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Preliminary communication

An open trial of pregabalin as an acute and maintenance adjunctive treatment for outpatients with treatment resistant bipolar disorder

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ABSTRACT

Background: Pregabalin is a structural analog of GABA, similar to gabapentin. It does not have a FDA indication for any psychiatric disorder in the USA. There has been one case report of the successful use of pregabalin as an augmenting agent in a patient with Bipolar Disorder (BD). In the present open label study, not subsidized by the manufacturer, the investigators prospectively evaluated the acute and maintenance efficacy of pregabalin as an adjunctive medication for a group of treatment refractory outpatients with BD.

Methods: Older adolescent and adult outpatients with any type of DSM-IV diagnosed BD, who were considered treatment nonresponders to multiple standard medications for BD, were treated with adjunctive pregabalin. The baseline mood state before initiation of pregabalin was compared to the mood state after an acute trial of pregabalin using the Clinical Global Impression-Bipolar Version Scale (CGI-BP). All acute responders were treated for a minimum of two months. Follow-up maintenance treatment data was obtained for the acute pregabalin responders for three years after the 18 month acute phase of the study.

Results: Fifty-eight total patients were treated adjunctively with pregabalin. Twenty-four (41%) were rated as acute responders. For the acute responders, pregabalin produced either a mood stabilizing effect, antidepressant effect or antimanic effect. Intolerable side-effects were the most common reason (79%) for a failed acute trial of pregabalin. None of the side effects resulted in serious medical complications. No patient abused pregabalin, and there were no adverse drug-drug interactions despite an average of 3.3 concurrent other psychiatric medications. The maintenance data revealed that 10 (42%) of the original 24 acute pregabalin responders were still taking pregabalin as an add-on medicine for an average of 45.2 months (range 42–48, SD: 2.35).

Limitations: This study has an open label observation design.

Conclusions: The results of this preliminary open study suggest that pregabalin is a safe and effective acute and maintenance adjunctive treatment for a significant number of treatment-resistant outpatients with any type of BPD. It appears to have mood stabilizing and antidepressant properties in addition to antimanic effects. Similar studies using a double-blind, randomly controlled design would be useful to confirm the reliability and validity of the results of this study.

1. Introduction

Pregabalin is a structural analog of GABA, similar to gabapentin. It was approved by the Federal Drug Administration (FDA) for neuropathic pain and adjunctive treatment of partial seizures in adults in 2005 (The Medical Letter on Drugs and Therapeutics, 2005) and for mono-therapeutic treatment of fibromyalgia in 2007 (The Medical Letter on Drugs and Therapeutics, 2007). The results of several studies indicate that pregabalin appears to be effective for Generalized Anxiety Disorder (GAD) (Baldwin et al., 2011), and it has been approved for GAD in the United Kingdom. A recent placebo-controlled study reported successful treatment of Social Anxiety Disorder with pregabalin (Feltner et al., 2011). Preliminary studies indicate that pregabalin may have antidepressant properties when used to treat anxiety disorders (Stein et al., 2008). A case study reported that pregabalin was an

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effective augmenting agent to paroxetine in a patient with chronic Major Depressive Disorder (Showraki, 2007). In the USA it is classified as a controlled medication, and it has yet to be FDA approved for any psychiatric disorder.

Several medications initially FDA-approved for seizure disorders, with similar anticonvulsant properties as pregabalin, are now considered standard treatment options for any type of Bipolar Disorder (BD) (Rosa et al., 2011). The only publication on the use of pregabalin for treatment of BD is a single case report of an adult patient experiencing an acute manic episode who was treated successfully with pregabalin in conjunction with quetiapine treatment (Pae, 2007). The manufacturer of pregabalin, Pfizer, Inc., conducted a double-blind, placebo-controlled, multicenter, 3-week study that evaluated the efficacy and safety of pregabalin (600 mg/day) as primary treatment of acute mania in hospitalized patients with Bipolar I Disorder ($N=59$; pregabalin $N=28$, placebo $N=31$). Standard research rating scales were used, and lorazepam was provided adjunctively. There were no clinically or statistically significant differences between the treatment groups for any efficacy variable (Letter from Pfizer, Inc., 3/16/09, Study #:1008-022). The unpublished study was terminated early based on results of an interim analysis.

Although the above study by the manufacturer indicates that pregabalin may not be effective in monotherapy for acute manic episodes, there are several reasons to assess its effectiveness as an adjunctive medication for BD. Another GABA analog, gabapentin, was not more effective than placebo in a monotherapy trial for refractory rapid cycling BD patients (Frye et al., 2000) and in an adjunctive trial for acute mania patients with Bipolar I Disorder (Pande et al., 2000). However, several published studies have demonstrated its usefulness as an add-on medication for different types of BD other than Bipolar I Disorder (Yatham et al., 2002). Moreover, the antianxiety effects of pregabalin may be useful for patients with BD just as the anxiolytic effects of benzodiazepines are helpful adjunctive medications for many BD patients. Lastly, several studies indicate that some older anticonvulsants which are used to treat partial seizures have also been effective as adjunctive medications for some patients who experience a partial but unsatisfactory monotherapy response to standard medications for BD (Grunze, 2010, Rosa et al., 2011).

