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ABUSE AND ADDICTION OF GABAPENTINOIDS VERSUS TREATMENT: TWO SHARP KNIFE EDGES

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ABSTRACT

Gabapentinoids (pregabalin, and gabapentin) are being used in a wide range of disorders effectively, and they are also known as euphoric drugs, and their usages are increasing day by day. However, we don't know their potentials of abuse or addiction, exactly. Here we tried to find an answer to this question by a brief, case-based, review of the literature. In this study, a 32 years old male prisoner using over dose pregabalin, and who complains of withdrawal symptoms was reported. The patient had started to hoard the pills, and had increased the number of pills (1200-1500 mg/day) that he took in unique dose. He had withdrawal symptoms like sweating, dither, bellyache, nausea, headache, nervousness, insomnia, nightmare, restlessness, and xerostomia when he didn't take the pills. A PubMed search was performed for studies relating to usage of gabapentinoids from 2005 to 2014. Relevant references from these studies were also retrieved. As well as the studies in the literature that are reporting no addiction or abuse of gabapentinoids, there are some studies stating the potential risk of abuse and addiction of gabapentinoids. Eventhough gabapentinoids seem effective in the treatment of addiction as well as the neuropathic pain, and the fibromyalgia; we have to keep in mind the potential risk of abuse and addiction of these drugs.

Key words: Pregabalin, Gabapentin, Abuse, Addiction.

INTRODUCTION

Pregabalin is an anticonvulsive drug which effects by binding to the α2δ subunit of the voltage-gated calcium channel on neurons, and 95% excreted unchanged in the urine. Gabapentin is an anticonvulsive drug which effects by modulating the N-type calcium channels, and 100% excreted unchanged in the urine [1-3]. By releasing calcium from the nerve endings of hyperexcited neurons they decrease the release of various excitatory neurotransmitters like glutamate, norepinephrin and substance P [3-7]. Furthermore, gabapentinoids are thought to possess GABA-mimetic properties whilst possibly presenting with direct, and indirect effects on the dopaminergic 'reward' system [8,9], may be associated with drugs' addictive liability levels [10]. Euphoric side effect was reported in 1-10% of the patients medicated with gabapentinoids [11]. At dosages exceeding the therapeutic dosages, gabapentinoids seem to have both sedative effects as well as dissociative effects [12,13]. Binding affinity of pregabalin to the α2δ subunit, and potency, are six times more than that of gabapentin [14]. Irrespective of the dosage, bioavailability of pregabalin remains at >90 % as the dosage increases, where the bioavailability of gabapentin drops from 60 to 33 % as the dosage increases from 900 to 3,600 mg/day [1]. This can be explicated as the higher therapeutic efficacy of pregabalin than gabapentin [15], but may also show the reason why the drug misusers accept pregabalin more powerful [12,13,16]. Pregabalin does not effect on GABA receptors and does not change the uptake or the catabolism of GABA [17,18]. Both drugs don't bind plasma proteins, and don't interact with liver enzymes or other drugs [19]. Most known side effects of gabapentin are somnolence,

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dizziness, ataxia, fatigue, nystagmus, gaining weight, and behaviour disorders in childhood. For pregabalin these are transient increase of liver enzymes, somnolence, fatigue, giddiness and gaining weight [20].

Primary indications for these drugs are focal, and secondary generalized epilepsy [20-23]. Primary usage fields are epilepsy, and neuropathic pain, but the usage for the treatment of addiction of alcohol, and benzodiazepine must be kept in mind [24]. Also, because of the central mechanisms in the etiopathogenesis of fibromyalgia, which is a common cause of chronic pain, central drugs like anticonvulsives were thought to be effective in fibromyalgia. In 2004, pregabalin was approved in Europe for the treatment of peripheric neuropathic pain, and combination treatment of the partial onset epilepsy, and it was approved in USA for the treatment of neuropathic pain related to diabetic polyneuropathy. In 2005, pregabalin was approved for the treatment of partial onset epilepsy in adults. Also, pregabalin is the first agent which was approved by FDA for the treatment of fibromyalgia syndrome [25]. There is also randomized placebo controlled study in the literature, evaluating the gabapentin treatment in fibromyalgia [26]. However, these drugs are also often prescribed off-label for a range of clinical conditions, including bipolar disorder, alcohol/narcotic withdrawal states, attention deficit/hyperactivity disorder, restless legs' syndrome, trigeminal neuralgia, and non-neuropathic pain disorders [27].

Pain emerges by the combination of various subjective and unknown factors. Accordingly, pain is the reflection of a reaction or a symptom, associated with an organic disorder or associated with a psychological stress. Pain can affect emotional status, and the character, and can cause changes at the level of carefulness [28]. Gabapentin and pregabalin are eligible agents for the treatment of neuropathic pain, and frequently they are preferred to use in painful conditions of patients with diabetic polyneuropathy [28]. Incidence of the neuropathic pain is about 1% in developed countries. Primary lesion of the peripheric nerves, dorsal root ganglions, and central nervous system that affects the sensory fibers or the functional disorders of nervous system cause neuropathic pain. Most frequent examples of the neuropathic pain encountered in the clinic are postherpetic neuralgia, diabetic neuropathy, posttraumatic neuralgia, and central poststroke pain. Common symptoms of the neuropathic pain are spontaneous pain, allodinia, hiperalgesia, and paresthesia in the painful area [29].

