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A three-year follow-up study of patients with the respiratory subtype of panic disorder after treatment with clonazepam

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Abstract

The demographic, clinical and therapeutic features of the respiratory subtype of panic disorder (PD) versus the non-respiratory subtype were studied in a prospective design. Sixty-seven PD outpatients (DSM-IV), who had previously been categorized into respiratory ($n=35$) and non-respiratory ($n=32$) subgroups, were openly treated with clonazepam for a 3-year period. The principal measure of efficacy was the number of panic attacks, obtained from the Sheehan Panic and Anticipatory Anxiety Scale. In the first 8 weeks of treatment (acute phase), the respiratory subtype group had a significantly faster response to clonazepam. During the follow-up (weeks 12-156), the two subgroups did not differ significantly in the number of panic attacks experienced from baseline to end point. Patients in the respiratory subtype were characterized by a later onset of disorder and a family history of PD. Patients in the non-respiratory subgroup had a significantly higher number of past depressive episodes than those in the respiratory subgroup. The respiratory subgroup had a faster response after 8 weeks of treatment and an equivalent response in the 3-year follow-up period. Clonazepam had a sustained therapeutic effect over the entire treatment period.

Keywords: Respiration; Panic attack; Follow-up; Benzodiazepine; Treatment; Anxiety disorder

1. Introduction

A link between the respiratory system and panic disorder (PD) has been widely reported (cf. Klein, 1993; Gorman et al., 2000). Biber and Alkin (1999) examined the sensitivity to CO_2 in PD patients and

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proposed two subtypes of the disorder defined by differential responses to CO_2 challenge. Patients who showed prominent respiratory symptoms were more sensitive to CO_2 challenge, had a significantly longer illness duration, had more severe panic and phobic symptoms, and were more likely to be heavy smokers than were patients without respiratory symptoms.

The choice of an optimal treatment for PD depends on a number of issues, including adverse effects, efficacy, and presence of concomitant syndromes. It is crucial to provide a risk-benefit assessment before treating each patient (Gorman, 1997; Sheehan, 1999). The subtype of PD can also influence therapeutic response (Nardi et al., 2003; Valença et al., 2003). Although many treatment options are effective in PD, the efficacy of clonazepam, a high-potency benzodiazepine with anticonvulsant and anxiolytic properties, was first noted in the 1980s and the early 1990s by Chouinard and Rosenbaum and their collaborators (for review, see Rosenbaum, 2004), and its effectiveness in PD has been confirmed in later studies (Valença et al., 2003). In addition to clonazepam's activation of the benzodiazepine-GABA receptor complex, clonazepam, unlike many other benzodiazepines, appears to have serotoninergic activity, which contributes to its psychotropic and antimyoclonic effects (Moroz, 2004).

Our group has been studying the therapeutic response to clonazepam and other medications in PD subtypes (Nardi et al., 2003; Valença et al., 2003). In a retrospective 6-week comparison of clonazepam versus placebo (Valença et al., 2003), we found no significant differences in therapeutic response between respiratory and non-respiratory subgroups of PD. In a prospective analysis of a 1-year open trial with nortriptyline, the respiratory PD subtype had a faster response to treatment than did the non-respiratory subtype and an equivalent response after 1 year of treatment (Nardi et al., 2003).

The present study extends our previous reports by examining the demographic, clinical and therapeutic features of patients with the respiratory PD subtype who had been treated for a 3-year period in the Laboratory of Panic & Respiration in Rio de Janeiro, Brazil. The respiratory subgroup was compared with a non-respiratory PD subgroup. All patients were openly treated with clonazepam.

2. Methods

2.1. Subjects

Participants were men and women, between the ages of 18 and 65 years, who met DSM-IV criteria (American Psychiatric Association, 1994) for PD, with or without agoraphobia, as determined by the Structured Clinical Interview for DSM-IV (First et al., 1997). Patients were required to have a minimum of four panic attacks, at least one of which was unanticipated, during the 4 weeks before treatment began. The clinical symptoms of the most severe recent panic attack were assessed at baseline to characterize the respiratory and non-respiratory subtype groups (Briggs et al., 1993).

At the initial visit, patients needed to score at least 18 on the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) and below 17 on the 21-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). Urinary screens for the presence of benzodiazepines and barbiturates were required to be negative on the first day of the treatment period.

To qualify for study, women of child-bearing potential had to use an effective method of birth control. Pregnant or nursing women were excluded from participating. Patients who met DSM-IV criteria for current major depression, bipolar disorder, obsessive–compulsive disorder, schizophrenia, delusional or psychotic disorders, organic brain syndrome, epilepsy, or substance abuse or dependence (during the last year) were also excluded. Patients with comorbid dysthymic or generalized anxiety disorders could be included if PD was judged to be the principal diagnosis. Other reasons for exclusion included the following: unstable medical conditions; hypersensitivity or other medical contraindications to antidepressant therapy; participation in an investigational drug study within the preceding 6 months; previous treatment with clonazepam; concomitant treatment with any psychotropic drug during the study or psychotherapy during the first 8 weeks of the study; use of monoamine oxidase inhibitors, typical antipsychotics, antidepressants, benzodiazepines or nonbenzodiazepine anxiolytics within 4 weeks; use of fluoxetine within 5 weeks of the first administration of the study medication; and the presence of suicidal risk.