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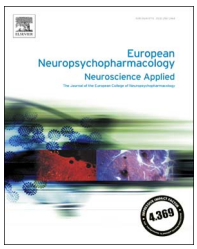

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REVIEW

How addictive are gabapentin and pregabalin? A systematic review

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Abstract
In the last ten years, gabapentin and pregabalin have been 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 106 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

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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.

1. Introduction

Pregabalin and gabapentin are approved pharmacotherapies for the treatment of some epileptic and pain disorders, and pregabalin also for generalized anxiety disorder (Bockbader 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 (Kapil et al., 2014; Calandre et al.; 2016; Chiappini and Schifano, 2016; Kwok 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., 2016a, 2016b; 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; Kapil 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 11,940 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

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