**Trends and variations in concurrent dispensing of prescription opioids and Benzodiazepines in Australia: a retrospective analysis**

**Abstract**

**Objective:** Concurrent use of opioids and benzodiazepines is a public health issue, as it may cause a range of adverse health outcomes including death. However, little is known about levels of concurrent use and its variation across jurisdictions. This study examined the population level prevalence of concurrent use in Australia.

**Methods:** 10% sample of unit record data of prescription opioids and benzodiazepines dispensed during 1st January 2013–31 December 2016 were analysed. Using prescription dispensing dates and days of supply in terms of defined daily dose (DDD), concurrent users were identified as those for whom the supply in DDD quantity for one medicine overlapped with the supply day of the other. Using direct standardization approach, and age and sex structure of overall population in Australia, the number of concurrent users in individual LGAs were adjusted. Multivariable and multilevel regression models were developed.

**Results:** During the four years 12.41% (0.99 million) individuals were identified as concurrent users of prescription opioids and benzodiazepines. Significantly more women were concurrent users than men, across all age-groups. On average 1.75 per 1000 people were estimated to be concurrent users per year. There was substantial variation in number of concurrent users across jurisdictions ranging from less than one to 126 per 1000 people (standardized with age and sex). Much of this variation was attributed to individual level circumstances.

**Conclusion:** Concurrent use of opioid and benzodiazepine was common in Australia. There were considerable variations across jurisdictions in terms of number of concurrent users per 1000 people. Women, senior citizens or those living in socio-economically disadvantaged areas were dominant groups of concurrent users. Further research is needed to examine the precise reasons of concurrent use.

**Keywords**

Concurrent use, opioid, benzodiazepine, dispensing, misuse

**Introduction**

Concurrent use of opioids and benzodiazepines may cause a range of adverse health outcomes including fatal overdose. Studies that examined fatal overdose deaths found evidence of concurrent use of opioids and benzodiazepines among 31%–61% of decedents [1-3]. Despite this fatal risk, concurrent use of prescriptions opioids and benzodiazepines is common in many settings [4-7]. In a study conducted in USA Hwang and colleagues found that approximately half of the concomitant users received both the opioid and benzodiazepine prescriptions from the same prescriber on the same day [8]. Given that concurrent use of these medicines has substantial public health implications, a guideline published in 2016 by the Centers for Disease Control for prescribing opioids for chronic pain recommends clinicians to avoid prescribing the combination of an opioid and benzodiazepine whenever possible [9]. In the same year the Food and Drug Administration announced its intent to revise and improve the labelling for warnings, precautions and drug interaction for opioids and benzodiazepines [10].

Concurrent use of opioids and benzodiazepines is not uncommon in Australia [7,11]. In a study of a national sample of chronic non-cancer pain patients, Nielsen and colleagues [7] found that 17% reported daily benzodiazepine use. Although in lesser extent than USA, harmful use of licit and illicit drug continues to be a serious public health problem in Australia. In 2016, 1,808 drug induced deaths were registered, which was the highest number of drug deaths in last twenty-year’s history of Australia [12]. Opioids and depressants (benzodiazepines and barbiturates) were the two most common classes of drug identified on toxicology reports in drug induced deaths [12]. Guidelines by The Royal Australian College of General Practitioners recommend that a pain specialist be involved in the care of patients with chronic pain who take multiple psychoactive medications including benzodiazepines [13].

Although some previous studies examined the extent of concurrent and potentially problematic prescribing of opioids and benzodiazepines in USA [8,14,15] and other settings [16], a clear picture of concurrent dispensing of these medicines in Australia is lacking. Also, as prescribing behaviours and subsequent dispensing of these medicines are likely to vary nationally and across locations [17-19], it would be useful to examine the variation in concurrent dispensing across small geographical areas. Using a large national administrative dataset this study examined the (i) levels of concurrent use of opioids and benzodiazepines between 2013 and 2016, (ii) variation in concurrent use across local government areas and states, and (iii) predictors of concurrent use.

