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Running Title: Benzodiazepine use in chronic pain

Abstract

Objective: Benzodiazepines are commonly used by chronic pain patients, despite limited evidence of any long term benefits and concerns regarding adverse events and drug interactions, particularly in older patients. This paper aims to: describe patterns of benzodiazepines use; the demographic, physical and mental health correlates of benzodiazepine use; and examine if negative health outcomes are associated with benzodiazepine use after controlling for confounders.

Subjects: A national sample of 1220 chronic non cancer pain (CNCP) patients prescribed long-term opioids.

Methods: We report on baseline data from a prospective cohort study comparing four groups based on their current benzodiazepine use patterns. General demographics, pain, mental and physical co-morbidity, and health service utilisation were examined.

Results: One-third (n = 398, 33%) of participants reported BZD use in the past month, and 17% (n = 212) reported daily BZD use. BZD use was associated with: 1) greater pain severity, pain interference with life and lower feelings of self-efficacy with respect to their pain; 2) being prescribed 'higher-risk' (> 200mg oral morphine equivalent) doses of opioids; 3) using antidepressant and/or antipsychotic medications; 4) substance use (including more illicit and injection drug use, alcohol use disorder and daily nicotine use) and 5) greater mental health co-morbidity. After controlling for differences in demographic characteristics, physical and mental health, substance use and opioid dose, BZD use was independently associated with greater past-month use of emergency health care such as ambulance or accident and emergency services.

Conclusions: CNCP patients using BZDs daily represent a high-risk group with multiple comorbid mental health conditions, and higher rates of emergency health care use. The high prevalence of BZD use is inconsistent with guidelines for the management of CNCP or chronic mental health conditions.

Keywords: Chronic non-cancer pain, opioid, benzodiazepines, mental health

1. Introduction

The prescription of opioids for people with chronic non-cancer pain (CNCP) has increased dramatically in the US, Canada and Australia (1-6). Benzodiazepine (BZD) use, while common, is reported at much lower rates in the general population than in chronic pain populations. A national household survey in the US study found 4% of respondents reported tranquilizer use and 6% reported using sleeping pills or other sedative use (7). General population studies in the UK estimate that 3% of the population use BZDs (8). Although there has been some reduction in BZD use (9, 10), BZDs continue to be prescribed despite there being few indications for their use.

Significant proportions (18-38%) of CNCP patients are concurrently prescribed opioids and BZDs (11-13). While there are a range of reasons why benzodiazepines may be prescribed to patients with CNCP, there are few indications for chronic BZD use specifically in the treatment of CNCP. One review, conducted two decades ago, identified a potential role for BZD in acute pain, but there is little evidence from controlled studies to support their general use in chronic pain (14). The exceptions were just three specific conditions where some evidence of their efficacy in treating pain was found: chronic tension headache, temporomandibular disorders and tic douloureux (14). Non-drug treatments and other medications such as antidepressants are considered first-line treatments for chronic anxiety or insomnia, with BZDs reserved for second line use when patients are unable to tolerate first-line medications, or after non-drug treatments have failed (14). Guidelines state that BZD are “not recommended" for use in non-

cancer persistent pain (15), while expert opinion is divided (16). Although BZD are effective when used acutely for generalized anxiety or panic disorders, they are not listed in clinical guidelines as first-line treatments for these conditions. These guidelines indicate short-term use, or only where antidepressants are not tolerated (17, 18).

Concurrent use of BZDs and opioids carries potential risks, particularly in older adults who are more vulnerable to adverse events and drug interactions (19). Combined BZD and opioid use may increase sedation, cognitive and psychomotor impairment, falls, respiratory depression and risk of overdose (20, 21). Chronic BZD and chronic opioid use are associated with additive effects in sleep-disordered breathing (22, 23), and have the additional well known clinical complications of physiological neuroadaptation with long term use, and the potential for development of substance use disorders amongst some patients.

Few studies have investigated the possible effects of BZD use on long-term outcomes for chronic pain patients. One study of chronic pain patients enrolled in a tertiary pain clinic found that BZD use was correlated with deteriorating physical functioning and depression, after controlling for opioid use(24). A longitudinal study of older adults found that new-onset chronic BZD use was predicted by increasing age, female gender, symptoms of depression, pain and poor physical health (25).

