Psychiatry Research 269 (2018) 251–257

Contents lists available at ScienceDirect

Psychiatry Research

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

The clinical correlates of comorbid anxiety symptoms and syndromal anxiety in patients with major depressive disorder

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ABSTRACT

This study explored the magnitude and clinical correlates of anxiety in three groups of patients with major depressive disorder (MDD): those with comorbid anxiety disorders (the COM group), those with subthreshold core anxiety disorder symptoms that are the screening items for anxiety disorders on the MINI (the SUB group), and those with neither anxiety disorders nor subthreshold core anxiety disorder symptoms (the NON group). Anxiety symptomatology of 1052 patients from 8 psychiatric settings in mainland China, who met DSM-IV TR criteria for MDD, was assessed using the MINI. The presence of core anxiety symptoms was determined by patient endorsement of any screening item of panic disorder, agoraphobia, social anxiety disorder, or generalized anxiety disorder. The prevalences of comorbid subthreshold core anxiety symptoms and anxiety disorders were 13% and 28.7%, respectively. The SUB and COM cases showed similar patterns of clinical presentation. Both were more likely than the NON cases to be characterized by younger age, concurrent dysthymia and OCD, suicidal ideation and attempted suicides. These findings highlight the importance of assessing both anxiety symptoms and anxiety disorders in the presence of MDD, and suggest the need for novel assessments capable of addressing different levels of anxiety in depressed patients.

1. Introduction

A growing number of studies based on community and clinical samples have reported that patients with major depressive disorder (MDD) experience a high level of co-occurring anxiety symptoms and/or at least one anxiety disorder. For example, in a European community-based study Braam et al. (2014) reported that up to 86.2% of participants with late life depression endorsed at least three distinct anxiety symptoms (Braam et al., 2014). Fava et al. reported 45.1% ~ 53.2% of patients with MDD had significant anxiety, recording scores of 7 or above on the Anxiety/Somatization factor of the 17-Item Hamilton Rating Scale for Depression (HRSD-17) (Fava et al., 2004; Fava et al., 2008; Fava et al., 2006). The proportion with anxiety symptoms was even higher (~70%) among Chinese patients with treatment-resistant depression (Wu et al., 2013).

Studies investigating comorbidity of anxiety disorders with MDD have also revealed high rates of co-occurrence. The National Comorbidity Survey Replication study found that 57.5% of participants with 12-month MDD had at least one comorbid anxiety disorder (Kessler et al., 2007). High one-month prevalence (63%) of comorbid mood and anxiety disorders in Chinese community populations (Phillips et al., 2009) has also been reported. For clinical populations with MDD, 42.3% in the STAR*D population (Howland et al., 2009), and 60.2% (Li et al., 2012) and 68.9% (Shi et al., 2009) in two Chinese clinical populations presented with comorbid anxiety disorders. Unsurprisingly then, comorbid anxiety at both the syndromal level and dimensional level has become an increasingly popular theme in depression research.

The importance of recognizing and diagnosing comorbid anxiety among those with MDD is demonstrated by the findings of studies that have compared MDD patients without anxiety symptoms ('*pure*' MDD) to those of MDD patients with any level of comorbid anxiety. These studies have found that relative to those in the former group, patients in the latter group are characterized by clinical features such as higher illness severity (Cyranowski et al., 2012; Fava et al., 2006; Howland et al., 2009; Johansson et al., 2013), adverse socio-demographic characteristics like unemployment and lower education level (Fava et al., 2006), poorer functioning (Gili et al., 2013), higher disability

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https://doi.org/10.1016/j.psychres.2018.07.019
Received 3 November 2017; Received in revised form 1 July 2018; Accepted 11 July 2018

(Bonham and Uhlenhuth, 2014), lower quality of life (Johansson et al., 2013; Mittal et al., 2006), and a tendency to worse outcomes (Fava et al., 2008; Howland et al., 2009; Penninx et al., 2011; van Beljouw et al., 2010; Wu et al., 2013). Results of these studies indicate that anxiety, determined by dimensional approaches, could be clinically useful in differentiating between depressed patients with and without anxiety (Braam et al., 2014; Fava et al., 2006; Gili et al., 2013). This proposition is supported by studies showing that the newly developed dimensional measure, the anxious distress specifier for depression in DSM-5, has been reliably used in assessing anxiety in depressed patients with or without anxiety disorders (Zimmerman et al., 2017a; Zimmerman et al., 2017b) and was more likely to be associated with higher prevalence of comorbid generalized anxiety disorder (GAD), panic disorders (PD), agoraphobia and social phobia (Gaspersz et al., 2017; Rosellini et al., 2018). However, dimensional measures of anxiety are usually based on general and nonspecific anxiety symptoms that are not identical to core features of specific anxiety disorders (e.g. panic attack, social anxiety, or agrophobic symptoms). The extent to which dimensional approaches could convey information accounted for by the presence of comorbid anxiety disorders remains unknown.