**Methods**

***Dataset***

We used 10% sample of de-identified unit record data of prescription opioids and benzodiazepines that were dispensed between 1st January 2013 – 31 December 2016. The dataset was extracted based on the date of prescription dispensing from the database of the statistics branch of the Australian Department of Human Services. In the database, medicines are recorded according to the World Health Organization (WHO) Anatomical and Therapeutic Chemical classification [20]. Medicines that were dispensed through private prescription were not included in this dataset. The dataset also contained information about three types of subsidy schemes: Pharmaceutical Benefits Scheme, Repatriate Pharmaceutical Benefits Scheme and under co-payment; users’ sex (male or female); age in years; date-month-year of dispensing; generic name of drug, form and strength; quantity dispensed; and the local government area (LGA) in which the medicines were dispensed.

Demographic data for individual states and territories, LGAs, and Socio-Economic Indexes for Areas (SEIFA) for LGAs were obtained from the Australian Bureau of Statistics. SEIFA is made-up of four indexes derived from the five-yearly national census. SEIFA ranks Australian areas according to relative socio-economic advantage and disadvantage [21]. We used the Index of Relative Socio-Economic Disadvantage (also known as IRSD). A higher score on the Index of Relative Socio-economic Disadvantage indicate a lower level of disadvantage and a lower score indicates a higher level of disadvantage. LGAs were categorized as urban or rural based on Australian Classification of Local Government in 2013 [22].

***Identification of concurrent users***

Concurrent users were identified using the prescription dispensing dates, and days of supply in terms of defined daily dose (DDD), which was introduced by the WHO Collaborating Centre, to quantify drugs dispensed across different types of opioids [20]. DDD corresponds to the estimated defined daily dose of a drug when used for its main indication in adults. Concurrent users are those where the supply in DDD quantity for an opioid overlaps with the supply of a benzodiazepine. For example, an individual dispensed 10 DDD opioids on 12 January followed by benzodiazepines dispensing on 19 January, then the person was identified as concurrent user for 3 days (i.e., 10+12 – 19).

***Data analysis***

The outcome measures included number of individual users and duration of concurrent use, most common type of opioid and benzodiazepine dispensing, and predictors of concurrent users. Number of users were computed for men and women, states and territories, and age-groups, stratified across the years (2013-2016). As the data was a 10% sample, for computing number of users per 1000 people, the numbers were multiplied by 10. Using direct standardization approach [23], the number of concurrent users in the individual LGAs were adjusted for the age and sex structure of the Australian national population. The standardised rates are hypothetical rates that would have been observed if the population we studied had the same age and sex distribution as the Australian national population, while all other factors remained unchanged. Based on tertile distribution of four-year average of standardized concurrent user numbers, all LGAs were categorized into three types: low, moderate and high and reflected on the Australian map.

To examine the variation in type of drug being dispensed among the concurrent and non-concurrent users, a drug of choice (both for opioid and benzodiazepine) was identified for everyone based on total amount of DDD dispensed during the four-year of study period. If someone was dispensed tramadol and codeine, and the DDD amount for tramadol was higher than codeine, then tramadol was identified as drug of choice for this person.

Two regression models were developed. Firstly, we ran a multivariable logistic regression to identify the significant covariates of concurrent users. Secondly, where the dataset had a hierarchical structure (e.g., LGAs are nested in states), we performed a likelihood test to compare random effects model against a fixed effects model. Statistically significant results (*p*<0.05) in this test implied that the random effect models were preferable for modelling this data. Accordingly, we conducted multilevel mixed effects negative binomial regression using *meqrlogit* commands of STATA program [24].

All analyses were performed using Stata 13 (Stata Corp LP, College Station, TX, USA, 2011) and R software version 3.4.4 [25] was used for mapping and the tidyverse and tmap packages [26,27] to generate the maps.

