



Critical Review Report: Pregabalin

Expert Committee on Drug Dependence

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Executive Summary

Substance identification

International Nonproprietary Name (INN)

Pregabalin

WHO Review History

Pregabalin was pre-reviewed by the 39th WHO- ECDD in 2017.

Chemistry

Chemical Name

IUPAC Name:

(3S)-3-(aminomethyl)-5-methylhexanoic acid

Ease of convertibility into controlled substances

No information was found on the conversion of pregabalin into other controlled substances.

Similarity to known substances / Effects on the central nervous system

Pregabalin is similar to gabapentin. Both are gabapentinoids and are 3-substituted derivatives of the neurotransmitter gamma-aminobutyric acid (GABA) and known inhibitors of alpha-2-delta -subunit-containing voltage-dependent calcium channels (VGCC).

General pharmacology

Pregabalin is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). It has been reported that it modulates the release of many neurotransmitters such as glutamate, noradrenaline, substance-P and calcitonin gene related peptide. In particular, the inhibitory modulation of overexcited neurons allows them to return to a normal state, including a decrease in the hyper excitability caused by tissue damage. Although pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABA or benzodiazepine receptors.

Pregabalin has linear and dose-proportional absorption with a steady state achieved at 24-48 hours. There are two different formulations of pregabalin with different pharmacokinetic profiles, including extended release. Pregabalin, in both its forms, is rapidly absorbed in the fasting state. Pregabalin is not metabolized and is almost entirely excreted unchanged in the urine (90%). It is not bound to plasma proteins and has virtually no pharmacokinetic drug-drug interactions. Other drugs do not affect the pharmacokinetics of pregabalin. The half-life of pregabalin ranges from about 4.5 hours to 7.0 hours (mean elimination half-life or pregabalin is 6.3 hours in subjects with normal renal function), thus requiring more than once-daily dosing in most patients. Therapeutic serum levels of pregabalin range between 0.15-7.5 mg/L.

Toxicology

Animal toxicology studies with exposures from 2 to 69 weeks have shown the following: ataxia and hypoactivity in rats and monkeys at repeated oral doses \geq 500 mg/kg; tail dermatopathy and urine staining in rats \geq 250 mg/kg and monkeys up to 500 mg/kg; urinary bladder changes and mortality with pyelonephritis/cystitis in rats at \geq 250 mg/kg; reversible platelet count decreases of 14-36% in rats at \geq 50 mg/kg in males and \geq 100 mg/kg in females. Epididymal hypospermia and spermatogenic epithelial degeneration were observed after 4 weeks at 1250 mg/kg in rats, but not in doses up to 500 mg/kg. There were no changes in sperm count, motility or morphology in monkeys at 500 mg/kg for up to 69 weeks. There were no effects on female rat fertility when given high doses. However, male rats had reversible decreased sperm motility and fertility at \geq 27 times human exposure.

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In humans, the highest reported serum pregabalin concentration in literature in a *living* patient, was 66.5 mg/L, after a self-reported ingestion of 8.4 g of pregabalin. The patient was handled with airway and general supportive care alone, assuming a spontaneous recovery. Another laboratory study analyzed pregabalin concentration in 70 *post mortem* pregabalin blood samples to determine therapeutic and fatal ranges. 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 included. (Goodman and Brett, 2017)

Adverse reactions in humans

The most common AEs seen among trials of pregabalin, occurring in at least 10% of any age or dosage group, are dizziness and somnolence, infection, ataxia, blurred vision, constipation, diplopia, dizziness, drowsiness, fatigue, headache, peripheral edema, tremor, weight gain, visual field loss, accidental injury, and xerostomia.

The incidence of the most common AEs increases with larger pregabalin doses. Dizziness and somnolence both arise with moderate frequency; dizziness takes place in 31% of patients treated with PGB compared with 9% of those receiving placebo. Somnolence is slightly less common, being experienced in 22% of patients treated with PGB compared with 7% of those receiving placebo (Pfizer, 2005). It was also noted that the threshold to experience AEs of pregabalin may be different in different disorders. (Zaccara et al., 2012).

Dependence potential

Tolerance and withdrawal symptoms have been reported in pregabalin dependence case reports and were found to be associated with symptoms of behavioral dependence. Evidence from preclinical and therapeutic clinical trials suggests the development of tolerance to the euphoric effects. Withdrawal symptoms are manifest in some patients following abrupt discontinuation of pregabalin treatment (e.g., insomnia, headache, nausea, anxiety, sweating and diarrhea). For this reason, it is recommended that patients undergo a short taper period (1 week) when discontinuing treatment.

Abuse potential

Pregabalin is not known to be directly active at receptor sites associated with drugs of abuse. However, pre-marketing clinical trials provided evidence that pregabalin can produce euphoria (pregabalin: 4% (and up to 12% in select cohorts) versus placebo: 1%; Pfizer, 2016) Meta-analysis of 38 trials noted euphoria to be the second most commonly reported pregabalin adverse event (Zaccara et al., 2012).

Since 2008, a number of 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, the vast majority describing patients being currently or previously dependent on other substances, too. This association was supported by the latest analysis of the EudraVigilance database, which included spontaneous reports from Europe, North and South America as well as East Asia.

Four systematic reviews on the abuse potential of pregabalin investigated the preclinical, clinical, and epidemiological data concerning abuse of pregabalin; the pharmacological characteristics of pregabalin abuse; extent of gabapentinoid abuse, characteristics of typical abusers, patterns of abuse, and potential harms, and evaluation of gabapentinoid dependence risk. In patients without a prior abuse history, Bonnet and Scherbaum (2017) found very few cases with gabapentinoid-related behavioral dependence symptoms (International Statistical Classification of Diseases and Related Health Problems–10th Revision [ICD-10]). A scoping review by Al-Husseini et al., (2018c) concluded that the risk of pregabalin misuse and abuse was especially evident among patients with a history of substance abuse, those with psychiatric disorders, and

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those who were opioid dependent (Lyndon et al., 2017). Physicians, their patients, and pharmacists all play a role in identifying, preventing, and addressing pregabalin abuse and dependence (NIDA, 2014). The review highlighted the need for enhanced surveillance, regulatory efforts, and prescriber and pharmacy vigilance.

Therapeutic applications / usefulness

Pregabalin is approved for the adjunctive treatment of partial seizures, with or without secondary generalization; controlled clinical trials have documented its effectiveness. It is available only in oral form, and the dosage ranges from 150 to 600 mg/d, usually in two or three divided doses. Pregabalin is also approved for use in neuropathic pain, including painful diabetic peripheral neuropathy and postherpetic neuralgia. It is the first drug in the USA approved for fibromyalgia. In Europe it is approved for generalized anxiety disorder. Moreover, pregabalin is widely used for off-label conditions such as substance use disorders, alcohol withdrawal syndrome, restless legs syndrome, migraine and vasomotor symptoms of menopause

Listing on WHO Model List of Essential Medicines

Pregabalin is not included in the WHO Model List of Essential Medicines. (WHO, 2017)

Marketing authorizations

Marketing authorizations for pregabalin as a medicine are held by many companies.

Industrial use

None

Non-medical use

Abuse of large doses of pregabalin (up to 20 times higher than the maximal dosage indicated) has been reported. This mostly seems to occur orally, but intravenous and nasal insufflation have also been reported.

Nature and magnitude of public health problems

The main public health problems reported from the non-medical use or misuse of pregabalin are overdose, suicidal ideation and impaired driving.

In a study of all medicolegal death cases in Finland, a total of 48.1% of the pregabalin positive cases, were associated with drug abuse and fatalities were associated with concurrent opioid use (Häkkinen et al., 2014).

Dizziness and somnolence, alone or together, can impair abilities for performance of potentially dangerous job functions, such as driving or operating complex or heavy machinery. These adverse events often occur when pregabalin is initiated, diminishing after weeks of therapy (Toth, 2014). In a study that measured the amount, nature of pregabalin abuse, and serum pregabalin levels of the drivers apprehended for driving under the influence of drugs (DUID) in Finland in 2012, 50% of the 206 cases had a serum concentration higher than the typical therapeutic range (Kriikku et al., 2014).

Licit production, consumption, and international trade

Pregabalin was approved in the European Union and the US in 2004.. As of October 2017, pregabalin was marketed under many brand names in other countries. In the UK, prescriptions for pregabalin have increased more than 11-fold in the last decade, from 476,102 in 2006 to 5,547,560 in 2016 (NHS, 2016). According to Pharma Marketing (2018), worldwide sales of pregabalin (Lyrica) in 2017 reached 10th position in terms of gross sales (about 5.1 billion USD), with an annual growth rate of about 2.8 %.

Illicit manufacture and traffic

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Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

Current international controls and their impact

Pregabalin is not currently under international control.

Current and past national controls

Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Pregabalin

B. *Chemical Abstract Service (CAS) Registry Number*

148553-50-8

C. *Other Chemical Names*

(S)-3-(aminomethyl)-5-methylhexanoic acid; (S+)-3-isobutyl-GABA
 (S)-(+)-3-isobutyl-gamma-aminobutyric acid
 (S)-(+)-4-amino-3-(2-methylpropyl)butanoic acid
 (S)-3-(Aminometyl)-5-metylhexanoic acid (WHO)
 (S)-3-(Aminometyl)-5-metylhexansäure (IUPAC)
 Hexanoic acid, 3-(aminometyl)-5-metyl-, (3S)-

D. *Trade Names*

Lyrica: Argentina; Australia; Austria; Belgium; Bosnia & Herzegovina; Brazil; Canada; Chile; China; Croatia (Hrvatska); Czech Republic; Denmark; Ecuador; Egypt; Finland; France; Georgia; Germany; Greece; Hong Kong; Hungary; Iceland; India; Indonesia; Ireland; Israel; Italy South Korea; Japan; Jordan; Latvia; Lebanon; Lithuania; Luxembourg; Malaysia; Myanmar; Netherlands; New Zealand; Norway; Oman; Peru; Philippines; Poland; Portugal; Romania; Russian Federation; Saudi Arabia; Serbia; Singapore; Slovakia; Slovenia; South Africa; Spain; Sweden; Switzerland; Thailand; Tunisia; Turkey; United Kingdom; United States; Vietnam.

