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Spontaneous adverse event reports associated with zolpidem in Australia 2001–2008

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SUMMARY A prominent media publicity cluster during 2007–2008 in Australia linked the common hypnotic zolpidem to adverse drug reaction reports of parasomnias, amnesia, hallucinations and suicidality. The collection of adverse drug reaction data through spontaneous reporting systems is a mainstay of drug safety monitoring, but a stimulated reporting event such as this often renders such data uninterpretable. As such, we aimed to investigate whether these associations were present before the media cluster and then to quantify the effect of stimulated reporting on those four specific outcomes. Using disproportionality analyses we compared zolpidem to all other drugs in the database, and then separately to each of all hypnotics, then all benzodiazepines, and then temazepam alone, and did so in every year from 2001 to 2008. Year-by-year analyses of Reporting odds ratios for zolpidem exposure and adverse events of interest, adjusted for a number of covariates, revealed an association between zolpidem exposure and parasomnias, amnesia and hallucination both before and after the cluster of media publicity beginning in early 2007. The odds ratios increased significantly after the media publicity for only parasomnias and amnesia. Suicidality was increased in some analyses, but limited data make this outcome difficult to interpret. We conclude that zolpidem adverse drug reaction reports have higher odds for parasomnia, amnesia, hallucination and perhaps suicidality compared to either all other drugs or hypnotics, even before the media publicity cluster. However, the extant literature and the limitations of these spontaneously reported adverse drug reaction data do not allow us to conclude that these events are related causally to zolpidem.

KEYWORDS insomnia, sleep, sleepdriving, sleepwalking

INTRODUCTION

Insomnia is the most common and costly sleep disorder, with both substantial direct and indirect costs (Institute of Medicine (USA), 2006; Ozminkowski *et al*., 2007). Prevalence estimates depend on the definition of impairment and the duration of the affliction (Simon and Vonkorff, 1997), but the disorder is nearly universally experienced over some part of the lifespan. It is often untreated or resolves spontaneously, but is also managed via pharmacological and non-pharmacological methods, sometimes in combination (Morin *et al*., 2009). While the American Academy of Sleep Medicine (AASM) guidelines for the management of insomnia recommend non-pharmacological cognitive behavioural approaches as first-line treatment (Schutte-Rodin *et al*., 2008), there is a shortfall in the clinical workforce required to provide this to the population (Espie, 2009).

Non-benzodiazepine gamma-aminobutyric acid (GABA) receptor agonists with names such as zolpidem, zopiclone and zaleplon (hence named colloquially the z-drugs) and the

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older benzodiazepine class are the major prescription hypnotics. In Australia, zolpidem was first marketed at the end of 2000 under the brand name Stilnox® and earlier in the United States as Ambien®. Recent Australian estimates rank zolpidem as the third most often-used hypnotic after the government-subsidized and substantially cheaper benzodiazepines, tempazepam and nitrazepam (Hollingworth and Siskind, 2010). The situation in the United States with the Medicaid fee-for-service population is somewhat different, in that zolpidem and trazodone are prescribed more often than the benzodiazepines (Roy and Smith, 2010).

Following the Australian market release, health professionals were alerted by the regulatory authority, as with other new drugs, to report suspected adverse drug reactions (ADRs) associated with zolpidem via the Australian Adverse Drug Reaction System (ADRS). This, like other spontaneous reporting systems (SRS), is considered an effective mechanism for detecting ADRs and forms an essential part of post-marketing drug surveillance (Salmerón-García *et al*., 2010). Conventionally, health care professionals play a major role in providing these spontaneous reports when they encounter ADRs. In addition, Australia is one of the few countries that now accept direct ADR reports from consumers (http://www.tga.gov.au/adr/bluecard.htm). A key vulnerability of any SRS is sensitivity to media publicity linking a particular drug to particular events, stimulating a rise in specific ADR reports. Called 'stimulated reporting', it typically renders ADR data uninterpretable because patients and health professionals have been influenced by media publicity to report specific side effects with specific drugs.

