Uncovering the potential risk of serotonin toxicity in Australian veterans using pharmaceutical claims data

Clare Ringland,¹ Andrea Mant,² Patricia McGettigan,³
Philip Mitchell,⁴ Christopher Kelman,⁵ Nicholas Buckley⁶ &
Sallie-Anne Pearson⁷

¹Biostatistician, UNSW Cancer Research Centre, University of NSW, Australia, ²A/Prof, Population Health and Use of Medicines Unit, University of NSW, Australia, ³Senior Lecturer, Hull York Medical School, University of Hull, ⁴Professor, School of Psychiatry, University of NSW, Australia, ⁵A/Prof, Australian National University, National Centre for Epidemiology and Population Health and ANU Medical School, Australia, ⁶A/Prof, Prince of Wales Clinical School, University of NSW, Australia and ⁷Senior Research Fellow and Cancer Institute NSW Fellow, UNSW Cancer Research Centre, University of NSW, Australia

Correspondence

Associate Professor Andrea Mant,
Population Health and Use of Medicines
Unit, School of Public Health and
Community Medicine, University of New
South Wales, 95 Adelaide Parade,
Woollahra, NSW 2025, Australia
Tel.: +614 1300 6537
E-mail: a.mant@unsw.edu.au

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Serotonin toxicity is greatly increased by the co-prescribing of serotonergic agents.
- Serotonin toxicity varies greatly in severity from mild to potentially life-threatening, however even mild cases can impair quality of life, especially for older people, by causing agitation and sleep disturbance. Combinations including MAOI are most likely to cause severe toxicity.
- Few studies have used pharmaceutical claims data to quantify the use of serotonergic medicines in combination.

WHAT THIS STUDY ADDS

- In a cohort of elderly Australian veterans and dependants, we found widespread use of serotonergic medicines: 115 969 (42%) of the study population ($n = 273\,228$) were dispensed at least one of these medicines between July 2000 and June 2004.
- Approximately 8% (20 658 individuals) experienced at least one episode of potential concomitant use of serotonergic medicine combinations.
- Potentially life-threatening combinations involving MAOIs were of concern: 1811 (0.7%) individuals had at least one episode with such combinations.
- This study demonstrates the utility and benefits of pharmaceutical claims data to provide insights into real-world prescribing.

AIMS

We examined potential risk of serotonin toxicity in Australian veterans by quantifying the concomitant use of serotonergic medicine combinations from claims data collected by the Department of Veterans' Affairs (DVA).

METHODS

This was a retrospective cohort study of 273 228 Australian veterans, war widows, widowers and dependants aged ≥ 55 years and holding full treatment entitlement for the period July 2000 to June 2004 or until death. The main outcome measure was potential concomitant use, estimated as the number of cohort members with an overlap in days of supply for serotonergic medicine combinations over the 4 year period for all medicine combinations and potentially life threatening combinations.

RESULTS

From July 2000 to June 2004, 115 969 (42%) cohort members were dispensed at least one serotonergic medicine. 20 658 (8%) had at least one episode of potential concomitant use. We identified 1811 (0.7%) cohort members with at least one overlapping period of potentially life-threatening serotonergic medicine combinations, 937 of whom had the combinations dispensed within the recommended washout period. Three hundred and seventeen of these individuals were dispensed potentially life-threatening medicine combinations on the same day. The most common combinations were moclobemide with a selective serotonin reuptake inhibitor or tramadol.

CONCLUSIONS

The individuals potentially at risk of mild to moderate serotonin toxicity were considerable and potentially life threatening combinations were not infrequent. While we were unable to determine how many individuals experienced serotonin toxicity this study indicates, for the first time, the potential size of the problem in a subgroup of elderly Australians. Clinicians and patients need to be vigilant regarding inadvertent concomitant use, especially that of moclobemide with a selective serotonin reuptake inhibitor or tramadol.

