

# Pregabalin abuse and toxicity and related factors

Walla Alelwani<sup>1</sup>, Abrar Alkhazindar<sup>2\*</sup>, Basmah Alqumaysh<sup>2</sup>, Dina Kutbi<sup>2</sup>, Raghad Tayeb<sup>2</sup> and Reem Altobaiqi<sup>2</sup>

<sup>1</sup>Department of Biochemistry, Collage of Science, University of Jeddah, Jeddah, Saudi Arabia.

<sup>2</sup>College of Applied Medical Science, University of Jeddah, Jeddah, Saudi Arabia.

Accepted 5 March, 2021

---

## ABSTRACT

Pregabalin is one of a group of gabapentinoids approved by the Food and Drug Administration (FDA) in 2004. It is a capsule medication taken by mouth that is used for the treatment of neuropathic pain. It is a structural analogue of the neurotransmitter gamma-aminobutyric acid (GABA), and it appears to have a spectrum of benefits and harms similar to those of other adjuvant analgesics used to treat neuropathic pain. The most common side effects mentioned in peripheral neuropathy studies are dizziness and somnolence. Pregabalin could cause liver toxicity by increasing the levels of liver enzymes. It can potentially cause vasodilatation and fluid retention in the heart and blood vessels. It may also lead to addiction. The use of Pregabalin is common among patients with a history of substance abuse and psychoactive drug dependence, as euphoria is one of its main side effects. However, abrupt discontinuation from using Pregabalin may cause nausea, insomnia, or headache. The present review evaluates the significant impact of Pregabalin toxicity on liver and heart in patients and misusers.

**Keywords:** Pregabalin, liver toxicity, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), heart failure, addiction.

---

\*Corresponding author. E-mail: Abrar.Alkhazindar@hotmail.com. Tel: +966 597301145.

---

## INTRODUCTION

Pregabalin is one of a group of gabapentinoid or antiepileptic drugs approved by the Food and Drug Administration (FDA) for neuropathic pain in 2004 (Halaby et al., 2015), as it has a strong structural similarity to Gabapentin. It is a lipophilic analogue of gamma-aminobutyric acid (GABA). It is a capsule medication taken by mouth that is used as a treatment for neuropathic pain, conditions such as diabetic peripheral neuropathy, post-herpetic neuralgia (PHN), and anxiety disorder, and it is also used as a second line in the management of partial seizures. When used before surgery, it improves pain but results in greater sedation and visual disturbances (Olaizola et al., 2006; Mishriky et al., 2015).

Pregabalin is usually a well-tolerated medication with no contraindications; however, it must not be given to any patient known to have hypersensitivity to Pregabalin or its components. The most common side effects mentioned in peripheral neuropathy studies are dizziness (22 to 38%) and somnolence (11 to 25%), which did not resolve in about one-third of patients. Side effects that appear

later carry a potential risk of accidental injury in the elderly. Other reported adverse effects include dry mouth, blurred vision, asthenia, peripheral edema, ataxia, and weight gain other than edema. These adverse effects are usually mild to moderate. There are limited data suggesting a withdrawal effect of the drug of the drug after long-term use, while abrupt discontinuation may cause nausea, insomnia, headache, or diarrhea, so it is recommended to taper off the dose during the treatment (Finnerup, 2008).

Prescribed drug abuse is an increasing issue, as 18 million Americans have used the prescribed medicine for non-treatment purposes (Center for Behavioral Health Statistics and Quality, 2018). High death rates have resulted from this, especially with opioid analgesics, but also with Gabapentin and Pregabalin (Young et al., 2016).

In a meta-analysis of Pregabalin's adverse effects based on 38 clinical trials, euphoria was reported in about 5% of patients; while in a study implemented by Grosshans found that the use of Pregabalin was common

among opioid-addicted patients (Young et al., 2016). A specific regulatory warning on the abuse potential of Pregabalin was issued by the European Summary of Product Characteristics as follows: "Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of Pregabalin misuse, abuse or dependence" (Bastiaens et al., 2016). On May 31, 2015, the Saudi Food and Drug Authority (SFDA) announced new regulations and restrictions related to Pregabalin-containing drugs in the country as a way to decrease its abuse rates. For example, it limited Pregabalin availability in pharmacies so it could only be found in hospitals or prescribed by registered physicians or consultants. It also required a record for all products containing Pregabalin to be kept in pharmacy and distributors. Later, on February 18<sup>th</sup>, 2018, the SFDA added Pregabalin to the updated list of controlled and narcotic medications in Saudi Arabia (Finnerup, 2008).