As early as 2001, the ADRS had received 72 reports describing 170 reactions associated with the use of zolpidem (Olson, 2008). Fifty-six of these reports described one or more neurological or psychiatric effects. The most common ADRs were confusion, depression, visual hallucinations and amnesia (Olson, 2008). In the United States, media interest in the side effects of zolpidem began in 2006 in conjunction with a class action suit and the high-profile involvement of Congressman Patrick Kennedy in a car crash, in May 2006, that he claimed was caused partially by zolpidem use. Significant media interest in Australia began later (February 2007), again in conjunction with a class action suit that proposed zolpidem as the precipitating factor in a number of adverse behaviours and events. Media reports in Australia focused on unusual adverse reactions including parasomnias, hallucinations, amnesia and suicide. This media publicity was associated with a very large and sharp rise in the raw number of ADR reports. Similar ADRs have been documented in the peer-reviewed literature (Hoque and Chesson, 2009; Hwang *et al*., 2010; Mendelson, 1994; Morgenthaler and Silber, 2002; Schenck *et al*., 2005; Wing *et al*., 2010).

Because spontaneous adverse reaction data can be biased once stimulated reporting has begun, we aimed to quantify the association between exposure to zolpidem and four categories of adverse events (parasomnias, amnesia, hallucination and suicidality) year-by-year both before and after the period of media publicity in Australia.

METHODS

Study design and data source

We used retrospective case/non-case time–series analysis of spontaneous reporting system data. We analysed a subset of data from the Australian ADRS database reported to the Therapeutic Goods Administration (TGA) from 2001 (the initial marketing year for zolpidem) to 2008. The final data set comprised 67 328 records after excluding records in which details were absent for patient age, gender, drug exposure or adverse reaction. Each report includes details of patient demographics (age, gender), drug exposure (generic and brand names, dose and dose form), adverse reaction terms and dates of exposure and of adverse reaction. Medical officers within the TGA reviewed and, using the *Medical Dictionary for Regulatory Activities* (MedDRA), coded ADR descriptions into 'preferred terms' (PT) and 'lower-level terms' (LLT), which reflect increasing levels of descriptive specificity.

Case/non-case method

Case/non-case methods are used to generate signals for drug–event associations (DEAs) using disproportionality analyses of spontaneous reporting system data (Van Puijenbroek *et al*., 2002). Cases are defined variously as reports that include any PTs or LLTs (using MedDRA version 12.1) within each of the following categories of ADR: parasomnias, amnesia, hallucination and suicidality (see Table 1 for a full list). Because these outcomes could be reported with one another, no defined case should be assumed to be independent of cases associated with any of the other three outcomes (which are investigated in separate analyses). However, multiple reports of adverse effects that fall inside the same category (e.g. a combination of sleep eating and sleepwalking under the parasomnias) are only counted as a single case. A reporting odds ratio (ROR) can be calculated with its 95% confidence interval (95% CI). The statistical null hypothesis is that there is no difference in the incidence of reported exposure to a drug of interest between cases and non-cases. If the lower limit for the 95% CI is greater than 1, then patients within the database with ADRs within a category of interest were more likely to have been exposed to the drug of interest compared to the patients within the database without ADRs in that category. This method was applied to investigate the association after adjusting for a number of covariates in a sequential time–series.

Exposure definition

Exposure was defined as the presence of zolpidem tartrate in a report, regardless of whether or not it was suspected of causing the reaction. A number of covariates, including potential confounders were also included as exposure categories. These include demographic variables [age: stratified as paediatric (< 18 years), working age (18–65 years), geriatric (> 65 years) and gender] and drugs within the following classes:

Table 1 Adverse Drug Reaction categories of interest and terms defining cases

Parasomnias	**Amnesia**	**Hallucination**	**Suicidality**
Parasomnias	Amnesia	Hallucination	Suicide
Abnormal dreams	Anterograde amnesia	Hallucination, auditory	Parasuicide
Abnormal sleep-related event	Dissociative amnesia	Hallucination, gustatory	Repeated parasuicide
Confusional arousal	Paramnesia	Hallucination, olfactory	Attempted suicide
Loss of dreaming	Retrograde amnesia	Hallucination, synaesthetic	Completed suicide
Dream delirium	Transient global amnesia	Hallucination, tactile	Suicide accomplished
Bad dreams	Transient amnesia	Hallucination, visual	Suicide attempt
Bizarre dreams	Aggravated Amnesia	Hallucinations, mixed	Suicide attempt by drug overdose
Frightening dreams	Amnesia NEC	Hypnagogic hallucination	Suicide attempt other than overdose
Morbid dreams	Loss of memory	Hypnopompic hallucination	Suicide gesture
Dream anxiety disorder	Losing memory in mornings	Somatic hallucination	Unsuccessful suicide
Bizarre dreams- unusual and frightening	Long-term memory loss	Kinesthetic hallucination	Accomplished suicide
Terrifying dreams	Partial loss of memory	Sensory hallucination	
Nightmare	Transient memory loss	Hallucination-like abnormal behaviour	
Nightmare disorder	Loss of memory ability	Hallucination-aggravated	
Brief nightmare	Short-term memory loss	Haptoc hallucination	
Rapid eye movements sleep abnormal	Total loss of memory	Pseudo-hallucination	
Sleep inertia	Confused memory and fantasy	Stump hallucination	
Sleep sex	Hysterical amnesia	Audio and visual hallucination	
Sleep talking	Psychogenic amnesia		
Sleep terror			
Sleep-related eating disorder			
Sleep driving			
Night terrors			
Paroniria			
Somnambulism			

