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Increasing rates of quetiapine overdose, misuse, and mortality in Victoria, Australia

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ABSTRACT

Background: Quetiapine is misused due to its anxiolytic and hedonic effects and has been associated with deliberate self-harm. This study analyzed quetiapine-related calls to the Victorian Poisons Information Centre (VPIC), coronial data from Victorian Institute of Forensic Medicine (VIFM) and prescribed data from the Pharmaceutical Benefits Scheme (PBS) to determine current trends in overdose, misuse and mortality.

Methods: This was a retrospective review of multiple databases. Calls to VPIC and coronial data from the VIFM were reviewed from 2006 to 2016. PBS prescription data from 2000 to 2015 was obtained from the Australian Statistics on Medicines website.

Results: VPIC data indicated a 6-fold increase in the number of quetiapine-related calls over the 11-year period of which most were overdose-related (77%). Overdose and misuse calls increased by 6-fold and 6.6-fold, respectively. Coronial data also indicated a rise in quetiapine-related harm; a 7.4-fold increase in quetiapine-related deaths was recorded for the same period. Similarly, Australian PBS data showed that quetiapine prescriptions increased 285-fold since 2000. There was a significant positive correlation between the increase in prescribing and overdose ($r = 0.75$, $p < 0.001$), and prescribing and mortality ($r = 0.82$, $p < 0.01$).

Conclusions: This study revealed an increasing trend of misuse, non-fatal and fatal overdoses in Victoria over the last decade. The increasing rates of prescriptions in Australia and thus increased quetiapine availability are likely to have contributed to increased poisoning and mortality. Further research is warranted to explore the reasons behind increased prescribing, including off-label use.

1. Introduction

Quetiapine is an antipsychotic available in Australia under the Pharmaceutical Benefits Scheme (PBS) for the treatment of schizophrenia, acute mania, and maintenance of bipolar disorder. Although not subsidized by the PBS, the Therapeutic Goods Administration (TGA) has also approved quetiapine use for the treatment of generalized anxiety disorder and refractory major depressive disorder (TGA, 2010). The normal therapeutic dose range for these indications is between 400 and 800 mg daily (Brett, 2015).

Quetiapine has been associated with deliberate self-poisoning and is increasingly responsible for emergency department presentations (Mattson et al., 2015) and mortality (Flanagan, 2008; Flammia et al., 2006). Indeed, reports from the US have shown that quetiapine overdoses increased by 90% between 2005 and 2011 (Mattson et al., 2015), and in England, quetiapine has caused 31.3 deaths per million prescriptions between 2000 and 2002 (Flanagan, 2008). Similarly, in Australia, ambulance attendance data indicated an 8-fold increase in quetiapine-related cases between 2001 and 2010 (Heilbronn et al., 2013).

There is growing evidence that quetiapine is being misused for its anxiolytic, hedonic and sedative effects (Fountain and Slaughter, 2016). The first report of misuse referred to incarcerated populations (Pierre et al., 2004); however, there is evidence that the problem has extended to the wider community. This is demonstrated by the increased prescribing of sub-therapeutic low-dose quetiapine (Brett, 2015; Hollingworth et al., 2010); its presence on the black market (Tarasoff and Osti, 2007); and reported cases of quetiapine withdrawal

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syndromes (Yargic and Caferov, 2011; Kohen and Kremen, 2009; Kim and Staab, 2005).

The epidemiology of quetiapine overdose, misuse, and mortality in Australia is currently unclear. While some studies have examined specific quetiapine-related harms such as mortality (Pilgrim and Drummer, 2013), the correlation with non-fatal poisonings and prescription trends has not yet been explored. This study aims to describe the epidemiology of quetiapine poisoning by examining data from the Victorian Poisons Information Centre (VPIC), Victorian Institute of Forensic Medicine (VIFM) and PBS. Specifically, it aims to provide current trends in use and misuse of quetiapine, identify the most common features of fatal and non-fatal poisonings, and determine any correlation between prescribing trends and quetiapine poisoning, in order to identify any opportunities for drug harm prevention.

2. Material and methods

This study was a retrospective review of data relating to quetiapine poisonings (VPIC), deaths (VIFM) and prescribing rates (PBS). Ethics approval was obtained from Austin Health Human Research Ethics Committee (LNR/16/Austin/327) and the VIFM Ethics Committee (RAC26/16, EC21/16).

