

Pregabalin Addiction in a Case with Synthetic Cannabinoid Use

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ABSTRACT

Pregabalin addiction in a case with synthetic cannabinoid use

Pregabalin is a gamma-aminobutyric acid (GABA) analog that is approved for the treatment of neuropathic pain and partial-onset seizures. Pregabalin selectively binds to the alpha 2 delta subunit of voltage-gated calcium channels. Thus, the release of excitatory neuro-transmitters are inhibited and neuronal GABA levels are increased. Pregabalin has also been approved in the European Union for treatment of Generalized Anxiety Disorder. The anxiolytic effects of pregabalin are similar to the benzodiazepines and occur rapidly after administration. However, the Food and Drug Administration in the USA (FDA) and European Medicines Agency (EMA) have included pregabalin in the "Schedule V Controlled Substances". This means that just like the benzodiazepines, pregabalin is considered to be a drug with a low potential for abuse.

Keywords: Addiction, pregabalin, substance abuse

ÖZET

Sentetik kannabinoid kullanımı olan bir olguda pregabalin bağımlılığı

Pregabalin nöropatik ağrı ve parsiyel nöbetlerin tedavisi için onaylanmış bir gama-aminobutirik asit (GABA) analogudur. Pregabalin seçici voltajda duyarlı kalsiyum kanallarının alfa 2 delta alt ünitesine bağlanır. Böylece eksitator nöro-transmitter salınımını inhibe ederken nöronal GABA düzeylerini artırır. Pregabalinin aynı zamanda Yaygın Anksiyete Bozukluğu'nun tedavisinde kullanımı Avrupa İlaç Komisyonu tarafından onaylanmıştır. Pregabalinin anksiyolitik etkisi benzodiazepinlerin etkisine benzer ve uygulamadan sonra hızla ortaya çıkar. Ancak, Amerika Gıda ve İlaç Dairesi (FDA) ile Avrupa Tıbbi Ürünler Ajansı (EMA) tarafından "Kontrollü Kullanılması Gereken Maddeler V" listesine alınmıştır. Bu, pregabalinin benzodiazepinler gibi kötüye kullanılma potansiyeli düşük olan ilaçlar arasında kabul edildiği anlamına gelmektedir.

Anahtar kelimeler: Bağımlılık, pregabalin, madde kötüye kullanımı

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Date of receipt / Geliş tarihi:
January 2, 2016 / 2 Ocak 2016

Date of the first revision letter /
İlk düzeltme öneri tarihi:
February 26, 2016 / 26 Şubat 2016

Date of acceptance / Kabul tarihi:
March 28, 2016 / 28 Mart 2016

INTRODUCTION

Pregabalin is a gamma-aminobutyric acid (GABA) analog anticonvulsant discovered at Northwestern University with great hope as an antiepileptic drug but later on it was found out that it is effective only on partial seizures (1). Although the mechanism of action is not fully understood, it affects the excitatory neuronal conduction by binding to the $\alpha 2-\delta$ subunit of voltage-sensitive calcium channels (2). Thus, the release of excitatory neuro-transmitters is inhibited and neuronal GABA levels are increased. Analgesic (3-6) and anxiolytic effects (7,8) have been shown to occur by reducing the release of neurotransmitters such as glutamate, noradrenalin, and substance P.

In the United States of America (USA), its use in diabetic peripheral neuropathy, neuropathic pain

associated with fibromyalgia and, postherpetic neuralgia was approved by the Food and Drug Administration (FDA) in 2005 (9). In 2006, the European Medicines Agency (EMA) approved it to be used in the treatment of generalized anxiety disorder (10). It is used at a dose of 150-600mg/day in peripheral neuropathic pain, general anxiety disorder, fibromyalgia, and in the treatment of adult patients with partial epilepsy, with the approval of the Ministry of Health in Turkey. However, there are case reports stating that pregabalin has potential for abuse and causes addiction (11-15). In this article, we present a patient who referred to outpatient clinic of the Research, Treatment and Training Center for Alcohol and Substance Dependence (AMATEM) with withdrawal symptoms following the use of pregabalin for a long time at high doses and at the same time, using synthetic cannabinoid intermittently.

CASE

Our case is a 34-year-old male, married, healthcare worker as an operating room technician. He referred to AMATEM with complaints of anxiety, tension, fatigue, weakness and sleep disturbances. He reported that he had been taking 4800mg/day pregabalin (32 tabletsx150mg) until a few days ago. Two years ago, the patient's wife, who had familial mediterranean fever (FMF), was prescribed pregabalin for the analgesic effect; and when she said that the drug made her joyous, the husband began to take the medication as well. Just a while before starting pregabalin, the patient had been using synthetic cannabinoid intermittently for about four years and been sentenced to probation for having been caught with a synthetic cannabinoid. In the past two years, due to its euphoric effects euphoric effect he has taken pregabalin, a legally prescribed drug, instead of cannabinoid. The patient, who describes himself as introverted and anxious, has been more active and talkative, and realized that the level of anxiety decreased when he used pregabalin, and he continued taking pregabalin because of these effects.

