Journal of Affective Disorders 136 (2012) 675–679

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Predictors of response among patients with panic disorder treated with medications in a naturalistic follow-up: The role of adult separation anxiety

M. Miniati [a], S. Calugi [a], P. Rucci [b], M.K. Shear [c], A. Benvenuti [a], D. Santoro [a], M. Mauri [a], G.B. Cassano [d,*]

[a] Department of Psychiatry, Neurobiology, Pharmacology, Biotechnology, University of Pisa, Pisa, Italy
[b] Department of Medicine and Public Health, Alma Mater Studiorum, University of Bologna, Bologna, Italy
[c] Columbia University, School of Social Work, New York, NY, USA
[d] University of Pisa, Italy

ARTICLE INFO

Article history:
Received 28 July 2011
Received in revised form 6 October 2011
Accepted 6 October 2011
Available online 30 November 2011

Keywords:
Panic disorder
Separation anxiety
Naturalistic follow-up
Panic–agoraphobic spectrum
Remission

ABSTRACT

Background: Efficacy of treatments for panic disorder is well established, but not all patients respond. Adult separation anxiety has been found to predict poorer response to CBT, but its effect on response to medication has not been previously explored.
Study aim: The aim of this study is to investigate if panic–agoraphobic spectrum factors, including '*separation anxiety*' factor predict treatment outcome in patients with panic disorder.
Study sample: Participants who met criteria for PD (n = 57) completed baseline assessment and 12 months follow-up. Patients were administered the Panic Agoraphobic Spectrum Self-Report (PAS-SR, Lifetime and Last-Month Versions), and the Panic Disorder Severity Scale (PDSS). We examined patients who met the following criteria at baseline: 1) PDSS total score > 7; 2) no current Axis I comorbidity with major depression; 3) no lifetime or current bipolar disorder. All patients were treated with evidence-based psychopharmacological treatment for panic disorder during the 12-month observation period.
Results: Twenty eight patients (48.1%) achieved remission during the follow-up period. In a logistic regression model, controlling for baseline severity, gender and age, only the last-month PAS-SR '*separation anxiety*' factor was associated with a lower likelihood of remission.
Conclusions: Signs and symptoms of separation anxiety in adulthood, as assessed with the PAS-SR Last Month version, are predictors of poor treatment outcome in patients with PD. We submit that the assessment of panic–agoraphobic spectrum features, including adult separation anxiety, should become routine of clinical assessment of patients with PD. It is likely that a better psychopathological characterization of patients may inform treatment selection, and result in better treatment outcome.

1. Introduction

Panic Disorder (PD), with or without agoraphobia, is characterized by a chronic or recurrent course (Goodwin et al., 2005), a resistance to spontaneous remission, and by high rates of comorbidity with several Axis I disorders, namely, unipolar depression, bipolar disorder, alcohol or substance abuse (Pollack and Smoller, 1995; Weissman et al., 1997). Difficulties in treating panic disorders are partially due to the paucity of information regarding the prognostic value of its heterogeneous clinical manifestations (Cassano et al., 1997). The most common classification of PD includes two main subtypes: one with a predominance of respiratory symptoms, and another with a predominance of cognitive symptoms. Studies have shown that the '*respiratory subtype*',

* Corresponding author at: University of Pisa, Via Roma 67-56100 Pisa, Italy. Tel.: +39 050 586378; fax: +39 050 532063.
E-mail address: cassano.gb@gmail.com (G.B. Cassano).

0165-0327/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2011.10.008

related to the theory of hyperventilation (Ley, 1985), and to the '*false suffocation alarm*' hypothesis (Klein, 1993), is characterized by later onset of panic, longer illness duration, and severe agoraphobic features (Biber and Alkin, 1999; Nardi et al., 2004). Conversely, patients belonging to the '*cognitive symptoms*' subtype, are characterized by a strong feeling of distress or fear together with cognitive symptoms. More recently, Kircanski et al. (2009) reviewed studies of different subtypes of panic disorder (namely, '*respiratory*', '*nocturnal*', '*non-fearful*', '*cognitive*', and '*vestibular*'), and found no evidence supporting the need of sub-typing.

These descriptions have been utilized not only to better define the clinical phenotypes of panic disorder, but also to correlate the presence of a subset of symptoms to specific outcomes, with inconclusive findings. Thus, in community studies as well as in clinical studies, only agoraphobic features proved to be reliable predictors of poorer course of PD (Allen et al., 2010; Katschnig and Amering, 1998; Roy-Byrne and Cowley, 1998).

