How addictive are gabapentin and pregabalin? A systematic review

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Abstract

In the last ten years, gabapentin and pregabalin have becoming dispensed broadly and sold on black markets, thereby, exposing millions to potential side-effects. Meanwhile, several pharmacovigilance-databases have warned for potential abuse liabilities and overdose fatalities in association with both gabapentinoids. To evaluate their addiction risk in more detail, we conducted a systematic review on PubMed/Scopus and included 104 studies. We did not find convincing evidence of a vigorous addictive power of gabapentinoids which is primarily suggested from their limited rewarding properties, marginal notes on relapses, and the very few cases with gabapentinoid-related behavioral dependence symptoms (ICD-10) in patients without a prior abuse history (N=4). In support, there was no publication about people who sought treatment for the use of gabapentinoids. Pregabalin appeared to be somewhat more addictive than gabapentin regarding the magnitude of behavioral dependence symptoms, transitions from prescription to self-administration, and the durability of the self-administrations. The principal population at risk for addiction of gabapentinoids consists of patients with other current or past substance use disorders (SUD), mostly opioid and multi-drug users, who preferred pregabalin. Pure overdoses of gabapentinoids appeared to be relative safe but can become lethal (pregabalin > gabapentin) in mixture with other psychoactive drugs, especially opioids again and sedatives. Based upon these results, we compared the addiction risks of gabapentin and pregabalin with those of traditional psychoactive substances and recommend that in patients with a history of SUD, gabapentinoids should be avoided or if indispensable, administered with caution by using a strict therapeutic and prescription monitoring.

Key words: gabapentin, pregabalin, liking, wanting, abuse potential, overdose fatalities

1. Introduction

Pregabalin and gabapentin are approved pharmacotherapies for the treatment of some epileptic and pain disorders, and pregabalin also for generalized anxiety disorder (Bocksbader et al., 2010; Calandre et al., 2016). Both pharmaceuticals are very closely related regarding their pharmacology (Bockbader et al., 2010; Calandre et al., 2016). Therefore, gabapentin and pregabalin can be placed in their own group of gabapentinoids (Rogawski and Bazil, 2008). They are 3-substituted derivatives of the neurotransmitter γ-aminobutyric acid (GABA) and known inhibitors of $\alpha_2\delta$-subunit-containing voltage-dependent calcium channels (VGCC), more precisely the $\alpha_2\delta$ type 1 and 2 proteins of the P/Q type of VGCCs (Tran-Van-Minh and Dolphin, 2010; Mico´ and Prieto, 2012). By this action, they inhibit the trafficking of the $\alpha_2\delta$ subunit complex to the plasma membrane and reduce the synaptic vesicle exocytosis (Tran-Van-Minh and Dolphin, 2010; Mico´ and Prieto, 2012). These VGCCs are located predominantly in presynaptic membranes and it was demonstrated that gabapentionids restrain stimulus-dependent synaptic transmitter release, mainly the excitatory transmitter glutamate and norepinephrine, but not dopamine (Dooley et al., 2000; Bockbader et al., 2010; Rogawski and Bazil, 2008). Thereby, gabapentinoids may act against aberrant neuronal “overexcitation” and, likely, also against sensitization (Eroglu et al., 2009; Mico´ and Prieto, 2012). Additionally, therapeutic doses of gabapentinoids are dose-dependently associated with a modest increase of the extracellular GABA-concentration in brain tissue (Peng et al., 2008.; Bockbader et al., 2010; Cai et al., 2012; Calandre et al., 2016) and, thus, have weak GABAmimetic features that most likely drive the relaxation and euphoria experienced especially in the beginning of the drug therapy and during an overdose. There is a substantial tolerance against this euphoric high which is typical for addictive GABAmimetics, e.g. benzodiazepines or propofol (Bonnet, 2011; Korpi et al., 2015). Pharmacokinetically, the gabapentinoids are nearly “ideal” pharmaceuticals with good tolerability (Zaccara et al., 2017), a low interaction potential (with the exception of combining with clozapine, opioids or sedatives (Englisch et al., 2012; Calandre et al., 2016;

Schjerning et al., 2016a; Quintero, 2017.; Abrahamsson, et al. 2017)), no metabolism and no protein binding (Bockbader et al., 2010; Calandre et al., 2016). However, they need dose reduction alongside increasing renal insufficiency (Verma et al., 1999; Calandre et al,, 2016).

Within the last decade, both, gabapentin and pregabalin, have become blockbuster prescription drugs with myriads of prescriptions worldwide (Kapril et al., 2014; Calandre et al.; 2016; Chiappini and Schifano, 2016; Kwork et al., 2017). Of note, a good portion of these drugs were prescribed “off-label” against anxiety, non-neuropathic pain, mood instability, insomnia, neurasthenia, somatoform disorders, and withdrawal symptoms from recreational drugs (Prescrire Int, 2012; Calandre et al., 2016; Freynhagen, et al., 2016; Kwok et al., 2017). Since gabapentin and pregabalin became also easily obtainable over the internet and were sold on black markets, gabapentinoids have been assumed to possess considerable abuse liability (Schifano et al., 2011; Prescrire Int, 2012; Kapril et al., 2014). This corresponds to pharmacoepidemiologic analyses of prescription data and a mounting number of records pointing to an abuse of gabapentinoids that have been spontaneously reported to pharmacovigilance databases, mainly in Scandinavia, the UK, and Germany (Chalabianloo and Schjøtt, 2009; Schwan et al., 2010; Gahr et al., 2013a; Bodén et al., 2014; Asomaning et al., 2016; Schjerning et al., 2016b). Notably, the vast majority of the registered patients were currently or previously dependent on other substances, too, mostly opiates or sedatives (Chalabianloo and Schjøtt, 2009; Schwan et al., 2010; Prescrire Int, 2012; Gahr et al., 2013a; Bodén et al., 2014; Asomaning et al., 2016; Schjerning et al., 2016b). This was supported by the latest analysis of the EudraVigilance database which included 11940 misuse reports of gabapentin (N=4301 records corresponding to 410 patients) and pregabalin (N=7639 records, 1315 patients) to the European Medicine Agency from Europa, East Asia, North and South America in the period 2004-2015 (Chiappini and Schifano, 2016). For both gabapentinoids, there was as considerable increase of those reports over time with a peak in 2013 (pregabalin, N=2154 records) and 2014 (gabapentin,

N=1001 records) (Chiappini and Schifano, 2016). These pharmacovigilance data were warning although, for reasons of methodology, remaining less specific towards the addiction risks of gabapentinoids, because it is cannot be excluded that they are simply innocent bystanders of other more powerful substance use disorders (SUD).

We attempt to estimate the addiction risks of gabapentinoids in several steps. Firstly, we conducted a review about animal and human studies focusing on rewarding properties (Panlilio and Goldberg, 2007) of gabapentinoids. Secondly, we evaluated clinical studies and case reports having been related to gabapentin or pregabalin misuse according to fulfilled ICD-10-criteria of dependence (Dilling and Freyberger, 2006), information about the magnitude and durability of self-administrations (Panlilio and Goldberg, 2007) including relapses, and treatment-seeking behavior of affected patients. Thirdly, we reviewed the overdose safety of gabapentin and pregabalin to assess the benefits and inconvenience to the consumer. Next, we discussed their addiction risks basing upon these findings and on a popular and useful explanation of how addiction can occur, i.e., the Incentive Sensitization Theory of Addiction (Berridge and Robinson, 2016). Finally, we provide an approach to compare the addiction risks of gabapentinoids with those of common substances of abuse.

2. Experimental procedures

2.2. Data sources

Following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (http://prisma-statement.org/documents/PRISMA 2009 flow diagram.pdf) we systematically searched in the electronic databases PubMed and Scopus for articles about gabapentinoids and focused on those which have been related to misuse, addiction and overdose safety of the gabapentinoids (gabapentin, pregabalin) and were published from their introduction into the markets (gabapentin 1997, pregabalin 2004) up to 03/31/2017. We used the following search terms: gabapentin or pregabalin AND addiction or abuse or misuse or dependence or substance use disorder (SUD) or withdrawal or tolerance or craving or drug-seeking

behavior or toxicity or safety or death or fatalities or overdose or suicide or delirium or coma or respiratory insufficiency or cardiac insufficiency or recreational or reinforcing or reward or self-administration or discrimination or treatment-seeking AND animal , rodents, primates, controlled study, clinical study, clinical trial, register study, epidemiologic study, case report, case presentation, register study.

Eligible articles reported i) rewarding behavior and self-administration of gabapentinoids, ii) clinical studies about gabapentinoid-addiction, iii) case-reports about gabapentinoid-addiction, iv) overdoses of and suicides/fatalities by gabapentinoids.

Studies were excluded if they i) are reviews, ii) are not related to rewarding, self-administration, misuse, abuse, dependence, addiction, overdoses, self-poisoning, or fatality and iii) dealt with the use of gabapentinoids in the treatment of other disorders than addictive diseases. The search strategy is shown in Figure 1. Identified articles were independently reviewed by the authors using the above criteria. After a screening of title and abstract, consensus was reached towards articles to be included for full-text screening. Useful publications identified from the reference list of retrieved articles were also considered in this review (additional hand search), Subsequent to the full-text screening, the final number of included articles was identified (N=104) and potential disagreement was resolved by discussion.

2.2. Determination the addiction risk (genuine addictive power A-E vs. overdose toxicity F) – inspired by Griffiths and Johnson (2006)

A. Addictive drugs have in common that they are voluntarily and avidly self-administered by laboratory animals and humans, thereby, disrupting and hijacking natural reward processes (Panlilio and Goldberg, 2007; Ernst and Luciana, 2015; Karoly et al., 2015; Volkow and Morales, 2015; Berridge and Robinson, 2016; Scofield et al, 2016). Therefore, we screened the literature for rewarding behavior and self-administrations inclusive information about transition from prescriptions to self-administration.

B. Behavioral symptoms, i.e. craving, loss of control, drug-seeking behavior, are regarded to be more decisive for relapses and the durability or chronicity of an addictive disorder than physical symptoms, i.e. tolerance or withdrawal (Panlilio and Goldberg, 2007; Bonnet et al., 2011; Karoly et al., 2015; Volkow and Morales, 2015; Korpi et al., 2015). We hypothesize that the number of those cases who showed symptoms of behavioral dependence on gabapentin or pregabalin without any prior experiences with other substances of abuse reflects the “genuine” addiction power of gabapentinoids the best. Therefore, we screened the clinical studies and case presentations for existing dependence criteria according to ICD-10 (Dilling and Freyberger, 2006) and their substance abuse history. In this context, we also screened the studies and case reports for information about relapses and long-term self-administrations.

C. The magnitudes of fulfilled ICD-10-dependence criteria were used to calculate the severity of an addiction (Dilling and Freyberger, 2006).

D. A simple but universal criterion for a substantial addiction is the need for treatment of this condition. Therefore, we also searched for reports on people who voluntarily sought treatment for problematic use, misuse of or dependence on gabapentinoids.

E. Own social hazards, i.e. social hazards being only attributed to the use of gabapentionoids, are also helpful in the assessment of their addictive power.

F. Information about overdose toxicity should gain first insight into the health hazard of an addictive drug which will be taken into account on the way to desirable experiences. Therefore, we screened the literature for non-fatal and fatal overdoses by gabapentinoids.

3. Results

3.1. Rewarding behavior of gabapentinoids including self-administration

We found 17 publications which were related to this topic. A few studies were about conditioned place preference tests with rats (Andrews et al., 2001; Rutten et al., 2011; Schjerning et al., 2016a) or mice (Shibasaki et al., 2009; Kurokawa et al. 2011). Oral doses of gabapentin (10-100 mg/kg) or pregabalin (3-30 mg/kg) being assumed to be similar to therapeutic dosages did not affect the conditioned place preference in the cages (Andrews et al., 2001; Schjerning et al., 2016a). In other experiments, however, pregabalin induced a conditioned place preference which occurred only with intraperitoneally applied doses about 3mg/kg while lower doses have been inactive (Rutten et al., 2011). On the other hand, gabapentin was demonstrated to block place conditioning. For instance, intracerebroventricular administrations of gabapentin (3, 10 and 30 nmol/mouse) dose-dependently inhibited morphine- and methamphetamine-induced place preference and behavioral sensitization in the limbic forebrain (including the nucleus accumbens) of mice via inhibition of the $\alpha_2\delta$-1-subunits of the VCGG (Shibasaki et al., 2009; Kurokawa et al., 2011).

