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Pregabalin Misuse and Abuse: A Scoping Review of Extant Literature.

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Abstract:	Background: Prescribing of pregabalin is increasing worldwide with public health concerns centring on misuse and abuse of prescribed and diverted pregabalin. Objectives: In order to describe and map what is known about misuse and abuse of pregabalin, a scoping review of available published literature was undertaken. Methods: A scoping review methodology was used to identify and map available literature on misuse and abuse of prescribed and diverted pregabalin. Results: Four themes emerged on the misuse and abuse of pregabalin: (1) Abuse potential, (2) Prevalence of abuse, (3) Risk and predisposition and (4) Consequences of abuse. Fifty four records were reviewed and charted. Of note was the dearth of research on the topic prior to 2005, with increased interest in pregabalin abuse potential from 2010 onwards. Conclusion: Available literature supports concern around abuse potential of pregabalin, especially among patients with a history of substance abuse. Prescribers should adopt more rational prescribing.

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Introduction

By definition, any medication can be misused, but few have abuse potential, and particularly those with mind-altering or body-shaping properties (Hughes et al., 1999). The most commonly abused prescription medications worldwide are stimulants (methylphenidate) used for treating Attention Deficit Hyperactivity Disorder (ADHD), central nervous system (CNS) depressants such as sedatives (benzodiazepines) (National Institute on Drug Abuse (NIDA), 2014) and anticonvulsants (pregabalin) (Loftus & Wright, 2014). The risk of dependence on such prescription drugs increases when they are used in ways other than prescribed, e.g., at higher doses, by different routes of administration, or with a combination of alcohol or other drugs (NIDA, 2014). Adverse health and social consequences of prescription medicine abuse and dependence are steadily worsening worldwide, and are reflected in increased treatment admissions, emergency room visits, and overdose deaths from drugs such as opioids, CNS depressants, and stimulants (NIDA, 2014). This is particularly evident in the United States (US), currently experiencing an opioid crisis. In Europe, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and European Medicines Agency (EMA) currently exchange warning trend information around abuse of medicinal products, and with key examples including (cafentanyil, pregabalin, etaqualone, zopiklone, phenibut, gabapentin, and tropicamide) (EMCDDA-Europol, 2013; EMCDDA, 2014).

Of interest for this scoping review is the drug known as pregabalin which is an analogue of the gamma-aminobutyric acid neurotransmitter, and approved for the treatment of partial epilepsy, generalized anxiety disorder, peripheral and central neuropathic pain, and fibromyalgia (Papazisis & Tzachanis, 2014). Pregabalin decreases central neuronal excitability by binding to

an auxiliary subunit (α2-δ protein) of a voltage-gated calcium channel on neurons in the central nervous system and reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P (Schwan et al., 2010). The potential for abuse and/or physical dependence on pregabalin was originally assessed to be low at the time of marketing authorization (Schwan et al., 2010). However, it was noted that euphoria occurred as an adverse event in clinical trials among 1–10% of patients depending on dose, compared with 0.5% for placebo (Schwan et al., 2010). Of particular concern is that global prescribing of pregabalin is increasing, with total sales projected to reach $3.3 billion by 2018 (Mackey, 2010). Pregabalin is controlled in Jordan, Norway and in the USA by the Jordan Food and Drug Administration, the European Medicines Agency and the American Drug Enforcement Administration report (Blommel & Blommel, 2007; Bramness et al., 2010; Jordan Food and Drug Administration, 2017). Diverted and off label use of pregabalin is also on the increase in Europe (EMCDDA-Europol, 2013; EMCDDA, 2014) and in the Middle East (Al-Husseini, et al., 2017). Profiles of pregabalin abuse generally involve individuals with a history of abuse of other medications (Papazisis & Tzachanis, 2014; Häkkinen et al., 2014). In order to describe and collate what is known about misuse and abuse of pregabalin, a scoping review of available published data on misuse and abuse of prescribed and diverted pregabalin was undertaken.

Methods

Scoping review methods are increasingly popular as an accepted review approach (Arskey & O'Malley, 2005; Hidalgo Landa et al., 2011) and are used to "*map the literature on a particular topic or research area and provide an opportunity to identify key concepts; gaps in the research; and types and sources of evidence to inform practice, policymaking, and research*." Daudt et al.

(2013). This form of descriptive synthesis is generally used to provide descriptive summaries of the literature, across a broad range of methodologies and study designs, summarize and publish findings of the research, and identify gaps in the current literature (Arskey & O'Malley, 2005; Brien et al., 2010; Rumrill et al., 2010). The scoping review was underpinned by the research question *' what do we know about the misuse and abuse of pregabalin?".* The research team adopted the five stage method as developed by Arskey and O'Malley (2005) which included: (1) identifying the essential research question, (2) searching for similar studies, (3) study selection, (4) charting the data, and (5) collecting, summarizing, and recording the results.

A thorough and systematic search of literature (1990-2017) was conducted by the team using the following university databases: Science Direct, Electronic Library of Medicine, Hinari, Google Scholar, Cochrane Library, and PubMed. A comprehensive list of search terms was created by the team, which consisted of two pharmacists and an addiction/public health specialist. Searches combined the terms "*pregabalin"* with *"abuse," "misuse," "dependence,"* and *"prescription drug."* For the purposes of this review, abuse was defined as the use of a drug for a non-medical reason (e.g., mental altering effect) and misuse as the use of a drug for a legitimate medical reason but wrongly used either in terms of dose or duration (Hughes et al., 1999). The team of three authors screened literature titles and abstracts to determine their inclusion status. Full text articles were reviewed and screened independently to ensure inclusion.

References were managed by the citation manager Endnote®. This software promoted the recording and organization of all related literature. This allowed cross-monitoring of data records, removal of duplicates, and extraction of information from the papers contained in the

review. The initial search identified 1,320 articles and excluded animal studies, duplicates, those not in the English language, articles where full text was not available, and lack of relevance specifically to the misuse and abuse of pregabalin. The disagreements of the relevance of data were resolved through discussion. (Figure 1).

Insert Figure 1 about here

A charting exercise was conducted by the team and was used to identify specific themes pertaining to misuse and abuse of pregabalin (Bergin et al., 2015).