**Results**

During the study period (2013-2016) 7.95 million distinct users were dispensed either opioids, benzodiazepines or both. Opioids alone were dispensed to 59.09%, benzodiazepines alone to 15.24% and both were dispensed to 25.66% of the users. Over the four years almost 12.41% (0.99 million) individuals concurrently used prescription opioids and benzodiazepines. Overall, the mean duration of concurrent use during the study period was 93 days (SD±319 days). Year-wise distribution of concurrent users across sex and age-group are presented in Table 1. Over the years, significantly and consistently more women were concurrent users than men, and this holds for all age-groups (Table 1). The mean age of opioid-only users was 50 years, benzodiazepine-only users was 52 years, both drug users was 56 years and concurrent users was 59.6 years. There was an age gradient in concurrent users – the population of concurrent users increased with age.

Table 1: Concurrent users (in 100,000 people) of prescription opioids and benzodiazepines – stratified by year, sex and age-group (0-19, 20-44, 45-64, 65+)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Year | Men | | | | Women | | | | Overall |
| 0-19 | 20-44 | 45-64 | 65+ | 0-19 | 20-44 | 45-64 | 65+ |
| 2013 | 19 | 875 | 2133 | 4364 | 24 | 1053 | 2722 | 6725 | 1763 |
| 2014 | 22 | 963 | 2180 | 4177 | 29 | 1146 | 2770 | 6456 | 1787 |
| 2015 | 25 | 978 | 2159 | 3886 | 31 | 1179 | 2745 | 6055 | 1751 |
| 2016 | 29 | 1029 | 2098 | 3649 | 41 | 1242 | 2733 | 5630 | 1722 |

Note: these are unadjusted numbers

Codeine and diazepam were the most popular items for all types of users, concurrent or other. Over the four years, 7,59,960 individuals were dispensed both opioids and benzodiazepines on the same day. Among those who were dispensed an opioid (n=6.74 million), 14.64% were dispensed opioid and benzodiazepine concurrently, 15.63% were dispensed these medicines non-concurrently, and the remaining 69.71% were dispensed opioid only. Similarly, among those who were dispensed a benzodiazepine (n=3.24 million), 30.35% were concurrent users, 32.39% were non-concurrent users and the remaining 37.26% were benzodiazepine-only users. There was little variation over the years in terms of number of individuals who were dispensed these two medicines on the same day.

Figure 1: Concurrent users per 1000 people in individual states and territories (standardized for age and sex)

Figure 1 represents age and sex adjusted numbers of distinct concurrent users over the years and across the states. Tasmania had the highest number of concurrent users followed by Victoria. Northern Territory had the lowest number of concurrent users. Among the concurrent users, the mean duration of concurrent use was highest for Tasmania (112 days) followed by South Australia (95 days), and lowest for Northern Territory (74 days).

Oxycodone, tramadol, buprenorphine, fentanyl and morphine were more popular among the concurrent users than others. On the other hand, codeine (and derivatives) was more popular among the “only opioid users” and those who were dispensed both opioids and benzodiazepines but not concurrently (Table 2). Diazepam, nitrazepam, alprazolam and clonazepam were more popular benzodiazepines among the concurrent users while temazepam was more popular among “only benzodiazepine users” and those who were dispensed both opioid and benzodiazepine but not concurrently.

Table 2: Variation in dispensing of drug of choice in four groups of users: concurrent, non-concurrent, opioids only and benzodiazepines only