From all laboratory models of addiction, self-administration paradigms are regarded to provide the most direct point-to-point correspondence with addictive behavior occurring in the natural environment (Panlilio and Goldberg, 2007). While we did not find any animal study on self-administration of gabapentin alone, there were two investigations about the effects of pregabalin on Rhesus monkeys trained to self-administer barbiturates (Schjerning et al., 2016a). In one set of experiments, pregabalin-injections had no reinforcing effects in the dose range 1-8 mg/kg and in another set, small positive reinforcement occurred with the 3.2 mg/kg and the 10 mg/kg injections which subsided within the first week (c.f. Table 1 in Schjerning et al., 2016a). Gabapentin (25-200 mg/kg, intraperitoneal, rats) was not able to influence intravenous cocaine self-administration or cocaine-triggered reinstatement of cocaine-seeking behavior (Peng et al., 2008) which was supported in two further studies on rats (Itzhak and Martin, 2000; Filip et al., 2007) and three studies on cocaine abusing or dependent humans (Hart et al., 2004; Haney et al., 2005; Hart et

al., 2007), the latter even with large therapeutic gabapentin doses (3200 mg/d) (Hart et al., 2007). Oral pregabalin (10 and 30 mg/kg) reduced the rats´ cocaine self-administrations and cocaine seeking (De Guglielmo et al., 2012). Controversial are the effects of gabapentinoids on the self-administration of alcohol in rats, both an increase (with gabapentin: Besheer et al., 2016) and a decrease (with gabapentin: Roberto et al., 2008; with pregabalin: Stopponi, et al., 2012) was described. In drug discrimination tests with rats, oral gabapentin (30 and 120 mg/kg) and alcohol had similar effects while lower gabapentin doses were ineffective. (Besheer et al., 2016).

Regular cannabis users (N=8) reported similar effects of gabapentin (600 and 1200 mg/d) and delta-9-tetrahydrocannbidiol (30 mg) in a selective drug-discrimination assay (Lile et al., 2016). Pregabalin administered in therapeutic doses (75 mg) and supratherapeutic doses (150 mg at its first use) did not impact on the psychomotor performance, liking and drug taking desire of healthy volunteers (Zacny et al., 2012).

In sum, gabapentin appeared to have no relevant rewarding properties. Those of pregabalin were low and occurred only in doses which were assumed to be supratherapeutic.

3.2. Clinical studies on gabapentinoid abuse and dependence with focus on ICD-10 dependence criteria, self-administration, long-term use, relapses, social hazards, and substance abuse history

The clinical studies about abuse and dependence of gabapentinoids are shown in Table 1. Most studies reported non-medical gabapentinoid use in patients being in opioid substitution programs or being dependent on opioid prescription drugs with up-to-6-month prevalence rates between 15% and 22% for gabapentin (Baird et al., 2013; Smith et al,, 2015; Bastiaens et al.; 2016) and between 3% and 26% for pregabalin (Grosshans et al., 2013; Baird et al., 2013; McNamar et al., 2015; Wilens et al., 2015; Snellgrove, 2016).

There were only two studies using a structured face-to-face interview considering operationalized dependence criteria (Snellgrove, 2016; Cossmann et al., 2016). In 2013, Cossmann et al (2016) found a 12-month prevalence-rate of 0.25 % of gabapentinoid dependence in a German hospital population who was ≥ 65 years old. In a German detoxification ward, Snellgrove (2016) described point- and 24-month-prevalence rates of pregabalin dependence in the magnitude of 3% and 7%; respectively. Of note, all patients identified to abuse or to be dependent on gabapentinoids were dependent on at least another substance, mostly opioids (Table 2). Via an online survey, Kapril et al. (2014) found life-time prevalence rates of 1.1% of gabapentin misuse and 0.5% of pregabalin misuse in a non-elderly adult population. Typical sources to obtain gabapentinoids were the family, acquaintances, drug dealers and physicians (Kapil et al., 2014; Table 1). Gapentinioids were used mostly oral, but also nasal, intravenous and rectal routes were described (Schifano et al., 2011; Snellgrove, 2016; Table 1).

One longitudinal study on gabapentinoid abuse/dependence described a massive increase of the non-medical gabapentin use in a cohort of adults misusing opioid prescription drugs within the last 5 years (Smith et al., 2015). In his retrospective interview, Snellgrove (2016) found that 13% of those patients who had experiences with non-medical pregabalin use fulfilled 3 DSM-IV dependence criteria for longer than 12 months. At the moment of the interview, 6% of this cohort was dependent on pregabalin (Snellgrove 2016). We found no further clinical studies that had investigated the longitudinal course or severity of the abuse of or dependence on gabapentinoids.

With the exception of Snellgrove (2016), none of the other clinical studies gained detailed insight into the pattern or magnitude of fulfilled operationalized dependence criteria of the participants (Table 1) or self-administration behavior. Typical incentives for non-medical gabapentinoid use (misuse) were to get high, to potentiate an opioid high or to dampen withdrawal symptoms or anxiety (Table 1). One recent study, however, did not find any case of pregabalin abuse/dependence in an urban Swiss

population of opioid substituted patients which was verified by hair toxicology analysis (Mutschler et al., 2015).

In sum, there were a couple of population based studies that showed different prevalence rates of gabapentinoid abuse/dependence with highest up-to-6 month prevalence rates in opioid substitution programs or cohorts misusing prescription opioids (up to every third or fourth patient misused gabapentinoids for recreational purposes). On the other hand, one recent study found no evidence of non-medical pregabalin use in a population of opioid substituted patents (Mutschler et al., 2015). There is a great paucity of research on the longitudinal course and severity of gabapentinoid abuse/dependence. There was no report about people who sought treatment for the abuse or dependence of gabapentinoids or relapsing behavior. Also, we found no relevant information about social hazards through the use of gabapentinoids.

3.3. Case studies related to gabapentinoid abuse and dependence with focus on ICD-10 dependence criteria, self-administration, long-term use, relapses, social hazards, and substance abuse history

We found 36 case presentations related to gabapentin abuse or dependence (Table 2). Among them, 25 cases were solely related to withdrawal symptoms or a rebound of psychiatric symptoms which had developed after stopping therapeutic gabapentin administrations (Corá-Locatelli et al., 1998; Rosebush et al:; 1999; Norton, 2001; Drabkin and Calhoun, 2003; Tran et al., 2005; Finch et al., 2010; See et al., 2013; Mah and Hart, 2013; Bonnet and Scherbaum, 2016). The remaining 11 cases typically had used markedly higher gabapentin doses than prescribed (Markowitz, et al., 1997: Barrueto et al., 2002; Reccoppa et al., 2004; Victorri-Vigneau et al., 2007; Pittenger et al., 2007; Kruszewski et al., 2009; Hellweg et al., 2010; Reeves and Burke, 2014; Reeves and Ladner, 2014; Satish et al., 2015). Regarding pregabalin, we found 19 case presentations being related to abuse or dependence (Table 2).

We evaluated these case presentations according to fulfilled ICD-10 dependence criteria (Dilling and Freyberger, 2006) and found that i) tolerance and withdrawal symptoms were common in gabapentinoid dependence (N=27 out of N=36 (75%) with respect to gabapentin, N=16 out of N=19 (84%) with respect to pregabalin), and ii) in comparison with pregabalin (N=15 from N=19, 79%), the gabapentin-related case presentations were far fewer associated with behavioral dependence symptoms (N=3 from N=36, 8%) (Table 2).

The frequently observed physical dependence on gabapentinoids, i.e. withdrawal symptoms and tolerance, were in line with previous reviews about this subject (Smith et al., 2016; Mersfelder and Nichols, 2016; Schjerning et al., 2016a; Evoy et al., 2017; Quintero, 2017). The described withdrawal symptoms resembled those of benzodiazepines (including withdrawal seizures and delirium) (Tyrer et al., 1990) or SSRIs (Fava et al., 2015) and appeared to respond poorly to benzodiazepines but improved after reinstating a gabapentinoid taper (Smith et al., 2016; Mersfelder and Nichols; 2016, Schjerning et al., 2016a; Table 2).

According to severity of gabapentinoid addiction, there were only three case presentations with more than 4 fulfilled (out of 6 possible) dependence criteria (Table 1). Two of which were related to pregabalin (Aldemir et al., 2013; Yazdi et al., 2015) and only one to gabapentin (Satish et al., 2015). More case reports with ≥ 3 dependence criteria were reported during pregabalin use (N=13 from 19, 68%) than with gabapentin (N=5 from 36, 14%) (Table 2). Also, more patients underwent a transition from prescribed therapeutic doses to self-administration of pregabalin (N=16 out of 19, 84%) compared to gabapentin (N=10 out of 36, 28%) (Table 2). Regarding relapses, one report was related to gabapentin dependence (Victorri-Vigneau et al., 2007), and two reports were related to pregabalin dependence (Grosshans et al., 2010; Yazdi et al., 2015) (Table 2). Regarding self-administration for longer than one year, there was no report on gabapentin and three reports on pregabalin - with durations between 2 and 4 years (Westin and Strom, 2010; Aldemir et al., 2013; Ashwini et al., 2015). The most case reports, however, described

gabapentin or pregabalin self-administrations over periods of a few weeks or months (Table 2).

Notably, the vast majority of the cases reporting a self-administration of gabapentinoids had a positive history of addiction of traditional psychoactive substances, too, mostly alcohol, benzodiazepines and opioids (Table 2). There were solely 4 patients who showed symptoms of behavioral dependence without having a positive history of addiction of other substances apart from nicotine in the past (Yargic and Ozdemiroglu, 2011; Ashwini et al., 2015; Halaby et al., 2015; Driot et al., 2016). All these “abuse-history-free” 4 cases were attributed to pregabalin (Table 2).

The validity of this evaluation is limited because an information about 177 (54%) of all 330 ICD-items was not given in the case presentations (c.f “U” in Table 2). This applies to 122 (56%) out of 216 gabapentin-related items and 55 (48%) out of 114 pregabalin-related items. However, it is more likely that an information is missing because an ICD-10 criterion was simply not apparent in the respective case than that corresponding symptoms had been prominent but not described.

In sum, the reports described evidence that the dependence on pregabalin is somewhat stronger and more sustaining than the dependence on gabapentin, taking into account the number and pattern of fulfilled ICD-10 dependence criteria, the number of transitions from prescriptions to self-administrations, and the durability of the self-administrations. This is supported by the finding that only for pregabalin (and not for gabapentin), cases of behavioral dependence were described in patients who had no positive substance abuse history previously, although these cases appeared to be quite rare (N=4). We found no report about people who sought treatment for the misuse or dependence of gabapentinoids and noconclusive information on related social hazards.

3.4. Gabapentinoid-related overdoses and fatalities

We found 9 case presentations (Table 3) and one case series (Klein-Schwartz et al., 2003) about non-fatal gabapentin overdoses, mostly following self-poisoning together with other pharmaceuticals. The highest described blood levels of gabapentin were nearly 4-fold the recommended maximum therapeutic blood level (30 mg/L, Schulz et al., 2012), that were 104.5 mg/L (Spiller et al., 2002) and 126.8 mg/L (Koschny et al., 2014). Both were related to coma, respiratory depression or cardiopulmonary resuscitation but also related to overdosing with concurrent medications (Spiller et al., 2002; Koschny et al., 2014). There were two case reports with lower blood levels ((62 mg/L (Fischer et al., 1994), 72.8 mg/L (Schauer et al., 2013)) which were attributed to gabapentin overdosing alone, and both were associated with sedation and nausea but stable vital signs (Fischer et al., 1994; Schauer et al., 2013). Verma et al. (1999) described a 30-year-old woman with epilepsy and renal insufficiency who developed mild resting tremor and cognitive deficits with gabapentin blood concentrations of 85 mg/L (nearly 3-fold the maximum therapeutic level) following a dose increase of gabapentin up to daily 1800 mg together with valproate anticonvulsion.

