Translated from ***Rev Prescrire*** **April 2012; 32 (342): 268**

Nicorandil: mucocutaneous ulceration (continued)

● **A very severe case report.**

In 2012, a summary of an exemplary case report of adverse effects attributed to *nicorandil* was published in the newsletter of the Regional Pharmacovigilance Centre in Angers, France (1). *Nicorandil* has minor efficacy as a symptomatic treatment for angina pectoris. It is known to cause sometimes severe ulceration of the skin and mucosae (2).

An 87-year-old woman who had been taking *nicorandil* since 2003 developed severe aphthous stomatitis in mid-2009 (1). *Nicorandil* was discontinued in July 2009 and the lesions healed within a month. In August, *nicorandil* was reintroduced.

In December 2009, a sigmoidouterine fistula was diagnosed. In March 2011, a colostomy was performed. Then, a vesicovaginal fistula was diagnosed. The stoma area became ulcerated in August 2011.

Nicorandil was withdrawn in August 2011. By late September 2011, the ulceration around the stoma had improved and the pain had stopped. By November 2011, it has almost completely healed.

In view of *nicorandil*'s minor efficacy in angina, these adverse effects are unacceptable: patients would be better served if *nicorandil* were neither prescribed, used nor licensed.

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Selected references from Prescrire's literature search.
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Varenicline and bupropion: suicide

● **An analysis of reports in the USA.**

In late 2011 a study based on reports made between 1998 and 2010 to the US Food and Drug Administration (FDA) analysed reactions in patients taking drugs used for smoking cessation, namely *varenicline*, *bupropion* and *nicotine* (1). It included 3249 cases of suicide, self-harm and severe depression, 90% involving varenicline, 7% bupropion, and 3% nicotine.

The authors calculated what proportion these adverse effects represented among all other serious adverse effects reported with each drug.

Compared to *nicotine*, this proportion was 8 times higher with *varenicline* (odds ratio 8.4, 95% confidence interval (95%CI): 6.8 to 10.4) and about 3 times higher with *bupropion* (95%CI: 2.3 to 3.7). The increase persisted after excluding reports in which the patient was also taking one or more of the other 58 drugs for which, according to the US summaries of product characteristics, suicide is an adverse effect.

In practice, *varenicline* and *bupropion* both have an unfavourable harm-benefit balance. When a smoker needs a drug to help him or her quit, it is best to use nicotine (2).

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Venlafaxine: preeclampsia and eclampsia

● **Gestational hypertension.**

In early 2012 the World Health Organization's pharmacovigilance centre in Uppsala published an analysis of 31 cases of hypertensive disorders attributed to *venlafaxine* in pregnant women (1). They derived from the international Vigibase database. There were 4 cases of eclampsia, 21 of preeclampsia, 6 of gestational hypertension and 2 of the Hellp syndrome (severe preeclampsia, haemolysis, thrombocytopenia and liver damage). Only 3 of the women were under 29 years old. The daily doses of *venlafaxine* ranged from 9 to 300 mg and the treatment period ranged from 19 days to several years.

A cohort study of 5731 women showed that the risk of gestational hypertension was roughly twice as high among women taking a selective serotonin reuptake inhibitor antidepressant as in women not taking such drugs (odds ratio 1.9, 95% confidence interval (95%CI) 1.4 to 2.7) (1). The frequency of preeclampsia was 9% in women taking an SSRI and 2.4% in controls, and the risk was even higher with *venlafaxine* (relative risk 4.9, 95% CI: 2.7 to 8.8).

Blood pressure elevation is a well-known adverse effect of *venlafaxine* (2) and is one more reason to use antidepressants sparingly during pregnancy.

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Selected references from Prescrire's literature search.
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Benfluorex: lesions on a bioprosthetic heart valve too

● **A troubling case.**

In early 2012, a French team published a troubling case report involving a 40-year-old woman who underwent heart valve replacement surgery twice while taking *benfluorex* (formerly marketed under the brand name Mediator° among other names) (1,2).

After 15 months of *benfluorex* therapy, the patient was diagnosed with mitral valve regurgitation, and a bioprosthetic valve was implanted.

Benfluorex was reintroduced, and the patient continued treatment for 33 months. Cardiac problems developed a second time. She was diagnosed with mitral and aortic regurgitation, and both valves were replaced with mechanical valves. The lesions on the bioprosthetic mitral valve resembled those on the native aortic valve, including thickening similar to lesions attributed to *benfluorex* or observed in patients with carcinoid tumours. No other possible causes of valvular heart disease were identified, such as the use of other amphetamine appetite suppressants or ergot derivatives.

