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REVIEW ARTICLE

Pregabalin for the Treatment of Drug and Alcohol Withdrawal Symptoms: A Comprehensive Review

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Abstract Treatments for physical dependence and associated withdrawal symptoms following the abrupt discontinuation of prescription drugs (such as opioids and benzodiazepines), nicotine, alcohol, and cannabinoids are available, but there is still a need for new and more effective therapies. This review examines evidence supporting the potential use of pregabalin, an α2δ voltage-gated calcium channel subunit ligand, for the treatment of physical dependence and associated withdrawal symptoms. A literature search of the MEDLINE and Cochrane Library databases up to and including 11 December 2015 was conducted. The search term used was '(dependence OR withdrawal) AND pregabalin'. No other date limits were set and no language restrictions were applied. Works cited in identified articles were cross-referenced and personal archives of references also searched. Articles were included based on the expert opinions of the authors. There is limited evidence supporting the role of pregabalin for the treatment of physical dependence and accompanying withdrawal symptoms associated with opioids, benzodiazepines, nicotine, cannabinoids, and alcohol, although data from randomized controlled studies are sparse. However, the current evidence is promising and provides a platform for future studies, including appropriate randomized, placebo- and/or comparator-controlled studies, to further explore the efficacy and safety of pregabalin for the treatment of withdrawal symptoms. Given the potential for pregabalin misuse or abuse, particularly in individuals with a previous history of substance abuse, clinicians should exercise caution when using pregabalin in this patient population.

Key Points

There is a need for new and effective treatments for withdrawal symptoms.

This review examines the role of pregabalin for withdrawal symptoms associated with multiple drug types and alcohol.

There is limited evidence supporting pregabalin for the treatment of withdrawal symptoms, but data are promising and more studies, including those from appropriate randomized controlled trials, are required to further determine pregabalin efficacy and safety.

The potential risk of pregabalin misuse or abuse in patients with a history of substance abuse should be considered.

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1 Introduction

The US National Institute on Drug Abuse (NIDA) defines physical dependence as "[a] physiological state that can occur with regular drug use and results in withdrawal symptoms when drug use is abruptly discontinued" [1]. Withdrawal symptoms are therefore a manifestation of physical dependence, and their severity depends on a number of factors including drug type, dosage, frequency of administration, and duration of treatment [1]. Many drugs and centrally acting agents are known to cause physical dependence and lead to withdrawal symptoms upon cessation.

Opioids are frequently used to treat chronic pain [2–4], and in most individuals prolonged use can cause physical dependence. Symptoms such as irritability, anxiety, apprehension, muscular and abdominal pains, chills, nausea, diarrhea, rhinorrhea, and insomnia occur upon withdrawal [5], and patients may continue to take opioids to avoid withdrawal symptoms. Benzodiazepines and other agents that bind to the benzodiazepine binding site (e.g., zolpidem) are used to treat anxiety and sleep disorders [6–8], and, like opioids, are associated with physical dependence. Upon treatment discontinuation, withdrawal symptoms can include anxiety or anxiety-related symptoms, somatic symptoms, cognitive dysfunction, perceptual distortions, and major events such as seizures or the precipitation of psychosis [9, 10], and are more common with long-term use [11]. Between 15 and 44% of long-term benzodiazepine users may experience moderate to severe symptoms upon withdrawal, including ~40% of individuals using benzodiazepines for more than 6 months [9]. Alcohol withdrawal syndrome may arise within 24–48 h after abrupt cessation or reduced alcohol consumption, with symptoms including sweating, tachycardia, insomnia, nausea, transient hallucinations, anxiety, agitation, and tremor, and in severe cases seizures or delirium tremens [12, 13]. Nicotine withdrawal symptoms peak within the first week after ceasing tobacco use, and may include anxiety and depression, anger, impatience, difficulty concentrating, and insomnia, amongst others [14]. The most common symptoms of cannabis withdrawal include anger, aggression or irritability, anxiety, weight loss, restlessness, and sleep problems, including insomnia [15].