Concerning pregabalin, there were 3 detailed case presentations about non-fatal overdosing showing blood levels of 20.8 mg/L (Miljevic et al., 2012), 45 mg/L (Braga and Chidley, 2007) and 66.5 mg/L (Wood et al., 2010) which are nearly 3 to 8 times higher than the recommended maximum therapeutic blood level (8 mg/L, Schulz et al., 2012). The latter case was attributed to a pure pregabalin overdose and showed coma and respiratory depression (Wood et al., 2010). A slight decrease of the respiration rate was demonstrated in healthy volunteers who had been exposed the first time with a therapeutic pregabalin dose of 75 mg (Zacny et al., 2012). Miljevic et al (2012) reported the case of a 59-year-old man with generalized anxiety disorder who self-poisoned himself with 4.2 g pregabalin (blood level: 20.8 mg/L) ingested together with therapeutic doses of bromazepam and clomipramine. This patient was conscious and alert with stable cardiovascular and respiratory functions. Individuals who had been apprehended for driving under the influence of drugs showed blood levels of pregabalin up to 111.6 mg/L (14.fold the maximum therapeutic level), mostly

detected together with other drugs of abuse (Kriikku et al 2014). A poison center database analysis of clinical outcomes of overdoses with newer anticonvulsants found no severe adverse event and no fatality associated with gabapentin (N=94) or pregabalin (N=18) overdosing, however, blood levels were not presented (Wills et al 2014). There were two recent case reports of psychiatric patients without a history of another SUD who self-administrated pregabalin in large supratherapeutic amounts (1500-3000 mg/day, i.e. 2.5-5-fold the recommended maximum therapeutic dose) to produce euphoria what finally led to sedation or confusion (Halaby et al., 2015; Ashwani et al., 2015). Similar information is available from emergency medicine (Millar et al., 2013) and methadone maintenance treatments (Schifano et al., 2011; Grosshans et al., 2013; Baird et al., 2013; Piralishvili et al., 2013; Wilens et al., 2015; Smith et al., 2015; McNamara et al., 2015; Bastiaens et al., 2016) where gabapentinoids were abused mainly together with opioids and sedatives (Table 2).

We found 19 publications about fatalities in association with gabapentinoids (Table 3). Among them, there were 6 detailed postmortem case reports with gabapentin assumed to be the main cause of death (Moore et al., 2005; Middleton, 2011; Cantrell et al., 2015; Chiappini and Schifano, 2016). Pregabalin was identified to be the main cause of death in 35 postmortem case reports which were described in more detail (Button et al., 2010; Priez-Barallon et al., 2014; Häkkinen et al., 2014; Eastwood and Davison; 2016; Chiappini and Schifano, 2016; Elliott et al 2017). Among the whole 19 publications about gabapentinoid-fatalities were 9 retrospective studies from regional or national postmortem toxicology registers in Finland (Launiainen et al., 2011; Launiainen et al., 2013; Häkkinen et al., 2014; Ojanperä et al., 2016), Sweden (Abrahamsson et al., 2017), Germany (Lottner-Nau et al., 2013) and the UK (Eastwood and Davison, 2016; Office of National Statistics, 2016), Europe (Chiappini and Schifano; 2016) - all pointing to increasing fatalities over the last 15 years in which gabapentinoids (mainly pregabalin) have been involved, nearly always in combination with other drugs, mostly opioids, benzodiazepines, alcohol and antidepressants. Ojanperä et al (2016) had analyzed the Finish postmortem

toxicology database by using a fatal toxicity index (FTI) which is defined as the number of deaths per million DDD (defined daily doses) per year and which did include drug mixtures. For pregabalin, Ojanperä et al (2016) found an increasing trend in FTI over the years: 2005 (0.54), 2009 (1.54), and 2013 (2.44) (Table 3). The mean FTI of pregabalin (1.92) and gabapentin (0.91) is located in the middle of a corresponding list which ranked the safety of 70 pharmaceuticals - being approximately on level with reboxetine (1.91) or nortriptyline (1.72) in the case of pregabalin and on level with paroxetine (0.93) or carbamazepine (0.85) in the case of gabapentin (Ojanperä et al 2016).

Whether a substantial overdose of gabapentin used in isolation is sufficient enough to induce life threatening respiratory or cardiac insufficiency is still controversial (Table 3), although two fatalities in association with excessive and pure gabapentin self-poisoning were described in postmortem case reports (Middleton 2011, Cantrell et al 2015). However, substantial pregabalin overdosing may have fatal consequences, especially if combined with opioids and sedatives (Häkkinen et al., 2014; Eastwood and Davison, 2016; Elliott et al., 2016).

The actual frequency of fatalities due to pure overdoses of gabapentinoids can be roughly estimated from large national or international online-registers. Therefore, we studied the annual reports of the American Association of Poison Control Centers from the years 2012-2015 (Mowry et al., 2013, 2014, 2015, 2016). These showed stable incidence rates of fatality records related to gabapentinoids in isolation between 0.05 and 0.07% (of all arriving fatality records) in the last 3 years, apropos: all have been related to gabapentin and none to pregabalin (Mowry et al., 2014, 2015, 2016, Table 3). Regarding all records in which gabapentinoids were involved, that means including those with drug mixtures (Mowry et al., 2014, 2015, 2016), there is a trend over the years from 2012 to 2015 in the USA: whilst the total amount of registered fatality records had been fallen continuously from 2576 (2012) to 1371 (2015), the number of gabapentinoid-related fatalities had increased from 1,5% (N=38) to 4.3% (N=59) (Table 3). This seems more stronger to be attributed to

gabapentin (2012: N=31, 1.2% - 2015: N=51, 3.7%) than to pregabalin (2012: N=7, 0.27% - 2015: N=8, 0.6%) (Table 3).

Suicides by using pregabalin in isolation have not been described yet, but vice versa, suicide attempts in the beginning of the gabapentinoid therapy were rarely reported (Mutschler et al., 2011, Kustermann et al 2014), a phenomenon which is known for other anticonvulsants, too (Mula et al 2013).

In sum, pure overdoses of gabapentinoids appeared to be relatively safe but can become lethal if used in mixture with other drugs of abuse, mostly opioids and sedatives. There are nearly 6 times more detailed postmortem case reports in which pregabalin was attributed to be the main cause of death (N=35) as with gabapentin (N=6). This corresponds with gabapentin´s lower FTI (Ojanperä et al., 2016). In Europe, pregabalin is the leading gabapentinoid to be involved in drug-related fatalities which actually applies to gabapentin in the USA, where the prescription of pregabalin is regulated by law.

4. Discussion

Pregabalin appeared to be somewhat more addictive than gabapentin, taking into consideration that the pregabalin use was more frequently associated with behavioral ICD-10-dependence symptoms, switches from prescription to self-administration and self-administrations themselves (Table 2). However, this review did not find convincing evidence of a substantial genuine addictive power of gabapentinoids in general which is primarily suggested from their limited rewarding properties and the very few cases with behavioral dependence symptoms of gabapentinoids without a prior substance abuse history (Yargic and Ozdemiroglu, 2011; Ashwini et al., 2015; Halaby et al., 2015; Driot et al., 2016; Table 2). In support, there were only 3 cases reports that mentioned relapses (Victorri-Vigneau et al., 2007; Grosshans et al., 2010; Yazdi et al., 2015; Table 2) and we could not found any publication reporting people who sought treatment for the use of gabapentinoids which appeared to be used mostly together with other substances of abuse (Table 1). Also, we could not

find any note on social hazards being attributed to the use of gabapentinoids in isolation. At this juncture, it should be mentioned that drugs of abuse were used rather infrequently in isolation from other substance dependences, which may point to contextual, social, and individual factors that maintain the substance use. Recently, some additional concerns about a substantial addictive power of gabapentinoids have arisen. Thus, a distribution analysis of the French Pharmacovigilance database found no significant association between the exposure to pregabalin and drug abuse or dependence, nevertheless, taking into account the limited specificity of a spontaneous reporting pharmacovigilance system (Bossard et al., 2016). Recently, Mutschler et al (2015) found no evidence of a non-medical pregabalin use in an opioid substitution program.

4.1. Impact on the mesolimbic reward system

Drugs of abuse are characterized by an increase of the dopamine activity in the mesolimbic reward system (Karoly et al., 2015; Volkow and Morales; 2015). Their repeated administrations drive neuroplastic changes in glutamatergic inputs to the striatum and midbrain dopamine neurons, which is associated with an increase of the motivational salience of drug cues, a reduction of the sensitivity to non-drug rewards, a weakening of self-control behavior; and an affection of the individual stress reactivity (Spiga et al., 2014; Karoly et al., 2015; Volkow and Morales, 2015; Fosnocht and Brand 2016; Scofield et al., 2016). As yet, there is no evidence for gabapentinoids to increase the extracellular dopamine activity in the mesolimbic reward system. The only microdialysis study to this subject found that gabapentin (25-200 mg/kg, intraperitoneal, rats) produced a modest increase (approximately 50%) in extracellular nucleus accumbens GABA levels but failed to alter either the basal or the cocaine-enhanced dopamine activity in this key region of the reward system (Peng et al., 2008). This might restrict the ability of gabapentinoids to develop a substantial addictive power. Neuroimaging studies on the human reward system (Ernst and Luciana, 2015) under the influence of gabapentinoids are warranted.

4.2. Prevalence rates and motives of non-medical gabapentinoid use

As yet, epidemiologic surveys have not measured the prevalence rates of gabapentinoid abuse and dependence in the general population. These rates can be roughly estimated from an elderly German hospital population (life-prevalence of dependence: 0.25%, Cossmann et al., 2016) and younger British internet-population (life-prevalence of misuse: 0.5-1.1%, Kapril et al., 2014).

Opioid using (self-administrating) patients and patients in opioid substitution programs are at particular risk for gabapentinoid abuse and dependence with up-to-6-month prevalence rates of up to 26% (Grosshans et al., 2013; Baird et al., 2013; McNamar et al., 2015; Wilens et al., 2015; Snellgrove, 2016; Smith et al., 2015; Bastiaens et al., 2016; Table 1). There is robust evidence that opioid users including multiple drug users selected gabapentinoids mainly due to their special features to boost an euphoric high and reduce withdrawal symptoms while producing only few adverse effects (Schwan et al., 2010; Schifano et al., 2011; Grosshans et al,. 2013; Baird et al., 2013; Wilens et al., 2015; Smith et al.,2015; Bastiaens et al., 2016; Snellgrove, 2016). These cohorts clearly preferred pregabalin allowing a more rapid and stronger euphoric high than being possible with gabapentin (Tables 1 and 2). Most likely, this results from pharmacological differences of gabapentin and pregabalin (Bockbader et al., 2010; Calandre et al., 2016). Firstly, pregabalin is absorbed more rapidly (reached its maximal blood level within 1.5 hours after oral intake) and possesses a greater bioavailability (gabapentin: 33%–66%, pregabalin: >90%). Secondly, while pregabalin is absorbed dose-independently gabapentin`s plasma concentrations have been found to have a non-linear relationship with increasing oral doses because its absorption underlies a saturation process in the gastrointestinal mucosa (Bockbader et al., 2010; Calandre et al., 2016). Thirdly, pregabalin has a stronger inhibitory action on the $\alpha_2\delta$-subunits containing VCGG compared to gabapentin (Bockbader et al., 2010; Calandre et al., 2016). Especially the faster onset of a euphoric high and the linear relationship between blood concentrations and oral intake are supposed to be the reasons why pregabalin is

preferably self-administered by patients with experiences in substance abuse, such as opioid addicts. At this juncture, pregabalin would be associated more closely with the hazards of this population, such as dependence and overdose death (Hser et al, 2017), than gabapentin (Table 1-3).

4.3. Durability of gabapentinoid self-administrations

Regarding the self-administration for longer than one year, we did not find any case report about gabapentin and three case reports mentioning pregabalin self-administrations over a period of 2 and 4 years (Westin and Strom, 2010; Aldemir et al., 2013; Ashwini et al., 2015) (Table 2). In a cohort of patients admitted to detoxify from other drugs, Snellgrove (2016) found that 13% of those patients, who had experience with non-medical pregabalin use had a period with pregabalin-dependence no longer than 2 years. As yet, only one prospective study on the longitudinal course of gabapentinoid has been published and this study found a considerable increase of gabapentin misuse in a special cohort of American prescription opioid dependents within 5 years (Smith et al., 2015) which support the view that opioid dependents are at particular risk for a non-medical co-use of gabapentinoids (Table 1). Using the Danish nationwide Prescription Registry, Schjerning et al (2016b) found evidence for a long-term use of pregabalin when they analyzed pregabalin dispensing to patients in the period from 2004 to 2013. Of 42350 pregabalin-recipients, there were 2765 (6.5%) and 137 (0.3%) persons who had received prescriptions ≥ 600 mg/d and ≥ 1200 mg/d for longer than 12 months, respectively (Schjerning et al., 2016b). This is interesting because those persons being dispensed pregabalin at higher than the maximum allowed dose most likely had other SUDs, too (Boden et al., 2014). Furthermore, it is not excluded that a good portion of the registered pregabalin dispensing is not used by the patients themselves and were diverted to others (e.g. family members, acquaintances) or to the black markets (Schifano et al., 2011; Kapil et al., 2014).