The presence of any preferred terms (PTs) or lower-level terms (LLTs) within a report defined a case for each ADR category.
NEC, not elsewhere classified.

benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants, other antidepressants, antipsychotics and opioids. Age categories were selected as zolpidem is not listed for use in people under 18 years of age in Australia. People over 65 often have pensioner status and drug use may be affected by cost, as zolpidem has not been subsidized. There were insufficient data to analyse associations with other z-class hypnosedatives.

Statistical analysis

Reporting odds ratios and 95% CIs were determined for each exposure category using univariate logistic regression analysis. Covariates for which RORs were significant were included in multivariate logistic regression analyses as a single step or using forward selection based on the likelihood ratio statistic as appropriate. Statistical analyses were conducted using SPSS® for Windows XP® (version 17.0; SPSS Inc., Chicago, IL, USA).

Year-by-year analyses were conducted for each category of ADR by stratifying the records by reporting year from 2001 to 2008 and determining annual RORs and 95% CIs for zolpidem adjusted for demographic and drug-class covariates. We also evaluated the drug–event associations for the whole 8-year period and tested whether there was an interaction between the two reporting periods of interest (when reporting period was treated as a dichotomous variable; 2001–2006 and 2007–2008) for each category of ADR using multivariate logistic regression analysis. Because these interactions were found to be significant, we then calculated (for zolpidem exposure) the RORs and 95% CIs (adjusted for covariates) for each ADR category separately for the two periods.

In addition, to account for the effects of some critical confounders, we conducted a number of sensitivity analyses. First, in an attempt to avoid potential confounding effects of polypharmacy, we repeated our analyses using a subset of data by including solely reports where a single drug was identified in each report – this analysis also restricts all drugs of interest to those that are directly suspected of causing the adverse event rather than being a bystander drug. Secondly, we conducted a series of analyses that aimed to control for confounding by indication (given the comorbid associations of insomnia); as control exposure categories, we used only hypnotic drugs, then only benzodiazepines, and then only the leading hypnotic in Australia, tempazepam (Hollingworth and Siskind, 2010). Each of these analyses generated annual RORs for zolpidem adjusted for other potential confounders (e.g. age category and other psychotropic drug exposure) where possible.

RESULTS

Univariate analyses

The characteristics of cases and non-cases for each ADR category are presented in Table 2. Parasomnias were reported more often by females and suicidality was associated more often with males. Adult age was associated with each of the ADR categories of interest when compared with reports from paediatric patients. Odds for reporting suicidality was greater among individuals of working age than among the other age categories. There was a trend towards reporting hallucination with advancing age. Exposure to benzodiazepines, opioids, anticholinergics and each antidepressant class (with the exception of moclobemide) was associated with reporting parasomnias. Odds for reporting antipsychotic exposure were lower among individuals reporting parasomnias than among others. Similar patterns of association with drug-class exposures were observed among cases of amnesia and hallucination. We do not report the crude ORs (and 95% CIs) for zolpidem for the entire 2001–2008 period because of the effect modification between pre- and post-publicity for three of the four outcomes (i.e. stimulated reporting). Readers should also be aware that the four outcome categories are not independent, and any single report could contain any or all of the three other outcomes.

Multivariate analyses

Annual ORs (adjusted for age (paediatric working age and retired), gender, selective serotonin reuptake inhibitors, anticholinergics, antipsychotics, other antidepressants, moclobemide and opioids) for zolpidem for each of the ADR categories of interest over the period 2001–2008 are presented in Fig. 1. While signals for DEAs were observed from 2001, the ORs for parasomnias and amnesia increased significantly in 2007 and remained elevated in 2008. Signals for association of zolpidem exposure and hallucination or suicidality were not altered significantly throughout the period of investigation.

