

Pregabalin Dependence: A Case Report



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SUMMARY

Pregabalin is a new generation antiepileptic that exerts its effect by decreasing the release of such neurotransmitters as glutamate, noradrenaline, and substance P. Pregabalin can be prescribed in Turkey at 150-600 mg to treat neuropathic pain, generalized anxiety disorder, fibromyalgia, and as concomitant therapy in adult patients with partial epilepsy. Experimental studies have shown that pregabalin could be beneficial in the treatment of benzodiazepine dependence and withdrawal, as well as for relapse prevention in patients with alcohol dependence. Nonetheless, the number of case reports on the abuse potential of pregabalin has increased.

Herein we present a patient with pregabalin dependence. The patient's underlying alcohol and polysubstance dependence, and symptoms of generalized anxiety were thought to contribute to the development of pregabalin dependence. The patient reported that he had experienced severe withdrawal symptoms when he tried to stop using pregabalin. Bupropion and low-dose quetiapine were added to his paroxetine treatment, and pregabalin was discontinued gradually. Following this treatment the patient had not exhibited any signs of pregabalin dependence for one month. Although pregabalin is a promising drug for various psychiatric disorders, it should be used carefully in patients with a history of substance dependence.

Keywords: Pregabalin, substance dependence, generalized anxiety disorder

INTRODUCTION

The gamma-aminobutyric acid analogue pregabalin is a new generation antiepileptic. Although its mechanism of action is not clearly understood, it is thought that it affects excitatory neuronal transmission via $\alpha 2-\delta$ ligands in voltage sensitive calcium channels (Stahl 2012) and decreases the release of such neurotransmitters as glutamate, noradrenaline, and substance P (Schwan et al. 2010). In Europe pregabalin has been approved by the European Medicines Agency (EMA) for the treatment of central and peripheral neuropathic pain, and generalized anxiety disorder, and as concomitant therapy in adult patients with partial epilepsy, the US Food and Drug Administration (FDA) approved its use for diabetic peripheral neuropathy, neuropathic pain associated with postherpetic neuralgia, fibromyalgia, and as concomitant therapy

in adult patients with partial epilepsy (Gahr et al. 2013a), and in Turkey the Ministry of Health approved pregabalin at doses of 150-600 mg for the treatment of peripheral neuropathic pain, generalized anxiety disorder, fibromyalgia, and as concomitant therapy in adult patients with partial epilepsy. As pregabalin has a broad range of indication, the number of reports on its potential for abuse is increasing (Gahr et al. 2013b, Carrus and Schifano 2012, Yargic and Alyanak Ozdemiroglu 2011, Filipetto et al. 2010, Grosshans et al. 2010).

Case

Mr. K is 34 years old, married, and works self-employed. He was referred for the first time to our outpatient clinic in July 2013. He has a history of substance abuse that began in early

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adulthood and he was diagnosed with alcohol, cannabis, and ecstasy dependence. He had spontaneously abstained from alcohol and substance use at age 27 years without professional help, and after 4 years of complete remission at age 31 started to use pregabalin following with the recommendation of a relative. He reported having a high level of anxiety since childhood due to stressful family-related life events and that as his anxiety was reduced with pregabalin he increased the dose to 300 mg over time. The patient reported that the highest dose of pregabalin he used at the time of admission was 15,600 mg (104 capsules $\times$ 150 mg), and that when he was able to obtain pregabalin he used at least 1,950 mg (13 capsules $\times$ 150 mg) and frequently used 7,800 mg (52 capsules $\times$ 150 mg).

He reported that when he used pregabalin he felt better and more energetic, required less sleep, had a lower level of anxiety, felt more self-confident, and had visual hallucinations. He also reported that when he tried to stop using pregabalin he experienced pessimism, aggression, anxiety, suicidal ideation, fatigue, excessive sleep, loss of appetite, palpitations, tremors, and vomiting, and therefore continued to use pregabalin. During the previous three years he did not stop using pregabalin for more than three days. Pregabalin use negatively affected his work performance and his family relationships. As pregabalin was sold over the counter in Turkey until March 2013, he did not have any difficulty obtaining pregabalin, but since the time it could only be obtained with a prescription he had difficulty getting it. This difficulty increased his motivation for treatment and he presented to a psychiatrist in April 2013. He reported his pregabalin use, but he did not provide detailed information on the dose. Paroxetine 20 mg and hydroxyzine 25 mg was initiated. This treatment regimen decreased his level of anxiety, but there was no change in his pregabalin use. He had used 1 g of cocaine six times within the last month, and when his family became aware of this he was referred to our clinic.

Psychiatric examination showed hypersomnia, anorexia, anergia, lack of attention and concentration, depressive mood, and anhedonia. He reported that his last used pregabalin 1,200 mg (8 capsules $\times$ 150 mg) 1 d earlier. His Beck Depression Inventory (Hisli 1989; Beck et al. 1961) score was 43 and Beck Anxiety Inventory (Beck et al. 1988; Ulusoy et al. 1988) score was 48. Liver, kidney, and thyroid function tests, and electrolyte and hemogram evaluations were normal. Based on these findings, according to DSM-IV-TR (Diagnostic and Statistical Manual IV-text revision), he was diagnosed as generalized anxiety disorder, other substance dependence (pregabalin), and other substance (pregabalin)-related mood disorder with onset during withdrawal. A schedule was arranged to terminate pregabalin use by tapering its dose by 150 mg. Hydroxyzine treatment was discontinued and bupropion 150 mg (to be increased to 300 mg 1 week later), and quetiapine 50 mg were added to paroxetine treatment.

