CNS Drugs (2016) 30:9–25
DOI 10.1007/s40263-015-0303-6

SYSTEMATIC REVIEW

Abuse Potential of Pregabalin

A Systematic Review

Ole Schjerning[1,2,6] · Mary Rosenzweig[3] · Anton Pottegård[4] · Per Damkier[4,5] · Jimmi Nielsen[1,2]

Published online: 14 January 2016

Abstract

Background Several case reports and epidemiological studies have raised concern about the abuse potential of pregabalin, the use of which has increased substantially over the last decade. Pregabalin is, in some cases, used for recreational purposes and it has incurred attention among drug abusers for causing euphoric and dissociative effects when taken in doses exceeding normal therapeutic dosages or used by alternative routes of administration, such as nasal insufflation or venous injection. The magnitude of the abuse potential and the mechanism behind it are not fully known.

Objective The aim of this study was to present a systematic review of the data concerning the abuse potential of pregabalin.

Methods We performed a systematic literature search and reviewed the preclinical, clinical and epidemiological data on the abuse potential of pregabalin.

Results We included preclinical ($n = 17$), clinical ($n = 19$) and epidemiological ($n = 13$) studies addressing the abuse potential of pregabalin. We also reviewed case reports ($n = 9$) concerning abuse of pregabalin. The preclinical studies indicated that pregabalin possesses modulatory effects on the GABA and glutamate systems, leaving room for an abuse potential. Further, clinical studies reported euphoria as a frequent side effect in patients treated with pregabalin. The majority of case reports concerning abuse of pregabalin involved patients with a history of substance abuse and, similarly, epidemiological studies found evidence of abuse, especially among opiate abusers.

Conclusions Overall, the available literature suggests an important clinical abuse potential of pregabalin and prescribers should pay attention to signs of abuse, especially in patients with a history of substance abuse.

Key Points

Preclinical, clinical and epidemiological studies have raised concern about the abuse potential of pregabalin. This concern is further supported by case reports about pregabalin being used in doses that exceed normal therapeutic dosages.

Euphoria is a frequent side effect of treatment with pregabalin and this may be of special importance to the abuse potential of pregabalin.

Clinicians should be cautious when prescribing pregabalin, especially to patients with a history of substance abuse.

✉ Ole Schjerning
o.schjerning@rn.dk

1 Department of Psychiatry, Aalborg University Hospital, Aalborg, Denmark

2 Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

3 Danish Health and Medicines Authority, Copenhagen, Denmark

4 Clinical Pharmacology, Department of Public Health, University of Southern Denmark, Odense, Denmark

5 Department of Clinical Chemistry and Pharmacology, Odense University Hospital, Odense, Denmark

6 Centre for Schizophrenia, Brandevej 5, 9220 Aalborg, Denmark

1 Introduction

Pregabalin is an alkylated analogue of γ-amminobutyric acid (GABA) and structurally related to gabapentin. Pregabalin binds to the α2δ type 1 protein of the *P*/*Q* voltage-dependent calcium channel and reduces the central release of excitatory molecules [1]. In addition, GABA mimetic properties have been shown in rats [2].

The use of pregabalin in Denmark has increased 10-fold during the last 10 years, and reached an estimated 6,500,000 daily defined doses (DDD) in 2013 (Data from National Institute for Health Data and Disease Control [3]). According to Pharma Marketing, worldwide sales of pregabalin (Lyrica®) in 2014 reached 12th position in terms of gross sales (about 5.4 billion USD), with an annual growth rate of about 12 % [4]. In Europe, pregabalin holds marketing authorizations for epilepsy, neuropathic pain and generalized anxiety disorder (GAD), while in the US, this includes fibromyalgia, postherpetic neuralgia and neuropathic pain following spinal cord injury or diabetes mellitus, but not GAD [5]. A substantial off-label use has materialized, such as hypnotic-dependent insomnia [6], withdrawal of benzodiazepines [7] and alcohol dependence [8].

Although, pregabalin is considered well tolerated, euphoria was reported in about 5 % of all patients in a meta-analysis of pregabalin adverse events based on 38 clinical trials [9]. Further, case reports have suggested an abuse potential of pregabalin [10], and a study by Grosshans et al. found that illicit use of pregabalin was common among opioid-addicted patients [11]. The European summary of product characteristics holds a specific regulatory warning on the abuse potential of pregabalin: "Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin misuse, abuse or dependence" [12].

Evaluating the abuse potential of a drug is a complex task that cannot be based on a single test but rather should be based on the overall pharmacokinetic and pharmacodynamic properties of the drug, as well as data from both preclinical and clinical studies [13]. In addition, empirical evidence from clinical use may also indicate abuse potential. Indications of abuse include non-prescribed use or use for non-medical purposes in patients with substance abuse as well as experimental use in higher dosages or in a modified administration form, such as snorting or intravenous injections.

The estimated abuse potential of a given drug is an important basis for clinicians' decision making. Additionally, abuse potential assessment can be beneficial to drug regulators and authorities to regulate and assess the patterns of drug use [14]. We performed a systematic review according to PRISMA guidelines on the abuse potential for pregabalin [15].

2 Methods

2.1 Literature Search

PubMed, Embase, European Medicine Agency (EMA) (http://www.ema.europa.eu/ema/) and the US Food and Drug Administration (FDA) (http://www.fda.gov) websites were searched from inception until November 29, 2014 using the term 'pregabalin'. We used this open search strategy without the use of Boolean operators, as abuse liability may not be the main topic of the articles and for this reason not indexed with an abuse liability term. All hits were exported to ENDNOTE in order to exclude duplicates. All remaining hits were screened for relevancy based on title and abstract. Full text was retrieved if the abstract was missing or not sufficient for decision making. Only articles written in English, German or any Scandinavian language were included. We excluded reviews and conference abstracts. Eligible articles were categorized into four groups: preclinical, clinical, case reports and epidemiological studies. The retrieved articles were cross-checked for additional references.

As adverse events suggesting abuse potential may be described heterogeneously, we screened the full text of all retrieved literature. At the end of the review process, all retrieved information had been searched for the following terms: 'feeling dazed', 'euphor*', 'feeling good', 'feeling drunk', 'overdose', 'abuse', 'misuse', 'withdrawal', 'addict*' and 'dependenc*'.

Preclinical studies were divided into the following groups: conditioned place preference (CPP) studies, self-administration studies and studies investigating pregabalin effect on other substances.

Published case reports concerning possible misuse and abuse related events (MAREs) were reviewed and categorized as described in the Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTTION) classification system [16]. According to these definitions, a misuse-related event is defined as any intentional therapeutic use of a drug product in an inappropriate way. Misuse-related events specifically exclude those events that meet the definition of an abuse-event indicator. An abuse-related event is defined as any intentional, non-therapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect. MAREs can be further clarified by supplemental

designations. Tampering is the inappropriate manipulation of a drug product (i.e. crushing tablets or emptying capsules). Diversion is any intentional act that results in transferring a drug product from lawful to unlawful distribution or possession. Withdrawal is symptoms or clinical signs due to the decline in blood concentration of a drug product after dose reduction, at the end of a dosing interval, after discontinuing treatment or due to administration of an antagonist. Overdose includes any act that results in drug exposure exceeding the generally recommended or medically accepted dose.

Epidemiological studies were divided into four categories: drug utilization studies, adverse drug reaction reports, studies in substance abuse populations and postmortem studies.

Finally, the Marketing Authorization Holder (MAH) was contacted in order to retrieve any unpublished data about the abuse potential of pregabalin.

3 Results

A selection tree from the literature search is shown in Fig. 1. The MAH declined to provide additional data.

3.1 Preclinical Findings

In total, we identified 17 preclinical studies directly or indirectly investigating abuse potential of pregabalin. This included seven unpublished studies from the manufacturer provided by an FDA report [17]. Table 1 shows an overview of the preclinical studies.