The ORs for zolpidem exposure for each ADR category of interest over the 8-year period, adjusted initially for demographic covariates, then additionally for drug-exposure covariates, are presented in Table 3. Table 3 also displays the fully adjusted ORs stratified by pre- and post-publicity periods, and the effect of this can also be seen visually in Figs 1 and 2.

When analyses are stratified by the reporting period (pre and post the point in 2007 of media publicity of ADRs in patients who were using zolpidem), the DEA signals for zolpidem for parasomnias and amnesia are significantly greater during the post-publicity period (Table 3). The trend for reporting suicidality is also increased with zolpidem during the post-publicity period; however, the increase from the pre-publicity period is not statistically significant.

Sensitivity analyses

Multivariate sensitivity analyses comparing zolpidem to all other hypnotics, to the benzodiazepines only and to temazepam only tended to confirm our primary analyses. The exceptions were where ORs were incalculable due to a lack of reports, particularly for suicidality, and in the temazepam-only analyses. Our sensitivity analyses also had less statistical power than the primary analyses, so while increased risk might be evident in the OR these were sometimes not statistically significant until the OR reached above 5. The comparison of zolpidem to all other benzodiazepines is illustrated graphically in Fig. 2. Our analyses of zolpidem-only versus one other drug only showed marked risk with ORs > 10 for all outcomes in all years except for suicidality between 2001 to 2005, where ORs were again non-calculable because of a lack of reports.

DISCUSSION

This study aimed to assess retrospectively the association between zolpidem exposure and the reporting of parasomnias, amnesia, hallucination and suicidality as adverse outcomes in the periods before and after the cluster of media publicity in Australia in 2007. Routinely collected adverse-event reporting data from the Australian Therapeutic Goods Administration [TGA: the US Food and Drug Administration (FDA) equivalent] indicate that there was a significant association between zolpidem exposure and each of the four outcomes before the media publicity of unusual behaviours in patients using zolpidem. In February, 2007 the TGA advised health professionals of reports received of distressing neurological and psychiatric reactions, including strange automatic behaviour while asleep, and suggested that patients using zolpidem should be warned of the possibility of such effects (ADRAC, 2007). This was soon followed by a cluster of media publicity highlighting bizarre behaviour. Both the numbers of ADR reports to TGA involving zolpidem and the odds for reporting parasomnias and amnesic events with zolpidem increased significantly following this cluster of publicity. These observational data do not, of course, allow us to conclude that zolpidem causes these outcomes, but treating clinicians should be aware that their patients being treated pharmacologically for insomnia may be at increased risk. Our data indicate that elevated risk for reports of parasomnias, amnesia, hallucinations and possibly suicidality existed before the stimulated reporting event.

Some arguments for the biological plausibility of the parasomnias link have been reviewed recently elsewhere (Dolder and Nelson, 2008; Hoque and Chesson, 2009), but an additional line of evidence might be through the anecdotally reported interaction between alcohol and zolpidem. Both zolpidem and alcohol have been reported to increase power density in low delta frequency (1.25–2.5 Hz) waves (Landolt *et al.*, 1996, 2000; Monti *et al.*, 2000). Alone or in conjunction (with the unstudied possibility of interaction), this enhancement of very slow wave activity might provide a background

Table 2 Demographic and drug-class exposure characteristics of cases and non-cases for each adverse drug reaction (ADR) category

