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Pregabalin versus sertraline in generalized anxiety disorder. An open label study

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Abstract. – OBJECTIVE: Generalized Anxiety Disorder (GAD) is a chronic mental illness with a prevalence of 5-7% in the general population. *t* GAD is characterized by extreme persistent worry, mostly about minor problems, involving pathological fear with high occurrences of vegetative disturbance. GAD leads to functional impairment and a significantly reduced patient's quality of life. According to the guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP), the first-line treatments for GAD are Serotonin selective reuptake inhibitors (SSRIs), Selective serotonin- and norepinephrine reuptake inhibitors (SNRIs) and pregabalin, an atypical anxiolytic. In this study, both efficacy and tolerability of pregabalin were evaluated and compared with efficacy and tolerability of sertraline, an SSRI antidepressant.

PATIENTS AND METHODS: 107 patients both male and female, aged 20-60 were included in the study. All patients were hospitalized outward at the Psychiatric Clinic. Patients fulfilled criteria for GAD, according to ICD-X and DSM-IV. Each patient was randomly assigned to 4 weeks of treatment with pregabalin (n=47) or sertraline (n=60). Patients treated with sertraline were previously treated with SSRIs and SNRIs without remission, according to the latest National Clinical Guideline issued by the National Institute of Health and Clinical Excellence for treating GAD (NICE). The primary analysis was the change in the Hamilton Rating Scale for Anxiety (HAMA), a total score from baseline to endpoint. The second indicator of efficacy was the change in the HAMA psychic (emotional) and somatic (physical) scores, weekly, till endpoint. Global clinical assessment was conducted by using the Clinical Global Impression change rating (CGI).

RESULTS: Both pregabalin and sertraline showed good results in treating symptoms of Generalized Anxious Disorder. The onset of action was shorter in treatment with pregabalin compared to the treatment with sertraline. In the patients treated with sertraline, the anxiolytic effect was detectable after at least 14 days while pregabalin showed initial good results during the first week of treatment. Adverse effects were reported in 28% patients treated with pregabalin and 27% of patients treated with sertraline, without significant differences. There were no dropout patients in neither group. Beside pharmacotherapy, each patient received 8 weeks of cognitive/behavior therapy. In concomitant therapy benzodiazepine was used (klonazepam, in low doses). In all patients adverse events were short-lasting withmild intensity and there were no withdrawal events during this study.

CONCLUSIONS: Efficacy and tolerability of pregabalin were high. Compared to sertraline, pregabalin showed more rapid onset of action and equal efficacy. Adverse reactions are short-lasting and the dose depends. Our investigation showed that pregabalin, an atypic anxiolytic is efficient and well tolerable in treatment of GAD.

Key Words:
Generalized anxiety disorder, Pregabalin, Sertraline-efficacy-adverse events.

Introduction

Generalised Anxiety Disorder (GAD) represents a chronic psychiatric disorder with a lifetime prevalence of 5-7% in the generalpopulation. Therefore, GAD is one of the most common psychiatric problems in Mental Health. This mental disorder is characterised by permanent and pervasive worrying and tension with great potential for comorbidity to other somatic or mental disorders, and it causes substantial personal distress[1-4]. The World Federation of Societies of Biological Psychiatry,WFSBP (2009) recommends SSRI (serotonin selective reuptake inhibitors-escitalopram, citalopram, fluoxetine, paroxetine), selective serotonin and norepinephrine reuptake inhibitors (SSNRI-venlafaxine) and pregabalin as first line treatments. Psychotherapy, like CBT, (cognitive/behavioral therapy, autorelaxing treatment), is recommended mostly in combination with pharmacotherapy[5,6].