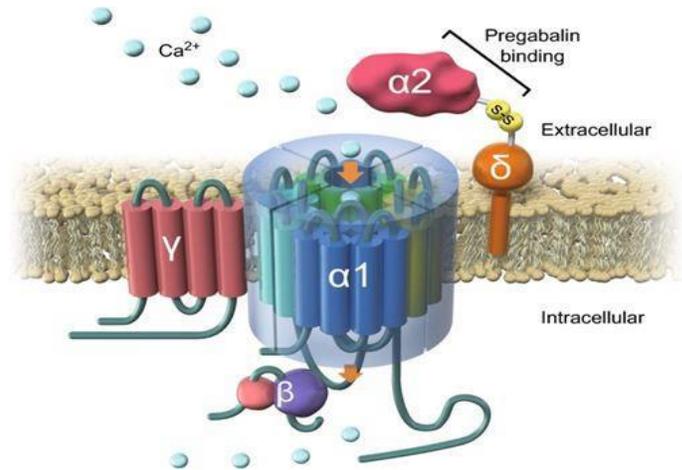
## PHARMACOLOGY OF PREGABALIN

### Mechanism of action

Pregabalin's mechanism of action has not been exactly determined, however, it interacts with the same binding site as Gabapentin (1-cyclohexane acetic acid) (Kumar et al., 2010; Rose and Kam, 2002). The main acting site is the 2-subunit of the pre-synaptic, voltage-dependent calcium channels (Figure 1) that are widely distributed throughout the peripheral and central nervous systems (Arikkath and Campbell, 2003). It is six times more potent in its binding affinity to the 2<sup>δ</sup> subunit than Gabapentin. This subunit may play an important role in hypersensitization processes (Li et al., 2004). Pregabalin produces an inhibitory modulation of neuronal excitability, especially in synaptic connection-dense areas of the central nervous system, such as the neocortex, amygdala, and hippocampus (McClelland et al., 2004). Ectopic activity is reduced, while the normal nervous function is unchanged (Chen et al., 2001). Pregabalin is well-absorbed, with a bioavailability of greater than 90% and a peak serum concentration in 1 h independent of dose (Randinitis et al., 2003).

### Dosage and administration

Therapeutic doses of pregabalin begin at 50 mg three times per day (150 mg/day) and can be increased up to 300 mg/day; however, the recommended dose for painful diabetic neuropathy is 100mg three times per day as a maximum. There are no significant benefits of increasing the dose more, according to studies, but side-effects, which are dose-dependent, do increase. The dose needs to be adjusted in renal impairment cases because



**Figure 1.** Structure of the voltage-gated L-type calcium channel (Ninomiya et al., 2020).

Pregabalin's primary excretory site is kidney.

In the case of post-herpetic neuralgia (PHN), Pregabalin dosage begins at 75 mg two times daily or 50mg three times daily and can be increased to reach 300 mg/day within one week, depending on the tolerability and efficacy. If the treatment is tolerated by a patient but the pain is not resolved completely, its dose can be increased up to 300 mg twice a day or 200 mg three times a day (600 mg/day) (Finnerup, 2008).

### Pregabalin overdose

In post-marketing research, fatalities have been reported when Pregabalin was combined with other medications in doses as low as 800 mg a day. None of these cases caused by Pregabalin monotherapy, and the lowest fatal dose of Pregabalin has yet been identified. The most commonly reported features of Pregabalin overdose (doses beginning at 800 mg/day up to 11,500 mg as a single dose) include affective disorder, somnolence, depression, agitation, confusion, and restlessness. Seizures have also been reported (APO-PREGABALIN Product Monograph, 2017).

The first reported case of Pregabalin dependence was in a 26-year-old woman who had a withdrawal symptom upon stopping the drug; she developed a tolerance to the anxiolytic effect, leading to an increase in the drug dosage (Halaby et al., 2015). She was abusing Pregabalin at a daily dose of approximately 1500 to 2400 mg over the previous four months. She was treated first with fluoxetine and quetiapine and then by venlafaxine and lithium carbonate. After six weeks, her craving for Pregabalin subsided, and she resumed working without anxiety symptoms (Halaby et al., 2015).

Two other cases were reported in 2011 in teenagers. A 16-year-old boy ingested nine tablets of pregabalin 300

mg while attempting to "get high" with a friend (Reedy and Schwartz, 2010). He developed generalized tonic-clonic seizure activity one hour later. He was admitted to the hospital for observation and was discharged the following day. In the other case, a 17-year-old boy who had ingested an unknown amount of Pregabalin, developed generalized tonic-clonic seizures. He was admitted for neurological observation following a second seizure. His plasma Pregabalin level was 43 µg/ml, and a urinary drug screen was positive for tetrahydrocannabinol (Reedy and Schwartz, 2010).

## TOXIC EFFECTS OF PREGABALIN

### Liver toxicity

In Latin America, the first case of idiopathic Pregabalin-induced toxicity was reported in a patient with radicular pain secondary to lumbar spinal stenosis who presented with jaundice and elevation of liver enzymes associated with the use of Pregabalin. A diagnosis of drug-induced liver injury was made. Liver function was normalized once the drug was discontinued without any complications. It is important to be aware of the potential hepatic toxic effects of Pregabalin. Liver injury mostly resolves upon pregabalin discontinuation (Quintero-Castellanos, 2017; Dogan, 2011).

Data on Pregabalin hepatotoxicity is limited. During the clinical trials of Pregabalin (before its final approval) on diabetic neuropathy and epilepsy patients, therapy with Pregabalin was not associated with an increase of serum aminotransferase or liver toxicity. Since its approval and increased use, Pregabalin has been linked to rare cases of liver injury. Cases were mostly mild and without jaundice. The onset latency of injury was short, and symptoms of liver injury appeared within 3 to 14 days (U.S. National Library of Medicine et al., 2018). Table 1 reviews some reported cases of hepatotoxicity.

### Cardiac toxicity

Pregabalin can potentially cause vasodilatation and fluid retention by inhibiting the  $\alpha_2\text{-}\delta$  subunit in the heart and blood vessels. Complete atrioventricular blockage has also been reported due to Pregabalin overdose, which suggests its inhibitory effects on L-type calcium channels of myocardium. The American Heart Association (AHA) recommends the use of Pregabalin with caution in patients that have heart failure class III to IV due to the risk of peripheral edema and heart failure exacerbation (Aksakal et al., 2012).