Introduction

Certain commonly prescribed medicines, used alone or in combination, carry a risk of serotonin toxicity [1, 2]. These medicines are often co-prescribed to treat pain, depression and anxiety, conditions which frequently coexist, and where more than one doctor is likely to be involved in treatment [3, 4]. In Australia, the use of serotonergic medicines is considerable. For example, in 2005 more than 7 million prescriptions for selective serotonin reuptake inhibitors (SSRIs) and 2 million tramadol prescriptions were dispensed from community pharmacies [5].

Serotonin syndrome is a predictable consequence of serotonin toxicity arising from increased concentrations of serotonin at neurological receptor sites [1, 3]. Serotonin toxicity varies greatly in severity from mild to potentially life-threatening [6–8]. However, even mild cases can impair quality of life, especially for older people, by causing agitation and sleep disturbance. Unfortunately such unrecognized cases may be managed by prescribing patients yet another medicine, further increasing the potential for an adverse event.

In principle, moderate to severe serotonin toxicity is largely avoidable [1, 9]. It is most often found in patients taking two or more medicines at therapeutic doses that increase CNS serotonergic activity by different mechanisms [2, 8, 9]. Although many drugs are stated to be serotonergic, there is a great deal of variation even within drug classes and some combinations which carry warnings probably have a very low likelihood of causing problems. For example, within the tricyclic antidepressant class serotonin re-uptake inhibition varies considerably, imipramine and clomipramine being by far the most potent and the only agents clearly linked to life-threatening interactions [10]. The most serious cases of serotonin toxicity following drug interactions have involved non-selective MAOIs or selective MAO-A inhibitors combined with another potent serotonergic drug with a different mechanism [10].

Currently in Australia, the primary source of information about the occurrence of adverse events including serotonin toxicity is the Therapeutic Goods Administration (TGA) voluntary reporting system. Clearly this is not a comprehensive list of cases and the database probably reflects the more serious end of the spectrum. However, risk quantification requires measurement of incidence of exposure, as well as strength of association between exposure and outcome. Such information is not available from adverse event reporting databases. Greater access to existing health administrative data sources to explore potential risks associated with medicine use would complement the existing pharmacovigilance strategies [11]. A recent study of Australian veterans [12] illustrated the potential of dispensing data in quantifying this risk over a 6 month period. The study examined the prevalence of duplicate antidepressant prescribing and potentially avoidable drug interactions such as anticholinergic agents with tricyclic

antidepressants and tramadol with antidepressants. Our study advances this research by examining a broader range of serotonergic drugs and drug combinations, over a longer observation period, and using different algorithms to quantify the extent of the problem.

Prescription data for dispensed medicines are held for all Australians who claim services under the Repatriation Pharmaceutical Benefits Schedule (RPBS). These data have recently become available for research and provide a unique opportunity for evaluation of medicines use, safety and outcomes [12, 13]. In this paper we examined exposure to serotonergic medicines, either as sole agents or in combination, for a cohort of elderly Australians, using pharmaceutical claims data collected by the Department of Veterans' Affairs (DVA).

Methods

Ethics

This study was approved by the Human Research Ethics Committees of the Department of Veterans' Affairs and the University of New South Wales.

Data holdings

We extracted data from the DVA client and pharmaceutical claims databases. The client database contains information on entitled veterans including: unique card holder identifier, dates of birth and death, sex, entitlement level and the start and end date of each continuous period at a specific entitlement level for each client. The pharmaceutical claims files contain data on dispensed pharmaceutical items including: unique card holder identifier, entitlement at time each item was dispensed, sex, date of birth, pharmaceutical item details (item code, name and strength, Anatomical Therapeutic Chemical (ATC) code, date of supply, packs supplied and number of repeats).

