Proportion of 1425 pregnant women reporting an adverse event within one week of receiving 2013 seasonal trivalent influenza vaccine

Symptom	No.	Proportion (95% CI)
Injection site reaction*	52	3.6% (2.5%–4.8%)
Fatigue	29	2.0% (0.9%–3.1%)
Fever	28	2.0% (0.9%–3.1%)
Respiratory symptoms	27	1.9% (0.8%–3.0%)
Headache	24	1.7% (0.6%–2.8%)
Vomiting/diarrhoea	8	0.6% (0–1.7%)
Myalgia	7	0.5% (0–1.6%)
Sore throat	5	0.4% (0–1.5%)
Rigors	5	0.4% (0–1.5%)
Rash	3	0.2% (0–1.3%)
Nausea	2	0.1% (0–1.3%)
Dizziness	2	0.1% (0–1.3%)
Arthralgia	2	0.1% (0–1.3%)
Lymphadenitis	2	0.1% (0–1.3%)
Convulsions	0	0 (0–1.1%)
Other events	3	0.2% (0–1.3%)
None	1271	89.2% (88.1%–90.3%)

* Injection site reaction was defined as swelling, redness or pain at the site of vaccine injection. ◆

detected during the same appointment that the vaccine was administered. The second was an episode of self-reported decreased fetal movement; subsequent medical evaluations did not corroborate a decrease in fetal movements, and a healthy infant was delivered at term. Both of these events were considered unlikely to be caused by influenza vaccination.

Using SMS technology, WA DOH established a rapid system for monitoring influenza vaccine safety in near real-time. The rates of reactions after vaccination are consistent with those of previously published data in pregnant women[5] and support the safety of the 2013 influenza vaccine for use in pregnant women.

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1 Munoz FM, Greisinger AJ, Whemanen OA, et al. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol* 2005; 192: 1098-1106.
2 Omer SB, Bednarczyk RA, Madhi SA, et al. Benefits to mother and child of influenza vaccination during pregnancy. *Hum Vaccin Immunother* 2012; 8: 130-137.
3 Taksdal SE, Mak DB, Joyce S, et al. Predictors of uptake of influenza vaccination — a survey of pregnant women in Western Australia. *Aust Fam Physician* 2013; 42: 582-586.
4 Wiley KE, Massey PD, Cooper SC, et al. Uptake of influenza vaccine by pregnant women: a cross-sectional survey. *Med J Aust* 2013; 198: 373-375.
5 Carcione D, Blyth CC, Richmond PC, et al. Safety surveillance of influenza vaccine in pregnant women. *Aust N Z J Obstet Gynaecol* 2013; 53: 98-99. ❑

Systematic postmarketing surveillance needed for misused psychoactive pharmaceutical drugs

To the Editor: I would like to thank Rintoul and colleagues for bringing together data from varied sources to highlight an important public health issue.[1] The 1426% increase in supply of alprazolam they identified over the 20-year period from 1990 to 2010 was particularly striking.

Alprazolam is indicated as a second-line treatment for panic disorder where other therapies are ineffective, or for short-term treatment of anxiety disorder. As these conditions have not had a >1400% increase in incidence, while alprazolam use reported by the Victorian Illicit Drug Reporting System increased more than eightfold from 2005 to 2011 and detection of alprazolam in heroin-related deaths has increased,[1] it is reasonable to believe that alprazolam prescriptions are increasingly being diverted for illicit purposes.

> “Many of my patients misuse alprazolam obtained through either doctor shopping or the black market”
>
> Soh

Certainly, increasing availability of alprazolam and its subsequent misuse is reflected in the patients I see presenting for drug treatment. Many of my patients misuse alprazolam obtained through either doctor shopping or the black market.

Other consequences of using alprazolam not captured in coronial data include non-lethal overdoses; destabilisation of drug treatment; impairment of judgement leading to greater injury risk, high-risk substance use or criminal behaviour; and memory difficulties that impair patients’ ability to self-care.

Limiting alprazolam supply by categorising it as a Schedule 8 medication (now scheduled to occur in February 2014), instituting real-time prescription monitoring of all drugs of dependence (not just opiates), and improving the capacity of drug treatment services to manage benzodiazepine dependence would help reduce the harms related to its misuse.

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1 Rintoul AC, Dobbin MDH, Nielsen S, et al. Recent increase in detection of alprazolam in Victorian heroin-related deaths. *Med J Aust* 2013; 198: 206-209. ❑

To the Editor: Rintoul and colleagues showed that alprazolam is being increasingly detected in heroin-related deaths.[1] One explanation provided is increased rates of alprazolam misuse among people who inject drugs.

My colleagues and I recently reviewed the role of alprazolam in Australian clinical practice,[2] focusing on the sole supported Pharmaceutical Benefits Scheme (PBS) indication: treatment of “panic disorder where other treatments have failed or are inappropriate”. Despite this narrow indication, PBS prescriptions

increased 93% between 1997 and 2007, and total drug intake increased from 3.88 mg to 5.12 mg per 1000 population per day between 2003 and 2007, while use of other benzodiazepines remained stable or fell. The increase occurred despite updated treatment guidelines recommending psychological treatment (eg, cognitive behaviour therapy) and alternative pharmacological treatments (eg, selective serotonin reuptake inhibitors) before benzodiazepines, with specific warnings against benzodiazepine use beyond the short term (4 weeks) due to risks of addiction and side effects.[3] These recommendations should have reduced alprazolam prescription, but this was not the case.

