Pregabalin in the Treatment of Alcohol and Benzodiazepines Dependence

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We review all available studies on the use of the newer anticonvulsant drug pregabalin (PGB) in the treatment of both alcohol dependence (AD) and benzodiazepine dependence (BD). In AD, the available evidence includes one open-label and one double-blind randomized studies, whereas in BD, only a few case reports and one open-label study are as yet available. In both conditions, PGB was found efficacious with significant improvement in withdrawal symptoms at the dosage ranges of 150–450 mg/day (AD) and 225–900 mg/day (BD). Moreover, its side effects were mild and transient. Despite the limited quality of the studies design, their findings suggest that PGB might constitute a novel efficacious and safe option in the treatment of both AD and BD.

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Introduction

Pregabalin (5-(+)-3-isobutyl γ -aminobutyric acid [GABA]) (PGB) was initially synthesized as a lipophilic analogue of GABA capable to cross the blood–brain barrier. However, PGB has been proved eventually devoid of any direct actions on GABA_A and GABA_B receptors. Moreover, it has been shown to lack any GABAergic metabolites or to interfere with GABA reuptake or degradation [1,2]. Instead, PGB binds potently to the α -2- δ regulatory subunit of voltage-gated calcium channels, inhibiting activity-dependent calcium influx in presynaptic neurons, which results in reduced release of excitatory neurotransmitters, especially glutamate, norepinephrine, and substance P [3–6]. It is presumed that this mechanism of action of PGB underlies its therapeutic efficacy.

PGB has a linear pharmacokinetic profile, including complete absorption with lack of subsequent binding to plasma proteins, lack of metabolites and interactions with other drugs, as well as elimination through the kidneys [7,8]. PGB has been found efficacious in a broad range of medical and psychiatric conditions; in refractory partial onset seizures as an adjunctive medication [9,10], in the management of neuropathic pain in diabetic

peripheral neuropathy [11,12], and postherpetic neuralgia [13] and fibromyalgia [12,14]. Moreover, it has been efficacious in several anxiety disorders, above all in generalized anxiety disorder (GAD) [15–18] rated as evidence of the highest quality—A level [19], and to a much lesser extent in social anxiety disorder [20,21] with overall inconsistent data [19]. Recent preclinical evidence suggests that PGB might be also useful in post-traumatic stress disorder (PTSD) [22] with encouraging results from a recent small clinical study [23]. Even in major depression, recent evidence from case reports and small open studies suggests that PGB might be a valuable adjunctive medication to SSRIs and SNRIs [24–28]. Furthermore, in one pooled analysis of six studies of patients with GAD, PGB has been found efficacious in reducing associated symptoms of depression [28].

In this short review, we shall concentrate on recent emerging evidence, suggesting the usefulness of PGB in the treatment of alcohol and BDZ dependence.

PGB in Alcoholism

One preclinical study has investigated the ability of PGB to reduce CNS hyperexcitability, following alcohol withdrawal in a mouse model of chronic ethanol dependence

[29]. PGB at 50–200 mg/kg was found efficacious in reducing convulsions, high-voltage synchronous EEG activity, as well as in blocking withdrawal sensitization.

At the clinical level, two recent studies by an Italian group provide encouraging evidence on PGB efficacy in treating alcohol dependence (AD) [30,31].

The first study enlisted 31 subjects (16 male and 15 female) with a history of at least 3 years of alcohol misuse and DSM-IV-TR AD with a mean daily alcohol intake of 12 ± 5.2 alcohol units. About one-third of patients had a comorbid affective or anxiety disorder (not further specified by the authors). Patients were initially detoxified for a period of 5–10 days with BDZ compounds. Eleven patients dropped out from the study at this stage. The remaining 20 underwent a 16-week treatment with PGB with incremental increase—within 1 week—of its dosage at the range of 150–450 mg/day (mean 262.5 mg/day, SD 117.9) and 15 completed the study. At the end of the study, 10 patients remained totally alcohol-free, whereas five relapsed. Withdrawal symptoms were assessed by the Clinical Institute for Withdrawal Assessment of Alcohol (CIWA-Ar), and the level of craving for alcohol was evaluated by both a 10-cm visual analogue scale (VAS) and the obsessive and compulsive drinking scale (OCDS). Finally, patients' clinical psychopathology was assessed by the Symptom Check List-90 revised (SCL-90-R). Besides their initial evaluation, patients were assessed after 2, 8, and 16 weeks of treatment. Subjecting their data to an analysis of variance for repeated measures using the last-observation-carried-forward method, the authors found statistically significant decrease of patients' scores both on the global severity index and the positive symptom total of SCL-90-R as well as its subscales of hostility—anger, obsessive—compulsive, and psychotism. Still more impressive were their findings with respect to patients' score decreases on OCDS, VAS for craving and CIWA-Ar. The respective effect sizes—calculated by us from authors' tabulated data whenever displayed—ranged from 0.63 to 5.42 (see Table 1).

