Pregabalin augmentation of antidepressants in patients with accident-related posttraumatic stress disorder: an open label pilot study

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This study evaluated the efficacy of pregabalin augmentation of antidepressant treatment in patients with posttraumatic stress disorder (PTSD). Nine patients meeting *Diagnostic and Statistical Manual*, fourth edition criteria for PTSD who were on stable doses of antidepressants were treated open label with flexibly dosed pregabalin for 6 weeks. All patients were assessed with the Short PTSD Rating Interview, Montgomery–Asberg Depression Rating Scale, Patient Global Impression-severity, Visual Analog Scale-pain, and Sheehan Disability Scale at baseline and weeks 2, 4, and 6. Significant reductions were observed in all effectiveness measures from week 4 to the end of the study. In particular, the numerical improvement of the Visual Analog Scale-pain score was most robust (−53.4%, *P*=0.007). Pregabalin augmentation was effective and well tolerated during the study. Our findings warrant adequately powered, placebo-controlled clinical trials to confirm the usefulness of pregabalin augmentation of antidepressants in patients with PTSD. *Int Clin Psychopharmacol* **24:29–33 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Posttraumatic stress disorder (PTSD) is characterized by distressful recollections of events associated with traumatic stressors, such as automobile accidents, rape, combat, and natural disasters (Cyr and Farrar, 2000).

The lifetime prevalence of PTSD has been estimated to be 8% in the United States, and the majority of PTSD patients suffer with a chronic course (Kessler *et al.*, 1995). A high proportion of these patients struggle with psychiatric comorbidities including major depressive disorder (Marshall *et al.*, 2001b).

The US Food and Drug Administration (FDA) has approved two selective serotonin reuptake inhibitor antidepressants, sertraline and paroxetine, for the treatment of PTSD. However, response rates of sertraline and paroxetine for patients with PTSD are approximately 53 (Brady *et al.*, 2000a) and 62% (Marshall *et al.*, 2001a), respectively. To increase response rates and overcome partial response to antidepressants in PTSD patients, augmentation strategies with antipsychotics and anticonvulsants have been explored and have been shown to be effective in open-label and randomized, placebo-controlled clinical trials (RCTs) (Kinrys *et al.*, 2006; Rothbaum *et al.*, 2006; Pae *et al.*, 2008; Rothbaum *et al.*, 2008; Stein *et al.*, 2002).

In this context, pregabalin warrants investigation as a potential augmentation agent in the treatment of PTSD. Pregabalin is FDA approved for the treatment of neuropathic pain, fibromyalgia, and partial complex seizures in adults (Arnold *et al.*, 2008; Crofford *et al.*, 2005, 2008; Mease *et al.*, 2008), and it has recently demonstrated efficacy in the treatment of generalized anxiety disorder (GAD) and social anxiety disorder (SAD). More specifically, in studies of GAD, pregabalin has been shown to be superior to placebo (Feltner *et al.*, 2003; Pande *et al.*, 2003, Rickels *et al.*, 2005, Montgomery *et al.*, 2006) and comparable with lorazepam (Feltner *et al.*, 2003; Pande *et al.*, 2003), alprazolam (Rickels *et al.*, 2005), and venlafaxine (Montgomery *et al.*, 2006). Pregabalin was shown to be superior to placebo in SAD (Pande *et al.*, 2004). In addition, pregabalin reduced anxiety-like behaviors in a rat model of acute traumatic stress, although it did not exhibit long-term protective effects (Zohar *et al.*, 2008).

The therapeutic benefit of pregabalin for multiple indications is believed to relate to the hyperpolarization

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of neuronal membranes and decreased release of excitatory neurotransmitters by the high-affinity binding of pregabalin to the α_2-δ subunit protein of voltage-gated calcium channels (Rickels *et al.*, 2005). Although the precise pathophysiology of PTSD remains unknown, preliminary evidence suggests that neuronal excitation may be partly involved in the development of PTSD. We therefore hypothesized that pregabalin augmentation would have efficacy in the treatment of PTSD. This study was designed to test the potential use of pregabalin augmentation in PTSD patients who showed a partial response to antidepressants.

Methods and patients

Nine patients at Kangnam St Mary's Hospital, Seoul, Korea diagnosed with chronic PTSD according to *Diagnostic and Statistical Manual*, fourth edition criteria (American Psychiatric Association, 1994) were included in this study. Eligible patients were those whose PTSD symptoms were prospectively judged to be partially responsive to ≥ 12 weeks of current antidepressant treatment (regardless of class) at maximum tolerated dose. Key exclusion criteria included a history of major psychiatric illnesses other than major depressive disorder as determined by the Mini International Neuropsychiatric Interview (Sheehan *et al.*, 1998), clinically significant medical and neurosurgical conditions such as head injury, and current or previous treatment with pregabalin.