4.4. Safety of gabapentinoids

Unlike other substance of abuse, such as cannabis which euphoric high is scarcely influenced by tolerance due to repeated dosing (Wu and French, 2000), gabapentinoids are characterized by a rapid tolerance towards their desirable euphorization (Schifano et al., 2011; Calandre et al., 2016). This is suggested to drive a considerable overdosing (Schifano et al., 2011; Calandre et al., 2016). It is controversial how toxic overdoses of gabapentinoids can be (Table 3). Overdosing of gabapentinoids in isolation appeared to be less toxic taking into account the cases reported to have ingested gabapentinoid amounts up to 25-fold their maximum therapeutic doses without developing serious sequelae (Fischer et al., 1994; Klein-Schwartz et al., 2003; FDA, 2004; Schauer et al., 2015). Otherwise, an intake of pregabalin in amounts 14 times higher than its maximum therapeutic dose was associated with coma and the necessity of mechanical ventilation (Wood et al., 2010). Gabapentinoid overdoses together with other substances are clearly more toxic (Table 3). Thus, in the last years, there were increasing fatalities associated with pregabalin overdoses mostly in opioid using populations and infrequently also without opioids but in mixture with overdosed benzodiazepines or antidepressants (Table 3). Parenteral applications of gabapentin and pregabalin have been described (Schifano et al., 2011, Snellgrove, 2016) but seemed to be rare and, in the case of pregabalin, would not be associated with a stronger euphoria than achievable with an oral intake due to its high bioavailability of >90% (Calandre et al., 2016). In comparison with propofol and benzodiazepines, gabapentinoids are certainly the safest GABAmimetics with a higher therapeutic index and wider dose margin between pleasure (euphoria/relaxation) and coma or death by overdosing (Bockbader et al., 2010; Bonnet, 2011; Calandre et al., 2016; Smith et al., 2016; Mersfelder and Nichols, 2016; Scherning et al., 2016a; Evoy et al., 2017; Quintero et al 2017). Regarding the FTI as a new measure of harm, gabapentin and pregabalin are located clearly below that of opioids and most antidepressants and antipsychotics according to an analysis of the Finish national database of medicolegal autopsies and the Finish consumption figure of a particular substance (Ojanperä et al., 2016). Of note, the FTI of clonazepam was calculated to be lower than that of the

gabapentinoids (Ojanperä et al., 2016) which should await reproduction in alternative forensic samples. To this aspect, it should be considered that analyzing large registers is well suited to uncover trends but is less helpful to verify causal relationships. To illustrate this point, we can take a look at the deaths being reported in relation to drug poisoning in England and Wales basing upon a register from 2011 to 2015 (Office of National Statistics 2015). This register reports increasing deaths related to gabapentinoids over the years but need to be interpreted with caution according to the limitations shown in the column of Table 3 which are all disclosed in detail on the official website (Office of National Statistics 2015). This quality of not being specific may explain the listed deaths related to cannabis and, most likely, a good portion of those being associated with gabapentinoids, too (Office of National Statistics 2015). The increasing deaths related to gabapentin and pregabalin (Table 3) might have mainly reflected their increasing use resulting from their “bystanding” of another waxing potential lethal substance abuse, mostly that of opioids (Hser et al., 2017). However, considerable overdoses of gabapentinoids can be associated with respiratory depression (Spiller et al., 2002) and cardiac conduction disturbances (Rasima and Burkhart, 2006) which can make the difference whether a mixture with other potentially more life-threatening drugs is lethal or not.

4.5. “Anti-adverse selection” process or Pandora´s box in at-risk-populations?

One might speculate even on an “anti-adverse selection” process in the population of substance dependents, if assuming that overdosing gabapentinoids is far less life-threatening than overdosing other widely misused GABAmimetics, such as benzodiazepines, which are involved in 30% to 50% of overdose deaths related to opioid analgesics (Park et al., 2015). This means that gabapentinoids might have the potential to replace more toxic benzodiazepines on the prescriptions and black markets and thereby, would help to decrease hazards in the population of opioid and multidrug users: “more safe drugs for the riskiest patients” - however, on costs of “ground noises” of this population, such as inclusion of gabapentinoids in drug taking behavior and extreme overdosing - but even with fewer fatal consequences than with

benzodiazepines or other more toxic drugs. A similar process might have been happened between the late 1950ies and the late 1980ies when barbiturates had been largely replaced by benzodiazepines which appeared to have a markedly higher therapeutic index compared to barbiturates (Morgan, 1990; Coupey, 1997). A presumptive signal for an anti-adverse selection might have come from the annual reports of the American Association of Poison Control Centers (Mowry et al., 2013, 2014, 2015, 2016). Therein, the total amount of registered fatality records had been fallen continuously from 2012 to 2015 whilst the number of gabapentinoid-related fatalities in drug mixtures became increased and this appeared to be much stronger attributed to gabapentin than to pregabalin (Table 3), although gabapentin is the lower toxic agent compared to pregabalin (Calandre et al., 2016). A further argument could come from a 5 year cross sectional times series analysis in Canada which described a nearly 20-fold increase in the rates of pregabalin use from 2006 to 2014 and a simultaneous trend to a decrease of the co-use of other prescription drugs including benzodiazepines (Kwok et al., 2017). Further pharmacoepidemiological research is needed to verify this hypothesis as well as the opposite view that gabapentinoids possess features of Pandora´s box in risk populations, such as patients with substance abuse history (Prescrire Int, 2012; Häkkinen et al., 2014; Chiappini and Schifano, 2016; Eastwood and Davison, 2016; Elliott et al., 2017).

4.6. Comparing the addictive risks of gabapentinoids with those of traditional substances of abuse

Unlike traditional psychoactive drugs, there is less evidence for gabapentinoids to be misused in a long-term manner and to be associated with tenacious relapses and social hazards (as outlined above). This would support the hypothesis that gabapentinoids can induce a “liking” (euphoric/relaxing high) due to their GABAmimetic action but no or only minimal “wanting” (Berridge and Robinson, 2016) which corresponds with no or only minimal rewarding properties of gabapentinoids in animal experiments (c.f. 3.1). Non-treatment seeking cocaine abusers did not alter their choice to self-administer cocaine while on gabapentin maintenance (up to 3200

mg/day) (Hart et al., 2007) which also did not emphasize a robust addictive power ("wanting") of gabapentinoids. However, the inhibition of presynaptic $\alpha_2\delta$-subunit-containing VGCCs could even hinder the transfer (sensitization?) from "liking" to "wanting" (Figure 2) through "anti-sensitizing" (Dooley et al., 2000; Eroglu et al., 2009) and thereby, "anti-wanting" actions (Shibasaki et al., 2009; Kurokawa et al, 2011) (Figure 2). Of note, there is first evidence for an up-regulation of α_2/δ subunits in the rodent limbic brain via repeated dopamine surges, e.g. mediated by methamphetamine administrations (Kurokawa et al., 2010, 2011).

Traditional drugs of abuse are characterized by a dominant "wanting" according to Berridge and Robinson´s "Incentive Sensitization Theory of Addiction" (Berridge and Robinson, 2016) (Figure 2). There are several further non-regulated medications being deemed to have less or no relevant addictive power ("wanting"), which were observed to be abused preferentially by patients with a history of another substance abuse disorder. These include some antidepressants (tranylcypromine, bupropion, tianeptine) (Haddad, 1999; Bernard et al 2011, Costa et al 2015), antipsychotics (quetiapine) (Montebello and Brett, 2015; Reeves and Burke, 2014; Reeves and Ladner, 2014) or pain relievers (flupirtine) (Gahr et al., 2013c).

On this background, we assume that gabapentin and pregabalin belong to those substances, which themselves have no relevant addictive power suis generis ("wanting"), but could become addictive in patients with prior substance abuse experiences These patients look for various options broadly being able to induce euphoria and to improve their affected stress reactivity that occur following substance addiction (Karoly et al., 2015; Volkow and Morales, 2015; Fosnocht and Brand, 2016). Unlike for nicotine, alcohol or opiates, there is yet no evidence for gabapentinoids to facilitate the misuse of other drugs in patients without a history of SUDs. Although gabapentinoids are widely distributed, we have found only 4 cases supporting a "wanting" of gabapentinoids in patients without an abuse history and these 4 cases referred to pregabalin and not to gabapentin (Yargic and Ozdemiroglu, 2011; Ashwini et al., 2015; Halaby et al., 2015; Driot et al., 2016; Table 1). This is still

below the frequency of cases having reported extremely rare clinical phenomena, such as the toxicologically relevant gut fermentation syndrome (“endogeneous auto-brewery”) (Cordell and McCarthy, 2013; Welch et al., 2016). Thus, we assume that gabapentinoids are usually not related to the development of behavioral dependence (“wanting”) in patients without prior experiences with traditional drugs of abuse. Unlike gabapentin, dispensing of pregabalin is regulated by law in two countries (USA, Norway) and actually listed in schedules which control psychoactive drugs with the lowest risk of abuse (Calandre et al 2016; Westin and Strøm, 2010). In Germany, prescription of gabapentinoids is hitherto not regulated by his narcotic law, just as in most other countries of the world.

Considering the safety concerns and addictive power of gabapentin and pregabalin as outlined above, we propose Table 4 to compare the addictive risks of gabapentinoid use with those of traditional substances of abuse.

5. Conclusion and recommendations

Altogether, the addiction risk of gabapentin is lower than that of pregabalin and depends on the exposed population. In patients without another current or past SUD, the risk to develop a dependence on gabapentinoids is very low. In these “abuse-history-free” patients, the treatment with gabapentinoids is advised to be managed similar to the treatment with other frequently prescribed medications. In patients with a history of SUD and especially in patients with an opioid use disorder, gabapentinoids (notably pregabalin) should be avoided or if indispensable, administered with caution by using a strict therapeutic and prescription monitoring. This is already stated in the package inserts. Prospective studies comparing the frequency and pattern of addiction criteria and drug safety alongside gabapentinoid use in patients with and without the experience of another SUD are missing and warranted to estimate the addictive power and hazardous potency of gabapentin and pregabalin more precisely.

6. Acknowledgements: none

7. Conflict of Interest: None to declare

8. Contributors

Conception: U.B., collection, analysis and interpretation of data: U.B., N.S., drafting the article: U.B., revising it critically for important intellectual content: N.S.