Medicines of interest

Based on the literature [1, 2, 6–10, 14–17] we identified medicines associated with serotonin toxicity (Table S1). Drug classes included tricyclic antidepressants (non-selective monoamine reuptake inhibitors, hereafter referred to as TCAs), SSRIs, non-selective monoamine oxidase inhibitors (MAOIs), monoamine oxidase A inhibitors (moclobemide), other antidepressants (ADs), and 5-hydroxytryptamine 1 agonists (5-HT₁ agonists). Tramadol, fentanyl, pethidine, selegiline, lithium, linezolid, pentazocine, dexamethorphan and sibutramine were also examined.

Cohort selection

For the period July 2000 to June 2004 we identified a cohort of veterans, war widows, widowers and dependants holding full treatment entitlement (Gold Card Holders; GCH) aged ≥ 55 years and enrolled for the duration of the

study period or until death. These veterans are entitled to claim health care, related services and pharmaceutical items for all health needs, whether related to military service or not. Therefore, data are available for all prescribed medicines dispensed to GCHs under the Repatriation and Pharmaceutical Benefits Schemes (R/PBS).

Period prevalence of serotonergic medicine use
We identified the number of cohort members dispensed serotonergic medicines of interest at least once during the four-year period, overall and according to specific medicine categories (as defined in Table S1). We also calculated the number of serotonergic medicine categories cohort members were dispensed over the period.

Concomitant use
We developed a model to determine potential concomitant use of medicine combinations of interest, based on the following assumptions: medicine use commenced on the date of supply; and all medicines were consumed at a rate of one Defined Daily Dose (DDD) per day or one tablet per day (if tablet strength was greater than one DDD). The DDD is the international unit of drug utilization and is the assumed daily dose of a medicine when used for its main indication by adults [18]. DDDs for the medicines of interest are listed in Table S1. We examined two possible scenarios regarding the dispensing of more than one prescription for the same medicine dispensed on the same day or prior to the expected completion of a previous prescription. In the first scenario, we assumed medicines were taken in parallel (for example, the medicine was consumed at twice the rate, or double the dose). In the second, we applied the assumption that medicines were consumed in sequence (i.e. the medicine was consumed at a rate of one DDD or one tablet per day). Our calculations show concomitant use estimates were similar for the two scenarios. Therefore, we only report estimates derived from the parallel consumption model.

Based on this model we calculated the use of serotonergic medicine combinations in the following ways:

- 1 The number of cohort members dispensed at least two serotonergic medicine categories (Table S1) on the same day or with any potential overlap in days supply.
- 2 The number of cohort members with any overlap in days supply for specific medicine combinations and potentially life-threatening combinations (namely MAO-inhibitors and other drugs which strongly inhibit the reuptake of serotonin [10]).
- 3 The number of cohort members with potentially life-threatening combinations dispensed on the same day or within the recommended wash-out period for that combination [19], (i.e. for which no assumption for drug interaction potential needed to be made other than current use at the time of dispensing).

All analyses were performed using SAS software, version 9 (SAS Institute Inc, North Carolina, USA).

Results

Demographic details of our study cohort are summarized in Table 1. Not unexpectedly, there were more males than females and more than 80% were aged 75 years and over.

Period prevalence of serotonergic medicine use
Over the four-year study period 115 969 (42.4%) cohort members received at least one serotonergic medicine and the proportion dispensed SSRIs, TCAs, ‘other antidepressants’ and moclobemide was 18%, 15%, 6% and 2% respectively. Further, 18% received at least one tramadol prescription, with fewer than 0.5% of cohort members dispensed non-selective MAOIs, selegiline, pethidine, 5-HT₁ agonists, lithium and fentanyl. No cohort members were dispensed linezolid, pentazocine, dextromethorphan, sibutramine or fenfluramine (Table 2).

We identified 76 621 (28%) cohort members dispensed medicines from only one serotonergic medicine category over the four-year period and 10% (28 179), 3% (8343) and 1% (2826) from two, three and four or more categories. However, this dispensing did not necessarily reflect concomitant use as the medicines could have been dispensed at any time during the period.