	ADR categories															
	Parasomnia				*Amnesia*				*Hallucination*				*Suicidality*			
Covariates	*Cases* (n = 961)	*Non-cases* (n = 66367)	*ROR*† *(95% CI)*	P-*value*	*Cases* (n = 805)	*Non-cases* (n = 66523)	*ROR*† *(95% CI)*	P-*value*	*Cases* (n = 1130)	*Non-cases* (n = 66198)	*ROR*† *(95% CI)*	P-*value*	*Cases* (n = 442)	*Non-cases* (n = 66886)	*ROR*† *(95% CI)*	P-*value*
Gender																
Female	625	38 771	1.32 (1.16–1.51)	<0.001	476	38 920	1.03 (0.89–1.18)	0.721	660	38 736	1.00 (0.88–1.12)	0.942	184	39 212	0.50 (0.42–0.61)	<0.001
Age																
Paediatric (<18 years)*	33	9178	1		17	9194	1		110	9101	1		50	9161	1	
Working age (18–65)	736	38 026	5.38 (3.80–7.64)	<0.001	650	38 112	9.22 (5.70–14.94)	<0.001	643	38 119	1.40 (1.14–1.71)	0.001	373	38 389	1.78 (1.32–2.39)	<0.001
Geriatric (>65)	192	19 163	2.79 (1.92–4.04)	<0.001	138	19 217	3.88 (2.35–6.43)	<0.001	377	18 978	1.64 (1.33–2.04)	<0.001	19	19 336	0.18 (0.11–0.31)	<0.001
Benzodiazepines	80	3160	1.82 (1.44–2.29)	<0.001	61	3179	1.63 (1.26–2.13)	<0.001	106	3134	2.08 (1.70–2.55)	<0.001	64	3176	3.40 (2.60–4.44)	<0.001
SSRI	150	3826	3.02 (2.53–3.61)	<0.001	123	3853	2.93 (2.41–3.56)	<0.001	136	3840	2.22 (1.85–2.67)	<0.001	127	3849	6.60 (5.36–8.13)	<0.001
TCA	48	1119	3.07 (2.28–4.12)	<0.001	41	1126	3.12 (2.26–4.29)	<0.001	51	1116	2.76 (2.07–3.67)	<0.001	7	1160	0.91 (0.43–1.93)	0.912
Anticholinergics	6	292	2.05 (1.09–3.87)	0.026	6	292	1.70 (0.80–3.61)	0.165	17	281	3.81 (2.44–5.95)	<0.001	1	297	0.87 (0.22–3.52)	0.850
Antipsychotics	47	5367	0.58 (0.44–0.79)	<0.001	38	5376	0.56 (0.41–0.78)	0.001	87	5327	0.95 (0.77–1.19)	0.670	141	5273	5.47 (4.47–6.70)	<0.001
Other antidepressants	148	3898	2.92 (2.44–3.49)	<0.001	107	3939	2.44 (1.98–2.99)	<0.001	139	3907	2.24 (1.87–2.68)	<0.001	97	3949	4.48 (3.57–5.63)	<0.001
MAO inhibitors; non-selective	3	33	6.30 (1.93–20.56)	0.002	2	34	4.87 (1.17–20.31)	0.030	1	35	1.67 (0.23–12.23)	0.611	1	35	4.33 (0.59–31.68)	0.149
Moclobemide	5	189	1.83 (0.75–4.46)	0.183	6	188	2.65 (1.17–5.99)	0.019	7	187	2.20 (1.03–4.69)	0.041	3	191	2.39 (0.76–7.49)	0.136
Opioids	123	4796	1.88 (1.56–2.28)	<0.001	87	4832	1.55 (1.24–1.94)	<0.001	247	4672	3.68 (3.19–4.26)	<0.001	31	4888	0.96 (0.66–1.38)	0.957

MAO, monoamine oxidase; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.

*Reference group.

†Crude reporting odd ratios (RORs) [95% confidence intervals (CIs)] for covariates from univariate logistic regression analyses. Cases within each ADR category are not necessarily independent of other categories, as a single report may include combinations of terms from any of the four outcome categories of interest.