While there are many possible explanations for increasing prescription rates,[2] it is most concerning that these trends have correlated with increasing alprazolam-related harm. Additionally, alprazolam appears easy to access[4] and is traded on the black market. At least four state and territory health departments and medical boards have identified increasing use of alprazolam as problematic and sought to engage practitioners in education,[5] resulting in some reduction in prescription rates.[6] However, escalating rates of harm suggest a more interventionist approach is required. The recent move to elevate alprazolam to Schedule 8 is one important step and, coupled with continuing prescriber education, will hopefully lead to a reduction in alprazolam-related harm.

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1 Rintoul AC, Dobbin MDH, Nielsen S, et al. Recent increase in detection of alprazolam in Victorian heroin-related deaths. *Med J Aust* 2013; 198: 206-209.
2 Moylan S, Giorlando F, Nordfjaern T, Berk M. The role of alprazolam for the treatment of panic disorder in Australia. *Aust N Z J Psychiatry* 2012; 46: 212-224.
3 National Institute for Health and Clinical Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. NICE clinical guideline 113. London: NICE, 2011.
4 Best D, Wilson A, Reed M, et al. Alprazolam and wider benzodiazepine misuse in Australia — sources of supply and evidence of harms. *Aust N Z J Psychiatry* 2013; 47: 94-95.
5 Medical Practitioners Board of Victoria. Warning: alprazolam (Xanax, Kalma, Zamhexsal). *Bulletin* 2009; (Jun): 11.
6 Galloway J. Newsletter number 42. Information circular for pharmacists in Tasmania. New restrictions on the prescribing of alprazolam. Hobart: Department of Health and Human Services, 2007. ❑

In reply: We thank Soh for her letter providing further evidence of harm relating to alprazolam misuse, which highlights deficiencies in postmarketing surveillance systems for pharmaceutical drugs. Reports of adverse drug reactions typically originate from therapeutic use; they seldom identify problems arising from misuse. Detection of misuse-related harm currently relies on ad-hoc epidemiological studies such as ours and that of Frei and colleagues, who documented problems with over-the-counter codeine–ibuprofen analgesics.[1] Given that pharmaceutical drug misuse and its consequences are becoming more prevalent in Australia,[2] a more systematic approach to identifying harm from misuse is required.

In the 1950s, several reports of aplastic anaemia associated with oral chloramphenicol emerged in the literature, but it was difficult to define the extent of the problem from these spontaneous reports.[3] An American Medical Association blood dyscrasia registry found that, while this was a rare adverse effect, the denominator of use was very high and the number affected was unacceptable. Oral chloramphenicol was removed from the market.

This example shows how a registry enables description of low-prevalence conditions. Other examples include the study by Frei et al[1] and the monitoring of uncommon diseases in children by the Australian Paediatric Surveillance Unit. A professional body such as the Royal Australasian College of Physicians Australasian Chapter of Addiction Medicine might serve to administer a funded registry for emerging pharmaceutical drug misuse problems.

Moylan highlights the inconsistency between alprazolam prescribing and treatment guidelines. Although alprazolam is not recommended as first-line treatment for anxiety or panic disorders, and despite significant risks of misuse and dependence, it remains widely prescribed for these conditions.

> “These recommendations should have reduced alprazolam prescription, but this was not the case”
>
> Moylan

> “Reports of adverse drug reactions typically originate from therapeutic use; they seldom identify problems arising from misuse”
>
> Rintoul et al

Regulatory and administrative changes can be effective in controlling pharmaceutical drug misuse problems. For example, flunitrazepam was moved to Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons in 1998,[4] and temazepam capsules were removed from the Australian market in 2004.[5] The 2010 report of the Victorian Illicit Drug Reporting System showed that benzodiazepine injection among people who inject drugs decreased from 40% in 2001 to 4% in 2010.[6]

We were encouraged to learn that as a result of many submissions to the Therapeutic Goods Administration describing harm from alprazolam misuse, alprazolam will also move to Schedule 8 in February 2014.

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1 Frei MY, Nielsen S, Dobbin MD, Tobin CL. Serious morbidity associated with misuse of over-the-counter codeine–ibuprofen analgesics: a series of 27 cases. *Med J Aust* 2010; 193: 294-296.
2 Rintoul AC, Dobbin MD, Drummer OH, Ozanne-Smith J. Increasing deaths involving oxycodone, Victoria, Australia, 2000–09. *Inj Prev* 2011; 17: 254-259.
3 Wright C, Schnoll S, Bernstein D. Risk evaluation and mitigation strategies for drugs with abuse liability: public interest, special interest, conflicts of interest, and the industry perspective. *Ann N Y Acad Sci* 2008; 1141: 284-303.
4 Rintoul AC, Nielsen S, Drummer OH, Dobbin MD. Benzodiazepine supply and heroin-related deaths in Victoria: the success of flunitrazepam regulation compared with escalating deaths involving alprazolam [abstract]. *Drug Alcohol Rev* 2010; 29 Suppl 1: 62.
5 Degenhardt L, Roxburgh A, van Beek I, et al. The effects of the market withdrawal of temazepam gel capsules on benzodiazepine injecting in Sydney, Australia. *Drug Alcohol Rev* 2008; 27: 145-151.
6 Reddel SE, Horyniak D, Dietze P, McElwee P. Victorian drug trends 2010: findings from the Illicit Drug Reporting System (IDRS). Sydney: National Drug and Alcohol Research Centre, University of New South Wales, 2011. ❑