Most studies assessing the therapeutic effects of anticonvulsants for BD have not addressed efficacy during the maintenance or continuation phase of treatment after a successful acute trial. In the present open label study, not subsidized by the manufacturer, the investigators evaluated the acute and maintenance efficacy of pregabalin as an adjunctive medication for a group of treatment resistant outpatients with any type of BD.

2. Methods

This study was approved by the Sutter Health Central Area Institutional Review Committee. All patients involved in this study were either adults or older adolescents in an outpatient private practice who met DSM-IV diagnostic criteria for some type of BD. The participants in this study were offered treatment with adjunctive pregabalin if they were clinically considered to be nonresponders or unsatisfactory partial responders to numerous standard medications for BD. The only two exclusion factors were pregnancy and patients under the age of sixteen. The treating physicians (LCS and CBS) are board certified psychiatrists, each with over 30 years of clinical experience, who specialize in the treatment of BD. Before beginning treatment with pregabalin, each adult patient and the parent/guardian of minor patients gave verbal informed consent after potential risks and benefits of taking pregabalin were explained. The consent process included informing each patient that pregabalin does not have an FDA indication for BD, and that it is not presently considered standard treatment for BD. All patients were offered off-label pregabalin as an option for clinical reasons (treatment-resistant BD) regardless of their participation in the study.

The mood state at the time of initiation of pregabalin was documented and compared to the mood state after a two-month acute trial of pregabalin treatment for BP symptoms. The following DSM-IV-defined mood categories were used to identify the baseline mood state of each patient: manic, hypomanic, depressed, mixed and rapid-cycling. A score of 1–3 on the Change Scale of the Clinical Global Impression-Bipolar Version Scale (CGI-BP) (Spearing et al., 1997) was considered a positive therapeutic response. All acute phase responders satisfied these CGI-BP rating criteria for a minimum of two months. Demographics, substance abuse history, side effects, and adverse drug–drug interactions were also documented. All patients were assessed by clinical evaluation to determine if they abused pregabalin as clinically defined by DSM-IV criteria for Substance Abuse. Lastly, for each participant, the number of unsuccessful medications for bipolar treatment, as well as the number of concurrent psychiatric medicines, were noted at the beginning of the study. Medicines that were considered as unsuccessful treatments for BD included: anticonvulsants, antipsychotics, antidepressants, and lithium.Some of these previous failed medication trials could have been experienced while the patient was under the care of a prior doctor.

Patients were entered into the acute phase of the study from June 2007 through December 2008. An attempt was made to gather follow-up maintenance treatment data on the original acute pregabalin responders who were continued on pregabalin after the acute phase of the study. The decision to continue the pregabalin as maintenance therapy after the two month acute phase of treatment was based on a persistent positive therapeutic response, as judged by both the patient and the treating psychiatrist. The following data was collected during the maintenance phase of the study: number of original acute responders who continue to be treated with pregabalin, total duration of treatment with pregabalin, dose of pregabalin, and number of concurrent psychiatric medications. The reason for discontinuing pregabalin was recorded for those patients who stopped taking it during the maintenance treatment period.

Descriptive statistics were utilized in the presentation of the results of the study. Simple two tailed t-tests were used in the comparison between responders and nonresponders in the acute trial to determine the presence of any demographic variables, number of treatment medications and age that might have contributed to the differences in response to pregabalin therapy.

3. Results

Fifty-eight total BD patients entered the acute treatment phase with adjunctive pregabalin. The average age was 47 (range 17–83). Forty-six (79%) were female. At the end of the two-month acute trial, twenty-four (41%) were rated as responders to adjunctive pregabalin. Twenty (83%) of the responders were female. The average age of the responders was 45, and the average age of the nonresponders was 49 ($t=0.9633$, $p=0.3396$, two tailed t test, NS). Twelve (50%) of these responders experienced a mood stabilizing effect for either mixed or rapid cycling symptoms; five (21%) had an antimanic effect, and seven (29%) had an antidepressant effect. Twenty (83%) of the acute responders did not have a Bipolar I Disorder. This compares with the 50 (86%) of the initial 58 subjects entering the acute trial that did not have Bipolar type I. The average dose ($\pm$SDs) for the acute responders was 72 mg (± 69) and for the nonresponders was 84 mg (± 74) ($t=0.6049$, $p=0.5477$, two tailed t test, NS).