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Pregabalin, a structural analog of y-aminobutric acid (GABA), is a relatively novel agent, and it has been used for treatment of GAD since 2002. Pregabalin acts as a presynaptic inhibitor of the release of excessive levels of excitatory neurotransmitters by selectively binding to the alpha-2- beta-subunit of voltage-gated calcium channels. Pregabalin does not exert its therapeutic effects by binding directly to GABA a, GABA b and benzodiazepine receptors and, moreover, it does not appear to have functional activity at serotonin, dopamine or norepinephrine receptors[7-9]. Pregabalin is rapidly absorbed in the gastrointestinal tract and achieves maximum plasma concentrations within 1.5 hours from oral administration. It does not exhibit any significant protein binding, has no known drug interactions and it is excreted renally as an unchanged drug[10-13]. Thus, at first, it was called an atypical anxiolytic. Pregabalin is also prescribed for management of neuropathic pain and for adjunctive therapy in patients with partial onset seizures[10,14].

Anxiolytic effects of pregabalin appear within one week, similar to the effects of benzodiazepines, but faster than SSRIs and SNRIs. Anxiolytic effects of pregabalin in generalized anxiety disorder have been demonstrated in many randomized, double-blind placebo-controlled studies[9,15-18], compared to SSRI antidepressants.

The purpose of this article was to identify effective treatment options and side effects in treatment of GAD with pregabalin, compare to treatment with sertraline (selective serotonin reuptake inhibitor).

Patients and Methods

Our sample consisted of 107 outward patients at the Psychiatric Clinic. Patients, both male and female, age range 20-60, with a diagnosis of GAD (according to ICD-X, and DSM-IV), were observed from October 2011 to February 2013. Inclusion criteria: at the beginning of the investigation, all observed patients had a HAMA total score > 20. A global clinical assessment was conducted by using the Clinical Global Impression rating (CGI). Patients with comorbid mental disorders (depression, alcoholism, personal disorders, psychotic disorders), or somatic dysfunction (diabetes mellitus, hypertension, cardiomyopathy, thyroid dysfunction) were not included in the study. The study protocol was approved by the local Ethical Committee and was carried out in accordance with the Declaration of Helsinki. Patients treated with pregabalin did not previously respond to sertraline and venlafaxine. All patients were monitored during a 4-week period and psychiatric control checks occurred every week. During each check, patients fulfilled both rating scales.

At each visit, patients were evaluated by one of two different psychiatrists, but the final effectiveness and side effects assessments were made by the same psychiatrist that did the baseline evaluations.

Statistical Analysis

The primary efficacy parameter was the baseline to endpoint change on the total score of the HAMA. This parameter was analyzed by using an analysis of covariance (ANCOVA) model that included the effects of treatment and the center, with the baseline Hamilton anxiety scale total score entered as a covariate[3]. The effect of pregabalin treatment relative to the treatment with sertraline, in terms of response (defined as > 50% decrease from baseline to endpoint in the Hamilton anxiety scale total score and a CGI change rating of "much improved" or "very much improved" at the endpoint) was evaluated by using logistic regression after we adjusted for the center.

The adverse events were counted only once (regardless of the number of times the patient experienced the event) by using the maximum intensity recorded. When $p < 0.05$, it was considered statistically significant.

Results

A total of 107 patients were screened. The first group of patients (n = 60) were treated with sertraline, with a mean daily dosage of 150 mg/day. The second group of patients (n = 47) were treated with pregabalin, with a mean daily dosage of 225 mg/day. Doses of psychoactive drugs were titrated during first week.

Patients treated with pregabalin were 67% female and 33% male and the mean age was 37.8 + 2.2. In the group of patients treated with sertraline, the gender and aged distributions were similar (69% female, and 31% male, mean age was 37.4 + 5.2) with no statistical difference between the two groups (Table I).

The Hamilton anxiety total score decreased in both treatment groups during the first month. This change occurred significantly faster in the group of patients treated with pregabalin (Table II).

Table I. Demographic and clinical characteristics of patients with generalized anxiety disorders.

SAMPLE (n=107)	Patients treated with pregabalin (n=47)		Patients treated with sertraline (n=60)		p
Gender	N	%	N	%	ns
Female	67	31	41	19	
Male	16	33	69	31	
Age (years)	X + SD 37.8 (2.2)		X + SD 37.4 (5.2)		ns
HAMA (total score)					
Baseline	X + SD 23.80 (5.8)		X + SD 23.50 (3.4)		ns
Endpoint	14.20 (2.4)		13.70 (3.0)		

Table II. Change in hamilton anxiety scale scores in patients with generalized anxiety disorder treated 4 weeks with pregabalin (225 mg/day) and sertraline (150 mg/day).