Results

Fifty four records were reviewed and charted. Of note was the dearth of research on the topic prior to 2005, with increased interest in pregabalin abuse potential from 2010 onwards. Eighteen clinical case reports of pregabalin misuse or abuse were identified, and were from the US (Filipetto et al., 2010), Turkey (Yargic & Ozdemiroglu, 2011; Aksakal et al., 2012; Aldemir et al., 2015; Sonmez, 2015), Austria (Yazdi et al., 2015), France (Driot et al., 2016), Greece (Papazisis et al., 2013), Germany (Olaizola et al., 2006; Grosshans et al., 2010; Skopp and & Zimmer, 2011; Gahr et al., 2013 a), Italy (Carrus & Schifano, 2012), United Kingdom (Braga & Chidley, 2006; Wood et al., 2010), India (Tandon et al., 2013), Ireland (Osman & Casey, 2014), and Lebanon (Halaby, 2015). Thirty six publications were obtained as peer reviewed journal articles from Germany (Gahr et al., 2014; Bonnet and Scherbaum, 2017), United Kingdom (Schifano et al., 2011; Baird et al., 2013; Kapil et al., 2014; Loftus & Wright, 2014; Eastwood & Davison, 2016), USA (Zacny et al., 2012; Papazisis & Tzachanis, 2014; Wilens, 2014), Finland

(Kriikku et al., 2014), Jordan (Wazaify et al., 2016; Al-Husseini et al., 2017), and Italy (Martinotti, 2012), and as reports from Germany (Gahr et al., 2013 b; Grosshans et al., 2013; Cossmann et al., 2016; Freynhagen et al., 2016), United Kingdom (Millar et al., 2013; Schifano, 2014; Asomaning et al., 2016), Sweden (Schwan et al., 2010; Bodén et al., 2014), Denmark (Schjerning et al., 2016 a; Schjerning et al., 2016 b), USA (Herman et al., 2012; Wills et al., 2014; Evoy et al., 2017; Dart et al., 2017), France (Bossard et al., 2016), Finland (Häkkinen et al., 2014; Heikman et al., 2016), Norway (Sugandiran & Bramness, 2014), Switzerland (Mutschler et al., 2016; Suardi et al., 2016), and Italy (Chiappini & Schifano, 2016). A summary is presented in Table 1.

Insert Table 1 about here

Four themes emerged from the charting exercise of data collected on the misuse and abuse of pregabalin: (1) Abuse potential, (2) Prevalence of abuse, (3) Risk and predisposition and (4) Consequences of abuse.

Abuse potential

Abuse of pregabalin (and gabapentin) occurs in several forms, by using the drug above the approved recommended doses (Loftus & Wright, 2014), or with opiates and other drugs (for example benzodiazepines) to potentiate the effect of the latter (Baird et al., 2013; Schifano, 2014). Pregabalin has also been claimed to be useful in the treatment of nicotine dependence, but it is important to note that pregabalin has some abuse potential and should be used cautiously especially in dependent individuals (Herman et al., 2012).

In Sweden, a study was conducted to measure the abuse liability of pregabalin by applying a Bayesian data-mining algorithm to the 16 available reports of possible abuse or dependence of pregabalin in the Swedish national register of adverse drug reactions (SWEDIS). This study concluded that more research was warranted to characterize its extent and nature (Schwan et al., 2010). Bossard et al., (2016) provided a disproportionality analysis of all currently available pharmacovigilance studies and reported pregabalin was not abused more intensely than amitriptyline, an antidepressant drug without abuse liabilities, and also found that pregabalin was abused significantly less than clonazepam, a drug with evident abuse liability (Bossard et al., 2016). While in Norway, the Norwegian version of M.I.N.I International Neuropsychiatric Interview was used to identify pregabalin abuse or dependence, according to DSM-IV diagnosis. Five of the six subjects achieved the DSM-IV criteria for pregabalin dependence, and with all five patients diagnosed with co-morbid psychiatric conditions. The study underscored how iatrogenic dependence in patients with chronic disease occurs in the case of pregabalin (Sugandiran & Bramness, 2014). In Germany, urine specimens were taken from patients with opiate dependence and other addiction disorders, and screened for pregabalin to measure its abuse potential in these patients. Only 12.1% of specimens were positive for pregabalin taken without medical indication (Grosshans et al., 2013).

Four systematic reviews on the abuse potential of pregabalin, and investigated the preclinical, clinical, and epidemiological data concerning abuse of pregabalin (Schjerning et al., 2016 b); the pharmacological characteristics of pregabalin abuse (Papazisis & Tzachanis, 2014); extent of gabapentinoid abuse, characteristics of typical abusers, patterns of abuse, and potential harms

(Evoy et al., 2017) and evaluation of gabapentinoid dependence risk (Bonnet and Scherbaum, 2017). Bonnet and Scherbaum (2017) found very few cases with gabapentinoid-related behavioural dependence symptoms (ICD-10) in patients without a prior abuse history. In Italy, an observational study revealed that pregabalin liability for abuse was an issue of concern, especially in doses prescribed above 600 mg/day more commonly seen in psychiatric conditions such as anxiety disorder (Martinotti, 2012). Two studies originated in the US. The first, by Zacny et al. (2012) explored the subjective effects of pregabalin used alone and pregabalin used with co-medication (various doses) in 16 healthy volunteers, and aimed to investigate if pregabalin used with co-medication changed the subjective effects of opioids (oxycodone). The second, assessed patients in a detoxification center and reported that a small proportion (7%) of opioid dependent patients were misusing pregabalin (Wilens et al., 2014).

Several case reports illustrated the abuse of pregabalin in patients prescribed for medical conditions such as pain management, generalized anxiety disorder (GAD), and treatment of neuropathic pain (Filipetto et al., 2010; Aksakal et al., 2012; Aldemir et al., 2015) and particularly evident among those individuals with previous histories of poly-substance abuse. Patients developed drug seeking behaviour and withdrawal symptoms when stopping or decreasing the dose of pregabalin (Gahr et al., 2013 a; Halaby, 2015). Two cases had no history of drug abuse but reported craving for pregabalin (Driot et al., 2016). A case of a patient with borderline personality disorder (Gahr et al., 2013 a) and history of alcohol abuse reported that pregabalin had the potential to stimulate the development of habit forming and dependence type behaviours. Two other case reports described the abuse of pregabalin as when used in high doses, and when crushed formulations of pregabalin were smoked, and described when ingested

the incidences of myositis (Carrus & Schifano, 2012). Three cases reported abuse of pregabalin in patients with a known history of drug abuse (Grosshans et al., 2010) and with one observing that that pregabalin had a lower abuse potential than benzodiazepines (Yargic & Ozdemiroglu, 2011). Upon discontinuation of pregabalin, patients suffered from withdrawal symptoms and were classified using the DSM-5 criteria for the pregabalin use disorder (Sonmez, 2015).