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Table 1: Clinical and epidemiological studies about gabapentinoid-abuse or -dependence

Study	Population	Methods	Results	Addiction history and Psychiatric comorbidity
Internet and hospital population				
Kapil et al., 2014 England and Wales	16-59-year-old internet users, N=1500, 50.9% females	online survey about the use of use of recreational substances including gabapentin and pregabalin	life-time prevalence of misuse: baclofen 1.3% (N=19), gabapentin 1.1% (N=17), pregabalin 0.5% (N=8) misuse of these GABAergic drugs more than once weekly in 13.1% (N=5) obtained from various sources, e.g. family or acquaintances (57.8%, N= 22) or from the Internet (47.3%, N=18) or abroad (7.8%, N=3) or legitimated prescriptions 13.1%, N=5)	unknown
Cossman n et al., 2016 Germany	≥ 65-year-old inpatients of a German general hospital in a metropolitan area, "Ruhrgebiet" 2013 (N=400)	structured DSM-IV-based face-to-face interview (SKID-I) focusing on the use of psychoactive substances including gabapentin and pregabalin	12-months prevalence 0% and life-time prevalence 0,25 % for gabapentinoid-abuse and dependence, N=1 with transient dependence on gabapentin, no case of pregabalin abuse or dependence	the male gabapentin-dependent was prior and currently dependent on an opioid pain reliever
Addicted populations or recreational drug users				
Schifano et al., 2011 Europe	anonymous recreational drug users	evaluation of 108 internet web-sites with reference to gabapentinoid and clonazepam use experiences, 8 European languages	Pregabalin was attributed to be an „ideal psychotropic drug for recreational purposes." incentives: to achieve alcohol/GHB/benzodiazepine-like effects mixed with euphoria; entactogenic feelings and DXM-like disassociation, and to cope with opiate/opioid withdrawal, similar effects with gabapentin but pregabalin	unknown

			seemed to be preferred (“far less dosage to get the same recreational high”) routes of misuse: mostly oral, but intravenous, rectal (‘plugging’), and ‘parachuting’ (emptying the content of the capsule into a pouch) were reported, too usual pregabalin dosages: 600 to 5000 mg/d, rapid tolerance	
Piralishvili et al., 2013 Georgia	adults in opioid substitution programs, Tbilisi, N=506 (two females)	self-report questionnaire of psychoactive substances	non-medical use: 8.17% pregabalin	all dependent on opioids at least
Grosshans et al., 2013 Germany	N=124 (34 female), 37.1±8.1 years old (range 20–55) in opioid substitution program vs control group: N=111 patients treated for non-opiate addiction, mostly alcohol or cannabis, Mannheim	pregabalin urine screen	non-medical pregabalin use: 12.1% of the patients substituted with opioids. In the control group were 2.7% positive (all had been prescribed pregabalin for medical purposes)	all had another substance use disorder at least
Baird et al., 2013 Scotland	adults dependent on substances attended to 6 detoxification clinics in the Lothian region, N=129	anonymous self-report questionnaire about psychoactive substances performed in 6 substance misuse clinics	non-medical use: N=25 (19%) gabapentin, N=4 (3%) pregabalin, N=19 (15%) methadone, N=61 (47%), buprenorphine N=2 (2%), cannabis N=55 (43%), heroin N=7 (5%). All patients admitting to using non-prescribed gabapentinoids (29/129 = 22%) were in opioid substitution programs incentives: to get “high”, to potentiate methadone effects	all dependent on opioids at least
McNamara et al., 2015 Ireland	adults being in 6 different opioid substitution programs, N=440, 21 to 61	drug urine screen including pregabalin in the National Drug Treatment Centre's (NDTC)	31 patients (7%) were found to use pregabalin for non-medical purposes, significantly more females (59%)	all dependent on opioids at least

	years old, 34% females	Drug Analysis Laboratory		
Smith et al., 2015 USA	adults using non-medical prescription opioids, Appalachian Kentucky, N=503, 78% females	prospective study, self-report questionnaire of psychoactive substances	6-months prevalence of non-medical gabapentin-use: 15%; – which represented a 165% increase in use compared to reports from one-year prior, and a 2950% increase since 2008 within this cohort. incentive: to get high gabapentin use in 25 of the past 30 days was associated with abusing immediate-release oxycodone, buprenorphine, benzodiazepines, females, and reporting chronic medical conditions The two major sources of gabapentin were physicians (52%) and drug dealers (36%)	all dependent on opioid pain relievers
Wilens et al., 2015 USA	adult opioid dependent inpatients detoxifying voluntarily at the Massachusetts General Hospital, Boston, N=162, 49% female, 33 ±10 years old	self-report questionnaire of psychoactive substances	28% reported using higher amounts of each medication than prescribed. Of opioid patients, 10% self-reported misusing clonidine, 22% gabapentin, 7% pregabalin, 25% clonazepam, and 11% amphetamine	all opioid dependent, at least anxiety 72%, ADHD 32%, depression 64%, PTSD 38%, bipolar disorder 28%
Bastiaens et al., 2016 USA	former inmates, living in a correctional community center, Pittsburgh, N= 250 adults, 37.2±12.1 years old, 36% females, 72% white	written questionnaire about the non-medical use in the past: opiates, gabapentin, buproprion, quetiapine, and fluoxetine	16% (N=41) reported having misused gabapentin in the past (quetiapine 21.8%, bupropion 6%, fluoxetine 0%). Of patients with an opioid use disorder (N=145), 26 % endorsed gabapentin abuse while 4 % of patients without an opioid use disorder (N=105) endorsed the non-medical use of gabapentin ($p<0.0001$) 26% of opiate dependent patients reported illegally obtaining, overusing, or malingering problems to obtain gabapentin only one of 30 patients (3 %)	all patients had further substance use disorders, 72 % two substance use disorders, at least depressive disorders (25 %), ADHD (25 %), adjustment disorders (22 %), anxiety disorders (18 %), PTSD (11 %), bipolar disorder (8 %), schizophrenia (3 %)

			with a cocaine use disorder and not comorbid with an opioid use disorder reported abusing gabapentin.	
Snellgrove, 2015 Germany.	adults voluntarily treated in a ward for qualified detoxification, Ulm (N=253), 33,1±8,8 years old, 21% female, 100% white	structured DSM-IV-based face-to face interview about pregabalin use, visual analogue scales of pregabalin effects, pregabalin urine screens	pregabalin use in the last 30 days: 26% (N=65), lifetime: 56% (N=142) 24-months-prevalence: 7% und point prevalence: 3% for pregabalin-dependence, every 10th patient had a false positive memory about a recent pregabalin use obtained from family or acquaintances for free (44% of all pregabalin users), drug dealers (41%), physicians (30%) minimum and maximum dose = 100 and 4500 mg/d in the last 30 days, respectively, median: 600 mg/d incentives: to potentiate opioid high, to dampen anxiety or withdrawal symptoms 9% of patients with pregabalin experience used pregabalin over 12 months at ≥ 25 days/month	all dependent on other substances, mostly opioids or benzodiazepines, cannabis use = negative predictor for pregabalin use co-use. with opioids (39%), sedatives (20%), alcohol (19%)
Alblooshi et al., 2016 United Arab Emirates	male adults with substance use disorders from seven emirates/principalities admitted to the National Rehabilitation Centre, Abu Dhabi 2015; N=250, mean age: 29.6 years, minimum: 18 years, maximum: 62 years	structured face-to-face interview about substance use	84.4% were polysubstance abusers, mostly opioids and alcohol. Of whom, over 60% used prescription drugs non-medically, such as meprobamate, prociclidine, and pregabalin. Pregabalin was used by 68% in this group which were mainly below 30 years old. Pregabalin (commonly 7 to 14 capsules á 75 or 150 mg/day) was used in 41% of these cases together with other prescription drugs and in 27% not together with other prescription drugs	all patients with another substance use disorder at least
Mutschler et al., 2016	adult patients in a methadone treatment	self-report measure focusing on	no case with pregaballin use could be identified by self-report and hair analysis	all dependent on opioids at least

Switzerland	program, Zurich (N=109)	pregabalin use, hair toxicology analysis		
Heikman et al., 2016 Finland	adult patients in a methadone substitution program, Helsinki (N=(82)	retrospective study of 200 urine samples collected consecutively between 10/2013 and 4/2014 drug urine screen including pregabalin and gabapentin	gabapentin and pregabalin in 1 (0.5%) and 8 (4%) of the samples; the gabapentin-positive sample showed also benzodiazepines, amphetamine and cannabis; no information about concurrent drugs in the pregabalin-positive samples, no information about potential prescriptions	all had another substance use disorder at least

Table 2: Differentiating case reports related to abuse and dependence of gabapentiniods according to the dependence-criteria of ICD-10[a], addiction history, self-administration, long-term use, relapses

Case reports	Craving (BD)	Loss of control (BD)	Narrowed behavior[b] (BD)	Tolerance (PD)	Withdrawal symptoms (PD)	Harmful use (PD)	Number of fulfilled dependence criteria[a]	History of other substance abuse or dependence apart from nicotine	Information about gender, comorbidity and patterns of consumption or relapses
Gabapentin (N=36)									
Markowitz et al., 1997 USA	U	U	U	None	None	unknown	0	Cocaine	41-year-old woman posttraumatic stress disorder 400-1600 mg/d for three months to reduce cocaine craving, self-administration
Corá-Locatelli et al., 1998 USA	U	U	U	U	Yes	U	1	Negative	five patients with obsessive-compulsive disorder and mood disorder receiving 900-3600mg/d for months

Rosebush et al., 1999 Canada	U	U	U	U	Yes	U	1	Negative	48-year-old man bipolar disorder prescription of 500mg/d for 4 weeks
Norton, 2001 USA	U	U	U	U	Yes	U	1	Negative	29-year-old man bipolar disorder prescription of 4800mg/d over 6 weeks
	U	U	U	U	Yes	U	1	Negative	36-year-old man bipolar disorder, chronic back pain prescription of 3600mg/d for 2 months
	U	U	U	U	Yes	U	1	Negative	28-year-old man migraine prescription of 2400mg/d for 6 months
Barrueto et al., 2002 USA	U	U	U	Yes	Yes	Yes	3	Negative	34-year.old male chronic back pain 8000 mg/d for 9 month to reduce pain, self-administration
Drabkin and Calhoun, 2003 Canada	U	U	U	Yes	U	U	1	Negative	35-year-old woman bipolar disorder prescription of 3600mg/d for 2 months
Reccoppa et al., 2004	U	U	U	U	U	U	0	Cocaine	five 29 to 45-year-old male inmates snorting the

USA									powder of opened gabapentin 300 and 400mg capsules to get high bipolar disorder, anxiety disorder, antisocial personality disorder, impulse control disorder, neuropathic pain self-administration
Tran et al., 2005 USA	U	U	U	U	Yes	U	1	Negative	81-year-old woman schizoaffective disorder, Parkinson´s disease, cerebrovascular disease prescription of 800mg/d over 5 years
Victorri-Vigneau et al., 2007 France	U	U	Yes	Yes	Yes	U	3	Alcohol	67-year-old woman mood disorder up to 7200 mg/d, self-administration, **relapse**
Pittenger et al., 2007 USA	U	U	U	U	Yes	U	1	Alcohol, cocaine, opioids	33-year-old man 3600 mg/d gabapentin over a few weeks, self-administration
	U	U	U	Yes	Yes	Yes	3	Alcohol	63-year-old man chronic back pain up to 4900 mg/d over

									several months, self-administration
Kruszewski et al., 2009 USA	**Yes**	U	U	Yes	Yes	Yes	4	Alcohol	33-year-old male physician depression, anxiety high self-administered doses over several weeks
Hellwig et al., 2010 USA	U	U	U	U	Yes	U	1	Alcohol	53-year-old woman liver cirrhosis 700 mg/d, prescribed over a few weeks
Finch et al., 2010 USA	U	U	U	U	Yes	U	1	U	41-year-old man with an orthotopic liver transplant neuropathic pain prescription of gabapentin for several weeks
See et al., 2011 USA	U	U	U	U	Yes	U	1	Negative	76-year-old woman depression, neuropathic pain prescription of 3600mg/d over 1 month
Di Fabio et al., 2013 Italy	U	U	U	U	Yes	U	1	Negative	76-year-old woman bipolar disorder, neuropathic pain prescription of 900mg/d over two years
Mah and Hart, 2013 Canada	U	U	U	U	Yes	U	1	Negative	75-year-old woman recurrent depression,

									fibromyalgia, postherpetic neuralgia long-term prescription of 1800mg/d
Reeves and Burke, 2014 USA	U	U	U	U	U	Yes	1	Cannabis, cocaine	42-year-old man Taking up to 5 tablets of gabapentin 300 mg with 3 to 4 tablets of quetiapine 200 mg simultaneously to produce a sensation of sedation and euphoria, self-administration
Reeves and Ladner, 2014 USA	U	U	U	U	U	U	0	Opioid-maintenance program	38-year-old man taking buprenorphine/naloxone simultaneously with up to 1000 mg of quetiapine or with up to 2400 mg of gabapentin. to get relaxed and euphoric which was experienced as not as intense as during opiates, self-administration
Satish et al., 2015 India	Yes	Yes	yes	yes	yes	U	5	opioids	26-year-old man ADHD substitution of a 3-years-lasting propoxyyphene dependence with gabapentin (up to 12 g/d alongside 2 years), self-administration gabapentin high was different from the opioid

									high
Bonnet and Scherbaum, 2016 Germany	None	None	None	Yes	Yes	None	2	Negative	six 35-76-year-old patients, among them 4 females anxious depression or generalized anxiety disorder prescription of gabapentin (1200-3200 mg/d) over several weeks
Pregabalin (N=19)									
Oaklander and Buchbinder, 2010 USA	U	U	U	U	Yes	U	1	Negative	80-year-old woman postherpetic neuralgia prescription of 375 mg/d for 49 weeks
Grosshans et al., 2010 Germany	**Yes**	U	**Yes**	Yes	Yes	U	4	Alcohol, cannabis, heroin	47-year-old man self-administration of up to 7500mg/d to get high, **relapse** serum level 29 mg/l (therapeutic range: (2–8 mg/L)
Filipetto et al., 2010 USA	U	U	**Yes**	Yes	Yes	U	3	Opioids	35-year-old woman neuropathic pain, anxious depression self-administration of 88500mg over a 28-day period
Westin and Strøm, 2010 Norway	U	**Yes**	U	Yes	Yes	U	3	Negative	30-year-old woman generalized anxiety disorder, insomnia

									self-administration to get euphoric - up to 1800mg/d for two years after a prescription of 600mg/d
Yargic and Ozdemiroglu, 2011 Turkey	U	None	**Yes**	Yes	Yes	U	3	Benzodiazepines, ketamine	37-year-old man bipolar disorder, grand mal epilepsy self-administration of up to 3000 mg/d to get euphoric, over a period of 2 month, afterwards the patient learned to take therapeutic doses
Karosin et al., 2012 Austria	U	U	U	U	Yes	U	1	Negative	28-year-old woman poststroke neuropathic pain prescription of 150 mg/d for 3 weeks
Skopp und Zimmer, 2012 Germany	U	**Yes**	**Yes**	Yes	U	U	3	Opioid maintenance program, cocaine, benzodiazepines	adult man taken into police custody due to maniform irritation and aggression self-administration serum level: 25mg/l pregabalin - in combination with diazepam and methadone
Carrus and Schifano, 2012 South-	U	U	U	Yes	Yes	U	2	Benzodiazepines, ecstasy, cocaine, cannabis	32-year-old man antisocial personality disorder,