Physical dependence is a significant healthcare issue that requires successful management. Treatments are available [10, 16–20], but there is still a need for new therapies due to lack of response, adverse effects (AEs), or risk of misuse (use of a medication other than as directed or indicated [21]) or abuse (intentional self-administration of a medication for a non-medical purpose [21]) of existing treatments [22]. Pregabalin is a high-affinity α2δ voltage-gated calcium channel subunit ligand [23, 24], indicated in different countries for the treatment of neuropathic pain associated with a variety of conditions, fibromyalgia, generalized anxiety disorder (GAD), and as adjunctive therapy for adults with partial-onset seizures [25, 26]. Previous reviews have examined pregabalin as a potential treatment option for benzodiazepine and alcohol withdrawal symptoms [27–29], but a comprehensive review of pregabalin for the treatment of withdrawal symptoms associated with other drugs, as well as benzodiazepines and alcohol, has not been conducted. The role of pregabalin in treating withdrawal symptoms is further complicated by reports of its possible misuse and abuse [30]. The objective of this review is to evaluate the potential therapeutic effects of pregabalin in the treatment of drug- and alcohol-related withdrawal symptoms.

2 Methodological Considerations

This qualitative review examines the evidence supporting pregabalin for the treatment of withdrawal symptoms associated with physical dependence due to drugs or alcohol. A literature search was conducted of the MEDLINE and Cochrane Library databases up to and including 11 December 2015. The search term used was '(dependence OR withdrawal) AND pregabalin'. No language restrictions were applied and there were no restrictions on the types of clinical studies reviewed. A total of 162 articles were returned from MEDLINE and eight from the Cochrane Library. Relevant articles were selected based on the expert opinion of the authors, and were identified for opioid, benzodiazepine and benzodiazepine site agonist, alcohol, nicotine, and cannabinoid physical dependence. The works cited in the identified articles were cross-referenced, and personal archives of references also searched. Evidence was obtained from both clinical and preclinical studies.

3 Opioid Withdrawal Symptoms

Clinical data on the treatment of opioid withdrawal symptoms with pregabalin are limited to a few individual case studies. Scanlon [31] reported successful detoxification of an opiate-dependent patient following pregabalin treatment (300 mg/day) over a 6-day period. Withdrawal symptoms were assessed by the Clinical Opiate Withdrawal Scale (COWS). At the end of the assessment, a COWS score of 0, equating to no withdrawal symptoms, was reported, and specific withdrawal symptoms including anxiety, insomnia, tremors, abdominal cramping, and joint pain were more effectively controlled than during previous detoxification episodes. Kammerer et al. [32] reported the

use of pregabalin in a patient who failed maintenance replacement therapy with buprenorphine for heroin use, rather than prescription opioids. Heroin intake and withdrawal symptoms were ameliorated with pregabalin at a dose of 300 mg/day for 2–3 days. In a separate case study, a patient with pain due to ankylosing spondylitis received pregabalin at a starting dose of 75 mg/day that was gradually increased over a period of 2 weeks to 300 mg/day while discontinuing from long-term opioid (codeine and fentanyl) treatment [33]. Pain symptoms progressively improved, and no opioid withdrawal symptoms were reported. No AEs were associated with pregabalin use in this individual.

Some preclinical evidence supports the use of pregabalin for opioid physical dependence and withdrawal. In a study by Hasanein and Shakeri [34], adult Wistar rats were rendered opioid dependent by administering escalating doses of subcutaneous morphine (2.5–50 mg/kg over a 7-day period), and the effect of pregabalin (50, 100, or 200 mg/kg subcutaneously) on signs and symptoms of withdrawal was assessed using naloxone precipitation withdrawal tests. Pregabalin dose-dependently attenuated most of the naloxone-induced morphine withdrawal signs, including weight loss, teeth chattering, penis licking, jumping, wet dog shakes, rearing, standing, sniffing, face grooming, and paw tremor.