Prevalence of abuse

Three studies measured the prevalence of pregabalin use at higher than recommended dosages. One study derived from the Swedish national registry reported that 8.5% of patients were dispensed pregabalin at high doses, and that epileptic patients in particular were more likely to be dispensed pregabalin at higher than recommended daily dosages (Bodén et al., 2014). The second study was based on the Danish nationwide registry and reported that 4,090 pregabalin users (9.6%) out of the total of 42,520 were treated with more than 600 mg/day for 6 months. Males and patients with prescriptions of antipsychotics and benzodiazepines were correlated with increased risk of use of higher than recommended dosage (Schjerning et al., 2016 a). The UK Drug Utilization Study (DUS) analyzed pregabalin prescription data from the UK Health Improvement Network primary care database and recently reported that only 1.0% of patients were prescribed pregabalin above maximum recommended doses of 600 mg/day (Asomaning et al., 2016).

The database of the Federal Institute for Drugs and Medical Devices (BfArM) in Germany recorded a total of 55 reports of pregabalin abuse by males and patients with a history of polytoxicomania, and which were correlated to risk of developing addictive behaviors in relation

to pregabalin (Gahr et al., 2013 b). A cohort study of older patients in a German hospital (400 randomly selected cases) reported that a fifth of the cohort were found to be dependent on nonopioid analgesics, and with one case identified with a history of dependence on gabapentin (Cossmann et al., 2016).

In the UK, a review of all cases admitted to the emergency departments after pregabalin abuse revealed that 10 patients presented to the ED following recreational pregabalin abuse with dosages ranging from 500–1400 mg (Millar et al., 2013). Also, an Internet-based survey was conducted to evaluate the prevalence, frequency, and sources of misuse of the GABA analogues (baclofen, gabapentin, and pregabalin). The prevalence of misuse was 1.3% for baclofen, 1.1% for gabapentin, and 0.5% for pregabalin (Kapil et al., 2014). This study highlighted the need for further work to understand the reasons for misuse in order to target appropriate harm-reduction activities (Kapil et al., 2014). Pregabalin use among opioid-addicted patients in Switzerland were assessed in 109 cases and quantified using 3-month hair toxicology analysis (Mutschler et al., 2016). None of the participants reported pregabalin use and pregabalin was undetectable in all samples. These findings contrast sharply with reports of pregabalin misuse by opioid-dependent patients in other countries (Mutschler et al., 2016).

Risk and predisposition

A meta-analysis study was conducted in regards to all published cases to measure the risk factors leading to the addictive behaviors, and the results proposed that males, young age, and current or previous substance abuse represent risk factors that contribute to patient vulnerability to adopting pregabalin correlated addictive type behaviors (Gahr et al., 2014; Sonmez, 2015). Reviews of

patient characteristics report that patients with past poly drug abuse histories abuse pregabalin (Heikman et al., 2016; Suardi et al., 2016). Availability also remains a risk factor. In countries such as Jordan, where the drug is available off prescription, pregabalin abuse is rising (Wazaify et al., 2016). Online sourcing of pregabalin additionally continues to represent a challenge (Schifano et al., 2011).

Hence, cautious use of pregabalin is advised in patients who have a history of substance abuse (Schifano, 2014). Pregabalin is also used to treat substance dependence. An internet search of all published data regarding the role of pregabalin in treating withdrawal symptoms associated with multiple drug types and alcohol, resulted in limited data supporting pregabalin for managing withdrawal symptoms and requires further studies to determine pregabalin efficacy and safety (Freynhagen et al., 2016). Pregabalin as treatment modaility for nicotine addiction reported mixed outcomes, in that it doesn't reduce smoking behaviours, but weakens withdrawal symptoms and the subjective ratings of "*liking*" smoking (Herman et al., 2012).

Consequences of abuse

Reports of abuse for intoxication purposes generally describe insufflation of crushed pregabalin tablets (Carrus & Schifano, 2012; Millar et al., 2013). User experiences were described in a qualitative study conducted in Jordan, where the positive outcomes of pregabalin use centered on its effect in making users sociable and talkative with others (Al-Husseini et al., 2017). Pregabalin was consumed in higher doses to reach intoxication and appeared enhanced when smoking cigarettes or when combining with sweet drinks (Al-Husseini et al., 2017). Enhancement of

sexual desire at higher doses was reported in a patient with a history of psychoactive drug abuse (Osman & Casey, 2014).

According to the National Poison Data System in the US, the rate of pregabalin abuse cases increased 4.3 fold in the period 2006 to 2014, with medical outcomes ranging from moderate health effects to death (Dart et al., 2017). Adverse drug reactions were more frequent in pregabalin abuse in comparison to gabapentin (Chiappini & Schifano, 2016). The Electronic Poison Center data in the US reported on 23 cases of pregabalin abuse contributing to impaired mental status (Wills et al., 2014). One case reported a patient suffering from psychotic symptoms with rhythmic EEG-changes after taking pregabalin at normal doses (Olaizola et al., 2006). Continuous use of pregabalin contributed to deliberate self harm in one case (Tandon et al., 2013). An intentional overdose case reported a patient taking pregabalin and lamotrigine and highlighted the need for clinical awareness around the adverse effects in both therapeutic and toxic doses of pregabalin (Braga & Chidley, 2007).). "Black outs" contribute to risk of fatal overdose (Häkkinen et al., 2014; Lyndon et al., 2017). Another report concluded that there was an effect of pregabalin on the heart as the patient who had used for 8 months experienced complete atrioventricular (AV) block on an ECG (Aksakal et al., 2012).