According to controlled trials among patients, the mean changes of creatine kinase (CK) were 60 U/l for Pregabalin-treated patients and 28 U/l for patients on placebo. Three times the upper normal limit of CK and

above was observed in 1.5% of patients on Pregabalin and 0.7% of placebo patients. Three individuals treated with Pregabalin developed rhabdomyolysis in premarketing clinical trials. The relation between Pregabalin and myopathy events is not completely understood due to the focus on documenting the factors that may be contributing to these events (Kaufman and Choy, 2012).

Post-marketing surveillance has noted an increasing number of reports of heart failure in patients using Pregabalin. A systematic review of randomized controlled trials involving Pregabalin found a fourfold increased incidence of peripheral edema, which may be associated with heart failure. The risk of edema or heart failure might be higher since these trials included patients who were healthier and more closely monitored than the general population. Furthermore, individuals for whom Pregabalin is often prescribed, such as diabetic patients, tend to have renal or cardiac disease, which are known risk factors for heart failure (Ho et al., 2013). Three patients reported with known chronic heart failure and left ventricular systolic dysfunction who had an exacerbation of heart failure after starting Pregabalin for neuropathic pain (Murphy et al., 2007). The detailed conditions of these three patients are explained in Table 2.

### Pregabalin abuse effect

Since 2008, numerous but unspecified cases of Pregabalin abuse have been reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), mainly via Scandinavian, British, French and German pharmacovigilance systems, with vast majority describing patients being currently or previously dependent on other substances (Bonnet et al., 2018). This association was supported by the latest analysis of the EudraVigilance database, which included spontaneous reports from Europe, North and South America, and East Asia (Chiappini and Schifano, 2016). Most of these cases presenting behavioral dependence symptoms on Pregabalin had a positive addiction history with traditional psychoactive drugs, mostly alcohol, benzodiazepines, and opioids. There were a few case reports of dependence with no positive addiction history; these cases may reflect the abuse potential of Pregabalin (Ashwini et al., 2015; Halaby et al., 2015; Driot et al., 2016; Al-Husseini et al., 2018). Amplification of a desired opioid high and relief of anxiety symptoms during opiate withdrawal were strong factors in promoting this misuse (Bastiaens et al., 2016; Wilens et al., 2015; Baird et al., 2014). Notably, there are two case reports of psychiatric patients without a history of another substance use disorder who self-administered Pregabalin in large supratherapeutic amounts (1500 to 3000 mg/day) to stimulate themselves and produce euphoria (Ashwini et al., 2015; Halaby et al., 2015).

**Table 1.** Pregabalin-induced hepatotoxicity review summary.

Author and title	Summary	ALT/AST reading changes	Finding
Manuel Quintero – Castellanos (2017)	53-year-old male with hypertension and Type II diabetes mellites who was an occasional user of alcoholic drinks. Patient admitted and diagnosed with severe acute lumbar pain lasting for 3 days. All lab results were within the normal values at the time of admission.	<b>ALT</b> value changed from 23.1 U/L to 1012.5 U/L. (43.8 times the first reading)	Based on the readings (ALT/AST: 1012.5/480), patient was diagnosed with drug-induced hepatitis, and Pregabalin was discontinued.
“Pregabalin-induced liver injury – Case report”	By the fourth day, Pregabalin 75mg was given to him twice daily. After eight days, the patient developed jaundice in the absence of any other associated causes. Pregabalin-induced liver injury was suggested and tests were performed again.	<b>AST</b> value changed from 10.4U/L to 480U/L. (46.1 times the first reading)	Two days after stopping Pregabalin, jaundice started to be resolved, AST/ALT readings dropped to 348.9/49.9, and liver function recovered to a normal condition.
Tolga Düzenli, Emre (2017)	78-year-old woman with chronic low back pain and no history or sign of liver problems or alcohol consumption planned to start Pregabalin 75mg twice daily. All blood tests were taken before Pregabalin administration and were within normal range.	No data available about ALT/AST readings before starting Pregabalin.	With the absence of any factor related to hepatic dysfunction, drug-induced liver dysfunction was suggested, and Pregabalin was stopped. Hepatic enzyme levels returned gradually (over three weeks) to normal levels.
“Pregabalin as a Rare Cause of Hepatotoxicity”	On her second day of Pregabalin, patient started to have severe fatigue and lab results showed high ALT/AST levels (12/14 times the normal range), which indicated liver damage.	After the third dose of Pregabalin, <b>ALT</b> : 701 U/L, and <b>AST</b> : 568 U/L,	
Doğan et al. (2011)	28-year-old woman with a history of acute disseminated encephalomyelitis on Pregabalin 150mg twice daily + glucocorticoid course of 1 g once for seven days with no history of smoking or alcohol.	On admission, <b>ALT/AST</b> results were 26 times the normal level ( <i>no specific number available</i> ).	Discontinuing Pregabalin therapy returned hepatic enzymes to normal ranges within two months.
“Pregabalin-induced hepatotoxicity”	After four months, she developed jaundice and was admitted to the hospital.		
Crespo et al. (2008)	61-year-old man who was hypertensive started Pregabalin 75 mg/day.	On day 11, <b>ALT</b> level was 307 U/L.	Discontinuing Pregabalin rapidly resolved all symptoms, except for mild fatigue.
“Cholestasis associated with pregabalin treatment”	Within two days, he developed dizziness, blurred vision, somnolence, and fatigue, which worsened when the dose was increased to 150mg/day one week later. On day 11, he revealed moderate enzyme elevations.	No data available about AST.	A few days later, Pregabalin was started once again. The abnormal enzyme values rapidly improved, but as symptoms returned immediately, Pregabalin was stopped again. The patient was normal two months later.
Sendra et al. (2011)	59-year-old man with mantle cell lymphoma developed neuropathic pain and started taking Pregabalin 25 mg daily.	<b>ALT</b> 907 U/L.	Pregabalin was discontinued and hepatic enzyme levels returned gradually (over 4 months) to baseline levels.
“Pregabalin-Induced Hepatotoxicity”	After 14 days elevations of liver enzyme levels occurred.	<b>AST</b> 1582 U/L.	