HAMA total score	Patients treated with pregabalin 225 mg/day (n=47)	Patients treated with sertraline 150 mg/day (n=60)
Baseline	23.60 + 2.6	24.00 + 1.2
1st week	18.10 + 2.2	23.50 + 0.9
2th week	16.40 + 1.2	19.20 + 1.1
3th week	15.20 + 1.3	14.70 + 1.0
4th week	14.20 + 0.7	13.90 + 0.2

In addition to the Hamilton anxiety total score, we examined the psychic and somatic subscales on the Hamilton anxiety scale. Both treatment with pregabalin, as well as treatment with sertraline, significantly reduced scores on the subscales (Table III).

In cases where the patients were treated with pregabalin, in terms of the CGI change rating, 97% showed ratings of "very much improved" at the endpoint. For the group treated with sertraline, 96% of patients showed ratings of "very much improved", and there were no non significant differences among the two groups of patients.

Adverse reactions during treatment were reported in 28% of patients treated with pregabalin. The most frequent events were nervous system related-dizziness (13%), and somnolence (10%). Among patients treated with sertraline, the frequency of side events was similar (27%) with no statistical difference between the two groups of patients. The most frequent reported adverse event among patients treated with sertraline was nausea (13%). Less frequent were dizziness, sleeping problems and vertigo (Table IV).

In all patients, the adverse events were short-lasting and of mild intensity and there were no withdrawal events during this study.

Discussion

This study demonstrates that pregabalin, an atypical anxiolytic, has good results when used for treatment of GAD[3,18-20]. When compared to

Table III. Change in Hamilton anxiety scale scores in patients with generalized anxiety disorder treated with pregabalin and sertralin monitoring during 4 weeks.

HAMA treatment groups	Adjusted mean change	Analysis T (df|=193)	p
Pregabalin 225 mg/day (n=47)	-9.11	-2.20	0.003
Sertraline 150 mg/day (n=60)	-1.29	-4.30	0.008
Psychic subscale pregabalin 225 mg/day (n=47)	-4.90	-1.20	0.08
Sertraline 150 mg/day (n=60)	-6.10	-1.70	0.001
Somatic subscale pregabalin 225 mg/day (n=60)	-4.56	-1.90	0.003
Sertraline 150 mg/day (n=60)	-5.75	-3.80	0.001

Table IV. Adverse events in patients with generalized anxious disorder treated with pregabalin (225 mg/die) and sertraline (150 mg/day).

Adverse events (reported in 26% patients)	Patients treated with pregabalin 225 mg/day (n = 47)	Patients treated with sertraline 150 mg/day (n = 60)
Dizziness	13%	5%
Somnolence	10%	–
Nausea	3%	13%
Diarrhea	–	5%
Vertigo	2%	1%
Insomnia	–	3%
Total	28%	27%

the treatment with sertraline, there is no evidence of superior efficacy, but the antianxiety effect of pregabalin was detectable within the first week after the start of treatment. In patients treated with sertraline, the anxiolytic effect was detectable after at least 14 days in the present study. So, the rapid onset of the anxiolytic effect is a feature of the treatment with pregabalin, compared to sertraline[21-27].

As this mental disorder interferes with everyday activities significantly, it is supposed to be very beneficial for a patient to notice that symptoms disappear within one week of use. This fact is important for good compliance as well. In this group of patients, pregabalin demonstrated superior efficacy, meaning shorter time of onset, compared to sertraline.

Although adverse events were reported in both groups of patients, they were of mild intensity, short time lasting and dose-related. There were no withdrawal events in this study.

This report confirmed the effectiveness and the rapid onset of action in pregabalin. The adverse events which were observed during treatment with pregabalin and sertraline were mild and dose-related. Regardless, after 3-4 days, they tended to resolve in this sample.

Conclusions

Pregabalin showed good efficacy and tolerability with rapid onset of action in the treatment of GAD, without the potential for withdrawal action.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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