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Case report

Monotherapy with reboxetine in amphetamine withdrawal syndrome

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Abstract

Amphetamine withdrawal can induce a condition with the symptoms of major depression. We report the case of a 46-year-old woman with antecedents of abuse of amphetamines and amphetamine derivatives from age 16 to age 41, who in the 5 years since withdrawal presented recurrent depression resistant to treatment. She was treated with maximum doses of selective serotonin reuptake inhibitors and lithium, but there was no remission of symptoms. On being treated with reboxetine, a selective noradrenaline reuptake inhibitor, euthymia was achieved, without negative after effects. Several studies have shown that noradrenaline plays an important role in the modulation of the response to amphetamines. The findings in this case suggest that reboxetine may constitute an interesting alternative for the treatment of amphetamine withdrawal syndrome (AWS).

Keywords: Amphetamines; Depression; Noradrenaline; Reboxetine; Withdrawal syndrome

1. Introduction

It has been reported that after chronic amphetamine abuse, withdrawal may lead to a mood disorder with the symptoms of major depression. This effect has indeed been reproduced in animal models (Swerdlow et al., 1991; Cryan et al., 2003).

According to the recent systematic review by Cochrane (Srisurapanont et al., 2001), the only treatment for amphetamines withdrawal syndrome (AWS) that has, up to now, produced any significant benefits has been amineptine, but this drug was withdrawn from the market after several cases of abuse came to light. Recently, however, the case has been reported of a woman who, after 30 years of amphetamine abuse, was successfully treated for a withdrawal condition with bupropion, an inhibitor of dopamine and serotonin reuptake (Tardieu et al., 2004).

Amphetamines are psychostimulant drugs whose action mechanism involves dopamine, noradrenaline and serotonin (Utrilla, 2000). Until recently, the majority of research had focused on the dopaminergic system, but there is growing evidence that noradrenaline plays an important role in the modulation of the response to amphetamines (Vanderschuren et al., 2003). In several studies with rodents, researchers have observed a relationship between the release of prefrontal noradrenaline stimulated by amphetamines and the release of dopamine in the nucleus accumbens and the ventral tegmental area (Drouin et al., 2002; Ventura et al., 2003). Likewise, other studies, also with rodents, have shown that chronic administration of amphetamines could produce persistent alterations in the noradrenergic system (neuroadaptation in the form of hyposensitivity) (Sorensen et al., 1982).

In the case presented here, treatment with reboxetine in monotherapy was successful for a patient who had an AWS condition with resistant depression. Reboxetine is a selective noradrenaline reuptake inhibitor (Montgomery, 1997) with low affinity for cholinergic, muscarinic, H_1 histaminergic and α_1-adrenergic receptors (Cuenca et al., 1999), so that its use is not associated with the typical adverse effects of the classic tricyclic

Abbreviations: ALT, alanine transaminase; AWS, amphetamine withdrawal syndrome; CNS, central nervous system; HIV, human immunodeficiency virus; LSD, lysergic acid diethylamide; MDMA, methyldioxyamphetamine.

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antidepressants. It has recently been observed, in a series of amphetamine abuse cases, that treatment with reboxetine may help patients to avoid the withdrawal syndrome (Cox et al., 2004). Research has also shown it to be highly effective in cases of depression resistant to conventional antidepressant treatment with serotonergic drugs (Rubio et al., 2004).

2. Case report

A 46-year-old woman was admitted to our acute inpatient unit with major depression resistant to various previous antidepressant treatments. Among her antecedents was a history of amphetamine abuse from age 16 to 41. No depressive episode had been diagnosed prior to beginning to abuse amphetamines.

The patient began consuming amphetamines (amphetamine resinate) as an anorexigenic drug at the age of 16, and was taking around 100 mg/day. The amphetamines ceased to have the anorexigenic effect after a few years, when she became tolerant to them; nevertheless, the patient reported a subjective need to continue taking the drug so as to be able to cope with her daily activities. She did not consume any other toxic substances, or alcohol. During this time, she had 4 children, and never took amphetamines during the pregnancies, when she suffered symptoms compatible with a withdrawal syndrome, such as an intense desire to consume the drug everyday and depressive symptoms. Indeed, after every birth, she asked her general practitioner for a pharmacological treatment to stop breast-feeding in order to begin the amphetamine consumption.

At the age of 25, she began to have difficulty obtaining amphetamines at the chemist, where they were no longer sold as anorexigenic drugs, and tried to acquire them on the black market, but was afraid of the marginal environment in which it operated. She therefore resorted to consuming amphetamine derivatives that were still sold as anorexigenic drugs: 120 mg/day of clobenzorex (*S*-*N*-2-chlorobenzylamphetamine) and 30 mg/day of fenproporex (*N*-2-cyanoethylamphetamine), substances with the same properties of stimulation of the CNS as amphetamines (Young et al., 1997). The consumption of these amphetamine-like drugs brought about euthymia, with a reduction in the need for sleep and increased capacity for work and concentration. When the amphetamine derivatives were also withdrawn from public sale, she fell into depression, finding herself unable to cope with everyday life, with anhedonia, anergy, difficulty of concentration, asthenia, reduced libido, inversion of circadian rhythm and thoughts of uselessness, despair and failure, all of these symptoms interfering in her family and working life.