We identified five CPP studies. The first study found that pregabalin did not induce CPP in doses up to 30 mg/kg [18]. Further, pre-treatment with pregabalin reduced morphine-induced CPP and also reversed established morphine-induced CPP [18]. The second study found that, in contrast to opioids, pregabalin showed no difference in CPP in painful

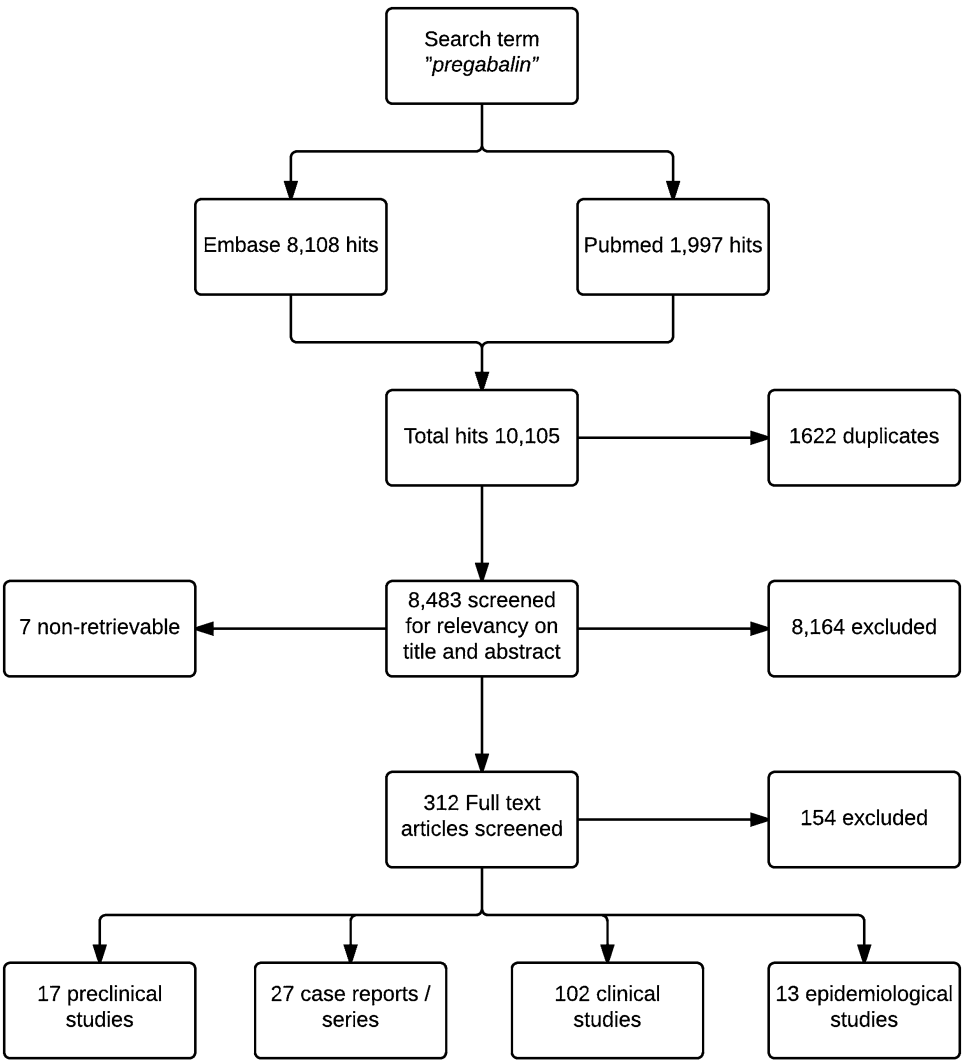

Fig. 1 Flow chart of literature search

Table 1 Preclinical studies of abuse liability of pregabalin

Study	Type	Design	Results and comments
Conditioned place preference (CPP) studies			
Andrews et al. [18]	CPP	Male Lister rats were tested in a CPP model with morphine, gabapentin and pregabalin. After this, morphine CPP was tested in rats pre-treated with pregabalin or gabapentin	Pregabalin alone, in doses up to 30 mg/kg, did not induce CPP. Pregabalin was shown to prevent the maintenance of CPP to morphine and pretreatment with pregabalin attenuated the induction of CPP by morphine
Rutten et al. [19]	CPP and CPA	Adult Sprague Dawley rats were given intraplantar injections with carrageenan to induce inflammatory pain. The direct nociceptive effects of the investigational drugs were tested. Increasing doses were used to reverse CPA and induce CPP. CPP was also tested in pain-free rats	Pregabalin reduced carrageenan-induced CPA at doses above 1 mg/kg. Pregabalin produced CPP at a dose of 3 mg/kg both in painful and pain-free conditions
FDA [17]	CPP study I	Rats were tested to see if morphine (0.1, 0.3, 1.0, 2.0 and 3.0 mg/kg, SC) or pregabalin (3, 10, 30 mg/kg, PO) induced a CPP	The results suggest that morphine induced CPP at all doses, but that no dose of pregabalin induced CPP. The route of administration differs, as oral absorption occurs more slowly, this may have favoured pregabalin
FDA [17]	CPP study II Pregabalin was tested for its ability to block the development of CPP with morphine	Rats received either pregabalin (1, 3, 10, 30 mg/kg, PO) or saline 60 min prior to administration of a submaximal dose of morphine (0.75 mg/kg, SC)	The 10 mg/kg dose of pregabalin was found to block the development of CPP from morphine
FDA [17]	CPP study III Pregabalin was tested for its ability to reverse CPP established by morphine	Pregabalin (10 mg/kg, PO) was administered 60 min prior to testing to investigate whether it would influence morphine-induced CPP	Pregabalin blocked the maintenance of morphine CPP. Rats were re-tested without further pregabalin administration on the following 2 days, but morphine-induced CPP returned in the absence of further pregabalin administration
Self-administration studies			
FDA [17]	Self-adminstration study I (methohexital vs pregabalin)	Rhesus monkeys were injected intravenously with methohexital (0.1 mg/kg/injection) following the presentation of a red light and 10 presses of the bar by the monkey, and subsequently received pregabalin in doses of 1.0, 3.2, 10 and 18 mg/kg/injection. Definition of positive reinforcing was >10 injections for 7 days	Pregabalin produced positive reinforcement with 14 injections/day with the 3.2 mg/kg dose and 11 injections/day with the 10 mg/kg dose. The reinforcing effect of pregabalin declined after the first week
FDA [17]	Self-adminstration study II (pentobarbital vs pregabalin)	Rhesus monkeys received pentobarbital (1.0 mg/kg/injection) until 16 injections per day was reached, when they were offered saline until daily injections returned to <10 and then offered pregabalin at doses of 1, 2, 4 and 8 mg/kg/injection. Definition of positive reinforcing was >10 injections/day for 7 days	Pregabalin produced no positive reinforcing in dose range 1–8 mg/kg as regards to at least 10 injections per day for 7 days. However, group and individual data showed that pregabalin showed >10 injections per day during the week
Drug-discrimination studies			
FDA [17]	Drug discrimination study I	Monkeys ($n = 4$) were trained to discriminate 0.56 mg/kg midazolam (SC, pretreatment time not given) under a stimulus-shock termination schedule. Challenge sessions with pregabalin (30, 100, 180, 300 mg/kg) were conducted with the drug administered orally 4 h prior to placement in the test cage	All doses of pregabalin were indistinguishable from saline (i.e. percent responding on the midazolam lever of <7 %)
FDA [17]	Drug discrimination study II	Monkeys ($n = 3$) were treated daily with a combination of diazepam (5.6 mg/kg, PO, administered 3 h prior to session) and flumazenil (0.32 mg/kg, SC, administered immediately prior to session). Thus, the discriminative cue is the effect of flumazenil in producing a benzodiazepine withdrawal syndrome. Monkeys were then tested with pregabalin (30, 100, 180 mg/kg, PO, administered 4 h prior to the session) and flumazenil (0.00032–0.32 mg/kg, SC, administered immediately prior to session)	A dose of 0.01 and 0.032 mg/kg of flumazenil in placebo-treated monkeys produced full generalization to the flumazenil cue in diazepam-dependent monkeys. No data are shown from the diazepam/flumazenil trials for comparison. The results with pregabalin-treated animals showed that pregabalin/flumazenil could produce full generalization to the flumazenil cue, although the dose of flumazenil necessary to produce this effect was larger than that at the 300-mg dose of pregabalin compared with placebo treatment. This indicates that pregabalin does not prevent the development of benzodiazepine withdrawal symptoms

