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Assessing anxious features in depressed outpatients

Shawn M. McClintock^{1,2}, Mustafa M. Husain¹, Ira H. Bernstein³, Stephen R. Wisniewski⁴, Madhukar H. Trivedi¹, David Morris¹, Jonathan Alpert⁵, Diane Warden¹, James F. Luther⁴, Susan G. Kornstein⁶, Melanie M. Biggs^{1,7}, Maurizio Fava⁵, and A. John Rush⁸

¹Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

²Department of Psychiatry, Columbia University/New York State Psychiatric Institute, New York, USA

³Department of Clinical Science, University of Texas Southwestern Medical Center, Dallas, TX, USA

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Correspondence: Shawn M. McClintock, Department of Psychiatry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390–8898, USA. Telephone: (+1) 214-648-2806, Fax (+1) 214-648-8030, shawn.mcclintock@utsouthwestern.edu.

Declaration of interest statement

Dr Alpert has served as in the advisor/consultative relationship role with Eli Lilly & Company, PamLab LLC, and Pharmavite LLC. Dr Biggs has served as a consultant for Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck, and Pfizer. Dr Fava has provided scientific consultation to or served on the Advisory Boards for Aspect Medical Systems, Astra-Zeneca, Bayer AG, Biovail Pharmaceuticals, Inc., BrainCells, Inc. Bristol-Myers Squibb Company, Cephalon, Compellis, Cypress Pharmaceuticals, Dov Pharmaceuticals, Eli Lilly & Company, EPIX Pharmaceuticals, Fabre-Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals Inc., GlaxoSmithKline, Grunenthal GmbH, Janssen Pharmaceutica, Jazz Pharmaceuticals, J & J Pharmaceuticals, Knoll Pharmaceutical Company, Lundbeck, MedAvante, Inc., Neuronetics, Novartis, Nutrition 21, Organon Inc., PamLab, LLC, Pfizer Inc, PharmaStar, Pharmavite, Roche, Sanofi/Synthelabo, Sepracor, Solvay Pharmaceuticals, Inc., Somaxon, Somerset Pharmaceuticals, Wyeth-Ayerst Laboratories. He has been on speaker bureaus for Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithKline, Novartis, Organon Inc., Pfizer Inc, PharmaStar, Wyeth-Ayerst Laboratories. He has received research/grant support from Abbott Laboratories, Alkermes, Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., Glaxo-SmithKline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Novartis, Organon Inc., PamLab, LLC, Pfizer Inc, Pharmavite, Roche, Sanofi/ Synthelabo, Solvay Pharmaceuticals, Inc., Wyeth-Ayerst Laboratories. He has equity holdings in Compellis, MedAvante. Dr Husain has served on Advisory Boards for Astra-Zeneca, VersusMed, Avinar, Boston Scientific, MEASURE, Bristol-Meyer-Squibb, and Clinical Advisors and on speakers bureaus for Cyberonics, Inc., Avinar, Inc., Cerebrio, Inc., AstraZeneca, Bristol-Meyers- Squibb, Optima/Forrest Pharmaceuticals, Glaxo-Smith-Kline, Forrest Pharmaceuticals, and Janssen. Dr Kornstein has served on Advisory Boards/received honoraria from Pfizer, Inc., Wyeth, Inc., Lilly, Inc., Bristol-Myers Squibb Company, Warner-Chilcott, Inc., Biovail Laboratories, Berlex Laboratories, Forest Laboratories, Neurocrine, and Sepracor, Inc. She has received book royalties from Guilford Press. Dr Morris has been a consultant for Pfizer. Dr Rush has provided scientific consultation to or served on Advisory Boards for Advanced Neuromodulation Systems, Inc.; Best Practice Project Management, Inc.; Bristol-Myers Squibb Company; Cyberonics, Inc.; Forest Pharmaceuticals, Inc.; Gerson Lehman Group; GlaxoSmithKline; Jazz Pharmaceuticals; Eli Lilly & Company; Merck & Co., Inc.; Neuronetics; Ono Pharmaceutical; Organon USA Inc.; Personality Disorder Research Corp.; Pfizer Inc.; The Urban Institute; and Wyeth-Ayerst Laboratories Inc. He has received royalties from Guilford Press and Healthcare Technology Systems and research/grant support from the Robert Wood Johnson Foundation, the National Institute of Mental Health, and the Stanley Foundation; has been on speaker bureaus for Cyberonics, Inc., Forest Pharmaceuticals Inc., Glaxo-SmithKline, and Eli Lilly & Company; and owns stock in Pfizer Inc. Dr Trivedi has received research support from Bristol-Myers Squibb Company; Cephalon, Inc.; Concept Therapeutics, Inc.; Cyberonics, Inc.; Eli Lilly & Company; Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutica; Merck; National Institute of Mental Health; National Alliance for Research in Schizophrenia and Depression; Novartis; Pfizer Inc.; Pharmacia & Upjohn; Predix Pharmaceuticals; Solvay Pharmaceuticals, Inc.; and Wyeth-Ayerst Laboratories. He has served on Advisory Boards for or provided consultation to Abbott Laboratories, Inc.; Akzo (Organon Pharmaceuticals Inc.); Bayer; Bristol-Myers Squibb Company; Cephalon, Inc.; Cyberonics, Inc.; Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutica Products, LP; Johnson & Johnson PRD; Eli Lilly & Company; Meade Johnson; Parke-Davis Pharmaceuticals, Inc.; Pfizer, Inc.; Pharmacia & Upjohn; Sepracor; Solvay Pharmaceuticals, Inc.; and Wyeth-Ayerst Laboratories and has been on speaker's bureaus for Akzo (Organon Pharmaceuticals Inc.); Bristol-Myers Squibb Company; Cephalon, Inc.; Cyberonics, Inc.; Forest Pharmaceuticals; Janssen Pharmaceutica Products, LP; Eli Lilly & Company; Pharmacia & Upjohn; Solvay Pharmaceuticals, Inc.; and Wyeth-Ayerst Laboratories. Dr. Warden currently owns stock in Pfizer and previously owned stock in Bristol Myers Squibb. Dr Wisniewski has served as a consultant for Cyberonics Inc. (2005–2005) and ImaRx Therapeutics, Inc. (2006). The remaining authors report no competing interests.