**Table 2.** Reported cases of chronic heart failure patients who developed complications after starting Pregabalin.

Patient profile	Recorded complications	Management strategy	Improvement progress
69-year-old man with ischemic cardiomyopathy, a documented 40% left ventricular ejection fraction, and stable heart failure status for six months.  He started Pregabalin for neuropathic pain related to diabetes.	Over the next four weeks, he became increasingly short of breath and noticed a weight gain.  On examination, he had raised jugular venous pressure, pitting ankle edema, and clear lung fields. His B-type natriuretic peptide (BNP) level increased to 611 pg/ml from a baseline of 293 pg/ml.	Discontinued Pregabalin and increased oral diuretic.	Three days later, he continued to be dyspneic and had developed paroxysmal nocturnal dyspnea. He was given a stat dose of intravenous frusemide 60 mg.  He developed strong symptomatic improvement and a 5.8 kg weight loss over the following days and remains well.
59-year-old man with nonischemic dilated cardiomyopathy and severe left ventricular systolic dysfunction. His heart failure status had been stable for one year.  He started Pregabalin for a peripheral neuropathy related to diabetes.	Over the next two months, he became increasingly dyspneic and noticed weight gain.  On examination, there were confirmatory signs of heart failure along with elevated jugular venous pressure, ankle edema, and bibasal lung crackles, with no significant change in BNP	Discontinued Pregabalin and increased oral diuretic.	He had an improvement in symptoms, a 3 kg weight loss, and resolution of all clinical signs of heart failure.
72-year-old man with a nonischemic cardiomyopathy, a 38% ejection fraction, and stable heart failure status for four months.  He started Pregabalin for paresthesia in his feet.	Over the next four weeks, his clinical status deteriorated. He developed symptoms of biventricular heart failure along with shortness of breath, fatigue, ankle edema, orthopnea, and paroxysmal nocturnal dyspnea, all associated with a significant weight gain.  On examination, his jugular venous pressure was raised. His BNP level increased significantly from a baseline of 461 pg/ml to 2110 pg/ml.	Discontinued Pregabalin and treated patient with intravenous diuretics and an increase in oral diuretics.	He had a good response, with improvement in symptoms, a weight loss of 5.8 kg, and a fall in BNP to 561 pg/ml over the next two weeks.

Source: Murphy et al. (2007).

To the best of our knowledge, one qualitative study on Pregabalin misuse has been conducted in the Middle East, and specifically, in Jordan in 2017 (Bastiaens et al., 2016). A total of 11 patients addicted to Pregabalin were interviewed. All were male patients aged 21 to 30 years. The majority (10 patients) were poly-drug abusers and had a previous history of substance abuse (tramadol, Captagon, synthetic cannabinoids, and marijuana) (Bastiaens et al., 2016).

Studies suggest that the sweet drinks activate the endogenous opioid system by inducing a release of  $\beta$ -endorphin and by increasing the binding affinity for opioids. A preference for stronger sweet solutions may represent a marker of alterations in brain systems that mediate rewarding responses to a variety of hedonic stimuli, including sucrose and alcohol (Kampov-Polevoy et al., 1997; Bonnet et al., 2018).

For reasons of methodology, the epidemiological

studies were primarily based on drug urine screenings, which have been found to be unsuitable for gabapentinoid use, even in supratherapeutic doses, and for true addictive behaviors or hazards induced by this usage (Bonnet et al., 2018). Additionally, lack of detection in urine screening facilitates abusers to continue on Pregabalin. The lack of detection might be due to the variability in urinary detection times of abused drugs, and differentiating new

drug use from residual drug excretion could be difficult, especially after repeated or chronic drug usage. In subjects with normal renal function, it seems highly unlikely that a urine specimen would remain positive for Pregabalin for more than 5 to 6 days after intake (Spigset and Westin, 2013).

Therefore, in patients having a prior history of substance abuse (principally for benzodiazepines) or

alcoholism, prescription of Pregabalin should be cautiously supervised by the clinician (Toth, 2014).

### ***Evaluating the addictive power of Pregabalin***

Table 3 compares the abuse potential and toxicity of Pregabalin with those of traditional psychoactive substances.

**Table 3.** Risk of dependence and hazards of Pregabalin and traditional psychoactive substances: a comparative appraisal (Bonnet et al., 2018).

<b>Characteristics/ Substance of abuse</b>	<b>Opiates</b>	<b>Alcohol</b>	<b>Benzodiazepines</b>	<b>Pregabalin</b>
Physical dependence (tolerance, withdrawal symptoms)	*****	****	****	***
Behavioral = psychological dependence (craving, loss of control, addictive behavior)	*****	*****	****	* (especially in patients with history of SUD)
Overall toxicity	***** (not in therapy)	****	****	*** (especially in the elderly or in overdose mixtures with opioids or sedatives)
Social hazards	*****	*****	****	Unknown

Abbreviations: SUD = Substance use disorder; - = no effects; \* = very weak effects; \*\* = weak effects; \*\*\* = moderate effects; \*\*\*\* = strong effects; \*\*\*\*\* = very strong effects.

