam C, Blind chart review</td>
<td>Non-randomised, Limited generality</td>
<td>No sig difference between A, C, or no BZD</td>
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Notes. Q.I. = quality indicator; RCT = randomised control trial; BZD = benzodiazepine; A = alprazolam; D = diazepam; Fl = flunitrazepam; T = temazepam; C = clonazepam; O = oxazepam; TZ = triazolam; CL = clorazepate; L = lorazepam; P = participants; DB = double-blind; PC = placebo-controlled; PSAP = Point Subtraction Aggression Paradigm; TAP = Taylor Aggression Paradigm; SOAS = Staff Observation Aggression Scale; RAGE = Rating Scale for Aggressive Behavior in the Elderly; FDS = flexible dose schedule; agg = aggression; F = female, M = male; CJS = criminal justice system; AOD = alcohol and drug; n.s. = non-significant; B/subjects = between subjects design; W/subjects = within-subjects design; f/up = follow up.
TAP involves participants administering and receiving electrical shocks under a competitive reaction time task, where the participant’s shock setting for a (fictional) opponent gives a proxy measure of behavioural aggression. Reaction to provocation is also measured, by providing participants with an indication of the shock set per trial by their opponent. Modifications involve using noise instead of shocks (e.g., Bond and Lader, 1988). The PSAP provides participants with a choice between escape responding, non-aggressive monetary-reinforced responding, and a proxy measure of aggression involving the subtraction of money from a (fictional) opponent, following provocation. It is noted that although laboratory proxy measures of aggression have demonstrated some external (Anderson & Bushman, 1997), and construct validity (e.g., Cherek, Lane, Dougherty, Moeller, & White, 2000; Giancola & Parrott, 2008; Golomb, Perez, Jaworski, Mednick, & Dimsdale, 2007), debate continues as to the empirical value and external validity of laboratory aggression paradigms (e.g., Ferguson & Rueda, 2009; Ferguson, Smith, Miller-Stratton, Fritz, & Heinrich, 2008). Eleven studies investigated undergraduate students or community members (18-46 years old), and one study each explored a clinical (28-40 years; Bond, Curran, Bruce, O’Sullivan, & Shine, 1995) and forensic (20-37 years; Pietras et al., 2005) sample.

Variable effects were reported both within and across benzodiazepine types. Diazepam was found to invariably increase responding indicative of behavioural aggression in five studies and produce mixed responses in one study; two studies demonstrated increased responding indicative of aggression following alprazolam consumption; lorazepam, oxazepam, and triazolam each demonstrated varied results between two studies; and one study demonstrated clorazepate to have no effect on responding. Study methodology may have influenced these findings, as responding
indicative of aggression generally increased in TAP studies and decreased in PSAP studies post-benzodiazepine consumption. Studies which utilised the original or modified TAP demonstrated enhanced aggressive responding following consumption of triazolam (Berman & Taylor, 1995), lorazepam, oxazepam (15mg, 30mg; Bond & Lader, 1988), alprazolam (Bond et al., 1995), combined alcohol and alprazolam (Bond & Silveira, 1993), and diazepam (Ben-Porath & Taylor, 2002; Gantner & Taylor, 1988; Wallace & Taylor, 2009; Weisman, Berman & Taylor, 1998; Wilkinson, 1985), but not clorazepate or oxazepam (50mg; Weisman et al., 1998), and self-reported ‘sedative’ use in healthy adults did not influence alcohol-related aggressive responding (Giancola & Parrott, 2005). The variation concerning oxazepam may reflect a dose effect or an insufficient absorption period by Weisman and colleagues (1998) (90 minutes versus 4 hours), as oxazepam has been found to have a later onset of action (Bond & Lader, 1988). Interestingly, Wilkinson (1985) reported that aggressive responding was enhanced in low-trait anxious participants compared to high-trait anxious participants. Comparatively, the PSAP studies demonstrated decreased responding indicative of aggression in the majority of participants following lorazepam (n = 8; Pietras et al., 2005), triazolam (n = 5; Cherek, Spiga, Roache, & Cowan, 1991), and diazepam consumption (n = 9; Cherek et al., 1990). Interestingly, response patterns in the latter study indicated increased aggressive responding in high hostile participants (n = 2). Personality characteristics were measured in a further four studies (Bond et al., 1995; Bond & Lader, 1988; Bond & Silveira, 1993; Pietras et al., 2005), however none discussed whether individual differences were related to patterns of responding.

The most common approximate DZM equivalent doses administered acutely were 5mg and 10mg (DZM range = 2-20mg), and each produced variable results.
Findings of two out of five studies using 5mg (Berman & Taylor, 1995; Bond & Lader, 1988) and five out of ten studies using 10mg (Ben-Porath & Taylor, 2002; Bond & Lader, 1988; Gantner & Taylor, 1988; Wallace & Taylor, 2009; Wilkinson, 1985) suggested increased aggression. Higher doses either failed to influence aggressive responding (DZM = 16.7mg; Weisman et al., 1998) or resulted in decreased responding indicative of aggression (DZM = 20mg; Pietras et al., 2005), and only one participant displayed increased aggressive responding following the low equivalent dose of 2.5mg (Cherek et al., 1991). Only one study considered chronic administration, where participants engaged in the laboratory task following eight weeks of alprazolam treatment (DZM = 10-100mg) or placebo (Bond et al., 1995). Although the findings indicated alprazolam use increased behaviour indicative of aggression compared to placebo the flexible dosing schedule precludes consideration of dose effects.

Overall, the experimental studies suggest that acute administration of certain benzodiazepines (i.e., diazepam, alprazolam) can result in an aggressive response in adults. However, the use of analogue representations of aggression greatly limits the ecological validity of the findings. Moreover, the studies cannot inform our understanding of chronic benzodiazepine use, and the reliance on healthy community samples reduces their ability to inform clinically pertinent prescribing practices.

3.4.2 Clinical studies.

The review identified six clinical studies of varying methodological rigor. In each instance, aggression following benzodiazepine use was a secondary consideration. The clinical populations varied widely, including individuals with panic disorder and agoraphobia (Noyes et al., 1988; O’Sullivan et al., 1994), chronic schizophrenia (Karson, Weinberger, Bigelow, & Wyatt, 1982), borderline personality
disorder (BPD; Gardner & Cowdry, 1985), hypoactive syndromes (Feldman, 1962), and psychogeriatric patients (Burgio et al., 1992). Across the combined samples, aggressive behaviour was reported following benzodiazepine consumption in less than one percent (0.6%) of participants.

Only two of the clinical studies reviewed were RCTs (Noyes et al., 1988; O’Sullivan et al., 1994). Both explored acceptance and side effects of alprazolam treatment over eight weeks in individuals with panic disorder and agoraphobia \((n = 525\); Noyes et al., 1988; \(n = 154\); O’Sullivan et al., 1994). Inspection of the data indicates that one (0.19%; Noyes et al., 1988) and two (1.3%; O’Sullivan et al., 1994) patients demonstrated elevated physical aggression during treatment, in one case following a DZM equivalent dose of 40mg (Noyes et al., 1988). Further interpretation of the role of alprazolam in these events is hampered by inadequate detail regarding dosing schedules and the length of alprazolam treatment prior to the aggressive incidents.

Two studies utilised double-blind and placebo-controlled methods in a within-subjects design to explore the effect of clonazepam on individuals with chronic schizophrenia \((n = 13\); Karson et al., 1982) and alprazolam on behavioural dyscontrol in females with BPD \((n = 16\); Gardner & Cowdry, 1985). Each of the studies reported aggressive responding in a single patient, following either an equivalent dose of 80mg (Karson et al., 1982) or twenty days of treatment (Gardner & Cowdry, 1985). Less rigorous designs and poor reporting characterised the final two studies. An unclear number of individuals with hypoactive syndromes demonstrated aggressive responding following an unreported dose of diazepam (Feldman, 1962), and collapsed treatment effects across oxazepam and haloperidol suggested no changes in aggressive behaviour during treatment (4-26 days) in a
sample of psychogeriatric patients \((n = 21; \text{Burgio et al., 1992})\). It is interesting, and potentially clinically pertinent, that the latter study utilised a substantially lower dose schedule \((\text{DZM} = 3.3-10\text{mg})\) than the above studies \((\text{DZM} = 10-100\text{mg})\) and reported no changes in aggression. However, any oxazepam-specific results are obscured by the authors’ decision to collapse the treatment effects.

The above findings suggest that instances of aggressive responding to benzodiazepines are rare in the clinical populations investigated. However, poor reporting makes consideration of control methods and dose schedules difficult. Moreover, although the results appear to suggest that higher doses may be more risky, it is difficult to draw conclusions regarding chronic administration of benzodiazepines, due to the large variation in treatment periods (i.e., four days to three months; Burgio et al., 1992; Feldman, 1962, respectively), and the potential of other drug interactions, with medication wash-out periods ranging from one (Burgio et al., 1992; Gardner & Cowdry, 1985; Noyes et al., 1988) to two weeks (Karson et al., 1982; O’Sullivan et al., 1994).

### 3.4.3 Prospective studies.

Only two prospective studies were identified, and both suggest an association between benzodiazepine consumption and aggressive behaviour. However, due to the associative nature of the studies, neither provide evidence of causality.

The association between benzodiazepine prescription and aggression lacked robustness in both papers, as the associative strength varied according to the operationalization of aggression. In a six month study of nursing home residents, the finding of an association between increased benzodiazepine prescription and heightened levels of aggression depended on the observation rating scale used to classify participants as aggressive (Shah, Chiu, Ames, Harrigan, & McKenzie, 2000).
As residents were assessed using both scales, this variation suggests some issues with scale validity. The second prospective study followed a random sample of help-seeking U.S. veterans with PTSD, of whom 23% were prescribed benzodiazepines, over 5-12 months (Shin, Rosen, Greenbaum, & Jain, 2012). The findings demonstrated that although benzodiazepine prescription did not explain overall variance between baseline and follow-up aggression scores, benzodiazepine prescription was related to increased aggressive behaviour in individuals who were aggressive at baseline. However, as the authors operationalized aggression as the sum of four items adapted from the Conflict Tactics Scale, where only one item referred to other-directed physical aggression, it is unclear which aspect/s of aggressive behaviour increased between baseline and follow-up. Combined, these studies indicate how variable measurement of aggression can affect findings, and in turn, our understanding of the relationship between benzodiazepine use and subsequent aggression. Tentatively, however, individuals with higher baseline aggression levels may be more likely to experience benzodiazepine-related aggression.

Overall, both studies indicate some level of association between benzodiazepine prescription and aggressive behaviour. However, as neither study can suggest temporal order, the associations may reflect increased benzodiazepine prescriptions to manage aggressive behaviour. Moreover, both studies investigated highly specific samples, limiting generalizability, and neither study explored variations in benzodiazepine type or dose, and therefore fail to inform clinical practice.
3.4.4 Cross-sectional studies.

The cross-sectional studies explored a range of sample types, including clinical (i.e., psychiatric, addiction, hospital; \( n = 7 \)), healthy or community (\( n = 7 \)), and forensic (i.e., criminal justice involvement or incidents, forensic psychiatric; \( n = 11 \)). Per sample type, a large proportion of studies suggested an association between benzodiazepine use and aggression (63.6-71.4%).

Overall, fourteen (56%) cross-sectional studies demonstrate positive associations between benzodiazepine consumption and aggressive behaviour (Afifi, Henriksen, Asmundson, & Sareen, 2012; Dåderman, Fredriksson, Kristiansson, Nilsson, & Lidberg, 2002; Dåderman, Edman, Meurling, Levander, & Kristiansson, 2012; Forsyth, Khan, & Mckinlay, 2011; Hakansson, Schlyter, & Berglund, 2011; Haller & Deluty, 1990; Hammersley & Pearl, 1997; Lundholm, Haggård, Möller, Hallqvist, & Thiblin, 2013; Moore Glenmullen, & Furberg, 2010; Nabors, 2010; Rouve et al., 2011; Ryden et al., 1999; Stalans & Ritchie, 2008; Whitty & O’Connor, 2006), and three studies provide mixed findings according to gender and level of aggression (Mattson, O’Farrell, Lofgreen, Cunningham, & Murphy, 2012), delinquent status (Friedman, Terras, & Glassman, 2003), and unclear differences in cognitive assessment scores (Rosenfeld, 1987). The final eight studies suggest that benzodiazepine use is not associated with physical aggression or violence (Bramness, Skurtveit, & Mørland, 2006; Dåderman & Edman, 2001; Dåderman & Lidberg, 1999; Dawson, 1997; Feingold, Kerr, & Capaldi, 2008; Haggård-Grann, Hallqvist, Långström, & Möller, 2006; Rothschild, Shindul-Rothschild, Viguera, Murray, & Brewster, 2000; Voyer et al., 2005). The latter point may relate to similar temperament and sensation seeking scores between benzodiazepine users and non-users (Dåderman & Edman, 2001), however other cross-sectional findings suggest
that certain personality traits assessed through empirically supported personality inventories (i.e., boredom susceptibility, verbal aggression, Dåderman & Lidberg, 1999; antisocial psychopathy characteristics, Dåderman et al., 2012) and file-based indicators of psychiatric vulnerability (e.g., anxiety, impulsivity; Dåderman et al., 2002) may influence an aggressive response to flunitrazepam.

Operationalization and measurement of benzodiazepines and aggression varied considerably across studies. Examination of specific benzodiazepines suggested that aggressive behaviour was associated with temazepam (Hammersley & Pearl, 1997) and diazepam (Forsyth et al., 2011), but not alprazolam (Rothschild et al., 2000), with mixed results for flunitrazepam (Bramness et al., 2006; Dåderman et al., 2002; Dåderman et al., 2012; Dåderman & Edman, 2001; Dåderman & Lidberg, 1999) and clonazepam (Rosenfeld et al., 1987; Rothschild et al., 2000). However, nine studies utilised poorly defined terms such as sedatives or tranquilizers (e.g., Afifi et al., 2012; Dawson, 1997; Feingold et al., 2008; Friedman et al., 2003), or grouped benzodiazepines with other substances (e.g., opiates, GHB; Mattson et al., 2012; Nabors, 2010; Stalans & Ritchie, 2008), reducing the specificity of results, and attenuating the associative or predictive strength of the findings (e.g., Dawson, 1997). Furthermore, many studies failed to statistically control for concurrent substance use (e.g., Dåderman et al., 2002; Dåderman & Lidberg, 1999; Hammersley & Pearl, 1997). Similarly, although some studies clearly defined aggression (i.e., violent crime including manslaughter, assault; Dåderman et al., 2002; Dåderman et al., 2012; Dåderman & Edman, 2001; Dåderman & Lidberg, 1999; Haggård-Grann et al., 2006; Lundholm et al., 2013; Moore et al., 2010), only two studies utilised the same questionnaire (Conflict Tactics Scale-Revised; Afifi et al., 2012; Mattson et al., 2012), and five studies inferred aggression from endorsement of one (Hakansson et
al., 2011; Hammersley & Pearl, 1997; Nabors, 2010; Stalans & Ritchie, 2008) or two
(Dawson, 1997) items, reducing the interpretability of findings. Such variable
operationalization limits the ability to compare findings and form accurate
conclusions about the benzodiazepine-aggression association.

Nonetheless, a tentative conclusion may be drawn regarding the role of dose
with reference to the findings of two similar forensic studies. Both case-crossover
designs, the studies operationalized violence as violent interpersonal crime (i.e.,
manslaughter, assault, murder), and employed structured interviews with convicted
male violent offenders undergoing forensic psychiatric evaluation ($n = 133$;
Håggård-Grann et al., 2006), and remand prisoners suspected of violent crime ($n =$
194; Lundholm et al., 2013). The studies demonstrated that benzodiazepines
consumed alone (i.e., without alcohol) and in regular doses were associated with a
reduced risk of violence (Håggard-Grann et al., 2006; Lundholm et al., 2013), but an
increased risk of violence was associated with unusually high intake of
benzodiazepines (Lundholm et al., 2013). However, these findings must be
considered in light of the following limitations. That is, they rely on ambiguous
definitions of ‘regular’ or ‘unusually high’ doses, and on uncorroborated
retrospective self-report from forensic samples.

3.5 Discussion

The literature review demonstrated a relative paucity of published papers
explicitly examining the benzodiazepine-aggression relationship given its clinical
importance. Of those papers which met inclusion criteria, the majority of findings
pertain to experimental studies of acute low doses of benzodiazepines, or cross-
sectional examination of self-report data. According to the reviewed papers,
benzodiazepine use is moderately associated with subsequent aggressive behaviour.
Nine (69.2%) of the experimental studies reported a significant increase in behaviour indicative of aggression. However, there are clear limitations in generalising from simulated responses in contrived experimental settings to interpersonal aggression. Indeed, the clinical studies reported aggressive responding in less than one percent of participants (0.6%) during benzodiazepine treatment. However, as aggressive responding was not a focus of these studies, many lacked detail which limited the ability to draw conclusions to inform clinical prescribing practices. Although an association between benzodiazepine use and aggressive behaviour was indicated in the majority of the cross-sectional studies ($n = 17$) and both prospective studies, the varied operationalization of aggression and benzodiazepines impedes consideration of the proportion of individuals reporting benzodiazepine-related aggression. Moreover, as the correlational nature of these studies precludes analysis of temporal causality, their findings may reflect increased benzodiazepine use in order to manage aggressive tendencies. The discrepancies within the literature regarding the benzodiazepine-aggression relationship likely relate to differing methodologies, samples, and benzodiazepines tested.

