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Clonazepam in the long-term treatment of patients with unipolar depression, bipolar and schizoaffective disorder

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Abstract

The value of a long-term treatment with clonazepam in the prophylaxis of affective disorder is discussed controversially in the scientific literature. Altogether there are only a few reports on the use of this compound as a mood stabilizer, most of them describing patients suffering from bipolar affective disorder. The aim of this investigation was to evaluate clonazepam as a phase prophylactic medication in affective disorder. We conducted a retrospective chart review in 34 out-patients of our lithium clinic (15 suffering from unipolar depression, 15 from bipolar disorder, four from schizoaffective disorder), who had been treated with clonazepam as a long-term medication. Clonazepam was either given as monotherapy, or as in the case of lithium non-responders, as adjunctive therapy. Patients with unipolar depression had significantly ($P=0.026$) less depressive episodes after initiation of treatment with clonazepam. Patients with bipolar disorder did not benefit from this therapy. Neither manic/hypomanic phases nor depressive episodes were reduced in this group of patients. Interestingly, clonazepam also reduced affective phases in our four schizoaffective patients on a trend level. Our results indicate that patients with unipolar depression may benefit from a maintenance treatment with clonazepam. Due to methodological limitations our results need to be replicated in controlled double-blind randomized clinical trials.

Keywords: Clonazepam; Mood-stabilizer; Maintenance treatment; Depression; Bipolar disorder; Schizoaffective disorder

1. Introduction

Affective disorder is recurrent in nature (Schatzberg, 1996) and can impose a significant impairment to patients' lives (Berndt et al., 2000; Murray and Lopez, 1997). Depression generally is under-treated in primary care and remains a substantial public health concern (Lin et al., 2000). Modern psychopharmacology is thus seeking ways to keep patients well after the initial remission from the affective episode (Winkler et al., 2002). Patients at risk should receive a maintenance pharmacotherapy, since affective illness appears to become more severe and potentially refractory with each new episode (Keller et al., 1992; Post, 1992; Rush and Thase, 1997). For patients with recurrent major depression it is recommended to use the same antidepressant agent that was effective during the acute and continuation therapy (Franchini et al., 2000). There is also strong evidence that lithium salts are efficacious in preventing depressive relapses and recurrences in unipolar depression (Bauer et al., 2000; Coppen, 2000). Lithium is considered as the first choice for patients with bipolar affective disorder (Bowden, 2000). Among the different treatment approaches as an alternative to lithium are the anticonvulsants carbamazepine, valproate and lamotrigine (Nolen and Bloemkolk, 2000).

Clonazepam (CNZP) is a unique high-potency 1,4-benzodiazepine derivative. It is proposed that its actions are not only mediated at the gamma-aminobutyric acid-sub(A) (GABA-sub(A)) receptor (Haefely, 1983), but also due to a modulation of central 5-hydroxytryptamine (5-HT, serotonin) metabolism (Lima, 1991). CNZP is approved by the US Food and Drug Administration (FDA) since 1976

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as an antiepileptic drug for the following types of seizures: absence, infantile spasm, atypical absence, myoclonic, and atonic (Browne, 1978). It is also used for the treatment of panic disorder (Valenca et al., 2000; Worthington et al., 1998) and has shown efficacy in case series and in a controlled trial for the acute treatment of mania (Adler, 1986; Chouinard et al., 1983; Pande, 1988). CNZP's long half-life of 20 to 80 h (Devane et al., 1991) might render this compound especially promising as a maintenance medication in affective disorder, because interdose fluctuation in mood state should be reduced and because it might diminish the likelihood or severity of rebound worsening of symptoms following the discontinuation of augmentation (Herman et al., 1987; Pecknold, 1990).

The aim of this investigation was to assess the value of CNZP as a long-term prophylactic treatment in affective disorder, an issue which was not sufficiently addressed in the available literature.

