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Brief report

Pregabalin in acute treatment of anxious depression: A case series

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ABSTRACT

Symptoms of anxiety are common in patients with depression. In this retrospective case series we investigated the effect of Pregabalin as an add-on medication in unipolar depressed patients with high levels of anxiety. The therapeutic effect of Pregabalin showed a fast onset and was comparable to the anxiolytic effect of benzodiazepines.

1. Introduction

Patients with unipolar major depression often also present symptoms of anxiety (Keller and Hanks, 1995). The U.S. National Comorbidity Study showed that 58% of patients with major depressive disorder were also diagnosed with comorbid anxiety disorder (Kessler et al., 1996). Additionally, depressed patients with a major depressive episode can report strong symptoms of agitation and anxiety without meeting the diagnostic criteria for anxiety disorder (Zinbarg et al., 1994). In a clinical setting, patients with a major depressive episode and symptoms of anxiety, restlessness, and somatic correlates of anxiety are often identified as patients suffering from *anxious depression* (Fava et al., 2004). This subtype of depressed patients may also fulfill the diagnosis of a comorbid anxiety disorder which might also be associated with certain Axis II clusters (Melartin et al., 2002). At the moment of treatment however the clinician faces a depressed patient with high levels of anxiety, which have to be accounted for in the immediate choice of procedure.

Relief of anxiety symptoms in depressed patients is of particular concern to clinicians since a comorbidity of symptoms of anxiety and depression predicts a poorer response towards pharmacological as well as psychotherapeutic treatment (McLean et al., 1998) and poses a higher risk for chronicity of the illness (Clayton et al., 1991; Pollack, 2005). Furthermore, patients with major depression and comorbid anxiety symptoms suffer from more severe depressive symptoms and have an increased risk for suicidality (Angst et al., 1999; Keller and Hanks, 1995).

First-line pharmacotherapy of comorbid symptoms of unipolar major depression and anxiety is often a combination therapy of an antidepressant agent, preferably from the group of SSRIs or SNRIs (Filteau et al., 1995; Kaufmann and Charney, 2000), which is augmented by benzodiazepines (Furukawa et al., 2001). SSRIs and SNRIs show a delayed onset of 2–4 weeks of the antidepressant therapeutic effect, a phase in which patients suffer and might become discouraged (Smith et al., 1998). Benzodiazepines are effective anxiolytics with a rapid onset of effect and they quickly relieve anxiety symptoms (Coplan and Gorman, 1990). However, benzodiazepines pose the drawbacks of being associated to cognitive and motor impairment (Wittenborn, 1979) and hold a significant risk for dependence (Schweizer and Rickels, 1998). Furthermore, benzodiazepines may actually cause a worsening of depressive symptoms in patients with major depression if used long term (Hicks et al., 1988).

Various anticonvulsant drugs, such as Carbamazepine or Valproate, have been used in the treatment of mood and anxiety disorders (Lipper et al., 1986; Tondo et al., 1989) as they have been found to be effective mood stabilizers in patients with bipolar disorder (Yatham et al., 2002) and are also beneficial in the treatment of anxiety disorders (Kinrys et al., 2003). Pregabalin, a gamma-aminobutyric acid analog, has been shown to have an acute anxiolytic effect in patients with generalized anxiety disorder (Pande et al., 2003; Pohl et al., 2005; Strawn and Geracioti, 2007) as well as being effective in long-term relapse prevention in patients with generalized anxiety disorder (Feltner et al., 2008). While its efficacy is comparable to benzodiazepines (Pande et al., 2003; Rickels et al., 2005), it is a well-tolerated drug with less cognitive and psychomotor side effects as well as less risk for dependence (Pande et al., 2003; Pohl et al., 2005), although latest data indicate that it does provide some potential for abuse

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or dependence (Gahr et al., 2013). Since there are no known drug interactions (Pfizer Incorporated, 2006), Pregabalin could provide an add-on strategy to antidepressant medication in depressed patients with high levels of anxiety and agitation and replace benzodiazepines during the acute treatment phase. A few studies have already indicated a beneficial add-on effect of Pregabalin in the treatment of depressed patients who do not or only partially respond to antidepressant medication (Showraki, 2007; Vitali et al., 2013) or in elderly patients who suffer from comorbid generalized anxiety disorder (Karaiskos et al., 2012).

2. Methods

In this retrospective study we report a sample of seven patients who were treated as inpatients in a psychiatric ward of the Charité Berlin, Campus Benjamin Franklin from February to May 2011, and who met a diagnosis of a unipolar major depressive episode according to DSM-IV criteria at the time of the study. All patients displayed agitation and they all experienced psychological as well as somatic symptoms of anxiety. All patients were treated with Pregabalin as an add-on strategy to their antidepressant therapy right from the beginning of their therapy. In a phase of 6 weeks, symptoms of depression and anxiety were routinely assessed (rated by a well-trained psychiatrist which is standard in our department). The severity of anxiety symptoms was measured by the clinician-administered Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959). Depressive symptoms were measured by the 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960). Patient characteristics, HAMA and HAMD baselines and change throughout the course of the treatment, as well as the maximal dose of Pregabalin and further psychiatric co-medication are reported in Table 1.

3. Results

To test for the acute anxiolytic effect of Pregabalin we compared HAMA and HAMD values at baseline and after one week of treatment with Pregabalin. Paired-samples *t*-tests show, in average, a highly significant reduction of HAMA scores, $t(6)=4.40$; $P=0.005$, and of HAMD, $t(6)=5.59$; $P=0.001$, within the first week of treatment.