Given the potentially serious adverse consequences of BZD use in chronic pain patients, we examined the prevalence and correlates of past, occasional and daily BZD use in a sample of

CNCP patients who are prescribed long-term opioid analgesics. Three a priori aims were defined for these analyses:

1. To describe patterns of BZD use amongst a sample of CNCP patients prescribed opioids;

2. To examine demographic, physical and mental health and substance correlates of BZD use; and

3. To examine if negative health outcomes, including emergency healthcare utilization, were independently associated with BZD use, after controlling for other patient characteristics.

2. Methods

2.1 Study design and setting

The sample comprised 1220 participants from the baseline data collected on a prospective cohort study of persons who have been prescribed opioids for chronic non-cancer pain (the POINT study). The parent study will collect prospective longitudinal data from this cohort at four time points over a two year follow up. A detailed description of the methodology is available elsewhere (26).

2.2 Eligibility criteria

POINT participants had to be: 18 years or older*;* competent in English; and mentally and physically able to complete telephone and self-complete interviews; without serious cognitive impairments; living with chronic non-cancer pain (by definition, of at least three months duration); prescribed a Schedule 8 opioid (an Australian classification of drugs of dependence that are subject to additional regulatory controls regarding their manufacture, supply, distribution, possession and use (27)); and having taken such opioids for CNCP for more than 6 weeks. Schedule 8 opioids include morphine, oxycodone, fentanyl, buprenorphine, methadone, hydromorphone, and codeine phosphate tablets as a single ingredient. Schedule 8 does not include codeine in combination with paracetamol or tramadol.

Patients currently prescribed pharmaceutical opioids for opioid substitution therapy (OST) for heroin dependence and those taking opioids for cancer pain were ineligible for this study.

2.3 Recruitment

A database of pharmacies and chemists across Australia and their contact details was purchased in May 2012 (28). The list included 7,136 pharmacies. After removing duplicates, those that had closed down, or were not suitable for the study (i.e. located in a hospital or were a compounding pharmacy), we had a final list of 5,994 pharmacies.

Pharmacies were invited to participate in the study and to refer eligible participants using a purpose-designed fax referral form. Pharmacists were asked to approach any customers who were prescribed a Schedule 8 opioid for CNCP for a period of greater than 6 weeks.

POINT staff determined the eligibility of interested customers who were referred to the study, or who contacted the POINT team. Eligible participants went through a voluntary informed consent process. After being given details of the study, those who were willing to participate were booked in for their initial interview which was conducted over the phone and took approximately 1-1.5 hours, and were sent a self-complete survey in the mail at the same time.

The study was approved by the Human Research Ethics Committee of the University of New South Wales (HREC reference: # HC12149).

2.4 Interview procedure

Baseline phone interviews were conducted by trained interviewers who had previously received suicide assistance training. They had a minimum 3-year health or psychology degree, and were provided with glossaries of chronic pain medications and conditions. Participants were reimbursed $40AUD for the baseline interview.

2.5 Measures

Key measures included: demographic characteristics, current pain (as measured by the Brief Pain Inventory (29)), opioid and BZD use and/or dependence (using ICD-10 dependence criteria assessed via the Composite International Diagnostic Interview (CIDI)(30)) pain self-efficacy (using the Pain Self-Efficacy Questionnaire (31, 32)), health service utilization, alcohol and illicit drug use, depression and generalized anxiety disorder (as measured by the PHQ-9 and GAD-7 modules of the Patient Health Questionnaire (33)). Previously validated cut-offs were used for screening tools as follows: symptoms indicating Major Depressive Disorder were defined at a score of ≥ 10 on the PHQ-9 (34), symptoms of Moderate to Severe Anxiety were defined as a score of ≥ 10 on the GAD-7 (35). A score of ≥ 3 on the Primary Care PTSD screen (PC-PTSD) was used to indicate presence of PTSD (36).

Weekly income was classified as greater or less than AUD $400/week, with less than $400/week comparable with unemployment or disability benefits.

In addition to reporting the number of days on which each medication was used in the past month, participants were also asked to return a medication diary that reported all medication taken over a seven day period. Of the 1220 participants, 853 had medication diaries available for analysis. Where BZD doses were reported, these data only represent the subset of patients that returned the medication diary. Oral morphine equivalent daily doses were calculated using available references (15, 37-39). A 'high risk' opioid dose variable was created, which was defined as more than 200mg/day oral morphine equivalents (40, 41).

2.6 Data analysis

We defined four distinct BZD use groups: patients who had used BZDs every day for the past month (referred to as 'Current Daily' users throughout) (n = 212), those who had used BZDs less than daily in the past month (referred to as 'Current Less Than Daily')(n = 186), those that had used BZDs previously but not in the past month (referred to as 'Past BZD Use') (n = 372) and those that had never used BZDs (referred to as 'Never BZD Use') (n = 450).