A study on the proportion of fatalities related to pregabalin or gabapentin abuse was conducted in all medicolegal death cases in Finland. A total of 48.1% of pregabalin positive cases were associated with drug abuse, and were fatal when mixed with opioids (Häkkinen et al., 2014). Most fatalities occur as a result of poly drug abuse, with high levels of up to 226 mg/L (Eastwood & Davison, 2016). Post mortem blood was analysed by Eastwood & Davison (2016) to obtain pregabalin therapeutic concentration and fatal ranges. A total of 70 post-mortem blood

samples of pregabalin was detected over a two-year period. Pregabalin concentrations ranged from 0.05 mg/L to 226 mg/L in the group as a whole and in one case a pregabalin concentration of 76 mg/L was detected to be the possible cause of death as no other drugs of importance were detected (Eastwood & Davison, 2016). Wood et al., (2010) reported a serum pregabalin concentration of 66.5 mg/L with the patient treated with supportive care alone (Wood et al., 2010). A concentration of 25 pg pregabalin/mL serum analyzed by LC/MS/MS following precipitation of serum proteins was reportd by Skopp & Zimmer (2011). Lastly, a study in Finland measured the amount, nature of pregabalin abuse, and serum pregabalin levels of the drivers apprehended for driving under the influence of drugs (DUID) in 2012. Pregabalin was discovered in 206 samples in the study, with 50% of the cases reporting a serum concentration higher than the typical therapeutic range (Kriikku et al., 2014).

Discussion

This review has mapped the available literature around what is currently known around misuse and abuse of pregabalin. It underscores the phenomenon of pregabalin misuse and abuse as a more recent trend, as evident in the increased literature available since 2010. Ultimately it highlights the need for enhanced pharmacovigilance and surveillance of pregabalin abuse trends, despite its more recent emergence as a drug to be monitored both on and off label (EMCDDA-Europol, 2013; EMCDDA, 2014).

Our mapping of the literature highlights the diverse range of those patients at risk of pregabalin abuse and dependence, and evident in certain special populations such as patients with legitimate therapeutic need and using it above the recommended dosages, and vulnerabilities particularly

concentrated among those with a history of psychiatric disorder, opioid dependence and poly-substance abuse or dependence (Filipetto et al., 2010; Schwan et al., 2010; Canadian Agency for Drugs and Technologies in Health, 2012; Carrus & Schifano, 2012; Gahr et al., 2013 a; Baird et al., 2013; Tandon et al., 2013; Wilens et al., 2014; Grosshans et al., 2013; Osman & Casey, 2014; Aldemir et al., 2015; Driot et al., 2016). Risks additionally centre on over the counter or off label availability (Wazaify et al., 2016), online retail (Schifano et al., 2011) and in the prescribing of high doses to patients (Bodén et al., 2014).

Pharmacodynamics of pregabalin may have direct/ indirect effects on the dopaminergic 'reward' system, with such effects typically related to abuse and dependence liability (Schifano, 2014).In their animal study pregabalin appears to have the efficacy to counteract both reinforcing and withdrawal effects of opioids, but also have a potentiating effect when given to mice with existing opioid levels (Vashchinkina et al., 2017). This enhances patient and pregabalin user vulnerabilities to development of abuse patterns and dependence, particularly among opioid dependent patients. Other studies raise concern around poly use with methadone (Baird et al., 2013) and other opiates (Loftus & Wright, 2014). Targetted awareness and support interventions are warranted (Yazdi et al., 2015; Evoy et al., 2017).

Limitations

The scoping review represents an initial step in mapping extant literature around what is known about misuse and abuse of pregabalin. Included records derive from retrospective reviews, survey data, and case reports. The review is hampered by difficulties in establishing accurate prevalence data, and the cases where pregabalin and gabapentin were analysed together.

Conclusion

The scoping review presents available literature around misuse and abuse of pregabalin. Risk of pregabalin misuse and abuse is especially evidnet among patients with a history of substance abuse, those with psychiatric disorders and those who are opioid dependent. Physicians, their patients, and pharmacists all play a role in identifying, preventing and addressing pregabalin abuse and dependence (NIDA, 2014). The review highlights the need for enhanced surveillance, regulatory efforts, prescriber and pharmacy vigilance.

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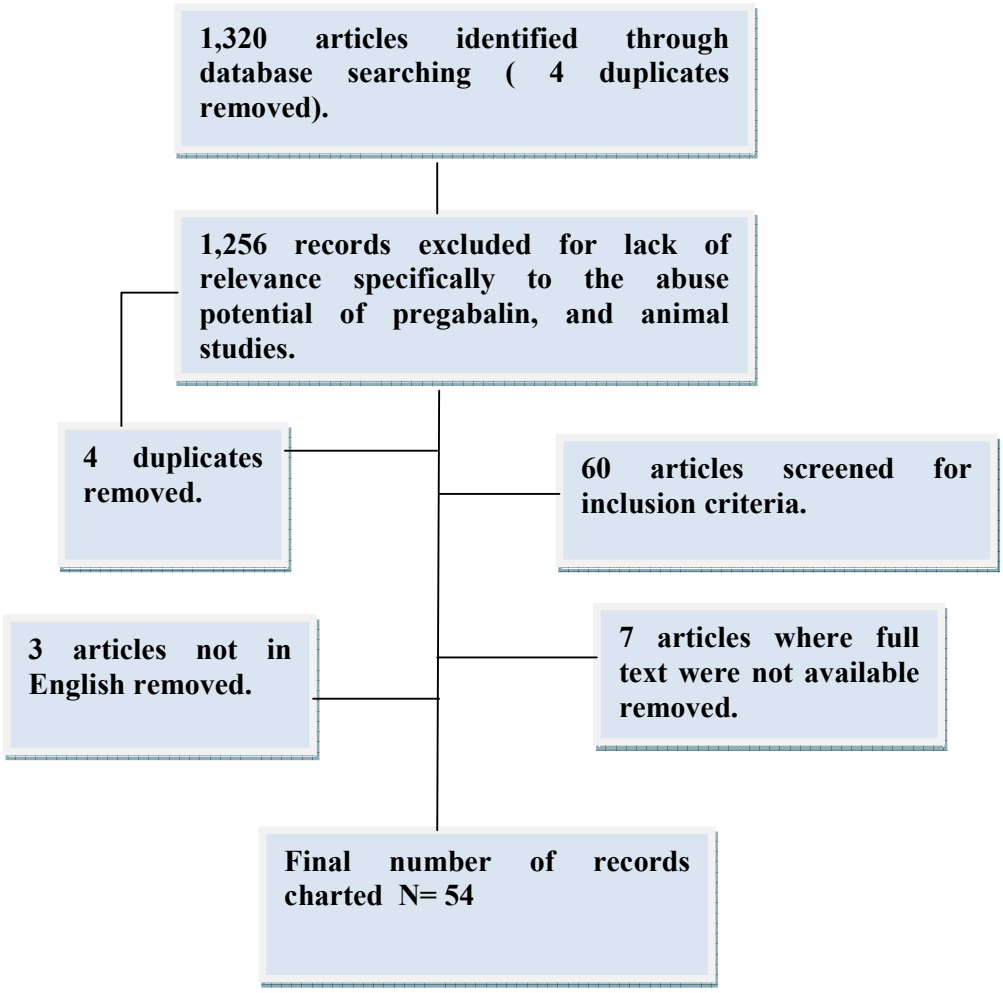