Two weeks later he reported that he completely stopped using pregabalin and that he had no symptoms of withdrawal and no craving for pregabalin. His anxiety and depression improved markedly, and there was no longer any suicidal ideation. He did feel sleepy, which he attributed to quetiapine. His Beck Depression Inventory score was 22 and Beck Anxiety Inventory score was 22. In agreement with the patient, it was thought that his somnolence was associated with quetiapine; therefore, the dose was decreased to 37.5 mg and he was scheduled for an outpatient clinical evaluation 15 d later. At his last evaluation he had no complaints other than sleeping excessively. There was no use of alcohol or any other substance, and his Beck Depression Inventory score was 16 and Beck Anxiety Inventory score was 15. Quetiapine was reduced to 25 mg and he was scheduled for a clinical evaluation three weeks later.

DISCUSSION

Herein we presented a patient with a history of alcohol and multiple substance abuse that after four years of not using any substances developed pregabalin dependence upon experiencing its anti-anxiolytic and euphoric effects. It was thought that the patient's development of pregabalin dependence was associated with the fact that it reduced the severity of his underlying generalized anxiety. The highest daily dose he used (15,600 mg) is much higher than that reported in earlier case reports (Gahr et al. 2013b, Carrus and Schifano 2012, Yargiç and Alyanak Ozdemiroglu 2011, Filipetto et al. 2010, Grosshans et al. 2010). It is possible the high dose he was using contributed to his inability to withstand the withdrawal symptoms he experienced when he repeatedly attempted to discontinue its use. His symptoms at presentation—hypersomnia, anorexia, anergia, lack of attention and concentration, depressive mood, anhedonia, and anxiety—might have been due to his high-dose cocaine abuse during the previous month; however, according to the patient, the symptoms were present before using cocaine.

Upon presentation to our clinic, pregabalin was discontinued gradually, and bupropion and low-dose quetiapine were added to his current paroxetine treatment. It was thought that bupropion would be effective for the patient's mood symptoms during withdrawal from pregabalin, and would decrease craving via stabilizing dopaminergic neurotransmission in the striatum and nucleus accumbens (Stahl 2012). Following initial presentation, he was re-evaluated twice, during which time he reported that he was able to abstain from pregabalin without any withdrawal symptoms. He was unable to attend a relapse prevention group at our clinic because of work-related issues, but remained abstinent for the last one month.

After pregabalin became indicated for the treatment of generalized anxiety disorder, the number of investigations on its use

for treating other psychiatric disorders- especially substance dependence- increased. There are reports that it helps to relieve benzodiazepine withdrawal symptoms (Bobes et al. 2012, Oulis et al. 2008). In addition, a placebo-controlled study reported that pregabalin was superior to placebo for diminishing benzodiazepine withdrawal symptoms, although the difference was not significant (Hadley et al. 2012). A review on pregabalin's use in treating alcohol dependence reported that findings concerning its effectiveness at 150-450 mg for alcohol withdrawal syndrome are inconsistent, but that it may be effective for relapse prevention (Guglielmo et al. 2012).

Despite the promising reports on pregabalin use for treating substance dependence, 198 adverse events related to substance abuse and dependence, of which 16 were associated with pregabalin, occurred between 1980 and 2009 according to the Swedish National Register of Adverse Drug Reactions (SWEDIS). In most of these cases pregabalin was administered as single dose of 300-4200 mg. In 13 cases there was a history of psychotropic substance abuse; one patient emptied pregabalin capsules and snorted the contents, one patient dissolved the drug in water and injected it, and the others used it orally (Schwan et al. 2010).

The German Federal Institute for Drugs and Medical Devices (BfArM) reported that as of 6 September 2012 there were 44 case reports of pregabalin dependence and 11 case reports of pregabalin abuse. The doses used varied between 400 mg and 6000 mg. Of the 35 patients whose files could be accessed, 27 had a history of and 22 had current other psychotropic substance abuse/dependence (Gahr et al. 2013a).

In addition, a review of anecdotal reports in eight European countries from 203 web sites reported that abusers described pregabalin as an ideal psychotropic drug that can be used for recreational purposes, with euphoric and dissociative effects similar to those of alcohol/GHB and benzodiazepine. This review also reported that oral use of pregabalin was common, but that it was also used intravenously, rectally, and by snorting (Schifano et al. 2011).

Case reports show that the most marked effect reported by abusers of pregabalin is euphoria (Yargic and Alyanak Ozdemiroglu 2011, Grosshans et al. 2010, Schwan et al. 2010). The euphoric effect of pregabalin was reported by more patients (1%-10%), as compared to placebo (0.5%). It is thought that pregabalin's euphoric effect increases the risk of its abuse (Baldwin et al. 2013). The symptoms of pregabalin withdrawal include tremors, craving, anxiety, irritability, sleeplessness, nausea, headache, and diarrhea. In addition, psychomotor agitation, arterial hypertension, and tachycardia may occur (Gahr et al. 2013b, Carrus and Schifano 2012, Filippetto et al. 2010).

Conclusion

Pregabalin is a new generation antiepileptic that has been approved for treating such disorders as peripheral neuropathic pain, generalized anxiety disorder, and fibromyalgia. Due to its mechanism of action, it is a promising drug for the treatment of other psychiatric disorders; however, its potential to cause dependence should be kept in mind when clinicians prescribe it, especially to patients with history of substance abuse.

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