Other Trade Names:

Argentina	Axual, Balifibro, Clasica, Dolgenal, Gavin, Kabian, Linprel, Mystika, Neuristan, Plenica, Prebanal, Prebictal, Prebien
Bangladesh	Gaba-PGabarol, Lyric, Neurega, Neurolin, Neurovan, PG, Prebalin, Pregaba, Pregaben, Pregadel, Pregan, Prelin, Pretor, Priga, Xablin, Xil
Bosnia & Herzegowina	Epica, Epiron, Pagamax
Canada	Apo-Pregabalin, PMS-Pregabalin, Pregabalin Sanis Health, RAN-Pregabalin, Sandoz Pregabalin, Teva-Pregabalin
Chile	Alivax, Neurum, Plenica, Prebictal, Prefaxil, Pregalex, Pregalin, Pregobin, Prestat
Colombia	Dolica, Martesia, Pregabalina Ecar, Pregabalina MK, Preludyo
Costa Rica	Martesia
Egypt	Andogablin, Averopreg, Convugabalin, Dapapalin,

	Dragonor, Gablovac, Glonervya, Hexgabalin, Irenyphatic, Kemirica, Lyrineur, Lyrolin, Neuragabalin, Painica, Pregaba, Pregatrend, Pregavalex, Pregdin Apex, Serigabtin, Vronogabic
El Salvador	Martesia, Pregabateg, Prelyx
Ecuador	Neurum, Prebictal, Pregobin
Estonia	Brieka, Pragiola, Pregabalin Alvogen, Pregabalin Teva, Pregagamma, Pregamid
France	Pregabaline Sandoz GmbH
Georgia	Helimon
Guatamala	Martesia, Pregabateg
Honduras	Martesia
Hong Kong	Apo-Pregabalin
Iceland	Pregabalin Krka
India	Gabanext, Nuramed, Pevesca, Prebel, Pregaba, Pregabin, Pregacent, Preganerve, Pregastar, Pregeb-OD, Prejunate, Preneurolin, Resenz
Indonesia	Aprion, Provelyn
Jordan	NeoGaba, Epigab, Regab, Zega, Galica
Lebanon	Gabrika, Plenica
Mexico	Dismedox, Gialtyn, Kineptia
Myanmar	Maxgalin
Netherlands	Lingabat
Nicaragua	Martesia
Panama	Martesia
Peru	Neurum, Prebictal, Pregalex, Pregobin
Poland	Pragiola, Pregabalin Pfizer
Portugal	Pregabalina Alter, Pregabalina Baldacci, Pregabalina Cinfa, Pregabalina Farmoz, Pregabalina Gática, Pregabalina Generis, Pregabalina Jaba, Pregabalina Kipa, Pregabalina Pentafarma, Pregabalina Pharmakern, Pregabalina Ratiopharm, Pregabalina Tetrafarma, Pregabalina Teva, Pregabalina ToLife
Netherlands	Pregabaline AET, Pregabaline Aurobindo, Pregabaline, CFPregabaline Hetero, Pregabaline Krka, Pregabaline Ranbaxy, Pregabaline Teva, Pregabaline Torrent, Pregabaline Wockhardt, Pregagamma, Pregamid
Russian Federation	Algerika, Pregabalin-Richter
Slovakia	Pregabalin Sandoz
Slovenia	Ecubalin, Pragiola
South Korea	Newrica, Pregalin
Spain	Pregabalina Apotex, Pregabalina Cinfa, Pregabalina Kern Pharma, Pregabalina Stada Genericos, Pregabalina Tarbis

Switzerland	Pregabalin Pfizer, Pregabalin-Mepha
Thailand	Pregabalin Sandoz
Turkey	Alyse, NeuricaPaden, Pagadin, Regapen, Symra
United Kingdom	Lecaent, Rewisca,
Vietnam	Gabica, Gablin, Pregobin, Premilin

(Drugs.com 2018)

E. Street Names

Budweiser (Millar et al., 2013); Lulu, Lalyse, the trip (Al-Husseini et al., 2018a); Gabbies, Bud light (drugs.ie, 2018); Fizers (Extern, 2018)

F. Physical Appearance

White to off-white crystalline solid
(Physicians' Desk Reference 2007)

G. WHO Review History

Pregabalin has been previously pre-reviewed by the 39th WHO- ECDD in 2017.

2. Chemistry (PubChem, 2018)

A. Chemical Name

IUPAC Name:

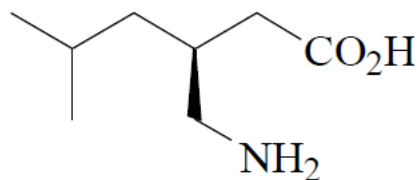
(3S)-3-(aminomethyl)-5-methylhexanoic acid

CA Index Name:

Hexanoic acid, 3-(aminomethyl)-5-methyl-, (3S)-

B. Chemical Structure

Free base:



(Pfizer, 2016)

Molecular Formula: C₈H₁₇NO₂

Molecular Weight: 159.23

C. Stereoisomers

Pregabalin is the (S)-(+)-isomer of 3-isobutyl-GABA

D. Methods and Ease of Illicit Manufacturing

No information was found on methods of illicit manufacturing. Published literature describes enantioselective synthesis methods. (Burk 2003, Yu 2012)

E. Chemical Properties (O'Neil, 2001)

Melting point 186-188°C

Boiling point 274°C at 760 mm Hg

Solubility Freely soluble in water and both basic and acidic solutions. (Physician's Desk Reference, 2007)

In water, 1.2X10+4 mg/L at 25 deg C (est) (US EPA, 2007)

F. Identification and Analysis

Several methods have been developed for identification of pregabalin. This includes liquid chromatography–tandem mass spectrometry (LC–MS–MS) methods in human urine (Heltsley et al., 2011) and human serum (Oertel et al., 2009); high-performance liquid chromatography (HPLC) methods in human serum (Vermeij et al., 2004) and for capsule contents (Kasawar et al., 2010); a high-performance liquid chromatography – mass spectrometry (HPLC-MS) method in post-mortem samples (Priez-Barallon et al., 2014); a spectrophotometric method for capsule contents (Bali 2011); nonaqueous CE-TOF-MS. Electrophoresis (Rodriguez et al., 2013) and immunoassay methods for human urine (Spigset and Westin, 2013).

3. Ease of Convertibility Into Controlled Substances

No information was found on the conversion of pregabalin into other controlled substances.

4. General Pharmacology

A. Routes of administration and dosage

Pregabalin pharmaceutical products are available to be taken orally

- **Capsule, Oral:**
- 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg
- **Solution, Oral:**
- 20 mg/mL (473 mL)
- **Tablet Extended Release 24 Hour, Oral:**
- 82.5 mg, 165 mg, 330 mg

<i>Diabetic Neuropathy</i>	-Initial dose: 50 mg orally 3 times a day -Titration: The dose may be increased to 100 mg orally 3 times a day within 1 week based on efficacy and tolerability -Maximum dose: 300 mg/day
<i>Postherpetic Neuralgia</i>	- Initial: 150-300 mg/day PO divided q8-12hr Maintenance: May increase to 300 mg/day divided q8-12hr after 1 week, as needed.
<i>Partial Seizure</i>	- Initial: 150 mg/day PO divided q8-12hr - Maintenance: Based on clinical response and tolerability, may increase dose in weekly increments, not to exceed 600 mg/day
<i>Fibromyalgia</i>	-Initial: 150 mg/day PO divided q12hr -Maintenance: May increase to 300-450 mg/day divided q12hr after 1 week, as needed
<i>Neuropathic Pain</i>	-- Initial: 150 mg/day PO divided q12hr; may increase within 1 week to 300 mg/day PO divided q12hr -If there is insufficient pain relief after 2-3 weeks and 300 mg/day dose is tolerated, may increase dose again up to 600 mg/day PO divided q12hr

- **Dosage of Pregabalin for non-medical purposes (*ie-Drug Abuse*):**

Other routes of pregabalin administration have been reported including injecting, smoking or inhaling. (Evoy et al., 2017). Dosages reported by those using non-medically are typically higher than therapeutic doses. In published case reports the dosages have ranged from 800 – 7500 mg/day. (Evoy et al., 2017)

B. Pharmacokinetics

Absorption

Pregabalin is well absorbed after oral administration: Oral bioavailability is 90% or more and peak plasma concentrations are achieved within 1.5 of oral administration.. Maximum plasma concentrations (C max) are proportional to the dose administered. When given with food, absorption is slowed, resulting in a decrease in Cmax and an increase in Tmax.

There are two different formulations of pregabalin with different pharmacokinetic profiles, including extended release. Pregabalin, is rapidly absorbed in the fasting state with Tmax of 0.7 hours, while pregabalin CR (extended release) has a Tmax of 8 hours. Pregabalin is absorbed from the small intestine. (Drug Bank, 2018)

Distribution

Pregabalin does not bind to plasma proteins. The apparent volume of distribution after oral administration is 0.5 L/kg. (Drug Bank, 2018). Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. (*Physicians' Desk Reference 2007*)

Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys. (Schulze-Bonhage, 2013).