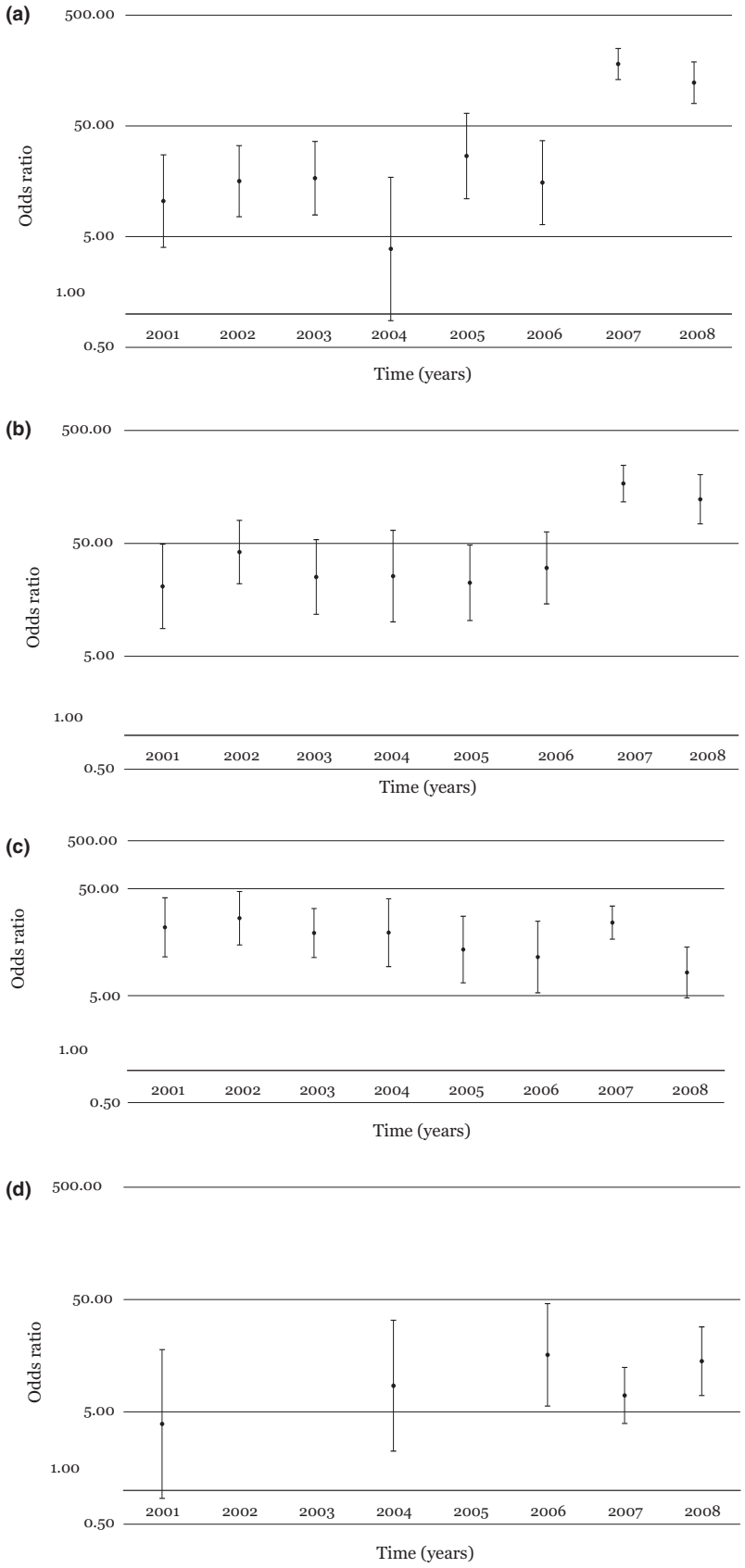

Figure 1. Year-by-year adjusted reporting odds ratios (and 95% confidence intervals) for (a) parasomnias, (b) amnesia, (c) hallucination and (d) suicidality for zolpidem exposure when compared to all other medications.

Table 3 Odds ratios for exposure to zolpidem tartrate adjusted for demographics, drug-exposure covariates and reporting period for each adverse drug reaction (ADR) category

	Odds ratios for exposure to zolpidem							
	Parasomnia		*Amnesia*		*Hallucination*		*Suicidality*	
Covariates in logistic regression models	*OR (95% CI)*	P-*value*	*OR (95% CI)*	P-*value*	*OR (95% CI)*	P-*value*	*OR (95% CI)*	P-*value*
Patient demographics	93.39 (80.38–108.50)	< 0.001	85.87 (73.30–100.59)	< 0.001	14.75 (12.48–17.42)	< 0.001	6.36 (4.72–8.56)	< 0.001
Patient demo graphics and drug exposures	87.37 (74.93–101.87)	< 0.001	79.40 (67.56–93.30)	< 0.001	12.87 (10.83–15.29)	< 0.001	5.07 (3.70–6.94)	< 0.001
Patient demographics and drug exposures stratified by reporting period								
Year 2001–2006	14.03 (9.86–19.97)	< 0.001	26.27 (19.27–35.23)	< 0.001	17.99 (13.91–23.27)	< 0.001	3.20 (1.68–6.10)	< 0.001
Year 2007–2008	154.88 (121.78–196.97)	< 0.001	154.87 (116.93–20 513)	< 0.001	15.52 (11.82–20.37)	< 0.001	8.30 (5.37–12.84)	< 0.001

Odds ratios (ORs) for zolpidem tartrate exposure were adjusted for demographics age (paediatric working age and retired) and gender as well as drug exposure covariates which included: selective serotonin reuptake inhibitors, anticholinergics, antipsychotics, other antidepressants, moclobemide and opioids.
CI, confidence interval.

onto which parasomnias may emerge in susceptible individuals even where these individuals have never been observed to have parasomnias previously. The potential role of alcohol as a confounder in our analysis cannot be ruled out because alcohol information is badly recorded in ADR data. However, readers should note that the idea that alcohol itself causes sleepwalking is regarded as unsupported scientifically (Pressman *et al*., 2008). We do not know whether this slow wave effect might plausibly induce either the amnesia or hallucinatory side effects.