4 Benzodiazepine and Zolpidem Withdrawal Symptoms

In an uncontrolled, observational study of pregabalin as tapering therapy for the management of benzodiazepine discontinuation in 282 long-term users (mean duration of dependence 2 years), 52% (95% confidence interval [CI] 46–58) of patients were benzodiazepine free at the end of the study (12 weeks) following pregabalin treatment [35]. Pregabalin (mean dose 315 mg/day at week 12) therapy resulted in significant reduction in withdrawal symptoms, from a score of 11 at baseline on the Benzodiazepine Withdrawal Symptom Questionnaire to 4.4 at endpoint, an effect considered clinically relevant by the authors. Anxiety symptoms on the Hamilton Anxiety Rating Scale (HAM-A) improved by 69% and pregabalin tolerability was rated as good or excellent by 90% of clinicians and 83% of patients. Pregabalin efficacy did not depend on the benzodiazepine that was being discontinued, or the presence of substance use disorders including opioid- and alcohol-related disorders. In a secondary analysis of the same study, pregabalin treatment led to a 55% improvement in sleep quality at study endpoint, and also improvements in sleep disturbance, snoring, shortness of breath, sleep adequacy, sleep quantity, and daytime somnolence [36].

Decreasing the number of patients who use benzodiazepines at large doses should decrease the number who become physically dependent and experience withdrawal symptoms upon their cessation. Pregabalin treatment may reduce benzodiazepine consumption. In a pharmacoepidemiological study of patients with psychiatric disorders ($n = 588$), epilepsy ($n = 589$), neuropathic pain ($n = 3933$), or non-specified conditions ($n = 7594$), 14.7–27.9% stopped using benzodiazepines after starting pregabalin treatment [37]. Moreover, in the psychiatric patients, pregabalin reduced consumption of benzodiazepines by 48% [37]. In a separate study, patients with GAD who had been treated with a benzodiazepine for 8–52 weeks were stabilized for 2–4 weeks to alprazolam 1–4 mg/day [38]. After this period, in a double-blind phase, patients were then randomized to pregabalin (300–600 mg/day) or placebo for 12 weeks while undergoing alprazolam taper, followed by 6 weeks of pregabalin or placebo treatment only. At study endpoint, 51.4% of patients were alprazolam free following pregabalin treatment, compared with 37.0% of placebo-treated patients, although because of greater than anticipated withdrawal from the study this difference was not statistically significant. The severity of withdrawal, as measured by the Physician Withdrawal Checklist, was significantly lower during the taper phase and at endpoint with pregabalin than with placebo. Anxiety symptoms on the HAM-A also significantly improved for pregabalin versus placebo during the taper phase and at endpoint. Overall, pregabalin was well-tolerated in this study. AEs were reported in 71.4% of pregabalin-treated patients, compared with 66.0% of patients who received placebo, and severe AEs were uncommon in both groups (5.4 and 8.0%, respectively). Dizziness (21.4%) and anxiety (19.6%) were the most frequently reported AEs in the pregabalin group.

Zolpidem is a non-benzodiazepine hypnotic that binds to the benzodiazepine-binding site [39] and is associated with dependence [40, 41]. Pregabalin has been assessed for the treatment of zolpidem physical dependence and withdrawal symptoms. In a prospective, open-label, single-arm interventional study of 40 patients with long-term insomnia (mean duration 5.2 years), the mean duration of hypnotic use was 2.6 years, and the majority (75%) had previously used zolpidem [42]. Of these patients, 52.5% successfully withdrew from hypnotic medication following 8 weeks of treatment with pregabalin 75–300 mg/day and had significant improvements in withdrawal symptoms (as measured by the Physician Withdrawal Checklist), sleep quality, and insomnia severity. Nausea and dizziness were the most common AEs reported with pregabalin treatment. In a single case study, a patient with dependence due to heavy zolpidem use (up to 1500 mg/day) was able to discontinue zolpidem successfully (for up to 9 months) with pregabalin

treatment (600–900 mg/day) on two occasions, with no noticeable discontinuation or craving symptoms, or AEs, despite its use at a higher than approved dose [43].