Table 1 continued

Study	Type	Design	Results and comments
Studies involving effects on other substances			
de Guglielmo et al. [2]	Investigating effects of pregabalin in cocaine addiction using self-administration stations, conditioned operant chambers	Male Wistar rats were used. Four experiments were conducted: (1) effect of pregabalin on self-administration of cocaine, (2) effect of pregabalin on food administration, (3) effect of pregabalin on yohimbine-induced reinstatement of cocaine seeking, (4) effect of pregabalin on discriminative-cue-induced reinstatement of cocaine seeking	The results showed that oral administration of pregabalin (0, 10 or 30 mg/kg) reduced self-administration of cocaine over an extended period (6 h), whereas it did not modify self-administration of food. In cocaine reinstatement studies, pregabalin (10 and 30 mg/kg) abolished the cocaine seeking elicited by both the pharmacological stressor yohimbine and the cues predictive of cocaine availability
Stopponi et al. [20]	Alcohol drinking reducing effect of pregabalin, two bottle choice test	Male rats genetically selected for alcohol excessive drinking (Marchigan Sardinian)	Pregabalin 30 and 60 mg/kg reduced voluntary ethanol intake and 10 and 30 mg/kg reduced operant responding for ethanol. Food and water intake was not affected by pregabalin. Pregabalin also reversed yohimbine-induced alcohol craving
Becker et al. [21]	Investigating effect of pregabalin on seizures during alcohol withdrawal, using behavioural signs of seizure activity or abnormalities in spontaneous EEG activity recorded from cortical and subcortical sites	Adult male C3H/He mice were chronically exposed to ethanol and, upon withdrawal, exposed to pregabalin (50–200 mg/kg) administered at 1 and 4 h	Pregabalin reduced severity of handling-induced convulsions in comparison with vehicle-treated mice. Similarly, pregabalin reduced the frequency in which EEG activity was interrupted by trains of high-voltage synchronous activity in a dose-related fashion. Finally, pregabalin treatment of repeated withdrawals was effective in blocking the development of withdrawal sensitization observed in vehicle-treated mice
Aracil-Fernandez et al. [22]	Cannabinoid withdrawal test by using rectal temperature and motor behaviour open field test and LDB test	Adult male Swiss Albino mice were treated with CB1 receptor agonist (CP55, 940) for 7 days to achieve cannabinoid dependency. CP55, 940 was discontinued and, at day 1 after last administration, pregabalin was administered orally in half of the rats	Pregabalin 40 mg/kg increased the time spent in the light box suggesting an anxiolytic effect. Pregabalin blocked anxiolytic effects of cannabinoid withdrawal, such as motor activity and rearing. Pregabalin blocked 82 % of the reduced time in light box during cannabinoid withdrawal
Hasanein and Shakeri [23]	Tail-flick and naloxone withdrawal precipitation test	Adult male Wistar rats were treated with morphine SC for 7 days to induce tolerance	Pregabalin 100 and 200 mg/kg prevented morphine tolerance development and attenuated naloxone-induced withdrawal symptoms, such as weight loss, teeth chattering and penis licking
Other studies			
Navarrete et al. [68]	Impulsivity and anxiolytic-like effects were studied using LDB, HBT and DRT	DBA/2 OlaHsd mice were exposed to acute and chronic administration of pregabalin (10, 20 and 40 mg/kg) and topiramate (12.5, 25 and 50 mg/kg)	Acute pregabalin administration showed a clear anxiolytic-like effect (LDB) but did not modify novelty-seeking behaviour (HBT). In the DRT, acute pregabalin had no effect but with chronic administration, pregabalin significantly increased motor impulsivity
Baastrup et al. [82]	Effect of pregabalin in spinal cord injury pain was evaluated by the place escape/avoidance behaviour paradigm (PEAP)	Sprague–Dawley rats were used in a modified T10 spinal cord contusion model. The effect of pregabalin (30 mg/kg) was tested in a randomized design	A decrease in escape/avoidance behaviour in response to treatment with pregabalin was seen
Errante and Petroff [67]	Brain GABA, glutamine and glutamate levels studies using proton magnetic resonance spectroscopy	Male Long Evans rats were exposed to intra-peritoneal pregabalin 50 mg/kg ($n = 12$), 250 mg/kg ($n = 12$) and 500 mg/kg ($n = 8$)	Cellular glutamate concentration was reduced by 4 % 2 h after administration of pregabalin. No differences in cellular GABA and glutamine concentration was observed

CPA conditioned place aversion, *CPP* conditioned place preference, *DRT* delayed reinforcement task, *HBT* hole board test, *LDB* light–dark box, *PO* oral, *SC* subcutaneous

or pain-free conditions [19]. The last three studies also found that pregabalin blocked development and maintenance of morphine-induced CPP [17], but did not find that pregabalin induced CPP, regardless of dose [17].

We identified two self-administration studies, both conducted by the manufacturer. In one of these studies, 3.2 g/kg and 10 mg/kg did produce positive reinforcing, while the other study did not find any positive reinforcing effects of pregabalin [17].

We identified two drug discrimination studies, both conducted by the manufacturer. The first study showed no discrimination between saline and pregabalin in midazolam-treated monkeys. The second study found that pregabalin could not prevent benzodiazepine withdrawal symptoms in diazepam/flumazenil-treated monkeys [17].

The effect of pregabalin on other substances was investigated in five studies. The first study found that pregabalin was able to reduce the self-administration of cocaine in rats [2]. The second study found that pregabalin reduced yohimbine-induced ethanol craving in rats [20]. The third study investigated the effect of pregabalin on seizures during alcohol withdrawal in mice chronically exposed to ethanol and found that pregabalin reduced severity of convulsions [21]. The fourth study tested the effect of pregabalin on cannabinoid withdrawal-induced anxiety-like behaviour in mice, and found pregabalin to have an anxiolytic effect [22]. The fifth study found that pregabalin prevented morphine tolerance development and attenuated naloxone-induced withdrawal symptoms [23].

3.2 Clinical Studies

In total, we identified 102 clinical studies, and 19 of them reported data on adverse effects suggesting abuse potential. A summary of the studies is shown in Table 2. Only one study investigated subjective effects of pregabalin in recreational sedatives and alcohol users [17]. The included studies involved the following indications/conditions: fibromyalgia [24–28], neuropathy [29–34], anxiety disorders [35, 36], restless legs syndrome [37], pancreatitis [38] and healthy volunteers [39–41]. Euphoria was described in 14 studies [24, 25, 27–34, 36, 40–42], feeling drunk in one study [38] and one study described feeling dazed as a side effect [37]. Withdrawal symptoms were not described in any of the clinical studies reviewed. One study reported overdosing as an adverse effect [35].

3.3 Case Reports/Series

We identified 27 case reports concerning treatment with pregabalin. MAREs were described in nine reports covering ten different patient cases [10, 43–50], as shown in Table 3. All cases were categorized as abuse-related events after the ACTTION definitions [16]. Pregabalin overdosing was described in all ten cases. Diversion was described in three cases [43, 48], tampering in one case [48] and withdrawal symptoms in two cases [44, 45]. Seven patients had a history of or ongoing substance abuse [44, 46–50] and four patients had no abuse history beside use of nicotine [10, 43, 45]. The first case report was published in 2010 [43]. Median age was 34 years (range 19–47). Median value of highest single dose reported was 2400 mg (range 800–7500 mg). Four patients were women and six patients were men.

3.4 Epidemiological Studies

We identified 13 epidemiological studies concerning misuse and abuse of pregabalin [11, 51–62]. An overview of these studies is presented in Table 4. Three studies were drug utilization studies. One study, based on the Norwegian prescription database, found a skewed utilization pattern as 0.6 % of patients who received pregabalin accounted for 5.6 % of total prescribed pregabalin [51]. Another study found that among 48,550 patients exposed to pregabalin from 2006 to 2009, 8.5 % received doses that exceeded the licensed dose recommendation [52]. One study performed an online survey concerning misuse of GABA analogues and reported a lifetime prevalence of pregabalin misuse of 0.5 % and reported that diversion occurred frequently as only 13.1 % of respondents with misuse of GABA analogues reported legitimately prescribed drugs as their sole source of the drug [53].

Three studies were reviews of adverse drug reaction reports, of which two studies concerned data from national adverse drug reaction (ADR) databases in Norway and Sweden. The first study investigated reports indicative of abuse or addiction and found that 8 % of these reports concerned pregabalin [54]. The second study reviewed any ADR related to pregabalin and found that 55 of 1552 reports (3.5 %) described pregabalin abuse or dependence and that previous or ongoing substance abuse was frequently occurring [55]. The third study reviewed cases concerning overdosing with newer antiepileptic drugs from a poison treatment centre and found that 23 of 347 cases (6.6 %) concerned overdosing with pregabalin. Median reported dosage was 2375 mg and highest dosage reported was 9000 mg. Indications or history of substance abuse were not reported [56].