2. Experimental procedures

Thirty-four adult out-patients from our lithium clinic, who either did not benefit from, or did not tolerate lithium, were included in a retrospective chart review. Non-response to lithium was defined as occurrence of affective phases while being on lithium with adequate plasma-levels. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994). Fifteen subjects were suffering from unipolar major depression (DSM-IV: 296.2, 296.3), 15 from bipolar affective disorder (DSM-IV: 296.4, 296.5) and four from schizoaffective disorder (DSM-IV: 295.70). Patients were physically in good health. Subjects with psychiatric comorbidity were not included in this evaluation. Prior to treatment with CNZP, patients consented orally after an explanation of the clinical profile and the side effects of the drug.

We used a mirror-image design (Grof, 1994) to evaluate the outcome with CNZP: the course of illness prior to the new treatment was compared to the time course during CNZP therapy. The main outcome parameter of our study was the mean number of episodes of affective illness per year (phase density) before and after treatment initiation with CNZP. The phase density was first calculated for each patient and then averaged across the group. Affective episodes were defined as major depressive episodes, manic or schizoaffective episodes, that had been diagnosed according to DSM-IV during the course of illness. Our patients were treated with CNZP as monotherapy or, as in the case of lithium non-responders, as an adjunctive maintenance medication. CNZP was administered as an open label medication. Mean dose was 2.0 ± 1.18 mg per day, patients were followed up for a mean duration of 1.5 years$\pm$7.5 months with CNZP therapy.

Statistical analysis was carried out with the Wilcoxon matched-pairs signed-ranks test using SPSS for Windows (1998). We preferred the Wilcoxon test over the Student *t*-test because it does not assume normal distribution of the data and it is almost as or even slightly more powerful than the latter for small numbers with unknown distribution (Bridge and Sawilowsky, 1999). The $P \leq 0.05$ level of significance was adopted. All statistical comparisons were two-tailed. In this article variables will be presented in the format: arithmetic mean$\pm$standard deviation.

3. Results

Of our patients, 56% were females ($n=19$), 44% were males ($n=15$). The mean age at presentation was 48.3 ± 17.1 years. Subjects with major depression were on average 43.5 ± 17.0 years old and their disorder had lasted for 11.6 ± 1.5 years. Patients with bipolar disorder were older (56.3 ± 16.5 years) and had suffered longer from their illness (17.5 ± 10.5 years). Subjects with schizoaffective disorder had a mean age of 41.8 ± 8.1 years, the mean duration of their illness was 12.8 ± 9.4 years. During the treatment period with CNZP, no drop-outs due to intolerance of medication and no cases of uncontrolled dose increase were observed.

Differences in phase density with and without CNZP are shown in Table 1. Patients with *unipolar depression* were observed 2.7 years before treatment with CNZP and 1.1 years afterwards. CNZP treatment led to a statistically significant reduction in affective episodes ($z=-2.220$, $P=0.026$): before treatment, patients had 1.51 ± 2.95 phases per year and 0.31 ± 0.54 throughout treatment. Eleven patients remained stable without any further depressive episodes during the observation period; four subjects experienced relapse, though two of them still seemed to

Table 1
Episodes of affective illness per year before and after patients were treated with clonazepam

N	Diagnosis		Without clonazepam (episodes per year)	With clonazepam (episodes per year)	*P*
15	Unipolar depressive disorder		1.51 ($\pm$2.95)	0.3 ($\pm$0.54)	0.026
15	Bipolar disorder	Manic episodes	0.29 ($\pm$0.22)	0.59 ($\pm$0.72)	0.909
		Depressive episodes	0.4 ($\pm$0.6)	0.44 ($\pm$0.69)	0.133
4	Schizoaffective disorder		0.75 ($\pm$0.43)	0.1 ($\pm$0.2)	0.068

Data is given as arithmetic mean$\pm$standard deviation. The Wilcoxon paired-sample signed-rank test (two tailed) was carried out to test for significance on the $P<0.05$ level.