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EXPERT OPINION

Pregabalin in clinical psychiatry and addiction: pros and cons

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Pregabalin acts as a presynaptic modulator of excitatory neurotransmitter release, binding to the α^2-δ subunit protein of voltage-gated calcium channels. Pregabalin use is becoming widespread in the psychiatric scenario. Data are encouraging, with some good evidence for efficacy in anxious spectrum, benzodiazepine abuse/dependence, and alcoholism. The abuse potential, however, is an issue that should be taken into account, mostly in subjects at risk for developing substance/alcohol misuse.

Keywords: addiction, anxiety, calcium channels, pregabalin

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Pregabalin acts as a presynaptic modulator of excitatory neurotransmitter release, preventing, in hyperexcited neurons, excessive release of several excitatory neurotransmitters, including glutamate, substance P, calcitonin gene-related peptide, and monoaminergic neurotransmitters. From a pharmacodynamic viewpoint, pregabalin is inactive at γ-aminobutyric or benzodiazepine receptors, does not bind to serotonin receptors and does not inhibit the reuptake of serotonin or norepinephrine [1]. Instead, pregabalin selectively binds to the α^2-δ subunit protein of voltage-gated calcium channels, as does gabapentin, although its binding is at least three times more potent than that of gabapentin [1].

Pregabalin has a broad-spectrum efficacy in the treatment of different medical conditions, as suggested by findings from studies on diabetic neuropathy, postherpetic neuralgia, fibromyalgia, and partial epilepsy [2]. In addition, evidence derived from different double-blind placebo controlled studies suggests that pregabalin may also be efficacious in the treatment of generalized anxiety disorder and social anxiety [3,4], while in different case series it showed some potential as augmentation therapy in obsessive compulsive disorder [5], post-traumatic stress disorder, schizophrenia, bipolar mania, and major depression [6,7]. Moreover, several findings suggest that pregabalin is a potential sleep modulating agent, improving sleep latency and the continuity of sleep in healthy volunteers [8]. Studies investigating pregabalin's role in alcohol dependence yielded contrasting results for the treatment of the withdrawal syndrome [9,10], while there is some preliminary evidence for its efficacy on relapse prevention [11,12]. These data are consistent with animal studies [13]. Its positive effects on benzodiazepine dependence, on the other hand, appear to be well-established both in the withdrawal phase [14] than for the discontinuation of long term use, with significant ameliorations in the cognitive functioning [15].

Several observations support the use of pregabalin in psychiatry and addiction: i) Its clear, rapid and well-documented efficacy in many psychiatric disorders in which anxiety is a core symptom or a relevant feature; ii) Its safety and tolerability, at least up to a dose of 600 mg/day, as confirmed in clinical trials and web-based surveys [16]; iii) It exhibits few drug – drug interactions and does not inhibit cytochrome P450 enzymes; iv) It is usually well accepted by patients, with a low incidence of unpleasant, and often transient, side effects. A recent review asserts that a weight gain > 7% afflicts one-in-six patients treated with pregabalin after 2 – 12 months of treatment [17].

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However, recent studies point to possible drawbacks that may limit pregabalin use. i) It is likely to be associated with an abuse potential, mostly in subjects with a previous diagnosis of alcohol and substance dependence [18]. Controlled clinical studies carried out in over 5500 patients have, in fact, demonstrated that 4% of pregabalin-treated patients versus 1% of placebo-treated patients develop abuse. Furthermore, following abrupt or rapid discontinuation of pregabalin some patients may report insomnia, nausea, headache, or diarrhea, which may be suggestive of physical dependence [19]. In this context, it is interesting to note that pregabalin's potential for misuse is not typically mentioned in prescribing information. However, pregabalin is not known to be active at receptor sites associated with drugs of abuse, though its precise mechanism of action in the area of nucleus accumbens is unclear; ii) Its misuse is becoming popular on the internet, in the so-called "web-scenario" [19], generally considered to be a predictor of future misuse in real life [20], where is possible to share information and buy drugs and illicit substances. Dosages most typically reported in the web clearly exceed (e.g., up to 5 g) the maximum recommended dose. iii) In some cases, although rare, as described in recent studies [19,21], pregabalin is associated with idiosyncratic hepatotoxicity.

In conclusion, pregabalin use, up to a dose of 600 mg/day, is becoming widespread in the psychiatric scenario. Data are encouraging, with some good evidence for efficacy in generalized anxiety disorder and benzodiazepine abuse/dependence. The abuse potential, however, is an issue that should be taken into account, mostly in subjects at risk for developing substance/alcohol misuse.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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