Five studies explored the abuse and misuse of pregabalin in substance abuse populations. The first study was conducted as a questionnaire to methadone users about their use of other substances. Among 129 responders, prescribed use of pregabalin was reported in two cases (1.5 %) and non-prescribed use of pregabalin was reported in four cases (3 %). Prescribed use of gabapentin was reported in nine

Table 2 Summary of clinical studies

Study	Indication	Design	Outcome
FDA [17]	Subjective response study	Single dose cross-over study, five treatment arms: placebo, diazepam 15 mg or 30 mg and pregabalin 200 mg or 450 mg. Comparing subjective response to pregabalin and diazepam in recreational sedative users or moderate alcohol users ($N = 15$)	Both doses of pregabalin produced "Good Drug Effects", "High" and "Drug Liking" equivalent to or greater than at least one dose of diazepam. Pregabalin 450 mg was liked better than either the dose of diazepam or the lower dose of pregabalin
Arnold et al. [24]	Fibromyalgia	14-week, double-blind study, placebo ($N = 184$) vs pregabalin 300 mg/day ($N = 183$), 450 mg ($N = 190$), 600 mg/d ($N = 188$). Patients with substance abuse were excluded	Euphoric mood was reported dose dependently in the pregabalin group: 300 mg/day—8 (4.4 %), 450 mg/day—11 (5.8 %), 600 mg—14 (7.4 %) and 0 (0 %) in the placebo group
Crofford et al. [25]	Fibromyalgia	8-week, double-blind randomized study, pregabalin 150 mg ($N = 132$), 300 mg ($N = 134$), 450 mg ($N = 132$) and placebo ($N = 131$). Not specified whether patients with substance abuse were included in the study	Two patients (1.5 %) in the 150-mg group reported euphoria, 11 (8.2 %) in the 300-mg group, 10 (7.6 %) in the 450-mg group and 1 (0.8 %) in the placebo group
Ohta et al. [26]	Fibromyalgia	15-week, double-blind randomized study, pregabalin ($N = 250$), placebo ($N = 248$). Patients with substance abuse were not excluded	The subscale of "feeling good" in the Fibromyalgia Impact Questionnaire was significantly improved with pregabalin treatment compared to placebo
Mease et al. [27]	Fibromyalgia	13-week, double-blind place controlled study, pregabalin 300 mg ($N = 185$), 450 mg ($N = 183$), 600 mg ($N = 190$) and placebo ($N = 190$)	Euphoria was reported in 5 (2.6 %) of the placebo users, whereas euphoria was reported in 6 (3.2 %), 11 (6.0 %) and 14 (7.4 %) patients treated with pregabalin 300, 450 and 600 mg/day, respectively
Nasser et al. [28]	Fibromyalgia	8-week, double-blind randomized study, pregabalin 300 mg daily dose, twice daily ($N = 88$) vs once nightly ($N = 89$). Not specified whether patients with substance abuse were included in the study	Five (5.7 %) in the twice-daily group reported euphoria vs 1 (1.1 %) in the once-daily group
Lesser et al. [29]	Painful diabetic neuropathy	5-week, double-blind randomized study, pregabalin 75 mg ($N = 77$), 300 mg ($N = 81$), 600 mg ($N = 82$) and placebo ($N = 97$). Not specified whether patients with substance abuse were included in the study	Five patients (6.2 %) in the 300-mg group and 4 (4.9 %) in the 600-mg group reported euphoria. None in the 75-mg or placebo group
Atalay et al. [30]	Painful neuropathy in haemodialysis patients	6-week, open-label, cross-over study ($N = 40$), pregabalin 75 mg and gabapentin 300 mg. Not specified whether patients with substance abuse were included in the study	Euphoria was reported by 1 (2.5 %) patient during exposure to pregabalin
Arezzo et al. [31]	Painful diabetic peripheral neuropathy	13-week, double-blind randomized study, placebo ($N = 85$), pregabalin 600 mg ($N = 82$). Not specified whether patients with substance abuse were included in the study	Three patients (3.7 %) reported euphoria during exposure to pregabalin. None in the placebo group
Stacey et al. [32]	Postherpetic neuralgia	4-week, randomized trial comparing flexible-dosed pregabalin (150–600 mg/d) ($N = 91$), fixed dose (300 mg/d) ($N = 88$) and placebo ($N = 90$). Not specified whether patients with substance abuse were included in the study	Two patients (2.2 %) in the flexible group and 2 patients (2.3 %) in the fixed group reported euphoria. None in the placebo group
Simpson et al. [33]	Painful HIV neuropathy	2-week, double-blind, randomized, placebo-controlled study, pregabalin ($N = 151$) and placebo ($N = 151$). Not specified whether patients with substance abuse were included in the study	Fifteen patients (9.9 %) reported euphoria in the pregabalin group and 1 (0.7 %) in the placebo group
Gilron et al. [34]	Peripheral neuropathic pain	4-week, open-label, flexible dose design, pregabalin ($N = 256$), followed by double-blind, randomized, placebo-controlled design, pregabalin ($N = 80$) and placebo ($N = 77$)	Euphoria was reported in 13 (5.1 %) in the single-blind study and 1 (1.3 %) in the pregabalin group in the double-blind design. None during exposure to placebo
Pande et al. [73]	Social anxiety disorder	10-week, double-blind randomized study, pregabalin 150 mg/d ($N = 42$), 600 mg/d ($N = 47$), and placebo ($N = 46$). Patients with substance abuse disorder were excluded	Four patients (8.5 %) reported overdose as an adverse event in the 600 mg/d group. None in the other groups

Table 2 continued

Study	Indication	Design	Outcome
Pohl et al. [36]	General anxiety disorder	6-week, double-blind randomized study, pregabalin 200 mg ($N = 78$), 400 mg ($N = 89$) and 450 mg ($N = 88$) and placebo ($N = 86$). Not specified whether patients with substance abuse were included in the study	Euphoria was reported by 8 (10 %) patients exposed to 200-mg pregabalin, 9 (10%) in the 400-mg group, 13 (15 %) in the 450-mg group and 1 (1 %) in the placebo group
Allen et al. [37]	Restless leg syndrome	6-week, double-blind, dose ranging study, pregabalin 50 mg ($N = 22$), 100 mg ($N = 23$), 150 mg ($N = 22$), 300 mg ($N = 24$), 450 mg ($N = 23$) and placebo ($N = 23$). Not specified whether patients with substance abuse were included in the study	'Feeling dazed' was reported among patients with adverse events leading to discontinuation of pregabalin. Not otherwise specified
Olesen et al. [38]	Chronic pancreatitis	3-week, double-blind randomized study, pregabalin 600 mg ($N = 34$) and placebo ($N = 30$). Patients with substance abuse were not excluded	Twelve patients (35 %) exposed to pregabalin reported the feeling of being drunk vs 2 (7 %) in the placebo group
Chew et al. [39]	Healthy volunteers	Pharmacokinetic single-dose study investigating effects of food on pregabalin controlled-release formula 330 mg vs immediate-release formula 300 mg	Euphoric mood was reported in 15 (11.7 %) in the controlled release group vs 11 (9.0 %) in the immediate-release group
Lang et al. [40]	Healthy volunteers	Investigating effects of pregabalin on transcranial magnetic stimulation. Double-blind, placebo-controlled, cross-over design ($N = 19$). Patients with substance abuse were excluded	Five patients (26.1 %) reported mild euphoria during exposure to pregabalin
Chua et al. [41]	Healthy volunteers	Cross-over study investigating the effect of pregabalin on acid-induced oesophageal hypersensitivity ($N = 15$), pregabalin and placebo. Patients with substance abuse were excluded	One patient (7 %) reported euphoria during pregabalin exposure

cases (7 %) and non-prescribed use in 25 cases (19 %). Patients who used non-prescribed pregabalin or gabapentin stated that they used it in order to become high (76 %) or in order to potentiate the effect of methadone (38 %) [57]. The second study reviewed data from a Swedish poison information centre regarding cases with crushed tablets being injected intravenously from January 2011 to June 2013. Pregabalin was crushed and injected intravenously in some cases (not further specified) [58]. The third study evaluated routine urine sample analysis from patients with opioid dependency ($n = 124$) and other substance abuse disorders ($n = 111$). Pregabalin was found in the urine of 12 % of opioid-dependent patients. None of these patients had received pregabalin for medical reasons. In the other group, 2.7 % had pregabalin in urine because of general anxiety or chronic pain [11]. The fourth study evaluated blood samples from persons convicted for driving under the influence of drugs in Finland (DUID cases). From a total of 3863 DUID cases in 2012, pregabalin was analysed in 459 cases and was detected in 206 cases. The median (range) serum concentration was 6.2 mg/L (0.68–112). In nearly 50 % of the cases, the serum concentration was above the typical therapeutic range. In most of the cases, the driver had also taken other drugs besides pregabalin, as the mean number of concomitant drugs was four [59]. In the fifth study, patients admitted to a public detoxification programme were asked to complete a self-report questionnaire related to co-use of prescription medication. In total, 196 patients responded to the questionnaire, of whom 162 were admitted due to opioid dependency. In this group, 7 % reported misusing pregabalin, either as non-prescribed use or using doses higher than prescribed [60].

Two post-mortem studies, both from Finland, concerned abuse of pregabalin. In one study, all medico-legal death cases from 2010 and 2011 were investigated. Toxicological analyses were performed in 13,766 cases and pregabalin was found in 316 cases (2.3 %). A total of 48 % of the pregabalin-positive cases were attributed to drug abuse. Pregabalin poisonings, in which pregabalin was the main toxicological finding, represented 10.1 % of all pregabalin-positive cases ($n = 32$) [61]. In another post-mortem study, drug use among deceased young adult nicotine users, aged 15–34 years, was evaluated ($n = 1623$). Of those, 68 had used pregabalin, among which legally obtained pregabalin could not be confirmed in 42 cases (62 %) [62].