Pregabalin half-life is approximately 6 hours and steady state is achieved within 24-48 hours of repeated administration.

C. Pharmacodynamics

Pregabalin is an analogue of the gamma-aminobutyric acid (GABA) mammalian neurotransmitter and its structurally related compound gabapentin are known as $\alpha 2$ - δ ligands. Pregabalin reduces central neuronal excitability by binding to an auxiliary subunit ($\alpha 2$ - δ protein) of voltage-gated calcium channels on neurons in the central nervous system and decreases the release of several neurotransmitters, including glutamate, noradrenaline and substance P. Endogenous ligands include the amino acids L-leucine, L-isoleucine, and L-valine. Despite similarities to gamma-aminobutyric acid (GABA), it does not act at GABA receptors or synapses. Pregabalin reduces the neuronal activation of hyperexcited neurons while normal activation remains unaffected (Papazisis and Tzachanis, 2014). Pregabalin is approved for the treatment of partial epilepsy; generalized anxiety disorder (GAD); post-herpetic neuralgia; peripheral and central neuropathic pain and fibromyalgia (in the USA but not in the UK; Morrison et al., 2017) with an accepted dosage range of 150 mg to 600 mg/day (Papazisis and Tzachanis, 2014). It appears that the therapeutic actions for all of

these conditions are mediated through pregabalin's actions on the $\alpha 2$ - δ protein. It has been suggested that these disorders may share neuronal hyperactivity in a variety of brain circuits that pregabalin helps to normalize. (Stahl 2013).

Pregabalin does not block sodium channels, is not active at opioid receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake. (Porter et al, 2018) Further study on the actions of pregabalin in different brain regions is needed. The exact mechanism for producing euphoric effects or physical dependence is not known at this time.

5. Toxicology

Preclinical Acute Toxicology

There were no deaths following administration of single oral doses of pregabalin of 5000 mg/kg or single IV doses of 300 mg/kg to mice and rats, nor changes in biochemical parameters, however, there were observations of hypoactivity, diarrhea and urine staining. Pregabalin was not genotoxic in vitro, nor in rats in doses up to 2000 mg/kg. (Pfizer, 2016)

Preclinical Chronic Toxicology

There was a dose-dependent increase in hemangiosarcomas in 2 strains of mice with 200 to 5000 mg/kg in their diet for 2 years. The exposure was considered to be similar to human exposure at 600 mg/day. Tumorigenic potential is included in the Warnings and Precaution section of the product monograph. Skin lesions were seen at exposures equivalent to 2 to 8 times that of human exposure at 600 mg/day, ranging from erythema to necrosis. Ocular lesions were detected in rats at exposures more than twice those in humans at 600 mg/day. The following have been observed in animal toxicology studies with exposures from 2 to 69 weeks: ataxia and hypoactivity in rats and monkeys at repeated oral doses \geq 500 mg/kg; tail dermatopathy and urine staining in rats \geq 250 mg/kg and monkeys up to 500 mg/kg; urinary bladder changes and mortality with pyelonephritis/cystitis in rats at \geq 250 mg/kg; reversible platelet count decreases of 14-36% in rats at \geq 50 mg/kg in males and \geq 100 mg/kg in females; no changes in hematology up to 500 mg/kg in monkeys; bone marrow total nucleated cell decreases 18-44% in rats at 150-1250 mg/kg, with no changes up to 50 mg/kg in rats nor in monkeys; no effects on body weight gain at 50 mg/kg or 150 mg/kg and no effects on monkeys up to 500 mg/kg; nasal discharge and diarrhea in monkeys at \geq 100mg/kg; and deaths in 3 days in monkeys at doses of 1000 or 2000 mg/kg. (Pfizer, 2016).

Teratogenicity

The evidence on possible fetal effects of pregabalin is currently limited and somewhat contradictory.

Studies conducted by Pfizer as part of the registration process for pregabalin found no evidence of teratogenic effects in mice, rats or rabbits (Morse 2016a, 2016b). However, a recent study in mice found evidence of dose-dependent increases in fetal resorptions and decreases in litter size, fetal length and weight. A range of minor malformations were also reported (Singh & Gupta 2018).

While one recent survey in women using pregabalin during pregnancy had suggested the possibility of congenital malformations, this was not confirmed in a larger sample (Patorno et al, 2017)

Reproduction

There were no effects on female rat fertility when pregabalin was given at high doses. Male rats had reversible decreased sperm motility and fertility at doses \geq 27 times human exposure, but the same effect was not observed in monkeys. (Pfizer, 2016)

Postmortem Toxicology

Data on prevalence of pregabalin in deceased persons is available from several countries. In Finland, 4.2% (68/1623) of deceased young adults had pregabalin detected over a 3 year period. (Launiainen et al., 2011). 2.3% (316/13,766) of all toxicologically investigated medico-legal cases from 2010-2011 in Finland had pregabalin involved. 48% (152/316) of pregabalin cases were attributed to abuse. (Hakkinen et al., 2014)

In Germany, 4.4% (43/982) of all postmortem toxicology cases had pregabalin detected from 2010-2012. In the first year studied, the rate was 2% (10/489), whereas by the second year it had substantially increased to 6.7% (33/493). Within drug dependent individuals, the rate went from 5.5% (4/72) to 29.8% (26/87) over the 2 year period. (Lottner-Nau et al., 2013)

Pregabalin was detected in 70 post-mortem blood samples in the UK over 2 years (2012-2014), of which 33% were at concentrations considered to be in excess of the reference range (above 17mg/L). 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 included. (Eastwood and Davison, 2016)

6. Adverse Reactions in Humans

In a meta-analysis of clinical trial data (Zaccara et al. 2012), 20 adverse events were associated with pregabalin use: dizziness, vertigo, incoordination, balance disorder, ataxia, diplopia, blurred vision, amblyopia, tremor, somnolence, confusional state, disturbance in attention, thinking abnormal, euphoria, asthenia, fatigue, edema, peripheral edema, dry mouth, constipation). The strongest associations were found for events related to cognition and coordination. The authors also reported no significant association between serious adverse events and use of pregabalin.

The incidence of these most common adverse events increases with larger pregabalin doses. From Pfizer clinical trial data, dizziness and somnolence appear to be the two most common adverse events: dizziness was reported by 31% of patients compared with 9% of those receiving placebo. Somnolence was reported by 22% of patients compared with 7% of those receiving placebo (Pfizer, 2005). These two symptoms are also the most common reasons given for discontinuance of pregabalin treatment. (Toth, 2014).

In doses above the normal therapeutic range, sedation, dissociation, relaxation, pleasure, drowsiness, disinhibition, improved sociability, empathy and auditory and visual hallucinations may occur. 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). The experience of euphoria might be the key factor that incites some patients to misuse large doses of pregabalin (Evoy et al., 2017). The meta-analysis of 38 trials described above noted euphoria to be the second most commonly reported pregabalin adverse event (Zaccara et al., 2012). Euphoria was reported in pregabalin but not in gabapentin pre-marketing trials (Schifano et al., 2011) This was anecdotally reported to be due to gabapentin being less potent, having slower onset and thus requiring higher doses to achieve the same effect. (Evoy et al., 2017).

Drug Interactions

The pharmacokinetic profile of pregabalin limits the potential for pharmacokinetic drug-drug interactions (i.e., it is not metabolized and does not exhibit plasma protein binding). In addition, in vitro evidence suggests pregabalin does not inhibit drug metabolizing enzymes. Nevertheless, a few papers suggest an interaction of pregabalin with clozapine (Englisch et al., 2012; Gahr et al., 2012) and opioids; Hasanein and Shakeri, 2014). For opioids, there is evidence of attenuation of the development of tolerance and physical dependence and reports of enhanced analgesia/opioid sparing effects from a combination of pregabalin and an opioid.

Potential pharmacodynamic interactions include additive effects of impaired cognition, impaired gross motor function, and respiratory failure and coma in combination with other CNS depressants, including ethanol and lorazepam.

Adverse Drug Reaction Reporting Databases

- 8% (16/198) of drug dependence reports were related to pregabalin (up to 2009) in the Swedish national register of adverse drug reactions (SWEDIS, Schwan 2010)
- 3.5% (55/1552) of reports for pregabalin were related to abuse (n=11) or dependence (n=44) reported from 2008-2012 to the German Federal Institute for Drugs and Medical Devices. (Gahr 2013a)
- 6.6% (7639/115,616) of reports for pregabalin were related to abuse/dependence/misuse from 2006-2015 in the European Medicine Agency Spontaneous Adverse Drug Reaction Reporting System. (Chiappini and Schifano, 2016)
- 1.5% (8/521) of abuse/dependence reports were related to pregabalin from 2010-2015 in the French Pharmacovigilance Database. (Bossard et al., 2016)
- A total of 4,152 intentional abuse cases exposed to pregabalin or gabapentin in data were extracted from the National Poison Data system in the USA (2006-2014). The rate increased 4.3 fold between 2006 and 2014. (Dart et al., 2017)
- 5421 Individual Case Safety Reports (ICSRs) from 42 countries for pregabalin reporting an adverse drug reaction related to drug abuse and dependence in WHO VigiBase® (1968-May 2018). The majority were from the US (71%), Germany (7%), UK (6%; WHO, 2018)
- There has been a marked increase in reports (3 fold) for pregabalin; from 216 ICSRs in 2013 to 680 in 2014. (WHO, 2018)

7. Dependence Potential

A. Animal Studies

Reviews by the US Centre for Drug Evaluation and Research for Pfizer's New Drug Application submission indicated that preclinical studies conducted in monkeys using a self-injection paradigm suggest that tolerance may develop to the reinforcing effects of pregabalin since self-administration decreased after one week. (Center for Drug Evaluation and Research, FDA 2004) There appears to be no systematic preclinical evaluation of withdrawal following chronic pregabalin administration.