Figure. 1 Flow chart of the search strategy used during the scoping review of pregabalin abuse

Table 1 A summary of all literature published about the abuse of pregabalin

Authors	Year/ country	Method	Summary of Findings	Conclusion
1. Filipetto et al.	2010/ New Jersey, USA	A case report.	A 35-year old woman with opioid history, prescribed pregabalin for pain control. After her physician denied her request, subsequently obtained pregabalin from other sources. Over a 28-day period the patient received a total of 88,500 mg of pregabalin.	This the first report diagnosed as a case of pregabalin abuse and referred to a local detoxification center.
2. Aldemir et al.	2015/ Turkey	A case report.	A 34 year old man with a history of alcohol and poly-substance	Pregabalin should be used carefully in patients with a history of substance

			dependence, and symptoms of GAD. He developed pregabalin dependence, then he experienced withdrawal symptoms when he tried to stop the drug.	dependence.
3. Yazdi et al.	2015/ Austria	A case report.	A male patient in his late 20s with GAD and a history of alcohol and benzodiazepine abuse. He exhibited similar drug-seeking behavior with pregabalin. With a daily intake 1050 mg. When there was no access to pregabalin, he experienced	need for an intense awareness when prescribing pregabalin to an individual with alcohol or benzodiazepine addiction.

			withdrawal symptoms.	
4. Driot et al.	2016/France	A case report.	A young female using pregabalin for anxiety, no history of substance abuse. But concurrent use with tobacco lead to synergic effect with craving for pregabalin, tolerance and withdrawal symptoms at usual doses (below 300 mg per day).	Authors concluded that health professionals should be conscious of this potential risk of concomitant use with tobacco in patients with no history of substance use disorder, submitting a psychiatric condition, and specifically, addiction susceptibility.
5. Papazisis et al.	2013/Greece	A case report.	A 19 year old man with a history of cannabis and alcohol abuse shows drug-seeking behavior with pregabalin. He used it for	This report highlights the abuse potential of pregabalin in a patient with a history of substance-seeking behavior.

			GAD, until he reached a dose of 1800 mg/day.	A better clarification of its abuse potential is essential. As considering that the drug has recently been proposed as a treatment for alcohol- and benzodiazepine-dependence.
6. Carrus & Schifano	2012/Italy	Two case reports	A male patients in his first 30s.Consumption of large dosages of pregabalin, (4500 mg) assumptions of drug smoking of the crushed tablet, and the possible incidence of myositis after pregabalin ingestion. Also sudden	Potential of pregabalin for diversion as rapid development of high tolerance and withdrawal signs and symptoms upon discontinuation, which may be a matter of particular interest and doctors should carefully

			stop of pregabalin, developed withdrawal symptoms that indicate its liability for physical dependence.	assess patients for a history of drug abuse and monitor them for signs of pregabalin abuse.
7. Grosshans et al.	2013/Germany	Quantitative study	A urine specimens were taken from 124 patients with opiate dependence and from 111 patients with other addiction disorders (alcohol, benzodiazepines, cannabis, amphetamines) were screened for pregabalin by means of a mass spectrometer analysis. To measure pregabalin abuse potential	Only 12.1% of all urine specimens from patients with opiate addiction to be positive for pregabalin without medical purpose for pregabalin use with a N =11of 15, bought it from other heroin addicts or drug dealers. The authors concluded that pregabalin is liable to be abused among individuals with

			in these patients.	opiate dependency syndrome and more cautious about this issue must be taken.
8. Loftus & Wright	2014/UK	Observational study	The author summarizes the drugs that used to manage neuropathic pain (pregabalin, gabapentin) for its potential misuse. As a suggestion that patients at high risk of addiction were prescribed higher than the recommended dose of pregabalin.	Reported that when used alongside opiates to potentiate opiate effects are increasing. Also can be used alone in higher than recommended doses to produce sedation and psychedelic effects. The author concluded that the quantities supplied should be limited because of the possibility of misuse.
9. Bodén et al.	2014/Sweden	To identify patient's	About 8.5 % were	The author concluded that

		dispensed pregabalin at higher than the maximum accepted dose in a cohort study based on data derived from Swedish national registers.	dispensing pregabalin in a dose that overridden the maximum daily accepted dose (600 mg).	patients at a high danger of addiction and patients with epilepsy are more possible to be dispensed pregabalin at higher than the maximum allowed daily dose.
10. Schjerning et al.	2016/ Denmark	Observational study	Using the Danish nationwide registers. To measure the predictor's pregabalin use above recommended dosage and to investigate the trends in the use of pregabalin. A total of 42 520 pregabalin users 4 090 (9.6 %) were treated with more than 600	The author concluded that use of pregabalin in Denmark increased 7-fold from its inception in 2004 to 2013. Use of pregabalin above recommended dose is uncommon. The physician should pay attention to signs of abuse when prescribing

			mg/day for 6 months and 2 765 (6.5 %) for more than 12 months. Also a male gender and prescription of antipsychotics and benzodiazepines were correlated with increased risk of use of above the recommended dosage.	pregabalin to patients already taking benzodiazepines, antipsychotics or opioids.
11. Baird et al.	2013/UK	A questionnaire-based survey	Carried out in six substance misuse clinics, looking for evidence of gabapentinoid abuse. A total of 22% (29/129) of respondents admitted to abusing gabapentinoids,	The study concludes that clinicians should be aware of the potential for gabapentinoid abuse, and of the apparent effects of their abuse along with methadone.