4 Discussion

4.1 Preclinical Findings

GABA-ergic properties, including allosteric modulation, are considered to hold a significant role in drug addiction

Table 3 Characteristics of published cases of pregabalin abuse and misuse

Study	Year	Number of cases	Age	Sex	Psychiatric diagnoses other than addiction	Ongoing substance abuse	History of substance abuse	Indication for pregabalin treatment	Maximum dose of pregabalin	MARE category	Short case description
Filipetto et al. [43]	2010	1	35	Female	Depression, anxiety	None	None	Neuropathic pain	88,500 mg over a 28-day period	Abuse event, diversion, overdose	The patient requested an increase in her medication 2 months after beginning treatment and, after her physician denied her request, subsequently obtained pregabalin from other sources
Grosshans et al. [44]	2010	1	47	Male	None	Alcohol, cannabis	Heroin	None	7500 mg/day	Abuse event, withdrawal, overdosing	pregabalin was recommended by a friend. The patient experienced euphoric feelings after pregabalin consumption. Tolerance and withdrawal symptoms emerged after continuous use. Pregabalin was reduced slowly after admission to addiction treatment unit. The patient experienced heavy craving and discontinued treatment prematurely and relapsed immediately afterwards
Westin and Strom [45]	2010	1	30–39 (exact age unknown)	Female	GAD, insomnia	None	None	GAD	1800 mg/day	Abuse event, overdosing, withdrawal	Treated with pregabalin for 2 years. Prescribed dose was 600 mg/day. Was admitted to a detoxification clinic. On admission she was taking 1800 mg/day in order to achieve a feeling of euphoria. She felt that pregabalin was taking over her life. Experienced withdrawal symptoms when pregabalin was tapered
Yargic and Ozdemiroglu [46]	2011	1	37	Male	BD, anxiety	BZD	Cannabis, ketamine	Anxiety	Up to 3000 mg/day	Abuse event, overdosing	Two months after starting pregabalin, his wife realized that he was abusing pregabalin. The patient admitted that he had consumed approximately 20 capsules (equivalent to 3000 mg) of pregabalin on 6–7 occasions. He said he felt euphoria while on high doses of pregabalin

Table 3 continued

Study	Year	Number of cases	Age	Sex	Psychiatric diagnoses other than addiction	Ongoing substance abuse	History of substance abuse	Indication for pregabalin treatment	Maximum dose of pregabalin	MARE category	Short case description
Skopp and Zimmer [47]	2012	1	Unknown	Male	None	BZD, methadone treatment	Various substances	Supportive therapy during abuse treatment	Unknown	Abuse event, overdosing	Developed delusional ideas after overdosing pregabalin
Carrus and Schifano [48]	2012	2	32	Male	ASPD	Alcohol, cannabis	BZD, cocaine, ecstasy	Neuropathic pain	4500 mg/day	Abuse event, overdosing, diversion	During a 4-week period, the patient gradually increased the dosage up to an alleged daily amount of 4500 mg. He managed to get access to these levels of pregabalin tablets through a new general practitioner's prescription or obtaining it from a friend
			33	Male	BD, GAD	Cannabis	Ecstasy, alcohol	GAD	1500 mg/day	Abuse event, overdosing, diversion, tampering	During a 4-week period, he gradually increased the dosage up to 1500 mg, and felt as being ''under the influence of an anesthetic,'' and ''very light.'' To achieve both a quicker and more intense effect, he also tried smoking crushed pregabalin tablets. He allegedly obtained the extra pregabalin tablets from a friend
Papazisis et al. [49]	2013	1	19	Male	Panic attacks, GAD	Alcohol	Cannabis, alcohol	GAD	1800 mg/day	Abuse event, overdosing	He described feelings of becoming high when taking pregabalin and had drug-seeking behaviour with pregabalin comparable to behaviour seen with illegal drugs. Obtained prescriptions for pregabalin through another doctor
Gahr et al. [50]	2013	1	38	Female	BPD	Nicotine	Alcohol	Anxiety	800 mg/day	Abuse event, overdosing	Experienced euphoric feelings after pregabalin intake, and subsequently increased the daily pregabalin dosage and consulted other physicians to receive additional pregabalin prescriptions

Table 3 continued

Study	Year	Number of cases	Age	Sex	Psychiatric diagnoses other than addiction	Ongoing substance abuse	History of substance abuse	Indication for pregabalin treatment	Maximum dose of pregabalin	MARE category	Short case description
Halaby et al. [10]	2014	1	26	Female	Depression, anxiety	Nicotine	None	Bought OTC	1500 mg to 2400 mg/day	Abuse event, overdosing	She started buying pregabalin and increased the dose progressively. She attributed her behaviour to the relaxation effect, the calmness as well as the numbness sensation delivered by this drug. The reported daily dose was approximately 1500–2400 mg over the 4 months prior to presentation

ASPD antisocial personality disorder, *BD* bipolar disorder, *BPD* borderline personality disorder, *BZD* benzodiazepines, *GAD* generalized anxiety disorder, *MARE* misuse and abuse related event, *OTC* over the counter

[63–66]. Binding affinity studies of pregabalin have demonstrated no or very little affinity towards opioid or GABA receptors [63], but administration of pregabalin to rats did decrease prefrontal glutamate levels [67].

The conflicting results with respect to CPP are likely a result of different study conditions [18, 19]. While dosing was similar, routes of administration differed substantially. Notably, in the MAH study, pregabalin was administered orally while morphine was administered subcutaneously [18]. In contrast, identical routes of administration (i.e. intraplantar injections) were used in the study by Rutten et al. [19]. In the unpublished data by Pfizer [17], the study on self-administration was subject to several limitations. The infusion rate was different between methohexital and pregabalin: 5 vs 25 s per injection. It was noted that it was not justified why the particular dose range was used and that the high doses were removed from the last self-administration study.

Interestingly, several preclinical studies have suggested that pregabalin might play a role in treatment of addiction disorders. Pregabalin was found to attenuate the CPP effect induced by morphine, including an increased release of dopamine in nucleus accumbens [18]. Additionally, in contrast to opioids, pregabalin showed no difference between CPP responses in painful as opposed to pain-free conditions [19]. Pregabalin reduced ethanol intake in rats predisposed to alcohol drinking [20] and attenuated opiate withdrawal symptoms and dependency development [23]. The interpretation of these findings in the context of abuse liability is not obvious. Although these effects may suggest a potential role of pregabalin in treatment of addiction disorders, these effects may also reflect direct or indirect effects of pregabalin on the reward system and support the view that pregabalin possesses potential for abuse. In addition, adding pregabalin to opioid treatment may increase the analgesic effect, but the mechanism and perspectives of this interaction, from an abuse liability point of view, remains largely unknown. The favourable effect of pregabalin on withdrawal symptoms seem non-specific as studies have shown this effect as related to opioids [23], ethanol intake [20] and cannabinoids [22]. Finally, pregabalin did not affect novelty seeking and impulsivity, characteristics that have also been associated with drug abuse [68].

4.2 Clinical Studies

The only study investigating subjective response to pregabalin included 15 patients in a cross-over design with diazepam 15 mg and 30 mg as active comparators [17]. Interestingly, the EMA concluded from this study that pregabalin did not share a profile of abuse liability similar to benzodiazepines [69], whereas FDA did find that