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Item** | **Concurrent users**  **%** | **Used both drugs but not concurrently**  **%** | **Only opioid users**  **%** | **Only benzodiazepine users**  **%** |
| ***Opioid*** |  |  |  |  |
| Codeine and derivatives | 46.03 | 59.89 | 62.65 | - |
| Oxycodone and derivatives | 22.29 | 21.43 | 20.36 | - |
| Tramadol | 16.05 | 13.17 | 12.44 | - |
| Buprenorphine | 5.67 | 2.04 | 1.81 | - |
| Fentanyl | 3.84 | 0.74 | 0.83 | - |
| Morphine | 3.56 | 1.70 | 1.07 | - |
| Tapentadol | 1.08 | 0.72 | 0.53 | - |
| Hydromorphone | 1.03 | 0.25 | 0.26 | - |
| Methadone | 0.45 | 0.05 | 0.06 | - |
| ***Benzodiazepines*** |  |  |  |  |
| Diazepam | 48.20 | 41.32 | - | 40.45 |
| Temazepam | 33.15 | 45.28 | - | 44.84 |
| Oxazepam | 9.51 | 9.14 | - | 9.31 |
| Nitrazepam | 3.89 | 1.91 | - | 1.96 |
| Alprazolam | 3.78 | 1.78 | - | 2.72 |
| Clonazepam | 1.18 | 0.48 | - | 0.60 |
| Zopiclone | 0.23 | 0.09 | - | 0.11 |
| Zolpidem | 0.03 | 0.01 | - | 0.01 |
| Flunitrazepam | 0.02 | 0.00 | - | 0.00 |
| Bromazepam | 0.01 | 0.00 | - | 0.01 |

Results of our multivariable model are consistent to that were found in the descriptive analysis. Odds of concurrent dispensing increased with age. Women were more likely than men to be dispensed both opioids and benzodiazepines concurrently. People living in relatively high disadvantaged or rural areas were more likely to be concurrent users (Table 3).

Table 3: Multivariable logistic model examining the factors associated with concurrent use of opioids and benzodiazepines

Number of observations = 786,587

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **OR** | ***p*** | **95% CI** |
| **Age-group** |  |  |  |
| 0-19 (ref.) | 1 | - | - |
| 20-44 | 5.19 | <0.01 | 4.78 – 5.63 |
| 45-64 | 8.89 | <0.01 | 8.19 – 9.65 |
| 65+ | 13.98 | <0.01 | 12.88 – 15.17 |
|  |  |  |  |
| **Sex** |  |  |  |
| Male (ref.) | 1 | - | - |
| Female | 1.17 | <0.01 | 1.15 – 1.19 |
|  |  |  |  |
| **SEIFA** |  |  |  |
| Very high (ref.) | 1 |  |  |
| High | 1.11 | <0.01 | 1.09 – 1.13 |
| Moderate | 1.16 | <0.01 | 1.14 – 1.19 |
| Low | 1.17 | <0.01 | 1.14 – 1.20 |
|  |  |  |  |
| **Urbanization** |  |  |  |
| Urban (ref.) | 1 |  |  |
| Rural | 1.03 | <0.01 | 1.01 – 1.06 |
|  |  |  |  |
| New South Wales | 1 | - | - |
| Victoria | 1.16 | <0.01 | 1.14 – 1.18 |
| Queensland | 1.30 | <0.01 | 1.28 – 1.33 |
| South Australia | 1.25 | <0.01 | 1.22 – 1.28 |
| Western Australia | 1.06 | <0.01 | 1.03 – 1.08 |
| Tasmania | 1.29 | <0.01 | 1.24 – 1.35 |
| Northern Territory | 0.78 | <0.01 | 0.69 – 0.89 |
| Australian Capital Territory | 0.93 | 0.03 | 0.87 – 0.99 |
|  |  |  |  |
| Constant | 0.01 | <0.01 | 0.01 – 0.01 |

The estimated standard deviation of the random intercepts, their standard errors and 95% confidence intervals suggest there were considerable variation in concurrent users across the states and LGAs. The random-intercept model offers significant improvement over the logistic regression (chi2 = 1834.91; *p*<0.01). Much of the urban-rural difference was eliminated in the multilevel model. Individual level coefficients remained largely similar to that in the logistic model. We estimate that the state and LGA random effects compose only 2% of the total residual variance in the final model, and most of the variation was due to individual level attributes. For instance, participants aged 65+ were 14 times more likely to be a concurrent user than those who were of 0-19 years old when other characteristics remained identical.