### 3.5.1 Sample.

The most methodologically rigorous studies (Levels 4 and 5) were conducted primarily on non-clinical samples (71%) such as undergraduates or social drinkers, with only two high level studies exploring a clinical or forensic sample. The lack of high-quality evidence pertaining to these latter populations greatly hinders our ability to understand the clinical and legal implications arising from the benzodiazepine-aggression relationship.
3.5.2 Benzodiazepine type.
Diazepam was the most commonly examined benzodiazepine, and was associated with increased responding indicative of behavioural aggression in five out of six methodologically strong experimental studies. Unfortunately, some benzodiazepines are examined in fewer than two studies, limiting our understanding of whether all benzodiazepines promote a risk of aggressive responding.

3.5.3 Benzodiazepine dose.
The inconsistent nature of the clinical and experimental dose-related findings suggests that a dose effect does not adequately explain benzodiazepine-related aggression. Aggression, or behavioural responses indicative of aggression, can result after both acute (single dose) and chronic (continuous treatment) administration of benzodiazepines. Examination of approximate DZM equivalent doses suggested that therapeutic doses (i.e., 5-10mg) may be more likely to be associated with aggressive responding when administered acutely, whereas higher doses (i.e., 40mg, 80mg) may be more risky following chronic administration.

3.5.4 Personality.
Four cross-sectional studies explicitly examined personality, however the use of targeted sampling (i.e., flunitrazepam using violent offenders; Dåderman et al., 2002; Dåderman & Lidberg, 1999) and the lack of non-violent control groups (Dåderman et al., 2012; Dåderman & Edman, 2001) precludes definitive conclusions that personality influences flunitrazepam-related violence. Controlled laboratory testing also demonstrated that diazepam-enhanced aggressive responding was associated with low levels of trait anxiety (Wilkinson, 1985) and high levels of hostility (Cherek et al., 1990). These findings suggest that trait levels of anxiety and hostility may indicate a vulnerability to the experience of benzodiazepine-related
aggression, however further research is needed to corroborate and clarify the role of interpersonal vulnerabilities in this response.

3.5.5 Limitations.

Due to the inclusion criteria, only the studies which explicitly examined the relationship between benzodiazepine consumption and subsequent aggressive behaviour were reviewed, and therefore clinical drug trials where aggressive behaviour was observed, but not explicitly measured or discussed in the design were not identified. Furthermore, the review was limited to English studies and published data, which can limit the generalizability of the data (Cole and Kando, 1993). Operationalization of aggression in the cross-sectional studies was considerably inconsistent, and studies often failed to control for concurrent substance use, use control or comparison groups, or clearly report methodological or statistical techniques. Overall, the quality of the included studies was poor, indicating a need for higher quality studies exploring the benzodiazepine-aggression relationship. Of concern, none of the clinical studies considered benzodiazepine-related aggression a primary focus. Furthermore, investigation of forensic participants and individual differences was rare, reducing our ability to draw conclusions regarding the forensic implications of this review. Moreover, the majority of the experimental studies examined male-only samples (Ben-Porath & Taylor, 2002; Berman & Taylor, 1995; Cherek et al., 1990; Cherek et al., 1991; Pietras et al., 2005; Wallace & Taylor, 2009; Weisman et al., 1998; Wilkinson, 1985), limiting generalizability to females, who have been demonstrated to use benzodiazepines for non-medical reasons at a high rate (DCPC, 2007; Loxley, 2007; McGregor, Gately & Fleming, 2011).
3.6 Conclusions

The benzodiazepine-aggression response is an urgent clinical issue with serious clinical and forensic implications. Although aggression has been noted to follow benzodiazepine use in a number of experimental and non-causational studies, inconsistency within the literature means that the circumstances under which aggressive behaviour is likely to follow benzodiazepine consumption remain poorly understood. The evidence base requires high quality and systematic investigation of the various benzodiazepines and doses. Jones and colleagues (2011) outline recommendations to reduce benzodiazepine-related harms when prescribing; however there is limited evidence to further inform practice policy or legal defences. Such examination is especially pertinent with increasing evidence that amnesia is a common consequence of benzodiazepine use (e.g., Chavant, Favrelière, Lafay-Chebassier, Plazanet, & Pérault-Pochat. 2011; Dåderman et al., 2003; Tannenbaum, Paquette, Hilmer, Holroyd-Leduc, & Carnahan, 2012), which, when coupled with their afore-mentioned disinhibitory properties, may lead to unprecedented use of benzodiazepine-related legal defences (i.e., impaired responsibility, consideration of mitigating circumstances) in cases involving interpersonal violence. Advances in the literature are pertinent at a time when Australia has recently re-scheduled alprazolam to a controlled drug and considers similarly up-scheduling other benzodiazepines to Schedule 8.

3.7 Chapter Summary

A systematic literature review was conducted to explore the benzodiazepine-aggression relationship. Results of this review indicated that the related literature base is flawed and has poor explanatory power. Alprazolam and diazepam are the most commonly researched benzodiazepines, presumably due to their preferential
use within community, clinical and forensic populations, and as such have been most closely associated with subsequent episodes of aggressive behaviour. One area which has been understudied is the role of intrapersonal factors in benzodiazepine-related aggression, despite arguments that such factors are highly important in understanding this response (Lion et al., 1975; Hoaken & Stewart, 2003). The following two original studies were designed in order to further our understanding of the role of intrapersonal factors such as personality, motivational traits, and mental health functioning in this response.
Chapter Four: Motivational drive and alprazolam misuse: A recipe for aggression?

Please note, the following chapter presents an expanded version of an original manuscript submitted for review to Psychiatry Research (May, 2015), due to copyright reasons. Details of the submitted article have been appended for your consideration (Appendix C).

4.1 Introduction

Benzodiazepines are commonly used to manage anxiety or agitated behaviour (Ashton, 2002). However, for an estimated 1-20% of users, benzodiazepine use is followed by an aggressive response (Lader, 2011). The somewhat paradoxical nature of this response, coupled with the high medical, financial and personal costs associated with aggressive behaviour, suggests that changes to prescribing policies and regulatory strategies may be required to reduce the likelihood of benzodiazepine-related aggression from occurring. However, surprisingly little attention has been paid to understanding the psychological processes associated with benzodiazepine-related aggression. Controlled laboratory studies have demonstrated that alprazolam and diazepam often result in an increased aggressive response in some participants (e.g., Ben-Porath & Taylor, 2002; Bond et al., 1995; Bond & Silveira, 1993; Wallace & Taylor, 2009), and animal studies have alluded to the possible influence of concurrent alcohol use (de Almeida, Saft, Rosa, & Miczek, 2010) and pre-existing aggressive tendencies (Ferrari, Parmigiani, Rodgers, & Palanza, 1997; Weerts, Miller, Hood, & Miczek, 2010) in benzodiazepine-related aggression. Yet, few human studies have examined potential contributory factors (i.e., dose, other substance use, psychological or intrapersonal factors, situation; see Albrecht et al., 2014, for systematic review). Of note, irrespective of a long-standing proposal that
intrapersonal factors are important in understanding this response (Hoaken & Stewart, 2003; Lion et al., 1975), only a handful of studies have investigated the role of various personality characteristics in benzodiazepine-related aggression (i.e., trait anxiety, hostility; Ben-Porath & Taylor, 2002; Cherek et al., 1990; Dåderman et al., 2002; Wilkinson, 1985). The absence of a clear theoretical framework with which to explore benzodiazepine-related aggression impacts our ability to develop meaningful, and testable, hypotheses and intervention strategies. We argue that current models of approach and avoidance motivational tendencies may be able to inform our understanding of benzodiazepine-related aggression.

Motivational systems are theorised to underlie a number of human behaviours, including violent and aggressive behaviour. Gray’s (1982) Reinforcement Sensitivity Theory and its’ recent revision (rRST; Gray & McNaughton, 2003) purports to explain behavioural output and emotional expression based on three separate but interacting motivational systems. The behavioural approach system (BAS) promotes movement towards incentives and rewards, often involving goal-directed behaviour and impulsive action. The fight-flight-freeze system (FFFS) promotes fearful avoidance of a threat, and over-activation clinically presents as phobia or panic (Corr & Perkins, 2006). The behavioural inhibition system (BIS) promotes risk assessment and conflict resolution (Corr, 2008), and is stimulated by simultaneous and similar activation of the other two systems (Pickering & Corr, 2008). As demonstrated by prior research, the independent and interactive effects of these motivational systems have informed our understanding of aggressive behaviour. It is therefore expected that the application of this theory to benzodiazepine-related aggression will provide meaningful insight into the response, on which intervention strategies can be based.
Aggression appears to involve a strong approach motivational component (i.e., BAS mediated action such as antagonism; Smits & Kuppens, 2005). That is, aggression may result due to a strong motivation towards desired goals or rewards. Indeed, studies with university students have reported that high levels of BAS are associated with anger and aggressive behaviour (Harmon-Jones, 2003; Harmon-Jones & Peterson, 2008). However, theoretical understanding of approach motivation (BAS) suggests that it involves multiple aspects, including behavioural restraint, planning and goal-directed behaviour (Segarra, Poy, López, & Moltó, 2014), and the use of a broad, unidimensional measure of BAS in the above studies fails to account for such complexity. Instead, greater specificity is afforded through the use of a multidimensional measure of approach motivation. The BIS/BAS scales (Carver & White, 1994) were designed to account for the dynamic and multifaceted nature of the BAS. The division of BAS into three subscales (fun seeking, drive, and reward responsiveness) has allowed for discrete exploration of how these motivational tendencies differentially relate to behavioural outcomes, including the expression of anger and aggression.

Empirical evidence suggests that Drive is the most important facet in our understanding of aggressive behaviour. Drive (BAS-Dr) involves persistent goal pursuit and functional impulsivity; whilst fun seeking involves dysfunctional impulsivity, with minimal thought to consequences; and reward responsiveness involves positive energy and affect in response to reward cues (Tull, Gratz, Latzman, Kimbre, & Lejuez, 2010). BAS-Dr has been positively associated with the experience of anger (Cooper, Gomez, & Buck, 2008; Harmon-Jones, 2003; Smits & Kuppens, 2005), anger arousal, displaced aggression, the tendency to not suppress angry feelings or prevent the expression of anger (Cooper et al., 2008), self-reported
physical aggression (Harmon-Jones, 2003), relational aggression (Miller, Zeichner, & Wilson, 2012), and laboratory proxies of aggressive behaviour (Seibert, Miller, Pryor, Reidy, & Zeichner, 2010). In addition, Beaver, Lawrence, Passamonti, and Calder (2008) identified that with increasing BAS-Dr, neural structures and dopaminergic pathways are activated in a similar pattern to that observed in relation to both reward processing and aggression, providing some explanation as to why BAS-Dr is so important in understanding aggression. Further conceptual understanding of the link between BAS-Dr and aggressive behaviour is afforded through the concept of frustrative non-reward, which is experienced when the expected reward is higher than the actual reward (Corr, 2002). Indeed, although predominantly associated with the experience of positive affect (i.e., through goal attainment), BAS-Dr has also been associated with the experience of negative affect, especially sadness, frustration and anger, experienced in the context of blocked or challenged reward attainment (Carver, 2004). Such scenarios may influence an aggressive response. Following such theorising, aggression may be especially likely if the individual also experiences sensitivity to cues of punishment or threat (i.e., avoidance motivational tendencies). Essentially, aggressive behaviour may involve a facilitative interplay between appetitive and aversive motivational systems, where aggression is more likely when an individual with high BAS-Dr also experiences strong avoidance tendencies.

Such an interaction may be especially important in the understanding of benzodiazepine-related aggression. Evidence suggests that benzodiazepines selectively interfere with the conflict resolution system (BIS) by making approach behaviour more likely (Pickering & Corr, 2008). Such movement away from risk averse behaviour, coupled with a strong BAS-Dr, may increase the likelihood an
individual engages in aggressive behaviour following benzodiazepine use. In addition, BIS has been associated with reactive aggression (Miller et al., 2012), potentially reflecting the frustration response, and at extremely high levels of BIS activation, the related emotional disturbance may increase aggression risk (Hatfield & Dula, 2014). As yet no studies have attempted to explore the role of these motivational tendencies, or their interactions, in substance-related aggression, particularly benzodiazepine-related aggression. Such investigation of the rRST motivational systems and their interactive effects should provide further insight into this relationship.

4.2 The Current Study

The current study aims to test the premise that motivational factors are important in understanding benzodiazepine-related aggression, through the application of the rRST to this response. Due to their prevalence, the current study explicitly focuses on diazepam and alprazolam in relation to both general aggressive behaviour (i.e., anger, hostility, verbal aggression) and specifically physical aggression. In order to ascertain a holistic picture of the participants, data regarding their substance use, mental health, and criminal history, and recent psychological functioning are also gathered. It is predicted that:

1. Motivational factors will significantly predict engagement in benzodiazepine-related aggressive behaviour over and above benzodiazepine type or use (e.g., Hoaken & Stewart, 2003; Lion et al., 1975).

2. BAS-Dr, or the tendency to persistently pursue appetitive goals, will significantly predict general aggression and physical aggression.
3. BAS-Dr will moderate the relationship between BIS and aggressive outcomes. Specifically, it is predicted that the relationship between BIS and aggressive behaviour will be stronger for individuals with high levels of BAS-Dr.

The current study is the first to explore the role of BAS-Dr in substance-related aggression, particularly benzodiazepine-related aggression. It is hoped that this study will provide a deeper, theoretically driven, conceptualisation of this response than that currently afforded by the literature base.

4.3 Method

4.3.1 Design and procedure.

Participants were recruited via a purposeful sampling method, which utilised an online electronic questionnaire and paper based questionnaires located at health services. Online participants were recruited through electronic, newspaper, and paper flyer advertising, and health clinic participants were recruited via flyers posted at two health clinics, or through discussion with their treating clinician. Each recruitment method included a brief summary of the research, the plain language statement (PLS), and questionnaire. The PLS detailed the expected use of the data, and participants’ freedom to end the questionnaire at any point, but the inability of researchers to remove their data once submitted due to the anonymity of the responses. Consent was implied by completion of the questionnaire. After completing the questionnaire, participants were invited to enter a draw for one of six shopping vouchers and to provide feedback on forms which were kept separate from their responses. At the completion of data collection, all draw entries were collated and the winning participants were notified and sent the vouchers.

Inclusion criteria were age of 18 years or older and use of benzodiazepines in the past 12 months. There were no additional exclusion criteria. The study was
approved by the Deakin University Human Ethics Advisory Group (HEAG-H 123_2012) and the Eastern Health Human Research Ethics Committee (E42-1213).

4.3.2 Materials.

Screening item. An item assessed whether participants had used benzodiazepines in the previous 12 months. Those who responded ‘no’ were not eligible for participation.

Demographics. A brief self-report questionnaire assessed participant age, gender, country of origin, student status and education, employment and occupation, whether they were currently taking prescribed medication, treatment history for drug, alcohol, and mental health issues, and whether they had been charged or convicted with an alcohol or drug offence or with physical crimes against another person. Participants were instructed to select the most appropriate answer or provide brief written responses.

Substance and benzodiazepine use. A modified version of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), an eight-item questionnaire designed to detect psychoactive substance use and related problems (WHO ASSIST Working Group [WHO], 2002), was used to assess lifetime substance involvement and benzodiazepine-related dependency and harms. The ASSIST usually covers frequency of use and associated problems for 10 substances (tobacco, alcohol, cannabis, cocaine, amphetamines type stimulants, inhalants, sedatives, hallucinogens, opioids, and ‘other drugs’), though the majority of the items were altered to refer only to the benzodiazepine the respondent selected as their preferred type for non-medically prescribed use (see below). Specific substance involvement scores (SSI) were therefore calculated in relation to the preferred benzodiazepine. Moderate-high to high test-retest coefficients have been established
over one to three days (WHO, 2002), and both internal consistency ($\alpha = 0.77-.94$) and convergent and concurrent validity has been established (Humeniuk et al., 2008).

A 15-item self-report questionnaire was constructed to examine prescribed and non-medically prescribed benzodiazepine use. The literature utilises various definitions to distinguish benzodiazepine use for medical reasons from abuse, and confusing terms (e.g., medical versus non-medical) may result in inaccurate responding (e.g., self-medication, even at a high rate, may be interpreted as medical use). Therefore, the definition utilised in research needs to clearly differentiate between what constitutes appropriate consumption of benzodiazepines and abuse, or over-consumption. In the current study, *medically prescribed use* is when an individual takes benzodiazepines in the amount and frequency prescribed by their doctor. *Non-medically prescribed use* (NMP) is when benzodiazepines are not prescribed by their doctor or are taken more frequently or at higher doses than their doctor has prescribed. NMP benzodiazepine use can include to feel better, get high, have fun, or to substitute a usual drug of choice. By separating medically-prescribed and NMP use, we were able to isolate data regarding the misuse of benzodiazepines, and specifically explore aggressive responses following such use. We focussed on NMP use in order to further our understanding of the sequelae of benzodiazepine use which may not be readily observed or monitored by prescribers or other health professionals (e.g., due to the frequent diversion of benzodiazepines onto the black market; Best et al., 2013), and therefore only these participants completed the aggression measure. Additional items regarding benzodiazepine and substance use patterns were developed through consultation with academics and clinicians within the alcohol and other drugs field, specifically regarding item wording, relevance and
exhaustiveness. Respondents were instructed to select the most appropriate answer/s or provide brief written responses.