Table 4 Overview of epidemiological studies

Study	Trial design	Primary findings
Drug utilization studies		
Landmark et al. [51], Norway	Drug utilization study using the Norwegian prescription database	In 2009, 17,111 individuals used pregabalin. Of those, 25 used >10 DDD. 118 persons used between 5 and 10 DDD accounting for 0.6 % of the patients and 5.6 % of total consumers of pregabalin
Bodén et al. [52], Sweden	Data was extracted from a nationwide health register. Multiple logistic regression was used to predict patients using dosages higher than the maximum licensed dosage (600 mg)	In the period 2006–2009, 48,550 individuals were exposed to pregabalin and 8.5 % of those exceeded the licensed dosage. Predictors for high use were male sex [adjusted odds ratio (aOR) 1.40, 95 % confidence interval (CI) 1.31–1.49], age between 18 and 29 years, compared with those aged ≥65 years (aOR 1.62, 95 % CI 1.45–1.82), low income (aOR 1.24, 95 % CI 1.10–1.40), epilepsy (aOR 1.41, 95 % CI 1.10–1.81), previous substance use disorder treatment or diagnosis (aOR 1.41, 95 % CI 1.31–1.52) and previously been dispensed high doses of drugs with abuse potential (aOR 1.77, 95 % CI 1.62–1.94)
Kapil et al. [53], UK	Online survey among 1500 persons from a consumer panel	Out of 1500 respondents, eight (0.5 %) reported lifetime misuse of pregabalin. Total lifetime misuse of GABA analogues was 38 (2.5 %) and only 5 (13.1 %) reported that they misused GABA analogues prescribed legitimately to them solely. Other reported multiple sources, from health services (63.1 %, $n = 24$), from family or acquaintances (57.8 %, $n = 22$) and from the Internet (47.3 %, $n = 18$), with only 7.8 % ($n = 3$) obtaining the medication from abroad
Adverse drug reactions report		
Schwan et al. [54], Sweden	Spontaneous adverse drug reaction reporting system analysed with data mining techniques for information component (IC) of abuse terms	Out of 198 reports indicative of abuse or addiction, 16 concerned pregabalin. The IC increased in 2008 to 3.99
Gahr et al. [55], Germany	Review of reported pregabalin cases with abuse or dependency	In total, there were 1552 patients with adverse reports related to pregabalin, including 55 reports on abuse or dependency of pregabalin. Mean age was 36 years and 63.6 % were male. In 49.1 % of cases, previous substance abuse was reported, and 40 % had a current substance abuse
Wills et al. [56], USA	Retrospective study investigating outcome of newer antiepileptics from 2002 to 2011 by using chart review from a poison centre	Out of 347 cases, 23 involved pregabalin. Mean age was 38.3 years and 16 (70 %) were females. Median reported dosage was 2375 mg and highest dosage reported was 9000 mg. Indications or history of substance abuse were not available
Studies in abuse/misuse population		
Baird et al. [57], Scotland	Questionnaire to methadone users about their use of other substances	Out of 129 respondents, two (1.5 %) reported prescribed use of pregabalin and 4 (3 %) reported non-prescribed use of pregabalin. Of the patients using non-prescribed gabapentinoids (pregabalin or gabapentin), 22/29 (76 %) stated that they used it in order to become intoxicated (high, stoned) and 11/29 (38 %) in order to potentiate the effect of methadone
Jonsson et al. [58], Sweden	Swedish poison information centre extracted from all cases with crushed tablets being injected intravenously from January 2011 to June 2013	Pregabalin was crushed and injected intravenously in some cases. This was not otherwise specified
Grosshans et al. [11], Germany	Routine urine sample analysis from patients with opiate dependency syndrome ($N = 124$) and other addiction disorders ($N = 111$)	In 12.1 % of patients with opiate dependency syndrome, pregabalin was found in urine. None of these patients had a medical indication for using pregabalin. In the other group, 2.7 % had pregabalin in urine because of general anxiety or chronic pain

Table 4 continued

Study	Trial design	Primary findings
Kriikku et al. [59], Finland	Analysis of the blood samples from persons convicted for driving under the influence of drugs in Finland	Pregabalin was detected in 206 samples in the study period. The median (range) serum concentration was 6.2 (0.68–111.6) mg/L. In nearly 50 % of the cases, the serum concentration was above the typical therapeutic range. In most of the cases, the driver had also taken other drugs besides pregabalin, the mean number of concomitantly taken drugs was four
Wilens et al. [60], USA	Self-report questionnaire to patients admitted to a public detoxification programme	In total, 196 responded to the questionnaire; 162 of those were admitted due to opioid dependency and 7 % of those reported having misused pregabalin. Fifty percent of patients using prescribed pregabalin reported that they had used a higher dosage than prescribed
Post mortem studies		
Hakkinen et al. [61], Finland	All medico-legal death cases were investigated for pregabalin in 2010 and 2011	In total, 316 cases with post-mortem pregabalin were identified, comprising 2.3 % of all medico legal death cases. A total of 48.1 % of the pregabalin-positive cases were attributed to drug abuse. pregabalin poisonings, in which pregabalin was the main toxicological finding, represented 10.1 % of all pregabalin cases
Launiainen et al. [62], Finland	Post-mortem database was searched for drug use in deceased aged 15–34 years	Of 1623 deceased, 68 had used pregabalin and in 42 (62 %) of those, prescribed use could not be confirmed

DDD daily defined doses

pregabalin had a similar abuse potential as diazepam [17]. Unfortunately, we did not have access to the full study report and therefore are not able to comment further on this.

Euphoria seems to be a dose-dependent adverse effect of pregabalin, occurring independent of indication and previous abuse of substances. Most studies report prevalence between 1–10 % [24, 25, 27–33, 36, 41, 70], but one study reported prevalence as high as 26 % [40]. The occurrence of euphoric mood as a frequent side effect of pregabalin treatment may be of special importance. The experience of euphoria may be the key factor that incites some patients to ingest large doses of pregabalin. Pharmacodynamically, and in comparison with gabapentin, the pharmacokinetic characteristics of pregabalin suggest a potential to induce euphoric mood. In vitro, pregabalin is 6-fold more potent than gabapentin with respect to effect on the calcium channel. Pregabalin has a rapid absorption with peak plasma concentration achieved within 1 h compared with 4–5 h with gabapentin [71], and a longer half-life, which may explain why less attention has been paid to the abuse liability of gabapentin [72]. Interestingly, administration of pregabalin in a controlled-release formulation did not reduce the occurrence of euphoric mood [39], while euphoric mood was more common during twice daily dosing than for night-time dosing only [28].

Euphoria did rarely lead to discontinuation [33, 39], and seems to be a transient side effect [34]. Although the mechanism remains unknown, the most likely reason for this reduction is the development of tachyphylaxis; that is, decreased responsiveness with repeat dosing. As a consequence, one would expect that overdose might be common in patients exposed to pregabalin. Surprisingly, overdose was only reported as an adverse event in one study [73]. However, it is important to notice that ongoing or prior substance abuse often will exclude patients from participating in clinical studies. Patients with a history of drug abuse might be more willing to overdose the treatment with pregabalin in order to achieve the euphoric experience. As a consequence, the clinical studies might underestimate the true magnitude of the abuse potential.

Several studies involved discontinuation of pregabalin and withdrawal symptoms were not reported in any of these studies [30, 34, 36]. Tolerance and withdrawal symptoms have been described in several case reports [44, 45, 74], but it is likely that the relatively short treatment duration in clinical trials is not long enough for tolerance to occur.

Some overlap between terms of symptoms may have occurred; one study reported ‘feeling drunk’ whereas other studies reported ‘feeling abnormal’ and gait disorders which may have covered the same issues. We used a conservative approach and only searched for ‘feeling drunk’, as the other symptom categories may have included symptoms not related to abuse potential.

The definition of euphoria may differ between different clinical studies. The WHO defines euphoria as “A sense of well-being” [16]. This definition is not sufficiently accurate to differentiate between the intended therapeutic effect of a given drug and the desired psychotropic effects when the

same drug is abused; that is, a patient with significant anxiety might describe proper anxiolytic effect of the drug as "giving a sense of well-being".

4.3 Case Report/Series

Abuse-related events were reported in all ten published case reports. Publication bias may have occurred. Misuse and abuse may have occurred for a while before it reached the threshold of reporting. The first three case reports were published in 2010 [43–45], more than 5 years after pregabalin became available on the market, but shortly after the first concerns about the abuse potential of pregabalin were conveyed [75]. Now the issue of potential abuse liability has emerged, it may stimulate increased misuse and abuse, but also increased focus and reporting of misuse/abuse with pregabalin. Additionally, there might be a certain threshold for publishing case reports describing pregabalin-related MAREs, as cases with misuse-related events might not be published as illustrated by the fact that all published case reports had descriptions of clear abuse-related events. As a consequence, the overall picture is likely distorted and may not provide an adequate overview on the abuse potential of pregabalin.

4.4 Epidemiological Findings

A skewed utilization pattern for a given drug can be indicative of drug abuse. A Norwegian utilization study found that a small number of patients were accountable for a large amount of the used pregabalin doses [51]. A population-based study of all first-time pregabalin users in Sweden found that 8.5 % of patients had an estimated daily dosage that exceeded the maximum approved dose [52], and factors associated with high use of pregabalin were male sex, young age, previous substance use disorder and having used large amounts of other drugs with abuse potential. None of the studies reported Lorenz curves or Gini coefficients, although these measures might have been helpful to clearly demonstrate a possible skewed utilization pattern of pregabalin [76, 77].

An online survey in the UK, with 1500 respondents aged 16–59 years, found a lifetime prevalence of pregabalin misuse of 0.5 % [53]. A study surveying anecdotal online reports found that a dissociative effect is noticed among pregabalin/gabapentin abusers and not in clonazepam abusers [78].