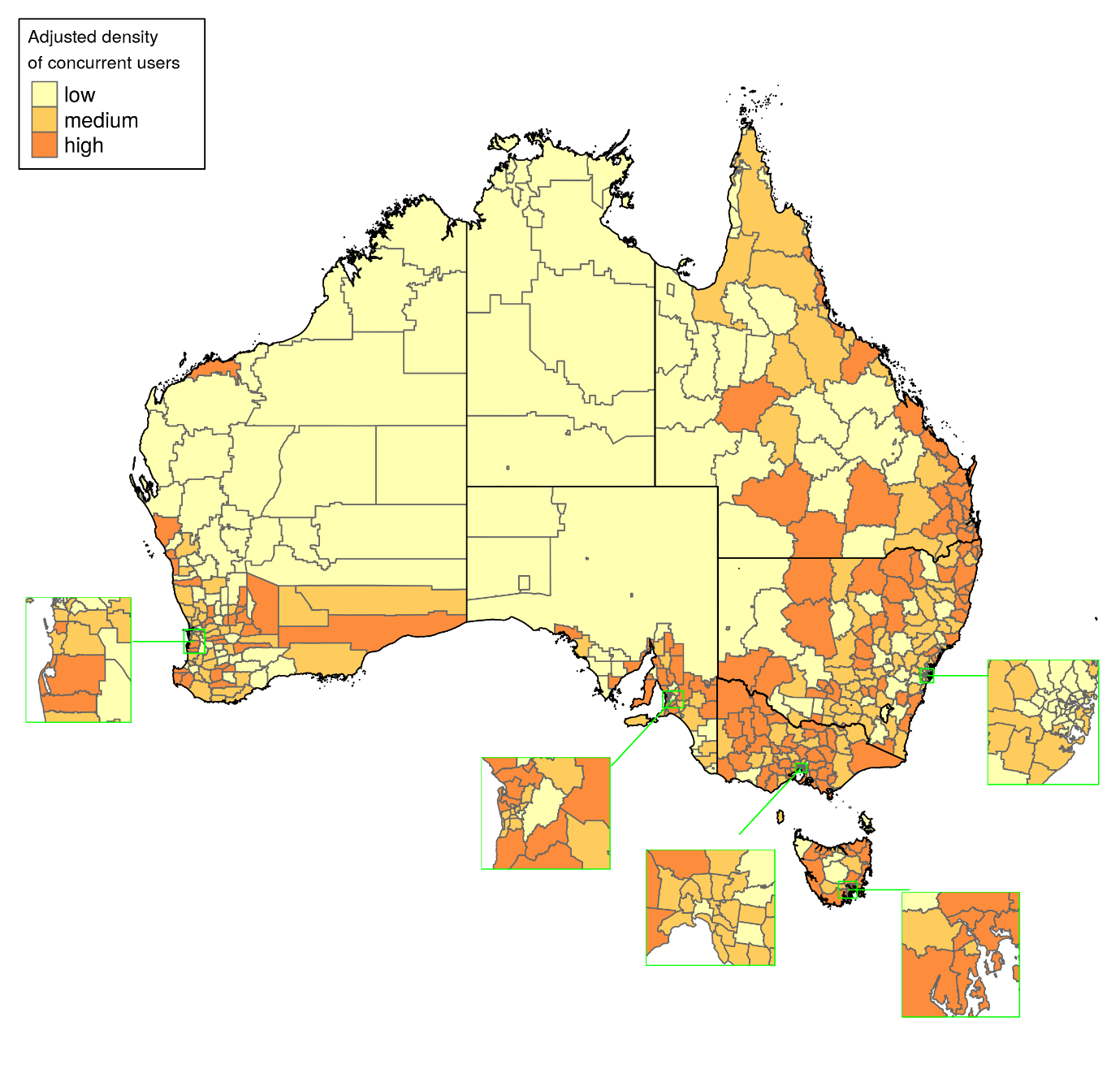
Table 4: Mixed-effect multilevel logistic regression model examining the factors associated with concurrent use of opioids and benzodiazepines