B. Human Studies

Tolerance

The latest VigiBase® report of WHO Global database in Uppsala in May 2018, reported 138 reports of “Drug Tolerance” codes for pregabalin from 12 countries in which 75% of cases were for pregabalin as the only suspected medicine. In addition, 23 reports from 5 countries were “Drug Tolerance increased”, in which 83% of cases were for pregabalin as the only suspected medicine. (WHO, 2018)

Reviews by the US Centre for Drug Evaluation and Research for Pfizer’s New Drug Application submission indicated that evidence from Phase2/3 clinical studies support the development of tolerance to the euphoric effects since the euphoria receded while patients were still taking pregabalin. (Center for Drug Evaluation and Research, FDA 2004)

An investigation for possible abuse liability of pregabalin were measured by a study conducted in Sweden in 2010. Done by applying a Bayesian data-mining algorithm to reports of possible drug abuse or addiction in the Swedish national register of adverse drug reactions (SWEDIS), the author calculated the information component (IC) for pregabalin and reports of abuse and addiction. Only 16/198 concerned pregabalin (Schwan et al., 2010). Two reports were coded as “tolerance increased” where patients increased their doses above the maximum recommended (1,200 and 3,000 mg/day) because of the waning of effect.

Withdrawal

The US Centre for Drug Evaluation and Research reviewed evidence from Pfizer’s New Drug Application submission in 2004 and summarized the following points which were suggestive of withdrawal symptoms and indicative of physical dependence (FDA center for Drug Evaluation and Research, 2004):

- Discontinuation-emergent symptoms from short- and long-term psychiatric studies that were more frequent in pregabalin treated patients compared to placebo treated patients were insomnia, headache, nausea, infections, diarrhea, and chills.
- Scores on the Physician’s Withdrawal Checklist in psychiatric studies were significantly different between pregabalin and placebo groups.
- Analysis of two pharmacokinetic studies showed discontinuation-emergent symptoms from pregabalin of headache, nausea and diarrhea, whereas from placebo the reports were of accidental injury, infection, skin disorder and ventricular extrasystole.

The current product monograph from Pfizer Canada Inc. indicates that following abrupt discontinuation of pregabalin in clinical studies some patients reported symptoms of insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea.

A withdrawal syndrome was reported in 4.3% of patients in the pregabalin group (n=70) at doses from 150 to 600 mg/day, with no reports in the placebo group (n=67). (Pfizer 2016) The apparent published paper of this study describes a serious adverse event in a patient one day following pregabalin discontinuation. The patient exhibited severe symptoms of spasticity with impaired coordination (more severe than previous episodes). (Siddall et al., 2006)

Published Pfizer-funded clinical trials using a discontinuation design rather than a placebo-control group have been conducted which incorporated a 1-week taper when pregabalin was stopped (i.e., for those randomized from pregabalin to placebo and at the end of the study for those taking pregabalin throughout). In general, the adverse event rates for nausea, headache, and diarrhea did not appear to be

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elevated for the placebo groups. However, treatment-emergent adverse events were reported globally for the treatment groups and not specifically during or after the taper periods, making interpretation of withdrawal effects difficult. (Gilron 2011, Arnold et al., 2014; Raskin et al., 2014)

Discontinuation effects following cessation of 12 and 24 wk of pregabalin treatment for generalized anxiety disorder (GAD) were evaluated in a placebo- and lorazepam-controlled, randomized, double-blind, multicentre trial conducted in 16 countries. Discontinuation effects were evaluated with the Physician Withdrawal Checklist (PWC) and reported discontinuation-emergent signs and symptoms. Rebound anxiety was measured with the Hamilton Anxiety Rating Scale. The study concluded that that risk of discontinuation symptoms and rebound anxiety were low for pregabalin after 12 and 24 weeks of treatment. The authors characterized these discontinuation symptoms as not clinically significant.

It is thought that the presence of psychiatric disorder may contribute to the development of drug dependence. (Aldemir et al., 2015; Gahr et al., 2015) Patients developed tolerance, drug seeking behaviour and withdrawal symptoms when stopping or decreasing the dose of pregabalin (Gahr et al., 2013 a; Halaby et al., 2015). There are a number of case reports of pregabalin withdrawal, most commonly in patients taking relatively high doses (eg, Sonmez 2015). A case of a patient with borderline personality disorder (Gahr et al., 2013a) and past alcohol abuse reported that pregabalin had the potential to stimulate the development of habit forming and dependence type behaviors. One case reported that the reason for shifting from benzodiazepine to pregabalin abuse was the ease of obtaining medical prescriptions for pregabalin in comparison to benzodiazepines (Gahr et al., 2015).

In Norway, the Norwegian version of the Mini-International Neuropsychiatric Interview was used to identify pregabalin abuse or dependence, according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; American Psychiatric Association [APA], 1994). Five of the six subjects fulfilled DSM-IV criteria for pregabalin dependence. All five of these patients had co-morbid psychiatric conditions. Two subjects met DSM-IV criteria for abuse previously, but not currently. The study concluded that patients with chronic disease were more or less "dependent" on pregabalin and may have problems with withdrawal which might falsely be labeled as addiction. These cases suggested that the use of pregabalin may lead to drug dependence, even without abuse (Sugandiran & Bramness, 2014)

8. Abuse Potential

A. *Animal Studies*

Schjerner et al (2016b) identified 17 preclinical studies directly or indirectly investigating the abuse potential of pregabalin. These included 7 unpublished studies from the manufacturer provided by an FDA report (Center for Drug Evaluation and Research, FDA 2004). Five of these studies investigated the effect of pregabalin on other substances (e.g. cocaine, opioids and alcohol), which is considered as beyond the main scope of this report.

Andrews et al (2001) found that pregabalin did not induce Conditioned place preference (CPP; which was used to measure the rewarding potency of a drug) in doses up to 30 mg/kg. Further, pre-treatment with pregabalin reduced morphine induced CPP and also reversed established morphine-induced CPP. CPP was induced only with higher ("supratherapeutic") intraperitoneal (but not oral) pregabalin doses in rats. (Bonnet et al., 2018) Another study found that, in contrast to opioids, pregabalin showed no difference in CPP in painful or pain-free conditions in rats. (Rutten et al., 2011)

In one self-administration study, 3.2 g/kg and 10 mg/kg of pregabalin did produce positive reinforcing effects, while another study did not find any positive reinforcing effects of pregabalin (Center for Drug Evaluation and Research, FDA 2004).

A drug discrimination study reviewed by Schjerner et al (2016b), conducted by the manufacturer (Center for Drug Evaluation and Research, FDA 2004) showed that pregabalin did not differ from saline when administered to midazolam-treated monkeys.

B. *Human Studies*

There is one published study that used an abuse liability study design to evaluate the effects of pregabalin alone and in combination with oxycodone. (Zacny et al., 2012) This was a double-blind, randomized study in 16 healthy volunteers. The participants were each administered single doses of pregabalin 75 mg, pregabalin 150 mg, oxycodone 10 mg, and pregabalin 75 mg combined with oxycodone 10 mg in a cross-over design. Neither dose of pregabalin alone increased ratings of "like drug" or "take drug again" and there was no significant change in abuse liability related subjective measures when pregabalin was co-administered with oxycodone compared to oxycodone alone. This study demonstrated low abuse liability associated with low doses of pregabalin in people without psychiatric and substance use disorders histories.

Despite the findings of this report, as noted above, euphoria has been recorded as one of the more common adverse effects of pregabalin administration and may be more likely to occur at higher doses. In the analysis of the Swedish national register of adverse drug reactions (Schwan et al. 2010) there were reports of people becoming "high" and of "a nice benzodiazepine effect". Others described an effect similar to that of an "amphetamine trip" with euphoria.

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., 2018b).

Pregabalin use in populations with substance use disorders

Web sites, case reports and the Swedish National Register of Adverse Drug Reactions proposed that the drug may be abused, specifically by substance-dependent individuals (Skopp and Zimmer, 2011; Grosshans, et al., 2013).

Several case reports illustrated the abuse of pregabalin in patients using this drug for medical conditions such as pain control, generalized anxiety disorder (GAD), and neuropathic pain (Filipetto et al., 2010; Aksakal et al., 2012) and with previous histories of poly-substance abuse.

Three cases reported abuse of pregabalin in patients with a history of drug abuse (Grosshans et al., 2010) and observed that pregabalin had a lower abuse potential than benzodiazepines (Yargic & Ozdemiroglu, 2011). Two cases had no history of drug abuse but reported craving for pregabalin (Driot et al., 2016).