## **WITHDRAWAL SYMPTOMS AND TREATMENT METHODS**

Withdrawal symptoms from abrupt discontinuation of Pregabalin include exhaustion, agitation, headache, depression, arthralgia, myalgia, shivering, lethargy, avoidance of social interaction, anxiety, confusion, GI distress, tachycardia, and palpitation. If weaning of Pregabalin fails, it will cause the following symptoms: sweating, restlessness, hypertension, tremor, and Pregabalin cravings. The larger the doses had been prior to abrupt quitting, the stronger the withdrawal syndrome. Benzodiazepines and clonidine help to reduce these withdrawal symptoms.

For clinical cases of acute Pregabalin withdrawal with the presence of hallucinatory features, benzodiazepines are not recommended due to the risks of paradoxical agitation. Instead, it is suggested that their use be withheld until the latter stages of withdrawal. Anticonvulsive protection could be used, as there are reports that seizures can occur during withdrawal treatment, even if seizures were not the reason for prescribing Pregabalin originally. Sleeping disorders could be eliminated by administering trazodone. All of the medications mentioned should be gradually reduced to

zero (Bonnet et al., 2018; Al-Husseini et al., 2018; Yazdi et al., 2015).

In a case conducted in 2006 with a patient with a long history of tranquilizer and alcohol dependency to suppress conditions of agitation and anxiety, he failed to respond to the detoxification treatments (for both alcohol and benzodiazepines) (Yazdi et al., 2015). The patient was first given Pregabalin in a daily dose of 300 mg to control his generalized anxiety disorder in 2012. The patient had an improvement of fear, mood, and agitation without further need for alcohol or benzodiazepines, but he soon began abusing Pregabalin by increasing the dose by himself to an average of 750 mg per day, with a daily intake up to 1050 mg in times of agitation. When Pregabalin was no longer available, he developed withdrawal symptoms, including severe tension and anxiety, which led to excessive drinking and benzodiazepine relapses. The patient lost control of his Pregabalin consumption. When the intake was gradually decreased by the inpatient clinic, withdrawal symptoms occurred. Benzodiazepines (oxazepam up to 60 mg/day) was used as a supportive medication, which helped reduce withdrawal symptoms. Anticonvulsive protection (levetiracetam in a daily dosage of 1,000 mg) was also given to prevent seizures. Sleeping disorder could be

eliminated by applying trazodone extended release 150 mg. All of the medications were gradually reduced to zero here as well. A year later, the patient continued to visit the outpatient clinic for regular check-ups with good health and no more addiction to Pregabalin (Yazdi et al., 2015).

According to Telles-Correia et al., Pregabalin does not inhibit human cytochrome P450 enzyme systems and does not metabolize by liver. Instead it depends mainly on renal excretion, and therefore it does not induce or reduce the level of hepatic enzymes (Telles-Correia et al., 2017). Moreover, Pregabalin was considered to have rare hepatotoxicity and to be of the safest medications for the liver. On a review on psychotropic drugs and liver disease (Telles-Correia et al., 2017), based on the case reports in Table 1, it was shown that Pregabalin-induced hepatic toxicity is an idiosyncratic reaction that could occur without any indication of hepatic toxicity.

In all cases, no one has been reported any hepatic problem, even when patients started to complain about symptoms. A full screening was performed to determine the exact cause of hepatic problems. Including a blood test, physical examination, and viral test and all the collected results were within the normal range; thus, Pregabalin-induced hepatotoxicity.

From a drug-drug interaction perspective, all medications used by the patient were checked by LexiComp Drug Interaction Analyzer, and the results were as follows: Amlodipine, Candesartan, Allopurinol, Losartan, Metformin, Vildagliptin, Metamizole, and Glucocorticoid showed no interactions that increased the level of the other medication. One study reported that when the patient received his first dose of Glucocorticoid, his ALT/AST levels increased slightly (125 and 68, respectively) and then returned back to normal (Doğan et al., 2011). It was concluded that drug-drug interaction was not a factor in causing this idiosyncratic reaction.

Additionally, from the perspective of drug-herb interactions all cases reported that there was no use of any herbal medication. For alcohol consumption, only one case reported being occasional user of alcoholic drinks, which could be affecting the liver through chronic use (Quintero-Castellanos, 2017). An interesting finding was that Pregabalins onset of action was considered to be dose-time depended; for example: in cases who received doses of 75mg twice daily, the onset of toxicity occurred within two to three days (Quintero-Castellanos, 2017; Tolga Düzenli et al., 2017; Doğan et al., 2011), while in patients who took 25 mg twice daily it occurred within 14 days (Sendra et al., 2011). The higher the doses, the more severe the symptoms.

Another interesting finding concerned the renal function of the patients. Pregabalin is known to be renally excreted, with half-life of 6.3 hours, according to LexiComp, and none of the cases reported the status of their renal functions at the time of toxicity (Crespo Pérez et al., 2008). Since all cases became better immediately

once Pregabalin was stopped, it was clearly demonstrated that Pregabalin toxicity is concentration-dependent. Hence, if a patient is with renal impairment, the half-life of Pregabalin concentration will increase and accumulate to the point that it starts to affect the liver enzymes. This is could be interpreted as the medication accumulating in the blood and producing hepatic toxicity, and once it is stopped, its concentration would also drop (Crespo Pérez et al., 2008).

