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

M Mofizul Islam

Dennis Wollersheim

**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 also common 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 alone, a total of 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 chronic pain patients 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 [17,18], it would be useful to examine the variation of 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 2013-2016, (ii) the variation in concurrent use across local government areas, 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 during 1st January 2013 – 31 December 2016. The dataset was extracted based on the date of supply 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 [19]. Medicines that were dispensed through private prescription were not included in this dataset. The dataset also contained information about three types of subsidy schemes: PBS, RPBS, or under co-payment; users’ sex (male or female); age in years; date-month-year of dispensing; drug generic name, 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. SEIFAranks Australian areas according to relative socio-economic advantage and disadvantage [20]. 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 [21].

***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 [19]. DDD corresponds to the estimated defined daily dose of a drug when used for its main indication in adults. Concurrent users consist of users for whom the supply in DDD quantity for one medicine overlaps with the dispensing day of the other. For instance, if an individual was 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, the most common type of concurrent 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). Using direct standardization approach [22] number concurrent users in the individual LGAs were adjusted for the population structure of Australia, stratified across age and sex. 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 standardized concurrent number of users, all LGAs were categorized into three types: low, moderate and high, and reflected in 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.

Two regression models were developed. Firstly, we run a multivariable logistic regression to identify the determinants of concurrent users. Secondly, given that there was a hierarchical structure (e.g., LGAs are nested in states) in the dataset, we performed likelihood test to compare random effects model against 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 [23].

All analyses were performed using Stata 13 (Stata Corp LP, College Station, TX, USA, 2011) and R software.

**Results**

During the study period (2013-2016) 7.95 million distinct users used either opioids, benzodiazepines or both. Only opioids were dispensed to 59.09%, only benzodiazepines to 5.24% and both to 25.66% users. During the four years almost 12.41% (0.98 million) individuals were identified as concurrent users of prescription opioids and benzodiazepines. Year-wise distribution of dispensing 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 is consistent 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 – numbers increased with the age.

Table 1: Concurrent users (in 100,000) 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 | 1.87 | 87.50 | 213.35 | 436.39 | 0.67 | 42.77 | 78.05 | 120.05 | 176.29 |
| 2014 | 2.21 | 96.35 | 218.02 | 417.74 | 0.83 | 46.52 | 79.67 | 117.31 | 178.66 |
| 2015 | 2.49 | 97.79 | 215.86 | 388.58 | 0.91 | 48.09 | 79.61 | 113.32 | 175.06 |
| 2016 | 2.88 | 102.94 | 209.81 | 364.92 | 1.18 | 51.01 | 80.28 | 108.24 | 172.19 |

Codeine and Diazepam were the most popular items for all types of users, concurrent or other. During the four years 7,59,960 individuals were dispensed both opioids and benzodiazepines on the same day. During four-year study period 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 benzodiazepines 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 the distinct number of individuals over the years and across the states, adjusted for age and sex. As per the adjusted numbers, Tasmania had the highest number of concurrent users followed by Victoria. Northern Territory at sits last in the league table. 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). In relation to benzodiazepine dispensing, diazepam, nitrazepam, alprazolam and clonazepam were more popular among the concurrent users while temazepam was more popular among “only benzodiazepine users” and those who were dispensed both opioid and benzodiazepine but no concurrently.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Item** | **Concurrent use**  **%** | **Used both drugs but not concurrently**  **%** | **Only opioid user**  **%** | **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 we 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 observation = 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 are considerable variation in concurrent users across the states and LGAs. The random-intercept model offers significant improvement over the linear 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.

