Benzodiazepine prescribing: A qualitative cross-national comparative pilot between Australia and South Africa

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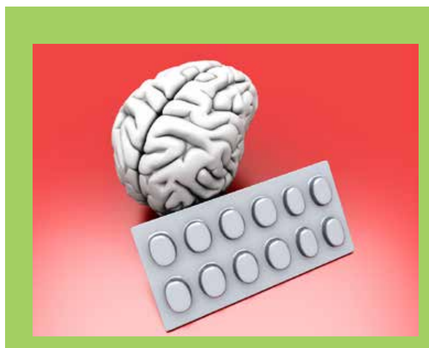
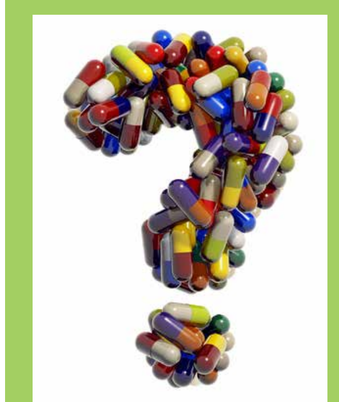
Nelson Mandela Metropolitan University
for tomorrow





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BACKGROUND TO THE STUDY

Benzodiazepines have anxiolytic, sedative, hypnotic and muscle relaxant effects and are used to treat anxiety, panic and sleep disorders. They may result in an altered mental state, including euphoria, resulting in misuse and abuse.[1] Misuse includes pharmacologic dependence, especially when used for more than one month. Drugs with a shorter half-life are associated with more severe withdrawal symptoms and dependence[2], although symptoms vary between patients.[3]

Abuse includes behaviour that accompanies psychological dependence[4], and includes drug diversion for illicit purposes. Legal restrictions on prescribing and dispensing limit misuse and abuse and in South Africa, benzodiazepines are Schedule 5 medicines. Although the abuse potential of benzodiazepines is low[2], alprazolam was rescheduled from a prescription drug to a Controlled Drug in Australia in 2014 due to its potential for illicit drug use.[5,6] Benzodiazepines used orally for recreational purposes include diazepam, alprazolam, temazepam, flunitrazepam and, to a lesser extent, triazolam and lorazepam.[7]

PRIMARY AIM

The primary aim of this pilot study was to investigate benzodiazepine prescribing patterns with a specific focus on cross-national comparative dispensing.

METHODOLOGY

- A retrospective, cross-sectional, cross-national comparative drug utilisation study was conducted on two datasets of prescriptions dispensed in 2010 and 2011.
- The South African database contained approximately 5 million records for medicines, medical devices and procedures, and was obtained from a medical insurance (medical aid) administrator in South Africa.
- The Australian data consisted of de-identified dispensing data that was extracted from three pilot sites (pharmacies) in a metropolitan city in Australia. This experimental dataset contained 1 311 669 dispensing records extracted over a 3-year period. In Australia, most medicines required to treat common conditions are subsidised by the government and Australian permanent residents pay a levy towards the cost of the medicine, similar to the patient contribution of medical aid schemes in South Africa. Data included dispensed prescriptions that were subsidised by the government as well as prescriptions for which patients paid the full amount.
- The Anatomical Therapeutic Chemical (ATC) Classification System[8], MIMS[9] and the South African Medicines Formulary[10] were used to identify medicines. For the South African data, all medication records for benzodiazepines and benzodiazepine-related drugs were extracted according to the MIMS classification system[9]. The Australian Medicines Handbook[11] and ATC were used to classify the Australian data.
- Each medication record contained a unique number that represented each de-identified dispensing record, the date of the prescription, detailed information on the dispensed drug (name, package size, formulation, strength and quantity).
- Microsoft Access® and Excel® were used to analyse the data.
- Ethical approval to conduct studies on prescription databases was obtained from the Research Ethics Committee (Human) of the Nelson Mandela Metropolitan University (ethics clearance number: H08-HEA-PHA-005), and the process to extract and de-identify data from three pilot sites in Australia received ethical approval from the University of Queensland (ethical clearance 2012000078).

Limitations of the study

- **South African database**: Only data of patients served by the private health care sector in South Africa were included in the study and no clinical information or diagnoses were available.
- **Australian dataset**: Only data from three participating pharmacies were included in this pilot study.

RESULTS AND DISCUSSION

Demographic information of patients

South Africa: In 2010 and 2011, a total of 71 390 prescriptions for benzodiazepines and benzodiazepine-related drugs were dispensed to 16 601 patients. In 2010, a total of 34 966 benzodiazepine prescriptions were dispensed to 9 606 patients (45.72% males) reflecting on average 3.64 benzodiazepine products per patient. Prescribing frequency decreased marginally the following year to an average of 3.45 products per patient, with 36 424 benzodiazepines prescribed to 10 556 patients of which 40.44% were males.