Although any level of comorbid anxiety is associated with the negative outcomes in individuals with MDD outlined above, syndromal/diagnostic comorbid anxiety is argued to be a more robust predictor of these clinical features than anxiety symptoms that do not meet diagnostic criteria. This may be because comorbidity of anxiety disorders and MDD may be a separate illness entity due to its differential illness trajectory from pure anxiety disorders and pure depression (Penninx et al., 2011). However, contrary to the assumption that MDD, anxiety disorders and comorbid anxiety-depression are different illness categories, the recently developed network perspective provides new insights in understanding comorbidity of MDD and anxiety disorders at the symptom level. It hypothesizes that MDD and anxiety disorders, rather than distinct illness entities, are substantially intertwined via symptoms that bridge the two disorders within a psychopathological network. Comorbidity of mental disorders arises when these bridging symptoms spread activation from one disorder to the other (Cramer et al., 2010; Fried and Nesse, 2015; Fried et al., 2017). For instance, it was reported that anxiety and depression domains in patients with comorbid GAD and MDD were linked by two strongly interconnected symptoms, interest loss and generalized anxiety, core symptoms of MDD and GAD, respectively. This suggests that there might be fuzzy boundaries between the two diagnostic categories (Cramer et al., 2010). The network perspective raises the challenge of making separate diagnoses of anxiety disorders and MDD in comorbid conditions and highlights the need to explore the clinical significance of comorbid anxiety at the symptom level in patients with MDD.

Furthermore, making comorbid diagnoses in real world settings is far from simple, especially when the mental health practitioner is inexperienced or the primary care physician has limited psychiatric knowledge. As a result, comorbidity of anxiety symptoms and disorders with MDD may be the most frequently undetected diagnosis in routine clinical practice (Zimmerman and Mattia, 1999). Underdiagnosis of comorbidity is exacerbated in areas of the world where psychiatric care is not readily available, or in regions where mental illness continues to carry cultural stigmas. In China for example, there is not only a paucity of research on the prevalence of comorbid anxiety disorders in patients with MDD, but also widespread neglect of anxiety disorders in clinical settings. In the busy environment of clinical settings in China, psychiatrists usually do not ask patients about anxiety symptoms when making a diagnosis of depression. Or in rare cases at best, they may make an informal diagnosis of 'depression with anxiety symptoms' or 'depression with anxious state' and simply prescribe anxiolytics in combination with antidepressants (Wu and Fang, 2014). As we have previously argued (Wu and Fang, 2014), the lack of careful assessment of comorbid anxiety disorders may seriously diminish the effectiveness of treatments for MDD in China . The introduction of routine thorough assessment of comorbid anxiety symptoms in the presence of MDD should help ameliorate underdiagnosis and inadequate assessment of anxiety in patients with MDD.

Even when diagnostic criteria are formally applied, only MDD patients who present with a certain number of symptoms of anxiety disorders may obtain diagnoses of comorbidity. However as such diagnoses are based on binary ('yes' or 'no') diagnostic criteria, they do not convey key clinical information of patients with MDD who do not meet the specified criteria for anxiety disorders, but have symptoms of anxiety disorders. For example, if a patient with MDD reports panic attack but does not meet other criteria for panic disorder, he/she cannot be diagnosed with comorbid panic disorder. In such a case, panic attack and its potential clinical significance may be missing. This is of concern because as reported above, compared to those without anxiety, distinctive clinical features (Fava et al., 2006; Gili et al., 2013; Johansson et al., 2013) and worse outcomes (Fava et al., 2008; Wu et al., 2013) have been reported in patients with comorbid symptomal/subthreshold anxiety and MDD. Furthermore, subthreshold anxiety symptoms (particularly, core symptoms of anxiety disorders) in a prodromal stage of full-fledged disorders may increase vulnerability to a specific anxiety disorder and/or a major depressive episode. For example, it has been reported that panic attack detected in non-psychiatric late adolescents predicted onset of both panic disorder and MDD in their early adulthood (Wolitzky-Taylor et al., 2014). Further evidence is provided in Batterham et al. (2013) study which explored the effects of 18 anxiety and depression symptoms assessed by the Goldberg Depression and Anxiety Scales on risk for subsequent onset of MDD and suicidal ideation in a 4-year follow-up community-based cohort study. They found anxiety symptoms (in particular, worrying) even contributed greater risk for both depression onset and suicidal ideation than core depressive symptoms did (e.g. interest loss) (Batterham et al., 2013). It is possible that these core anxiety symptoms persist but do not evolve into fully-fledged disorders in the presence of MDD yet influence the presentation and outcomes of MDD. To our knowledge, aside from these few studies, there is a paucity of research investigating the magnitude and clinical correlates of subthreshold anxiety disorders in the absence of full-fledged disorders in patients with MDD. Clearly, more research is needed in this area.

In the present study, we aimed to identify and compare the magnitude and clinical correlates of anxiety in three groups of patients with MDD: (1) those with core symptoms of anxiety disorders (subthreshold anxiety disorders), determined by the presence of screening items of panic disorder (PD), agoraphobia without panic attack, social anxiety disorder (SAD) and GAD in the absence of full disorders on the Mini-International Neuropsychiatric Interview (the MINI) [the SUB group], (2) those with syndromal/diagnostic level comorbid anxiety disorders [the COM group], (3) those with neither core anxiety symptoms nor anxiety disorders [the NON group]. We defined subthreshold anxiety disorders by core anxiety symptom endorsement for several reasons. First, those symptoms are common and more easily identified than anxiety disorders in patients with MDD. Second, core anxiety symptoms may impact on illness trajectory of MDD due to their predictive value for onset of both MDD and anxiety disorders. Finally, these symptoms represent core features of specific anxiety disorders and they may influence the current presentation of MDD, even without evolving into fully-fledged disorders. We hypothesized that both SUB and the COM cases would have differential clinical meaningfulness compared to the NON cases.

2. Methods

2.1. Participants

Data in this preliminary report were derived from participants consecutively enrolled into the screening stage of the *Algorithm Guided Treatment Strategies for Major Depressive Disorder (AGTs-MDD)*,