There is robust evidence in the literature that populations such as multiple drug users or patients in methadone treatment programs, have selected gabapentinoids due to their special features to boost a euphoric high and reduce withdrawal symptoms (Schwan et al. 2010, Schifano et al. 2011, Grosshans et al. 2013, Baird et al. 2013, Piralishvili et al. 2013, Wilens et al. 2015, Smith et al. 2015, Bastiaens et al. 2016; Bonnet et al., 2018). Of the gabapentinoids, there is a preference for pregabalin since it allows a more rapid and stronger euphoric high and relaxation than would be possible with gabapentin (Bockbader et al. 2010, Calandre et al. 2016). However, tolerance to these reinforcing effects of pregabalin encourage users to escalate the dose, which may lead to overdosing. At this juncture, pregabalin has been associated more closely with the hazards of these populations, such as behavioral dependence (Grosshans et al. 2010, Filipetto et al. 2010, Yargic & Ozdemiroglu 2011, Skopp & Zimmer 2012, Carrus & Schifano 2012, Aldemir et al. 2013, Papazisis et al. 2013, Gahr et al. 2013a, Barrett et al. 2015, Yazdi et al. 2015, Gahr et al. 2015) and even death (Häkkinen et al. 2014) in comparison with gabapentin.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

In Europe, pregabalin is licensed for epilepsy, neuropathic pain and generalized anxiety disorder (GAD), while in the US, the indications include fibromyalgia, postherpetic neuralgia and neuropathic pain following spinal cord injury or diabetes mellitus, but not GAD (Wattermark et al., 2014). Substantial off-label use is occurring for indications such as hypnotic-dependent insomnia (Cho et al., 2014), withdrawal from benzodiazepines (Papakosta et al., 2014), alcohol dependence (Martinotti et al., 2012), restless legs syndrome, migraine and vasomotor symptoms of menopause (Schjerning et al., 2016a; Evoy et al., 2017).

There is limited evidence supporting pregabalin for the treatment of opioid, benzodiazepine, nicotine and alcohol withdrawal symptoms, but data are promising and more studies, including those from appropriate randomized controlled trials, are required to further determine pregabalin efficacy and safety. (Freyenhagen et al., 2016). Given the potential for pregabalin misuse or abuse, (described below), particularly in individuals with a previous history of substance abuse, clinicians are advised to exercise caution when using pregabalin in this patient population. (Freyenhagen et al., 2016; Morrison et al., 2017). Pregabalin has also been claimed to be useful in the treatment of nicotine dependence, but because of its abuse potential, pregabalin should be used cautiously (Herman et al., 2012).

Drug Utilization Reviews

As greater risks are associated with higher doses it is important to examine statistics on prescribing practices:

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- In the UK, 1% (136/13,480) of outpatients prescribed pregabalin by general practitioners, were prescribed greater than 600 mg/day from 2004-2009. (Asomaning et al., 2016)
- In Denmark, 9.6% (4090/42,520) of pregabalin users were treated with more than 600 mg/day for 6 months in the time period 2004-2013. (Schjerning et al., 2016a)
- In Sweden, 8.5% (4130-48,550) of pregabalin users were prescribed greater than 600 mg/day. (Boden et al., 2014)

There is also evidence of increased rates of prescribing more generally:

- Digital Data provided by NHS shows that prescriptions for pregabalin have increased more than 11-fold in the last decade, from 476,102 in 2006 to 5,547,560 in 2016 (NHS, 2016)
- The use of pregabalin in Denmark has increased 10-fold during the last 10 years, and reached an estimated 5,858,000 daily defined doses (DDD) in 2016 (Data from National Institute for Health Data and Disease Control (Medstat.dk, 2018).
- Worldwide sales of pregabalin in 2017 reached 10th position in terms of gross sales (about 5.1 billion USD), with an annual growth rate of about 2.8 % (Pharma Marketing, 2018).

10. Listing on the WHO Model List of Essential Medicines

Pregabalin is not included in the WHO Model List of Essential Medicines. (WHO, 2017)

11. Marketing Authorizations (as a Medicinal Product)

Marketing authorizations for pregabalin as a medicine are held by many companies. Examples (not limited) are: Pliva Pliva Hrvatska, Laboratorio Chile, Abdi Ibrahim, Andalous, Apotex, Pharos, Averroes, Ivax, Buxton, Actavis Baltics Eesti, Craveri, Al Rowad, Debeiky, Pisa, Beta, Medley, Bioxell, Ecupharma, Actavis, Bosnalijek, AHPL, Renata, ACI, Getz Pharma, CCL, Gast Ph, Benta, Gador, Teva, Globe, Aversi, GNP, Amoun, Temis Lostalo, Chemi ph, Sandoz, Actavis UK, PharmaSwiss, Baliarda, Healthcare, Elite Ph, Hikma, Roemmers, Sun Pharma, Penn Pharmaceut, Grand Pharma, Ibn Sina, Koçak, Casasco, Square, Aristopharma, Laboratorio Saval, Icarus, Dong-A, Zydus, Wockhardt, Invision, Innokon, Bilim, Gen, Nobel, Alpha Gp, Peerage, USV, Eskayef, Laboratorios Raffo, Pharmascience, Krka, General Pharma, LKM, Johnlee, Johnlee, Medicamenta Ecuatoriana, Ariston, Andic, Royal Pharma, Egpi, Alvogen, Krka, Pfizer, Sandoz, Sanis Health, Teva Eesti, Alter, Apotex, Baldacci, Cinfa, Ecar, Farnoz, Alter, Generis, Jaba, Kern, Kipa, MK, Pentafarma, Pharmakern, Ratiopharm, STADA, Tarbis, Tetrafarma, Teva Pharma, ToLife, Alfred E. Tiefenbacher, Aurobindo, Centrafarm, Hetero, Krka, Ranbaxy, Sandoz, Teva, Torrent, Wockhardt, Mepha Pharma, Gedeon Richter, Laboratorio Tecnoquímicas, Incepta, Molekule, Crescent, Crescent, Delta, Wörwag, ABL Pharma, ITF - Labomed Farmaceutica, AHPL, G.L. Pharma, Navana, East West, East West, Invision, Lupin, Trend Ph, Eva, Apex, Torrent, Torrent, Little Greave, Drugtech, Molekule, Molekule, Drug International, Tecnoquimicas, Pail, Hasan, Franco-Indian, Franco-Indian, Laboratorio Bago, Malody, Sanofi-Aventis, Monico, Kalbe, Ranbaxy, Ilko, Sanofi Aventis, Strides Arcolab, Orchid, Consilient Health, Sanify, Sandoz, Serio Pharm, Sanovel, Teva Canada, FDC, Marcyrl, Novartis, and Orion.

12. Industrial Use

None.

13. Non-Medical Use, Abuse and Dependence

Abuse of pregabalin, at dosages up to 20 times higher than the maximal therapeutic dosage, mostly seem to occur orally, but intravenous, nasal insufflation (Ozturk and Morkavuk, 2018), rectal (“plugging”), smoking and “parachuting” (emptying the content of the capsule into a pouch) have also been reported (Schifano, 2014). Two case reports describe the abuse of pregabalin when used in high doses, when crushed formulations are smoked, and when ingested there were incidences of myositis (Carrus & Schifano, 2012).

Zellner et al. (2017) suggested that pregabalin was the fifth most frequently abused substance in a study conducted at the Poison Information Centre (PIC) in Munich. The study aimed at searching the database for all cases of pregabalin abuse admitted between 2008-2015. In addition, pregabalin users consumed additional substances significantly more than other patients. The most co-abused drugs were benzodiazepines (66.3%), methadone (48.8%), buprenorphine (32.5%) and heroin (22.5%; Zellner et al., 2017). Studies specifically assessing patients with opioid use disorder demonstrated that pregabalin abuse varied widely among this cohort, from 3% to 68%. (Grosshans et al., 2013; Wilens et al., 2015; Schjerning et al., 2016b).

A query of the entire database of the German BfArM regarding reports of pregabalin abuse or dependence between 2008 and 2012 was done. 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 mean pregabalin dosage of 1,424 mg. A withdrawal syndrome was noted in 32.7% (18/55) of pregabalin abuse/dependence-related reports to the German Federal Institute for Drugs and Medical Devices from 2008-2012. (Gahr et al., 2013a)

There have been 19 published case reports of pregabalin abuse from a range of different countries, including the USA (Filipetto et al., 2010), Turkey (Yargic & Ozdemiroglu, 2011; Aksakal et al., 2012; Aldemir et al., 2015; Sonmez, 2015; Ozturk and Morkavuk, 2018), 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 et al., 2015). **The characteristics of users include:**

- 12 males/7 females, with an age range of 19-65 years.
- Pregabalin maximum daily doses ranged from 800-7500 mg/day.
- 17/19 had a history of substance abuse.

In a separate case series of 10 inpatients from Switzerland, all patients tested positive for: cocaine, alcohol and/heroin in drug urine screening at admission. The major symptoms assessed were euphoria, psychomotor activation and sedation. (Suardi et al., 2016)

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

A lifetime prevalence of 0.25% for gabapentinoid abuse and dependence was reported in a German geriatric non-demented hospital population (Cossmann et al. 2016). In the UK, Kapil et al. (2014) found a 0.5% self-reported lifetime prevalence of misuse of pregabalin (Kapil et al. 2014).