**BIS/BAS.** The Behavioural Inhibition System and Behavioural Activation System Scales (BIS/BAS; Carver & White, 1994) is a 24-item self-report questionnaire designed to assess Gray’s (1982) reward and punishment sensitivities. A five factor model was used to reflect the revised theory; the three BAS factors, BIS, and FFFS (Heym, Ferguson, & Lawrence, 2008). Items are rated on a 4-point Likert scale (1 = strongly agree, 4 = strongly disagree) with four filler items (i.e., not included in the analysis). Moderate test-retest coefficients have been demonstrated over an eight week period (Carver & White, 1994), and each subscale has demonstrated moderate to high internal reliability ($\alpha = .54-.82$), although BIS-FFFS demonstrates low to high coefficients between various populations ($\alpha = 0.17-0.73$; Dissabandara et al., 2012; Heym et al., 2008). Convergent and discriminant validity has also been established (Carver & White, 1994; Heym et al., 2008). In the current study, moderate to high internal consistency was demonstrated per subscale ($\alpha = .67 -.82$), and the revised five-factor model was confirmed (see Appendix B).

**Mood state.** The Depression, Anxiety, and Stress Scales (DASS-21; Lovibond & Lovibond, 1995) is a 21-item self-report questionnaire assessing state levels of depression, anxiety, and stress, with seven items per factor. Participants rate the degree to which each statement applied to them over the past week on a 4-point Likert scale (0 = did not apply to me at all, 3 = applied to me very much). Scale scores range from 0 to 21, and Australian norms are available (Crawford, Cayley, Lovibond, Wilson, & Hartley, 2011). High internal consistency has been demonstrated for each subscale and the total score ($\alpha = 0.79-.94$; Crawford et al., 2011; Henry & Crawford, 2005; Osman, Wong, Bagge, Freedenthal, Gutierrez, &
Lozano, 2012; Sinclair, Siefert, Slavin-Mulford, Stein, Renna, & Blais, 2012). Reliability coefficients were also high for each subscale in the current study (α = .853-.928). Convergent (Henry & Crawford, 2005; Osman et al., 2012) and concurrent validity has been established (Antony, Bieling, Cox, Enns, & Swinson, 1995).

**Aggression.** The Aggression Questionnaire (AQ; Buss & Perry, 1992) is a 29-item self-report questionnaire which measures various components of aggression; physical aggression (9 items), verbal aggression (5 items), anger (7 items), and hostility (8 items). Items are rated on a 5-point Likert scale (1 = extremely uncharacteristic of me, 5 = extremely characteristic of me). A total aggression score can be calculated by summing all subscale scores. The AQ has demonstrated moderately high to high internal consistency (α = .70-.92; Buss & Perry, 1992; Harris, 1997; O’Connor, Archer, & Wu, 2001), and temporal stability over nine weeks (Buss & Perry, 1992) and seven months (Harris, 1997). Moreover, convergent (Harris, 1997; McMurray, 2009; O’Connor et al., 2001) and concurrent validity have been established (Garcia-León, Reyes, Vila, Pérez, Robles, & Ramos, 2002). The instructions were altered to prompt participants to respond to the questionnaire in relation to the last time they had used NMP benzodiazepines as defined above, on an occasion when they were not consuming other drugs or alcohol. Internal consistency for the current study was high for the total score (α = .946) and across all factors (α = .838-.880).

**4.3.3 Statistical analyses.**

The data were cleaned and analysed using SPSS PASW Statistics 18. Where possible, parametric analyses were conducted, and means, standard deviations, and 95% confidence intervals (CI) are reported. Non-parametric chi-square tests of
independence are used where assumptions are violated and with categorical variables. Hierarchical multiple regressions were used to investigate the primary research questions. The dependent variables pertaining to aggressive behaviour reflect the AQ total score (i.e., a measure of general aggression) or the physical aggression factor score (i.e., a measure of physical aggression specifically). A total of 297 participants were recruited, though eight cases were removed due to the absence of benzodiazepine use detail, and 85 cases reported never using benzodiazepines for NMP reasons and therefore did not complete the AQ. The final sample size was therefore 204 participants. Preliminary screening of the data indicated a number of random item responses across the standardised questionnaires were missing (0.34%), and each item’s sample median was imputed to fill this missing data. In order to retain the originality of the data, due to its uniqueness in the literature base, violations of normality were either dealt with by pulling in extreme outliers, or by recoding into categorical variables. The variables used to compose the interaction term (BAS-Dr, BIS-Anx) were centered prior to forming the interaction term, in order to reduce multicollinearity, and categorical variables included in the regression analyses were standardized using dummy-coding.

**4.3.3.1 Model specification and invariance testing.** Model specification was purely conceptual, and based on understandings of the aggression and rRST literature. Therefore, age, gender, previous drug and alcohol use, and prior violent convictions were statistically controlled. However, due to the use of two recruitment methods, it was necessary to determine whether the data could be pooled without deleterious effects on the main analyses. It was determined through bivariate analyses that the internet and health centre recruitment subsamples differed on a number of demographic variables, including age ($t(286) = -8.041, p = .000, 95\% CI$:}
-13.19 to -8.01, Cohen’s $d = -1.21$), education ($\chi^2(2) = 39.131, p = .000$, Cramer’s V = .37), employment status ($\chi^2(1) = 26.885, p = .000$, Phi = .32), previous violent ($\chi^2(1) = 17.789, p = .000$, Phi = -.27) and AOD convictions ($\chi^2(1) = 26.048, p = .000$, Phi = -.31), and prior engagement in alcohol ($\chi^2(1) = 112.281, p = .000$, Phi = -.65) or drug treatment ($\chi^2(1) = 50.662, p = .000$, Phi = -44), but not gender ($\chi^2(1) = .000$, $p = .989$, Phi = -.11). Therefore, invariance analyses using the Chow test (Demaris, 2004) were conducted, at the $p < .05$ standard. Based on the outcome of these tests, the prediction of both general aggression ($\Delta \chi^2 (15) = 9310.373, p < .05$) and physical aggression ($\Delta \chi^2 (15) = 1368.56, p < .05$) varied according to whether the data was pooled or separated into recruitment samples. However, due to the size of the health centre subsample relevant for the aggression analyses (i.e., NMP use of benzodiazepines with AQ scores; $n = 30$), it is likely that the lack of power in the health centre subsample may have artificially led to a significant difference from the pooled sample model. The planned model on such a small subsample would likely inflate the chance of Type 2 error, due to the lack of statistical power available. It was therefore decided to pool the data and include a sample recruitment variable in the analyses.

4.4 Results

4.4.1 Participant characteristics.

The final sample consisted of 204 adult community members (62.7% male) who regularly use benzodiazepines, recruited via the internet ($n = 174; 63.2\%$ male) and health services ($n = 30; 60.0\%$ male), aged between 18 and 51 years old ($M = 27.12, SD = 8.21$). Participant demographic characteristics are displayed in Table 1.
The sample reported moderate to high scores across the BIS/BAS scales, and moderate levels of psychological distress (see Table 2). The sample reported high rates of poly-substance use, with the two most commonly used substances in the month prior to reporting (other than tobacco) being alcohol and cannabis (see Table 1). Less than a third of the sample admitted previously injecting an illicit substance ($n = 61; 29.9\%$), though almost half of these participants had done so in the last three months ($n = 27; 44.26\%$). In the three months prior to survey completion, half (54.4\%) of the sample reported drinking alcohol on at least a weekly basis, whilst 82.4\% reported using illicit drugs on at least a weekly basis. Of these, the majority reported using one or two types of illicit drugs per week (77.4\%), with 17.9\% using three types, and only 4.8\% ($n = 8$) using 4 or more types of illicit drugs per week.

Table 1

*Participant demographic characteristics.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>128</td>
<td>62.7</td>
</tr>
<tr>
<td>Female</td>
<td>76</td>
<td>37.3</td>
</tr>
<tr>
<td><strong>Country of Origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>74</td>
<td>36.3</td>
</tr>
<tr>
<td>New Zealand</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>Asia</td>
<td>6</td>
<td>2.9</td>
</tr>
<tr>
<td>Europe/UK</td>
<td>21</td>
<td>10.3</td>
</tr>
<tr>
<td>USA/Canada</td>
<td>96</td>
<td>47.1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Student</strong></td>
<td>Yes</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>112</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before year 12</td>
<td>31</td>
<td>15.2</td>
</tr>
<tr>
<td>Year 12</td>
<td>79</td>
<td>38.7</td>
</tr>
<tr>
<td>University/TAFE</td>
<td>94</td>
<td>46.1</td>
</tr>
<tr>
<td><strong>Employed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100</td>
<td>49.0</td>
</tr>
<tr>
<td>Yes</td>
<td>100</td>
<td>49.0</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>86 (42.2)</td>
<td>42 (20.6)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>31 (15.2)</td>
<td>23 (11.3)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>140 (68.6)</td>
<td>83 (40.7)</td>
</tr>
<tr>
<td><strong>Criminal History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOD</td>
<td>66 (32.4)</td>
<td>39 (19.1)</td>
</tr>
<tr>
<td>Violence</td>
<td>16 (7.8)</td>
<td>10 (4.9)</td>
</tr>
<tr>
<td><strong>Substance Use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>183 (89.7)</td>
<td>124 (60.8)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>194 (95.1)</td>
<td>156 (76.5)</td>
</tr>
<tr>
<td>Cannabis</td>
<td>189 (92.6)</td>
<td>121 (59.3)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>122 (59.8)</td>
<td>27 (13.2)</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>168 (82.4)</td>
<td>76 (37.3)</td>
</tr>
<tr>
<td>Inhalants</td>
<td>67 (32.8)</td>
<td>15 (7.4)</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>143 (70.1)</td>
<td>41 (20.1)</td>
</tr>
<tr>
<td>Opioids</td>
<td>148 (72.5)</td>
<td>85 (41.7)</td>
</tr>
</tbody>
</table>

*Note*. Unless where specified, sample percentages are enclosed in brackets.

*Note*. AOD = Alcohol and other drugs; convict = convicted.
**Benzodiazepine profile.** On average, participants began using NMP benzodiazepines at 20.46 years old (SD = 6.17). NMP benzodiazepines were most frequently acquired through friends (53.4%) or the black market (34.3%), and only 13.7% reported to have engaged in doctor shopping. Most participants (72.5%) reported using benzodiazepines with other substances; especially alcohol (17.6%), cannabis (11.3%), or both (8.3%). As expected, diazepam and alprazolam were most likely to be used for NMP reasons (52.9% and 54.3% respectively; see Table 3), and were explicitly preferred for NMP use by 23.5% and 39.7% of participants, respectively. ASSIST scores generally reflected a moderate risk of dependence (see Table 2). Although used relatively infrequently over the year prior to survey completion (Table 3), participants consumed diazepam and alprazolam at high average doses (see Table 4). Alprazolam was used at the highest average doses, and at a level considerably higher than recognised prescribing guidelines\(^1\) (i.e., up to 33mgs; ‘Alprazolam’, 2013). Diazepam and alprazolam were mostly used to reduce anxiety and tension (29.8%, 30.0% respectively) or to get high (14.5%, 24.6% respectively), as well as to reduce withdrawal from other substances (11.3%) for diazepam and to assist sleep (8.5%) for alprazolam.

**4.4.2 Main analyses.**

Bivariate correlations between the variables of interest demonstrated that both general and physical aggression scores were significantly associated with higher risk of alprazolam and diazepam dependence, psychological distress (DASS), BAS-Drive, and having a violent conviction (see Table 5). Physical aggression was also positively associated with having a substance-related conviction. Increased alprazolam doses were significantly associated, albeit at a low strength, with weaker

\(^1\) Prescribing guidelines suggest a daily range of 0.5-4.0mg per day (‘Alprazolam’, 2013).
### Table 2

**Standardised questionnaire score ranges, means and standard deviations.**

<table>
<thead>
<tr>
<th>Tool</th>
<th>Total</th>
<th>Range</th>
<th>M (n)</th>
<th>SD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASSIST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSI diazepam (n = 45)</td>
<td>2-36</td>
<td>12.76 (9)</td>
<td>10.20 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>0-3</td>
<td>(9)</td>
<td></td>
<td>(20.0)</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>4-26</td>
<td>(30)</td>
<td>(66.7)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>27+</td>
<td>(6)</td>
<td>(13.3)</td>
<td></td>
</tr>
<tr>
<td>SSI alprazolam (n = 77)</td>
<td>0-39</td>
<td>15.74 (8)</td>
<td>11.22 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>0-3</td>
<td>(8)</td>
<td></td>
<td>(10.4)</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>4-26</td>
<td>(52)</td>
<td>(67.5)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>27+</td>
<td>(17)</td>
<td>(22.1)</td>
<td></td>
</tr>
<tr>
<td><strong>DASS-21</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0-21</td>
<td>10.12</td>
<td>6.44</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0-21</td>
<td>7.78</td>
<td>5.57</td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td>0-21</td>
<td>10.01</td>
<td>5.38</td>
<td></td>
</tr>
<tr>
<td><strong>BIS/BAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAS-Dr</td>
<td>5-16</td>
<td>10.66</td>
<td>2.47</td>
<td></td>
</tr>
<tr>
<td>BAS-FS</td>
<td>6-16</td>
<td>12.11</td>
<td>2.37</td>
<td></td>
</tr>
<tr>
<td>BAS-RR</td>
<td>11-20</td>
<td>15.99</td>
<td>2.11</td>
<td></td>
</tr>
<tr>
<td>BIS-Anx</td>
<td>6-16</td>
<td>13.09</td>
<td>2.41</td>
<td></td>
</tr>
<tr>
<td>BIS-Fear</td>
<td>4-12</td>
<td>9.21</td>
<td>2.08</td>
<td></td>
</tr>
<tr>
<td><strong>AQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29-137</td>
<td>69.99</td>
<td>23.90</td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>9-43</td>
<td>19.06</td>
<td>7.91</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* ASSIST = Alcohol, Smoking and Substance Involvement Screening Test (WHO, 2002); AQ = Aggression Questionnaire (Buss & Perry, 1992); BIS/BAS = Behavioural Inhibition System and Behavioural Activation System Scales (Carver & White, 1994); BAS-Dr = Drive, BAS-RR = Reward Responsiveness; BAS-FS = Fun Seeking; BIS-Anx = Anxiety; DASS-21 = Depression, Anxiety, and Stress Scales (Lovibond & Lovibond, 1995); SSI = Specific Substance Involvement score.

BIS-related anxiety and fear, a history of a substance-related conviction, and a tendency to use multiple other substances when consuming benzodiazepines. Higher
diazepam doses were associated with having violent and substance-related convictions. Increased risk of dependence to alprazolam and diazepam was associated with increased psychological distress, though alprazolam risk was not associated with DASS-anxiety.

Table 3

*Lifetime NMP use per benzodiazepine, frequency of alprazolam and diazepam use in past year.*

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Ever NMP</th>
<th>Frequency of use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Alprazolam&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>157 (54.3)</td>
<td>Never</td>
</tr>
<tr>
<td>Temazepam</td>
<td>61 (21.2)</td>
<td>Once/twice</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>39 (13.5)</td>
<td>Monthly</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>71 (24.6)</td>
<td>Weekly</td>
</tr>
<tr>
<td>Diazepam</td>
<td>153 (52.9)</td>
<td>Daily</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>70 (24.2)</td>
<td></td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>27 (9.3)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Percentages reflect those reporting ever using selected benzodiazepine for NMP reasons.

4.4.2.1 *Predicting benzodiazepine-related aggression.* Two hierarchical multiple regressions were conducted, to explore whether BIS/BAS variables could predict benzodiazepine-related aggression over and above control and benzodiazepine variables. In both models, control variables were entered at Step 1, diazepam and alprazolam use at Step 2, BIS/BAS main effects at Step 3, and the interaction term at Step 4. Preliminary analyses were conducted to explore the
assumptions of normality, linearity, multicollinearity, and homscedasticity. Two multivariate outliers were identified via Mahalonobis’ distance, and case summaries indicated these cases placed substantial leverage on both aggression models (Field, 2009). These cases were therefore removed from the following analyses. For general aggression, casewise diagnostics demonstrated that only 1.4% of cases had standardised residuals of ± 2.0, and only 0.9% of ± 2.5, with none ± 3.0 (Field, 2009). For physical aggression only one case (.05%) had a standardised residual of ± 2.5 (Field, 2009). Examination of this specific case indicated that it was not having undue influence on the model and it was retained in the analysis.

Table 4

Typical and maximum daily alprazolam and diazepam doses, with approximate diazepam equivalent doses (DZM).

<table>
<thead>
<tr>
<th>BZD</th>
<th>Typical</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>Alpraz</td>
<td>119</td>
<td>0-15.0</td>
</tr>
<tr>
<td>Diaze</td>
<td>111</td>
<td>0-61.0</td>
</tr>
</tbody>
</table>

Note. BZD = benzodiazepine; Alpraz = alprazolam; Diaze = diazepam; DZM = approximate diazepam equivalent dose; mgs = milligrams.

<sup>a</sup> Approximate DZM computed using a 1:10 ratio for alprazolam, as suggested by dosing conversion table outlined by Farinde (2014).
Table 5

Bivariate correlations between factors of interest.