5 Alcohol Withdrawal Symptoms

There is clinical evidence for pregabalin in the treatment of alcohol physical dependence and withdrawal symptoms. In a pilot open-label study, 20 detoxified alcohol-dependent patients received pregabalin at a starting dose of 50 mg/day, gradually titrated over 1 week to a flexible dose of 150–450 mg/day (mean dose 262.5 mg/day) [44]. During the 16-week study, 50% of patients remained completely alcohol free for the study duration. Both symptoms of withdrawal (assessed by the Clinical Institute Withdrawal Assessment for Alcohol) and alcohol craving (assessed by a visual analog scale and the Obsessive and Compulsive Drinking Scale) were significantly reduced by pregabalin. A single incidence of confusion leading to pregabalin cessation was reported. At the end of the study, no symptoms or AEs due to pregabalin discontinuation were seen. A follow-up open-label, prospective, 14-day study of 40 alcohol-dependent patients with mild-to-moderate alcohol withdrawal syndrome examined the efficacy, safety, and practicability of pregabalin for outpatient detoxification [45]. Pregabalin, at doses of 200–450 mg/day (mean dose 289 mg/day), significantly reduced withdrawal symptoms and craving scores by the end of the study. Pregabalin also significantly improved comorbid psychiatric symptoms, including depression, anxiety, psychoticism, and obsessive–compulsive behavior (assessed on the Symptom Check List 90 Revisited) and quality of life (assessed on the quality of life index). In total, 62.5% of patients remained alcohol free during the study period. No pregabalin-associated AEs were observed, and at pregabalin discontinuation no symptoms or side effects were seen.

Comparative studies of pregabalin with other possible treatments for alcohol physical dependence and withdrawal symptoms have been conducted. A randomized, single-blind study compared pregabalin with tiapride and lorazepam, for the treatment of alcohol withdrawal syndrome (Table 1) [46]. After 14 days of treatment, all groups showed a significant improvement in withdrawal symptoms, craving, quality of life, and comorbid psychiatric symptoms. Significantly more patients remained alcohol free in the pregabalin group than in the tiapride and lorazepam groups, and significantly more patients remained on treatment in the pregabalin group than in the tiapride group but not the lorazepam group. AEs occurred in one (2.7%) patient in the pregabalin group, which led to discontinuation from the study, and one (2.7%) patient in the lorazepam group. No AEs were reported with tiapride. At the end of the study, no AEs were observed due to the cessation of pregabalin treatment.

A separate randomized, double-blind trial compared the efficacy of pregabalin with naltrexone (Table 1) [47]. A greater proportion of patients remained alcohol free with pregabalin than naltrexone, and pregabalin-treated patients remained abstinent from any amount of alcohol for significantly longer than naltrexone-treated patients. Both treatment groups showed significant improvements in withdrawal symptoms, which were significantly greater for pregabalin versus naltrexone. Also, both pregabalin- and naltrexone-treated patients showed significant improvement in craving, which was not different between treatment groups, and psychiatric symptoms, but only pregabalin-treated patients showed significant improvements in phobic anxiety, hostility, and psychoticism. Only pregabalin-treated patients showed a significant improvement in quality of life. AEs were reported in one patient (3.2%) in the pregabalin group, which led to treatment discontinuation, and 11 patients (39.2%) in the naltrexone group, five of whom (17.8%) discontinued treatment. Treatment discontinuation at the end of study did not cause any AEs.

A third randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of pregabalin in patients with alcohol withdrawal syndrome (Table 1) [48]. Pregabalin and placebo significantly reduced withdrawal symptoms and alcohol craving. However, the effects of pregabalin were not significantly different to those of placebo. The incidence of AEs did not differ between treatment groups, and none were categorized as severe. Discontinuation of treatment at the end of study did not lead to any AEs or symptoms.