PGB treatment was also accompanied by patients' improvement in several markers of liver function, such as GGT, AST, ALT, and cholesterol levels as well as on MCV. Confusion was the only reported adverse event leading to treatment cessation. In cases of treatment discontinuation, neither withdrawal symptoms nor other side effects attributable to it were noted. Among the limitations of their study, the authors stressed its open-label design, its small sample size, and the lack of a matched control group.

In a second, double-blind 16-week study by the same group, from a total of 102 patients of both sexes with long-term AD (mean duration 14.8 ± 6.7 years), 71 were initially detoxified with diazepam at 6–40 mg/day for

Table 1 Pregabalin in alcohol dependence (30): results and effect sizes

Measures of clinical improvement	Mean (SD) Initial–final	<i>P</i>	Effect size Cohen's <i>d</i>
VAS	6.0 (2.1)–1.2 (1.9)	<0.001	2.53
OCDS			
Total	^a	<0.001	5.42 ^b
Obsessive	^a	^a	3.12 ^b
Compulsive	^a	^a	3.33 ^b
CIWA-Ar	14.6 (4.7)–9.1 (0.7)	<0.001	1.72
SCL-90-R			
General severity index	0.84 (0.5)–0.57 (0.4)	<0.05	0.63
Positive symptom total	43.5 (18.5)–32.0 (15.4)	<0.05	0.71
Hostility—anger	0.82 (0.8)–0.29 (0.2)	<0.05	1.02
Obsessive—compulsive	0.81 (0.5)–0.48 (0.4)	<0.05	0.77
Psychotism	0.55 (0.5)–0.30 (0.3)	<0.05	0.64

VAS, visual analogue scale (for alcohol craving); OCDS, obsessive compulsive drinking scale; CIWA-Ar, Clinical Institute for Withdrawal Assessment for Alcohol; SCL-90-R, Symptom Check List-90-Revised. Effect sizes calculated by us from authors' published data.

^aInformation not provided by authors.

^bRough estimate.

5–10 days and thereafter, 59 of them who completed successfully this stage were assigned after randomization into two groups. Patients with comorbid Axis I—affective or anxiety disorders—and Axis II conditions—mainly personality disorders of DSM-IV-TR cluster B—were evenly distributed across the two groups. The first group (28 patients) received naltrexone (NAL), titrated up to 50 mg/day within 1 week, whereas the second group (31 patients) underwent treatment with PGB titrated within 1 week up to 150–450 mg/day (mean dosage 275.8, SD 95.6). Forty-eight patients completed the 16-week study, 21 in the NAL group, and 27 in the PGB group. Besides their initial assessment after randomization, patients were reassessed after 2, 8, and 16 weeks. The clinical assessment instruments included the VAS for alcohol craving, the OCDS, the CIWA-Ar, the SCL-90-R, and the quality of life (QOL) index.

The results are displayed in Table 2. As seen in this table, in both treatment groups craving for alcohol scores as assessed by the VAS and OCDS scales decreased significantly, moreover with large effect sizes, ranging from 1.53 to 3.35. Likewise, patients' withdrawal total scores as assessed by the CIWA-Ar scale decreased in both groups significantly, with large effect sizes (1.21 in the NAL group, 2.14 in the PGB group). However, the effect size in the PGB group was significantly superior to that in the NAL group ($P < 0.025$). Moreover, as the authors stated, the improvement of patients in the PGB group with respect to their CIWA-Ar scores, emerged earlier than that in the NAL group.

Table 2 Pregabalin versus naltrexone in alcohol dependence (31): results and effect sizes