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</tbody>
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### Table 1

| A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U |
| L | .00 | .07 | .05 | .07 | .03 | -.02 | -.16* | .00 | .03 | .40* | .38* |   |   |   |   |   |   |   |   |   |   |
| M | .04 | .13 | -.25^ | -.28^ | -.06 | -.14 | .24^ | .29^ | .36^ | -.17^ | -.19* | .11 |   |   |   |   |   |   |   |   |   |   |
| N | -.01 | .08 | -.21* | -.25^ | .05 | -.12 | .30^ | .30^ | .36^ | -.24^ | -.32^ | -.00 | .54^ |   |   |   |   |   |   |   |   |   |
| O | .04 | -.03 | .09 | .08 | .14 | .17 | .33^ | .33^ | .46^ | .21^ | -.01 | .05 | .08 | .08 |   |   |   |   |   |   |   |   |
| P | .04 | -.06 | .10 | .10 | .14 | .16 | .22^ | .22^ | .34^ | .22^ | .03 | .05 | -.04 | -.07 | .87^ |   |   |   |   |   |   |   |   |
| Q | .10 | -.03 | .07 | .14 | .16 | .40^ | .04 | .12 | .15^ | .28^ | .18^ | .08 | -.05 | -.23^ | .17^ | .21^ |   |   |   |   |   |   |   |   |
| R | .25^ | -.06 | .24^ | .28^ | .19 | .30^ | .05 | .11 | .04 | .13 | .14* | .04 | -.11 | -.15* | .05 | .14* | .35^ |   |   |   |   |   |
| S | -.04 | -.07 | .25^ | .25^ | .15 | .03 | .10 | .15^ | .14^ | .22^ | .25^ | .14* | -.02 | -.05 | .13 | .12 | .14* | .05 |   |   |   |   |
| T | .24* | -.17 | .38^ | .41^ | .50^ | .50^ | .27* | .17 | .31^ | .16 | .04 | -.01 | .02 | -.12 | .33^ | .28* | .21 | .30^ | .24* |   |   |   |
| U | .33^ | .28 | -.18 | -.22 | .39* | .46^ | .30^ | .43^ | .54^ | .28 | -.05 | .05 | .25 | .07 | .53^ | .48^ | .26 | .13 | .11 | .a |   |   |
| V | -.07 | -.02 | .18 | .13 | .02 | -.06 | .15 | .05 | .10 | .12 | .21^ | .02 | -.15 | -.10 | .14 | .14 | .03 | .13 | .22^ | .23 | -.14 |   |

**Note.** A = age; B = gender; C = alprazolam typical dose; D = alprazolam maximum dose; E = diazepam typical dose; F = diazepam maximum dose; G = DASS Depression; H = DASS Anxiety; I = DASS Stress; J = BAS-Drive; K = FAS-Fun Seeking; L = BAS-Reward Responsiveness; M = BIS-Anxiety; N = BIS-Fear; O = general aggression; P = physical aggression; Q = violent conviction; R = substance-related conviction; S = use of other substances
when taking non-medically prescribed benzodiazepines; T = ASSIST score for those who prefer alprazolam; U = ASSIST score for those who prefer diazepam; V = number of substances regularly (at least weekly) used.

* correlation unable to be computed as discrete subsamples based on preferential benzodiazepine used for non-medically prescribed reasons.

* $p < .01$

^ $p < .001$
General aggression. Inclusion of the control variables at Step 1 explained 5.5% of the variance in general aggression ($F_{\text{change}} (6, 195) = 1.903, p = .082$). Entry of the benzodiazepine variables at Step 2 significantly improved the model, explaining an additional 3.7% of the variance; $F_{\text{change}} (2, 193) = 3.910, p = .022$. Entry of the BIS/BAS main effects at Step 3 again significantly improved the model, explaining an additional 6.7% of the variance; $F_{\text{change}} (5, 188) = 3.009, p = .012$. The inclusion of the interaction term at Step 4 did not significantly improve the model ($\Delta R^2 = .008$); $F_{\text{change}} (1, 187) = 1.769, p = .185$. However, the final model, with all the variables in the equation, was significant and accounted for 16.7% of the total variance in general aggression; $F(14, 187) = 2.682, p = .001$. Alprazolam and diazepam use, and BAS-Dr significantly attributed unique variance to general aggression, whilst recruitment group and BAS-FS approached significance (see Table 6). Inspection of the data indicates that BAS-Dr and alprazolam use made the strongest unique contributions to general aggression. Combined, BAS-Dr (5.29%) and alprazolam use (4.04%) contributed just under 10.0% towards the explanation of variance in general aggression, as calculated from the part correlation coefficients (Pallant, 2007).

It is notable that prior to the inclusion of the recruitment variable in the first step, the pooled data model indicated a significant effect of the interaction term ($p = .044$), accounting for 1.8% unique variance. Upon entering the recruitment variable the influence of the interaction term fell just outside significance ($p = .075$), before moving further from significance in the final model (i.e., following final case removal). This suggests that an extremely weak, but potentially clinically meaningful moderation of BAS-Dr on the BIS-Anx and general aggression relationship may exist, and may benefit from further research.
Table 6

*Hierarchical multiple regression predicting benzodiazepine-related general aggression.*

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<th>Part cor coef</th>
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*Note.* Part cor coef = part correlation coefficient; Viol Conv = violent conviction; Reg Drg = regular drug use (previous 3 months); Reg Alc = regular alcohol use (previous 3 months); BAS-Dr = drive subscale, BAS-RR = reward responsiveness subscale; BAS-FS = fun seeking subscale; BIS-Anx = anxiety subscale; BIS-Fear =
fear subscale; AnxXDr = interaction term. ^ centered variables.

Due to the significant findings pertaining to diazepam and alprazolam, it was explored whether general aggression differed according to benzodiazepine dose. Two follow-up independent samples t-tests (two-tailed) indicated that levels of general aggression did not differ between those using alprazolam within the prescribing range or above ($t(116) = -1.054, p = .294$, 95% C.I. = -13.52 to 4.13, Cohen’s $d = -.20$), or between those using diazepam within the prescribing range or above; $t(108) = -.849, p = .398$, 95% C.I. = -14.25 to 5.71, Cohen’s $d = -.18$.

Physical aggression. Inclusion of the control variables at Step 1 explained 6.4% of the variance in physical aggression; $F_{\text{change}}(6, 195) = 2.209, p = .044$. Entry of the benzodiazepine variables at Step 2 did not significantly improve the model ($\Delta R^2 = .015$); $F_{\text{change}}(2, 193) = 1.542, p = .217$. Entry of the BIS/BAS variables at Step 3 did however significantly improve the model ($\Delta R^2 = .057$); $F_{\text{change}}(5, 188) = 2.459, p = .035$. The inclusion of the interaction term at Step 4 did not significantly improve the model ($\Delta R^2 = .000$); $F_{\text{change}} (1, 187) = .000, p = .991$. However, the model remained significant at each step, and the final model, with all the variables in the equation, accounted for 13.5% of the total variance in physical aggression; $F(14, 187) = 2.084, p = .014$. Again, alprazolam and BAS-Dr significantly attributed unique variance to physical aggression, although recruitment group and BAS-FS approached significance (see Table 7). As calculated from the part correlation coefficients (Pallant, 2007), BAS-Dr (4.6%) and alprazolam use (1.8%) contributed a combined 6.4% towards the explanation of variance in physical aggression.
Table 7

Hierarchical multiple regression predicting benzodiazepine-related physical aggression.

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Note. Part cor coef = part correlation coefficient; Viol Conv = violent conviction; Reg Drg = regular drug use (previous 3 months); Reg Alc = regular alcohol use (previous 3 months); BAS-Dr = drive subscale, BAS-RR = reward responsiveness subscale; BAS-FS = fun seeking subscale; BIS-Anx = anxiety subscale; BIS-Fear = fear subscale; AnxXDr = interaction term.

^ centered variables.
A follow-up independent samples t-test (two-tailed) indicated that levels of physical aggression did not differ between those using alprazolam within the prescribing range or above \((t(116) = -1.658, p = .100, 95\% \text{ C.I.} = -5.36 \text{ to } .48, \text{Cohen’s } d = -.31\)).

**4.5 Discussion**

Benzodiazepine-related aggression is poorly understood. In an effort to understand this response in greater depth, the current study aimed to explore the role of motivational tendencies in benzodiazepine-related aggression. It was proposed that such characteristics would predict aggressive responding over and above benzodiazepine type, and that BAS-Dr specifically would be important in understanding this response. It was also predicted that BAS-Dr would moderate an association between risk averse motivational tendencies and benzodiazepine-related aggression. The data generally supported these predictions, however the moderation effect was not observed.

**4.5.1 Role of BAS-Dr in benzodiazepine-related aggression.**

The tendency to pursue appetitive goals in a persistent manner (BAS-Dr) has been consistently associated with aggression and related tendencies (i.e., anger; Cooper et al., 2008; Miller et al., 2012; Seibert et al., 2010). The current study extends this literature, by hypothesising that BAS-Dr is important in benzodiazepine-related aggression. In support of this hypothesis, BAS-Dr was the strongest unique predictor of both general aggression and physical aggression, over and above the influence of benzodiazepine type (diazepam and alprazolam). Such outcomes align with research indicating the importance of BAS-Dr in the prediction of aggressive behaviour compared to other intrapersonal factors (Seibert et al., 2010), and importantly, support the contention that our understanding of benzodiazepine-related
aggression may be enhanced via recourse to intrapersonal differences (Hoaken & Stewart, 2003; Lion et al., 1975).

Individuals with strong BAS-Dr have been described as antagonistic, competitive, and willing to work hard to achieve goals, even if at the expense of others (Segarra et al., 2014). Such individuals hold high expectations of rewards following goal attainment (Harmon-Jones, 2003) and their experienced affect is strongly reflective of their perceived progress towards their goal (Carver, 2004). For example, in the context of challenged or blocked goal attainment, individuals with high BAS-Dr may experience frustration or anger (Carver, 2004), such as frustrative non-reward (Corr, 2002). Aggressive behaviour then becomes increasingly likely, as during frustration, such individuals display reduced impulse control (Beaver et al., 2008) and attention to risk or punishment cues (Avila, 2001). Their ability to respond appropriately to stressors or frustrations may become further disinhibited in the context of benzodiazepine use (Paton, 2002). Indeed, the current data indicate that individuals with stronger BAS-Dr tendencies experienced greater anxiety and stress, which may reflect difficulty attaining desired outcomes (Carver, 2004), and tended to consume benzodiazepines in the context of other substances, which may further impact their coping or self-regulation ability. However, the absence of appropriate causal testing limits the conclusions able to be drawn from such associations, though the findings do clearly support the role of persistent action towards desired goals in benzodiazepine-related aggressive behaviour. As such, prescribers may benefit from exploring patients’ ability to engage in effective impulse control and frustration tolerance strategies prior to prescribing benzodiazepines. Such information may be gleaned from knowledge of the patient’s psychosocial background, or by specifically enquiring into their coping strategies, tendency to act without consideration of
consequences, engagement in risky behaviour, and ability to respond to frustration in a pro-social manner (i.e., delayed consult time, smaller prescription than requested).

Interestingly, the expected moderation effect between a strong appetitive and strong aversive motivational system on benzodiazepine-related aggressive behaviour failed to significantly influence either aggression model. Given that our sample displayed only moderate levels of aggression, such an effect may be more likely in a more violent sample, against clearly defined violent incidents. Furthermore, aggression risk may be associated with extremely high levels of BIS activation (Hatfield & Dula, 2014), whilst our sample displayed only moderately-high BIS activation. The moderating effect may therefore only be relevant to investigations of benzodiazepine-related aggression in individuals with more complex motivational presentations than those observed in the current sample.

4.5.2 Role of benzodiazepine type in benzodiazepine-related aggression.

The current findings suggest that alprazolam poses a greater risk than diazepam for subsequent aggressive behaviour. As described elsewhere (Horyniak, Reddel, Quinn, & Dietze, 2012; Rintoul, Dobbin, Neilsen, Degenhardt, & Drummer, 2013), alprazolam is one of the most problematic benzodiazepines, and has recently been rescheduled to a controlled substance within Australia, in order to mitigate the risks associated with it. Given its short acting effects, association with poly-substance use in the current sample, and the common goal to become intoxicated (25.6%), alprazolam-related aggression may reflect the context of use, rather than the physiological effects of alprazolam. Indeed, aggressive behaviour did not differ according to alprazolam dose. When considered with our finding that intrapersonal factors accounted for greater amounts of variance than alprazolam use alone, the current data appear to support Lion and colleagues’ (1975) supposition that it is the
interaction between benzodiazepine use, the situation and intrapersonal factors that influences subsequent aggressive behaviour. However, further research using urinalysis and an in-depth analysis of substance use patterns is required.

Interestingly, general aggression was significantly negatively predicted by diazepam use. Within the current sample, diazepam is used more for alleviation of negative emotional and physical states (i.e., anxiety, tension, or effects of withdrawal; 41.1%), rather than to get high (14.5%), whereas alprazolam use is more evenly attributed to both reasons. This differentiation further highlights the role that approach motivations (rather than avoidance motivational tendencies) may have in the experience of benzodiazepine-related aggression. Furthermore, unlike alprazolam, diazepam appears to be infrequently used within the context of poly-substance use, and therefore may be generally used in scenarios less conducive to aggressive interactions. In addition, only when diazepam-preferring participants were examined in isolation, of whom predominately displayed a moderate or high risk of dependence (i.e., difficulty managing diazepam use, experience of problematic diazepam-related outcomes), did we find a positive association with aggressive outcomes. Comparatively, the regression analyses were conducted with all participants who had reported historically using diazepam for NMP reasons (i.e., not necessarily frequent, ongoing, dependent use). Therefore, it could be concluded that diazepam poses a risk for benzodiazepine-related aggression only in those who display increasingly problematic patterns of diazepam use, rather than to the majority who use diazepam on a less regular basis. This has important implications for the continued prescription of diazepam, highlighting the importance of prescribers carefully monitoring patient adherence to low dose, short term use, and the potential benefits of prioritising non-medicinal approaches in assisting patients (Dobbin, 2014;
Lader, 2014). Comparatively, alprazolam appears to be a risk for aggression at both dependent (problematic) levels and for those with less frequent use, and may be best prescribed only after exhausting other treatment options.

4.5.3 Limitations and strengths.

A number of limitations must be acknowledged. Due to the cross-sectional nature of the study, causality cannot be implied, and data collection relied on uncorroborated, retrospective self-report which may be vulnerable to attributional biases and memory decay. In addition, the study did not involve a manipulation check to ensure that the modification to the aggression questionnaire was successful, meaning that conclusions should be considered with an element of caution, especially given the lack of measurement of aggressive tendencies in the absence of benzodiazepine use. The questionnaire was considered already burdensome (on average more than 45 minutes to complete) that to also include such a measure (possibly the AQ without the modified instructions) would result in increased participant dropout. The temporal duration between benzodiazepine consumption and the aggressive response was also not assessed, and therefore the possibility that the response occurred during benzodiazepine withdrawal (Votava, Kršiak, Podhorná, & Miczek, 2001) cannot be discounted. Benzodiazepine use was also assessed through a non-standardised and non-piloted questionnaire. Participant feedback indicated that the questionnaire was lengthy and failed to include an exhaustive list of street names for various licit and illicit substances. Furthermore, the predictive models were unable to be explored based on recruitment type, due to the insufficient sample size of the health centre subsample. In addition, the findings are limited in generality, and cannot be reliably applied to individuals who commit more severe violence. Moreover, it cannot be discounted that other substances used in combination with
benzodiazepines may have impacted the findings (Sweeney & Payne, 2012). Finally, the current study did not permit direct examination of frustrative non-reward as this can only be examined when reward pathways are activated.

Despite these caveats, the current study has a number of important and unique strengths. First, specific benzodiazepines are explored, allowing greater specificity than the majority of cross-sectional studies available. Greater specificity is also permitted through the separate examination of general aggressive tendencies and physical aggression specifically. Third, the sample is relatively large, with an almost even gender split; the latter feature absent in a number of well-designed, though male-only, examinations of benzodiazepine-related aggression (see Albrecht et al., 2014 for a review). The most important contribution of the current study, however, is that it is the first study to have a theoretically informed examination of benzodiazepine-related aggression, thus offering a clear model against which such behaviour can be more greatly understood, and interventions can be designed. The application of the rRST at the facet level provides additional specificity in order to inform such implications (Jones, Miller, & Lynam, 2011; Miller et al., 2012; Segarra et al., 2014).

4.6 Implications and Conclusions

Lion and colleagues (1975) suggested that it is the interaction between benzodiazepine use, intrapersonal factors, and context which can explain benzodiazepine-related aggression. Our data alludes to the influence of goal-driven tendencies and certain benzodiazepine use, though the situational context remains unclear. Future investigations could therefore benefit from an exploration of the context surrounding the aggressive act (i.e., presence of frustration or goal challenge), as well as consideration of beliefs and attitudes regarding the
acceptability of aggressive behaviour (i.e., aggressive scripts; Anderson & Bushman, 2002).

In lieu of these aspects receiving further attention, the current findings do demonstrate the importance of intrapersonal factors in understanding benzodiazepine-related aggression (Hoaken & Stewart, 2003; Lion et al., 1975). Notably, benzodiazepine users may be more likely to engage in aggressive behaviour if they exhibit persistent tendencies to pursue desired goals. In addition, general diazepam use (i.e., not in the context of dependency) appears to reduce the risk of general aggressive behaviour (i.e., anger, hostility, verbal aggression), whilst alprazolam increases the risk of aggression, regardless of dose. Although further work is necessary to confirm the mechanisms underlying the association between motivational drive and benzodiazepine-related aggression, the findings highlight the benefit of attending to frustration tolerance and aggression scripts in individuals with high BAS-Dr, and support the rescheduling of alprazolam to a controlled substance.

4.7 Chapter Summary

The application of a theory-driven research approach has highlighted the importance of intrapersonal factors in understanding benzodiazepine-related aggression. Notably, persistent approach of desired goals was associated with increased aggressive behaviour. In addition, alprazolam was highlighted as more risky than diazepam in regards to self-reported physical aggression, aligning with recent national and international concerns about the benzodiazepine. Community based studies are important in the examination of this response, as they provide insight into the population likely to access community-based health centres and drug and alcohol clinics. However, the low base rate of aggressive behaviour in such samples suggests that a clearer understanding of this response may be afforded by
investigation of a violent criminal justice sample. As will be discussed in the following chapter, such samples have received minimal attention in related literature, despite the potential that such examination has to inform the use of prescribed benzodiazepines in justice health contexts, and the development of appropriate violent offender rehabilitation strategies.