Finally, a preclinical study has examined pregabalin for alcohol physical dependence. In mice chronically exposed to ethanol, pregabalin (50–200 mg/kg) dose-dependently reduced the severity of behavioral convulsions upon ethanol withdrawal compared with vehicle-treated animals [49]. Since seizures are a potential serious manifestation of alcohol withdrawal [12, 13], an anticonvulsant such as pregabalin that can ameliorate withdrawal symptoms may be particularly beneficial in this case

6 Withdrawal Symptoms Associated with Nicotine

A single randomized, double-blind clinical study has evaluated pregabalin for nicotine physical dependence (Table 1) [50]. Pregabalin treatment significantly attenuated some nicotine withdrawal symptoms, but not others, versus placebo as well as reducing "drug-liking." Discontinuation due to pregabalin-related AEs occurred in three patients.

Table 1 Summary of results from randomized controlled trials of pregabalin for the treatment of withdrawal symptoms

Drug or substance	Sample	Comparator(s)	Pregabalin dose	Time of assessment	Efficacy measures of interest	Key findings
Alcohol [46]	111 alcohol-dependent patients with AWS	Tiapide (maximum dose 800 mg/day) Lorazepam (maximum dose 10 mg/day)	Maximum 450 mg/day	14 days	Freedom from alcohol use Withdrawal symptoms (CIWA-Ar) Craving (VAS; OCDS) Psychiatric symptoms (SCL-90-R) Quality of life (QL-index)	Significantly more patients remained alcohol free with pregabalin (62.2%) than with tiapide (37.8%) or lorazepam (56.8%; $\chi^2 = 4.19$; $P = 0.04$) Patients receiving pregabalin remained alcohol free for significantly longer than those on tiapide (log-rank test = 3.87; $P = 0.04$) but not those on lorazepam (log-rank test = 0.82; $P = 0.34$) Significant reduction in CIWA-Ar, VAS, OCDS, SCL-90-R, and QL-index for all treatments (all $P < 0.01$), with no differences between groups except for CIWA-Ar items headache/fullness in head (Kruskal–Wallis test = 7.5; $P = 0.02$) and orientation/clouding of sensorium (Kruskal–Wallis test = 8.8; $P = 0.01$) in favor of pregabalin
Alcohol [47]	59 detoxified alcohol-dependent patients selected for randomization	Naltrexone (50 mg/day)	150–450 mg/day	16 weeks	Freedom from alcohol use Withdrawal symptoms (CIWA-Ar) Craving (VAS; OCDS) Psychiatric symptoms (SCL-90-R) Quality of life (QL-index)	Similar numbers remained alcohol free with pregabalin (48.4%) and naltrexone (39.3%; $\chi^2 = 0.76$; $P = 0.86$) Patients receiving pregabalin remained abstinent from alcohol for significantly longer than those on naltrexone ($Z = -2.27$; $P < 0.05$) Significantly greater reduction in CIWA-Ar scores with pregabalin than with naltrexone ($P < 0.025$) Significant reduction in VAS, OCDS, and SCL-90-R scores for pregabalin and naltrexone (all $P < 0.05$), with no difference between groups Significant improvement in QL-index with pregabalin only ($t = 2.9$; $P < 0.05$)
Alcohol [48]	42 diazepam detoxified alcohol-dependent patients with AWS	Placebo	300 mg/day (days 1 and 2), 200 mg/day (days 3 and 4), and 100 mg/day (days 5 and 6)	6 days	Withdrawal symptoms (CIWA-Ar; AWSS) Craving (VAS)	Significant reduction in scores for CIWA-Ar, AWSS, and VAS for pregabalin and placebo (all $P < 0.01$), but no significant difference between treatment groups
Nicotine [50]	24 smokers with moderate nicotine dependence	Placebo	150 mg/day (day 1), 200 mg/day (day 2), and 300 mg/day (days 3 and 4)	4 days	Withdrawal symptoms (MNWSC) Subjective responses (DEQ)	Significant reductions ($P < 0.05$) for 'frustration,' 'anxiety,' and 'restlessness,' but not 'craving,' 'concentration,' 'appetite,' 'depressed,' or 'insomnia' for pregabalin vs. placebo on the MNSWC Significant reduction in 'drug liking' ($P < 0.05$) but not 'drug strength,' 'good effects,' bad effects,' and 'jittery' for pregabalin vs. placebo on the DEQ