One study found that illegal use of pregabalin was present among 12.1 % of patients with opiate addictions [11]. Wilens et al. report similar findings [60]. In a sample of patients seeking treatment for opioid dependence, 7 % of patients were using pregabalin without prescription or in higher amounts than prescribed.

Abuse of pregabalin was more common among patients with a history of substance abuse. This may suggest that abuse only occurs in this predisposed subgroup, pointing towards a minor abuse potential of pregabalin in the general population. On the other hand, being a preferred drug among drug abusers could point towards a higher abuse potential, as these patients know what they prefer.

4.5 Overall Evaluations and Clinical Implications

Based on small, and to some extent inconsistent, preclinical studies that were not replicated, it appears that pregabalin possesses modulatory properties relevant to the GABA and the glutamate system. While the predictive value of such studies with respect to clinical occurrence of addictive behaviour remains unknown, the finding does leave theoretical room for clinical abuse potential of pregabalin. A substantial number of the preclinical studies were conducted by the MAH. Data on pregabalin used in high doses were omitted from a self-administration study. This is an important limitation, as the abuse potential of pregabalin is more likely to appear at higher dosages and to a larger extent would reflect the conditions under which abuse potential is tested in real life by persons with ongoing substance abuse. As the MAH declined to provide additional data, a selection bias may have occurred.

Clinical studies have revealed that transient feelings of euphoria occurred in 1–10 % of patients treated with pregabalin, which clearly supports the concern about the abuse potential of pregabalin. Epidemiological studies confirmed tampering and diversion as reported in the published case reports. Drug utilization studies found heavy use among a minor group of patients. Non-prescribed use of pregabalin was commonly reported among opiate-addicted patients, which may indicate a potentiating effect on other psychotropic drugs or an independent abuse potential of pregabalin. Clinicians should stay vigilant and be aware of euphoria as a possible side effect, either if reported by the patient or if overdosing is suspected.

Pregabalin has been suggested to play a role in the treatment of alcohol or benzodiazepine addiction. However, the role of pregabalin in the treatment of addiction disorders remains largely unclear. Furthermore, using pregabalin in populations with addiction disorders may be problematic, as prior or ongoing substance abuse seems to be an important risk factor for abusing pregabalin. Some data suggest that pregabalin might impose the same risk of abuse as benzodiazepines, wherefore use of pregabalin to treat these conditions might be contraindicative.

There are different diagnostic systems that describe substance abuse disorders, such as the ICD-10 system developed by the World Health Organization (WHO) and the DSM-IV system. However, the definitions used in these

systems are made for diagnostic purposes and are not suitable for describing single abuse or misuse-related events. The terminology used to describe MAREs in clinical research is not always consistent and differs in the published literature. This lack of consistency might pose a limitation to this and other systematic reviews, although broad search terms were used initially to address this problem. A set of broadly accepted definitions, like the ones suggested by the ACTTION group, might improve future research concerning abuse potential of drugs.

The findings in this systematic review support the conclusions made in other papers addressing the abuse potential of pregabalin [79–81]. The strength of this study is the systematic search strategy and detailed review of the retrieved data. Although it is clear that pregabalin holds potential for abuse, further studies concerning the underlying mechanism are warranted.

5 Conclusion

This literature review suggests an important abuse potential of pregabalin. Prescribers should pay attention to signs of abuse, especially in patients with a history of substance abuse. Further studies should address the extent of abuse and individual factors that may increase liability towards abuse of pregabalin.

Compliance with Ethical Standards

Funding No sources of funding were used to assist with the preparation for this paper.

Conflict of interest Ole Schjerning has received speaker honoraria from Lundbeck. Jimmi Nielsen has received research grants from Lundbeck, Pfizer and speakers honoraria from Hemocue, Lundbeck and Bristol Myers Squibb. Anton Pottegård, Mary Rosenzweig and Per Damkier state no conflicts of interest.

References

1. Montgomery S, Emir B, Haswell H, Prieto R. Long-term treatment of anxiety disorders with pregabalin: a 1 year open-label study of safety and tolerability. Curr Med Res Opin. 2013;29:1223–30.
2. de Guglielmo G, Cippitelli A, Somaini L, Gerra G, Li H, Stopponi S, et al. Pregabalin reduces cocaine self-administration and relapse to cocaine seeking in the rat. Addict Biol. 2013;18:644–53.
3. Medstat.dk-National Institute for Health Data and Disease Control. Usage data on Lyrica. 2014. http://medstat.dk/en. Accessed 29 Nov 2014.
4. Pharma Marketing. Top 50 pharmaceutical products by global sales. 2015. http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales. Accessed 28 Oct 2015.
5. 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.
6. Cho YW, Song ML. Effects of pregabalin in patients with hypnotic-dependent insomnia. J Clin Sleep Med. 2014;10:545–50.
7. Oulis P, Kalogerakou S, Anyfandi E, Konstantakopoulos G, 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, Martinotti G, Clerici M, Janiri L. Pregabalin for alcohol dependence: a critical review of the literature. Adv Ther. 2012;29:947–57.
9. 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. 2011;52:826–36.
10. Halaby A, Kassm SA, Naja WJ. Pregabalin dependence: a case report. Curr Drug Saf. 2015;10:184–6.
11. Grosshans M, Lemenager T, Vollmert C, Kaemmerer N, Schreiner R, Mutschler J, et al. Pregabalin abuse among opiate addicted patients. Eur J Clin Pharmacol. 2013;69:2021–5.
12. European Medicine Agency. Summary of product characteristics for pregabalin. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003880/WC500166172.pdf. Accessed 29 Nov 2014.
13. Expert P. Abuse liability assessment of CNS drugs: conclusions, recommendations, and research priorities. Drug Alcohol Depend. 2003;70(3 Suppl.):S107–14.
14. Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. Drug Alcohol Depend. 2003;70:S13–40.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
16. Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, Comer SD, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain. 2013;154:2287–96.
17. Center for Drug Evaluation and Research US. Consult on abuse potential for NDA review, Lyrica (Pregabalin). In: FaDAP, editor. Review. USA: US Food and Drug Administration; 2004.
18. Andrews N, Loomis S, Blake R, Ferrigan L, Singh L, McKnight AT. Effect of gabapentin-like compounds on development and maintenance of morphine-induced conditioned place preference. Psychopharmacology (Berl). 2001;157:381–7.
19. 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 anti-nociceptives in the rat. Eur J Pain. 2011;15:299–305.
20. Stopponi S, Somaini L, Cippitelli A, de Guglielmo G, Kallupi M, Cannella N, et al. Pregabalin reduces alcohol drinking and relapse to alcohol seeking in the rat. Psychopharmacology (Berl). 2012;220:87–96.
21. Becker HC, Myrick H, Veatch LM. Pregabalin is effective against behavioral and electrographic seizures during alcohol withdrawal. Alcohol Alcohol. 2006;41:399–406.
22. Aracil-Fernandez A, Almela P, Manzanares J. Pregabalin and topiramate regulate behavioural and brain gene transcription changes induced by spontaneous cannabinoid withdrawal in mice. Addict Biol. 2013;18:252–62.
23. Hasanein P, Shakeri S. Pregabalin role in inhibition of morphine analgesic tolerance and physical dependency in rats. Eur J Pharmacol. 2014;742:113–7.
24. Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP Jr, Sharma U, et al. A 14-week, randomized, double-blinded, placebo-