Number of observations = 786,587

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **OR** | ***p*** | **95% CI** |
| **Age-group** |  |  |  |
| 0-19 (ref.) | 1 | - | - |
| 20-44 | 5.21 | <0.01 | 4.80 – 5.66 |
| 45-64 | 8.89 | <0.01 | 8.19 – 9.65 |
| 65+ | 13.93 | <0.01 | 12.83 – 15.12 |
|  |  |  |  |
| **Sex** |  |  |  |
| Male (ref.) | 1 | - | - |
| Female | 1.17 | <0.01 | 1.15 – 1.19 |
|  |  |  |  |
| **SEIFA** |  |  |  |
| Very high (ref.) | 1 |  |  |
| High | 1.11 | <0.01 | 1.06 – 1.16 |
| Moderate | 1.19 | <0.01 | 1.13 – 1.26 |
| Low | 1.24 | <0.01 | 1.17 – 1.32 |
|  |  |  |  |
| **Urbanization** |  |  |  |
| Urban (ref.) | 1 |  |  |
| Rural | 1.00 | 0.86 | 0.96 – 1.05 |
|  |  |  |  |
| Constant | 0.01 | <0.01 | 0.01 – 0.02 |
|  |  |  |  |
| Random-effects parameters | Estimate | Standard Error | 95% CI |
| States (SD, constant) | 0.13 | 0.04 | 0.06 – 0.25 |
| LGA (SD, constant) | 0.15 | 0.01 | 0.13 – 0.17 |

LR test vs. logistic model: chi2 = 1834.91; *p*<0.01

There were considerable variations in four-year’s average density of concurrent users across LGAs, ranging from less than one to 54 per 1000 people (standardized by age and sex). LGAs with relatively high (n=189), moderate (n=188) and low (n=188) levels of concurrent users were presented in Figure 2. Number of concurrent users over the years in each LGAs remain largely similar during the study period.



**Figure 2:** Variation in terms of concurrent users of opioids and benzodiazepines across LGAs during the study period.

**Discussion**

Opioid- and benzodiazepine-related morbidity and mortality present a serious public health problem and therapeutic challenge [12,28]. To our knowledge, this is the first study in Australia that analysed a large, population level and longitudinal data to examine the concurrent use of prescription opioids and benzodiazepines. Our results suggest concurrent use of opioids and benzodiazepines is not uncommon in Australia. Concurrent use was significantly more prevalent among women than men, and its likelihood increased with age and area level disadvantages. There was considerable variation in terms of standardized number of concurrent users across the small geographical areas.

Women and senior citizens were the largest group of concurrent users. This observation is consistent to studies conducted in other settings [29,30]. This is attributed to a number of factors that include seeking frequent medical care by women and senior citizens, relatively high prevalence of both chronic pain and mental health conditions for which these medications are often prescribed [8,31], and perceived easy pharmaceutical fixes [32]. Apart from risk of overdose death from concurrent use of opioids and benzodiazepines, other adverse health outcome such as falls, and fractures are prevalent among seniors [8,33].

Our results suggest a considerable geographical variation in concurrent dispensing of opioids and benzodiazepines. Although the reasons for this variation is outside the scope of this study, findings of our regression models suggest that apart from demographic composition of the population, the problem is greatly associated with social disadvantages. Literature suggests these disadvantages are a likely product of the rate of unemployment, socio-economic inequality, urban-rural locations and their impacts on access to health care [34]. Part of this variation could also be attributed to prescribing practices by the clinicians [14]. It is not unlikely that in regional areas and small communities prescribing and dispensing may be relatively relaxed because of a long-term and trusted relationship between patients and providers. Given that the state- or territory-level variation can mask local-level variation [17], in addition to current federal and state level policy intervention, tailored program is needed for small geographical locations such as local government areas.