2.1. Poisonings (VPIC)

The VPIC receives poison exposure calls within the state of Victoria, Australia, which has a population of almost 6 million people. Every call to the VPIC is documented in a purpose-designed database. Information including demographics, overdose details, intent, co-ingested drugs, and Poisoning Severity Score (PSS) (Persson et al., 1998) is recorded. All quetiapine-related calls between 1 January 2006 and 31 December 2016 were extracted and then categorised according to poisoning type: overdose, misuse, therapeutic error or accidental ingestion. In this study, 'overdose' refers specifically to deliberate self-harm and 'misuse' encompasses the terms 'diversion', 'off-label use', and 'recreational abuse'.

2.2. Mortality (VIFM)

Deaths reported to the Coroner in Victoria, Australia, between 1 January 2006 and 31 December 2016 were identified using the VIFM Integrated Case Management System, where quetiapine was detected by routine toxicological analysis. Post-mortem femoral blood provides the most accurate drug concentration (Drummer and Gerostamoulos, 2002); hence, results from other sites were excluded from analysis when calculating the range and median blood concentrations of quetiapine. Coronial cases include all unnatural, unexpected or suspicious deaths, including intentional and unintentional poisonings. Only overdose data was examined therefore deaths caused by natural disease and homicides were excluded from further analysis. Given this study aimed to examine recent mortality trends involving quetiapine and did not seek to examine individual case data, deaths that were still under investigation by the Coroner were included.

2.3. Prescriptions (PBS)

National PBS prescription data since the introduction of quetiapine into Australia in 2000 was obtained through the Australian Statistics on Medicines Government website (ASM, 2017). This included all 9 formulations prescribed between 2000 and 2015. Data for 2016 was not yet available at the time of analysis. A longer study period was chosen for this dataset to examine the overall prescription trend in Australia.

2.4. Data analysis

All data was analyzed descriptively using medians, percentages and interquartile ranges. The chi-square test was used for categorical data to examine VPIC trends. Pearson correlation was used to compare prescription rates to overdose and mortality rates. Excel (Version 14.00, 2010, Microsoft, USA) and SPSS (23.0, 2015, IBM, USA) were used to analyse the data.

Table 1
Demographic, overdose and misuse information (VPIC), 2006–2016.

Information	Number of calls/(%)
Call types	
Total	4412
Overdose	3410 (77.3%)
Therapeutic errors	517 (11.7%)
Accidental	247 (5.6%)
Misuse	221 (5.0%)
Miscellaneous (drug information, adverse reactions)	17 (0.4%)
Callers	
Doctors	2250 (51%)
Family/friends	587 (13.3%)
Nurses	536 (12.2%)
Self	299 (6.8%)
Ambulance personnel	284 (6.4%)
Others (carers, pharmacists, counsellors)	456 (10.3%)
Poisoning Severity Score (PSS)	
None	1472 (33.4%)
Minor	2384 (54%)
Moderate	327 (7.4%)
Severe	128 (2.9%)
Unknown	101 (2.3%)
Overdose demographics	
Total	3410
Females	2307 (68%)
Males	1084 (32%)
Child (5–14 years)	37 (1.1%)
Adolescent (15–19 years)	325 (9.5%)
Adult (20–74 years)	2152 (63.1%)
Elderly (> 75 years)	7 (0.2%)
Unknown	889 (26.1%)
Misuse demographics	
Total	221
Females	121 (54.8%)
Males	100 (45.2%)
Child (5–14 years)	4 (1.8%)
Adolescent (15–19 years)	25 (11.3%)
Adults (20–74 years)	127 (57.5%)
Elderly (> 75 years)	1 (0.5%)
Unknown	64 (29%)
Common reasons for misuse	
Insomnia	84
Recreational abuse	29
Anxiety	17
Agitation	12
Stress	11
Analgesia	6
Feeling 'unwell'	5
Common clinical features in sole quetiapine overdose	
Sole quetiapine overdoses	1411
Asymptomatic	248 (17.6%)
Drowsiness	1021 (72.4%)
Tachycardia	351 (24.9%)
Altered conscious state	218 (15.4%)
Hypotension (< 100 systolic or < 60 diastolic)	65 (4.6%)
Prolonged QT	57 (4%)

3. Results

3.1. Poisonings

There were 431,723 calls to VPIC over the 11-year period from 2006 to 2016. Of these calls, 4412 (1%) were quetiapine-related. A 6-fold increase was observed in the total number of quetiapine-related calls,

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