The patient had physicians admitted different specialties to get pregabalin prescription by stating that he had a low back pain. When it became to difficult to obtain the medication at higher doses due to the tolerance development, he admitted to a psychiatrist for treatment. The patient was prescribed antidepressant medication and he has not taken pregabalin for three days, thereafter severe withdrawal symptoms such as, vomiting, sweating, restlessness, tachycardia and agitation appeared; his wife took him to emergency service and he was referred to Bakirkoy AMATEM by the emergency physician.

At the first visit, decreased attention and concentration, depressed mood, anhedonia, anxiety, agitation, fatigue, weakness and sleep disturbance were noted. The speech was tangential. He had intense thought about how to get pregabalin. Routine laboratory examinations showed no pathological findings. According to DSM-5, the patient was diagnosed with other substance use disorder

(pregabalin) and depressive disorder caused by other substance (pregabalin). Benzodiazepine 15mg/day was started for withdrawal symptoms and decreased by dosing schedule. Bupropion 150mg/day, carbamazepine 400mg/day treatment were added because of the effect of reducing craving during withdrawal. When cannabis metabolite was detected in the urine at the follow up one week after, he told that he felt so uncomfortable enough to cry and he once used cannabis to cope with this feeling. Bupropion dose was increased to 300mg. The patient did not come for the follow up appointments.

DISCUSSION

In this article, we report a healthcare worker with synthetic cannabinoid abuse and having been sentenced to probation for possessing and using substance, later on being dependent of pregabalin upon noticing its anxiolytic and euphoric effects.

The use of pregabalin in psychiatry is not limited to the treatment of anxiety disorders. In particular, studies are being carried out in relation to its use in addiction treatment. In the treatment of benzodiazepine withdrawal syndrome, pregabalin has been shown to be superior to placebo even though it was not statistically significant (16,17). A report of 14 cases with long-term use of benzodiazepines at an average of 15 years, neurophysiological symptoms showed improvement in the 2-month follow-up period after benzodiazepine was discontinued (18). In a review article on clinical studies published between 2000 and 2012 regarding pregabalin therapy in alcohol dependence, pregabalin was reported to be effective in the prevention of relapse when used at 150-450mg/day (19).

A significant number of case reports of pregabalin dependency refer to the fact that users have previously had at least one substance or drug abuse (12,14,20,21). In a study, 12.1% of 124 patients with opiate dependence were found to be pregabalin positive in urine test, and none of these patients reported using pregabalin because of medical indications (22). The common features of the cases in the literature are: pregabalin is used at much higher doses than treatment

doses; even though there have been uses via intravenous or rectal routes, most of the cases take orally; the effect occurs within 10 minutes to 2 hours; tolerance and withdrawal develops very rapidly (23,24).

The most pronounced effect expressed by pregabalin users is euphoria. The literature suggests that although pregabalin abuse could be related with its euphoric effects euphoric effect, this effect is weak and can take place after a long time; it is emphasized that the reward effect is important in those with a history of substance use (11,14,25). The present case is similar to previous cases with the history of synthetic cannabinoid use and taking pregabalin for the euphoric effect. Our patient was admitted to the psychiatrist for the first time because of pregebalin withdrawal and he has not had any diagnosis of anxiety disorder before, but he stated that his level of anxiety was always high and it was considered that he continued to pregabalin abuse because of the anxiolytic effect. Having a four-year substance abuse history, the subject headed towards pregabalin to suppress the increased anxiety during the period when he had to quit the substance because of legal problems.

An article reported the potential toxic effects of pregabalin from 10 cases who were observed at an emergency service in the United Kingdom for a year because of taking pregabalin at doses as high as 500-1400mg just for fun. Intubation and ventilation were required in 2 patients while seizures were observed in 6 patients (26). GABAergic effect and stimulant properties of pregabalin are considered to play a role in

the abuse of the drug (27). In the light of the reports in the literature, pregabalin has been included in the "Schedule V Controlled Substances" by the FDA in the USA and the EMA (28). Taking into consideration the increasing case reports, new regulations could be suggested on pregabalin, which is still a regular prescription drug in our country.

The publications that draw attention to the addictive effect of pregabalin emphasize the fact that there has been another drug or substance dependency in the history of these cases. The presented case had a history of synthetic cannabinoid use, he also used once in the treatment period and cannabis was positive in his urine analysis. In this article, the addiction measures such as craving for the drug because of the euphoric effect, development of tolerance and, onset of withdrawal symptoms, are emphasized and it is suggested to investigate substance use history of the patients before prescribing pregabalin.

Contribution Categories	Name of Author
Follow up of the case	G.K.
Literature review	G.K.
Manuscript writing	G.K.
Manuscript review and revision	G.K.

Conflict of Interest: Author declared no conflict of interest.

Financial Disclosure: Author declared no financial support.

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