Efficacy measures included the Short PTSD Rating Interview (SPRINT) (Connor and Davidson, 2001), Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), Patient Global Impression-severity (PGI-S) (Guy, 1976), Visual Analog Scale-pain (VAS-pain) (Katz and Melzack, 1999), and Sheehan Disability Scale (SDS) (Sheehan, 1983), which were performed at baseline and weeks at 2, 4 and 6 after treatment. Adverse events were collected by using the Systematic Assessment for Treatment Emergent Events (Levine and Schooler, 1986). Pregabalin was started at a daily dosage of 75 mg and flexibly titrated upward or downward at the discretion of attending clinician (C.U.P.) based on patients' clinical response and tolerability; after the first week, the recommended dose increment was 75–150 mg/day by a week; maximal target dose=450 mg/day. Preexisting antidepressant medications were continued without dose change, and no other psychotropics were permitted during the study. All patients provided informed written consent and the institutional review board of Kangnam St Mary's Hospital approved the study.

Statistical analysis was done by using SPSS 12.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics and nonparametric paired *t*-test were carried out according to variable characteristics where appropriate, and statistical significance was determined at *P* value of less than 0.05 (two-tailed).

Results

The patients included were four males and five females with an average age of 37.8 years. The causes of trauma included: motor vehicle accidents in seven patients, bicycle crash in one patient, and riding a free-falling elevator in one patient. The detailed descriptions of the patients and clinical parameters are presented in Table 1.

The scores of the SPRINT, PGI-S, VAS-pain, MADRS, and SDS at week 4 (-18.2, -34.8, -40.0, -18.9, -11.9%, respectively, all *P* values < 0.001) and week 6 (-29.8, -47.8, -53.4, -24.7, -16.1%, respectively, all *P* values < 0.001) showed statistically significant reduction from baseline, whereas these parameters were not significantly reduced at week 2 (Table 1). Furthermore, five (55.6%) and six (66.7%) patients showed a ≥ 50% reduction in PGI-S and VAS-pain scores at week 6, although this trend was not observed in the scores of the SPRINT, MADRS, and SDS during the study.

All patients completed the study. The adverse events (AEs) observed included: dizziness ($n=4$), somnolence ($n=3$), blurred vision ($n=2$), and dry mouth ($n=2$), which mainly appeared and resolved within the first 2 weeks. The severity of all AEs was mild, and no serious AEs were reported. No abnormal laboratory findings were detected during the study.

Discussion

Short-term adjunctive treatment of antidepressants with pregabalin was effective and well tolerated in patients with PTSD. Further research is warranted to confirm the usefulness of pregablin in this patient population. The anticonvulsant, anxiolytic, and analgesic effects of pregabalin have been well documented (Gajraj, 2007). Pregabalin has shown efficacy for anxiety disorders and depression in numerous RCTs (Feltner *et al.*, 2003; Pande *et al.*, 2003, 2004; Rickels *et al.*, 2005; Stein *et al.*, 2008), and it has been determined that its analgesic effects are independent of improvements in anxiety and depression (Arnold *et al.*, 2007).

Data regarding the effectiveness and tolerability of pregabalin in the treatment of PTSD have not been reported. Therapeutic benefit of pregabalin in PTSD is plausible, based on pregabalin's mechanism of modulating calcium channels leading to reduced release of excitatory neurotransmitters (Gajraj, 2007). RCTs have been conducted to evaluate anticonvulsants as monotherapy or adjunctive therapy in the treatment of PTSD, but trials have largely been negative with topiramate (Lindley *et al.*, 2007), valproate (Davis *et al.*, 2008), and gabapentin (Stein *et al.*, 2007). Several preliminary open-label studies and RCTs have found that atypical antipsychotics may have benefit as adjunctive agents in the treatment of PTSD (Pae *et al.*, 2008; Rothbaum *et al.*, 2008; Stein *et al.*,

Table 1 Baseline characteristics of the patients ($n=9$)

	Age (years)	Sex	NT	DAA (months)	Medications (mg/day)	Baseline/posttreatment parameters					PG mg/day[a]
						SPRINT	PGI-S	VAS-pain	MADRS	SDS	
1	32	M	2	9	PRXCR 25 and LZP 1.5	19–16	5–3	8–3	18–15	16–15	150
2	25	F	2	24	PRXCR 25 and APZ 0.75	17–12	4–2	6–4	15–12	16–14	150
3	37	M	2	7	MIR 30 and LZP 0.75	20–15	5–3	6–3	19–14	17–14	150
4	49	F	3	11	MIP 100, ET 10, and LZP 1.5	22–19	5–2	8–3	23–16	18–14	300
5	45	F	2	15	PRXCR 37.5 and LZP 1.5	21–13	5–2	7–3	19–13	17–15	150
6	26	M	2	14	PRX 20, MIR 15, and LZP 1	22–10	4–2	8–4	22–15	18–15	300
7	39	F	2	15	PRXCR 25 and APZ 1.0	18–4	4–2	8–2	19–14	16–14	150
8	29	F	2	12	PRXCR 25 and LZP 1.5	19–13	4–3	8–5	20–17	16–15	300
9	58	M	3	10	ET 20, LZP 1.5, and PPL 15	20–13	5–3	7–4	16–13	17–14	150
Mean	37.8		2.2	13		19.8 (1.7)–13.9 (2.6)	4.6 (0.5)–2.4 (0.5)	7.3 (0.9)–3.4 (0.9)	19 (2.5)–14.3 (1.6)	16.8 (0.8)–14.4 (1.6)	200