Questionnaires/Surveys

- 22% (29/129) of respondents in 6 substance misuse clinics in UK, admitted to abusing gabapentinoids, out of which 38% (11/29) reported reason of abuse is to potentiate “high” they obtained from methadone. (Baird et al. 2013)

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- 0.5% (8/1500) of respondents to an online survey reported misuse of pregabalin. These respondents had a lifetime prevalence of use of recreational drugs that was comparable to national UK data. (Kapil et al., 2014)
- 7% of opioid dependent patients admitted for inpatient detoxification reported pregabalin misuse. (Wilens et al., 2015)
- 3% (4/129) of substance use disorder population in Scotland used non-prescribed pregabalin. (Baird et al., 2013)
- 68% of polysubstance use disorder patients in the United Arab Emirates used pregabalin. (Alblooshi et al., 2016)
- 20% (76/372) of reported prescription drugs suspected of abuse in community pharmacies in Jordan were for pregabalin. (Wazaify et al., 2017). Most suspected cases were for males with no age or socioeconomic status preference.
- 8.17% of 506 patients attending opioid substitution clinics admitted to using pregabalin (Piralishvili et al., 2013)

Urine/Hair Drug Screening

- 9.2% (39/425) of urine samples from opioid dependence treatment patients tested positive for pregabalin over a 3 month period in 2014 in Ireland, with only 10 patients prescribed the medication, giving an estimation of pregabalin abuse of 7.0% (McNamara et al., 2015)
- 12.1% (15/124) of urine samples from opioid dependence treatment patients tested positive for pregabalin, compared to 2.7% (3/111) in a cohort of patients with other substance use disorders. (Grosshans et al., 2013)
- Pregabalin use among opioid-addicted patients in Switzerland was 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.

Overdose

According to the National Poison Data System in the USA, the rate of pregabalin abuse cases increased 4.3 fold between 2006 to 2014 with medical outcomes ranging from moderate health effects to death (Dart et al., 2017). 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 the pregabalin positive cases were associated with drug abuse and can be fatal when mixed with opioids (Häkkinen et al., 2014). Electronic Poison Center data in the US have reported 23 cases of pregabalin abuse leading to impaired mental status (Wills et al., 2014). A suicidal case reported of a patient taking pregabalin and lamotrigine in overdoses highlights the need for clinical awareness around the adverse effects in both therapeutic and toxic doses (Braga & Chidley, 2007).

Suicidal Ideation

Suicides by pregabalin alone have not yet been described, although suicidal ideations have been reported after initiating gabapentinoid therapy (Mutschler et al. 2011)

Impaired Driving

Dizziness and somnolence, alone or together, can impair the ability to drive a motor vehicle or operate complex. These adverse events often occur when pregabalin is initiated, but frequently diminish after weeks of therapy. (Toth, 2014).

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).

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Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Illicit Manufacture and Traffic and Related Information

Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Current International Controls and Their Impact

Pregabalin is not currently under international controls.

17. Current and Past National Controls

Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

18. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None

References

- Aksakal, E., Bakirci, E. M., Emet, M., & Uzkeser, M. (2012). Complete atrioventricular block due to overdose of pregabalin. *The American journal of emergency medicine*, 30(9), 2101.e1-2101.e4.
- Alblooshi H, Hulse GK, El Kashef A, Al Hashmi H, Shawky M, Al Ghaferi H, et al. The pattern of substance use disorder in the United Arab Emirates in 2015: results of a National Rehabilitation Centre cohort study. *Subst Abuse Treat Prev Policy*. 2016;11:19.
- Aldemir, E., ALTINTOPRAK, A. E., & COŞKUNOL, H. (2015). Pregabalin dependence: a case report. *Turk Psikiyatri Dergisi*, 26 (3), 217-20.
- Al-Husseini, A., Wazaify, M., & Van Hout, M. C. (2018a). Pregabalin dispensing patterns in Amman-Jordan: An observational study from community pharmacies. *Saudi Pharmaceutical Journal*.;26(3):306-310
- Al-Husseini, A., Wazaify, M., & Van Hout, M. C. (2018b). Pregabalin Misuse and Abuse in Jordan: a Qualitative Study of User Experiences. *International Journal of Mental Health and Addiction*; 16: 642. 642-54.
- Al-Husseini, A., Van Hout, M. C. & Wazaify, M. (2018c). Pregabalin Misuse and Abuse: A Scoping Review of Extant Literature. *Journal of Drug Issues*;48 (3):1-21
- Andrews N, Loomis S, Blake R, Ferrigan L, Singh L, et al: Effect of gabapentin-like compounds on development and maintenance of morphine-induced conditioned place preference. *Psychopharmacology* 2001; 157:381–387
- Arnold LM, Arsenault P, Huffman C, Patrick JL, Messig M, Chew ML, Sanin L, Scavone JM, Pauer L, Clair AG. Once daily controlled-release pregabalin in the treatment of patients with fibromyalgia: a phase III, double-blind, randomized withdrawal, placebo-controlled study. *Curr Med Res Opin*. 2014;30(10):2069-83.
- Asomaning, K., Abramsky, S., Liu, Q., Zhou, X., Sobel, R. E., & Watt, S. (2016). Pregabalin prescriptions in the United Kingdom: a drug utilisation study of The Health Improvement Network (THIN) primary care database. *International journal of clinical practice*, 70(5), 380-388.
- Baird, C. R., Fox, P., & Colvin, L. A. (2013). Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers. *European addiction research*, 20 (3), 115-118.
- Berridge KC & Robinson TE: Liking, wanting, and the incentive-sensitization theory of addiction. *Am Psychol* 2016; 71:670-679
- Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet*. 2010;49(10):661-9.
- Bodén, R., Wettermark, B., Brandt, L., & Kieler, H. (2014). Factors associated with pregabalin dispensing at higher than the approved maximum dose. *European journal of clinical pharmacology*, 70 (2), 197-204.
- Bonnet, U., Scherbaum, N. (2017). How addictive are gabapentin and pregabalin? A systematic review. *European Neuropsychopharmacology*.
- Bonnet U, Richter EL, Isbruch K, Scherbaum N. On the addictive power of gabapentinoids: a mini-review. *Psychiatria Danubina*. 2018 Jun;30(2):142-149.

- Bossard, J. B., Ponté, C., Dupouy, J., Lapeyre-Mestre, M., & Jouanjus, E. (2016). Disproportionality analysis for the assessment of abuse and dependence potential of pregabalin in the French Pharmacovigilance Database. *Clinical drug investigation*, 36 (9), 735-742.
- Braga, A. J., & Chidley, K. (2007). Self-poisoning with lamotrigine and pregabalin. *Anaesthesia*, 62(5), 524-527.
- Burk MJ, de Koning PD, Grote TM, Hoekstra MS, Hoge G, Jennings RA, Kissel WS, Le TV, Lennon IC, Mulhern TA, Ramsden JA, Wade RA. An Enantioselective Synthesis of (S)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation. *J Org Chem*. 2003;68:5731-4.
- Calandre EP, Rico-Villademoros F & Slim M: Alpha2delta ligands, gabapentin, pregabalin and mirogabalin: a review of their clinical pharmacology and therapeutic use. *Expert Rev Neurother* 2016; 16:1263-1277

- Carrus, D., & Schifano, F. (2012). Pregabalin misuse–related issues; intake of large dosages, drug-smoking allegations, and possible association with myositis: two case reports. *Journal of clinical Psychopharmacology*, 32 (6), 839-840.
- Center for Drug Evaluation and Research. (2004). Pharmacology Review. In: Lyrica (pregabalin) capsules. Application No.:21-446 (FDA drug approval package). Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021724s000_PharmR.pdf (accessed Sep 24th, 2018)
- Chiappini S, Schifano F. A decade of gabapentinoid misuse: an analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' database. *CNS Drugs*. 2016 ;30(7):647-54
- Cho YW, Song ML. Effects of pregabalin in patients with hypnotic-dependent insomnia. *J Clin Sleep Med*. 2014;10(5):545–50.
- Cossmann JC, Scherbaum N & Bonnet U: Substance addiction in old age: A cross-sectional study in a German Hospital. *GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry* 2016; 29 :17-27
- Dart, R. C., Bartelson, B. B., Severtson, S. G., Bau, G., & Green, J. L. (2017). Increasing abuse of gabapentin and pregabalin as reported to US poison centers 2006 through 2014. *Drug & Alcohol Dependence*, 171, e51.
- 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.
- Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: placement of pregabalin into schedule V. Final rule. *Federal Register*. 2005;70(144):43633-5.
DrugBank. Record Name: Pregabalin. Retrieved from URL: <http://www.drugbank.ca/drugs/DB00230> (Accessed Aug 27th, 2018)
- Drugs.com. Pregabalin: <https://www.drugs.com/international/pregabalin.html> Accessed Sept 7, 2017
- DRUGS.ie Pregabalin Fact Sheet. Retrieved from: <http://www.drugs.ie/downloadDocs/2017/Pregabalin%20FactSheet%20Revision%20-%204.pdf>. (Accessed Sept 7, 2017)
- Eastwood, J. A., & Davison, E. (2016). Pregabalin concentrations in post-mortem blood—A two year study. *Forensic science international*, 266, 197-201.
- Englisch S, Alm B, Meyer-Lindenberg A & Zink M: Pregabalin-associated increase of clozapine serum levels. *J Clin Psychopharmacol* 2012; 32:127
- Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs*. 2017;77(4):403– 426.
- Extern. Pregabalin. Guidance for people working with pregabalin users. Ireland. <http://www.extern.org/news/extern-publishes-new-guidance-booklet-people-working-pregabalin-lyrica%C2%AE-users> (Accessed Sept 7, 2017)
- Filipetto, F. A., Zipp, C. P., & Coren, J. S. (2010). Potential for pregabalin abuse or diversion after past drug-seeking behavior. *The Journal of the American Osteopathic Association*, 110 (10), 605-607.
- Freynhagen 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.
- Fuzier R, Serres I, Guitton E, Lapeyre-Mestre M, Montastruc J (2013). Adverse drug reactions to gabapentin and pregabalin: a review of the French pharmacovigilance database. *Drug Saf*. 2013 Jan;36(1):55-62.
- Gahr M, Franke B, Freudenmann RW, Kölle MA & Schönfeldt-Lecuona C (2013a): Concerns about pregabalin: further experience with its potential of causing addictive behaviors. *Journal of Addiction Medicine*;7:147-9