AWS alcohol withdrawal syndrome, *AWSS* alcohol withdrawal syndrome scale, *CIWA-Ar* Clinical Institute Withdrawal Assessment for Alcohol, *DEQ* Drug Effects Questionnaire, *MNSWC* Minnesota Nicotine Withdrawal Symptom Checklist, *OCDS* Obsessive and Compulsive Drinking Scale, *QL-index* quality of life index, *SCL-90-R* Symptom Check List 90 Revisited, *VAS* visual analog scale, χ^2 Chi-squared

7 Withdrawal Symptoms Associated with Cannabinoids

A single preclinical study has examined the effect of pregabalin on withdrawal symptoms due to cannabinoid dependence. In mice tolerant to cannabinoids following administration of the synthetic cannabinoid CP-55,490 at a dose of 0.5 mg/kg/12 h for 7 days, pregabalin (40 mg/kg/12 h) improved withdrawal symptoms, including the appearance of anxiety-like symptoms and reduced motor activity, 1 and 3 days after cessation of CP-55,940 treatment [51].

8 Discussion

In this comprehensive, qualitative review, we have highlighted evidence supporting the use of pregabalin for the treatment of withdrawal symptoms associated with physical dependency to opioids, benzodiazepines, nicotine, cannabinoids, and alcohol. There is only limited evidence supporting the benefit of pregabalin for opioid, nicotine, or cannabinoid dependence, but these are clearly areas of great interest that would benefit from suitably designed clinical studies. More robust data are available for pregabalin in the treatment of benzodiazepine or alcohol dependence, but here, too, there is the need for additional studies, particularly large, appropriately controlled randomized studies that assess the efficacy and safety of pregabalin.

The mechanisms by which pregabalin may alleviate withdrawal symptoms associated with other substances is not clear, but what is known about its pharmacokinetic and pharmacodynamics profile may be of benefit for the treatment of physical dependence. Pregabalin is rapidly absorbed, has high bioavailability that is ≥90% independent of dose, and exhibits linear and predictable pharmacokinetic properties [25, 26]. It lacks protein binding and experiences negligible metabolism so that ~90% of the dose is recovered unchanged in the urine [25, 26]. It is therefore unlikely to be affected by pharmacokinetic drug–drug interactions, although pharmacodynamic interactions with oxycodone, lorazepam, and ethanol have been seen with coadministration, resulting in additive effects on cognitive and gross motor function [26]. Pregabalin is an anticonvulsant and anxiolytic [25, 26], which may be beneficial for the treatment of seizures associated with benzodiazepine [11, 52] or alcohol [53] withdrawal and anxiety-related withdrawal symptoms. Pregabalin has an established, well-tolerated safety profile [25, 26]. In addition, pregabalin has a fast onset of efficacy [54, 55], and evidence from perioperative studies of pregabalin indicate that it can significantly reduce acute pain after only a few hours [56]. This fast onset of pregabalin activity may be ideal for attenuating withdrawal symptoms. Further evidence supporting the use of pregabalin for the treatment of withdrawal symptoms comes from randomized controlled studies of gabapentin, another α2δ subunit ligand. These studies have shown the potential of gabapentin for the treatment of opioid [57, 58], alcohol [59, 60], and cannabis dependence [61].