The physician must be conscious of this idiosyncratic reaction to Pregabalin and have a full awareness of the medical history of the patient, especially concerning their hepatic and renal functions.

The patients with a history of heart failure mentioned in Table 2 had established clinical evidence of worsening heart failure within one month of the initiation of Pregabalin. In the two relevant cases, the diagnosis was supported by a substantial increase in B-type natriuretic peptide (BNP). The failure to observe an increase in BNP in the other patient does not dilute the accuracy of the clinical diagnosis because of the high intra-individual variability and adequate specificity, but poor sensitivity to BNP increase in establishes a clinical decline (Lewin et al., 2005). Furthermore, there are data in the potential for Pregabalin to interact with thiazolidinediones, causing weight gain or fluid retention when co-administered and possibly exacerbating or causing heart failure (Brunton et al., 2018). However, the mechanism of Pregabalins interaction with thiazolidinediones remains unclear and is likely pharmacodynamics (Murphy et al., 2007). Moreover, all patients had been stable for between four and six months in New-York-Heart-Association (NYHA) class II at the time that Pregabalin was initiated, no other cause of collapse could be identified, and all patients had a satisfactory clinical response to the increase in diuretics and discontinued Pregabalin.

Pregabalins abuse potential is lower in patients without a past or current substance use disorder. For patients with a previous history of substance abuse, Pregabalin should be avoided or administered with caution by using a strict therapeutic and prescription monitoring. The majority of participants were poly-drug abusers and had a previous history of substance abuse (Schwan et al., 2010; Yazdi et al., 2015). In the 2010s, it was reported that Pregabalin abusers were synchronizing the inhibitory and anxiolytic effects of Pregabalin by mixing Pregabalin with sedatives (Baird et al., 2014 (Baird et al., 2014; Schwan et al., 2010; Schifano et al, 2011; Grosshans et al., 2013). This is also unsurprising, as it has been documented that Pregabalin may be effective in treating withdrawal symptoms of drugs and alcohol associated with physical dependency (Freyenhagen et al., 2016). Combining Pregabalin with sedative drugs is dangerous and unpredictable, since the user might feel more sedated and relaxed when taking them (Yazdi et al., 2015). The substances frequently mixed with Pregabalin include natural hashish, opioids, benzodiazepines, and

alcohol; this is attributable to the claim that Pregabalin potentiates the effects of these drugs, which may have a similar effect as Pregabalin (Baird et al., 2014; Carrus and Schifano, 2012). Users also combine Pregabalin with sweet drinks to enhance its effect. The literature suggests that the sweetness activates the endogenous opioid system by inducing a release of  $\beta$ -endorphin and by increasing the binding affinity for opioids (Dum et al., 1983). Nonmedical use of a prescription drug may also be seen as being more socially acceptable than the use of illicit drugs, such as cocaine or heroin (Hernandez and Nelson, 2010). The impossibility of urine detection in screening analysis presents an additional motivation for users to continue on Pregabalin. This lack of detection might be due to the variability of urinary detection times for abused drugs, and differentiating new drug use from residual drug excretion could be difficult, especially after repeated or chronic drug usage (Spigset and Westin, 2013).

## CONCLUSION

The studies reviewed here showed that Pregabalin increases alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK) levels, causing liver and heart toxicities. It can cause a complete atrioventricular (AV) block in overdoses due to its inhibitory effects on L-type calcium channels of myocardium. The studies reported many cases of Pregabalin abuse and addictive effects, especially in patients with histories of substance abuse and psychoactive drug dependence, as euphoria is one of its main side effects. The lack of data related to Pregabalin in the Middle East, especially in Saudi Arabia demands further investigation, and more awareness is needed for Pregabalin side effects among users.

## Conflict of interest

There is no conflict of interest.

