Profound weight loss associated with reboxetine use in a 44-year-old woman

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We report a case of significant weight loss experienced by a 44-year-old Caucasian woman treated with reboxetine. She was treated with this drug at 12 mg daily for a total duration of 11 months. During the corresponding period her body mass index (BMI) decreased from a baseline of 21.4 kg m⁻² to a low of 16.8 kg m⁻². Withdrawal of the drug led to a full recovery of her BMI. The strongest evidence linking reboxetine to this woman's weight loss laid in the fact that the re-introduction of the drug subsequently caused a similar negative impact in her BMI.

Introduction

Reboxetine is a selective noradrenaline reuptake inhibitor. It is used as a second-line agent in the treatment of major depression [1]. A recent study has advocated its role as an adjunct therapy to attenuate olanzapine-induced weight gain in patients with schizophrenia [2]. We report a case of profound weight loss experienced by a 44-year-old woman treated with reboxetine.

The subject was a 44-year-old Caucasian female with a baseline body weight of 55.0 kg and height of 1.6 m (body mass index 21.4 kg m⁻²).

The woman's medical history included inactive

chronic hepatitis C infection with normal liver function, quiescent rheumatoid arthritis, gastroesophageal reflux disease, hypertension and bipolar mood disorder. Drug therapy included hydroxychloroquine 200 mg bid, rabeprazole 20 mg daily, and felodipine 2.5 mg daily. She was started on lamotrigine 100 mg daily and reboxetine 12 mg daily in July 2003.

The woman did not consume alcohol and was a life-long nonsmoker. Her dietary history was unremarkable. She did not suffer from abnormal eating behaviour. In addition, there was no family history of occult malignancies.

Figure 1

Body mass index and body weight changes during reboxetine treatment and withdrawal. BMI (●), weight (◆)

The woman began to experience a decrease in her body weight two months after initiation of reboxetine. She was losing on average 0.5 kg per fortnight between September 2003 and June 2004. During the corresponding period her weight decreased dramatically from a baseline of 55.0 kg to a low of 43.0 kg (Figure 1).

The patient reported loss of appetite though she kept up three meals per day. She did not vomit or feel nauseated. Several investigations were performed to exclude organic causes for the weight loss. These included thyroid function tests, a short synacthen test, and imaging of the abdomen and pelvis. The woman also underwent upper and lower endoscopies to exclude an occult gastrointestinal malignancy. The results were essentially normal. Despite high caloric dietary supplements recommended by a dietitian her body weight failed to increase.

In June 2004 the woman underwent a supervised withdrawal of reboxetine and lamotrigine over a 3-week period. By early July 2004 both drugs had been ceased and alternative mood-stabilizing agents (mirtazapine 30 mg daily and olanzapine 5 mg daily) were introduced. A gradual and full recovery in the woman's body weight ensued (Figure 1).

Later on, however, it was felt that the control of this woman's bipolar disorder was becoming suboptimal. Therefore, reboxetine alone was reintroduced by her psychiatrist in early October 2004 at the same dose of 12 mg daily. This coincided with yet another decrease in her body weight and body mass index (BMI). In early November 2004 the woman's body weight was 51.0 kg (Figure 1). Despite treatment the woman's mood

remained deeply depressed. She was withdrawn from reboxetine once again in mid-November 2004. At the time of writing in early December her body weight was trending back to its baseline level (Figure 1).

Discussion

Reboxetine is a relatively new psychotropic drug [1]. The main indication for its use is as a second-line agent in the treatment of major depression [1]. Although the drug is generally well tolerated, this report identifies one serious adverse event which, up to this date, has not been reported in the literature.

The relationship between reboxetine usage and reduction in BMI is strongly implicated in this case study as reboxetine treatment and withdrawal represented a crucial factor during each phase of weight fluctuation. Reboxetine treatment correlated with a significant negative effect on BMI while its withdrawal was associated with full recovery. In particular, the decrease in BMI following re-challenge with this drug strengthens the probabilistic evidence in favour of a reboxetine-induced adverse event [3]. A score of 7 on the Naranjo adverse drug reaction scale indicates the adverse event to be at least probable [4].

The reduction in BMI is very unlikely to be attributed to other factors as they have remained stable throughout the case scenario. There was no alteration in other drugs; the woman's mood and eating habit did not fluctuate; and organic causes have been excluded by a set of fairly thorough investigations. The only uncertainty is whether lamotrigine might have contributed to the adverse drug event. A search of the current literature through PubMed

failed to find any supporting evidence for a possible role of lamotrigine. Moreover, at the time of the second introduction of reboxetine with following weight loss, the patient did not receive lamotrigine.

We have searched the World Health Organization database for reports of weight loss and/or anorexia associated with reboxetine. Current to October 2004, there have been 11 unpublished case reports of this sort [5]. However, there is no information about the exact sequence of events in these reports [5]. The most dramatic description is that of a male weighing 100 kg developing anorexia and weight loss of 20 kg. Again, the time period was not specified.

Accepting the odds that the negative effect on BMI is due to reboxetine usage in this case, one must attempt to offer a pharmacological explanation. One possible mechanism is the drug's ability to partially inhibit serotonin re-uptake in the central nervous system. Serotonin has been implicated in the regulation of eating behaviour and appetite control [6]. Disruption of this system might lead to clinical symptoms of anorexia and subsequent weight loss [6]. Therefore, reboxetine is perhaps not as selective a noradrenaline reuptake inhibitor as claimed. Another possible mechanism relates to potential interaction at the enzyme level. Reboxetine is primarily metabolized by CYP3A4 isozyme of cytochrome P450. *In vitro* studies have shown that it is also a weak inhibitor of CYP3A4 [7]. In this subject it is possible that, at the dose of 12 mg daily, self-inhibition of metabolism occurs. This could then lead to excessively high concentrations of reboxetine, which then overcomes its noradrenaline selectivity. On the other hand, we have found no evidence that either rabeprazole or felodipine causes CYP3A4 inhibition. Furthermore, the subject was not a consumer of grapefruit juice.

It needs to be stated that while the recommended therapeutic dose for reboxetine is 8 mg daily, higher doses of up to 20 mg daily have been trialled and tolerated in cases of incomplete clinical response [8]. Therefore, the dose of reboxetine administered to this subject (12 mg daily) cannot be assumed to be an overdose.

In terms of the management of this clinical problem, we offer the advice of withdrawing reboxetine as the most expedient method of reversing the weight loss. High caloric dietary supplement appears to be ineffec-

tive in addressing this issue. Subsequent regaining of weight can be expected to occur within weeks of drug cessation.

In summary, reboxetine is a new psychotropic drug used in the treatment of major depression and schizophrenia [1]. In addition, pilot studies involving reboxetine in the treatment of eating disorders are also advocating the use of this drug in these conditions [9, 10]. This case report of profound weight loss associated with reboxetine use highlights one serious adverse event which has the potential to cause significant morbidity. More evidence of its safety profile is warranted before such promotions become widely accepted.

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