Pregabalin has been reported within the 30 most prescribed medications in the USA in 2011 [13,30]. Graphic 1 shows the increasing usage of pregabalin, and gabapentin, and the Graphic 2 shows the increasing cost of these drugs (This data was obtained by the investigation of commercial records of drug markets in USA, and Europe).

PATIENT AND METHODS

Accordance with the requirements of ethical standards (Helsinki Declaration), a 32 years old male using over dose pregabalin, and who complains of withdrawal symptoms was reported in this study. He was a prisoner, and he was in penitentiary for about 6 years. Before his penalty, he had had a crush injury, and he had been operated for the C3 fracture with instrumentation. After this surgical intervention, pregabalin 300 mg/day had been started for the treatment of neuropathic pain in his upper limbs that he suffered from. He stated that, by the time he had started to hoard the pills, and take more than 2 pills in unique dose. Also he stated that, he had realised both the euphoric effect of the medication when he took the pills, and the withdrawal symptoms like sweating, dither, bellyache, nausea, headache, nervousness, insomnia, nightmare, restlessness, and xerostomia when he didn't take the pills. By the years he had increased the number of pills (1200-1500 mg/day) that he took in unique dose. There were no toxic side effects. When he couldn't attain the medication he had used violence to gaolers, other prisoners, physicians, and especially himself. In physical examination, we found no weakness of muscle strength, there was hypoesthesia in C6 dermatome, and tendon reflex was normal. He stated that he was consuming alcohol before his penalty, but he wasn't an alcohol addict or narcotic addict. An antipsychotic therapy was started in psychiatry clinic.

Based on this case, a PubMed search was performed for studies relating to abuse, and addiction of gabapentinoids from 2005 to 2014. Relevant references from these studies were also retrieved. No filters were applied to limit the retrieval by study type.

Figure 1. Sale amount (pillbox) of pregabalin, and gabapentin in USA, and Europe drug market from 2011 to 2014.

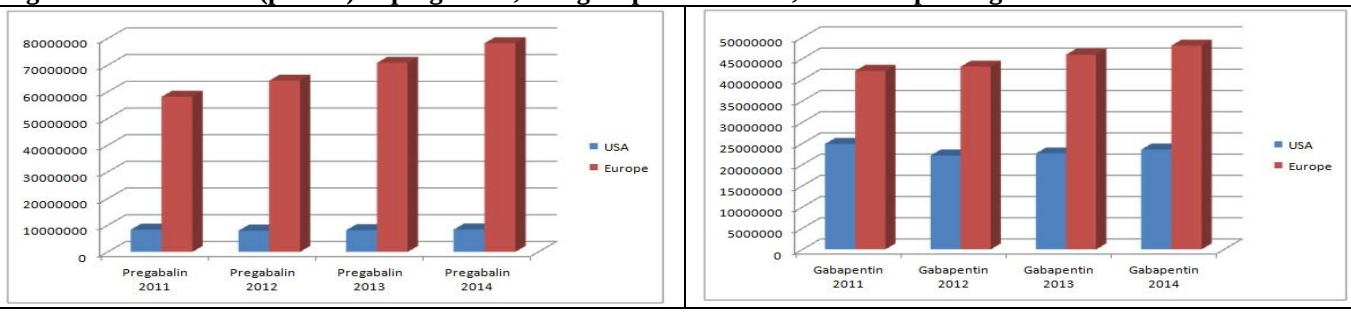
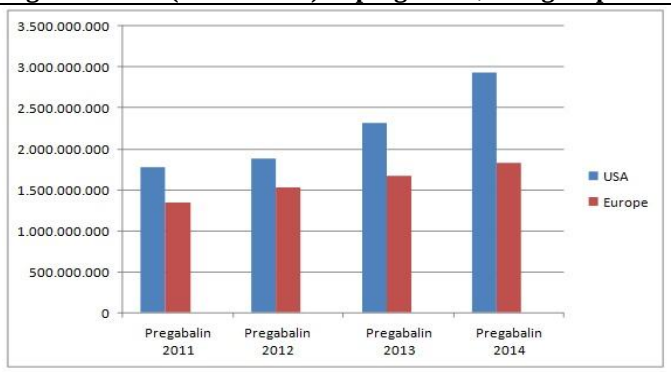
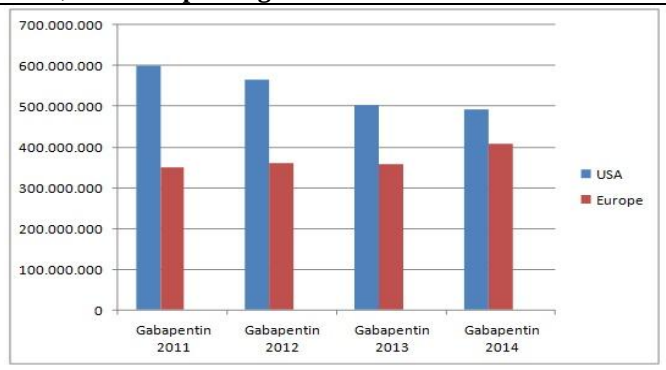


Figure 2. Cost (USA Dollar) of pregabalin, and gabapentin in USA, and Europe drug market from 2011 to 2014.