Multinomial regression was used to compare the four use groups. Medians and non-parametric statistics were used to compare groups where the distribution was non-normal. ANCOVA was used to examine whether pain self-efficacy differed between the BZD use groups, after controlling for pain severity as the covariate. Multivariate logistic regression models were used to determine whether patterns of BZD use were independently associated with ambulance and accident and emergency attendance, after controlling for differences between the BZD use groups identified through univariate analyses.

3. Results

3.1 Benzodiazepine (BZD) use patterns

Four hundred and fifty participants (36.9%) reported never having used a BZD ('Never BZD Use'). Three hundred and seventy two (30.5%) reported past BZD use only ('Past BZD Use'), 186 (15.2%) reported current less than daily use ('Current Less Than Daily'), and 212 reported current daily use ('Current Daily') in the past month (17.3%; Table 1). Of those currently using benzodiazepines (n = 398), 53% were using them daily.

Those reporting current less than daily BZD use had used BZDs on a mean of 8.2 days in the previous 28 days (SD 6.8, range 1-25 days). Multinomial logistic regression did not detect a significant difference in age of first BZD use between the groups: the mean age of first use for the Past BZD Use group was 38.8yrs (SD 14.7yrs), 39.7yrs (SD 15.1yrs) for the current less than daily group, and 40.4yrs (SD 16.8yrs) for the current daily group.

62 people (5.1% of the sample) endorsed the CIDI BZD screening question (i.e., 'was ever used so regularly that they could not stop using the sedative or tranquilizer prescribed' to them) and were further assessed using the CIDI for a BZD use disorder (using ICD-10 criteria). Those using BZDs daily in the past month were more likely to meet criteria for a BZD use disorder (8.5%, n = 18, OR: 3.36, 95%CI .152 – 7.42) than past BZD users (2.7%, n = 10)).

3.2 Demographic differences by BZD use group

Participants who reported any BZD use were younger than those in the Never BZD Use (reference) group (Table 1). Current daily BZD users reported lower levels of current employment/study compared with the Never BZD use reference group.

Insert Table 1 about here

3.3 Types of BZDs used

Diazepam was the most common BZD reported by the subset of participants that used a BZD in the past month and returned a medication diary (n = 254). Its use was reported by 48% (n = 122, mean daily dose 9.1mg, SD 8.8mg), followed by temazepam (22%, n = 56, mean daily dose 10.3mg, SD 7.0mg), oxazepam (12%, n = 30, mean daily dose 28.4mg, SD 14.4mg), nitrazepam (10%, n =25, mean daily dose 6.9 mg, SD 7.6mg), alprazolam(5%, n=12, mean daily dose 2.0 mg, SD 1.8mg) and clonazepam (5%, n =12, mean daily dose 2.4mg, SD 2.75mg). A small number of participants also reported use of BZD-like drugs zopiclone (n = 8) and zolpidem (n = 11). Twenty nine (11%) reported using two BZDs in the same week, and two participants (1%) reported using three BZDs in the same week.

3.4 Aberrant BZD Use

Participants were asked if they had ever used BZDs in a range of unsanctioned ways. Of those who had ever used benzodiazepines (n = 770), 5.5% (n = 42) reported ever using someone else's BZDs, and 4.5% (n = 35) reported using their own prescribed BZDs in a way that was not as prescribed, (i.e. injected, or used for recreational purposes). Having ever used someone else's BZDs was reported by more of those currently using BZDs less than daily (8.1%, OR 2.26 (95%CI 1.07 - 4.78), compared with past BZD users (Reference category, 3.8%). The difference was not significant between past and daily BZD users (6.3% OR: 1.72, 95%CI 0.79 -3.74). Those using BZDs daily were more likely to report recreational or intravenous use (7.8%, OR: 2.15, 95%CI 1.03 – 4.51) compared with past BZD users (3.8%) and less than daily BZD users (2.7%, OR: 0.71, 95%CI 0.25 - 2.00).

3.5 Pain

There was no difference in the duration of pain experience, or of duration of opioid prescription between the groups, although BZD users had received their first opioid prescription at a younger age than those who did not report using BZDs. The types of pain conditions reported within the past 12 months were broadly comparable across the three categories of BZD use groups, except that the current daily BZD use group reported the highest mean number of pain conditions. The current daily BZD use group reported the highest Pain Severity and Pain Interference scores on the BPI.