In the United States, in line with a low rate of ADR reports in clinical trials and post-marketing studies, in a 2005 National Institutes of Health Chronic Insomnia Treatment in Adults Consensus Statement the drug was considered of limited risk (NIH, 2005). For example, two post-marketing studies of zolpidem have reported parasomnias (sleepwalking) in seven of 1972 patients (0.3%; Ganzoni *et al*., 1995) and one of 96 patients (1%; Sauvanet *et al*., 1988). Systematic reviews of controlled trials of z-drugs have not indicated the adverse effects reported by patients in Australia, and certainly the data do not indicate that risks for such effects are higher for z-drugs compared to traditional benzodiazepines (Olson, 2008).

Despite potential utility, voluntary ADR reporting (by both health care professionals and patients) is subject to bias, as reporting consumers or professionals may demonstrate a 'bandwagon' effect (Edwards and Aronson, 2000). The media also play a role in stimulating adverse drug reaction reports. However, in this case these signals existed before media involvement, which seems to have increased not only the number of reports received but also their likelihood of involving a parasomnia or amnesia ADR. While data on the date of onset of ADRs within the database are incomplete, analyses of the association between zolpidem exposure and the outcomes of interest using onset dates revealed a similar pattern of time dependence (with RORs rising in 2007 and 2008). Furthermore, the distribution of time-lag between onset and reporting of ADRs is extended significantly (Mann–Whitney *U*-test) for reports involving zolpidem (compared with all other drugs) in 2007 and 2008, this effect not being evident in any of the preceding years. This suggests that the media reports not only raised awareness for new users (and prescribers), but probably also prompted existing or past users to report. Post-marketing surveillance outside Australia or the United States has not generally revealed a high prevalence of behavioural adverse events with z-drugs, but ADR systems might be particularly insensitive to parasomnias (Hajak and Bandelow, 1998; Mancini *et al*., 2006; Markowitz and Brewerton, 1996; Tsai *et al*., 2009).

However, the data we obtained from the Australian ADRS indicated that these effects are reported when the drug is used in real-life populations, which may differ substantially from the carefully selected and monitored clinical trials patients who are also exposed to much shorter treatment periods. Causality cannot be inferred from routinely collected data such as these because there remain numerous uncontrolled potential