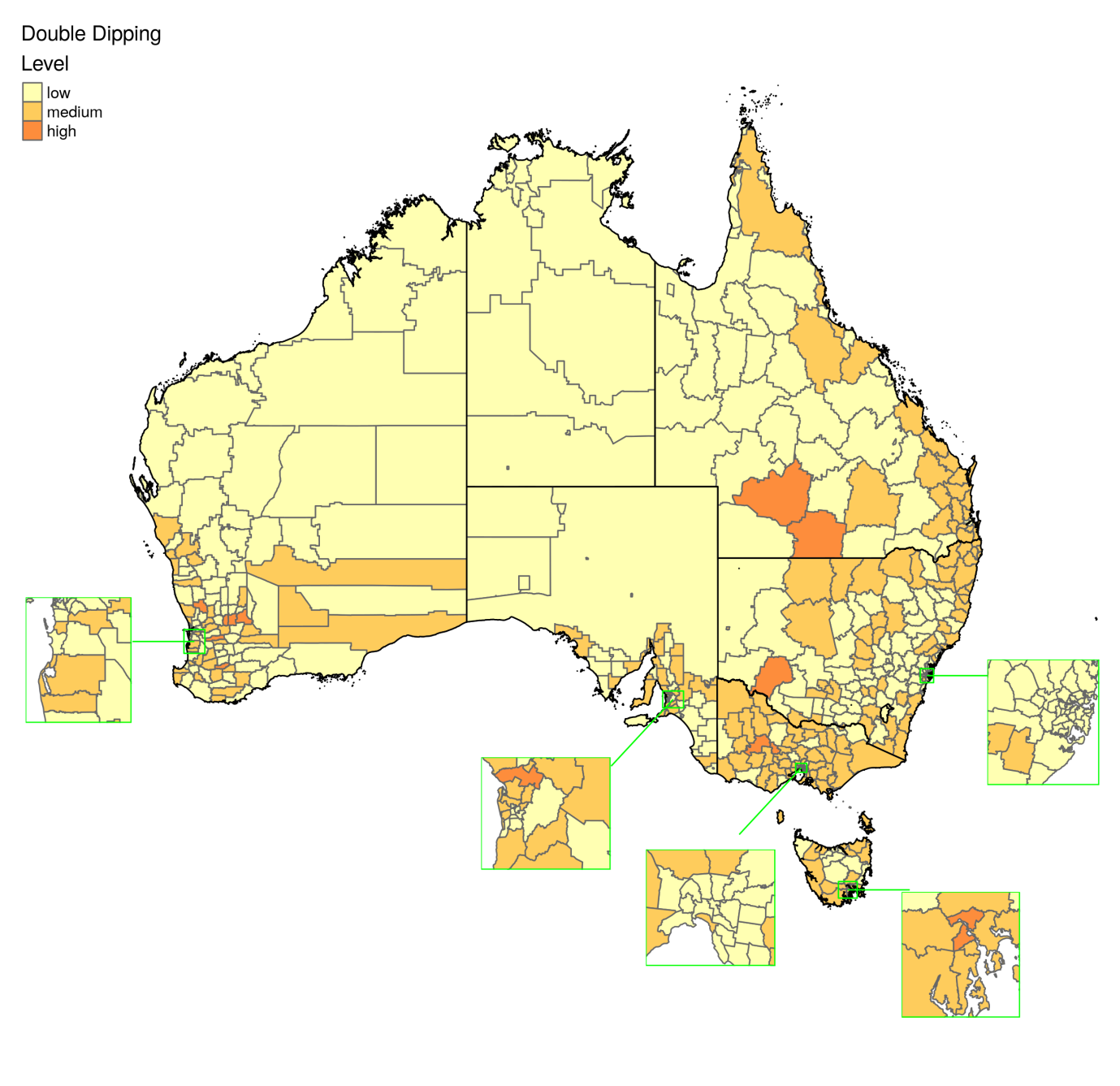
Table 4: Mixed-effect multilevel logistic regression model examining the factors associated with concurrent use of opioids and benzodiazepines

Number of observation = 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 the level of concurrent use (Figure 2), ranging from 0 to 55.0 per 1000 people (standardized with age and sex). Among all the LGAs, 2.8% were identified as high, 39.7% as moderate and 57.4% as low levels of concurrent using. Total number of concurrent users over the years in each LGA remained largely similar during the study period.



**Figure 2:** Variation in terms of concurrent users of opioids and benzodiazepines across LGAs in 2013

**Discussion**

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. Opioid- and benzodiazepine-related morbidity and mortality present a serious public health problem and therapeutic challenge [12,24]. 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 [25,26]. 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 [8,27], and perceived easy pharmaceutical fixes [28]. Although overdose death from concurrent use of opioids and benzodiazepines are lower in seniors than younger population (find a good reference), other adverse health outcome such as falls andfractures are prevalent among seniors [8,29].

Our results suggest 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 [30]. 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 masks 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 [31,32]. 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. Due caution is required, as the benefit may outweigh the harm from concurrent use. The CDC guideline says 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 prescriber education, 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 sufficient.

Although it is unknown as to what proportion of these concurrent dispensing were 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 [33]. 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, a range of challenges are involved in it [34]. These, together, possibly demonstrate the important role that fragmentation of care plays in the inappropriate and concurrent use of opioids and benzodiazepines and in the 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 [35]. 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” [36]. The NSW government is awaiting a nation-wide implementation of this program [37].

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 varies from “contraindicated” to “only discussing the risk” [38]. Given that the risk of overdose was highest on the first days of concurrent opioid and benzodiazepine use [33], 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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