Concomitant use
Eight percent (20 658) of cohort members were dispensed medicines from different medicine categories with some temporal overlap in use. Five percent (12 222), 2% (5919) and 1% (2517) of cohort members were dispensed two, three and four or more medicines types with at least one period of overlap in the four-year period. Furthermore, of those who had at least one episode of temporal overlap from different medicine categories, 50% had at least one

Table 1
Demographic characteristics of study cohort* (n = 273 228)

		n	%
Sex	Male	165 324	60.5
	Female	107 904	39.5
Age group (at July 2000)	55–59	6 046	2.2
	60–64	5 031	1.8
	65–69	9 570	3.5
	70–74	31 355	11.5
	75–79	113 480	41.5
	80–84	72 039	26.4
	85+	35 707	13.1

*study cohort = veterans, war widows, widowers and dependants holding full treatment entitlement (Gold Card Holders; GCH) aged ≥55 years and enrolled continuously for the duration of the study period or until death.

Table 2

Period prevalence of serotonergic medicine use in study cohort ($n = 273\,228$), July 2000 to June 2004

	<i>n</i>	%
Monoamine oxidase inhibitors (MAOIs), non-selective	141	0.1
Moclobemide	5 710	2.1
Selective serotonin reuptake inhibitors (SSRIs)	48 149	17.6
Other antidepressants (Other ADs)	16 389	6.0
Venlafaxine*	8 041	2.9
Others (mianserin, nefazodone, mirtazapine)	9 328	3.4
Pethidine	912	0.3
Tramadol	49 912	18.3
Fentanyl	4 210	1.5
Lithium	921	0.3
Selegiline	398	0.1
Tricyclic antidepressants (TCAs)	40 595	14.9
Imipramine, clomipramine*	5 852	2.1
Others (desipramine, amitriptyline, nortriptyline, doxepin, dothiepin)	35 873	13.1
Selective serotonin (5HT₁) agonists	643	0.2
Linezolid	0	0.0
Pentazocine	0	0.0
Dextromethorphan	0	0.0
Sibutramine	0	0.0
Fenfluramine	0	0.0
Any serotonergic medicine	115 969	42.4

*Subcategorization of these medicines has occurred as they are more clearly implicated in serotonin syndrome.

Table 3

Number of cohort members with temporal overlap and same day dispensing by number of serotonergic medicine categories* dispensed

Number of medicine categories	<i>n</i>	Same day dispensing		Any temporal overlap	
		<i>n</i>	%	<i>n</i>	%
0	157 259	–	–	–	–
1	76 621	–	–	–	–
2	28 179	5 497	19.5	12 222	43.4
3	8 343	3 118	37.4	5 919	70.9
4	2 179	1 123	51.5	1 895	87.0
5	534	335	62.7	511	95.7
6+	113	85	75.2	111	98.2
All	273 228	10 158	3.7	20 658	7.6

*Medicine categories are detailed in Table S1.

episode of same day dispensing. Twenty percent (5497) of cohort members supplied medicines from two categories and 38% of those supplied medicines from three categories had at least one episode of same day dispensing (Table 3).

Medicines most commonly used concomitantly included SSRIs ($n = 14\,326$), tramadol (11 777) and TCAs other than imipramine and clomipramine (9173). We identified 1811 cohort members with at least one period of

overlap of potentially life threatening serotonergic medicine combinations. Specifically, we identified those with at least one episode of overlap between moclobemide and SSRIs ($n = 1069$), tramadol ($n = 561$), venlafaxine ($n = 298$), imipramine/clomipramine ($n = 71$) and pethidine ($n = 4$). In addition, we found cohort members with at least one period of overlap between MAOIs and SSRIs ($n = 18$), tramadol ($n = 17$), venlafaxine ($n = 11$) and imipramine or clomipramine ($n = 1$) (Table 4).

