Duration of untreated illness in panic disorder: a poor outcome risk factor?

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Objective: The aim of this naturalistic study was to evaluate the impact of the duration of untreated illness (DUI) on the outcome and treatment response of panic disorder (PD).

Methods: Ninety-six outpatients with PD who underwent an 8-week open-label treatment with serotonergic antidepressants were subdivided into two subgroups: those with DUI ≤ 1 year and those with DUI > 1 year. The main baseline demographic and clinical variables were calculated and compared between the two subgroups of patients (chi-square test or t-test for independent samples). The effect of the antipanic medication was evaluated by analysis of variance with repeated measures considering Hamilton Rating Scale for Anxiety, Clinical Global Impression rating scores, and the number of panic attacks/week as the dependent variables (outcome measures), while the subgroups were the independent ones. Comorbidity with onset later than PD was also considered.

Results: There were no differences between patients with DUI ≤ 1 year and patients with DUI > 1 year with respect to the outcome measures considered. However, patients with DUI > 1 year (N = 64) had a higher frequency of comorbid major depressive disorder (MDD) with onset later than PD (p = 0.006).

Conclusions: Results from this study suggest that the DUI may be a predictor of the development of comorbid MDD in PD. Further investigations on larger samples and with longer follow-up are warranted.

Keywords: panic disorder, duration of untreated illness, treatment, outcome

Introduction

Panic disorder (PD) is considered a chronic and debilitating illness characterized by recurrent, severe, and spontaneous anxiety attacks accompanied by a wide variety of autonomic symptoms (Dannon et al 2004). Some population-based epidemiological studies showed that approximately 15% of subjects experience isolated panic attacks and up to 3.8% develop full-syndromal PD during the course of their life (Eaton et al 1994).

PD is often comorbid with other psychiatric disorders such as bipolar disorder, major depressive disorder (MDD), and other anxiety disorders (Diler et al 2004; Westenberg et al 2004). In addition, PD is associated with a significant impact on global functioning and quality of life (Starcevic et al 1993; Carpiniello et al 2002). The functional disability and risk of suicidal ideation and behavior associated with comorbid panic and depression far exceed those associated with either disorder alone (Markowitz et al 1989; Goodwin et al 2001). Recently, Bittner et al (2004) suggested that anxiety disorders (including panic disorder) act as risk factors for the first onset of MDD. Furthermore, the presence of several clinical characteristics of anxiety disorders (eg, specific phobia, social phobia, panic disorder, agoraphobia, and generalized anxiety disorder), and the presence of more than one anxiety disorder with severe impairment of global functioning appear to play a substantial role in determining the susceptibility to MDD.

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Although several effective pharmacological treatments do exist for PD, up to 20%–40% of patients can be considered nonresponders to pharmacotherapy, thus accounting for most of the individual and society costs associated with the illness (Slaap and den Boer 2001). Some clinical variables have been most consistently identified as predictors of poor outcome in PD: panic severity, presence of agoraphobia, comorbid depression, comorbid personality disorder, duration of illness, and female gender (Pollack et al 2000).

Duration of untreated illness (DUI), defined as the time elapsing from the onset of an illness and the first adequate treatment, has been considered an important predictive variable for the course of some psychiatric disorders such as schizophrenia (Altamura et al 2001). However, the role of the DUI in mood disorders is still controversial (Craig et al 2000; Mundo et al 2002). Only few studies exist on the possible association between a longer DUI and a poorer outcome in PD (Scheibe and Albus 1997; Katscing et al 1998; Shinoda et al 1999).

The primary aim of this study was to evaluate the impact of the DUI on the course and the pharmacological treatment response in PD.

Methods

This naturalistic study included 96 patients (26 males and 70 females) with PD, with or without agoraphobia, diagnosed by a semistructured psychiatric interview based on DSM-IV criteria, and treated with SSRIs, venlafaxine or clomipramine. Treatment was chosen and administered by the treating psychiatrists at flexible doses, adjusted according to clinical needs and tolerability. For the 8-week study duration no concomitant treatment (pharmacological or nonpharmacological) was allowed except for previously stabilized doses of benzodiazepines (not exceeding 5 mg diazepam eq/day). After a complete description of the study, written informed consent to participate was obtained from all subjects.

At baseline, the following clinical variables were collected: age, age at onset, DSM-IV Axis I diagnoses, family history (FH) for anxiety or mood disorders in first-degree relatives, and the duration of untreated illness (DUI) defined as the interval (months) between the onset of PD and the first adequate (considering time and doses) antipanic pharmacological treatment.

Data on the DUI were collected using semistructured clinical interviews and further confirmed using the clinical charts available for each patient. Patients were also subdivided into two subgroups: with DUI ≤ 1 year and with DUI > 1 year. Clinical assessment was done at baseline and after 8-weeks of treatment by administration of the Hamilton Rating Scale for Anxiety (HAM-A) (Guy 1976), the Clinical Global Impression rating scale (CGI) (severity item) (Guy 1976), and by evaluation of the number of panic attacks/week.