- Gahr M, Freudenmann RW, Hiemke C, Kolle MA, Schönfeldt-Lecuona C. (2013b). Pregabalin abuse and dependence in Germany: results from a database query. *European Journal of Clinical Pharmacology*;69(6):1335–42.
- Gahr, M., Freudenmann, R. W., Kölle, M. A., & Schönfeldt-Lecuona, C. (2014). Pregabalin and addiction: lessons from published cases. *Journal of Substance Use*, 19(6), 448-449.
- Gahr M, Freudenmann RW, Kölle MA, Schönfeldt-Lecuona C. (2015). From benzodiazepine to pregabalin dependence: Different agents, similar problems. *Indian J Psychiatry* ;57(1):111-2
- Gahr M, Schmid MM, Schönfeldt-Lecuona C. Pregabalin-associated elevation of clozapine serum levels. *Pharmacopsychiatry*. 2012 Nov;45(7):297-9.
- Gilron I, Wajsbrot D, Therrien F, Lemay J. Pregabalin for Peripheral Neuropathic Pain: A Multicenter, Enriched Enrollment Randomized Withdrawal Placebo-controlled Trial. *Clin J Pain*. 2011;27:185-93.
- Goodman CW, Brett AS. (2017) Gabapentin and Pregabalin for Pain — Is Increased Prescribing a Cause for Concern? *N Eng J Med*;377(5):411-4
- Grosshans M, Mutschler J, Hermann D, Klein O, Dressing H, Kiefer F, et al. (2010) Pregabalin abuse, dependence, and withdrawal: a case report. *American Journal of Psychiatry*;167(7):869.
- Grosshans, M., Lemenager, T., Vollmert, C., Kaemmerer, N., Schreiner, R., Mutschler, J., ... & Hermann, D. (2013). Pregabalin abuse among opiate addicted patients. *European journal of clinical pharmacology*, 69 (12), 2021-2025.
- Häkkinen, M., Vuori, E., Kalso, E., Gergov, M., & Ojanperä, I. (2014). Profiles of pregabalin and gabapentin abuse by postmortem toxicology. *Forensic science international*, 241, 1-6.
- Halaby, A., Abou Kassm, S., & J Naja, W. (2015). Pregabalin dependence: a case report. *Current drug safety*, 10(2), 184-186.
- Hasanein, P. & Shakeri, S. (2014) Pregabalin role in inhibition of morphine analgesic tolerance and physical dependency in rats. *European Journal of Pharmacology* 742: 113-7.
- Heltsley R, Depriest A, Black DL, Robert T, Caplan YH, Cone EJ. Urine drug testing of chronic pain patients. IV. Prevalence of gabapentin and pregabalin. *J Anal Toxicol*. 2011;35(6):357-9.
- Herman, A. I., Waters, A. J., McKee, S. A., & Sofuoglu, M. (2012). Effects of pregabalin on smoking behavior, withdrawal symptoms, and cognitive performance in smokers. *Psychopharmacology*, 220(3), 611-617.
- Iversen. Pregabalin and Gabapentin Advice. Advisory Council on the Misuse of Drugs (2016). <https://www.gov.uk/government/publications/advice-on-the-anticonvulsant-drugs-pregabalin-and-gabapentin> (Accessed Sept 7, 2017)
- Jordan Food and drug Administration (JFDA). (2017), Pregabalin scheduling in Jordan. Can be obtained from URL: <http://www.ifda.jo/EchoBusV3.0/SystemAssets/PDF/AR/LawsAndRegulation/Drug/DrugsAndPsychotropicSubstances.pdf> (accessed Aug 25th, 2018)
- Kapil, V., Green, J. L., Le Lait, M. C., Wood, D. M., & Dargan, P. I. (2014). Misuse of the γ -aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. *British journal of clinical pharmacology*, 78 (1), 190-191.
- Kasawar GB, Farooqui MN. Development and Validation of HPLC Method for the Determination of Pregabalin in Capsules. *Indian J Pharm Sci*. 2010;72(4):517–9.
- Kasper S, Iglesias-García C, Schweizer E, Wilson J, DuBrava S, Prieto R, Pitman VW, Knapp L. Pregabalin long-term treatment and assessment of discontinuation in patients with generalized anxiety disorder. *Int J Neuropsychopharmacol*. 2014 May;17(5):685-95.
- Knake S, Klein KM, Hattemer K, et al. Pregabalin-induced generalized myoclonic status epilepticus in patients with chronic pain. *Epilepsy Behav*. 2007;11 (3):471–473.
- Kriikku, P., Wilhelm, L., Rintatalo, J., Hurme, J., Kramer, J., & Ojanperä, I. (2014). Pregabalin serum levels in apprehended drivers. *Forensic science international*, 243, 112-116.

- Launiainen T, Broms U, Keskitalo-Vuokko K, Pitkaniemi J, Pelander A, Kaprio J, et al. Nicotine, alcohol, and drug findings in young adults in a population-based postmortem database. *Nicotine Tob Res.* 2011;13(9):763–71.
- Loftus, H., & Wright, A. (2014). Potential misuse of pregabalin and gabapentin. *BMJ*, 348, g1290.
- Lottner-Nau S, Ovguer B, Paul LD, Graw M, Sachs H, Roeder G. Abuse of pregabalin—results of the postmortem toxicology from 2010–2012. *Toxichem Krimtech.* 2013;80:339.
- Lyndon, A., Audrey, S., Wells, C., Burnell, E. S., Ingle, S., Hill, R.,Henderson, G. (2017). Risk to heroin users of polydrug use of pregabalin or gabapentin. *Addiction*, 112, 1580-1589.
- Martinotti G, Clerici M, Janiri L. (2012). Pregabalin for alcohol dependence: a critical review of the literature. *Advances in Therapy*;29:947–57. 9.
- McNamara S, Stokes S, Kilduff R, Shine A. Pregabalin abuse amongst opioid substitution treatment patients. *Ir Med J.* 2015;108(10):309–10.
- Medstat.dk-National Institute for Health Data and Disease Control. Usage data on Lyrica. 2014. <http://medstat.dk/en>. (Accessed Sep 25th, 2018)
- Mersfelder TL & Nichols WH: Gabapentin: Abuse, Dependence, and Withdrawal. *Ann Pharmacother* 2016; 50:229-33
- Millar, J., Sadasivan, S., Weatherup, N., & Lutton, S. (2013). Lyrica nights—recreational pregabalin abuse in an urban emergency department. *Emergency Medicine Journal*, 30 (10), 874
- Morrison EE, Sandilands EA, Webb DJ. Gabapentin and pregabalin: do the benefits outweigh the harms? *J R Coll Physicians Edinb* 2017; 47: 310–3
- Morse, D. C. (2016a). Embryo-Fetal Developmental Toxicity Studies with Pregabalin in Mice and Rabbits. *Birth Defects Research Part B: Developmental and Reproductive Toxicology*, 107(2), 85–93. Morse DC, Henck JW, Bailey SA (2016b). Developmental Toxicity Studies with Pregabalin in Rats: Significance of Alterations in Skull Bone Morphology. *Birth Defects Res B Dev Reprod Toxicol.* 107(2):94-107.
- Mutschler J, Grosshans M, Herwig U, Heekeren K, Kawohl W & Brühl A: Pregabalin-induced suicidal ideations. *Pharmacopsychiatry* 2011; 44:119
- Mutschler, J., Gastberger, S., Baumgartner, M. R., Grosshans, M., Seifritz, E., Quednow, B. B., & Herdener, M. (2016). Pregabalin use among opioid-addicted patients in Switzerland. *The Journal of Clinical Psychiatry*, 77, 1202-1203.
- National Institute on Drug Abuse (NIDA). (2014). Commonly Abused Drugs Charts. Retrieved from. <https://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs> charts. (Last accessed 10 May 2017).
- Oertel R, Arenz N, Pietsch J, Kirch W. Simultaneous determination of three anticonvulsants using hydrophilic interaction LC–MS. *J Sep Sci.* 2009;32(2):238–43.
- 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.
- O'Neil, M.J. (ed.). (2001). *The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals*. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., p. 1381
- Osman, M., & Casey, P. (2014). Pregabalin abuse for enhancing sexual performance: case discussion and literature review. *Irish Journal of Psychological Medicine*, 31(04), 281-286.
- Oulis P, Konstantakopoulos G, Kouzoupis AV, Masdrakis VG, Karakatsanis NA, Karapoulos E, Kontoangelos KA, Papadimitriou GN. Pregabalin in the discontinuation of long-term benzodiazepines' use. *Hum Psychopharmacol.* 2008b Jun;23(4):337-40.
- Ozturk HM & Morkavuk G (2018): Nasal pregabalin overdose and myoclonus: a new way of misuse, *Psychiatry and Clinical Psychopharmacology*, DOI: 10.1080/24750573.2017.1422959
- Papakosta VM, Masdrakis V, et al. Cognitive effects of pregabalin in the treatment of long-term benzodiazepine-use and dependence. *Hum Psychopharmacol.* 2014;29:224–9. 8. Guglielmo R,
- Papazisis, G., Garyfallos, G., Sardeli, C., & Kouvelas, D. (2013). Pregabalin abuse after past substance-seeking behavior. *International journal of clinical pharmacology and therapeutics*, 51 (5), 441-442.