Any BZD use (past or current) was associated with poorer pain self-efficacy (i.e. less confidence in their ability to do a range of activities including household chores, socializing, work and to cope with their pain) as measured with the PSEQ, where lower scores reflect poorer self-reported efficacy in managing pain. The current daily use group had the lowest pain self-efficacy scores (See Table 2). BZD use was independently associated with significantly lower mean pain self-efficacy scores after controlling for pain severity ($F(2, 1127) = 14.86$, $p < .001$). Adjusted means for the pain self-efficacy score were 31.8 (SD 12.3) for the Never BZD Use group, 29.4 (SD 18.8) for the past BZD use group, 27.5 (SD 8.5) for the current less than daily group and 25.6 (SD 12.9) for the current daily use group. The lower level of self-efficacy in the daily use group compared with the Never BZD Use group was of moderate magnitude (Hedges' $g= 0.49$). Differences between other groups were either small (poorer self-efficacy in the less than daily group compared to never use $g=0.37$) or not meaningful (all others $g<0.22$).

3.6 Other medication use

A higher proportion of BZDs users had been also prescribed anti-depressant and/or antipsychotic medication (Table 2). Two-thirds (68.4%) of the current daily use group had used antidepressants and 11.2% had used an antipsychotic medication in the past month, compared with 44.9% and 3.1% in the Never BZD Use group.

Participants who had used BZDs were also prescribed more opioids, and reported a greater median opioid dose. We examined the proportion of each group prescribed a 'high risk' opioid dose (> 200mg/day oral morphine equivalents). The two current BZD use groups (daily and less than daily) had higher proportions of 'high risk' opioid doses in past month (21.4% in the current less than daily and 27.9% in current daily BZD use) compared with 8.9% in Never BZD Use group).

Insert Table 2 around here

3.7 Substance use and mental health

BZD users were more likely to report lifetime illicit drug use, injection drug use and an alcohol use disorder (using ICD-10 definitions) than those who had never used BZDs (Table 3). Current daily nicotine use was more likely amongst current BZD users (whether using daily or less than daily) compared with those who had never used benzodiazepines.

Most BZD users reported a lifetime diagnosis or development of a mental health condition, and a more mental health conditions than non-users (Table 3). BZD users reported more symptoms of moderate to severe depression, anxiety, and were more likely to meet criteria for PTSD and past month panic attacks. The daily BZD use group had the highest proportion reporting symptoms that met criteria for each of these conditions (Table 3).

Insert table 3 around here

3.8 BZD use and emergency health service utilization

At a univariate level, the daily BZD use group reported more visits to the General Practitioner (GP) in the past month and were more likely to use emergency healthcare compared with those who had never used BZDs. Those who reported daily BZD use were more likely to have used an ambulance in the past month (OR 2.7, 95% CI 1.12 – 6.41) and more likely to have attended a hospital emergency department (OR 2.01, 95%CI 1.06 -3.81) than those who had not used BZDs, after controlling for differences in age, gender, income, number of pain and other chronic conditions, moderate to severe anxiety and depression symptoms and history of illicit drug use and drug injection, and receiving a 'high risk dose' of opioids. The three BZD-use groups were more likely to report a lifetime drug overdose compared with the group that had never used BZDs.

4. Discussion

In this national sample of CNCP patients prescribed opioids, approximately one-third (33%) had used a BZD in the previous month and half of those (53%) reported daily BZD use. Although a high proportion of these CNCP patients reported using BZDs regularly, most participants reported using only one type of BZD. This was most often diazepam, temazepam, oxazepam or nitrazepam, which jointly accounted for approximately 90% of all recent BZD use. These are the most commonly utilized BZDs in routine prescribing data for the general Australian population (9).

The mean self-reported BZD doses used were within therapeutic norms and few participants reported aberrant BZD use. Nearly one in ten (9%) of current daily BZD users met diagnostic criteria for a lifetime BZD use disorder, compared with below 3% in all other groups. In short, although many patients had recently used BZDs, there was little evidence of patients using them other than as prescribed and few endorsed criteria for substance use disorder or reported non-medical use.

Nonetheless, the high rates of BZD use in this population are at odds with clinical guidelines that do not recommend the long-term prescription of BZDs for the vast majority of chronic pain or mental health conditions. Few patients suffered from the short list of chronic pain conditions for which BZDs may have some therapeutic role (14) . Although being unable to tolerate antidepressants is identified as a possible indication for using BZDs (17), the large number of

patients concurrently prescribed antidepressants and BZDs suggests that this is not the reason for BZD use.

