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Anxious distress predicts subsequent treatment outcome and side effects in depressed patients starting antidepressant treatment

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ABSTRACT

Evidence has shown that the DSM-5 anxious distress specifier captures a clinically valid construct that predicts a worse clinical course. Although of importance for treatment planning and monitoring, however, the specifier's ability to predict treatment outcome is unknown. This is the first study to examine the ability of the DSM-5 anxious distress specifier to predict treatment response and side effects in depressed patients who recently initiated antidepressant treatment. Patients were from the Netherlands Study of Depression and Anxiety, an ongoing longitudinal cohort study. Baseline, 1-year and 2-year follow-up data were used from 149 patients (18–65 years) with current Major Depressive Disorder (MDD) who recently started adequately dosed antidepressant medication. Five self-report items were used to construct the DSM-5 anxious distress specifier. Treatment outcomes were depression severity after 1 year and 2 years, remission of MDD after 2 years and antidepressant side effects during treatment. For comparison, analyses were repeated for comorbid DSM-IV-based anxiety disorders as a predictor. In depressed patients who received antidepressant treatment, the anxious distress specifier (prevalence = 59.1%) significantly predicted higher severity (1 year: B = 1.94, $P = 0.001$; 2 years: B = 1.63, $P = 0.001$), lower remission rates (OR = 0.44, $P = 0.0496$) and greater frequency of side effects (≥4 vs. 0: OR = 2.74, $P = 0.061$). In contrast, the presence of comorbid anxiety disorders did not predict these treatment outcomes. The anxious distress specifier significantly predicts poorer treatment outcomes as shown by higher depression severity, lower remission rates, and greater frequency of antidepressant side effects in patients with MDD on adequate antidepressant treatment. Therefore, this simple 5-item specifier is of potential great clinical usefulness for treatment planning and monitoring in depressed patients.

1. Introduction

Major depressive disorder (MDD) is among the most disabling disorders worldwide (Mathers and Loncar, 2006; Murray and Lopez, 1997), yet the heterogeneity of the MDD diagnosis has not been reflected in approaches to classification, diagnosis and treatment (Parker, 2005; Carragher et al., 2009; Lamers et al., 2010). A body of evidence has underscored the clinical importance of the concept of anxious depression, as it is associated with greater symptom severity, chronicity of MDD and greater functional disability (Goldberg and Fawcett, 2012). Moreover, anxious depression was found to be associated with poorer treatment outcomes (Davidson et al., 2002; Fava et al., 2008; Wu et al., 2013; Ionescu et al., 2014; Domschke et al., 2010a) and with a higher rate and burden of side effects (Fava et al., 2008; Wu et al., 2013; Ionescu et al., 2014), although these results were not found in all studies (Tollefson et al., 1994; Nelson, 2010; Russell et al., 2001). A review by Ionescu and colleagues suggested that anxious depression is more difficult to treat. (Ionescu et al., 2014). This may be the result

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of an underlying differential biological profile of anxious depression (Ionescu et al., 2013) or due to trait anxiety which is difficult to treat with current interventions. The lack of a uniform definition of anxious depression in the literature has made comparisons of results across studies difficult. However the introduction of the anxious distress specifier in DSM-5 (American Psychiatric Association, 2013) may help overcome this problem.

Two studies have shown that the DSM-5 anxious distress specifier is a reliable and valid measure, with significant discriminant and convergent validity (Zimmerman et al., 2014; Gaspersz et al., 2016). Our previous work has shown that the specifier is longitudinally predictive of a worse clinical course and outcomes in a large cohort of depressed persons. Furthermore, it has shown that the specifier outperforms comorbid DSM-IV-based anxiety disorder diagnoses as a longitudinal predictor (Gaspersz et al., 2016). Since the introduction of the anxious distress specifier, no studies have evaluated whether depressed patients meeting the DSM-5 specifier have differential treatment response. If the specifier is found to be predictive of worse treatment outcomes, then it is of great clinical usefulness for treatment planning and monitoring in depressed patients with significant anxiety.

Our previous work aimed to test the longitudinal validity of the DSM-5 anxious distress specifier and validated it against comorbid DSM-IV-based anxiety disorder diagnoses in a large cohort of depressed persons (N = 1080) regardless of treatment status (Gaspersz et al., 2016). We now aim to examine whether the DSM-5 anxious distress specifier predicts treatment outcomes and frequency of side effects in a group of patients with MDD on recently initiated adequate antidepressant treatment, and how the predictive validity is compared to that of comorbid DSM-IV-based anxiety disorders.