Europe									neuropathic pain self-administration of up to 4500mg/d over a period of 4 weeks to get energetic, empathic and relaxed – after an initial prescription of 600mg/d
	Yes	U	U	U	Yes	Yes	3	Ecstasy, alcohol, cannabis	33-year-old man generalized anxiety disorder, bipolar disorder self-administration of up to 1500 mg/d within 4 weeks to get euphoric and relaxed "as with cannabis" – after an initial prescription of 300 mg/d
Aldemir et al 2013 Turkey	**Yes**	U	**Yes**	Yes	Yes	Yes	5	Alcohol, cannabis, ecstasy, cocaine	34-year old woman anxiety self-administration of up to 16000mg to feel more energetic and self-confident, visual hallucinations, for 3 years
Papazisis et al., 2013 Greece	U	U	**Yes**	Yes	U	U	2	Cannabis, alcohol	19-year-old man generalized anxiety disorder self-administration of up to 1800 mg to get high, longer than 3 months after a

									prescription of 600 mg/d, no motivation to detoxify
Gahr et al., 2013b Germany	U	U	**Yes**	U	yes	U	2	Alcohol	38-year-old woman bipolar disorder, borderline personality disorder, unspecific anxiety self-administration of 800 mg/d to get euphoric, for 4 months - after an initial prescription of therapeutic doses
Barrett et al., 2015 USA	U	**Yes**	U	U	Yes	Yes	3	Opioid painkillers	61-year-old man neuropathic pain self-administration of more than the prescribed 300mg/d for 8 months
Ashwini et al., 2015 India	U	U	**Yes**	Yes	Yes	Yes	4	Negative	30-year-old man neuropathic pain self-administration of up to 3000 mg/d, for 4 years, brought by his mother to admission due to suicidal ideations
Yazdi et al., 2015 Austria	U	**Yes**	**Yes**	Yes	Yes	Yes	5	Benzodiazepines, alcohol, tramadol	29-year-old man major depression, generalized anxiety disorder self-administration of up to 3000

									mg/d in combination with benzodiazepine or tramadol or quetiapine overdoses,, three admissions due deep sedation/mixed intoxication, **two relapses** within a year
Gahr et al., 2015 Germany	**Yes**	U	**Yes**	Yes	U	U	3	Benzodiazepines	33-year-old woman anxiety, borderline personality disorder self-administration of up to 3000 mg/d to get euphoric and relaxed, for 6 month
Halaby et et 2015 Lebanon	**Yes** (subsided within 6 weeks of abstinence)	U	U	Yes	Yes	Yes	4	Negative	26-year-old woman bipolar disorder, generalized anxiety disorder self-administration to calm negative feelings – up to 2400mg/d within 4 months
Nordgaart and Jürgens 2015 Denmark	U	U	U	Yes	Yes	U	2	Alcohol, opioid maintenance program	38-year-old man generalized anxiety disorder self-administration of up to 8400 mg/d, bought 21 times
Driot et al 2016 France	**Yes**	U	**Yes**	Yes	Yes	U	4	Negative	young woman anxiety, depression, anorexia,

									personality disorder prescription of < 300 mg/d – synergistic stimulating effects together with secondary tobacco use

Notes: [a]Dilling and Freyberger, 2004,[b] e.g. gabapentinoid seeking behavior.

Abbreviations: PD=physical dependence, BD=behavioral dependence, U=unknown; abuse = harmful use, dependence = ≥ 3 criteria within a year (Dilling and Fryberger, 2004)

Fulfilled BD-criteria in bold letters, negative addiction history is accentuated by shadowed boxes, relapses are highlighted in bold letters in the column on the right edge of the table

Table 3: Overdoses and fatalities associated with gabapentinoids

Study	Population	Methods	Results	Addiction history and Psychiatric comorbidity	Limitations
			Non-fatal overdosing		
Fischer et al., 1994 USA	16-year-old male swallowed father´s gabapentin, approximately 50 g	case study	sedation, stable vital signs, plasma level 62 mg/L	cocaine	no estimation of period between ingestion and determination of blood levels
Fernandez et al., 1996a USA	31-year-old man, self-poisoning with large amounts of valproic acid and gabapentin	case study	coma, shock, plasma concentrations: valproic acid 1306.9 mg/L (peak), gabapentin 60 mg/L, resolved during aggressive supportive care and concurrent hemoperfusion and hemodialysis to enhance elimination of valproic, negative urine drug screen	epilepsy	
Fernandez et al., 1996b	32-year-old man, self-poisoning with approximately	case study	dizziness, somnolence, nystagmus, slurred speech,	unknown	

USA	91 g gabapentin and 54g valproic acid, beer and whiskey, he denied other coingestions		stable vital signs, normal respiratory rate of 24/minute, negative urine drug screen; plasma concentrations valproic acid 139.9 mg/L, gabapentin 44.5 mg/L		
Stopforth, 1997 South Africa	17-year-old girl swallowed approximately 40 gabapentin capsules á 300mg (12 g) together with 20 lamotrigine tablets á 100 mg	Case study	sedation, drowsiness, ataxia and lethargy, low serum potassium levels	epilepsy	no blood levels
Verma et al., 1999 USA	30-year-old-female with epilepsy and chronic renal failure was treated with valproic acid 1250 mg/d which was augmented with 1800 mg/d gabapentin	case study	mild resting tremor, slight difficulty with naming objects and difficulty with performing three step commands, gabapentin plasma level 85 mg/L, valproate may have contributed to the symptoms	lupus erythematodes, at the age of 24 years left middle cerebral artery stroke which resulted in a right hemiparesis and expressive aphasia, chronic renal failure requiring hemodialysis three times per week, generalized tonic clonic seizures at the age of 27 years	
Klein-Schwartz et al., 2003 USA	pure gabapentin intoxications 20 patients ranging from 12 months to 83 years old, estimated doses of gabapentin ingestion	case series, 2-year multicenter prospective observational study of all gabapentin exposures reported to three poison	ten cases involved children and adolescents, 9 of the 20 cases were symptomatic with drowsiness, dizziness, nausea and vomiting,	unknown; of gabapentin exposures, 65% were acute-on-chronic, indicating that most cases involved the patient´s own	no information about blood levels, no conclusive information about addiction history and comorbidity

	between 50 mg (child) and 35 g (48 years old)	centers from 4/1/1998 to 4/1/2000	tachycardia, hypotension, none of the patients were admitted to medical care	medication	
FDA, 2004 USA	premarketing clinical trials	medical review about pregabalin	six patients with reported ingested doses from 1500 to 8000 mg showed typical adverse effects (confusion, somnolence, dizziness, ataxia, diplopia, blurred vision), no death – one patient with an reported intake of 15g which had "resulted in no consequences"	unknown	no conclusive information about mixtures, comorbidity or serum levels
Spiller et al., 2002 USA	61-year-old female; self-poisoning with gabapentin and quetiapine	case study	massive gabapentin and presumptive quetiapine overdose with a recorded serum gabapentin concentration of 104.5 mg/L associated with coma, respiratory depression requiring mechanical ventilation, and hypotension	unknown	no information about addiction history
Rasimas and Burkhart 2006 USA	44-year-old female multiple prescription drug overdose plus alcohol and cannabis	case study	lethargy, drowsiness, tachycardia, hypotension, ataxia, dizziness, never lost consciousness, QRS widening and QTc prolongation attributed to a reported self-induced overdose with gabapentin and	alcohol, cannabis	no information about the ingested gabapentin and nefazodone amounts

			nefazodone, serum levels of both substances obtained 2 hours post-ingestion were both within the therapeutic range (gabapentin 7 mg/L)		
Braga and Chidley, 2007 UK	29-year-old man, self-poisoning with 32 g lamotrigine and 11.5 g pregabalin	Case study	agitated, unresponsiveness, hemibalistic movements, facial grimacing, tachycardia, urinary retention, stable vital signs, pregabalin´s plasma level 45 mg/L	epilepsy	No conclusive information about addiction history and psychiatric comorbidity
Wood et al., 2010 UK	54-year-old male, self-poisoning with 8.4 g of pregabalin, denied ingestion of other drugs	case study	significant neurological depression and coma approximately 3 h post-ingestion, remained cardiovascularly stable, serum concentration of pregabalin 66.5 mg/L; supportive care including mechanical ventilation	HIV, peripheral neuropathy, diabestes mellitus	no conclusive information about addiction history
Zacny et al., 2012 USA	healthy volunteers between the age of 31 and 39 years	double-blind, randomized, crossover design; in separate sessions, participants were exposed to 75 and (supratherapeutic at first dosing) 150 mg pregabalin, 10 mg oxycodone and 75 mg pregabalin & 10 mg oxycodon	respiration rate (placebo: 12.9±0.6): significantly reduced with pregabalin 75 mg (10.3±0.7) and 150 mg (10.6±0.8), oxycodone 10 mg (10.5±0.7), oxycodone 10 mg & pregabalin 75 mg (9.6±0.5) pregabalin did not impact on psychomotor performance or	15 volunteers reported use of cannabis, and some subjects also the use of stimulants, club drugs, hallucinogens, opioids	no information about the results of urine drug screens, although in the methods section is mentioned that upon arrival, breath alcohol, urine toxicology, and pregnancy (for females) tests had

			liking or drug taking desire experimental combining 150 mg pregabalin with oxycodone 10 mg was not further studied because two subjects reported excessive drowsiness		been given no information about serum levels of the tested drugs
Miljevic et al., 2012 Serbien	54-year-old man, self-poisoning with 4.2 g pregabalin together with 21 mg bromazepam and 125 mg clomipramine	case study	conscious, alert, stable condition of cardiovascular and respiratory systems serum level: 20.8 mg/L	generalized anxiety disorder	no information about addiction history
Schauer et al., 2013 USA	59-year-old man, self-poisoning with approximately 90 g gabapentin	case study	nausea, mild sedation, stable vital signs, normal cQT-interval negative urine drug screen gabapentin plasma level 72.8 mg/L, approximately 3 hours after ingestion	unknown	no information about addiction history and comorbidity
Millar et al., 2013 Northern Ireland, UK	10 young adults presented to a Belfast emergency department following recreational pregabalin abuse	observational retrospective study	reported dosages ranged from 500–1400 mg pregabalin. Six (60%) patients presented with seizures (5 of which were 'first' seizures). Two patients (20 %) required intubation and ventilation and were admitted to the Intensive Care Unit.	unknown	no information about addiction history, comorbidity and the contribution of concurrent drugs of abuse or pharmaceutic als
Koschny et al., 2014	21-year-old female with	case study	asystole, cardiopulmonary	no information	no conclusive information