In order to address this question from a different point of view, Cassano et al. (1997, 1998) suggested an alternative strategy for sub-typing panic disorder. They observed that patients with panic disorder usually exhibit a wide range of clinical features surrounding the '*core*' psychopathological features of PD, and not included in the categorical criteria sets. This '*panic spectrum model*', shares the basic idea, proposed by other authors (Meuret et al., 2006), that dimensions of clinical features can occur within the same diagnostic category. They further posit that clinical phenotypes of panic disorder, and the identification of possible predictors of clinical course, might be related to such dimensions, and that failure to recognize spectrum features might explain continued impairment, even when core Axis I symptoms have been successfully treated (Shear et al., 2002). The proposed '*panic–agoraphobic spectrum*' includes several psychopathological dimensions surrounding the typical panic manifestations, such as separation sensitivity, stress sensitivity, medication and substance sensitivity, typical and atypical agoraphobic features, anxious expectation, illness phobia and hypochondria, and reassurance orientation (Cassano et al., 1997; Rucci et al., 2009). In order to operationalize these dimensions, a Structured Clinical Interview for Panic–Agoraphobic Spectrum (SCI-PAS) and the corresponding self-report form (PAS-SR) that matches exactly its content were developed in the framework of the 'Spectrum Project' (Cassano et al., 1999).

The present study is a 12-month naturalistic follow-up aimed at assessing the role of the Panic–Agoraphobic Spectrum signs and symptoms in predicting treatment response of patients with Panic Disorder. The factor structure of PAS-SR is described in detail elsewhere (Rucci et al., 2009). In this study, we administered two versions of the PAS-SR: the 'Lifetime Version', that investigates the presence of panic/agoraphobic signs and symptoms during the lifetime, and the 'Last Month' Version, that explores panic/agoraphobic symptoms experienced in the past month. We were especially interested in assessing the role of adult separation anxiety as outcome predictor of PD, considering that in a previous study, patients experiencing signs and symptoms of adult separation anxiety were less likely to respond to CBT (Aaronson et al., 2008), but no information was provided on patients treated with medications.

2. Method

2.1. Study sample

A total of 102 individuals, referred by primary care physicians, underwent a preliminary psychiatric screening at the outpatient section of the Psychiatric Clinic of the University of Pisa, Italy. Those who met DSM-IV criteria for current Panic Disorder with or without agoraphobia, and who were interested in participating in a naturalistic follow-up study were provided with a complete description of the study and gave written informed consent for participation. We included only patients who met the following criteria at baseline: 1) Panic Disorder Severity Scale (PDSS) total > 7, 2) no current Major Depression, 3) no current or lifetime Bipolar Disorder (BPD). Patients with BPD were excluded for three reasons: the hierarchical position of BPD; the potential implications of treatment with antidepressants in patients with BPD; the heterogeneity of clinical presentation of PD, when a BPD has been diagnosed even in the past.

Fifty seven of the 102 patients meeting criteria for Panic Disorder completed a baseline diagnostic interview and participated in follow-up evaluations at 1, 3, 6 and 12 months. Forty-five patients did not complete the follow-up procedures, for the following reasons: 21 (20.6%) did not complete baseline assessment; and 24 (23.5%) dropped out during the follow-up period, with a mean duration of treatment of 58.3 days (±82.0; range: 1–270). No differences were found between patients who dropped out and patients who completed the 1-year follow-up period, regarding demographic and baseline clinical features.

At baseline, the following clinical variables were collected: age, age at onset, DSM-IV Axis I diagnoses, duration of illness and history of pharmacological treatments. Baseline clinical assessment was completed by the administration of the PDSS.

All patients received an evidence-based psychopharmacological treatment, according to published international standards (AJP guidelines 2000), provided by psychiatrists not involved in the study assessment protocol, and with the supervision of a senior psychiatrist (M.M.). Psychopharmacological treatments are described in Table 1. No psychotherapy was added to pharmacological treatment. Follow-up procedures were approved by the Ethical Committee of the Azienda Ospedaliero-Universitaria of Pisa, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Diagnostic assessment

The diagnostic assessment was carried out using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, APA, 2000) by trained and certified interviewers. Certification was obtained when high levels (>0.90) of inter-rater reliability were achieved.

The Panic Disorder Severity Scale (PDSS) was administered at each time point of the study by raters not involved in treatment. The PDSS is a 7-item interview rating scale utilized to provide an overall rating of severity of panic disorder, including the frequency and severity of panic and limited symptom episodes, severity of anticipatory anxiety, phobic avoidance and functional impairment (Shear et al., 1997).