Understanding the underlying causes of concurrent use of opioids and benzodiazepines is an important step towards any efforts to reduce it. Literature suggests comorbidities such as anxiety, depression, insomnia and substance use are common among patients with chronic pain [35,36]. As a result, along with pain relief, treatment for anxiety, depression and sleep disorder are also important and requires co-prescription of medications such as benzodiazepines [16]. However, it is not clear as to what extent the concurrent use of benzodiazepines and opioids is caused by psychiatric problems or as a therapeutic treatment of pain. Most guidelines on prescription opioids and benzodiazepines say that although there are circumstances when it might be appropriate to concurrently prescribe opioids and benzodiazepines, clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible [9].

Our dataset did not have information about the prescribers or dispensers. As a result, we are unable to say as to what proportion of these concurrent prescribing were from the single provider. However, literature suggests, a majority of concurrent cases involved a single provider prescribing both drugs within a short time window [8]. This suggests the necessity for improved education for prescriber, information about better alternative treatments and support in managing patients who use both of these drugs concurrently. In addition, further research is needed to assess the strategies to reduce co-prescribing and concurrent use of these drugs, as prescriber guidelines and education may not be enough.

Although it is unknown as to what proportion of this concurrent dispensing was attributable to prescription by several clinicians in a small period, literature suggests a considerable part of these are due to inadequate information of the history of prescribing. A recent study showed that the risk of overdose increases with the numbers of opioid and benzodiazepine prescribers [37]. If the clinicians or pharmacists are unaware of the previous prescription/dispensing, they often need to rely on the information they receive from the patients. Although drug urine test is recommended when there are reasons for suspicion, this involves a range of challenges [38]. These, together, possibly highlight the important role that fragmentation of care plays in the inappropriate and concurrent use of opioids and benzodiazepines and subsequent risk of overdose, and warrant the necessity of introducing real-time prescription drug monitoring program. This computer based program helps physicians and pharmacists to check the history of prescription drugs of dependence before prescribing and dispensing [39]. The good news is that some states are now implementing this program. Tasmania initiated such program first. Currently the Victorian government is implementing a similar program known as “SafeScript” [40]. The NSW government awaiting a nation-wide implementation of this program [41].

Our findings have some important implications from clinical, policy and research perspectives. Firstly, one of the important reasons for concurrent dispensing is a lack of consensus on co-prescribing of these medicines. The consensus opinions on the concurrent use of opioids and benzodiazepines vary from “contraindicated” to “only discussing the risk” [42]. Given that the risk of overdose was highest on the first days of concurrent opioid and benzodiazepine use [37], clinicians should avoid: concurrent prescribing of these medicines, prescribing benzodiazepines to patients using opioids or other way around. Secondly, from the policy perspective, it is important to ensure that the clinicians have access to the history of medication use by the patients, and clinicians are aware of risks involved. Also, policymakers and healthcare systems should equally focus on benzodiazepine prescribing and dispensing practice along with the current focus on opioid prescribing [4]. Thirdly, further research is needed to identify the precise reasons for co-prescribing in population level, reasons for prescribing one drug category while a patient is using the other, and evaluate interventions which can reduce such practice.

Our study has several strengths. Firstly, we examined concurrent use in a national sample that is broadly representative of the entire population in Australia. Secondly, we analysed national, state and LGA level dispensing. Thirdly, four-year’s unit-record data helped to examine the temporal variation of concurrent use. Our study has also some limitations. The DDD does not always correspond to the recommended daily dose for everybody. Also, opioids and benzodiazepines that were dispensed through private prescriptions or in hospitals were not captured in this dataset. We collected only limited set of variables. The spatial measure in concurrent use offers only a summary index and does not equally apply to everybody, as all people living an area are not similar.

In summary, concurrent use of opioid and benzodiazepine was common in Australia. There were considerable variations across the states/territories and LGAs in terms of users who were dispensed these medicines concurrently. Women, senior citizens or those who were living in socio-economically disadvantaged areas were dominant groups of concurrent users. Further research is needed to examine the precise reasons of concurrent use and the interventions that can ameliorate those causes.

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