Due to local restrictions on new research protocols with justice populations, the following study involved analysis of a previously-acquired database, developed in the absence of strong theoretical reasoning. It is hoped that the uniqueness of the database (i.e., benzodiazepine-using offenders) provides valuable insight into this response, and informs the development of future, more theoretically rigorous, research protocols exploring benzodiazepine-related aggression in violent samples.
Chapter Five: Violent crime: A complex interplay of benzodiazepine use, psychological distress, and problematic impulsive behaviours.

Please note, this chapter presents an expanded version of an original manuscript submitted for review to Journal of Substance Abuse (September, 2015), due to copyright reasons. Details of the submitted article have been appended for your consideration (Appendix D).

5.1 Introduction

Why any individual commits a violent act is a question that generally frightens and confronts us. Years of research and investigation have shown that violence involves a complex interplay of social, environmental, biological and situational elements (Anderson & Bokor, 2012; Steinert & Whittington, 2013). However, in spite of examinations of the construct from a broad array of disciplines, including neurobiology, mental health, sociology, criminology, and addiction (for reviews, see Anderson & Bokor, 2012; Chereji, Pintea, & David, 2012; Friedman, 1998; Schenk & Fremouw, 2012), a number of questions still remain. One of these questions involves identifying the role of various substances in the commission of violent behaviour. Despite knowing that pharmacological properties of substances can have a profound influence on neurobiology, mental state, and behaviour, we know relatively little about how this differs between substances to effect violent behaviour (i.e., both stimulants and depressants have been associated with violence; e.g., Lennings, Copeland, & Howard, 2003; McKetin et al., 2014). While the role of alcohol in violent behavior has been studied at length, benzodiazepine use on the other hand has been surprisingly under-researched. Given the increasing misuse of benzodiazepines (ACC, 2014), particularly amongst those with mental health issues
and forensic backgrounds (Ng & Macgregor, 2012; Stafford & Burns, 2013; Sweeney & Payne, 2012), further research is warranted.

A recent systematic review (Albrecht et al., 2014) suggests that benzodiazepines may play a role in aggressive behavior and violent crimes (e.g., French, 1989; Ben-Porath & Taylor, 2002; Lundholm, Haggård, Möller, Hallqvist, & Thiblin, 2013; Moore, Glenmullen, & Furberg, 2010). For example, an estimated 1-20% of benzodiazepine users report experiencing some form of increased anger or aggression following use (Lader, 2011). While this may seem counter-intuitive given the sedating effects of benzodiazepines, neurobiological theories suggest that such paradoxical effects may arise due to disinhibition following benzodiazepine use (Bond, 1998; Longo & Johnson, 2000). This unlikely effect has been repeatedly demonstrated in experimental laboratory studies, where increased responding indicative of aggression has followed consumption of acute doses of benzodiazepines (e.g., alprazolam, diazepam) compared to placebo (e.g., Wilkinson, 1985; Bond, Curran, Bruce, O’Sullivan, & Shine, 1995). However, the use of analogue representations of aggression in highly controlled circumstances greatly limits the ecological validity of such findings.

### 5.1.1 Benzodiazepines and violent crime.

Criminal justice samples have been found to misuse benzodiazepines more than the general community (e.g., AIHW, 2011; Ng & Macgregor, 2012). Yet, empirical literature examining the association between benzodiazepine use and subsequent violent crime is rare (see Albrecht et al., 2014, for a review). Although benzodiazepines, either alone or in combination with other substances, have been empirically associated with criminal behaviour, including acquisitive and property crime (Bradford & Payne, 2012; Darke & Ross, 1994; Darke, Ross, Mills, Teesson,
Williamson, & Havard, 2010; Payne & Gaffney, 2012; Smith, Miller, O’Keefe, & Fry, 2007), comparatively little attention has been paid to their association with violent offences. To date, no research has explored the relationship between benzodiazepine use and actual violent crime in an adult community criminal justice sample. This is despite recent research demonstrating young community based offenders (aged 16-20 years) attribute their violent crimes most commonly to diazepam (often in conjunction with alcohol; Forsyth, Kahn, & McKinlay, 2011). Furthermore, studies of remanded and incarcerated violent offenders report positive associations between violent crime and higher doses of (unspecified) benzodiazepines (and combined alcohol use; Haggård-Grann, Hallqvist, Långström, & Möller, 2006; Lundholm et al., 2013). The focus of this study is to examine in detail how community-based offenders engaged in violent crime differ from those engaged in non-violent crimes across a range of mental health and substance abuse behaviours with a particular focus on their use of benzodiazepines. Findings will have particular relevance to law enforcement and addiction treatment services in the community, at a time when recent rescheduling of alprazolam to a controlled substance (Schedule 8) in Australia may impact the already increasing diversion of benzodiazepines onto the black market (ACC, 2014).

Importantly, the available literature provides little insight into the specific dose schedules or types of benzodiazepines which present increased risk of violence. That is, the nature of the benzodiazepine-violence relationship appears to vary according to administration and dosing schedules of specific benzodiazepines. For example, methodologically diverse investigations have provided evidence both for and against the role of alprazolam in violent behaviour (e.g., Bond et al., 1995; Bond & Silveira, 1993; O’Sullivan et al., 1994). In addition, existing cross-sectional
studies often group benzodiazepines together (ignoring concepts such as the half-life or function of specific benzodiazepines), fail to consider dose, and at times do not include non-violent controls (e.g., Dåderman, Fredriksson, Kristiansson, Nilsson, & Lidberg, 2002). Such methodological limitations have hampered our understanding of the relationship between benzodiazepine use and subsequent violent crime. Improving our understanding of these relationships may have important medical and legal implications for prescribing practices, especially when benzodiazepines are commonly used to manage agitation (Ashton, 2002), often in public spaces such as hospital emergency rooms.

5.1.2 The current study.

In order to address some of these gaps, the present study aims to examine the relationship between benzodiazepine use and engagement in violent crime within a benzodiazepine-using, community-based criminal justice sample. Previously gathered data are re-analysed with this specific research question in mind. The current study uses a non-violent offender comparison group, and uniquely explores whether benzodiazepine type or dose level is more closely associated with violent than non-violent crimes. Alprazolam and diazepam are specifically examined due to their frequent misuse in forensic populations (McGregor, Gately, & Fleming, 2011; Sweeney & Payne, 2012), and benzodiazepine use during the month and day preceding a recent crime is explored. It is predicted that individuals engaged in violent crime will report greater benzodiazepine use, and higher doses, than non-violent offenders. In order to attend to the complexity of violent behaviour (DeWall, Anderson, & Bushman, 2011), core factors understood to play a role in violent crime are also assessed. Based on prior literature, it is expected that individuals engaged in violence will exhibit a heightened level of impulsivity (Derefinko, DeWall, Metze,
Walsh, & Lynam, 2011; Smith & Waterman, 2006), increased psychological distress or disorder (e.g., Swogger, Walsh, Houston, Cashman-Brown, & Connor, 2010; Umberson, Williams, & Anderson, 2002), poly-substance use (Friedman, 1998), and prior criminality (Rice, Harris, & Lang, 2013).

5.2 Method

5.2.1 Participants.

Participants were recruited through purposive sampling techniques via drug treatment programs and initiatives within the criminal justice system in Melbourne, Australia, including the Court Integrated Services and other drug treatment services, through liaison with service managers and forensic counsellors. Eligibility criteria were (i) 18 years and over, (ii) committed a crime within six months of the interview, and (iii) used benzodiazepines (prescribed or non-prescribed) at least once per month in the last six months. The current study uses the term ‘index offence’ to refer to the participants’ most recent crime, to which eligibility criteria (ii) relates. Participants were divided into violent and non-violent groups based on this offence.

5.2.2 Design and Procedure.

The study involved a specifically developed semi-structured interview protocol. Participants provided demographic information, mental health and substance use history, and the context of their index charge (i.e., employment and residential information). Interviews lasted 45-60 minutes and were conducted either face-to-face or over the telephone, and were audio recorded and transcribed verbatim. Analysis of the de-identified data was approved by the relevant ethics committees.
5.2.3 Measures.

**Psychological distress.** The Kessler Psychological Distress Scale (K-10; Kessler et al., 2002) is a 10-item questionnaire designed to measure self-reported psychological distress over the most recent 4-week period, or in this case the month before the crime. A score of 30 or more has been demonstrated to be the most accurate indicator for a severe mental disorder (Andrews & Slade, 2001). The K-10 has demonstrated predictive validity in a national Australian sample (Furukawa, Kessler, Slade, & Andrews, 2003).

**Impulsivity.** The UPPS Impulsive Behaviour Scale (UPPS; Whiteside & Lynam, 2001) is a 45-item questionnaire measuring impulsivity across four subscales, with higher scores indicating greater levels of impulsivity. The subscales are Urgency (12 items; e.g., “when I am upset I often act without thinking”), (lack of) Premeditation (11 items; e.g., “I like to stop and think things over before I do them”), (lack of) Perseverance (10 items; e.g., “I concentrate easily”), and Sensation Seeking (12 items; e.g., “I’ll try anything once”). The four factor model has demonstrated construct and differential validity (Miller, Flory, Lynam, & Leukefeld, 2003; Whiteside, Lynam, Miller, & Reynolds, 2005), and concurrent validity within a sample of alcohol-consuming college students (Magid & Colder, 2007). The subscales have shown good internal consistency ($\alpha = 0.82-0.91$; Whiteside & Lynam, 2001).

**Substance use and dependence.** The Severity of Dependence Scale (SDS; Gossop & Darke, 1995) is a five-item questionnaire providing a score indicating the degree of dependence to a certain substance. Data was collected regarding dependence to benzodiazepines, in the month prior to the index offence. The items

2 The original study utilised a 5-point Likert scale (0 = not at all, 2 = sometimes, 4 = very much). It is recognised that this departs from the standardised application of the UPPS, which uses a 4-point Likert scale (1 = strongly agree, 4 = strongly disagree).
are scored on a 4-point scale (0-3) with a total score obtained by the sum of all item ratings. A score of 7 or higher indicates benzodiazepine dependence (de las Cuevas, Sanz, de la Fuente, Padilla, & Berenguer, 2000).

A 28-day timeline follow back method (Sobell & Sobell, 1992; Sobell, Brown, Leo, & Sobell, 1996) was used to measure benzodiazepine, alcohol, pharmaceutical opiate and illicit drug use in the month prior to the index crime. Participants were asked about drug type and amount used, route of administration, days of no use/withdrawal, days of increased use, and days of different drug combinations or administration methods.

**Criminality.** The Criminality Index from the Opiate Treatment Index (OTI; Darke, Hall, Wodak, Heather, & Ward, 1992) was used as a measure of criminal behaviour in the month prior to the index offence. The Criminality Index explores the frequency of recent property crime, drug dealing, fraud, and violent crime using a 5-point Likert scale (0 = no crime, 2 = once a week, 4 = daily). Scores are summed to form a total score (0-16), with higher scores indicating greater criminal involvement. The Criminality Index has demonstrated test-retest reliability over a one week period (0.96), and construct validity with official criminal records and the Addiction Severity Index (ASI) crime days measure, but limited internal reliability ($\alpha = 0.38$; Darke et al., 1992), potentially due to the nature of the items all referring to specific and disparate crime types. The violent crime item has demonstrated agreement between a person’s self-report and collateral report (94% agreement, kappa: -0.03) and conviction records (89.2% agreement; kappa = .071$^3$; Darke et al., 1992). The tool has been successfully applied in a study exploring benzodiazepine use (Darke & Ross, 1994).

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$^3$ Low kappa figures with a high agreement may reflect the low base rate of the behaviour under the agreement analysis (Viera & Garrett, 2005)
5.2.4 Statistical analyses.

The data were analysed in SPSS PASW Statistics 18. Preliminary screening informed the deletion of six cases due to no data, and indicated that there was a proportion of incomplete data for the dose variables ($n_{\text{range}} = 44-60$; $53.70-73.17\%$). Due to the unique nature of the data, statistical imputation was not conducted, though pairwise case exclusion was applied to analyses. This may have attenuated the statistical power available, and influenced the choice of statistical analyses that were conducted. Where normality was violated, variables were recoded, including number of mental health diagnoses (zero; one; two or more diagnoses), OTI Violence (violent vs non-violent), and benzodiazepine dose (within or above the standard dosing range$^4$ outlined in the MIMS; “Alprazolam”, 2013; “Diazepam”, 2013). Inspection of bivariate correlations indicated an absence of multicollinearity. The final sample size was 82.

Due to concerns of the veracity of the impulsivity data provided (i.e., pre-computed scale scores), a research assistant not involved in the current research study extracted the item-level impulsivity data from the raw data, into a de-identified electronic spreadsheet. Impulsivity data for 76 cases were provided. Inspection of this item-level data by the first author indicated that the scale scores provided in the de-identified database were incorrect. In order to align the final scores with those possible within the standardized version of the UPPS (i.e., zero scores are not possible), 7.25% ($n = 248$) of the data points required re-scoring from zero to one. Inspection of missing data indicated that less than 1% ($n = 35$) of the data points were missing, and these were imputed with the sample median per item. Items were reverse-scored, taking into consideration the already reversed scale direction (i.e., $4 = \ldots$)

$^4$ Alprazolam: 0.5-4.0mg per day; Diazepam: 5-40mg per day.
very much, whilst standardized UPPS uses 4 = strongly disagree\(^5\), and scale totals were calculated using SPSS Compute Variable. Only impulsivity data of 74 cases were transferred into the main database, due to the prior deletion of two cases above. All scale scores were normally distributed, with no univariate outliers, and the assumption of multicollinearity was upheld.

Sample characteristics were explored using descriptive and frequency analyses. Where possible, group differences were explored using independent samples t-tests (two-tailed), and means, standard deviations, and 95% confidence intervals (CI) are reported. For categorical variables, or when assumptions are violated, non-parametric tests were conducted.

### 5.3 Results

#### 5.3.1 Participant characteristics.

The final sample consisted of 82 individuals, aged between 21-56 years old (\(M = 34.6, SD = 7.1\); see Table 1 for sample demographics).

#### 5.3.2 Crime profile.

Eleven (13.4%) participants were charged with a violent index offence, which included assault, armed robbery, aggravated burglary, serious threats, and sexual assault. In the month prior to the index offence, 64 (78.0%) participants reported engaging in criminal activity of some kind, most commonly property crime (69.5%), followed by drug dealing (36.6%), violent crime (22.0%), and fraud (20.7%). Total frequency of crime (OTI total) was positively associated with urgency and a total impulsivity score, as well as increased use of substances and benzodiazepines in the 12-24 hours prior to the index offence.

---

\(^5\) It is noted that the scale used may have conceptual implications both when impacting the participant’s answer, and for over-all interpretability (i.e., estimation of frequency versus degree the participant agreed with each statement).
Table 1

Demographic characteristics of the sample population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
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<td>Gender</td>
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<tr>
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<td>Yr 9 or below</td>
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<td>42.7</td>
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<tr>
<td>Torres Strait Islander</td>
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<td>Yr 10-11</td>
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<tr>
<td>Neither</td>
<td>70</td>
<td>85.4</td>
<td>Yr 12</td>
<td>9</td>
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<td></td>
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<td>Diploma/Tafe</td>
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<td>AOD treatment residence</td>
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<td></td>
<td></td>
<td>Other</td>
<td>22</td>
<td>26.8</td>
</tr>
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Table 2

*Participant substance use and mental health histories, and recent distress ratings.*

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<tr>
<th>Previous AOD treatment</th>
<th>Lifetime substance use</th>
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</thead>
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<td>Opiate substitution</td>
<td>68 82.9 Cannabis</td>
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<tr>
<td>AOD counselling</td>
<td>67 81.7 Amphetamines</td>
</tr>
<tr>
<td>Inpatient detoxification</td>
<td>54 65.9 Tobacco</td>
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<tr>
<td>Self-help programs</td>
<td>38 46.3 Alcohol</td>
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<tr>
<td>Residential rehabilitation</td>
<td>35 42.7 Heroin</td>
</tr>
<tr>
<td>Supported accomm</td>
<td>27 32.9 Ecstasy</td>
</tr>
<tr>
<td>Outreach worker support</td>
<td>17 20.7 Hallucinogens</td>
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<tr>
<td>Unspecified/other</td>
<td>17 20.7 Cocaine</td>
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</tbody>
</table>

<table>
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<tr>
<th>Self-reported diagnosis</th>
<th>Psychological distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>51 62.2 Likely well</td>
</tr>
<tr>
<td>Anxiety</td>
<td>37 45.1 Mild mental disorder</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>20 24.4 Mod mental disorder</td>
</tr>
<tr>
<td>Drug-induced psychosis</td>
<td>18 22.0 Severe mental disorder</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>18 22.0</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>13 15.9</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>9 11.0</td>
</tr>
</tbody>
</table>

*Note.* ATSI = identify as Aboriginal or Torres Strait Islander; FT/PT = full time or part time; AOD = alcohol and other drugs; accomm = accommodation’ mod = moderate.

*a*status refers to the month prior to index offence.
5.3.3 Benzodiazepine use profile.