We examined the temporal relationship between the dispensing of potentially life-threatening medicine combinations to find 317, of the 937 cohort members dispensed potentially very serious interactions up to ten days apart, were dispensed these medicines on the same day (Table 5). An additional 20% ($n = 205$) were dispensed medicines before the recommended washout period had elapsed from the previous dispensing.

Discussion

This study illustrates how pharmaceutical claims data can help assess the risk of serotonin toxicity in a defined population. While we were unable to determine how many individuals actually experienced serotonin toxicity the study indicates, for the first time, the potential size of the problem in the Australian veteran population. Quantification of the number of individuals who may be at risk will help guide regulatory and educational bodies in alerting prescribers, patients, carers, and pharmacists to be vigilant.

During the four-year study, over 40% of the cohort received at least one serotonergic medicine. Concomitant use of serotonergic medicines (as indicated by one or more overlapping periods of prescription supply) was frequent. The numbers of individuals at risk of mild to moderate serotonin toxicity were therefore considerable. The most common combinations were: tramadol and a SSRI; tramadol and a TCA; a TCA and a SSRI; a SSRI and a medicine from the other antidepressants class; and a combination of two SSRIs. Potentially lethal combinations were also observed, including moclobemide/MAOI with a SSRI or venlafaxine or tramadol. Many of these were co-dispensed without any possible time for the recommended wash-out period to have occurred (Table 5). That 317 patients received such combinations on the same day is of concern, suggesting that the interaction risk was overlooked by both prescribers and pharmacists.

Overall, 20 658 people had overlapping combinations of serotonergic drugs. It is unlikely all were due to oversights. Many combinations are relatively safe and experienced prescribers may have decided the benefits outweighed the risks of co-prescription. For example, two prescriptions for medicines from different antidepressant drug classes [12, 20] might commonly occur transiently while switching medications [2, 7, 9, 21].

Table 4
Number of cohort members potentially using medicine combinations concomitantly*

	MAOIs	Modobemide	SSRIs	Venlafaxine	Imipramine, clomipramine	Other TCAs	Other ADs	Pethidine	Tramadol	Fentanyl	Lithium	Selegiline	5HT1 agonists
MAOIs	4†												
Moclobemide	8	–											
SSRIs	18	1069	2 295†										
Venlafaxine	11	298	1 748	–									
Imipramine, Clomipramine	1	71	543	77	3†								
Other TCAs	8	450	3 786	599	214	548†							
Other ADs	10	313	1 983	657	91	696	137†						
Pethidine	0	4	23	9	1	25	7	–					
Tramadol	17	561	5 752	901	368	4021	1080	78	–				
Fentanyl	0	76	721	114	28	407	162	44	495	–			
Lithium	10	45	295	160	34	171	128	0	75	6	–		
Selegiline	0	10	74	13	4	46	12	0	37	3	1	–	
5HT1 agonists	0	15	104	23	9	96	20	3	56	2	4	0	11†
All [^]	62	2270	14 326	3547	1248	9173	4239	157	11 777	1659	667	156	252

*Cohort members can appear in more than one cell. †An overlap within a medicine grouping means there is an overlap in dispensing of two different medicines within that category. Shading identifies potentially life threatening combinations. [^]Corresponds to the number of cohort members in the column and row for a medicine category.

Some combinations are more likely than others to occur inadvertently. One in five individuals in this elderly cohort was dispensed at least one SSRI or tramadol prescription at least once over the four-year period. Combinations involving overlap of antidepressants with tramadol were consequently very common and were unlikely to represent planned switching of prescribed medication. In the four years following its marketing in Australia in late 1998, tramadol gave rise to 20 reports of serotonin syndrome, in 16 of which the patient was taking potentially interacting medicines such as antidepressants, sibutramine and St John's Wort [21].