			and of these, 38% (11/29) abused gabapentinoids in order to potentiate the 'high' they obtained from methadone.	
12. Schwan et al.	2010/Sweden	Quantitative study	Apply a Bayesian data-mining algorithm to reports of possible drug abuse or addiction in the Swedish national register of adverse drug reactions (SWEDIS), and calculate the information component (IC) for pregabalin and reports of abuse and addiction. To investigate abuse potential of	The author concludes that pregabalin is likely to be associated with an abuse liability and that further studies are urgently needed to characterize its extent and nature.

			pregabalin. A total of 198 reports indicate of abuse or addiction to any drug, only 16 reports concerned pregabalin.	
13. Skopp & Zimmer	2011/ Germany	A case report of pregabalin misuse. Pregabalin was analyzed by LC/MS/MS following precipitation of serum proteins. Vigabatrin was used as internal standard.	A concentration of 25 pg pregabalin/mL serum determined in the present case is the second highest value published so far after misuse of the substance.	The author concluded that additional studies are needed to assess the actual abuse potential of pregabalin.
14. Schjerning et al.	2016/ Denmark	A systemic review study	Perform a systematic literature search and reviewed the preclinical, clinical and epidemiological data on	The author concluded that the available literature suggests an important clinical abuse potential of pregabalin and prescribers

			the abuse potential of pregabalin. A total of (n = 17) preclinical, (n = 19) clinical and (n = 13) epidemiological studies addressing the abuse potential of pregabalin. Also reviewed case reports (n = 9) concerning abuse of pregabalin.	should pay attention to signs of abuse, especially in patients with a history of substance abuse.
15. Papazisis et al.	2014/USA	A systemic review study	To review all published data signaling pregabalin's abuse liability considering on the pharmacological characteristics. Result in different article, case series, screening study and	The author concluded that is essential to make a good illustration of pregabalin abuse potential and further studies are essentially needed to identify the pathophysiological and

			several case reports.	molecular basis of the setting pharmacological features that pregabalin shares with addictive drugs.
16. Bossard et al.	2016/France	A case/non case study was performed in the FPVD .	A total of 184,310 reports in the database, 521 were abused or dependence cases. Among theme 8 cases (1.5 %) concerned pregabalin, 18 cases (3.5 %) clonazepam and 0 case amitriptyline. No statistically significant association between pregabalin and abuse or dependence was observed	That pregabalin abuse potential still an issue that clinicians should recognize when prescribing this drug.

			in the disproportionality analysis.	
17. Millar et al.	2013/UK	Observational study	A one year review of all patients presenting to the emergency department after recreational drug abuse of pregabalin. A total of 10 patients presented to the ED following recreational pregabalin abuse with a dosages ranged from 500–1400 mg.	The author concluded that emergency physicians should be aware of the current use of pregabalin as a recreational drug.
18. Gahr et al.	2013/Germany	Quantitative study	A query of the entire database of the German Federal Institute for Drugs and Medical Devices	The author concluded that the cases of pregabalin abuse or dependence reported in the BfArM

			(BfArM) regarding reports of pregabalin abuse or dependence. A total of 55 reports of pregabalin abuse or dependence were identified (mean age 36 years, 64 % of the reports involved males). With a daily pregabalin dosage was 1424 mg.	since 2008, and increasing. Male sex and a history of polytoxicomania may be possible risk factors for the development of addictive behaviors related to pregabalin.
19. Häkkinen et al.	2014/ Finland	Observational study	They examined all medico legal death cases in Finland in which pregabalin or gabapentin was formed in postmortem toxicology during 2010–2011. A total of 316 cases	The author concluded that in postmortem material, pregabalin was a more common finding than gabapentin and pregabalin abuse with large doses is increasingly frequent and

			were pregabalin and 43 cases were gabapentin. Drug abuse was combined with 48.1% of the pregabalin and 18.6% of the gabapentin findings.	can be fatal when mixed with opioids.
20. Kriikku et al.	2014/ Finland	Quantitative study	The samples were analyzed by an LC–MS/MS system and the results were compared with the typical therapeutic range of pregabalin also the age and gender of the driver. A total of 206 samples from pregabalin was detected. In about 50% of the cases the serum	The author concluded that pregabalin is being used in large doses, apparently for recreational purposes. Also that pregabalin contributed in their driving deterioration, but to what extent stayed unclear.

			concentration was higher the typical therapeutic range.	
21. Kapil et al.	2014/UK	Internet-based survey study	To evaluate the prevalence, frequency and sources of misuse of the GABA analogues (baclofen, gabapentin and pregabalin). A total of 1500 individuals was completed the online survey and the lifetime prevalence of misuse of any of the three surveyed GABA-analogue medications were 2.5% (n = 38); for each drug, this	The author concluded that there is a definite misuse of baclofen, gabapentin and pregabalin in the UK, and we need further work to understand the reasons for misuse, to enable suitable targeted harm-reduction activities by multi-agency responses.

			was 1.3% (n = 19) for baclofen, 1.1% (n = 17) for gabapentin, and 0.5% (n = 8) for pregabalin.	
22. Wazaify et al.	2016/Jordan	A questionnaire-based survey study	To measure the abuse and misuse of drugs sold with or without a prescription in community pharmacies. New products have appeared on the list such as: ophthalmic drops (n=39, 13.4%) and the anti-epileptic; Lyrica (pregabalin; n=19, 6.5%).	The author concluded that the patterns of suspected prescription and nonprescription drug abuse/misuse have slightly changed in Jordan over time, with the appearance of new drugs on the list which liable for abuse.
23. Dart et al.	2017/USA	Observational study, Data from the Nation Poison Data System were	A total of 4152 Intentional Abuse cases revealed to gabapentin or pregabalin.	The study concluded that the rates of intentional gabapentin and pregabalin

		examined for gabapentin and pregabalin product codes and were employed to decide if the category of Intentional Abuse cases were increasing in the US, and different outcomes from abusing them.	The rate increased 4.3 fold between 2006 to 2014. Medical outcomes range from moderate effect, major to death.	abuse has been increasing since 2006.
24. Olaizola et al.	2006/Germany	A case report	A 44-year-old female used pregabalin for her neuropathic pain, after an unexpected increase in pregabalin dose, the patient suffers from psychotic symptoms with rhythmic EEG-changes. After discontinuation of	So physicians must be aware of psychotic symptoms in patients using pregabalin even in normal doses.