Throughout the course of 6 weeks, in which our patients were treated with Pregabalin as an augmentation therapy to their respective antidepressant medication, in half of our patients, anxiety levels, as assessed via the HAMA, declined by more than 50%. Repeated measures ANOVA showed, that anxiety levels, measured by the HAMA, significantly declined throughout the course of treatment, $F(1,4)=7.91$, $P=0.017$ (Greenhouse–Geisser corrected).

HAMD scores also declined during the course of the study, although the effect was less pronounced. Two out of seven patients reached a 50% reduction in their HAMD scores. Repeated measures ANOVA also revealed a significant reduction of depressive symptoms, as assessed by the HAMD, in the 6 week treatment phase, $F(1,4)=9.08$, $P=0.003$ (Greenhouse–Geisser corrected).

The three patients who had relied on a fixed dose of Lorazepam before the Pregabalin treatment scored in a range from 10 to 13 points on the HAMA and a range of 12 to 14 on the HAMD at the end of the study phase without treatment with Lorazepam. Doses at which we found Pregabalin to be effective varied between 150 mg/day and 450 mg/day. One patient reported dizziness at a dose of 150 mg/day. No further side effects occurred during the phase of the study.

Three of the seven patients were diagnosed with a comorbid anxiety disorder. One suffered from obsessive-compulsive disorder and two received the comorbid diagnosis of generalized anxiety disorder. These diagnoses became evident in the course of the treatment and were based on biographical data as well as the symptoms that remained, once the depressive symptoms receded.

4. Discussion

In this retrospective case study we investigated the effectiveness of Pregabalin as an add-on medication in patients with agitated and anxious depression with particular interest to the acute treatment phase. In a majority of patients we observed a decline of anxiety within the first week of treatment with Pregabalin which proceeded over the following 5 weeks. We also observed a decline of depressive symptoms throughout the course of the study, although this effect was less pronounced and might be an effect of the standard antidepressant treatment. The relatively low response rate is in concordance with other studies that have shown lower response and remission rates in patients with anxious depression compared to non-anxious depression towards pharmacological as well as psychotherapeutic treatment (Farabaugh et al., 2012). No patients required treatment with Lorazepam by the end of the study phase.

Our data indicate that Pregabalin might be an effective way of targeting symptoms of anxiety experienced in the course of a depressive episode—especially in the first weeks of treatment,

Table 1
Psychotropic medication, HAMD-Scores, and HAMA-Scores over the course of the study.

DSM-IV diagnoses	Sex	Age	Psychiatric co-medication during Pregabalin treatment (mg/d)	Lorazepam dose before Pregabalin treatment (mg/d)	Maximal dose of Pregabalin (mg/d)	HAMD/HAMA						
						Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
296.34 301.4	F	70	Bupropion 450 Olanzapine 10	2	150	23/15	17/11	10/7	10/14	12/13	12/14	13/13
296.33 300.4	F	46	Bupropion 300 Escitalopram 20	2	450	26/26	20/19	20/20	20/13	11/13	13/13	12/11
296.32 300.81	F	44	Escitalopram 15	–	150	26/29	21/25	18/20	15/21	14/20	18/21	11/9
296.22	F	74	Citalopram 40 Duloxetine 60 Quetiapine 75	1	250	19/22	18/20	17/17	15/16	13/14	17/10	14/10
296.22 300.02	F	76	Mirtazapine 30 Agomelatine 50	–	150	27/31	18/18	20/18	16/17	17/12	–	–
296.22 300.3	M	60	Trazodone 150 Venlafaxine 225	–	300	20/29	16/24	14/25	16/19	13/20	16/17	15/15
296.22 300.02	F	59	Escitalopram 10	–	300	27/23	19/13	11/16	11/18	–	–	–

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comparable to treatment with benzodiazepines. The anxiolytic effect Pregabalin showed in our patients, had a rapid onset compared to the delayed onset of treatment with SSRIs or SNRIs. Other depressive symptoms also declined in our patients throughout the phase of the study.

With the decline of depressive symptoms comorbid anxiety disorders became evident in three patients. This matches the data of a life time comorbidity of depression and anxiety between 40 and 50% (Regier et al., 1990; Fava et al., 2000). While the choice of treatment with Pregabalin was syndrome-orientated and targeted anxious depression, these comorbid diagnoses will especially be relevant for the patients' future psychosocial treatment.

Our retrospective case study has several drawbacks and may contain various biases. We investigated a very heterogeneous and small sample where the severity of depressive and anxiety symptoms varied as well as the comorbid diagnoses. While this sample naturally reflects the patients clinicians are presented with in psychiatric wards, the small sample size is especially a drawback when it comes to the statistical analysis, as is the absence of a control group to control for time effects. We cannot make any conclusions about causalities between the improvement of symptoms in our patients and the treatment with Pregabalin.

The aim of this case study can therefore be understood as to generate rather than test hypotheses about the efficacy or effectiveness of Pregabalin as an augmentation therapy in unipolar depressed patients with symptoms of agitation and anxiety, particularly in the acute treatment phase. In further, placebo-controlled trials, this acute effect should be confirmed in order to recommend Pregabalin instead of benzodiazepines in this subgroup of depressed patients. The advantage of Pregabalin is that is causes less cognitive and motor impairment and shows a lower risk for respiratory depression. It also shows a lower addiction potential than benzodiazepines although especially in middle aged, male patients with known polytoxicomania the prescription of Pregabalin should be monitored more closely to avoid abuse (Gahr et al., 2013). For general risk management, clinicians should be alert for signs of tolerance or withdrawal.

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