Measures of clinical improvement	Pregabalin			Naltrexone			Difference between groups
	Mean (SD) Initial-final	<i>P</i>	Effect size Cohen's <i>d</i>	Mean (SD) Initial-final	<i>P</i>	Effect size Cohen's <i>d</i>	
VAS	6.0 (1.6)–1.3 (1.3)	<0.001	3.35	5.4 (1.7)–2.8 (1.9)	<0.05	1.53	n.s.
OCDS							
Total	22.1 (10.2)–5.5 (7.2)	<0.001	1.95	26.8 (9.7)–7.1 (6.0)	<0.001	2.56	n.s.
Obsessive	^a	<0.005	^b	^a	<0.001	^b	n.s.
Compulsive	^a	<0.005	^b	^a	<0.001	^b	n.s.
CIWA-Ar	14.9 (6.7)–2.9 (4.7)	<0.001	2.14	15.6 (7.2)–8.9 (4.0)	<0.05	1.21	<0.025
SCL-90-R							
General severity index	0.85 (0.5)–0.52 (0.6)	<0.05	0.62	0.81 (0.4)–0.63 (0.3)	<0.05	0.53	n.s.
Positive symptom total	^a	<0.05	^b	^a	<0.05	^b	n.s.
Phobic anxiety	^a	<0.05	^b	^a	n.s.	^b	^a
Hostility-anger	^a	<0.05	^b	^a	n.s.	^b	^a
Psychotism	^a	<0.05	^b	^a	n.s.	^b	^a
QOL	^a	<0.05	^b	^a	n.s.	^b	^a
	Pregabalin		Naltrexone		Difference between groups		
Measures of efficacy					<i>P</i>		Effect size
Alcohol free/relapsed	15/11		11/7		$\chi^2 = 0.76$	0.86	OR = 0.87
Alcohol free patients with dual diagnosis	50%		15%		$\chi^2 = 98.12$	<0.01	OR = 5.68
Number of abstinent days	81.6 ± 43.7		74.1 ± 41.2		^a	n.s.	<i>d</i> = 0.18
Heavy drinking days	16.8 ± 9.2		21.2 ± 16.8		^a	n.s.	<i>d</i> = –0.34
Duration of abstinence	^a		^a		$Z = -2.27$	<0.05	^b
Measures of safety and tolerability					<i>P</i>		Effect size
Patients who completed the study	27/31		21/28		^a $\chi^2 = 0.15$	^a 0.70	OR = 2.25
Adverse events	1/31		11/28		^a $\chi^2 = 7.87$	^a <0.01	OR = 0.05
Discontinuation due to adverse events	1/31		5/28		^a $\chi^2 = 2.80$	^a 0.09	OR = 0.15

n.s., not significant; VAS, visual analogue scale (for alcohol craving); OCDS, obsessive compulsive drinking scale; CIWA-Ar, Clinical Institute for Withdrawal Assessment for Alcohol; SCL-90-R, Symptom Check List-90-Revised; QOL, quality of life index; OR, odds ratio.

Effect sizes calculated by us from authors' published data.

^aInformation not provided by authors.

^bCannot be estimated.

In addition, although both groups improved significantly on their overall clinical psychopathology measures as assessed by both the general severity index and the positive symptom total of the SCL-90-R, only the PGB group exhibited significant score decreases on its subscales of phobic anxiety, hostility-anger, and psychotism. Likewise, only the PGB group showed statistically significant improvement on the QOL index. In the same vein, the proportion of PGB patients with dual diagnosis who remained completely abstinent from alcohol until the end of the study was significantly higher than that in the NAL group ($P < 0.01$) with large relative effect size (odds ratio 5.68). No significant between-groups differences were found with respect to alcohol abstinence for the entire study period. However, the survival analysis of data showed that patients treated with PGB

remained abstinent from any amount of alcohol for a significantly longer time compared to those in the NAL group ($z = -2.27$, $P < 0.05$). Moreover, with respect to patients who completed the study, the rates in the PGB group were much higher than those in the NAL group, despite the lack of statistically significant differences (odds ratio 2.25).

Finally, rates of treatment discontinuation owing to adverse drug events were significantly lower in the PGB group ($P < 0.01$). Patients in both groups improved also in several indices of liver and blood functions. Patients' drug treatments were discontinued within 5 days after the completion of the study at 16 weeks. Of note, no rebound anxiety was noted after PGB discontinuation within 5 days following the completion of the 16-week trial. This finding is of paramount clinical importance

because both BDZ and alcohol abrupt discontinuation give rise to severe withdrawal syndromes. Thus, the use of PGB in their discontinuation does not carry the risk of subsequent development of tolerance and dependence, nor—a fortiori—of withdrawal symptoms.

Among the limitations of their study, the authors stressed its small sample size and the absence of a placebo group. Both limitations warrant further research.

PGB in BDZ-dependence

The clinical usefulness of PGB in BDZ withdrawal was initially suggested by the findings of a case report [32] and a small series of four patients [26]. In the latter study, four female patients with a long history of uninterrupted high-dosage BDZ dependence (ranging from 5 to 27 years) were incrementally switched to PGB within 3–7 weeks (mean duration of the substitution process 5 weeks). The final required dosage of PGB ranged from 225 to 600 mg/day (mean dosage 390 mg/day). Besides their BDZ discontinuation, patients anxiety levels decreased by 60–80%.