The main baseline demographic and clinical variables were calculated and compared between the two subgroups of patients (chi-square test or t-test for independent samples). The treatment efficacy and the difference between the two patient subgroups were evaluated using analysis of variance (ANOVAs) with repeated measures. In these analyses the HAM-A score, CGI score (impairment item), and number of panic attacks/week were the dependent variables.

Results

The main demographic and baseline clinical variables in the two subgroups of patients are summarized in Table 1. Patients with DUI ≤ 1 year and patients with DUI > 1 year did not differ with respect to baseline clinical characteristics, including FH for anxiety or mood disorders in first degree relatives.

The clinical assessment after 8-weeks treatment with serotonergic antidepressants (venlafaxine, n = 6, mean 100 ± 38.7 mg/day; sertraline n = 34, mean 88.9 ± 26.9 mg/day; clomipramine n = 9, mean 86.1 ± 13.2 mg/day; paroxetine n = 43, mean 27.0 ± 8.3 mg/day; citalopram n = 1, 20 mg/day; fluoxetine n = 3, mean 40 ± 20 mg/day) showed a significant improvement in the whole sample, with no differences

Table 1 Baseline demographic and clinical characteristics in the whole sample and in the two subsamples defined by the duration of untreated illness (DUI)

Variables	Total (N = 96)	DUI ≤ 1 year (N = 32)	DUI > 1 year (N = 64)
Gender	26 M, 70 F	12 M, 20 F	14 M, 50 F
Age	40.14 (13.05)	35.6 (12.4)	42.5 (12.8)
Age at onset	32.26 (12.75)	34.00 (11.12)	31.39 (13.49)
Panic attacks/week	3.86 (2.16)	3.44 (1.90)	4.08 (2.26)
Positive FH for anxiety disorders	34	14	20
Positive FH for mood disorders	12	5	7
HAM-A baseline	19.90 (3.56)	19.22 (3.65)	20.23 (3.50)
CGI baseline (severity)	3.76 (0.83)	3.59 (0.91)	3.84 (0.78)

NOTE: SDs for continuous variables are shown in parentheses.
Abbreviations: CGI, Clinical Global Impression Scale; DUI, duration of illness; FH, family history in first degree relatives; HAM-A, Hamilton Rating Scale for Anxiety.

between patients with DUI ≤ 1 year and patients with DUI > 1 year on the HAM-A total score (time effect: $F = 306.314$, $p < 0.00001$; group effect: $F = 3.127$, $p = 0.08$; time × group effect: $F = 0.334$, $p > 0.50$), on the number of panic attacks/week (time effect: $F = 156.457$, $p < 0.00001$; group effect: $F = 1.525$, $p > 0.020$; time × group effect: $F = 0.992$, $p > 0.30$), and on the CGI improvement item score (time effect: $F = 244.314$, $p < 0.00001$; group effect: $F = 3.304$, $p > 0.07$; time × group effect: $F = 0.127$, $p > 0.70$).

Patients with DUI > 1 year had a higher frequency of comorbid MDD with onset later than PD (chi-square = 7.518, $dF = 1$, $p = 0.006$) than patients with DUI ≤ 1 year. These results did not change when we categorized patients according to gender, diagnostic subtype (presence/absence of agoraphobia), or presence/absence of positive FH for anxiety or mood disorders in first degree relatives.

Discussion

The results from this study do not appear to confirm that a longer DUI is a predictor of poorer response to pharmacotherapy, as it has been reported in previous studies (Slaap and den Boer 2001).

On the other hand, in this sample, PD patients with DUI > 1 year had a course complicated by the occurrence of comorbid major depression (44%) more often than PD patients with DUI ≤ 1 year (31%). According to the literature, MDD is highly comorbid with anxiety disorders, which commonly have earlier onset and represent a significant risk factor for the development of depression itself (Hettema et al 2003; Bittner et al 2004). The association between a delay in the treatment of PD and the development of depressive episodes has been suggested by previous studies (Scheibe et al 1997; Katscing et al 1998; Shinoda et al 1999). The exact nature of this association and the pathogenetic mechanism underlying the comorbidity between PD and MDD are still obscure. The presence of common biological characteristics between the two clinical conditions (eg, alterations in the hypothalamic-pituitary-adrenal axis function, in serotonergic neurotransmission, and in growth hormone response to challenges) suggests some shared biological susceptibility (Johnson et al 1995).

In any case, the results from this preliminary naturalistic study suggest that early PD diagnosis and treatment may positively affect the risk of developing MDD. In addition, preventing the development of MDD in PD patients by early pharmacological treatment may have important clinical implications. As an example, high rates of suicide attempts or suicidal behavior have been observed in PD patients with comorbid depression (Goodwin et al 2001), and early antipanic treatment may be a critical prevention strategy.

Limitations of this study are represented by the relatively small sample, the naturalistic design, and the relatively short follow-up. Future research will consider larger samples, controlled treatments, and longer follow-up.

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