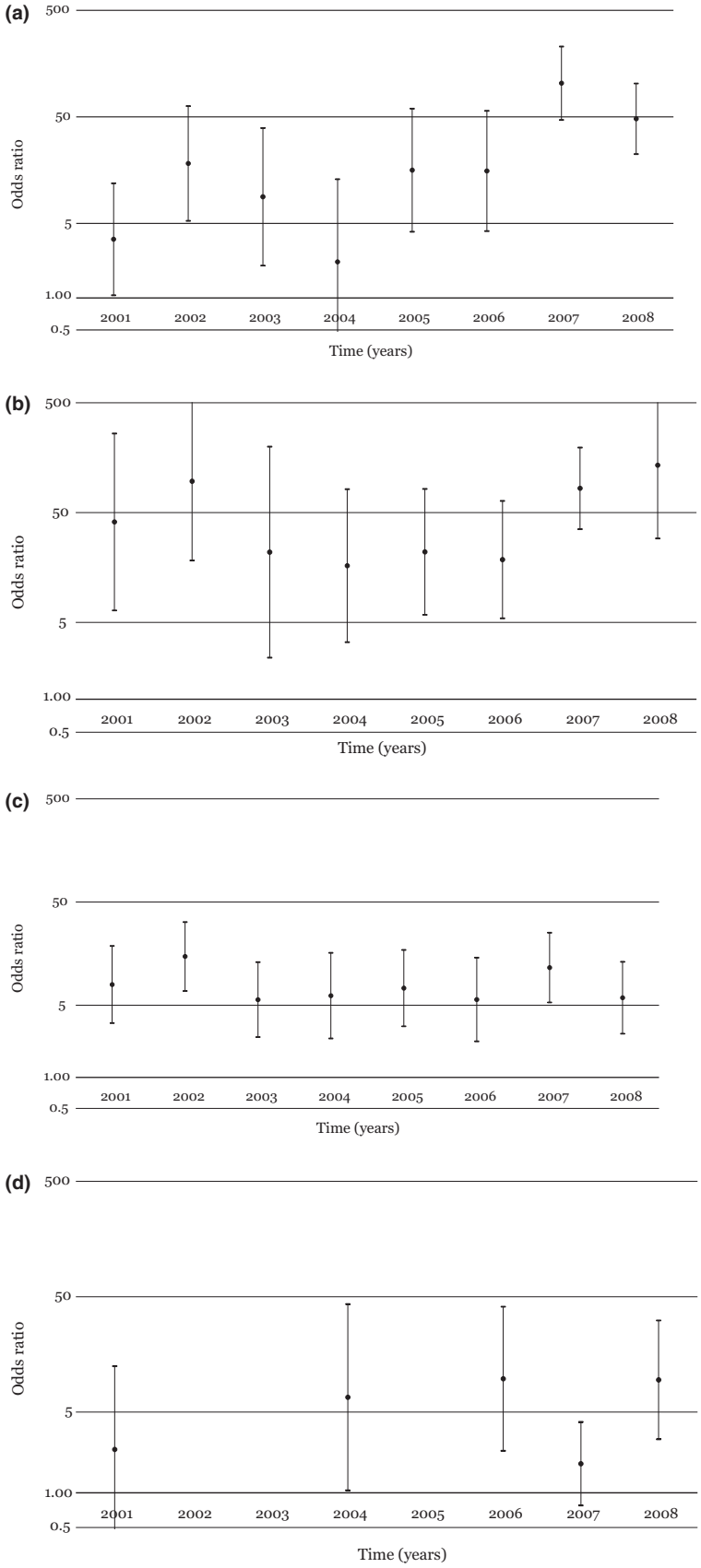

Figure 2. Year-by-year adjusted reporting odds ratios (and 95% confidence intervals) for (a) parasomnias, (b) amnesia, (c) hallucination and (d) suicidality for zolpidem exposure when compared to all benzodiazepines.

confounders, and the unresolved issue as to why this has only been observed systematically so far in Australia, and perhaps the United States (Li *et al*., 2010). However our pre-media data may still be valuable. There is a clear elevation in signals obtained from the ADRS. Importantly, valid signals for well-established risk factors were also detected in the ADR data, such as male gender for suicidality and female gender for parasomnia reports (Matwiyoff and Lee-Chiong, 2010). Exposure to benzodiazepines, opioids, anticholinergics and each antidepressant class (with the exception of moclobemide) were also associated with higher odds of reporting parasomnias compared with exposure to other medications. This might indicate that depression itself could be responsible for the increased risk of these outcomes.

The voluntary nature of ADR reporting in Australia combined with it being the third most popularly prescribed hypnotic, despite its additional cost (Hollingworth and Siskind, 2010), would have facilitated the upsurge in reports; but the types of unusual nocturnal activities combined with amnesia reported by patients may well have several other possible diagnostic explanations such as epilepsy, rapid eye movement (REM) behaviour disorder, micro-sleeps, confusional arousals and dissociative states. Parasomnias are also poorly understood, even at a descriptive level.

There are numerous other weaknesses in ADR data of which cautious readers should be aware: self-report, absence of lifestyle covariates such as alcohol use in zolpidem ADR reports, limited numbers of reports for very specific ADRs, the analyses per force had to include broader ADR terms (such as parasomnia which includes many specific conditions, e.g. sleep-related eating disorder, somnambulism, etc.). Information on important concurrent diagnoses such as depression was not available. It is also unknown whether zolpidem, like some benzodiazepines, may have been prescribed to manage patients who were experiencing parasomnias. We are unaware of the proportion of patients who were prescribed and using hypnotics according to label instructions for appropriate therapeutic purposes versus those using medication that has been diverted for recreational or other illicit use.

CONCLUSION

In Australia zolpidem ADR reports are disproportionately likely to include reports of parasomnia, amnesia, hallucination and perhaps suicidality when compared with all other drugs listed or with other hypnotics. This increased risk was evident even before the media publicity events of 2007–2008, although this event increased markedly not only the absolute numbers of reports but also the strength of association with two of the four adverse outcomes: parasomnias and amnesia. We do not claim that this effect is causal: the extant literature and the limitations of ADR data do not give us that level of evidence. There is also the largely unexplored but anecdotally reported possibility that alcohol and zolpidem may interact perniciously. However, poor recording of the ADR data and high use of alcohol generally make this impossible to investigate using this data set. Demonstrating causality may be best undertaken in controlled laboratory settings or in a clinical trial environment. Regardless, practising clinicians should be aware that patients to whom they prescribe zolpidem may be at increased risk for hallucination, amnesia, parasomnia and possibly suicidality.

DECLARATIONS OF INTEREST

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