CASE REPORT

doi:10.1111/j.1360-0443.2008.02266.x

Venlafaxine dependence in a patient with a history of alcohol and amineptine misuse

Gianluca Quaglio[1], Fabrizio Schifano[2] & Fabio Lugoboni[1]

Medical Service for Addictive Disorders, Department of Internal Medicine, University of Verona, Verona, Italy[1] and University of Hertfordshire School of Pharmacy and Postgraduate Medical School, Hatfield, Hertfordshire, UK[2]

ABSTRACT

Background Venlafaxine is an inhibitor of neuronal serotonin and noradrenaline re-uptake and a weak inhibitor of dopamine re-uptake. There was no indication of problems of abuse/dependence during the clinical trials. **Case description** A 53-year-old client with a history of alcohol and amineptine misuse and a long history of recurrent depression, for which he was prescribed venlafaxine tablets. Over time, he increased the dosage to 50 tablets daily (3750 mg). Large venlafaxine dosages produced amphetamine-like effects, due possibly to the related increase in dopamine turnover. Once hospitalized for detoxification, the patient had a symptomatology which was consistent with a serotonergic discontinuation syndrome. **Conclusions** Physicians should be aware that patients with a history of drug and alcohol abuse might develop venlafaxine dependence.

Keywords Addiction, antidepressants, dependence, substance abuse, substance dependence, venlafaxine, withdrawal symptoms.

Correspondence to: Gianluca Quaglio, Medical Service for Addictive Disorders, University of Verona, Policlinico G. B. Rossi, 37134 Verona, Italy.
E-mail: gianluca.quaglio@azosp.vr.it

Submitted 9 October 2007; initial review completed 14 February 2008; final version accepted 2 April 2008

INTRODUCTION

Both venlafaxine and its active metabolite, o-desmethylvenlafaxine, are potent inhibitors of neuronal serotonin and noradrenaline re-uptake and weak inhibitors of dopamine re-uptake [1]. While no venlafaxine drug-seeking behaviour has been described in formal clinical trials [1], a case of venlafaxine abuse has been described previously [2]. To the best of our knowledge, however, no venlafaxine dependence reports have been published so far.

CASE REPORT

The patient, a white European 53-year-old male, was referred to our unit to be detoxified from venlafaxine. He had a history of alcoholism, treated successfully with a 3-year prescription of disulfiram. Furthermore, he showed a long history of recurrent depression and had been diagnosed previously with borderline personality disorder. Between 1995 and 2000 he had been abusing with amineptine, reporting an intake level of up to 120 tablets (e.g. 12 g) a day. When amineptine was withdrawn from the Italian market, and in concomitance with a further depressive episode, he was put on 75 mg, normal-release, venlafaxine tablets, which he took regularly for about 1 year. Eventually, presumably to cope with a further depressive relapse, he increased his venlafaxine dosage spontaneously to 10 tablets (i.e. 750 mg) a day. With this dosage, he was allegedly able to experience an amineptine-like 'high'. This continued for about 6 months but, in parallel with what appeared to be a tolerance to venlafaxine, he increased his intake levels further. When his general practitioner (GP) refused to prescribe him with the drug, the patient started purchasing it from amenable pharmacists.

After having taken an unusually large dose of venlafaxine, he went to a accident and emergency unit. On that occasion, he was experiencing a state of intense psychomotor agitation which had not resolved within a few hours, unlike previously. He managed to continue to self-administer venlafaxine, at an average daily dosage of 28 tablets (i.e. 2100 mg), with peaks of up to 50 (i.e. 3750 mg) tablets. He gave preference to normal-release formulation tablets, as the extended-release ones were associated with decreased psychoactive properties. On a

typical day, he was ingesting 16–17 tablets in the morning on an empty stomach ('it had a stronger effect'), seven to eight tablets at lunchtime and seven to eight tablets in the afternoon. Occasionally, he ingested a further seven tablets late in the afternoon and a another seven in the evening. During his 5 years of venlafaxine misuse a few spells of non-consumption occurred, the longest being of about 6 months.

The patient reported that, during his high levels of venlafaxine intake, he felt more empathic and sociable and his mood was elated. Conversely, he experienced a number of side effects, including weight loss (up to 13 kg, without dieting), trembling (accompanied by the inability to both write and perform tasks which required precise movements), dizziness and intense muscular asthenia, which caused several falls.

When hospitalized in our unit the patient was diagnosed with venlafaxine dependence, according to DSM-IV criteria [3]: he sought unsuccessfully to discontinue or control consumption, developed tolerance, continued use despite the recurrent harm and raised the doses, etc. During his 10-day admission, venlafaxine was discontinued and he was switched to duloxetine, 120 mg per day. In the first 3–4 days, the patient suffered from nausea, drowsiness and hypotension. Initially, his electrocardiogram (ECG) showed a prolongation of QTc interval to 500 milliseconds, but this normalized within a few days. Blood tests [haemoglobin, haematocrit, white blood cells, platelets (PLTS), electrolytes (Na^+, K^+, Cl^-, $HCO3^-$), Ca^+, blood–urea–nitrogen (BUN), creatinine, liver function, thyroid hormones, cholesterol] showed only a small increase in gamma glutamyl transferase (GGT) (57 U/l), alanine aminotransferase (ALT) (61 U/l) and total cholesterol (204 mg/dl).