DISCUSSION

Addiction is a chronic neurobiological disease which includes genetic, psychosocial, and environmental factors. Characteristics of addiction are: using the substance off-label; gaining tolerance to that substance; incremental usage amount; despite the deteriorated daily living, continuing to take that substance; and by the decrease of usage amount or stop the usage, possessing withdrawal symptoms. Common characteristic of these substances is reinforcement effect on taking the substance again. Effects on the central 'reward' system cause the euphoric effect, and reinforcement effect on taking the substance again, and this condition is associated with drugs' addictive liability levels. Addicts continue to take the drugs as a compulsive behaviour, despite the negativeness in their lives. It is known that anticonvulsives are being used widely in the treatment of alcohol dependence for reducing the withdrawal symptoms, and epileptic seizures [31]. Also, it is reported that in patients with bipolar disorders, valproate, and lamotrigine decrease the desire, and consumption of alcohol [31-33]. Probably, GABA, and gabapentinoids will be in use for the treatment of alcohol dependence, especially for reducing the withdrawal symptoms [34,35]. In some studies, it is expressed that pregabalin does not interact with other drugs, and does not have tolerance or abuse risks [36]; however, Grosshans et al. [37] reported the first addiction case of pregabalin in a patient using pregabalin for alcohol dependence, in 2010.

Gabapentinoids are widely used in physical therapy, neurology, and psychiatry but are increasingly being reported as having potential risk of abuse. In USA, trend of gabapentinoid prescription is shifting from gabapentin to pregabalin. But in Europe, both the gabapentin, and the pregabalin prescriptions increase (See Graphic 1, and 2.). Beside the increasing level of prescriptions, black market is growing very fast, and gabapentinoids seem available without prescriptions through online in many countries [12,13]. In line with this, gabapentinoids first emerged in the UK mortality databases in 2006, and most gabapentinoid victims were not being prescribed in UK, as well as USA, France, and Finland [13,38-41]. Gabapentinoid users possess a medical history of polydrug abuse, who self-administer the drug with exceeded doses (three to twenty times more than the clinically advisable dose). Schwan et al. [11] reported the addictive liability levels of pregabalin to be low. Bode´n et al. [42] found the amount of patients who exceeded the advisable dose as 8.5 %, and 31 % of these patients had medical history of drug abuse. Kapil et al. [43] reported the prevalence of gabapentin abuse 1.1 %, and pregabalin abuse 0.8 %, where the prevalence of cocaine use was 8.1 %, and cannabis use was 28.1 %. In Germany, pregabalin was detected in 12.1 % of urine samples from opiate-addicted patients with no indication for pregabalin prescribing [30]. Similarly, Baird et al. [44] investigated the data from Scottish substance misuse clinics, and found the amount of patients who abuse gabapentinoids as 22 %. Similar to our case, in England pregabalin is widely used in prisons, and is in some cases being preferred to heroin [16]. Associated experiences with gabapentin abuse are: euphoric effect; improved sociability; marijuana-like 'high'/ relaxation, 'zombie-like' effects, sedative/'opiate buzz', and psychedelic/3,4-methylenedioxy-N-methyl amphetamine-like effects [12,13,45]. Abuse of pregabalin, up to 20 times higher dose than the maximal dosage indicated [46], mostly taken orally. Also, other reported self-administration techniques are intravenous, rectal ('plugging'), smoking, and 'parachuting' (emptying the content of the capsule into a pouch) techniques [12,13].

Withdrawal symptoms like restlessness, insomnia, and nervousness occur when the addict didn't take the medication, and in our patient these symptoms showed the potential risk of addiction as well as the risk of abuse. Rapidly decreased usage amount of pregabalin is associated with withdrawal symptoms [12,13]. But pregabalin, at clinically advisable dose, possesses beneficial effects for reducing alcohol withdrawal symptoms [47]. Additionally, pregabalin has been shown beneficial for the cocaine relapse [48], withdrawal symptoms of both benzodiazepine [49], and opiate [50]. Similarly, gabapentin has been indicated for the management of some addictions including opiates [51], cannabis [52], and alcohol [53]. According to literature, potential of abuse or addiction of gabapentinoids

seems low in patients without medical history of addiction or abuse of other substances, and medicated at therapeutic doses [15,54]. Contrary to this opinion, we have to keep in mind the reward pathways [8].

CONCLUSION

Even though gabapentinoids seem effective in the treatment of addiction as well as the neuropathic pain, and the fibromyalgia, we have to keep in mind the potential risk of abuse and addiction of these drugs. Tight control of the patients using these medications is needed.

Physicians considering prescribing gabapentinoids for various disorders should carefully evaluate the patients for a possible previous medical history of drug abuse, and try to identify symptoms of gabapentinoid abuse or addiction promptly.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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