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Changes in anxiety sensitivity with pharmacotherapy for panic disorder

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Abstract

Fear of anxiety symptoms (anxiety sensitivity) has been implicated in the etiology and maintenance of panic disorder, and has been shown to improve with cognitive-behavioral treatment. The impact of pharmacotherapy on anxiety sensitivity is less clear. We administered the Anxiety Sensitivity Index (ASI) during a 12-week randomized controlled trial investigating the relative efficacy of paroxetine, paroxetine plus sustained clonazepam, and paroxetine plus brief clonazepam for patients with panic disorder. We found a mean reduction in ASI scores of 9.6 points, which correlated with symptomatic improvement, and did not differ significantly between groups. Our data provides further evidence that pharmacotherapy leads to significant acute reductions in fears of anxiety symptoms in patients with panic disorder, albeit at levels that may be somewhat less than the changes associated with CBT. Implications of these findings are discussed relative to optimizing pharmacologic treatment of panic disorder.

Keywords: Anxiety sensitivity; Panic; Pharmacotherapy; Benzodiazepines; ASI; Treatment outcome

1. Introduction

Anxiety sensitivity (AS) is a dispositional construct defined by an excessive fear of anxiety-related sensations, based on beliefs that these sensations are harmful (Reiss, 1991; Reiss and McNally, 1985). Although anxiety sensitivity, as measured by the Anxiety Sensitivity Index (ASI; Reiss et al., 1986) is elevated in a number of anxiety disorders, scores are particularly prominent in panic disorder and agoraphobia, where anxiety sensitivity is thought to contribute to the maintenance and amplification of anxiety symptoms (Taylor et al., 1992; Reiss, 1991). Accordingly, the ASI has been found to be useful for identifying individuals at risk for the emergence (Ehlers, 1995; Schmidt et al., 1997) or re-emergence of panic attacks in prospective, longitudinal studies, as well as in panic prevention programs (Gardenswartz and Craske, 2001).

The ASI is also sensitive to clinical improvement. In a review of the literature, Otto and Reilly-Harrington (1999) identified seven outcome studies providing data on anxiety sensitivity. Based on a weighted average of the 160 participants in these studies, ASI scores dropped an average of 14 points following short-term, therapist-directed cognitive-behavior therapy (CBT). Moreover, preliminary evidence suggests that symptomatic improvement following CBT is mediated by a reduction in fear of anxiety-related symptoms (Smits et al., in press). Two studies of patients undergoing benzodiazepine discontinuation indicated high ASI scores despite control of panic (Fava et al., 1994; Bruce et al., 1995). Upon taper of these medications in the context of treatment with CBT, ASI scores decreased significantly. In one trial, the degree of change in ASI was linked with protection from relapse; patients who had greater ASI change scores with CBT were less likely to relapse (Bruce et al., 1995). These findings underscore contemporary accounts of panic disorder emphasizing that a

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change in fear of anxiety related symptoms is critical for panic disorder symptom reduction (Barlow, 1988; Clark, 1986; Goldstein and Chambless, 1978; McNally, 1994).

Considering their respective treatment rationales, one might expect that pharmacotherapy might not operate on anxiety sensitivity as CBT does. Only a few studies have examined changes in anxiety sensitivity during pharmacotherapy. Otto et al. (1995) reported a mean reduction of 6.1 points on the ASI among patients with a principal diagnosis of depression in a longitudinal study receiving fluoxetine. Mavissakalian et al. (1998) reported a mean reduction of 11.4 points in a last-visit-carried-forward analysis, and 20.9 points in a completer sample of panic disorder patients treated with imipramine. Similarly, Perna and colleagues (Romano et al., in press) recently demonstrated the efficacy of citalopram in reducing anxiety sensitivity in a sample of panic disorder patients. They reported a reduction of 9.4 on the ASI over a 6-week treatment period. Taken together, preliminary results suggest that pharmacotherapy is associated with significant reductions in anxiety sensitivity. However, Fava (1996) argued that anxiety sensitivity reduction is not as likely to occur with benzodiazepines. According to Fava, long-term administration of benzodiazepines blocks anxiety symptoms, which decreases the patient's tolerance to anxiety and discomfort.

Building on aforementioned studies, the present study sought to address the following questions regarding the relationship of anxiety sensitivity and pharmacotherapy. First, is there additional evidence supporting the notion that pharmacotherapy leads to significant changes in ASI scores? Second, do ASI scores change differentially with benzodiazepine treatment versus other pharmacotherapy? Finally, does benzodiazepine taper in the context of acute treatment aid further reductions in ASI scores? A recently completed outcome trial (Pollack et al., 2003) provides the ideal context for addressing these questions in the acute treatment phase. In this 12-week randomized trial, Pollack et al. (2003) examined outcome for panic disorder in patients randomized to one of three groups: paroxetine, paroxetine plus sustained clonazepam, and paroxetine plus brief clonazepam tapered from weeks 5 to 8. Accordingly, the trial provides a context for: (1) examining the general effects of pharmacotherapy on ASI scores; (2) comparing the acute effects of benzodiazepine and non-benzodiazepine treatment on these scores; (3) examining the impact of benzodiazepine taper relative to continued benzodiazepine treatment.

2. Materials and methods

2.1. Participants and methods

Participants, 39 women and 20 men with current panic disorder with or without agoraphobia, were drawn from a randomized controlled trial investigating the relative efficacy of paroxetine, paroxetine plus sustained clonazepam, and paroxetine plus brief clonazepam for patients with panic disorder with or without agoraphobia. Concurrent CBT was an exclusion criterion. Clinicians experienced in the diagnosis and treatment of anxiety and affective disorders used the Structured Clinical Interview for the DSM-IV (First et al., 1996) to establish diagnoses. Patients could have comorbid mood and anxiety disorders, as long as the panic disorder was considered the primary diagnosis (i.e., it was the principal source of a patient's distress and the disorder for which the patient was seeking treatment). This study was conducted in accordance with the latest version of the Declaration of Helsinki and was reviewed by the institutional review board of the Massachusetts General Hospital. Informed consent was obtained from willing participants after a full explanation of study procedures.

2.2. Measures

2.2.1. Anxiety sensitivity index

The ASI is a 16-item scale measuring fears of physical sensations and cognitive fears of loss of control on a 0–4 severity scale per item, with high internal consistency (established coefficient alpha in the range of 0.80–0.90) (Peterson and Reiss, 1992; Taylor et al., 1992). The normative mean is 19, while panic patients have been reported with a mean score of 36.6 (Peterson and Reiss, 1992). In the pharmacotherapy trial, ASI was administered weekly and is here examined at baseline, week 5 just prior to initiation of benzodiazepine taper, and week 12 (or study endpoint). Baseline and week 12 scores were examined in completer analyses while the ASI rating most proximate to endpoint was used in the intent-to-treat analyses.

2.2.2. The panic disorder severity scale

The PDSS was the primary continuous outcome measure for the parent trial of this study. The PDSS consists of seven items assessing multiple dimensions of panic disorder severity: (1) frequency of panic attacks; (2) distress during panic attacks; (3) anticipatory anxiety; (4) agoraphobic fear and avoidance; (5) interoceptive fear and avoidance; (6) impairment of work functioning; (7) impairment of social functioning. Interrater reliability has been found to be adequate (0.87) when assessed in the context of use in a controlled outcome study (Shear et al., 1997) and two-day test-retest reliability has been reported as 0.71 (Shear et al., 2001).

2.3. Statistical analyses

Paired *t*-tests were used to examine mean change in ASI across treatment. Group differences were examined