controlled monotherapy trial of pregabalin in patients with fibromyalgia. J Pain. 2008;9:792–805.
25. Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005;52:1264–73.
26. Ohta H, Oka H, Usui C, Ohkura M, Suzuki M, Nishioka K. A randomized, double-blind, multicenter, placebo-controlled phase III trial to evaluate the efficacy and safety of pregabalin in Japanese patients with fibromyalgia. Arthritis Res Ther. 2012;14:R217.
27. Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP Jr, Martin SA, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol. 2008;35:502–14.
28. Nasser K, Kivitz AJ, Maricic MJ, Silver DS, Silverman SL. Twice daily versus once nightly dosing of pregabalin for fibromyalgia: a double-blind randomized clinical trial of efficacy and safety. Arthritis Care Res (Hoboken). 2014;66:293–300.
29. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology. 2004;63:2104–10.
30. Atalay H, Solak Y, Biyik Z, Gaipov A, Guney F, Turk S. Crossover, open-label trial of the effects of gabapentin versus pregabalin on painful peripheral neuropathy and health-related quality of life in haemodialysis patients. Clin Drug Investig. 2013;33: 401–8.
31. Arezzo JC, Rosenstock J, Lamoreaux L, Pauer L. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. BMC Neurol. 2008;8:33.
32. Stacey BR, Barrett JA, Whalen E, Phillips KF, Rowbotham MC. Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. J Pain. 2008;9:1006–17.
33. Simpson DM, Schifitto G, Clifford DB, Murphy TK, Durso-De Cruz E, Glue P, et al. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology. 2010;74:413–20.
34. 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.
35. Pande AC, Crockatt JG, Feltner DE, Janney CA, Smith WT, Weisler R, et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. Am J Psychiatry. 2003;160:533–40.
36. Pohl RB, Feltner DE, Fieve RR, Pande AC. Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled comparison of BID versus TID dosing. J Clin Psychopharmacol. 2005;25:151–8.
37. Allen R, Chen C, Soaita A, Wohlberg C, Knapp L, Peterson BT, et al. A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. Sleep Med. 2010;11:512–9.
38. Olesen SS, Bouwense SA, Wilder-Smith OH, van Goor H, Drewes AM. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Gastroenterology. 2011;141:536–43.
39. Chew ML, Alvey CW, Plotka A, Pitman VW, Alebic-Kolbah T, Scavone JM, et al. Pregabalin controlled-release pharmacokinetics in healthy volunteers: analysis of four multiple-dose randomized clinical pharmacology studies. Clin Drug Investig. 2014;34:627–37.
40. Lang N, Sueske E, Hasan A, Paulus W, Tergau F. Pregabalin exerts oppositional effects on different inhibitory circuits in human motor cortex: a double-blind, placebo-controlled transcranial magnetic stimulation study. Epilepsia. 2006;47:813–9.
41. Chua YC, Ng KS, Sharma A, Jafari J, Surguy S, Yazaki E, et al. Randomised clinical trial: pregabalin attenuates the development of acid-induced oesophageal hypersensitivity in healthy volunteers—a placebo-controlled study. Aliment Pharmacol Ther. 2012;35:319–26.
42. Chew ML, Plotka A, Alvey CW, Pitman VW, Alebic-Kolbah T, Scavone JM, et al. Pharmacokinetics of pregabalin controlled-release in healthy volunteers: effect of food in five single-dose, randomized, clinical pharmacology studies. Clin Drug Investig. 2014;34:617–26.
43. Filipetto FA, Zipp CP, Coren JS. Potential for pregabalin abuse or diversion after past drug-seeking behavior. J Am Osteopath Assoc. 2010;110:605–7.
44. Grosshans M, Mutschler J, Hermann D, Klein O, Dressing H, Kiefer F, et al. Pregabalin abuse, dependence, and withdrawal: a case report. Am J Psychiatry. 2010;167:869.
45. Westin AA, Strom EJ. Yes, pregabalin can be abused! Tidsskr Nor Laegeforen. 2010;130:2108.
46. Yargic I, Ozdemiroglu FA. Pregabalin abuse: a case report/Pregabalin kötüye kullanımı: Bir olgu sunumu. Bull Clin Psychopharmacol. 2011;21:64–6.
47. Skopp G, Zimmer G. Pregabalin—a drug with abuse potential? Arch Kriminol. 2012;229:44–54.
48. Carrus D, Schifano F. Pregabalin misuse-related issues; intake of large dosages, drug-smoking allegations, and possible association with myositis: two case reports. J Clin Psychopharmacol. 2012;32:839–40.
49. Papazisis G, Garyfallos G, Sardeli C, Kouvelas D. Pregabalin abuse after past substance-seeking behavior. Int J Clin Pharmacol Ther. 2013;51:441–2.
50. Gahr M, Franke B, Freudenmann RW, Kolle MA, Schonfeldt-Lecuona C. Concerns about pregabalin: further experience with its potential of causing addictive behaviors. J Addict Med. 2013;7:147–9.
51. Landmark CJ, Fossmark H, Larsson PG, Rytter E, Johannessen SI. The prescription registry and abuse of pregabalin. Tidsskr Nor Laegeforen. 2011;131:223.
52. Boden R, Wettermark B, Brandt L, Kieler H. Factors associated with pregabalin dispensing at higher than the approved maximum dose. Eur J Clin Pharmacol. 2014;70:197–204.
53. Kapil V, Green JL, Le Lait M-C, Wood DM, Dargan PI. Misuse of the γ-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. Br J Clin Pharmacol. 2014;78:190–1.
54. Schwan S, Sundstrom A, Stjernberg E, Hallberg E, Hallberg P. A signal for an abuse liability for pregabalin–results from the Swedish spontaneous adverse drug reaction reporting system. Eur J Clin Pharmacol. 2010;66:947–53.
55. Gahr M, Freudenmann RW, Hiemke C, Kolle MA, Schonfeldt-Lecuona C. Pregabalin abuse and dependence in Germany: results from a database query. Eur J Clin Pharmacol. 2013;69: 1335–42.
56. Wills B, Reynolds P, Chu E, Murphy C, Cumpston K, Stromberg P, et al. Clinical outcomes in newer anticonvulsant overdose: a poison center observational study. J Med Toxicol. 2014;10:254–60.
57. Baird CR, Fox P, Colvin LA. Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers. Eur Addict Res. 2014;20:115–8.
58. Jonsson B, Backman E, Salmonson H, Hojer J. Injection of crushed tablets–a prospective observational study. Clin Toxicol (Phila). 2014;52:982–3.
59. Kriikku P, Wilhelm L, Rintatalo J, Hurme J, Kramer J, Ojanpera I. Pregabalin serum levels in apprehended drivers. Forensic Sci Int. 2014;243:112–6.

60. Wilens T, Zulauf C, Ryland D, Carrellas N, Catalina-Wellington I. Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. Am J Addict. 2014;24:173–7.
61. Hakkinen M, Vuori E, Kalso E, Gergov M, Ojanpera I. Profiles of pregabalin and gabapentin abuse by postmortem toxicology. Forensic Sci Int. 2014;241:1–6.
62. 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;13:763–71.
63. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res. 2007;73:137–50.
64. Filip M, Frankowska M, Sadakierska-Chudy A, Suder A, Szumiec L, Mierzejewski P, et al. GABAB receptors as a therapeutic strategy in substance use disorders: focus on positive allosteric modulators. Neuropharmacology. 2015;88:36–47.
65. Vlachou S, Markou A. GABAB receptors in reward processes. Adv Pharmacol. 2010;58:315–71.
66. Tan KR, Brown M, Labouebe G, Yvon C, Creton C, Fritschy JM, et al. Neural bases for addictive properties of benzodiazepines. Nature. 2010;463:769–74.
67. Errante LD, Petroff OA. Acute effects of gabapentin and pregabalin on rat forebrain cellular GABA, glutamate, and glutamine concentrations. Seizure. 2003;12:300–6.
68. Navarrete F, Perez-Ortiz JM, Manzanares J. Pregabalin- and topiramate-mediated regulation of cognitive and motor impulsivity in DBA/2 mice. Br J Pharmacol. 2012;167:183–95.
69. European Medicine Agency (EMA). Scientific discussion—Lyrica. In: Agency EM, editor. European Medicines Agency. 2005. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000546/WC500046605.pdf. Accessed 28 Nov 2015.
70. Arnold LM, Arsenault P, Huffman C, Patrick JL, Messig M, Chew ML, et al. 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;30:2069–83.
71. 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;49:661–9.
72. Bockbrader HN, Radulovic LL, Posvar EL, Strand JC, Alvey CW, Busch JA, et al. Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol. 2010;50:941–50.
73. Pande AC, Feltner DE, Jefferson JW, Davidson JR, Pollack M, Stein MB, et al. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. J Clin Psychopharmacol. 2004;24:141–9.
74. Sugandiran NBJ. Pregabalin may cause dependence even if it is not abused. Arc Cas Rep CMed. 2014;1:1.
75. Chalabianloo F, Schjott J. Pregabalin and its potential for abuse. Tidsskr Nor Laegeforen. 2009;129:186–7.
76. Hallas J, Nissen A. Individualized drug utilization statistics. Analysing a population's drug use from the perspective of individual users. Eur J Clin Pharmacol. 1994;47:367–72.
77. Hallas J, Stovring H. Templates for analysis of individual-level prescription data. Basic Clin Pharmacol Toxicol. 2006;98:260–5.
78. Schifano F, D'Offizi S, Piccione M, Corazza O, Deluca P, Davey Z, et al. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom. 2011;80:118–22.
79. Bramness JG. Abuse of pregabalin. Tidsskr Nor Laegeforen. 2010;130:1703–4.
80. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs. 2014;28:491–6.
81. Papazisis G, Tzachanis D. Pregabalin's abuse potential: a mini review focusing on the pharmacological profile. Int J Clin Pharmacol Ther. 2014;52:709–16.
82. Baastrup C, Jensen TS, Finnerup NB. Pregabalin attenuates place escape/avoidance behavior in a rat model of spinal cord injury. Brain Res. 2011;1370:129–35.