Germany	polyintoxication (approximately 1.75 g carvediol, 300 mg amlodipine, 6g amitriptyline, 500 mg torasemide, 1.5 g ketoprofen, 28 g nicotinic acid, 16 g gabapentin), self-poisoning		resuscitation, coma gabapentin´s peripheral blood concentration: 126.8 mg/L to facilitate drug removal, therapeutic plasma exchange was performed, after extubation without neurologic sequelae		about addiction history and comorbidity
Kriikku et al 2014 Finland	drivers apprehended for driving under the influence of drugs in 2012, N=206 pregabalin positive samples	retrospective review	pregabalin serum concentration-range: 0.68-111.6 mg/L, median: 6.2 mg/L, nearly 50% cases had serum concentrations above the recommended therapeutic range (2.7-8.5 mg/L); no further substance besides pregabalin in three cases (0.7 mg/L, 17.9 mg/L, 18.2 mg/L)	additional use: benzodiazepines (91%), cannabis (54%), amphetamines (44%), opioids (40%), alcohol 20%, in 43.2% > 5 substances simultaneously	no information about comorbidity or prescribed medications
Wills et al., 2014 USA	poison center data evaluating clinical outcomes from newer anticonvulsant overdoses	retrospective study using the Toxicall™ database from 1/1/2002 to 31/12/2011	94 cases with gabapentin (maximal dose 96g, median 6g) and 18 cases with pregabalin (maximal dose 9 g, median 2,4 g), no severe outcome, no fatality	unknown	no information about blood levels, addiction history, comorbidity
			Fatalities		
Moore et al., 2005 USA	54-year-old female, self-poisoned with metaxalone and	case study	postmortem central (heart) blood concentrations:	no drugs of abuse were found	

	gabapentin		gabapentin 24 mg/L, metaxalone (21 mg/L) and therapeutic concentrations of acetaminophen and citalopram		
Button et al., 2010 England, UK	49-year-old female, 50-year-old male, self-poisoning with pregabalin	case-study, unpreserved femoral blood	pregabalin serum concentrations: 25.3 mg/L, 180 mg/L	additional use: benzodiazepines, Z-drugs, opioids; antidepressant	causality douptful due to a mixture of contributing substances and missing information about comorbidities
Launiainen et al., 2011 Finland	population-based sample of deceased young adults aged 15-34 years, 75% male, November 2006 to October 2008, N=1623	register study, review of postmortem toxicology, background information from case referrals was used to distinguish the abuse of medicines from their therapeutic use	postmortem analyses found pregabalin positive in 68 cases (42 with abuse); for comparison: cannabis was positive in 221 cases (221 with abuse), morphine 149 (64), codeine 148 (55), tramadol 154 (84); any drug 677 (509)	blood alcohol was positive in 52% of the cases	no conclusive information about mixtures, comorbidity or serum levels; cases of known opioid substitution treatment and cases classified as suicides with the drug in question were not included
Middleton, 2011 USA	82-year-old female, self-poisoning with gabapentin	case study	postmortem peripheral blood concentration of gabapentin 88 mg/L, clonazepam concentrations within the therapeutic range,residual gastric gabapentin dose was estimated to be 2210 mg	depression, several previous episodes of suicidal ideation, obesity, cardiomegaly	no conclusive information of period between ingestion and determination of blood levels, autopsy was performed ca. 22 h after her discovery
Lottner-Nau et al., 2013 Germany	autopsies of drug-related deaths within 2 years (October 2010 –	register study, retrospective observational study	pregabalin was found in 43 (4.4%) cases. The concentration	additional illicit and licit drugs in each case, opioids (100%),	causality douptful due to a mixture of contributing

	September 2012), Munich, N=982		range in femoral or heart blood was between 0.04 mg/L and 22.8 mg/L, median 5.18 mg/L	benzodiazepines (77%), neuroleptics (33%), alcohol (30%)	substances and missing information about comorbidities
Llauniainen et al., 2014 Finland	population-based sample of 57903 Finish autopsy cases from the period between 01/01/2000 and 31/12/2010. Among them, there were 135 (0.23%) and 380 (0.66%) autopsy cases in which gabapentin and pregabalin were involved	register studies	8 of the 135 (6%) records were related to gabapentin to be the main cause of death and 12 of the 380 (3.2%) records were related to pregabalin in this sense – as taken from death certificates	unknown	no conclusive information about mixtures, comorbidity
Priez-Barallon et al., 2014 France	18 cases of deaths in which pregabalin was involved	case series	no significant differences between central and peripheral blood pregabalin concentrations, concentrations in peripheral blood ranged between 0.4 and 206.7 mg/L, pregabalin was suggested to be a likely factor in the cause of death in 3 cases, which used also opioids	unknown	no conclusive information about addiction history and comorbidity
Häkkinen et al., 2014 Finland	all medico-legal death cases in Finland in which gabapentin (N=43) and pregabalin (N=316) was found in postmortem toxicology from 2010 to 2011	register study, 2-year retrospective observational study	median femoral blood concentrations of pregabalin were 15 mg/L in the abuser group and 5.8 mg/L in the other cases. For gabapentin, those concentrations were 12 mg/L (abuser group) and 8.3 mg/L (non-abuser	positive addiction history and drug abuse in 48.1% of pregabalin and 18.6 % of gabapentin cases; 91.4 of pregabalin abusers and 87.5 of gabapentin abusers had concomitant	

			group)	opioid use, other psychoactive substances were found in the remaining cases	
	"only" pregabalin case, 31-year-old male, no valid pregabalin prescription	case study	femoral blood concentrations: pregabalin 110 mg/L – and ethanol (0.24%); traces of quetiapine and levomepromazine; benzodiazepines were within therapeutic ranges	unknown addiction history, coronary disease	
	"pregabalin and opioid" case, 26-year-old male, no valid pregabalin prescription	case study	femoral blood concentrations: pregabalin 48 mg/L, concentrations of buprenorphine and benzodiazepines were within the therapeutic ranges	abuser of buprenorphine and amphetamine	
Cantrell et al., 2015 USA	47-year-old female deceased after the ingestion of approximately 26 tablets of 600 mg (15.6 g) gabapentin	case study	postmortem peripheral(femoral) gabapentin blood concentration 37 mg/L, central (heart) blood 32 mg/L (therapeutic concentrations 2-20 mg/L), liver 26 mg/kg, vitreous 32 mg/L, gastric contents 6 mg concurrent medication: ibuprofen in therapeutic doses	chronic pain, obesity, no history of alcohol or illicit drug use, no other drugs including prescribed hydrocodone were detected	
Ojanperä et al., 2016 Finland	39 (0.2%) and 6 (0.03%) fatalities were related to pregabalin and	register study, postmortem toxicology cases,	Mean FTI: pregabalin 1.92, gabapentin 0.91	unknown	no information about possible

	gabapentin, respectively, out of 19670 drug-related deaths	database review using the fatal toxicity index (FTI), expressed as the number of deaths per million DDD (defined daily doses) in 3 years, 2005, 2009, 2013	increasing trend in FTI over the years for pregabalin (0.54, 1.54, 2,44) superior mean FTIs: methadone 42.65, dextropropoxyphene 31.84, levomepromazine 21.92, doxepine 13.99, chlorprothixene 7.11, oxycodone 6.76, amitriptyline 6.54, trimipramine 6.32, tramadol 5.69, sulpiride 4.66, propranolol 3.83, quetiapine 2.51, trazodone 2.44		mixtures and comorbidities
Eastwood and Davison, 2016 UK	70 cases over a two year period, analyses was carried out if use was suspected, mostly due to information about known prescription of pregabalin	register study, postmortem toxicology analyses	whole blood concentration: 0.005 to 225 mg/L, median: 8 mg/L. Of the cases, 67% had pregabalin concentrations within the assumed therapeutic range (0.4-17mg/L). All cases had concurrent use of other substances, mostly opioids and benzodiazepines, One potential case (19-year-old male) where pregabalin (76 mg/L) appeared to be the cause of death; but contribution of low levels of	13% heroin, 28% morphine, methadone 19%, cocaine 20%, 55% diazepam, alcohol 24%	No conclusive information about comorbidity

			diazepam and sertraline detected could not be excluded		
Chiappini and Schifano, 2016	EudraVigilance database, misuse reports of gabapentin (N=410 patients) and pregabalin (N=1315 patients)	database review	gabapentin: 86 (21%) fatality reports, in 3 (3.5%) of these reports no other drug was reported pregabalin: 27 (2%) fatality reports, in 5 (18.5%) of these reports no other drug was reported	unknown	no conclusive information about possible mixtures, comorbidities, serum levels
Office for National Statistics, 2016 England and Wales, UK	death related to drug poisoning in England and Wales from 1993 onwards	register study	increasing deaths in which gabapenoids are involved; gabapentin 2011 (4), 2012 (8), 2013 (9), 2014 (26), 2015 (49) and pregabalin 2011 (4), 2012 (4), 2013 (33), 2014 (38), 2015 (90) - All drug poisoned deaths 2011 (2652), 2012 (2597), 2013 (2955), 2014 (3346), 2015 (3674) – any opioid 2011 (1439), 2012 (1290), 2013 (1592), 2014 (1786), 2015 (1989) – any benzodiazepine 2011 (293), 2012 (284), 2013 (342), 2014 (372), 2015 (366) - any new psychoactive substance 2011	unknown	i)the data are based only on information reported on the coroner's death certificate and may not include every substance involved in the death, ii) in around 1 in 8 drug poisoning deaths, only a general description is recorded on the coroner's death certificate (such as drug overdose or multiple drug toxicity), iii) in an additional third of all drug poisoning deaths, the death certificate mentions more than 1

			(31), 2012 (55), 2013 (63), 2014 (82), 2015 (114) – any amphetamine 2011 (62), 2012 (97), 2013 (120), 2014 (151), 2015 (157) – cocaine 2011 (112), 2012 (139), 2013 (169), 2014 (247), 2015 (320) - cannabis 2011 (7), 2012 (14), 2013 (11), 2014 (28), 2015 (21) – z-drugs 2011 (71), 2012 (83), 2013 (86), 2014 (100), 2015 (87) – antipsychotics 2011 (104), 2012 (102), 2013 (107), 2014 (126), 2015 (101) – propranolol 2011 (32), 2012 (39), 2013 (46), 2014 (54), 2015 (55) - tricyclic antidepressants 2011 (200), 2012 (233), 2013 (235), 2014 (253), 2015 (215) – SSRI 2011 (127), 2012 (158), 2013 (150), 2014 (159), 2015 (150) – paracetamol 2011 (207), 2012 (182), 2013 (226), 2014 (200), 2015 (197) Over half of the reported deaths involved an opoid		specific drug (where more than 1 drug is mentioned, it is not possible to tell which was primarily responsible for the death) iv) where more than 1 drug is mentioned on a death certificate, the death may be counted in more than one substance category; v) approximatel y 30% of all drug-related poisoning deaths also contain a mention of alcohol or long-term alcohol abuse (for example, cirrhosis) in addition to a drug, vi) no conclusive information about addiction history and comorbidity
Mowry et al., 2013 USA	2576 nonpharmacolog ical and pharmacological	national register of prehospital, hospital and	38 fatalities in which gabapentinoids are involved	unknown	blood levels were presented only in 10

	exposures reported to the national poison data system from 57 of the nation´s poison centers in the period of 01/01/2012 and 12/31/2012 (30nd Annual Report)*	autopsy records or indirect cases reported through other sources	(1.5% of the whole 2576 records). The 7 (0.27%) pregabalin-involved fatalities were always contaminated with other pharmaceuticals, mostly antidepressants (N=3), opioids (N=3), benzodiazepines (N=3) – one record with blood level (0.44 mg/L). The 31 (1.2%) gabapentin-involved fatalities were always contaminated with other substances, mostly antidepressants (N=15), benzodiazepines (N=18), opioids (N=17) – 9 records with blood levels (0.8 – 29 mg/L)		records, no information about individual comorbidity or addiction history, autopsy in 19 of the 38 records
Mowry et al., 2014 USA	2113 nonpharmacological and pharmacological exposures reported to the national poison data system from 57 of the nation´s poison centers in the period of 01/01/2013 and 12/31/2013 (31nd Annual Report)*	national register of prehospital, hospital and autopsy records or indirect cases reported through other sources	41 fatalities in which gabapentinoids were involved (1.9% of the whole 2113 records). The 7 (0.33%) pregabalin-related fatalities were always contaminated with other pharmaceuticals, mostly antidepressants (N=3), opioids (N=2), benzodiazepines (N=3). The 34 (1.6%)	unknown	blood levels were presented only in 5 records, no individual information about comorbidity or addiction history; autopsy only in 14 of the 41 records. One fatality (2.4%) of the 41 gabapentinoid records (or 0.05% of the whole 2113

			gabapentin-related fatalities were nearly fully (N=33) contaminated with other pharmaceuticals, mostly antidepressants (N=22), benzodiazepines (N=12), opioids (N=13) – 5 records with blood levels (1.1 – 34 mg/L) – one of the 34 records was related to gabapentin alone		fatality records) was attributed solely to a gabapentinoid alone (gabapentin), however, this record provided no information about blood levels, autopsy results, comorbidity or addiction history
Mowry et al., 2015 USA	1408 nonpharmacological and pharmacological exposures reported to the national poison data system from 56 of the nation´s poison centers in the period of 01/01/2014 and 12/31/2014 (32nd Annual Report)*	national register of adult prehospital, hospital and autopsy records or indirect cases reported through other sources	41 fatalities in which gabapentinoids were involved (2.9% of the whole 1408 records). The 11 (0.8%) pregabalin-related fatalities were always contaminated with other pharmaceuticals, mostly antidepressants (N=4), opioids (N=4), benzodiazepines (N=4) – 2 records had blood levels (24 and 21.3 mg/L). The 30 (2.1%) gabapentin-related fatalities were nearly fully (N=29) contaminated with other substances, mostly antidepressants (N=14), benzodiazepines (N=10), opioids	unknown	blood levels were presented only in 9 records, no information about individual comorbidity or addiction history, autopsy only in 16 of the 41 gabapentinoid records. One fatality (2.4%) of these 41 records (or 0.07% of the whole 1408 fatality records) was attributed solely to a gabapentinoid alone (gabapentin), however, this record provided no information about blood levels, autopsy