The most commonly used benzodiazepine over the lifetime (including prescribed and non-prescribed) was diazepam (98.8%), followed by temazepam (95.1%), alprazolam (93.9%), oxazepam (92.7%), and clonazepam (62.2%). More than one third (39.0%) had used six types of benzodiazepines (including ‘other’), whilst more than half (59.8%) regularly used four or more types. Nearly half (46.3%) exhibited benzodiazepine dependence, and participants specifically referenced difficulty with diazepam (39.0%) or alprazolam (37.8%) when responding to the SDS. As shown in Table 3, benzodiazepine dependence was significantly, positively associated with urgency, sensation seeking, psychological distress, and the number of other substances used on a regular basis. Non-medical acquisition methods (i.e., without a prescription) were extremely common (91.5%), though 70.7% of the sample reported using both non-medical and medical sources during their lifetime.

In the 12-24 hours immediately prior to the index offence, 84.1% of the sample reported using a benzodiazepine, with high rates of diazepam (61.0%) and alprazolam (57.3%) use. More than a third (36.6%) reported using two types of benzodiazepines prior to the index crime. Examination of approximate diazepam equivalent doses (DZM) indicates that alprazolam was consumed at the highest doses both in the day and month prior to the offence, at levels more than twice, and triple, national prescribing recommendations, respectively (“Alprazolam”, 2013; see Table 4).

5.3.4 Substance use profile.

As shown in Table 2, all participants reported lifetime use of cannabis and amphetamines, while other drug use was also high. The entire sample had used five or more drugs in their life ($M = 17.9$, $SD = 3.5$), and reported a large number of
Table 3

Means (M), standard deviations (SD) and bivariate correlations between factors of interest

<table>
<thead>
<tr>
<th></th>
<th>M (SD)</th>
<th>Age</th>
<th>OTI Total</th>
<th>SDS BZD</th>
<th>K-10</th>
<th>UPPS PRE</th>
<th>UPPS URG</th>
<th>UPPS SS</th>
<th>UPPS PER</th>
<th>Sub Reg</th>
<th>BZD Reg</th>
<th>Sub 12-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTI Total</td>
<td>3.8 (3.3)</td>
<td>-.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDS BZD</td>
<td>6.6 (4.3)</td>
<td>.01</td>
<td>.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-10</td>
<td>31.5 (9.5)</td>
<td>.06</td>
<td>.20</td>
<td>.51**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPPS PRE</td>
<td>30.5 (7.0)</td>
<td>.21</td>
<td>.20</td>
<td>-.20</td>
<td>-.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPPS URG</td>
<td>33.5 (8.0)</td>
<td>.09</td>
<td>.31**</td>
<td>.32**</td>
<td>.53**</td>
<td>.30**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPPS SS</td>
<td>31.2 (8.8)</td>
<td>-.11</td>
<td>.12</td>
<td>.37**</td>
<td>.17</td>
<td>-.13</td>
<td>.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPPS PER</td>
<td>26.1 (5.4)</td>
<td>-.10</td>
<td>.19</td>
<td>-.20</td>
<td>.06</td>
<td>.51**</td>
<td>.26*</td>
<td>-.33**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>Age</td>
<td>OTI Total</td>
<td>SDS BZD</td>
<td>K-10</td>
<td>UPPS PRE</td>
<td>UPPS URG</td>
<td>UPPS SS</td>
<td>UPPS PER</td>
<td>UPPS Total</td>
<td>Sub Reg</td>
<td>BZD Reg</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>-----</td>
<td>-----------</td>
<td>---------</td>
<td>------</td>
<td>-----------</td>
<td>-----------</td>
<td>---------</td>
<td>----------</td>
<td>------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>UPPS Total</strong></td>
<td>121.3</td>
<td>.04</td>
<td>.36**</td>
<td>.19</td>
<td>.34**</td>
<td>.66**</td>
<td>.74**</td>
<td>.42**</td>
<td>.48**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-24</td>
<td>.07</td>
<td>.17</td>
<td>.24*</td>
<td>.15</td>
<td>-.13</td>
<td>.23</td>
<td>.05</td>
<td>-.09</td>
<td>.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BZD Reg</strong></td>
<td>3.8</td>
<td>.03</td>
<td>.09</td>
<td>.27*</td>
<td>.13</td>
<td>-.02</td>
<td>.07</td>
<td>.05</td>
<td>.06</td>
<td>.07</td>
<td>.79**</td>
<td></td>
</tr>
<tr>
<td>12-24</td>
<td>.01</td>
<td>.25*</td>
<td>.12</td>
<td>.177</td>
<td>-.07</td>
<td>.11</td>
<td>-.13</td>
<td>-.08</td>
<td>-.08</td>
<td>.35**</td>
<td>.33**</td>
<td></td>
</tr>
<tr>
<td><strong>BZD 12-24</strong></td>
<td>1.22</td>
<td>.69</td>
<td>.26*</td>
<td>.20</td>
<td>.174</td>
<td>-.20</td>
<td>.10</td>
<td>-.14</td>
<td>-.15</td>
<td>-.17</td>
<td>.20</td>
<td>.21</td>
</tr>
</tbody>
</table>

Note. OTI Total – frequency of crime in last month; SDS BZD – total Severity of Dependence score for benzodiazepines; K-10 – Kessler distress scales total score; UPPS PRE – (lack of) premeditation; UPPS URG – urgency; UPPS SS – sensation seeking; UPPS PER – (lack of) perseverance; UPPS Total – total impulsivity score; MH DX – number of mental health diagnoses; Sub Reg – number of substances regularly used; BZD Reg – number of benzodiazepines regularly used; Sub 12-24 – number of substance used 12-24 hours prior to index crime; BZD 12-24 – number of benzodiazepines used 12-24 hours prior to index crime.

* p < .05  
** p < .01
substances regularly used ($M = 12.8$, $SD = 3.9$). In addition, the majority of the sample (96.3%) had previously sought treatment for alcohol and/or drug (AOD) difficulties, predominantly in the form of opiate substitution programs (82.9%). In the 12-24 hours immediately prior to the index offence, 98.8% of the sample reported using a substance in addition to benzodiazepines.

5.3.5 Mental health profile.

Scores on the K-10 indicated that the sample was highly distressed, with more than half of the sample (52.4%) scoring 30 or above (see Table 2). The majority of the sample reported being diagnosed with a mental illness in their life (82.9%), with 64.6% reporting more than one mental health diagnosis ($M = 2.2$, $SD = 1.7$). The most commonly reported diagnoses were depression (62.2%) and anxiety (45.1%), followed by bipolar disorder (24.4%), drug induced psychosis (22.0%), panic disorder (22.0%), schizophrenia (15.9%), and personality disorder (11.0%).

5.3.6 Group differences.

Benzodiazepine use. As shown in Table 5, the degree of benzodiazepine dependence significantly differed between those who committed violent and non-violent index offences. Individuals who committed a violent offence reported a greater degree of benzodiazepine dependence than those who committed a non-violent index offence ($t(76) = -2.120$, $p = .037$, 95% C.I.: -5.84 to -.18, Cohen’s $d = 0.73$). The use of non-prescribed (i.e., illicit) benzodiazepines did not differ between violent and non-violent offenders ($p = .186$; OR = 0.27, 95% CI: .04-1.71).

Alprazolam use. Non-parametric Fisher’s exact tests (two-tailed) found that individuals who committed a violent index offence were significantly more likely to use alprazolam at doses above the SDR (90.0%) in the month prior to the index offence, than individuals who committed a non-violent offence (54.0%; $p = .040$; OR
Indeed, violent offenders reported average alprazolam doses substantially higher than the SDR ($M = 26.60$, $SD = 31.13$), compared to the high, though less extreme, average doses reported by non-violent offenders ($M = 9.54$, $SD = 14.92$). However, although a similar trend was observed, alprazolam dose used in the 12-24 hours prior to the index offence did not significantly differ between violent ($M = 14.57$, $SD = 16.56$) and non-violent groups ($M = 9.95$, $SD = 16.54$); $p = .416$; OR = 2.76, 95% CI: .48-15.95. Neither group was significantly more likely to have used alprazolam in the month ($p = .441$, OR = 3.21, 95% CI = .38-26.91) or day ($p = .754$, OR = 1.31, 95% CI: .35-4.90) prior to the index offence.

**Table 4**

*Benzodiazepine use the month and day prior to the index offence*

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Month prior to offence</th>
<th>12-24 hours prior to offence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N$ (%)</td>
<td>$M$ ($SD$)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>68 (82.9)</td>
<td>19.5 (10.7)</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>63 (76.8)</td>
<td>14.2 (11.0)</td>
</tr>
</tbody>
</table>

*Note. Approx DZM = approximate diazepam equivalent dose; Est = estimated; mgs = milligrams.*

*a Approximate DZM computed using a 1:10 ratio for alprazolam, as suggested by dosing conversion table outlined by Farinde (2014).*
Table 5

**Independent t-tests pertaining to substance use and commission of a violent index offence**

<table>
<thead>
<tr>
<th></th>
<th>Violent Index M (SD)</th>
<th>Non-violent Index M (SD)</th>
<th>df</th>
<th>( t ) statistic</th>
<th>( p ) (two-tailed)</th>
<th>Mean difference</th>
<th>95% C.I. Lower</th>
<th>95% C.I. Upper</th>
<th>( d )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDS BZD</td>
<td>9.20 (3.52)</td>
<td>6.19 (4.27)</td>
<td>76</td>
<td>-2.120</td>
<td>.037</td>
<td>-3.01</td>
<td>-5.84</td>
<td>-.18</td>
<td>.73</td>
</tr>
<tr>
<td>No. BZD Reg Used</td>
<td>4.45 (1.69)</td>
<td>3.73 (1.29)</td>
<td>80</td>
<td>-1.657</td>
<td>.101</td>
<td>-.72</td>
<td>-1.59</td>
<td>.14</td>
<td>.54</td>
</tr>
<tr>
<td>No. BZD 12-24</td>
<td>1.27 (.79)</td>
<td>1.21 (.68)</td>
<td>79</td>
<td>-.260</td>
<td>.796</td>
<td>-.06</td>
<td>-.51</td>
<td>.39</td>
<td>.08</td>
</tr>
<tr>
<td>No. Sub Reg Used</td>
<td>13.64 (5.39)</td>
<td>12.72 (3.70)</td>
<td>80</td>
<td>-.717</td>
<td>.476</td>
<td>-.92</td>
<td>-3.47</td>
<td>1.63</td>
<td>.24</td>
</tr>
<tr>
<td>No. Sub 12-24</td>
<td>3.73 (1.56)</td>
<td>4.29 (1.24)</td>
<td>79</td>
<td>1.340</td>
<td>.184</td>
<td>.56</td>
<td>-.27</td>
<td>1.39</td>
<td>.44</td>
</tr>
</tbody>
</table>

*Note.* C.I. = Confidence Interval; SDS = Severity of Dependence Scale total score (benzodiazepines); BZD = benzodiazepine; No. Sub = number of substances; 12-24 = 12-24 hour period prior to the index offence.

**Diazepam use.** Non-parametric Fisher’s exact tests (two-tailed) failed to find significant group differences relating to diazepam average dose in the month prior to the offence (\( p = .616; \ OR = 1.75, \ 95\% \ CI: .30-10.27 \)) or in the 12-24 hours preceding the offence (\( p = .369; \ OR = 2.33, \ 95\% \ CI: .44-12.45 \)). Neither group was significantly more likely to have used diazepam in the month (\( p = 1.000, \ OR = .84, \ 95\% \ CI = .16-4.42 \)) or day (\( p = 1.000, \ OR = 1.06, \ 95\% \ CI = .28-3.97 \)) prior to the index offence.
**Mental health.** Although those who committed a violent index offence \((M = 37.25, SD = 9.97)\) reported higher distress scores than those who committed a non-violent index offence \((M = 30.81, SD = 9.31)\), this difference failed to reach statistical significance; \(t(75) = -1.839, p = .070\) (two-tailed), 95% CI: -13.41 to .53, Cohen’s \(d = 0.70\). Fisher’s exact tests (two-tailed) found that individuals who committed a violent offence were significantly more likely to be diagnosed with depression (90.9% vs 57.7%; \(p = .045\); OR = 7.32, 95% CI: .89-60.29) and personality disorder (36.4% vs 7.0%; \(p = .016\); OR = 7.54, 95% CI: 1.64-34.77) than those who committed a non-violent index offence. There were no significant group differences based on anxiety \((p = .210\); OR = 2.39, 95% CI: .64-8.91), panic disorder \((p = .246\); OR = 2.33, 95% CI: .60-9.07), or bipolar \((p = .449\); OR = 2.29, 95% CI: .51-7.57), although the analyses regarding schizophrenia \((p = .068\); OR = 3.94, 95% CI: .96-16.18) and short-term psychosis \((p = .058\); OR = 3.72, 95% CI: .98-14.07) approached significance.

**Criminality.** Frequency of reported crime involvement (OTI total) in the month prior to the index offence did not significantly differ between those who committed violent and non-violent index offences; \(t(79) = -.043, p = .966\), 95% CI = -2.19 to 2.10, Cohen’s \(d = .01\). However, Fisher’s exact test (two-tailed) found that individuals who committed a violent index offence were more likely to have engaged in violence in the month prior (54.5%) than those who committed a non-violent index offence (17.1%; \(p = .012\); OR = 5.8, 95% CI: 1.52-22.15).

**Impulsivity.** Individuals who committed a violent index offence \((M = 37.38, SD = 7.54)\) displayed significantly higher sensation seeking tendencies than non-violent offenders \((M = 30.42, SD = 8.72)\); \(t(72) = -2.157, p = .034\), 95% C.I.: -13.38 to -.53, Cohen’s \(d = .82\). No further group differences were observed (see Table 6).
Table 6

*Independent t-tests pertaining to impulsivity and commission of a violent index offence*

<table>
<thead>
<tr>
<th></th>
<th>Violent Index M (SD)</th>
<th>Non-violent Index M (SD)</th>
<th>df</th>
<th>t statistic</th>
<th>p (two-tailed)</th>
<th>Mean difference</th>
<th>95% C.I.</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>(lack of) Premed</td>
<td>27.00 (8.02)</td>
<td>30.97 (6.86)</td>
<td>72</td>
<td>1.519</td>
<td>.133</td>
<td>3.97</td>
<td>-1.24 - 9.18</td>
<td>.58</td>
</tr>
<tr>
<td>Sensation Seeking</td>
<td>37.38 (7.54)</td>
<td>30.42 (8.72)</td>
<td>72</td>
<td>-2.157</td>
<td>.034</td>
<td>-6.95</td>
<td>-13.38 - .53</td>
<td>.82</td>
</tr>
<tr>
<td>Urgency</td>
<td>34.63 (8.85)</td>
<td>33.32 (7.93)</td>
<td>72</td>
<td>-.435</td>
<td>.665</td>
<td>-1.31</td>
<td>-7.29 - 4.68</td>
<td>.17</td>
</tr>
<tr>
<td>(lack of) Persev</td>
<td>25.00 (5.63)</td>
<td>26.24 (5.41)</td>
<td>72</td>
<td>.611</td>
<td>.543</td>
<td>1.24</td>
<td>-2.81 - 5.30</td>
<td>.23</td>
</tr>
</tbody>
</table>

*Note. C.I. = Confidence Interval; Premed = premeditation; Persev = perseverance.*

### 5.4 Discussion

The relationship between benzodiazepine use and violent crime was explored in a benzodiazepine using, community criminal justice sample. Consideration was also given to factors understood to play a role in the commission of violent crime, notably mental health, impulsivity, substance use, and prior criminal behaviour. Of note, our sample was highly distressed, at levels substantially greater than that reported by persons entering Australian custodial settings (AIHW, 2013), a national sample of injecting drug users (Stafford & Burns, 2013), and the general Australian population (AIHW, 2014). Taken with the sample’s high rate of poly-substance use and strong tendency towards impulsive action, such complex presentations are however common in community criminal justice and AOD services; indeed, nearly all of the participants reported having sought AOD treatment in the past.
In line with the violence literature, our findings demonstrate that violence is multiply-determined, influenced by both unchanging and dynamic factors (DeWall, Anderson, & Bushman, 2011). Individuals who committed a violent index offence were significantly more likely to report benzodiazepine dependence, use alprazolam doses above the recognized standard prescribing range, display strong sensation seeking tendencies, report engaging in violent behaviour in the month prior to the index offence, and report diagnoses of depression and personality disorder, than those who committed a non-violent index offence. The use of non-prescribed (i.e., illicit) benzodiazepines or other substances did not differ between violent and non-violent offenders. Importantly, it appears that a general tendency towards high dose benzodiazepine use is insufficient to indicate violence risk; it is the constellation of risk indicators which is important (Lion, Azcarate, & Koepke, 1975).

Individuals who committed a violent index offence exhibited significantly higher levels of benzodiazepine dependence than those who committed a non-violent offence. This indicates that violent offenders were more likely to report difficulty controlling their use, and greater concern about their use of benzodiazepines. Such difficulties may have reduced their ability to effectively negotiate other situational stressors, increasing their likelihood of responding to stressors in an emotional, rash manner (e.g., violence). Enhanced disinhibition following benzodiazepine use (Paton, 2002) may underlie this response. However, this response may also be influenced by a series of indirect mechanisms, as suggested by significant correlations found with benzodiazepine dependence in our study, but which were unable to be investigated due to insufficient statistical power. For example, impulsive action in the context of negative emotions (urgency) may influence the relationship between benzodiazepine dependence and violence, by increasing the likelihood that
an individual who is experiencing distress and using high levels of benzodiazepines may act spontaneously and violently without considering the consequences (see Figure 2). Urgency was found to associate with general offending, though in the context of problematic benzodiazepine use may heighten the risk of violent behaviour. Such a model aligns with research associating urgency with negative substance use outcomes (Coskunpinar, Dir, Cyders, 2013), and as influential in the relationship between emotional lability and violence (Dvorak, Pearson, & Kuvaas, 2013). Testing of such models would improve our understanding of this response, and offer individually tailored treatment options.

