Health and Drug Alerts

Venlafaxine (Effexor): concerns about increased risk of fatal outcomes in overdose

Reason for posting: A change in the prescribing information for venlafaxine has been issued by the US manufacturer, based on concerns that the antidepressant drug has been associated, in cases of overdose, with an increased risk of death compared with selective serotonin reuptake inhibitors (SSRIs).

The drug: Venlafaxine, a serotonin and noradrenalin reuptake inhibitor, is widely used in Canada for the treatment of DSM-IV–defined major depressive, generalized anxiety and social anxiety disorders in adults. It is generally well tolerated but shares several of the adverse effects of SSRIs, including gastrointestinal upset, sweating, dry mouth, sedation and sexual dysfunction. Additionally, venlafaxine has a known association with blood pressure elevation in some 3%–4% of patients who use the sustained release format and 2%–13% of those who take the immediate-release preparation. Concerns about a higher fatality rate in overdose has emerged over the past 4 years from information provided by administrative database studies.[1–4]

Relative risk estimates for fatal overdose vary within and between classes of antidepressants. Tricyclic antidepressants (TCAs) have consistently been associated with the highest toxicity in overdose. SSRIs, on the other hand, are the least toxic in overdose, with approximately one-tenth the death rates associated with TCAs.[1] Venlafaxine appears to fall somewhere in between (Table 1). Putting the numbers into perspective, the annual suicide rate in Canada is about 13.5 per 100 000 in the general population; higher, among patients receiving psychiatric treatment. Deliberate antidepressant overdoses account for 4%–7% of all suicides;[1] one-third of fatal antidepressant overdoses also include alcohol or other drugs.[2]

The reasons for the increased overdose fatalities associated with venlafaxine are not entirely clear. Competing explanations include a true toxicity effect versus a "spurious" effect related to its use in higher-risk groups than those prescribed SSRIs. Some combination of these is also possible. The former explanation is supported by case reports linking cardiac illness and venlafaxine overdose.[3] The latter is supported by a study of data from the United Kingdom's General Practice Research Database, in which patients prescribed venlafaxine were more likely than patients prescribed SSRIs to have been admitted to hospital for depression, to have displayed suicidal behaviour and to have received co-prescriptions of antipsychotic medications.[5] Unfortunately, the data did not include specifics on the doses consumed, duration of drug use or comorbid illnesses.

What to do: The US manufacturer has issued a warning stating that "prescriptions for Effexor should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose." This is difficult to apply across a wide spectrum of prescribing patterns. If venlafaxine is used as a second- or third-line drug for the treatment of depression, its use may signal the need for a more in-depth assessment of suicide risk and perhaps more intensive treatment.

Regardless of the role of patient risk factors, it is important to be aware of plausible arguments that venlafaxine is more toxic in overdose than SSRIs but less so than TCAs. A definitive explanation of the observed effect will have to wait upon more specific information.

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Table 1: Database studies of antidepressant-related deaths in relation to antidepressant prescriptions

Study	Administrative database	Risk measure	Type of antidepressant (95% CI)		
			Tricyclics	Venlafaxine	SSRIs
Buckley and McManus 2002	General Register Office for Scotland; Office for National Statistics (England and Wales) 1993–1999	Deaths per million prescriptions	34.8 (33.5–36.2)	13.2 (9.2–18.5)	1.6 (1.3–2.0)
Morgan et al 2004	Office for National Statistics (England and Wales) 1993–2002	Deaths per million prescriptions	30.1 (29.0–31.3)	8.5 (6.6–11.0)	1 (0.7–1.2)
Cheeta et al 2004	National Programme of Substance Abuse Deaths (England and Wales, coroner's data) 1998–2000	Mentions in death reports per million prescriptions	12*	13*	2*
Koski et al 2005	Finnish National Agency of Medicine: autopsy lab results, national prescription data 1995–2002	Fatal toxicity index (deaths/1000 people per defined daily dose per year)	Doxepin† 22 (19–25) Amitriptyline 12 (10–13)	4.4 (3.0–6.3)	Citalopram† 1.2 (1.0–1.5) Fluoxetine 0.33 (0.19–0.53)

Note: CI = confidence interval, SSRIs = selective serotonin reuptake inhibitors.
*Raw datum; no confidence interval given.
†Summary data unavailable for antidepressant category.

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