Australia: The dataset did not contain reliable gender information. The surrogate marker for gender was the title of the patient (mr/mrs/miss/ms/master) and indicated that 30.70% of anxiolytic, sedative and hypnotic prescriptions were dispensed to females and 21.32% to males; however, gender was unknown for the remaining 52.02% of benzodiazepine prescriptions. Date of birth was not extracted from the database for privacy reasons.

Active ingredients dispensed

In the South Africa dataset, benzodiazepines constituted 64.79% of prescriptions, sedative hypnotics (other) accounted for 29.17% and anxiolytics (other) for 6.04%. In the Australian dataset there were 1 311 669 dispensed prescriptions that were extracted in a 3-year period. During 2010 and 2011, a total of 3 960 dispensing records were analysed for this study including the non-benzodiazepine hypnotics zolpidem (n=362) and zopiclone (42). Clonazepam is indicated for epilepsy and was excluded from the study; 19 active ingredients are reported in Table 1.

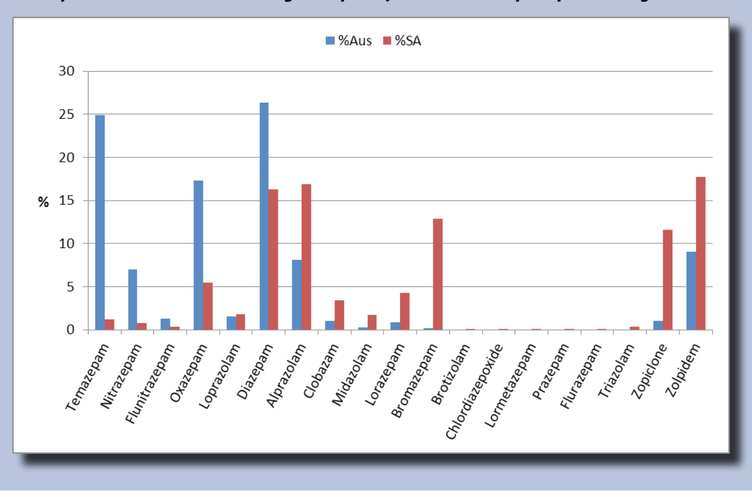
TABLE 1
Comparative relative percentage frequency of active ingredients dispensed 2010 and 2011

ACTIVE INGREDIENTS	Half-life	% Australia / South Africa data	Australian dataset %			South African data %		
			2010 n=2030	2011 n=1930	Total n=3960	2010 n=32775	2011 n=34579	Total n=67354
Temazepam	Short	21:1	24.51	25.28	24.89	1.12	1.20	1.16
Nitrazepam	Long	9:1	6.76	7.16	6.96	0.88	0.68	0.77
Flunitrazepam	Long	4:1	1.02	1.48	1.25	0.38	0.29	0.34
Oxazepam	Short	3:1	18.73	15.81	17.31	6.13	4.84	5.47
Loprazolam	Short	1:1	0	3.12	1.52	1.84	1.68	1.76
Alprazolam	Short	1:2	7.98	8.24	8.10	17.45	16.39	16.91
Diazepam	Long	1:2	25.24	27.53	26.36	17.85	14.88	16.33
Clobazam	Long	1:3	1.02	0.97	1.00	2.88	3.86	3.38
Midazolam	V.Short	1:7	0.29	0.20	0.25	1.89	1.59	1.74
Lorazepam	Medium	1:5	1.65	0	0.85	4.33	4.13	4.23
Triazolam	V.Short		0	0	0	0.40	0.32	0.36
Bromazepam	Medium	1:65	0.10	0.31	0.20	9.35	16.23	12.88
Flurazepam	Short		-	-	-	0.01	0	0.01
Brotizolam	Short		-	-	-	0.03	0.02	0.02
	Long		-	-	-	0.01	0	0.02
Lormetazepam	Short		-	-	-	0.08	0.05	0.06
Prazepam	Long		-	-	-	0.10	0.06	0.08
OTHER								
Zolpidem		1:2	9.87	8.14	0.03	17.77	17.71	17.74
Zopiclone		1:11	1.56	0.511	1.05	12.17	11.01	11.58

Cross-national comparison

In this exploratory comparative cross-national pilot the datasets were not directly comparable; therefore, we designed a method that permitted qualitative comparisons. **Comparative Relative Percentage Frequency** was calculated by expressing the relative percentage frequency of dispensing in each dataset as a ratio of dispensed prescriptions from Australia:South Africa datasets. Six active ingredients accounted for more than a four-fold difference in prescribing between the two countries: temazepam and nitrazepam were dispensed more frequently at the Australian pilot sites (21 times and nine times, respectively), while bromazepam, midzalom and lorazepam were dispensed more frequently in South Africa (65 times, seven, and five times, respectively). Zolpidem was dispensed twice as frequently in South Africa compared to the Australian sites, while zopiclone was dispensed 11 times more frequently (Figure 1). Prazepam, brotizolam, flurazepam and chlordiazepoxide were not available or were not subsidised medicines in Australia at the time of the study.