After discharge from hospital, the patient was followed as an out-patient. After several weeks he attempted to increase the dosage of duloxetine (double the normal dose), without reward, and returned to the therapeutic dose. Later he abandoned duloxetine, resuming the abuse of venlafaxine.

DISCUSSION

Given the hundreds of millions of patients treated with antidepressants, the number of antidepressant dependence case reports is extremely small [4]. Most reports involve drugs with amphetamine-like properties, such as tranylcypromine and amineptine [5,6]. Reports of misuse with other antidepressants are rare indeed [7–10]. Typically, previously described clinical vignettes of antidepressant misuse referred to personality disordered male patients with a previous history of drug and/or alcohol abuse [4–9]. The present venlafaxine dependence case report seems to conform to previous observations.

The mechanisms of addiction to venlafaxine are unknown. Large dosages may produce amphetamine-like effects [2], which might be related to a venlafaxine-related increase in dopamine and noradrenaline synaptic concentration. Consistent with this hypothesis, the patient reported that venlafaxine reminded him of amineptine, 'although amineptine was much better'. Therefore the patient, on his own initiative, seems to have used venlafaxine to replace amineptine. Unlike in this case, the only other venlafaxine misuse case report involved the ingestion of crushed, extended-release, formulation tablets [2].

Among side effects, the patient did not mention tachycardia, retrosternal weight or an increase in blood pressure, as described in the previous case of venlafaxine abuse [2]. For several years the patient had been treated with nebivolol and amlodipine for essential hypertension, which might have masked these cardiovascular effects. Part of his anti-hypertensive therapy was suspended upon hospitalization. Before increasing the dose gradually, the patient took venlafaxine at the therapeutic dosage for about 1 year: perhaps the lack of anticipated symptoms of serotonin toxicity was a consequence of partial tolerance.

Following the discontinuation of venlafaxine, the patient had a symptomatology (i.e. nausea, dizziness, hypotension) which was consistent with a mild serotonergic discontinuation syndrome. Discontinuation symptoms may reflect a combination of functional deficit of both serotonin and noradrenaline at the receptor level [11,12]. Symptoms of withdrawal were, on the whole, mild only if the high levels of intake identified here were considered. The patient was put on replacement pharmacotherapy with duloxetine, which has a similar mechanism of action to, but is more potent than, venlafaxine [13]. This would have alleviated at least part of the withdrawal symptoms associated with venlafaxine discontinuation. It should, however, be remembered that the US Food and Drug Administration reports that the severity of withdrawal reactions from venlafaxine increases with both dose and time [14].

Finally, it is interesting to note that the patient's blood test results did not have any significant alterations. Physicians should evaluate patients with a history of drug and alcohol abuse and follow them, focusing upon the development of tolerance, the increase in the dose of venlafaxine and related drug-seeking behaviour. Despite potential abuse, it should be pointed out that venlafaxine remains a very valuable antidepressant.

Declarations of interest

None.

References

1. Wyeth. Venlafaxine hydrochloride. Product's label. Philadelphia, PA, USA 2006.
2. Sattar S. P., Grant K. M., Bhatia S. C. A case of venlafaxine abuse. *N Engl J Med* 2003; **348**: 764–5.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington, DC: American Psychiatric Association; 1994.
4. Haddad P. Do antidepressants have any potential to cause addiction? *J Psychopharmacol* 1999; **13**: 300–7.
5. Prieto J. M., Gost A., Obiols J., Caycedo N. Amineptine dependence and schizophrenia. *Biol Psychiatry* 1994; **36**: 266–8.
6. Davids E., Roschke J., Klawe C., Grunder G., Schmoldt A. Tranylcypromine abuse associated with delirium and thrombocytopenia. *J Clin Psychopharmacol* 2000; **20**: 270–1.
7. Prahlow J. A., Landrum J. E. Amitriptyline abuse and misuse. *Am J Forensic Med Pathol* 2005; **26**: 86–8.
8. Taieb O., Larroche C., Dutray B., Baubet T., Moro M. R. Fluoxetine dependence in a former amineptine abusers. *Am J Addict* 2004; **13**: 498–500.
9. Leterme L., Singlan Y. S., Auclair V., Le Boisselier R., Frimas V. Misuse of tianeptine: five cases of abuse. *Ann Med Interne* 2003; **154**: S58–63.
10. Lepping P., Menkes D. B. Abuse of dosulepin to induce mania. *Addiction* 2007; **102**: 1166–7.
11. Pinzani V., Ginies E., Robert L., Peyriere H., Abbar M., Blavac J. P. Venlafaxine withdrawal syndrome: report of six cases and review of the literature. *Rev Med Interne* 2000; **21**: 282–4.
12. Johnson H., Bouman W. P., Lawton J. Withdrawal reaction associated with venlafaxine. *BMJ* 1998; **317**: 787.
13. Bymaster F. P., Dreshfield-Ahmad L. J., Threlkeld P. G., Shaw J. L., Thompson L., Nelson D. L. *et al*. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters *in vitro* and *in vivo*, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology* 2001; **25**: 871–80.
14. Medwatch. *The FDA Medical Products Reporting Program. Summary of Safety-Related Drug Labelling Changes Approved by FDA*. Rockville, MD: US Food and Drug Administration; 2000.