			pregabalin the patient return to normal.	
25. Braga& Chidley	2006/UK	A case report	A 29-year-old male used lamotrigine and pregabalin in overdoses as he attempted to suicide by ingesting 32 g of lamotrigine and 11.5 g of pregabalin.	So physicians must be aware of all anti-epileptic drugs adverse effects in both therapeutic and toxic doses.
26. Wood et al.	2010/UK	A case report	A 54-year-old male presented to the Emergency Department (ED) after a self-reported ingestion of 8.4 g of pregabalin. Determined that the patient should be handled with airway and	The highest reported serum pregabalin concentration in literature is in this patient, which is 66.5 mg/L. The physicians should be aware of this case of pregabalin toxicity to be treated with supportive care alone.

			general supportive care alone, assuming a spontaneous recovery.	
27. Yargic & Ozdemiroglu	2011/Turkey	A case report	A 37 year old man with a history of benzodiazepine and drug abuse, complaining of anxiety, then he used pregabalin and start to abuse it by taking 20 capsules to get euphoric.	So physicians must be cautious when using pregabalin to treat patients with a history of drug abuse and that pregabalin having abuse potential lower than that of the benzodiazepines.
28. Herman et al.	2012/USA	Crossover study was obtained on 24 smokers in 4 days treatment with pregabalin 300 mg or placebo, during the experiment the findings	Pregabalin treatment in smokers didn't lower the smoking behavior but it weakens some of smoking withdrawal symptoms and weaken the subjective	Author concluded that pregabalin has fixed support as a treatment for smoking addiction.

		were collected. To measure pregabalin's effects on smoking in general.	ratings of "liking" in response to smoking.	
29. Zacny et al.	2012/USA	A randomized, crossover study was conducted in 16 healthy volunteers were grouped in five sessions taking capsules of placebo, 75 mg pregabalin, 150 mg pregabalin, 10 mg oxycodone, and 75 mg pregabalin mixed with 10 mg oxycodone. Then subjective, psychomotor, and physiological measures were evaluated.	Pregabalin has no impact on psychomotor performance and has no increase on drug liking effects of the dose testing. While oxycodone has an increase in drug liking effects. When mixed together drug liking of oxycodone was not elevated by 75 mg pregabalin.	The author concluded that this drug is bused and need more psychopharmacological studies with pregabalin are allowed.
30. Aksakal et al.	2012/Turkey	A case report	A 65-year-old woman	This is the first report

			admitted with dizziness and syncope that revealed she was taking pregabalin 300 mg daily for 8 months for her neuropathic pain. On ECG found that there is complete atrioventricular (AV) blocked, once stoped using pregabalin the patient turn to normal.	concluded there is effects of pregabalin on the heart.
31. Gahr et al.	2014/Germany	A meta-analysis study was conducted to all published cases, as a result of inadequate data in the evaluation of abuse liability of pregabalin is not finished, specifically	Different cases and published literature.	The author proposed that male sex, young age, and current or previous substance abuse may be risk factors that lead patients to become pregabalin correlated

		the risk factors leading to the addictive behaviors.		addictive behaviors.
32. Tandon et al.	2013/India	A case report	A 21-year-old male patient taking pregabalin for his back pain with no history of drug abuse. After continuous use of pregabalin, the patient suffers from behavioral changes with self- harm in the forearm.	From this reported side effect focuses the probability of abuse potential of pregabalin in young individuals and possible to cause self-harm behavior on a constant use.
33. Gahr	2013/Germany	A case report	A 38-year-old female patient with borderline personality disorder and past alcohol abuse and nicotine dependence who become pregabalin abuse	During the decline of pregabalin dose, the patient progressed a moderate withdrawal symptoms.

			up to 600 mg/day.	
34. Wills et al.	2014/USA	It is a retrospective study utilizing electronic poison center data, measuring clinical outcomes from newer anticonvulsant overdose.	A total of 501 cases found, 347 cases met the inclusion criteria, 23 cases of them were pregabalin.	The author concluded that overdose of newer anticonvulsants leads to impaired mental status and there was no significant effect of dose on the intensity of outcome. No significant result regarding pregabalin.
35. Osman & Casey	2014/Ireland	A case report	A 55-year-old male patient with a history of various psychoactive substances abuse, later on he abused pregabalin as he used it for his anxiety by consuming 2250 mg/day in	So physicians should be aware of prescribing pregabalin in patients with a history of substance abuse and more studies are needed regarding pregabalin and sexual

			over 2 days. Then patient noticed an enhancement in sexual desire and excitement in psychological phase of the sexual response cycle, when using pregabalin in higher doses.	cycle.
36. Sonmez	2015/Turkey	A case report	A 31-year-old man with a history of drug abuse (cannabis, alcohol and others) and consuming 25–30 capsules of pregabalin per day. Upon discontinuation of pregabalin the patient suffers from withdrawal	So the report concluded that pregabalin is possibly abused for its positive psychological effects and should be cautiously used in patients with a history of substance use disorders.

			symptoms and achieves the DSM-5 criteria for the pregabalin use disorder.	
37. Sugandiran& Bramness	2014/Norway	Qualitative study, semi-structured interviews with six psychiatric patients at an outpatient clinic in Norway for a case series. The Norwegian version of M.I.N.I International Neuropsychiatric Interview was used to identify pregabalin abuse or dependence, according to DSM-IV diagnosis.	Five of the six subjects achieved DSM-IV criteria for pregabalin dependence. All of these five patients had co-morbid psychiatric conditions.	The author concluded that patients with chronic disease has more or less dependence liability to their medication and proposed that the use of pregabalin may cause drug dependence without abuse.
38. Wilens et al.	2014/USA	A quality assurance program by assessing the	A total of 162 patients admitted with opioid	The author concluded that clinician working with