2. Methods

2.1. Study sample

Participants were selected from The Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008), an ongoing longitudinal cohort study designed to examine the long-term course of depressive and anxiety disorders. A total of 2981 participants (18–65 years) were included in the baseline assessment (2004–2007), consisting of healthy controls (n = 652; 22%) and participants with a past or current depressive and/or anxiety disorder (n = 2329; 78%). Recruitment took place in the community (19.0%), primary care (54.0%), and specialized mental health care settings (27.0%), reflecting different settings and stages of psychopathology. Uniform inclusion and exclusion criteria were used. Patients with an age of 18 through 65 years were included. Patients with a primary clinical diagnosis of a psychiatric disorder other than depressive or anxiety disorders, and those not fluent in Dutch were excluded. At baseline and at 2-year follow-up (n = 2596; 87.1%), data were obtained by trained research staff during a broad assessment, consisting of a face-to-face interview, self-reported questionnaires, a medical examination and cognitive computer tasks. In addition, antidepressant medication use was recorded based on inspection of participants' prescription drug containers, which were brought to the interview (75.2%, n = 112 patients). Only when drug containers were not brought in, did we rely on self-report (which, if felt necessary, was also re-checked by later inspection of drug container labels during phone contact). In the Netherlands, all drug containers are provided with a registered label that shows the patient's name, the prescriber name, frequency and dose of the drug as a standard procedure by all pharmacies. Data of 1-year follow-up (n = 2445; 82.0%) were acquired by a self-reported questionnaire including measures of depression symptom severity and medication use. The research protocol was approved by the ethics committees of all participating universities and all participants provided written informed consent after the study procedures were fully explained. The rationale, objectives and recruitment strategy of the NESDA study can be found elsewhere (Penninx et al., 2008).

We aimed to include patients with new-onset MDD episodes and a recent start of antidepressant treatment to optimally determine treatment outcomes. We achieved this by carefully selecting timeframes to include patients who are most likely to meet these criteria. First, we selected patients with a current diagnosis of MDD (defined by the 6-month recency criteria on the CIDI assessment) at baseline. Second, of these current cases, we selected only patients who recently started a) around baseline (but were not on medication long enough to expect a therapeutic effect at baseline) or b) started antidepressant treatment in the period from baseline to 2-year follow-up. Third, we included only patients with an adequate dose and duration of use (i.e. an adequate Defined Daily Dose [DDD] of $\geq$1 and a minimum duration of antidepressant use of $\geq$3 months; see also next section), in order to insure selection of patients for whom a therapeutic effect could be expected (see Supplementary Fig. S1). At baseline and follow-up, the Composite International Diagnostic Interview (CIDI) version 2.1 (World Health Organization, 1997) was used to assess a diagnosis of MDD according to DSM-IV algorithms. At each assessment, medication was coded according to the Anatomical Therapeutic Chemical (ATC) classification (World Health Organization, 2007). Antidepressants were classified as selective serotonin reuptake inhibitors (SSRIs, ATC-code N06AB), tricyclic antidepressants (TCA, ATC-code N06AA) and other antidepressants (ATC-code N06AF/N06AG/N06AX). Antidepressant dosages were expressed in WHO DDD, which is the assumed average maintenance dose per day for a drug used for its main indication in adults (World Health Organization Collaborating Centre for Drug Statistics Methodology, 2012). Duration of antidepressant use was assessed in months between baseline and 2-year follow-up.

Adequate antidepressant treatment was defined as frequent use of an antidepressant with a DDD of $\geq$1 and a total duration of antidepressant use of $\geq$3 months in the period around baseline to 2-year follow-up. Patients who already fulfilled the duration criterion (i.e. $\geq$3 months) for the adequate antidepressant treatment definition at baseline were excluded from the analyses, as treatment outcome is most reliably evaluated among patients who recently initiated treatment. By using this approach, all long-term antidepressant users were excluded, as well as patients with suboptimal dosages of antidepressants, for whom treatment outcomes cannot be interpreted accurately. Furthermore, the recent onset of both the MDD episode and the start of treatment makes the assumption that the antidepressant medication was prescribed specifically for that particular MDD episode fairly strong. We were then able to optimally determine treatment outcomes subsequently in a group of patients with depression who recently initiated antidepressant medication at an adequate dose.

Of the 2981 participants included in the NESDA study, 1115 participants had a current (past 6 months) MDD diagnosis at baseline, of which 1090 participants had enough information present to construct the anxious distress specifier. Of these 1,090, 53.3% (581 persons) frequently used an antidepressant in the period from baseline to 2-year follow-up. Three hundred fifty-one of these patients already met the duration criterion of $\geq$3 months of antidepressant treatment at baseline (and thus were considered long-term users) and were therefore excluded. Of the remaining 230 patients, 168 patients initiated adequate antidepressant treatment between baseline and 2-year follow-up and met all inclusion criteria of this study. Of these, 19 patients had missing