## REFERENCES

- Aksakal E, Bakirci EM, Emet M, Uzkeser M, **2012**. Complete atrioventricular block due to overdose of pregabalin. *Am J Emerg Med*, 30(9): 2101.e1-4. doi:10.1016/j.ajem.2012.02.008.
- Al-Husseini A, Wazaify M, Van Hout MC, **2018**. Pregabalin Misuse and Abuse in Jordan: a Qualitative Study of User Experiences. *Int J Ment Health Addict*, 16(3): 642-654. doi:10.1007/s11469-017-9813-4.
- APO-PREGABALIN Product Monograph, 2017**. Pregabalin capsules - Analgesic Agents. Control no. 204819. [https://pdf.hres.ca/dpd\\_pm/00039815.PDF](https://pdf.hres.ca/dpd_pm/00039815.PDF).
- Arikath J, Campbell KP, **2003**. Auxiliary subunits: essential components of the voltage-gated calcium channel complex. *Curr Opin Neurobiol*, 13(3): 298-307.
- Ashwini S, Amit DR, Ivan NS, Alka PV, **2015**. Pregabalin dependence with pregabalin induced intentional self-harm behavior: A case report. *Indian J Psychiatry*, 57(1): 110-111. doi:10.4103/0019-5545.148550.
- Baird CRW, Fox P, Colvin LA, **2014**. Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers. *Eur Addict Res*, 20(3): 115-118. doi:10.1159/000355268.
- Bastiaens L, Galus J, Mazur C, **2016**. Abuse of Gabapentin is Associated with Opioid Addiction. *Psychiatr Q*, 87(4): 763-767. doi:10.1007/s11126-016-9421-7.
- Bonnet U, Richter E-L, Isbruch K, Scherbaum N, **2018**. On the Addictive Power of Gabapentinoids: A Mini-Review. *Psychiatr Danub*, 30(2): 142-149. doi:10.24869/psyd.2018.142.
- Brunton LL, Hilal-Dandan R, Knollmann BC, **2018**. Goodman & Gilman's the pharmacological basis of therapeutics - NLM Catalog - NCBI. Accessed April 15, 2019. <https://www.ncbi.nlm.nih.gov/nlmcatalog/101708739>.
- Carrus D, Schifano F, **2012**. Pregabalin misuse-related issues; intake of large dosages, drug-smoking allegations, and possible association with myositis: two case reports. *J Clin Psychopharmacol*, 32(6): 839-840. doi:10.1097/JCP.0b013e318272864d.
- Center for Behavioral Health Statistics and Quality, **2018**. Results from the 2017 National Survey on Drug Use and Health: Detailed Tables. Rockville (MD): SAMHSA.
- Chen S-R, Xu Z, Pan H-L, **2001**. Stereospecific Effect of Pregabalin on Ectopic Afferent Discharges and Neuropathic Pain Induced by Sciatic Nerve Ligation in Rats: *Anesthesiology*, 95(6): 1473-1479. doi:10.1097/00000542-200112000-00029.
- Chiappini S, Schifano F, **2016**. A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's "Suspected Adverse Drug Reactions" Database. *CNS Drugs*, 30(7): 647-654. doi:10.1007/s40263-016-0359-y.
- Crespo Pérez L, Moreira Vicente V, Manzano Fernández R, García Aguilera XA, **2008**. Cholestasis associated with pregabalin treatment. *Med Clin (Barc)*, 130(4): 157-158.
- Doğan S, Özberk S, Yurci A, **2011**. Pregabalin-induced hepatotoxicity. *Eur J Gastro Hepato*, 23: 628.
- Doğan S, Doğan S, Özberk S, Yurci A, **2011**. Pregabalin-induced hepatotoxicity. *Eur J Gastroenterol Hepatol*. 23(7): 628. doi: 10.1097/MEG.0b013e328346df7a.
- Driot D, Chicoulaa B, Jouanjus E, Dupouy J, Oustric S, Lapeyre-Mestre M, **2016**. Pregabalin use disorder and secondary nicotine dependence in a woman with no substance abuse history. *Therapie*, 71(6): 575-578. doi:10.1016/j.therap.2016.04.006.
- Dum J, Gramsch Ch, Herz A, **1983**. Activation of hypothalamic  $\beta$ -endorphin pools by reward induced by highly palatable food. *Pharmacol Biochem Behav*, 18(3):443-447. doi:10.1016/0091-3057(83)90467-7.
- Düzenli T, Ata E, Kösem M, Bayram Çarli A, **2017**. Pregabalin as a Rare Cause of Hepatotoxicity. *Pain Med*, 18(7): 1407-1408.
- Finnerup N, **2008**. Clinical use of pregabalin in the management of central neuropathic pain. *Neuropsychiatr Dis Treat*, 3: 885-891. doi: 10.2147/NDT.S1715.
- Freyenhagen R, Backonja M, Schug S, Lyndon G, Parsons B, Watt S, Behar R, **2016**. Pregabalin for the Treatment of Drug and Alcohol Withdrawal Symptoms: A Comprehensive Review. *CNS Drugs*, 30(12): 1191-1200. doi:10.1007/s40263-016-0390-z.
- Grosshans M, Lemenager T, Vollmert C, Kaemmerer N, Schreiner R, Mutschler J, Wagner X, Kiefer F, Hermann D, **2013**. Pregabalin abuse among opiate addicted patients. *Eur J Clin Pharmacol*, 69(12): 2021-2025. doi:10.1007/s00228-013-1578-5.
- Halaby A, Kassm S, Naja W, **2015**. Pregabalin Dependence: A Case Report. *Curr Drug Saf*, 10(2):184-186. doi:10.2174/1574886309666141022101956.
- Halaby A, Kassm SA, Naja WJ, **2015**. Pregabalin dependence: a case report. *Curr Drug Saf*, 10(2): 184-186.
- Hernandez SH, Nelson LS, **2010**. Prescription drug abuse: insight into the epidemic. *Clin Pharmacol Ther*, 88(3): 307-317. doi:10.1038/clpt.2010.154.
- Ho JM, Tricco AC, Perrier L, Chen M, Juurlink DN, Straus SE, **2013**. Risk of heart failure and edema associated with the use of pregabalin: a systematic review. *Syst Rev*. 2(1): 25. doi:10.1186/2046-4053-2-25.
- Kampov-Polevoy A, Garbutt JC, Janowsky D, **1997**. Evidence of preference for a high-concentration sucrose solution in alcoholic men. *Am J Psychiatry*. 154(2): 269-70. doi: 10.1176/ajp.154.2.269.