A recent systematic review [30] examined the misuse and abuse potential of pregabalin in detail and we refer the reader to this article for more information on the subject. Such an in-depth assessment of the topic is beyond the scope of this review, but a brief discussion of the misuse/abuse potential of pregabalin in the current context is warranted. Despite being structurally similar to γ-aminobutyric acid (GABA), pregabalin does not exhibit any GABA-mimetic activity [62, 63] and is not known to be active at receptor sites associated with drugs of abuse [26, 64]. The European Summary of Product Characteristics notes that "Cases of misuse, abuse and dependence have been reported" [25], while in the USA, pregabalin is listed as a Schedule V drug, denoting a low potential for abuse and misuse relative to opioids, stimulants, benzodiazepines, and other Schedule I–IV drugs. A misuse/abuse potential of pregabalin has been reported in multiple epidemiological studies including drug utilization studies [65–68], adverse drug reaction reports [69–73], postmortem reports [74–76], and studies in populations with a previous history of other substance misuse or abuse [77–80], as well as in multiple case studies [81–92]. Results from controlled clinical studies have reported AEs suggestive of a potential for misuse or abuse, notably euphoria, which has an incidence of 4% across all approved indications [26]. Symptoms associated with pregabalin discontinuation have been reported [69, 82, 84, 86, 91–93], although individuals who use pregabalin at indicated doses appear to be at a low risk of developing such symptoms [94]. Gradual discontinuation over a period of at least 1 week is recommended [25, 26]. Potential for pregabalin misuse and abuse therefore exists, particularly with very high doses [95], and previous substance abuse appears to be an important risk factor [30, 96]. This suggests that pregabalin may have a potentiating effect on other substances of abuse, and that pregabalin misuse or abuse may be limited to this population of individuals already predisposed to substance abuse, rather than this issue widely occurring in the general population [30]. In the experience of some of the authors, and according to anecdotal evidence in this population and online information, pregabalin is sometimes abused to stop the long-lasting 'kicks' of stimulating drugs, or in rare cases is solely used for 'kicks'

itself. Also, those authors who are practicing clinicians have identified some individuals who have realized that pregabalin reduces withdrawal symptoms and use it to bridge periods of limited access to their usual substance(s) of abuse. In general, clinicians should watch for drug-seeking behavior, repeated requests for pregabalin, or requests for high doses, and caution should be exercised in patients with a history of substance abuse.

We can hypothesize on the mechanisms by which pregabalin may attenuate physical dependence. Withdrawal symptoms associated with opioids, benzodiazepines, alcohol, and cannabinoids have been linked to hyperactivity in the locus coeruleus, a highly divergent neuron population that provides the majority of norepinephrinergic input to the central nervous system [97–102]. One hypothesis is that pregabalin may reduce the synaptic release of excitatory neurotransmitters including norepinephrine and glutamate [103, 104], and may restrict functional calcium channel expression [105]. These two modes of action may combine to reduce central hyperexcitability. However, this hypothesis would need to be confirmed by further experimentation. Supporting evidence comes from animal models of neuropathic pain where pregabalin has been shown to target the descending norepinepheric pain inhibitory system to produce analgesia [106]. The proposed mechanism of action of pregabalin is different to that of benzodiazepines, which reduce central hyperexcitability by allosteric augmentation of $GABA_A$ receptor-mediated inhibition [107]. The possible different mechanisms of action between pregabalin and benzodiazepines are one reason why pregabalin may be a useful option in treating benzodiazepine withdrawal symptoms, but, as noted elsewhere, the efficacy and safety of pregabalin would need to be demonstrated in large clinical studies. It is also important to note that, although rare, there have been reports of fatal withdrawal from benzodiazepines and alcohol. Patients with tachycardia, unstable blood pressure, or prominent neurological or psychiatric changes must be treated with standard detoxification protocols for these agents.

9 Conclusion

Physical dependence associated with drugs and alcohol is a global health concern, and its treatment is an important clinical question. There is limited evidence that pregabalin may be effective in treating withdrawal symptoms associated with physical dependency, but it does show some promise. Large-scale, rigorous, appropriately controlled clinical studies are required to further demonstrate the efficacy and safety of pregabalin in these patient populations. The potential risk of pregabalin misuse or abuse needs to be addressed and clinicians need to exercise caution when prescribing pregabalin to patients with a history of previous substance abuse.

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