BZD use in this sample was broadly associated with three factors: (a) *pain* (including number and type of pain conditions, greater self-reported recent pain severity and pain interference, and poorer pain self-efficacy), (b) *mental disorders* (including current depression and generalised anxiety disorder); and (c) *substance use* (including alcohol use disorders, tobacco use, injecting drug use and illicit drug use).

One way of understanding the high prevalence of BZD use in this sample is to consider how CNCP patients who use BZD might differ from other patients in their approach to treatment. Daily BZD users reported the highest levels of current antidepressant and antipsychotic medications, were more likely to be taking high opioid doses (>200mg oral morphine equivalent mg daily) and reported the lowest self-efficacy in managing their pain. BZD users also reported higher rates of alcohol and other illicit drug use. In summary, BZD users also used more prescribed and recreational drugs which may suggest a pattern of 'chemical coping' (42) or may reflect the high levels of substance use and comorbid mental disorders in this group.

It is unclear whether the greater use of medication and other substances among benzodiazepine users is in response to, or contributes to more severe pain and psychological distress. Alternatively, it may be that current approaches to pain treatment using opioid medications and antidepressants fail to satisfactorily address these patients' pain and distress,

and so that higher opioid doses and a wider variety of medications are used in an attempt to achieve better pain relief. This raises the value of comprehensive approaches to pain management that broadly address the range of bio-psycho-social aspects of chronic pain and reduce reliance upon psychoactive medication for symptom control as the predominant intervention (43, 44). Indeed, the triple co-morbidities of chronic pain, mental health and substance use disorders highlight the many needs of this patient population. The complexity of the population not only demands a multifaceted rather than only a medication-based approach to pain, but also suggests the need for additional strategies that may address patients' mental health or substance use problems.

Those using BZDs generally reported poorer health outcomes, greater utilization of health services, and in particular greater use of emergency services such as ambulance, emergency department presentations and a higher likelihood of having a history of accidental overdose than those who did not use BZDs. A history of overdose was reported in approximately a quarter of daily BZD users (compared with 10% of non-BZD users). The high rates of polypharmacy are of particular concern, especially in older patients who are more vulnerable to drug interactions and related adverse events.

The high prevalence of BZD use in CNCP is an issue that requires more clinical and research attention in light of the limited number of accepted indications for long term BZD prescribing for either pain or mental health conditions and the poorer health outcomes in these patients. While it is not possible from this cross sectional study design to identify whether BZD use is

safe, effective or appropriate in CNCP patients, the high prevalence of BZD use is clearly inconsistent with therapeutic guidelines recommendations on the management of CNCP or chronic mental health conditions. This raises questions about the adequacy of the assessment and clinical decision making in these patients. There have been many approaches to identifying high risk CNCP patients in whom opioid medication should be used cautiously (41), where a personal or family history of substance abuse is a constant theme. We are unaware of similar approaches to identifying risk factors for BZD use in CNCP patients.

There are some study limitations that need to be considered. Although a clear strength of the study was that all Australian community pharmacies were approached and many assisted with recruitment, we have limited data on those pharmacists and patients who did not participate. Further, we rely on self-report data which, while being generally reliable when there are no disincentives for being honest (45), may be subject to biases. All participants were informed that their responses would be de-identified and confidential, which traditionally results in more valid reports of substance use (46). Further, we do not know the indications for each of the medications used by participants. Future work that can explore reasons for benzodiazepine initiation and continued use in these patients would be a valuable addition to the literature. Finally, as this is a cross- sectional analysis, we are not able to assess causality. We do not know what the outcomes for these patients would have been had they not been prescribed benzodiazepines. The longer-term findings for this study will provide important data on outcomes for those that use BZDs over time.

This study identified a high prevalence of BZD use in CNCP patients, with approximately one-third of patients reporting use within the past month. CNCP patients with daily BZD use represent a highly distressed group of patients: they reported greater pain severity and more interference with daily life, multiple mental health problems and a higher rate of substance use disorders. They are at risk of adverse events from polypharmacy, and report higher rates of emergency health care use and opioid-related overdose. Careful consideration needs to be given to the role of BZDs in the treatment of CNCP and there is a need for ongoing monitoring of BZD use. In light of the current concerns with opioid related harms, those using opioids and benzodiazepines appear to represent a particularly high-risk group.

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