- Kaufman MB, Choy M, 2012.** Pregabalin and Simvastatin. *Pharm Ther*, 37(10): 579-595.
- Kumar N, Laferriere A, Yu JSC, Leavitt A, Coderre TJ, 2010.** Evidence that pregabalin reduces neuropathic pain by inhibiting the spinal release of glutamate. *J Neurochem*, 113(2): 552-561. doi:10.1111/j.1471-4159.2010.06625.x.
- Lewin J, Ledwidge M, O'Loughlin C, McNally C, McDonald K, 2005.** Clinical deterioration in established heart failure: what is the value of BNP and weight gain in aiding diagnosis? *Eur J Heart Fail*, 7(6): 953-957. doi:10.1016/j.ejheart.2005.06.003.
- Li C-Y, Song Y-H, Higuera ES, Luo ZD, 2004.** Spinal Dorsal Horn Calcium Channel  $\alpha 2\delta$ -1 Subunit Upregulation Contributes to Peripheral Nerve Injury-Induced Tactile Allodynia. *J Neurosci Off J Soc Neurosci*, 24(39): 8494-8499. doi:10.1523/JNEUROSCI.2982-04.
- McClelland D, Evans RM, Barkworth L, Martin DJ, Scott RH, 2004.** A study comparing the actions of gabapentin and pregabalin on the electrophysiological properties of cultured DRG neurones from neonatal rats. *BMC Pharmacol*, 4: 4:14. doi: 10.1186/1471-2210-4-14.
- Mishriky BM, Waldron NH, Habib AS, 2015.** Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. *Br J Anaesth*, 114(1): 10-31. doi:10.1093/bja/aeu293.
- Murphy N, Mockler M, Ryder M, Ledwidge M, McDonald K, 2007.** Decompensation of chronic heart failure associated with pregabalin in patients with neuropathic pain. *J Card Fail*, 13(3): 227-229. doi:10.1016/j.cardfail.2006.11.006.
- Ninomiya W, Mizobuchi K, Hayashi T, Okude S, Katagiri S, Kubo A, Masuhara N, Tadashi Nakano T, 2020.** Electoretinographic abnormalities associated with pregabalin: a case report. *Doc Ophthalmol*, 140, 279–287.
- Olaizola I, Ellger T, Young P, Bösebeck F, Evers S, Kellinghaus C, 2006.** Pregabalin-associated acute psychosis and epileptiform EEG-changes. *Seizure*, 15(3): 208-210. doi:10.1016/j.seizure.2006.02.004.
- Quintero-Castellanos M, 2017.** Pregabalin-induced liver injury. Case report. *Revista Colombiana de Anestesiología* 45(4): 349-352.
- Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN, 2003.** Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol*, 43(3): 277-283.
- Reedy S, Schwartz M, 2010.** A case serie 2017 seizures. *Clin Toxicol*, 48(6): 616–617.
- Rose MA, Kam PCA, 2002.** Gabapentin: pharmacology and its use in pain management: Gabapentin. *Anaesthesia*, 57(5): 451-462. doi:10.1046/j.0003-2409.2001.02399.x.
- Schifano F, D'Offizi S, Piccione M, Corazza O, Deluca P, Davey Z, Di Melchiorre G, Di Furia L, Farré M, Flesland L, Mannonen M, Majava A, Pagani S, Peltoniemi T, Siemann H, Skutle A, Torrens M, Pezolesi C, van der Kreeft P, Scherbaum N, 2011.** Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. *Psychother Psychosom*, 80(2): 118-122. doi:10.1159/000321079.
- Schwan S, Sundström A, Stjernberg E, Hallberg E, Hallberg P, 2010.** A signal for an abuse liability for pregabalin--results from the Swedish spontaneous adverse drug reaction reporting system. *Eur J Clin Pharmacol*, 66(9): 947-953. doi:10.1007/s00228-010-0853-y.
- Sendra JM, Junyent TT, Pellicer MJR, 2011.** Pregabalin-induced hepatotoxicity. *Ann Pharmacother*, 45(6): e32. doi:10.1345/aph.1Q032.
- Spigset O, Westin AA, 2013.** Detection times of pregabalin in urine after illicit use: when should a positive specimen be considered a new intake? *Ther Drug Monit*, 35(1): 137-140. doi:10.1097/FTD.0b013e31827789dd.
- Telles-Correia D, Barbosa A, Cortez-Pinto H, Campos C, Rocha NBF, Machado S, 2017.** Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. *World J Gastrointest Pharmacol Ther*, 8(1): 26. doi:10.4292/wjgpt.v8.i1.26.
- Toth C, 2014.** Pregabalin: latest safety evidence and clinical implications for the management of neuropathic pain. *Ther Adv Drug Saf*, 5(1): 38-56. doi:10.1177/2042098613505614.
- U.S. National Library of Medicine, Rockville Pike, Bethesda, 2018,** Pregabalin Hepatotoxicity. National Institutes of Health, U.S. Department of Health & Human Services.
- Wilens T, Zulauf C, Ryland D, Carrellas N, Catalina-Wellington I, 2015.** Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. *Am J Addict*, 24(2): 173-177. doi:10.1111/ajad.12159.
- Yazdi KS, Hemetsberger U, Baier CM, 2015.** Pregabalin abuse of benzodiazepine and alcohol addicted patient. *Psychiatr Danub*, 27(3): 278-279.
- Young KH, Ehman M, Reves R, Maddox BLP, Khan A, Chorba TL, Jereb J, 2016.** Tuberculosis Contact Investigations — United States, 2003–2012. *MMWR Morb Mortal Wkly Rep*, 64(50-51): 1369-1374. doi:10.15585/mmwr.mm6450a1.

---

**Citation:** Alelwani W, Alkhazindar A, Alqumaysh B, Kutbi D, Tayeb R, Altobaiqi R, 2021. Pregabalin abuse and toxicity and related factors. *Int Res J Med Med Sci*, 9(1): 34-42.

---