We also found that sensation seeking tendencies were associated with increased benzodiazepine dependence and engagement in violent offending; however given the cross-sectional nature of the data causality cannot be inferred. Nevertheless, sensation seeking has been associated with violent behaviour in samples of undergraduate students (Derefinko et al., 2011; Dvorak et al., 2013; Miller, Zeichner, & Wilson, 2012) and violent prisoners (Shoham, Askenazy, Rahay, Chard, & Addl, 1989), and is often an observed characteristic in substance-using

![Figure 2](image_url)  
*Figure 2.* Proposed relationships between psychological distress, impulsive coping, benzodiazepine dependence and violence.
samples (e.g., Horvath, Millch, Lynam, Leukefeld, & Clayton, 2004; Knafo, Jaffee, Quinn, & Harden, 2013). Such tendencies may predispose individuals to situations which place them at a greater risk of violence, particularly when using drugs that can further disinhibit behaviour. Further research would benefit from exploring the combined influence of sensation seeking and benzodiazepine use on violent crime in a more violent sample.

Further research is needed to clarify the key factors underlying the benzodiazepine-violent crime relationship. Nonetheless, there is a growing body of evidence suggesting that high doses of alprazolam in particular may play a significant role in violent criminal behavior. Alprazolam is arguably the most concerning benzodiazepine due to its short-acting nature and potential for harm (Nicholas, Lee, & Roche, 2011; Rintoul, Dobbin, Nielsen, Degenhardt, & Drummer, 2013), and is frequently abused in clinical and forensic populations (Horyniak, Reddel, Quinn, & Dietze, 2012; Sweeney & Payne, 2012). Notably, widespread evidence of alprazolam’s harm potential has led to its recent rescheduling to a controlled substance (Schedule 8) in Australia. Specifically pertaining to violence, alprazolam has been associated with instances of increased aggression in clinical studies (Gardner & Cowdry, 1985; Noyes et al., 1998; O’Sullivan et al., 1994), typically involving high dose regimes. Our data extend these findings, as general use of higher doses of alprazolam by non-clinical, criminal-justice involved individuals also appear to be associated with a greater likelihood of engaging in violent behaviour. Our findings also appear to tentatively support the idea that acute high doses of alprazolam may pose a proximal risk of violence. The identified trend suggests that, in contrast to laboratory findings (Bond & Silveria, 1993), higher acute doses of alprazolam may pose a greater risk of violence than regularly prescribed
doses. Indeed, although their case-crossover study did not specify benzodiazepine type, Lundholm and colleagues (2013) identified an association between acute, ‘unusually high’ benzodiazepine doses and violent crime. It is emphasized, however, that this latter conclusion is based on a non-significant trend in the data, and merely identifies an area in need of further research. Moving forward, an additional consideration is the accessibility of the various benzodiazepines, as increased restrictions on alprazolam (in Australia) may create a domino effect where other benzodiazepines (or substances) are substituted to harmful levels.

The diagnoses of personality disorder and depression may present further risk indicators for benzodiazepine-related aggression. Personality disorders, especially antisocial (ASPD) and borderline (BPD) types, have been consistently associated with violent behaviour (Gillies & O’Brien, 2006; Latalova & Prasko, 2010; Yu, Geddes, & Fazel, 2012), and there is some evidence to suggest that comorbid substance abuse increases the risk of violence in people with such diagnoses (Fountoulakis, Leucht, & Kaprinis, 2008). The association between violence and personality disorders may be due to problematic enduring cognitive and affective characteristics, such as aggression-related and maladaptive cognitions and anger (Gilbert & Daffern, 2011), or a need for excitement (Howard, 2011), as well as the presence of diagnostic traits such as a callous disregard for others’ rights and lack of empathy (ASPD), and impulsive tendencies and emotional dysregulation (BPD; American Psychiatric Association, 2014). The association between depression and aggressive behaviour may reflect common underlying factors (e.g., low serotonin, impaired attachment), violence resulting from depressive sequelae (e.g., reduced social support, increased alcohol use, angry rumination, impaired self-regulation or impulsivity; Dutton & Karakanta, 2013), or depression developing in response to
guilt, rumination and regret following an aggressive act (Graham, Bernards, Flynn, Tremblay, & Wells, 2012). The progression between depression and aggressive behaviour may also be non-linear, reflecting a complex dynamic progression over time, influenced by factors such as gender or violence type or severity (e.g., Angkaw, Ross, Pittman, Kelada, Valencera, & Baker, 2013; Graham et al., 2012; Sadeh, Javdani, Finy, & Verona, 2011; Stith, Smith, Penn, Ward, & Tritt, 2004). Although our measure of lifetime diagnoses cannot suggest that active symptoms of depression were directly associated with violent offending, our data does suggest that a predisposition towards emotional disturbance, disrupted interpersonal functioning, and reduced executive functioning may be important in the assessment of violence risk, especially in substance-using samples.

5.4.1 Limitations and strengths.

The study has a number of limitations. Of note, the small sample size with some variables of interest having missing data (i.e., impulsivity characteristics, dose information), as well as the low base rate of violent offending, greatly precluded the types of analyses that were able to be performed, prompting reliance on non-parametric analyses which have less stringent criteria. Such sampling issues may have also attenuated the statistical power available. In addition, due to the unique nature of the data, an a priori decision was made that non-normal variables would be recoded into categorical variables, and no correction was made to protect against Type 1 error. The measurement protocols used may have impacted our results, including the non-standardised UPPS response scale, a non-specific substance use variable which may have attenuated the effects of specific drugs (Sweeney & Payne, 2012), and a criminal involvement scale with limited scope (i.e., beyond one month). Furthermore, data collection relied on retrospective self-report which is vulnerable to
memory decay and potential reporter bias, without any method to corroborate substance use (i.e., urinalysis), benzodiazepine dose, crime involvement (i.e., official data), or the accuracy and currency of reported mental health diagnoses. Indeed, a proportion of the sample neglected to provide crime information (i.e., non-specified ‘other’ crime). In addition, the findings may have limited generality to individuals with less complex presentations, and greater insight may have been afforded through the use of a non-benzodiazepine using control group. It is noted that the observed relationship may reflect increased dependence to benzodiazepines arising from efforts to effectively manage pre-existing violent tendencies, or the occurrence of aggression and agitation during benzodiazepine withdrawal (Votava, Kršiak, Podhorná, & Miczek, 2001). It is further noted that benzodiazepine dependence was also significantly associated with poly-substance use, indicating that other substances may have influenced the identified relationship between benzodiazepine dependence and violent crime. The findings may have limited generality to individuals with less complex presentations.

While acknowledging these limitations, the current study adds to the limited literature regarding the relationship between benzodiazepine use and violence in a criminal justice sample. First, our examination of a community-based criminal justice sample with regular benzodiazepine use and recent offending is unique within the literature. Previous research has predominantly focused on healthy community samples, clinical or substance using samples, or forensic samples in custodial settings (Albrecht et al., 2014), greatly reducing the ecological validity of their findings. Second, the research protocol offered numerous avenues of exploration, by way of the range of data that was collected. Notably, 84.1% of the sample reported using benzodiazepines in the day prior to committing an offence, and our data permitted
specific examination of the roles of diazepam and alprazolam in violent offending. With a less constrained sample size, the study had the potential to explore numerous points of interest.

5.4.2 Implications and conclusions.

Recent literature, including a letter written regarding the benzodiazepine acquisition practices of those included in the current database (Best, Wilson, Reed, Lloyd, Eade, & Lubman, 2013), has demonstrated that benzodiazepines are being frequently sought through illegal, or non-medically prescribed, means (Nielsen et al., 2013). Of interest, although the majority of the current sample reported such a preference, every individual who engaged in violence in the month prior to the index offence reported preferring non-medically sourced benzodiazepines. This suggests that people at risk for violence may be less likely to be identified at the point of prescription, and intervention efforts should focus on management of the black-market trade in benzodiazepines, with prevention efforts tailored towards (1) enhancing prescription selectivity, (2) reducing large prescriptions, and (3) strategies to reduce the ease of doctor and pharmacy shopping. Essentially, a two-tiered policy approach involving enhanced control over the prescription of benzodiazepines and greater regulation around the diversion of benzodiazepines onto the black market is required. The latter directive may involve further up-scheduling of all benzodiazepines to controlled substances.

The findings highlight the importance of adhering to recognized prescribing protocols (e.g., Jones, Nielsen, Bruno, Frei, & Lubman, 2011), and addressing reasons for benzodiazepine use (i.e., to manage negative affect). Our findings also promote the use of psychological approaches that target mental health and adaptive coping strategies (e.g., emotion identification and regulation techniques,
consequential thinking and impulse control strategies) in violent offenders. Such strategies can hopefully reduce the association between benzodiazepine consumption and being detained for violent offending (Australian Institute of Criminology, 2013).

5.5 Chapter Summary

Research exploring the benzodiazepine-violence relationship is rare in community samples with a recent criminal justice and benzodiazepine use history. Investigation of such a sample identified risk factors of benzodiazepine dependence, high alprazolam doses (i.e., above 4mg daily), sensation seeking, previous violence, depression, and personality disorder. The current findings detail a complex picture of psychiatric and impulsive functioning as influencing the relationship between benzodiazepine (notably alprazolam) use and subsequent involvement in violent crime. This picture highlights the need to take a holistic, multifaceted approach to the prevention and intervention of benzodiazepine-related aggressive behaviour. As will be discussed in greater detail in the following chapter, concurrent attention to limiting the widespread diversion of benzodiazepines, addressing reasons for benzodiazepines misuse, and promoting psychological approaches that target mental health and adaptive coping strategies among violent offenders is required in order to effect change and reduce the continued occurrence of benzodiazepine-related violence.
Chapter Six: Outcomes, Implications, and Future Directions

Benzodiazepines are widely prescribed, used, and diverted through the black market. Yet, benzodiazepine use has been associated with an increased risk of harm, behavioural disinhibition, and aggressive behaviour. It is this latter response which is poorly understood, and has prompted further exploration within this thesis using both general community and criminal justice samples. As identified through a systematic review, the currently available literature is flawed and has limited explanatory power, though benzodiazepine-related aggressive responses appear to be linked most closely with alprazolam and diazepam use.

In a study with a community sample, benzodiazepine-related aggression was more likely to be experienced by those who used alprazolam and exhibited persistent approach tendencies, or motivational drive. It was posited that frustration (in)tolerance and difficulties regulating impulses when pursuing desired goals may influence aggressive responding. Examination of general and physical aggression allowed for the comparison of predictive models in this sample, and it was observed that for the general community, diazepam (used not to excess) may inhibit general aggressive tendencies such as anger, hostility or verbal aggression, but may not impact physically aggressive behaviour. Problematic use of diazepam (and alprazolam), however, was associated with increased general and physical aggression, highlighting the concerning sequelae that can result from problematic benzodiazepine use or dependence.

In a study with an offender population, this response was associated with a complex picture of emotional, impulse control and interpersonal difficulties. Violent offenders were significantly more likely to present with benzodiazepine dependence, alprazolam use at higher doses, depression and personality diagnoses, sensation
seeking, and a history of violent behaviour than non-violent offenders. The findings highlighted the need to take a holistic, multifaceted approach to the prevention and intervention of benzodiazepine-related aggressive behaviour, and consider the reasons underlying benzodiazepine use whilst promoting adaptive coping strategies.

Taken together, the systematic review and two studies showed alprazolam use to pose a greater risk of subsequent aggression than diazepam use, and demonstrated that intrapersonal factors can further our understanding of benzodiazepine-related aggression. Specifically, the two empirical studies highlighted the role of impulse control and maladaptive coping responses to negative affect in this response. Although the above findings do require replication and extension through further research, a number of pertinent clinical and forensic implications can be drawn from these outcomes.

6.1 Clinical Implications

6.1.1 Role of alprazolam.

Alprazolam misuse has consistently been associated with problematic sequelae. The research conducted as part of this thesis supports national and international concern about alprazolam (Horyniak et al., 2012; Isbister et al., 2004; Rintoul et al., 2013), by highlighting its association with benzodiazepine-related aggression. However, the currently available findings cannot specify that it is the psychophysiological effects of alprazolam that result in aggressive behaviour. Instead, the link between alprazolam use and benzodiazepine-related aggression may be due to the context in which alprazolam is frequently used (i.e., poly-substance use, personality factors, high doses, unknown situational factors). Nevertheless, a positive association has been consistently observed between alprazolam and this response,
suggesting that those who consume alprazolam may be at an increased risk of experiencing benzodiazepine-related aggression.

Alprazolam has recently been up-scheduled in Australia to a controlled substance (Schedule 8), in an effort to reduce alprazolam access, use, and related harms. However, as noted by Islam and colleagues (2014), it cannot be discounted that re-scheduling may result in increased black market trade in alprazolam, or a rise in misuse of a substitute benzodiazepine (or other substance). This will likely have implications for ambulance attendants, emergency departments and substance use treatment clinics, where clinicians should be aware of a possible rebound effect in benzodiazepine-related overdoses, health complications and/or mortality. Prescribers would also benefit by attending to the medicinal requests of patients who had previously received alprazolam prescriptions. In addition, acquisitive crime to fund black-market alprazolam use may increase, and border controls may see an increase in attempts to traffic alprazolam and/or a substitute benzodiazepine. Therefore, whilst it is important to continue monitoring the use of alprazolam, restricting its use, and engaging in further well-controlled examination of this response following alprazolam use, it is also imperative that policy approaches are broadened to the regulation and monitoring of all benzodiazepines, so as to reduce this substitution effect (Islam et al., 2014).

6.1.2 Prescribing policy.

Across both studies, benzodiazepine dependence was associated with aggressive (or violent) behaviour in a proportion of participants. As introduced in Chapter 5, the most appropriate course of action may involve a two-tiered policy system for the regulation of benzodiazepines. It is recommended that such a strategy would involve targeting the point of prescription whilst also targeting the point of
diversion. Such dual focus enhances the likelihood of accessing those who are unlikely to use health care services to obtain benzodiazepines.

The first tier, targeting the point of prescription, is recommended to involve a number of strategies. These include increasing the selectivity of benzodiazepine prescriptions, which may involve a review of the indications appropriate for benzodiazepine treatment, reducing available prescription size and dosing strength (i.e., Ibañez et al., 2013), increased training regarding prescription protocols (and common side effects and risks associated with benzodiazepines), and greater consequences for off-label prescribing of benzodiazepines. Off-label prescribing to individuals already at increased risk of aggressive behaviour (i.e., violent offenders) or in contexts more conducive to interpersonal violence (i.e., prison) is especially concerning. The high dependence potential of benzodiazepines (i.e., physiological dependence; O’Brien, 2005) further warrants the development of national regulations regarding the upskilling or continuing professional development for benzodiazepine prescribers, and emphasises the importance of non-pharmacological (i.e., psychological) approaches to treatment (Dobbin, 2014; Lader, 2014). By targeting the point of prescription, it is expected that fewer inappropriate prescriptions (in dose or indication) will be made, resulting in reduced access to benzodiazepines for personal misuse, as well as a reduced market of prescribed benzodiazepines (Ibañez et al., 2013). Although some psychiatrists (n = 20) already consider both benzodiazepine factors (i.e., abuse and dependence potential) and person factors (i.e., suspicion of who takes the medication, history of abuse, feeling manipulated) when prescribing benzodiazepines (Marienfeld, Tek, Diaz, Schottenfeld, & Chawarski, 2012), it is apparent that greater awareness (through enhanced regulation or training) is required.
The second tier, targeting the point of diversion, aims to further decrease the ease of which benzodiazepines are diverted onto the black market. Strategies could involve further up-scheduling of benzodiazepines, a nation-wide database to provide real-time information to pharmacies regarding the dispensing of benzodiazepines, and increased ramifications for those caught trafficking benzodiazepines or in possession of large quantities of benzodiazepines. Community health promotion strategies may be helpful in reaching individuals who are less likely to be accessed through health centres (i.e., lower income; Ibañez et al., 2013), and offer rehabilitation opportunities without negative consequences (i.e., misdemeanours for illicit drug use). It is noted that each of the above recommendations requires notable financial and personnel resources, and further research as recommended below may assist in garnering support for the provision of such resources.

6.1.3 Poly-substance use.

A complicating factor in the regulation of benzodiazepines, especially alprazolam, is the high rate of poly-substance use associated with benzodiazepine misuse. As demonstrated in Chapter 4, benzodiazepines are often used to enhance the effects of another drug, or to attenuate the negative effects of substance withdrawal. Therein, drug and alcohol interventions may involve concurrent treatment of benzodiazepine use and other substance use, and rely strongly on a comprehensive functional assessment as to why the individual (mis)uses benzodiazepines.

6.1.4 Chicken-egg intervention.

Due to the absence of well-controlled longitudinal studies of this response, the progression between intrapersonal factors, benzodiazepine misuse, and the development of aggressive behaviour is currently unable to be determined. Therefore, intervention for an individual who has experienced benzodiazepine-
related aggressive behaviour will likely depend on a comprehensive individual assessment. Such an assessment should inform the manner in which treatment is provided, and the prioritisation of the various components. For example, underlying anxiety may be prioritised as it leads to problematic benzodiazepine use, or aggressive or hostile attitudes may be targeted as this prompts benzodiazepine use and disinhibited violence, or benzodiazepine and other substance misuse may be targeted as the cycle of use increases distress and agitation, culminating in aggressive outbursts. Although the progression is still unclear in the general literature, core high risk intrapersonal factors requiring assessment have, however, been indicated by the current research (i.e., violent histories, sensation seeking, antisocial or borderline traits, psychiatric distress, and persistent pursuit of goals).