After 2 years without taking amphetamines or its derivatives, the patient made her first visit to a psychiatrist. She reported neither previous depression nor other psychiatric antecedents apart of amphetamine abuse. She was treated with amitryptiline and flunitrazepam, but gave up the treatment after 3 months due to the excessive sedation and a lack of improvement in her mood. It was then that she began to abuse alcohol, seeking its euphoric effect. Four years after giving up amphetamines she made a suicide attempt with benzodiazepines and alcohol. She was diagnosed with recurrent depression and treated with fluoxetine (up to 80 mg/day) and venlafaxine (up to 300 mg/day) for 6 months, without success, so that lithium was incorporated into the treatment. However, there was still no improvement, and she gave up this treatment after 6 months. She began once more to abuse alcohol and benzodiazepines, and a few months later made a second suicide attempt, with overdose of benzodiazepines and slashed wrists.

She was admitted to our acute psychiatric inpatient unit, where we began treatment with reboxetine in monotherapy (6 mg/day), observing clinical improvement in the first week and gradual disappearance of the symptoms over 4 weeks. Neither group nor supportive therapy was provided to the patient at this moment. She did not report any previous medical illness, apart from allergies to sulfamides and to aminosalicylates. Premenopause symptoms occurred 1 year before she was admitted to our unit, but symptoms did not affect the previous reported depressive state, that began 5 years before, following complete amphetamine withdrawal. During her stay in our hospital, a complete clinical history and physical examination, with a battery of screening tests, was carried out in order to rule out psychiatric and physical conditions, related or not to substance use, which might otherwise accounted for the patient's persistent depression. Pathological laboratory test findings were as shown: cholesterol 274 mg/dL; triglycerides 298 mg/dL, ALT 47 UI/L. Values for thyroid hormones were in normal, and serology for HIV, hepatitis C virus and hepatitis B virus were negative. She was discharged with the same pharmacological treatment—reboxetine 6 mg/day. She remained on the same treatment during outpatient follow-up. Two months later she was re-evaluated and she was found to be euthymic and capable of carrying out her everyday activities, just as she had been at the time of discharge. No significant side effects were reported by the patient. At this time, another blood analysis was carried out. Cholesterol was 271 mg/dL and LDL cholesterol was 158 mg/dL. No other pathological findings (including both thyroid and liver function) were found. Urine drug analysis was negative both during her hospitalization in our acute inpatient unit and 2 months after her discharge.

3. Discussion

Withdrawal from amphetamines and the onset of depressive conditions appear to be closely related. In the case reported here, the patient was euthymic while she was consuming amphetamines, and it was in the periods in which she was unable to do so–because she was pregnant or due to lack of access to the drug–that the depressive symptoms emerged. Moreover, there are reports of the persistence of neuropsychological problems after years of abstinence in cases of abuse of amphetamine derivatives, such as methyldioxyamphetamine (MDMA) (MacInnes et al., 2001; Soar et al., 2004). These findings could be compatible with the fact that, after 5 years without consuming the drug, our patient continues to present an affective disorder.

There are several studies supporting the theory that the noradrenergic system has a special involvement in the effects

mediated by amphetamines, even to a greater extent than the dopaminergic system (Drouin et al., 2002; Ventura et al., 2003; Muñoz et al., 2003). A comparative study on the effects of amphetamine, cocaine and apomorphine on the modulation of noradrenergic transmission found that amphetamine had a more marked effect than the other drugs (Vanderschuren et al., 2003). Moreover, in diverse studies with rodents, lasting changes have been observed in noradrenergic neuronal activity as a result of chronic administration of amphetamine (Sorensen et al., 1982; Paulson et al., 1991), and this may reflect a phenomenon of neuroadaptation to continued consumption of this substance.

Thus, it would appear that reboxetine acts on the noradrenergic pathways themselves, giving rise to adaptive changes in adrenergic receptors, including the presynaptic α_2-adrenoreceptors, which would increase its functional response (Rogóz et al., 2002). Similarly, it has been hypothesized that long-term treatment with subtherapeutic doses of reboxetine may produce a desensitization of the presynaptic α_2-adrenergic heteroreceptors in serotonergic neurons, which would translate into a strengthening of serotonergic neurotransmission. This modulatory effect may also be involved in the therapeutic response process (Lucca et al., 2000).

Moreover, from the clinical perspective, it has been reported that reboxetine may be useful in the treatment of dependence on other substances, such as cocaine (Szerman et al., 2005), nicotine (Rauhut et al., 2002) and LSD (Lerner et al., 2002), and, in combination with escitalopram, in the treatment of depressions associated with substance abuse (Camarasa et al., 2005). As regards our patient, she had spent 5 years with a depression that failed to respond to maximal doses of selective serotonin reuptake inhibitors associated with lithium; however, with reboxetine, at therapeutic doses and in monotherapy, she responded satisfactorily, without significant negative after-effects.

4. Conclusion

This case, together with basic research studies that propose a shared neurobiological basis, suggests that reboxetine may constitute an interesting alternative for the treatment of AWS. Moreover, it should be borne in mind that the symptoms improvement may also be due to the inner and well-known antidepressive properties of reboxetine. Nevertheless, controlled clinical trials are necessary in order to confirm this hypothesis.

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