- Patorno et al. (2017) Pregabalin use early in pregnancy and the risk of major congenital malformations. *Neurology* 88: 2020–2025.
- Pfizer Canada Inc. Lyrica® Product Monograph. December 6, 2016. http://www.pfizer.ca/sites/g/files/g10028126/f/201612/LYRICA_DC_PM_198215_6Dec2016_E.pdf Accessed September 7, 2017.evers
- Pfizer UK 2017. Lyrica Capsules. <http://www.medicines.org.uk/emc/print-document?documentId=14651> Accessed Sept 7, 2017.
- Pfizer USA Lyrica. December 2016. <http://labeling.pfizer.com/showlabeling.aspx?id=561> Accessed Sept 7, 2017.
- Pharma Marketing. Top 50 pharmaceutical products by global sales. 2018. http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales. (Accessed Sep 25th, 2018)
- Physicians Desk Reference 61st ed, Thomson PDR, Montvale, NJ 2007., p. 2539
- Porter RJ, Rogawski MA. Antiseizure Drugs. 2017 In: Katzung BG. eds. *Basic & Clinical Pharmacology*, 14e New York, NY: McGraw-Hill;
- Piralishvili G, Gamkrelidze I, Nikolaishvili N & Chavchanidze M: Needs assessment and treatment compliance at state opioid substitution treatment programmes in Georgia. *Georgian Med News* 2013; 214:28-32
- PubChem: Open Chemistry Database. Compound Summary for CID 5486971. Can be obtained from URL: <https://pubchem.ncbi.nlm.nih.gov/compound/Pregabalin#section=Top> (Last accessed on Sep 30th, 2018)
- Priez-Barallon C, Carlier J, Boyer B, Benslimma M, Fanton L, Mazoyer C, Gaillard Y. Quantification of Pregabalin Using Hydrophilic Interaction HPLC-High-Resolution MS. in *Postmortem Human Samples: Eighteen Case Reports*. *J Analytical Toxicol*. 2014;38:143–8
- Raskin P, Huffman C, Toth C, Asmus MJ, Messig M, Sanchez RJ, Pauer L. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. *Clin J Pain*. 2014 May;30(5):379-90.
- Rodriguez J, Castaneda G, Munoz L: Direct determination of pregabalin in human urine by nonaqueous CE-TOF-MS. *Electrophoresis*. 2013 May;34(9-10):1429-36.
- Rutten K, De Vry J, Robens A, Tzschentke TM & van der Kam EL: Dissociation of rewarding, anti-aversive and anti-nociceptive effects of different classes of antinociceptives in the rat. *Eur J Pain* 2011; 15:299-305
- Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? *CNS Drugs*. 2014;28 (6):491–496.
- Schifano, F., D’Offizi, S. T. E. F. A. N. O., Piccione, M., Corazza, O., Deluca, P., Davey, Z., & Mannonen, M. (2011). Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. *Psychotherapy and psychosomatics*, 80(2), 118-122.
- Schjerning, O., Pottegård, A., Damkier, P., Rosenzweig, M., & Nielsen, J. (2016a). Use of Pregabalin—A Nationwide Pharmacoepidemiological Drug Utilization Study with Focus on Abuse Potential. *Pharmacopsychiatry*, 49 (04), 155-161.
- Schjerning, O., Rosenzweig, M., Pottegård, A., Damkier, P., & Nielsen, J. (2016b). Abuse Potential of Pregabalin: A Systematic Review. *CNS drugs*, 30 (1), 9-25.
- Schulze-Bonhage A. Pharmacokinetic and pharmacodynamic profile of pregabalin and its role in the treatment of epilepsy. *Expert Opin Drug Metab Toxicol*. 2013;9(1):105-15.
- 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. *European journal of clinical pharmacology*, 66 (9), 947-953.
- Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: A placebo-controlled trial. *Neurology*. 2006;67:1792-1800.

- Silverman RB. From Basic Science to Blockbuster Drug: The Discovery of Lyrica. *Angew Chem Int Ed*. 2008;47:3500-4.
- Singh K.P. & Gupta K. (2018) Teratogenic effects of third-generation antiepileptic drug, pregabalin: an in vivo study. *Current Drug Safety* 13: 113-121.
- Skopp, G., & Zimmer, G. (2011). [Pregabalin--a drug with abuse potential?]. *Archiv fur Kriminologie*, 229 (1-2), 44-54.
- Smith RV, Lofwall MR & Havens JR: Abuse and diversion of gabapentin among nonmedical prescription opioid users in Appalachian Kentucky. *Am J Psychiatry* 2015; 172:487-8
- Sonmez, M. B. (2015). Pregabalin use disorder. *Archives of Neuropsychiatry*, 52(4), 421-423.
- Spigset O1, Westin AA. Detection times of pregabalin in urine after illicit use: when should a positive specimen be considered a new intake? *Ther Drug Monit*. 2013 Feb;35(1):137-40.
- Stahl SM, Porreca F, Taylor CP, Cheung R, Thorpe AJ, Clair A. The diverse therapeutic actions of pregabalin: is a single mechanism responsible for several pharmacological activities?. *Trends in Pharmacol Sci*. 2013;34(6):332-9.
- Suardi, N. E., Preve, M., Godio, M., Bolla, E., Colombo, R. A., & Traber, R. (2016). Misuse of pregabalin: Case series and literature review. *European Psychiatry*, 33, S312.
- Sugandiran N, Bramness JG (2014) Pregabalin May Cause Dependence Even if It is Not Abused. *Arc Cas Rep CMed* 1(1): 001.
- Tandon, V. R., Mahajan, V., Gillani, Z. H., & Mahajan, A. (2013). Pregabalin-induced self-harm behavior. *Indian journal of pharmacology*, 45(6), 638.
- Toth C. (2014). Pregabalin: latest safety evidence and clinical implications for the management of neuropathic pain *Ther Adv Drug Saf*; 5(1) 38–56
- Tujii T, Kyaw WT, Iwaki H, Nishikawa N, Nagai M, Kubo M, Nomoto M. Evaluation of the effect of pregabalin on simulated driving ability using a driving simulator in healthy male volunteers. *Int J Gen Med*. 2014 Jan 29;7:103-8.
- Vashchinkina E, Piippo O, Vekovischeva O, Krupitsky E, Ilyuk R, Neznanov N, Kazankov K, Zaplatkin I, Korpi ER. Addiction-related interactions of pregabalin with morphine in mice and humans: reinforcing and inhibiting effects. *Addiction Biology*. 2017; doi:10.1111/adb.12538.
- Vermeij TAC, Edelbroek PM. Simultaneous high-performance liquid chromatographic analysis of pregabalin, gabapentin and vigabatrin in human serum by precolumn derivatization with o-phthalaldehyde and fluorescence detection. *J Chromatogr B*. 2004;810(2):297–303.
- Wazaify, M., Abood, E., Tahaine, L., & Albsoul-Younes, A. (2017). Jordanian community pharmacists' experience regarding prescription and nonprescription drug abuse and misuse in Jordan—An update. *Journal of Substance Use*; 22(5):463-8.
- Westin AA & Strøm EJ: [Yes, pregabalin can be abused!]. *Tidsskr Nor Laegeforen* 2010; 130:2108. [Article in Norwegian]
- Wettermark B, Brandt L, Kieler H, Boden R. Pregabalin is increasingly prescribed for neuropathic pain, generalised anxiety disorder and epilepsy but many patients discontinue treatment. *Int J Clin Pract*. 2014;68:104–10
- WHO. 20th WHO Model List of Essential Medicines (2017) http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1. (Accessed on Sep 29th, 2018)
- WHO. Descriptive analysis of reports of suspected adverse drug reactions for psychotropic medicines in the WHO global database of reports of adverse drug reactions, Vigibase®. Uppsala Monitoring Centre. Sweden. 2018
- Wilens T, Zulauf C, Ryland D, Carrellas N, Catalina-Wellington I. Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. *American Journal of Addiction*. 2015;24(2):173–7.

- Wood, D. M., Berry, D. J., Glover, G., Eastwood, J., & Dargan, P. I. (2010). Significant pregabalin toxicity managed with supportive care alone. *Journal of medical toxicology*, 6(4), 435-437.
- Yargic, I., & Ozdemiroglu, F. A. (2011). Pregabalin abuse: A case report. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology*, 21(1), 64-66.
- Yazdi, K., Hemetsberger, U., & Baier, C. (2015). Pregabalin Abuse Of Benzodiazepine And Alcohol Addicted Patient. *Psychiatria Danubina*, 27 (3), 0-279.
- Yu HJ, Shao C, Cui Z, Feng CG, Lin GQ. Highly Enantioselective Alkenylation of Cyclic α,β -Unsaturated Carbonyl Compounds as Catalyzed by a Rhodium–Diene Complex: Application to the Synthesis of (S)-Pregabalin and (-)- α -Kainic Acid. *Chem Eur J*. 2012;18:13274–8.
- Zaccara G, Gangemi P, Perucca P, Specchio L. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. *Epilepsia*. 2012;52:826–36.
- Zacny JP, Paice JA, Coalson DW. Subjective, psychomotor, and physiological effects of pregabalin alone and in combination with oxycodone in healthy volunteers. *Pharmacol Biochem Behav*. 2012;100(3):560–5.
- Zellner N, Eyer F, Zellner T. Alarming pregabalin abuse in Munich: prevalence, patterns of use and complications. *Dtsch Med Wochenschr*. 2017;142(19): e140–e147