Intrapersonal factors have long been argued to be important in the understanding of benzodiazepine-related aggression. The findings contained within this thesis support this premise, and highlight the importance of considering emotional identification and regulation, including identification of prosocial, solution-focused problem solving and coping strategies; impulse control, frustration tolerance, and consequential thinking training; and interpersonal conflict resolution training, when developing interventions following benzodiazepine-related aggression. Such factors can be considered regardless of whether the intervention is targeting underlying aggressive tendencies, problematic substance use, or psychiatric health, and may indicate responsivity issues which need to be addressed. It has been argued that effective substance use treatment needs to consider individual personality factors (Staiger, Kambouropoulos, & Dawe, 2007), and it is argued that this premise should extend to consideration of other intrapersonal factors (i.e., motivational tendencies) and to other forms of intervention (i.e., violent offender treatment).
Indeed, Davison and Janca’s (2012) review of the relationship between personality and criminal behaviour highlight that effective risk assessment, management, and treatment involves the integration of personality traits, substance misuse, and other intrapersonal factors such as attitudes, beliefs, anger and arousal.

**6.2 Theoretical Implications**

This thesis is the first to apply the rRST to substance-related aggressive behaviour, and the first to apply the theory to benzodiazepine use. Therefore, in the absence of similar studies, comparisons of the current data to the relevant literature relies on studies which explore general aggressive behaviour only. A number of important conclusions can be drawn from such comparisons. First, BAS-Dr is important in the understanding of aggressive behaviour. As discussed in Chapter 4, this may be due to frustrative non-reward, increasing neurological activation mimicking that of aggressive behaviour, the role of attitudes condoning the use of aggression in order to achieve desired goals, or a combination of these factors. However, by aligning with other violence research using the BIS/BAS scales, the role of BAS-Dr in aggression has been supported, indicating that even in the presence of intoxicating substances, underlying intrapersonal factors are important in the treatment of violent offenders. As such, interventions targeting this motivational tendency may involve frustration tolerance training, including impulse control, and solution-focused coping, as well as challenging any beliefs or attitudes condoning the use of aggression. Mindfulness or acceptance and commitment based strategies may also be involved, in order to assist the client to more effectively manage goal challenges.

Reasoning regarding the role of frustrative non-reward (and aggression-based attitudes) is based on untested hypotheses, and therefore should be considered
cautiously. In the absence of follow-up research, the current findings can only highlight potentially relevant treatment targets for assessing and treating clinicians. It is notable, however, that such considerations do align with the frustration-aggression hypothesis (Dollard et al., 1939), and later expansions to the theory, that frustrations generate aggressive behaviour only to the degree to which they arouse negative affect (Berkowitz, 1989). According to Carver (2004), frustrative non-reward is dependent on the person’s perception of the imminence of goal attainment. Unfortunately, empirical investigation of the frustration-aggression hypothesis cannot currently provide further insight into benzodiazepine-related aggression, as the limited recent research (i.e., since 2000) explores bullying among Japanese school girls (Wai-ming Tam & Taki, 2007), aggression post sporting losses (Priks, 2010), and a socio-economic argument of aggression (de Gaay Fortman, 2005); with no apparent application of the hypothesis to situations involving substance use.

The role of affect regulation and coping capacity was in fact inferred by both empirical studies, despite their methodological differences. As noted above, the community sample study, through application of the rRST, posited that benzodiazepine-related aggression involves a problematic response to negative affective experiences (i.e., aggression in response to frustration or anger). Similarly, the findings from the criminal justice study prompted the argument that violent offending reflected impulsive action (urgency) in response to negative symptoms of distress. Although based on different measures and outcome variables, the similarity in results suggests that benzodiazepine-related aggression may involve problematic responding to negative affective experiences, highlighting the importance of emotional regulation and coping strategies, including problem-focused strategies, in both violent and substance use intervention. Difficulties regulating emotion have
frequently been linked with both problematic substance use (e.g., Berking & Wupperman, 2012) and violence (e.g., Roberton, Daffern, Bucks, 2015); however the current findings suggest that enhanced awareness and prioritisation of such treatment targets may reduce the risk of benzodiazepine-related aggression recurring.

Although problematic responses to negative affect appears to be consistent across the two studies, it is notable that divergent findings were observed in relation to sensation seeking. Fun seeking (BAS-FS) negatively influenced the prediction of physical aggression in Chapter 4 (albeit non-significantly), whilst sensation seeking was positively associated with violent crime in Chapter 5. It is acknowledged that the studies used different measures of sensation seeking and aggression, and it can be argued that BAS-FS is not a pure measure of sensation seeking, instead also tapping into dysfunctional impulsivity (Leone & Russo, 2009; Segarra et al., 2014), thus likely explaining the divergence. However, it is interesting that the direction of the effect differs between the studies, especially as BAS-FS has been positively associated with physically aggressive behaviour (Harmon-Jones, 2003; Smits & Kuppens, 2005), and has predicted both direct and indirect aggression in a sample of pharmacy workers (Cooper et al., 2008). Sensation seeking tendencies have also been positively associated with aggression in both general community (Derefinko et al., 2011; Dvorak et al., 2013; Miller, Zeichner, & Wilson, 2012) and violent offender samples (Shoham, Askenasy, Rahav, Chard, & Addl, 1989). It is therefore tempting to infer that benzodiazepine-related aggression operates differently to general aggression, especially given that the findings relating to BAS-FS further support the role of persistent, planned approach behaviour in benzodiazepine-related aggression (in the community sample), and that rash impulsivity or sensation seeking tendencies are only relevant in antisocial or violent (i.e., criminal justice) samples.
However, given the methodological inconsistencies leading to this inference, further research comparing violent offender and general community samples on this response, using a standardised measure of sensation seeking, is required.

6.3 Forensic Implications

Disinhibition potentially due to benzodiazepine misuse has been previously suggested to result in criminal justice system involvement (Redman, 1994). Indeed, offenders have attributed their criminal, and violent, behaviour to the psychopharmacological effects of benzodiazepines (Forsyth et al., 2011; Payne & Gaffney, 2012), though limited corroboration has been provided for such physiological effects. However, it is likely that the current, and future, academic interest in benzodiazepine-related aggression will result in attempts to seek decreased culpability for violent offending. It is emphasised that the aim of this research is not to excuse violence, or to provide an avenue under which a violent offender escapes punishment for a violent crime. Instead, the aim is to help inform whether the violent offender requires targeted treatment relating to his or her use of benzodiazepines, and whether there may be responsivity factors or intervention targets which may improve the offender’s rehabilitative prognosis (i.e., improve offender wellbeing, reduce risk of reoffending, improve community safety). Consideration of this research, indeed in the context of diminished responsibility due to intoxication, may enhance the awareness of the professionals receiving the violent offender pre- or post-sentence. Such awareness may, for example, inform decisions regarding further prescription of benzodiazepines, especially in the presence of related risk factors (i.e., psychological distress, impulsivity).

Similar to the discussion above regarding clinical intervention planning, the outcomes of this research may aid discussion and planning about the offender’s
rehabilitation needs. This would hopefully include an assessment of whether continuing benzodiazepine treatment is the most appropriate option for the offender, and tailoring of intervention techniques to meet responsivity factors or treatment targets. This will culminate in recommendations regarding the priority of violent offender rehabilitation or substance use or mental health treatment. In addition, it is acknowledged that such consideration may inform the inclusion of specific conditions (i.e., excluding or enforcing certain intervention pathways) on high risk violent offenders’ parole orders, where parole is successfully attained. It would be highly recommended, based on findings of Chapter 5, that the prescription of benzodiazepines to violent offenders, or within highly violent contexts (i.e., incarceration), be limited and follow only comprehensive assessment and exhaustion of alternative treatment methods.

6.4 Future Research

Due to the current state of related literature, there are a number of methodological improvements which would assist our understanding of benzodiazepine-related aggression (e.g., Albrecht & Staiger, in press). Of note, well-designed and controlled longitudinal research would prove valuable in determining true contributors to this response. In addition, regardless of study design (i.e., cross-sectional, experimental), the use of appropriate control groups would enhance our ability to be confident in findings. For example, a four-group design using violent/non-violent and benzodiazepine using/non-using groups would be optimal (i.e., B+V+, B+V-, B-V-, B-V+). In addition, larger samples, with a focus on gender equality, would improve the generality of the literature base, and provide greater foundations on which to develop prescribing and regulatory policies. Larger samples will also provide additional statistical power in which more comprehensive and
rigorous statistical modelling can be used. Such modelling ability is imperative for the testing of the various mechanisms posited throughout this thesis (i.e., the role of frustrating non-reward, BIS/BAS interactions, or impulsive action in response to depressive symptoms). As noted in Chapter 1, misuse of benzodiazepines is an international concern, and researchers could endeavour to explore benzodiazepine-related aggression cross-culturally.

A core limitation of the current research and prior studies is the ability to effectively measure, and statistically control, other substance use. Future research could benefit by systematically exploring the role of substances such as heroin, marijuana, and alcohol (i.e., closely associated with benzodiazepine use) in benzodiazepine-related aggression. Physiological research could also provide insight into how the various substances in combination with benzodiazepines affect an individual’s responding. In addition, systematic examination of the different benzodiazepines and dosing schedules requires further attention. As noted in Chapter 1, and replicated in the current research, alprazolam and diazepam have received the most empirical attention, likely due to their frequent use in both community, clinical and forensic populations. Further examination of the less-frequently used benzodiazepines is therefore required. Such examination would greatly benefit from the use of appropriate methods to corroborate self-report (i.e., urinalysis, systematic testing (using double blind methods) of various doses). Such techniques would increase the level of control of related studies, and improve our confidence in relying on research findings.

Building on Lion and colleagues’ (1975) premise, an aspect which has been overlooked in the current literature is the role of context in understanding this response. Aggression is by definition an interpersonal behaviour (Baron &
Richardson, 1994), and is highly influenced by situational factors (Anderson & Bushman, 2002). However, no research has explored the context or situational factors associated with benzodiazepine-related aggression, or how situational factors may interact with intrapersonal responding and benzodiazepines (and other substance) use (Lion et al., 1975). Blending quantitative and qualitative approaches would likely provide greater understanding of these factors.

Finally, there are a number of additional intrapersonal factors which have yet to be investigated in the benzodiazepine-aggression literature. Based on the current findings, and what is understood about violent behaviour in general (i.e., the general aggression model; Anderson & Bushman, 2002), individual goals, expectations, attitudes, and desires seem important. A number of questions could be asked, especially regarding perceptions of how substance use may vary the acceptability of aggressive behaviour, and tested through well-controlled experimental studies.

As demonstrated throughout this thesis, the benzodiazepine-aggression literature base has a number of limitations, and the above areas for further research are suggested in order to reduce such flaws. It is hoped that further research adhering to the above points and following the above questions will improve the statistical and methodological rigour of the related literature base, and increase the specificity and explanatory power of related outcomes. This includes the replication and expansion of the findings included in this thesis.

6.5 Conclusion

Much remains to be understood about benzodiazepine-related aggressive behaviour. This thesis has highlighted the increased risk that alprazolam poses in the commission of violent or aggressive behaviour, though it is currently unclear whether this is due to the physiological effects of alprazolam, or the increased
disinhibition which may result from using alprazolam in combination with other substances. It is also important to consider whether individuals who engage in aggression merely have a tendency to select alprazolam over other benzodiazepine options, possibly for its fast-acting effects, or whether the aggressive response may occur during the withdrawal phase of alprazolam abuse. This thesis has also highlighted the importance of intrapersonal factors in understanding this response, and will hopefully inspire further research into the proposed interaction between benzodiazepine, intrapersonal, and situational factors (Lion et al., 1975). In order to reduce the incidence of this response, it is necessary to increase the regulation of benzodiazepine prescription and diversion onto the black market, and a two-tiered prescribing policy has been suggested. Violent offender and substance use treatment programs should explore notable intrapersonal factors in order to determine their relevance as responsivity factors and/or treatment targets. Although risks may differ between violent offenders and the general public, attention should be paid to impulsive tendencies in response to frustration or negative affect, persistent motivational tendencies, violent histories, problematic personality traits and disrupted interpersonal functioning, and regular, heavy consumption of alprazolam, especially in the context of poly-substance use. It is through attention to the above risks and recommendations that the incidence of benzodiazepine-related aggression may be reduced, reducing the financial and personal injury toll on the community, and improving community safety.
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Appendices
Appendix A


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# AUTHORSHIP STATEMENT

## 1. Details of publication and executive author

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<td>Benzodiazepine-related aggression: Consideration of intrapersonal factors.</td>
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Conception of research question, design systematic review search protocol, run search protocol, independently review abstracts of articles, qualitative analysis and synthesis of articles, drafted manuscript, editing of manuscript

I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.

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## 4. Description of all author contributions

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<td>Associate supervision DPsych candidate, clinical implications, editing of manuscript</td>
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<td>Peter Miller</td>
<td>Expertise regarding method to assess study quality, editing of manuscript</td>
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Appendix B

Confirmatory Factor Analysis of BIS/BAS scales

A confirmatory factor analysis (CFA) was conducted to assess the reliability of the BIS/BAS scales with the recently revised 2-factor BIS (i.e., into fear- and anxiety-mediated avoidance motivation; Dissabandara et al., 2012; Heym et al., 2008), in line with the revised RST. The analysis was conducted in IBM SPSS AMOS 22, on 288 participants as one case did not have a complete BIS/BAS scale, providing more than a 10:1 ratio of cases to unknowns. The CFA was conducted only to assess whether the two-factor or one-factor BIS scale was most appropriate for the current sample, not to modify the BIS scale, and therefore the modification indices were not examined and no changes to the BIS scale were made. Although neither model demonstrated great fit to the data, the two-factor model ($\chi^2(13) = 56.496, p < .001$, CFI = .913, TLI = .860, RMSEA = .108, standardised RMR = .062) was a significantly better fitting model than the one-factor BIS ($\chi^2(14) = 90.814, p < .001$, CFI = .847, TLI = .770, RMSEA = .138, standardised RMR = .072); $\Delta \chi^2 (1) = 34.317, p < .05$. Both BIS and FFFS demonstrated adequate internal reliability ($\alpha = .73, .67$, respectively). A moderate association between the subscales was observed ($r = .519, p < .001$), supporting the separation of the scales.
Appendix C

Albrecht, B., Staiger, P. K., Hall, K., Kambouropoulos, N., & Best, D.

Motivational drive and alprazolam misuse: A recipe for aggression?

Submitted to: Psychiatry Research

Submission date: 27 May 2015
# AUTHORSHIP STATEMENT

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If there are multiple authors, give a full description of HDR thesis author’s contribution to the publication (for example, how much did you contribute to the conception of the project, the design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)

Conception of research question, statistical analysis plan, questionnaire development, preparing relevant ethics applications, cleaning and analysis of data, drafting of manuscript, editing of manuscript.

*I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.*

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<td>Expertise regarding theoretical assumptions, editing of manuscript</td>
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Abstract

Benzodiazepine-related aggression is understudied in the literature, in particular little is known about the motivational factors which may contribute to the development of this paradoxical response. The revised Reinforcement Sensitivity Theory (rRST) provides a theoretical framework from which to understand the relevant underlying motivational processes. The current study aimed to identify the role of approach and avoidance motivational tendencies in relation to benzodiazepine-related aggression. Data regarding benzodiazepine and other substance use, approach and avoidance motivation, and general and physical aggressive behaviour were collected via self-report questionnaires. Participants were a convenience sample ($n=204$) who reported using benzodiazepines in the previous month. Participants were primarily male (62.7%), aged 18-51 years old. General and physical aggression were predicted by alprazolam use and Drive, a facet of approach motivation reflecting persistent goal-directed action. Overall, lower use of diazepam significantly predicted higher levels of general aggression. However, when diazepam-preferring participants were examined in isolation of the larger sample (23.5% of sample), problematic (dependent) diazepam use was associated with greater aggression scores, as was dependence risk for alprazolam-preferring participants (39.7% of sample). The findings highlight the importance of motivational factors and benzodiazepine use patterns in understanding benzodiazepine-related aggression, with implications for violent offender rehabilitation.

Keywords: benzodiazepines, aggressive behaviour, Reinforcement Sensitivity Theory
Appendix D

Albrecht, B., Staiger, P. K., Best, D., Hall, K., Nielsen, S., Miller, P., & Lubman, D.

I.

Violent crime: Could benzodiazepine use be playing a role?

Submitted to: *Journal of Substance Abuse*

Submission date: September 2015
AUTHORSHIP STATEMENT

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Suzanne Nielsen | Development of the original study, editing of manuscript

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Abstract

Objective:
To examine the relationship between benzodiazepine use and violent crime in a sample of offenders.

Methods:
Data regarding benzodiazepine and other substance use, mental health, personality characteristics, and crime involvement was collected through semi-structured interviews. Participants ($n = 82, 79.3\%$ male) were 21-56 years old, and, in the previous six months, had been charged with a criminal offence and used benzodiazepines at least monthly.

Results:
Individuals charged with violent offences were significantly more likely to use higher average doses of alprazolam, exhibit benzodiazepine dependence and report high levels of sensation seeking, have committed prior violence, and report the diagnoses of depression and personality disorder, than individuals charged with non-violent offences.

Conclusions:
The findings suggest the existence of a complex dynamic between mental health and violent offending that may be influenced by benzodiazepine use (in particular alprazolam). Implications for prescribing and continued efforts to reduce benzodiazepine diversion are discussed.

Key words: benzodiazepines, alprazolam, violence, impulsive behaviour, mental health