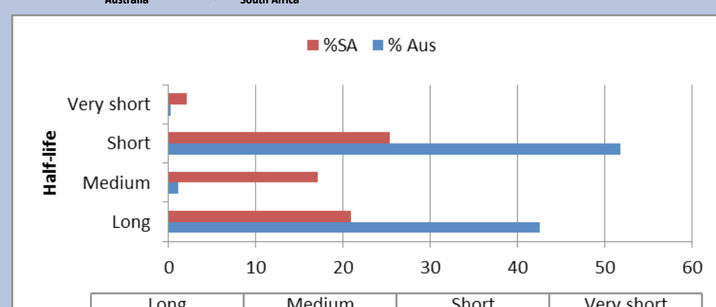
FIGURE 1
Comparative Relative Percentage Frequency of benzodiazepine prescribing



Benzodiazepine prescribing according to half-life

A visual comparison of the relative percentage frequencies of benzodiazepines dispensed in South Africa and in the Australian sites is shown in Figure 2, classified according to half-life as short half-life is associated with withdrawal effects and hence dependence.[2] There was a greater percentage of short or very short acting benzodiazepines in the Australian data (52.07%) compared to South African data (27.49 %).

FIGURE 2
Relative percentage frequency of benzodiazepine prescriptions according to half-life ($n_{Australia}$=3 960; $n_{South\ Africa}$=67 354)



	Long	Medium	Short	Very short
%SA	20.92	17.11	25.38	2.11
% Aus	42.52	1.05	51.82	0.25

% of dispensed benzodiazepines

Benzodiazepine active ingredients

- ***Alprazolam***

In the South African database, most (89.34%) prescriptions for alprazolam were prescribed in quantities of 14 or more tablets/capsules per prescription. It was noteworthy that one South African patient (a 51 year old female) received 30 prescriptions for alprazolam during this period. The prescriptions were, however, for a quantity of only ten 0.5 mg tablets per prescription, and the restricted quantity may have been an attempt to control the use. Also of interest: in the Australian data, on two occasions a quantity exceeding 120 tablets was dispensed. Medicines are dispensed in fixed pack sizes and at the time of the study, alprazolam was available in packs of 50 tablets. Alprazolam was rescheduled to a Controlled Drug in Australia in February 2014 due to concerns over misuse[12] - in higher dosages and mixed with alcohol, alprazolam enhances the "high" feeling that the drug generates.

- ***Bromazepam***

The medium-acting benzodiazepines bromazepam was dispensed 65 times more frequently in South Africa. This is most likely due to restrictions on its use in Australia, as its subsidised use is limited to patients with terminal disease or refractory phobic or anxiety states.

- ***Temazepam***

The short-acting temazepam was dispensed more than twenty times more frequently at the Australian experimental sites. It is prescribed for short-term insomnia and is dispensed in packs containing 25 units.

- ***Diazepam***

Diazepam was the most frequently dispensed benzodiazepine at the Australian sites and the third most frequently prescribed active ingredient in South Africa. Although it has a longer half-life, diazepam has abuse potential due to its rapid onset of action.[2]

The findings support those of other studies: in Cape Town, benzodiazepines are the most widely misused medicines in treatment centres[13] and were the primary substance of abuse among women,[14] and they are known to be subject to misuse in Australia.[15]

CONCLUSIONS AND RECOMMENDATIONS

- There are differences in benzodiazepine dispensing patterns between South African data and data from the experimental Australian sites; these differences may have been influenced by local administrative, financial or therapeutic restrictions.
- Benzodiazepine prescribing may influence intentional and unintentional misuse and, ultimately, abuse. Although overuse is difficult to prove in studies conducted on databases, medicines usage studies are an important tool that can be used to monitor for potential misuse.
- Studies in cross-national trends may play a role in identifying potential drug misuse and future comparative studies with Australia and other countries may yield important results. The length of therapy, dosages and, where possible, indication for use are aspects that could be investigated.

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