These encouraging findings motivated a subsequent open-label clinical study [27] in 15 further patients with chronic BDZ dependence and a concomitant affective disorder, mainly major depressive episode or dysthymic disorder, diagnosed according to DSM-IV-TR criteria. Twelve patients were females and three males with a mean duration of BDZ use of 13.23 years. Concomitantly, patients were evaluated with the Hamilton anxiety rating scale (HARS), the Hamilton depression rating scale (HDRS), and the mini mental state examination (MMSE) scale both before and after the BDZ's discontinuation process. Patients' remaining psychopharmacological regimen was held constant throughout the study, whereby PGB was substituted incrementally for BDZ. The duration of substitution process ranged from 2 to 14 weeks (mean 5.53 weeks) whereas the mean PGB dosage required was 465 mg/day (range 225–900 mg/d). PGB's side effects were transient and included dizziness and fatigue in 12 patients, sedation and leg cramps in 2 patients, and dysarthria in 1 patient, subsiding in all cases within 2 weeks.

On completion of the transition process, patient's scores on the HARS and HDRS dropped by 53.2% and 51.5%, respectively, whereas their MMSE score increased by 9.4%. All relevant effect sizes were quite robust, ranging from 1.14 to 1.81 (see Table 3). These findings suggest that PGB, besides its robust anxiolytic action, might also have antidepressant effects. On this score, our findings converge with those in the Stein et al. study cited in "Introduction" section of this review. Furthermore, our

Table 3 Pregabalin in benzodiazepines dependence [27]: results and effect sizes

Measures of clinical improvement	Mean (SD) Initial-final	P	Effect size Cohen's d
HARS	30.2 (12.1)–14.7 (5.9)	0.001	1.81
HDRS	30.2 (13.3)–14.3 (4.5)	0.001	1.55
MMSE	26.3 (2.8)–28.7 (1.3)	0.002	1.14

HARS, Hamilton anxiety rating scale; HDRS, Hamilton depression rating scale; MMSE, mini-mental state examination.

Effect sizes calculated by us from authors' published data.

findings with respect patients' cognitive functioning are in line with those of other studies, whereby PGB effects in both healthy volunteers and patients with GAD were found to be minimal or far less severe than those brought about by BDZ [33,34].

Obvious limitations of this study were its open-label design and the lack of matched control group as well as its small sample size.

Discussion and Conclusions

Despite their small sample sizes as well as the limitations in their design—categories B–C of the A–D gradation system of quality of evidence [19], the studies reviewed here provide suggestive evidence that PGB might constitute a novel efficacious and safe pharmacological treatment in both chronic and heavy alcohol and BDZ abuse and dependence. Moreover, PGB could also help in the treatment of symptoms of protracted withdrawal from alcohol, which extend up to 1 year beyond its cessation, such as anxiety and sleep disturbances [35]. This could enrich the available pharmacological armamentarium, which as far, includes virtually only carbamazepine [36].

On the face of the reviewed evidence, PGB's required dosage range in BD seems to be much higher (by more than 70%) than that in AD. In the PGB study in BD, patients exhibited high initial anxiety levels as assessed by HARS in addition to and despite their chronic heavy BD. In the PGB studies in AD, no initial anxiety levels were specified. Perhaps, the different dosage ranges of PGB required in the two conditions might reflect patients' initial severity of anxiety symptoms. At any rate, the issue of possible PGB dosage difference in the treatment of AD and BD warrants further investigation.

With respect to the common neurobiological pathway in AD and BD on which PGB might exert its therapeutic action, we should note that increased anxiety levels—common in both AD and BD withdrawal—express increased oscillatory theta activity of the hippocampal—limbic circuitry. Both ethanol and BDZ, along with PGB

among other drugs, reduce the frequency of theta oscillations in this circuitry [37]. This mode of action of PGB might well underlie its efficacy in both AD and BD.

One issue of great concern hinted at previously is whether PGB—on its own—could give rise to abuse, leading to dependence, especially in patient-populations particularly prone to addiction, such as those with chronic alcohol or BDZ dependence. On this score, we should note that in the product monograph of PGB it is stated that, from the currently available clinical data, very rarely (<0.001%), following abrupt or rapid discontinuation of PGB, some patients reported symptoms including insomnia, nausea, headache, or diarrhea suggestive of physical dependence [38].

Thus, overall, available evidence suggests that PGB's potential for physical and psychological dependence is much lower than that of BDZs [39]. At any rate, the manufacturer warns that PGB should be tapered gradually over a minimum of 1 week rather than discontinued abruptly. On this score, we remind of the relevant findings reported from the available studies of PGB in AD, whereby PGB was gradually discontinued within 5 days after the completion of the 16-week clinical study, without the occurrence of any symptoms suggestive of withdrawal reaction [30,31]. Overall, despite the scarcity and severe limitations of the primary studies reviewed here, the available evidence suggests that PGB might be a promising efficacious and safe novel agent in the treatment of both alcohol and BDZ dependence.

Author Contributions

Both authors contributed equally to writing this review.

Conflict of Interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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