		admitted patients in detoxification center, applying a self-report questionnaire to ask for particular psychotropic medication use, one of them pregabalin.	dependency, 28% noted the use of medication in amounts higher than prescribed. Of opioid patients, 7% self- noted misusing pregabalin.	opioid dependent patients should be cautious of the high levels of medication misuse of both controlled and non-controlled agents.
39. Halaby	2015/Lebanone	A case report	A 26-year-old woman, who established dependence and withdrawal symptoms after stopping pregabalin as she abused it in a daily dose of 1500–2400mg.	After 6 weeks of treatment the patient turn to normal and this is the first report of pregabalin dependence.
40. Suardi et al.	2016/ Switzerland	Ten inpatients with pregabalin misuse were evaluated and regulate a	All patients exist were having a history of drug abuse and pregabalin	So pregabalin should be cautiously prescribed in patients have a history of

		systematic review of all published literature.	misuse were by sniffing with a symptom of euphoria, psychomotor activation and sedation.	drug abuse.
41. Heikman et al.	2016/ Finland	Two hundred urine samples collected from 82 opioid maintenance treatment, patients were studied by liquid chromatography/time-of-flight mass spectrometry screening method to detect the bused substances.	Ninety-two (45.8%) samples were positive for the abused substances from the sample pregabalin was bused in 4.0%.	The author reported all new psychoactive drugs that being recently abused and recognize these patients as a poly drug abuser.
42. Eastwood & Davison	2016/UK	The laboratory analyzes pregabalin concentration in post mortem blood to determine therapeutic and	A total of 70 post-mortem blood samples of pregabalin was detected. Pregabalin concentrations	The author concluded that most fetal condition as a result of multi-drug abuse and reported the highest

		fatal ranges.	ranged from 0.05 mg/L to 226 mg/L in the group as a whole and in one case a pregabalin concentration of 76 mg/L was detected to be the possible cause of death as no other drugs of importance were included.	pregabalin level in blood to date of 226 mg/L.
43. Freynhagen et al.	2016/Germany	A literature search of the MEDLINE and Cochrane Library databases were conducted with different keywords regarding dependence, withdrawal and pregabalin.	There is limited data supporting pregabalin for managing of withdrawal symptoms, but the recent data are promising and more studies are needed regarding pregabalin safety and efficacy.	So physician should be aware when prescribing pregabalin in patients with a history of substance abuse.
44.Chiappini & Schifano	2016/ Italy	All reports of both	A total of 7639 reported	The author concluded that

		gabapentin and pregabalin relevant to abuse, misuse and dependence were analyzed and discussed.	adverse drug reactions of pregabalin cases related to abuse, misuse and dependence. A total of 27 deaths linked with pregabalin abuse, misuse and dependence. Proportional analysis reveals that adverse drug reactions are more frequent for pregabalin in comparison to gabapentin.	gabapentinoids misuse may be a matter of interest, specifically in patients with previous history of drug misuse.
45. Asomaning et al.	2016/UK	An observational drug utilization study (DUS) analysis pregabalin prescription data from the UK Health Improvement	A total of 13,480 patients, prescribing pregabalin was available. Only 1.0% of patients, prescribing pregabalin above	The author concluded that most of pregabalin prescribing in the UK was symmetric with product labeling and the percent of

		Network primary care database.	maximum recommended dose 600 mg/day and 18.4% of patients have a history of drug abuse.	patients prescribing pregabalin in high doses was low.
46. Martinotti	2012/Italy	An observational study	Pregabalin has high efficacy in psychiatric disorders as it useful in anxiety, but it has an abuse liability.	As a conclusion that pregabalin at a dose above 600 mg/day more seen in psychiatric conditions and an abuse potential of pregabalin is an issue of concern.
47.Grosshans et al.	2010/Germany	A case report	A 47-year-old man with a history of drug and alcohol abuse who abuse pregabalin and become tolerant to it and has withdrawal symptoms	So pregabalin may have an abuse liability and must be used cautiously in treating patient with previous drug abuse.

			when he stop using it as he consume 25 capsules per day.	
48. Schifano et al.	2011/UK	An analysis of both anecdotal online reports of pregabalin misuse and its online purchase availability levels. Pregabalin data were compared with related clonazepam and gabapentin online information. Qualitative Google searches of 203 websites have been carried out in 8 European languages using specific	A total of 52 websites was examined and 32 identified as relevant. More interesting findings of the present report is the dissociation effect noticed among pregabalin/gabapentin abusers and not in clonazepam abusers.	The author concluded that an increase in online trafficking/debate about a specific psychoactive drug typically precedes the occurrence of clinical incidents at the population level and a careful of pregabalin misuse.

		key words.		
49. Schifano	2014/UK	An internet search of all available literatures was obtained and gabapentinoid experimenters are summarized here as individuals with a history of recreational polydrug misuse of higher doses.	Different published literatures have obtained.	So physicians should be aware of pregabalin misuse in a patient who has a history of drug abuse.
50. Evoy et al.	2017/ USA	A systemic review study	Assessing the extent of gabapentinoid abuse, characteristics of typical abusers, patterns of abuse, and potential harms in order to bring this trend to providers' awareness.	Concluded that gabapentinoids possess potential for abuse, particularly in individuals with a history of opioid abuse.

51. Bonnet and Scherbaum	2017/Germany	A systemic review study	To evaluate gabapentinoid addiction risk in more detail.	Cautious use of gabapentinoid in a patient with a history of substance use disorder.
52. Al-Husseini et al.	2017/Jordan	A qualitative study	Semi-structured interviews were conducted to explore and describe pregabalin users' experiences.	The study concluded that the problem of pregabalin abuse and misuse in Amman, Jordan, exists with many challenges and several complicating factors.
53. Cossmann et al.	2016/Germany	A cohort study	An older patients in a German hospital (400 randomly selected cases) reported that a fifth of the cohort was found to be dependent on nonopioid	The study concluded that the identification and management of addiction disorders should be considered as part of the basic geriatric assessment.

			analgesics, and with one case identified with a history of dependence on gabapentin.	
54. Mutschler et al.	2016/ Switzerland	Quantitative study	Pregabalin use among opioid-addicted patients were assessed in 109 cases and quantified using 3-month hair toxicology analysis.	None of the participants reported pregabalin use and pregabalin was undetectable in all samples. Also the study recommended more caution regarding pregabalin use when treating patients with a history of opioid dependence.