Tramadol is readily available and recommended in pain management guidelines [22]. Patients and doctors need to be aware that tramadol can contribute to the risk of serotonin toxicity and be watchful for symptoms and signs [21–24]. Based on our findings, particular attention should be paid to the quite high possibility that older patients may be taking tramadol (or fentanyl) in combination with a serotonergic antidepressant. The risk-benefit of such combinations is very likely to be much worse in terms of both safety and efficacy than when these drugs are prescribed on their own.

Medicines such as linezolid [9, 16, 17], lithium, dextromethorphan, selegiline, pethidine and 5-HT₁ agonists for use in migraine have been implicated as placing patients at high risk of serotonin toxicity [1, 7, 9], but were dispensed rarely or not at all in this cohort.

A limitation of our study is that we cannot know if cohort members actually took the medicines dispensed, and if so, for how long the medicine was taken and the actual daily doses. Concomitant medicine use can only be inferred by the overlap in supply of medicines as estimated from the recorded dispensing intervals. Such methodological limitations are common to pharmacoepidemiological studies using dispensing and other healthcare databases to determine medicine exposure. However, even using the most conservative assumptions about duration of use (current at time of dispensing), there were more than 20 000 people with overlap in duration of two serotonergic drugs, and 1800 people who had overlaps of the most potentially serious combinations, with more than 300 people receiving such combinations on the same day.

Given the limited data on the incidence of serotonin toxicity [1, 7] we were not able to compare the observed frequency of potential concomitant use with the observed incidence of serotonin toxicity. With respect to the generalizability of our findings, our study population is older than the general Australian population as we selected those 55 years and over. However, in 2003 DVA beneficiaries represented approximately 10% of the total number of Australians aged 65 years and above, and 25% of Australians aged 80 years and over [25]. As such these findings may well reflect an important clinical issue for all elderly Australians. Clearly, as polypharmacy increases with age this is the population at greatest risk.

Table 5

Number of cohort members dispensed potentially life-threatening medicine combinations within recommended washout periods

Medicine 1	Medicine 2	Medicine 1/medicine 2	Medicine 1 followed by medicine 2		Medicine 2 followed by medicine 1	
		0 days	1–3 days	4–10 days	1–3 days	4–10 days
Moclobemide	Tramadol	211	50	101	45	102
	Pethidine	4	3	3	1	3
	Imipramine Clomipramine	0	3	15	0	0
	SSRI*	72	47	114	32	137
	Fluoxetine	11	5	13	3	14
	Venlafaxine	21	14	48	13	36
MAOI	Tramadol	4	1	3	1	2
	Pethidine	0	0	0	0	0
	Imipramine Clomipramine	0	0	0	0	0
	SSRI*	0	0	1	0	1
	Fluoxetine	0	0	1	0	0
	Venlafaxine	2	0	1	0	0
Total		317	115	275	93	267

*Excluding fluoxetine. Shaded cells correspond to those where supply was within the recommended washout period. Cohort members can appear in the table more than once as they may have received more than one medicine combination. Therefore, the total is not the sum of the cells above. However, individuals can appear in only one cell within a medicine combination – the one that equates to the episode with the minimum duration between supply days for that individual. Nine hundred and thirty-seven cohort members were dispensed at least one potentially life threatening medicine combination within 10 days.

Our study highlights the utility of person level data in informing pharmacovigilance. The Department of Veterans' Affairs database is unique in Australia in that it can, subject to ethical approval, provide comprehensive person level data with the appropriate safeguards to protect the identity of patients and their treating doctors. Improved pharmacovigilance in Australia demands a national effort to overcome the barriers to undertaking these and other pharmacoepidemiological studies using the Medicare Australia databases [11, 26, 27]. Such studies provide an estimate of the potential size of a clinically relevant problem and therefore inform educational strategies to reduce numbers at risk. Given limited funding for dedicated pharmacovigilance studies, it is imperative that existing data repositories are used effectively to help ensure safe use of medicines.

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Supporting information

The following supporting information is available for this article online:

Table S1

Medicines associated with serotonin toxicity

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