			(N=9), ethanol (N=6) – 7 records had blood levels (1.9 – 26 mg/L) – one of the 30 records was related to gabapentin alone		results, comorbidity or addiction history
Mowry et al., 2016 USA	1371 nonpharmacological and pharmacological exposures reported to the national poison data system from 55 of the nation´s poison centers in the period of 01/01/215 and 12/31/2015 (33nd Annual Report)*	national register of adult prehospital, hospital and autopsy records or indirect cases reported through other sources	59 fatalities in which gabapentinoids were involved (4.3% of the whole 1371 records). The 8 (0.6%) pregabalin-related fatalities were always contaminated with other pharmaceuticals, mostly opioids (N=5) and antidepressants (N=6). The 51 (3.7%) gabapentin-related fatalities were nearly fully (N=50) contaminated with multiple other pharmaceuticals, mostly opioids (N=22), benzodiazepines (N=16), antidepressants (N=21) – gabapentin blood levels were presented in in 7 records (11-35.9 mg/L) – one of the 51 records was related to gabapentin alone	unknown	blood levels were presented only in 7 records, no information about comorbidity or addiction history, autopsy in 20 of the 59 gabapentinoid records. One (1.7%) of these 59 records (or 0.07% of the whole 1371 fatality records) was attributed solely to a gabapentinoid alone (gabapentin), however, this record provided no information about blood levels, autopsy results, comorbidity or addiction history
Abrahamsson et al., 2017 Sweden	nation-wide register data including all individuals who were dispensed methadone or	retrospective register-based open cohort study	356 patients died (7.9%); 193 deaths were caused by overdoses (54.2%);	all opioid dependent	observational study not allowing conclusions about causalities;

	buprenorphine as opioid maintenance for opioid dependence between July, 2005 and December, 2012, N=4501		Z-drugs and pregabalin prescriptions were associated with overdose-death while benzodiazepine prescriptions were not associated with overdose-death but with non-overdose death		no information about socio-economic situation and comorbidity
Elliott et al., 2017 UK	requested and routine diagnostic investigation, pregabalin analysis was made in cases where pregabalin was prescribed or suspected to have been abused	case series	pregabalin was detected in 93 postmortem cases with 71 drug-related deaths among them. Pregabalin was attributed to be the main cause of death in 9 adult cases (blood levels 28-182 mg/L). Of the 9 cases, al had additional substance abuse, mostly opiates (N=6), benzodiazepines (N=5), antidepressants (N=4), pregabalin prescription in 5 from the 9 cases.	all currently abusing or being dependent on traditional substances of abuse, mostly opiates and benzodiazepines	no autopsy in 4 out of the 9 cases

*only the annual reports to the US-register from the years 2012 to 2015 were considered, Annual reports are available as of 1999 (http://www.aapcc.org/annual-reports/) [accessed on 04/04/17]

Table 4: Addictive risks of gabapentinoids and traditional substances of abuse: a comparative appraisal[a]

Characteristics/substances of abuse	Opioids	Alcohol	Gabapentin	Pregabalin	Benzodia-zepines	Cannabis

Self-administration behavior (animals) "Wanting"[a]	*****	****	none	* (only on "overdose")	***	**
Physical dependence (tolerance, withdrawal symptoms)	*****	****	***	***	****	**
Behavioral = psychological dependence (craving, loss of control, addictive behavior) "Wanting"[a]	*****	*****	(*) (only in patients with history of SUD)	* (especially in patients with history of SUD)	****	***
Severity of addiction[b]	*****	****	*	**	****	***
Transitions from prescription to self-administration Wanting"[a]	*****	n/a	*	**	**	(**)[e]
Relapsing behavior/durability "Wanting"[a]	*****	*****	*	**	****	****
Voluntary treatment-seeking behavior "Wanting"[a]	*****	*****	none	none	***	***
Overdose toxicity	*****	***	*	**	****	*
Social hazards (independent on co-use of other substances of abuse) "Wanting"[a]	*****	*****	n/a[c]	n/a[c]	***	***
Rapid euphorization "Liking"[a]	***** (especially intravenous)	****	** (especially on overdose)	**** (especially on overdose)	**** (especially on overdose)	***
Easy to obtain	****	*****	****	****	****	****
Legal control of prescription/dispensing	***** (most countries)	(**)[d]	none	* (Norway, USA)	** (e.g. flunitrazepa	***** (most countries

					m in Germany)	**)**

The addictive power is expressed in the shadowed boxes. Notes: [a]according to Berridge and Robinson, 2016; [b]according to the mean number of fulfilled operationalized dependence-criteria (ICD-10; DSM-IV), [c]no relevant information in the literature, [d]considering predominantly Muslim countries, laws about young people and drinking alcohol, [e]strong overlap between medicinal and recreational cannabis users (Pacula et al., 2016). Abbreviations: SUD = substance use disorder.

= no effects, * = very weak effects, ** = weak effects, *** = moderate effects, **** = strong effects, ***** = very strong effects. The estimation of the addictive power toxicity and safety of the gabapentinoids is based upon the present review. The estimation of the addictive power and safety of traditional drugs of abuse is based upon comprehensive reviews (e.g. Morgan, 1990; Coupey, 1997; Karoly et al., 2015; Korpi et al., 2015; Volkow and Morales, 2015; Brett and Murnion, 2015; Weaver; 2015; Bluth and Pincus, 2016; Quednow and Herdener, 2016) and the authors' expertise in the treatment of drug- and alcohol addiction (e.g. Bonnet et al., 1999; Bonnet and Gastpar, 1999; Bonnet, 2011; Bonnet et al., 2015; Scherbaum, 2016).

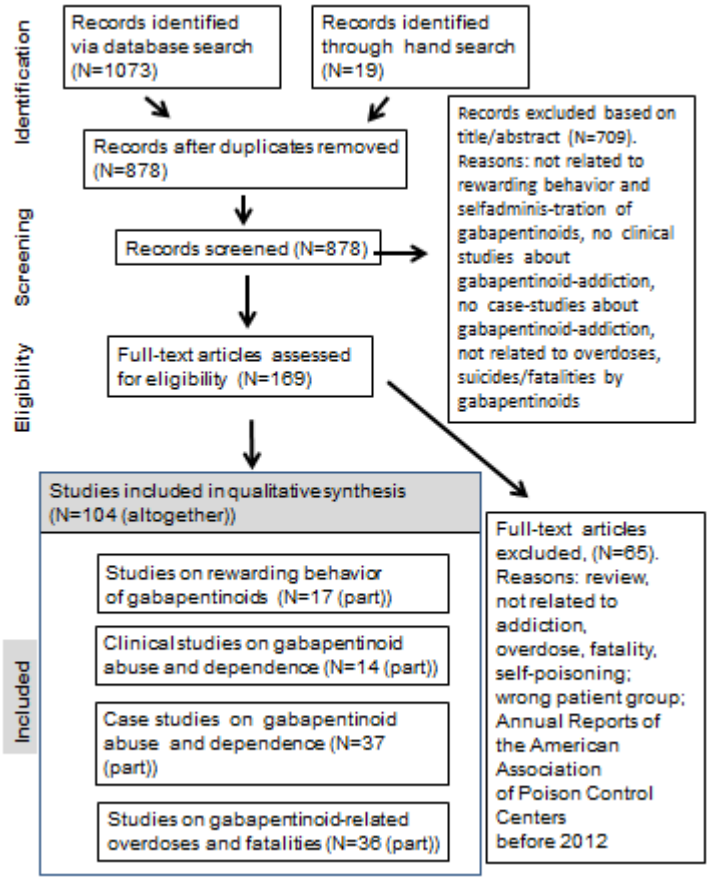

Figure 1 : PRISMA flow diagram

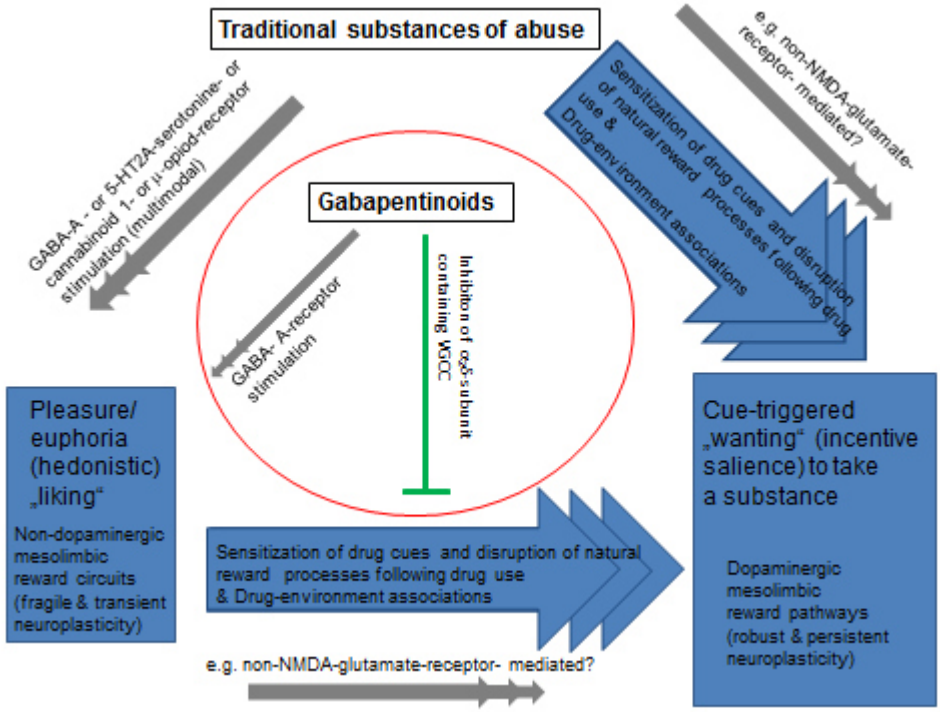

Figure 2: Gabapentinoids and reward: simplified hypothethic scheme of subcortical sensitizing (grey) and de-sensitizing (green) actions of traditional drugs of abuse and gabapentinoids, adapted to parts of the Incentive Sensitization Theory of Addiction (Berridge and Robinson, 2016) and to parts of the Glutamate Homeostasis Theory of Addiction (Spiga et al., 2014; Scofield et al., 2016). The sensitization of drug cues and associations of drug-use and environmental (external) cues were considered to be primarily driven by the repeated stimulation of non-NMDA glutamate receptors in key regions of the mesolimbic reward system, more precisely, by the repeated activation of the AMPA- and metabotropic glutamate receptors (Spiga et al., 2014; Volkow and Morales, 2015; Scofield et al., 2016). Unlike traditional substances of abuse, gabapentinoids are hypothesized to act also de-sensitizing (Dooley et al., 2000; Eroglu et al., 2009) via inhibiton of α2□-subunit containing VGCC and, thereby, are not able to induce a sustaining “wanting” (addictive power).