APZ, alprazolam; DAA, duration after accident; ET, escitalopram; F, female; LZP, lorazepam; M, male; MADRS, Montgomery–Åsberg Depression Rating Scale; MIP, milnacipran; MIR, mirtazapine; NT, number of trials with antidepressants; PG, pregabalin; PGI-S, Patient Global Impression-severity; PPL, propranolol; PRX, paroxetine; PRXCR, paroxetine controlled release; PTSD, posttraumatic stress disorder; SDS, Sheehan Disability Scale; SPRINT, Short PTSD Rating Interview; VAS-pain, Visual Analog Scale-pain.
[a]Dose at study endpoint (week 6).

2002). Such agents are, however, linked to long-term side effects such as metabolic disturbance and infrequent tardive dyskinesia, which are particularly relevant to patients with chronic PTSD who require long-term pharmacotherapeutic treatment.

This study is the first to test the role of pregabalin in patients with PTSD. Results indicate that open-label pregabalin augmentation of antidepressants led to improvement in core PTSD symptoms. Pregabalin augmentation also improved depressive symptoms, functional impairment, and pain, which has been shown to be highly comorbid with PTSD and a cause of increased morbidity (Brady *et al.*, 2000b) In fact, many of the symptoms of PTSD are reminiscent of fibromyalgia, one of the FDA-approved indications for pregabalin. Symptoms common to both disorders include: depression, sleep disturbance, anxiety, fatigue, impaired concentration, and diffuse pain (Owen, 2007). Our finding of a robust response in pain severity indicates that pregabalin may be particularly of benefit in PTSD patients with significant pain (particularly neuropathic or fibromyalgia). The magnitude of improvement in scores on the SPRINT, MADRS, and SDS was, however, relatively small compared with those of the PGI-S and VAS-pain scores. This may suggest that the effect of pregabalin might be more sensitive in subjective outcome measures than objective scales. In addition, the applied PTSD and depression rating scales may be less sensitive to the effect of pregabalin. These findings should be further investigated in future RCTs. Although our sample was too small to subanalyse by symptom cluster, pregabalin was not associated with differential improvement in three domains of PTSD symptoms (i.e. intrusion, avoidance, and numbness).

The mean dose of pregabalin at study endpoint was 200 mg/day, which is less than doses showed to be of benefit in RCTs of primary pain syndromes and anxiety disorders, such as diabetic neuropathy (300 mg/day) (Freeman *et al.*, 2008), fibromyalgia (300–450 mg/day) (Arnold *et al.*, 2008; Crofford *et al.*, 2005, 2008; Mease *et al.*, 2008), and SAD and GAD (200–450 mg/day) (Pande *et al.*, 2004; Bech, 2007). This may reflect that this study used pregablin as adjunctive treatment as opposed to monotherapy. Investigating the dose–response relationship of pregabalin augmentation is important given that RCT data have clearly shown that AEs and discontinuation of treatment are dose related (Arnold *et al.*, 2008; Crofford *et al.*, 2005, 2008; Mease *et al.*, 2008).

Similar to other trials with pregabalin, the most widely reported AEs were dizziness and somnolence, which were mild in severity, early and transient, and did not lead to treatment discontinuation.

A few methodological limitations restrict generalization of the present results. Most notably, the open-label design limits causal inferences about the effects of pregabalin treatment; improvement may reflect general placebo effects. In addition, improvements over the course of the study may be related to spontaneous waning of symptoms; this is less likely to be based on the stable and enduring nature of chronic PTSD symptomatology, although the effects of episodic depressive disorder comorbidity can not be ruled out. The sample size was small, and it is unclear whether these results would persist in a larger study sample. Another limitation of this study is inherent in the augmentation paradigm; delayed response to antidepressant therapy is a possibility, although we attempted to minimize this by excluding patients whose current antidepressant trial was less than 12 weeks duration. Still, previous research has shown delayed treatment effects of antidepressants in patients with PTSD, such that 20–25% of improvement in PTSD symptoms occurred during the continuation phase

(beyond 24 weeks) over the 36-week trial (Londborg *et al.*, 2001). At the same time, we posit that augmentation studies are of critical importance in identifying optimal treatment strategies for PTSD, and agents that have benefit adjunctively may not be identified in monotherapy studies. Such is the case with benzodiazepines, which have showed their use in reducing anxiety associated with PTSD but have failed to show benefit as monotherapy (Feldmann, 1987). Hence, interventions with adjunctive agents that can potentiate the effects of antidepressants in PTSD should be explored in well-designed, randomized, controlled clinical trials. Additional studies are warranted to determine whether benefits of adjunctive agents such as pregabalin are persistent in long-term studies.

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