Benfluorex therefore also appears to provoke serious valvular injury, even to porcine bioprosthetic valves.

In cases of valvular insufficiency, even those involving a bioprosthetic valve, *benfluorex* should be systematically suspected as the causative agent, along with other drugs known to damage heart valves.

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SSRI antidepressants: persistent pulmonary hypertension in newborns (continued)

● **Consistent data.**

In January 2012, the results of a European cohort study including 1.6 million neonates born after 33 weeks of gestation were published (1). About 11 000 women had used a selective serotonin reuptake inhibitor (SSRI) antidepressant after week 20 of pregnancy. Three per 1000 exposed newborns had persistent pulmonary hypertension, versus 1.2 per 1000 unexposed newborns (statistically significant difference). Two studies conducted since 1996 had already demonstrated this increased risk (2). All of the SSRIs used carried a similar risk (1).

In 2010, the European Medicines Agency (EMA) reported that the incidence of persistent pulmonary hypertension after *in utero* exposure to an SSRI antidepressant was 5 cases per 1000 births (3). The incidence in the general population is 1 to 2 per 1000 births. According to the EMA, the same precautions should be taken during pregnancy with other serotoninergic antidepressants: *duloxetine*, *mirtazapine* and *venlafaxine.*

This is yet another reason to frequently weigh the benefits against the potential harms of antidepressant therapy throughout pregnancy.

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Methylphenidate: abuse and addiction

● **In young adults and adolescents.**

Methylphenidate is an amphetamine marketed for the treatment of some forms of attention deficit-hyperactivity disorder and narcolepsy (1,2). Its use is only justified in rare, severe cases.

In February 2012 the French Health Products Agency released a report on the 16 June 2011 meeting of the National committee on narcotics and psychotropics concerning *methylphenidate* (2).

Between 2006 and 2011, 83 cases of abuse, addiction or off-label use were reported to the network of French Centres for Evaluation and Information on Pharmacodependence or to the companies. Only 21 such reports were received between 2000 and 2006.

This misuse involved the immediate- and sustained-release formulations. Most of the individuals concerned were young adults (19 to 29 years, 28%) or adolescents (20%).

The reported reasons for *methylphenidate* consumption included attention deficit disorder, sleep disorders, anxiety and depression, agitation, improved mental performance, cocaine replacement, stimulant effects, weight loss, and doping.

The doses ranged from 10 mg to 2520 mg per day. *Methylphenidate* was taken for various periods (up to 20 years in one case). The route of administration was intravenous in 10 cases, subcutaneous in 1 case, and intranasal in 6 cases.

Systemic adverse effects included neuropsychological and cardiac disorders. Withdrawal symptoms were also reported, along with local adverse effects at the site of administration.

The French committee on narcotics and psychotropics concluded that *methylphenidate* "*is trivialised, both by prescribers and by students in schools, where the product is already circulating*".

What measures are being taken to warn them of the dangers?

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Pelargonium: severe liver damage

● **Harmful plants.**

Root extracts of *Pelargonium sidoides* and *P. reniforme* are sometimes used to treat certain respiratory or ENT disorders, despite the lack of proven efficacy. In France, these products are marketed as dietary supplements (1,2).

In late 2011, the independent German pharmacovigilance centre Arznei-Telegramm reported a case of liver damage attributed to a plant belonging to the genus *Pelargonium* (3).

A 30-year-old woman took *Pelargonium* root extracts (unknown species) for 4 days. One day after the end of treatment, she developed liver damage with jaundice, dark urine, hyperbilirubinaemia and transaminase levels more than 35 times the upper limit of normal. No other potential causes of hepatitis were found.

In March 2012, the German drug regulatory agency published a review including approximately 30 reports of liver damage that were attributed to *Pelargonium* and registered in the German national database up to January 2012 (4). There were 11 cases of hepatitis and 8 cases of jaundice. One patient received a liver transplant. Some of the patients were also taking known hepatotoxic drugs (*paracetamol*, *ibuprofen*, *aspirin*).

In practice, "natural" is not synonymous with safe, even when it comes to plants. Patients with unexplained symptoms should also be asked whether they use herbal preparations (5).

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