⁴Epidemiology Data Center Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

⁵Massachusetts General Hospital, Harvard University, Boston, MA, USA

⁶Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA

⁷Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

⁸Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

Abstract

Both the 17-item Hamilton Rating Scale for Depression (HRSD₁₇) and 30-item Inventory of Depressive Symptomatology – Clinician-rated (IDS-C₃₀) contain a subscale that assesses anxious symptoms. We used classical test theory and item response theory methods to assess and compare the psychometric properties of the two anxiety subscales (HRSD_{ANX} and IDS-C_{ANX}) in a large sample ($N = 3453$) of outpatients with non-psychotic major depressive disorder in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Approximately 48% of evaluable participants had at least one concurrent anxiety disorder by the self-report Psychiatric Diagnostic Screening Questionnaire (PDSQ). The HRSD_{ANX} and IDS-C_{ANX} were highly correlated ($r = 0.75$) and both had moderate internal consistency given their limited number of items (HRSD_{ANX} Cronbach's alpha = 0.48; IDS-C_{ANX} Cronbach's alpha = 0.58). The optimal threshold for ascribing the presence/absence of anxious features was found at a total score of eight or nine for the HRSD_{ANX} and seven or eight for the IDS-C_{ANX}. It would seem beneficial to delete item 17 (loss of insight) from the HRSD_{ANX} as it negatively correlated with the scale's total score. Both the HRSD_{ANX} and IDS-C_{ANX} subscales have acceptable psychometric properties and can be used to identify anxious features for clinical or research purposes.

Keywords

depression; anxiety; rating scales; STAR*D; measurement-based care

Introduction

Major depressive disorder (MDD) has a lifetime prevalence rate of 15% to 20% and is a significant cause of disability worldwide (Murray and Lopez, 1996; McKenna *et al.*, 2005; Moussavi *et al.*, 2007). Individuals with MDD often have anxiety and sympathetic nervous system arousal, which characterizes anxious symptom features. Although depression with anxious features is not codified in the DSM-IV-TR (American Psychiatric Association, 2000), it has been defined in the literature as either MDD with high levels of anxiety symptoms, or the concurrent (not lifetime) presence of depression and anxiety (Fava *et al.*, 2004).

Anxiety disorders are frequently comorbid with MDD. Studies have found comorbid anxiety (lifetime) in 60% to 65% of individuals with MDD in a community sample (Kessler *et al.*, 1996) and comorbid anxiety disorder in 59.2% of individuals with MDD based on DSM-IV criteria (Kessler *et al.*, 2003). In clinical trial populations, prevalence rates of concurrent (not lifetime) anxious features of approximately 40% to 60% have been documented. Thus, roughly half of all patients who have MDD experience anxious symptoms and consequently suffer from increased levels of impairment (Fava *et al.*, 2004; Lydiard and Brawman-Mintzer, 1998).

While no standard measure exists for systematically identifying depressed outpatients with “anxious features” (Bramley *et al.*, 1988), the six-item anxiety/somatization factor within the 17-item Hamilton Rating Scale for Depression (HRSD₁₇) (Hamilton, 1960, 1967; Cleary and Guy, 1977) has been used to assess anxiety as it contains items that measure psychic and somatic anxiety symptoms (Fava *et al.*, 2008). However, no studies to date have assessed the psychometric properties of this anxiety/somatization factor (HRSD_{ANX}) in depressed patients with and without anxious features (Bagby *et al.*, 2004). The 30-item Inventory of Depressive Symptomatology – Clinician-rated (IDS-C₃₀) (Rush *et al.*, 1986, 1996) also assesses anxious features through the inclusion of items that assess anxious mood, somatic complaints, and sympathetic arousal. Again, no psychometric studies have yet assessed the anxiety subscale (IDS-C_{ANX}).

The current study assessed the psychometric performance of both the HRSD_{ANX} and the IDS-C_{ANX} in depressed outpatients enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. We hypothesized that both scales would have satisfactory psychometric properties.

Materials and methods

Study overview

The STAR*D study aimed to define prospectively the comparative effectiveness of several antidepressant treatments in individuals with non-psychotic MDD who have an unsatisfactory clinical outcome to an initial and, if necessary, subsequent treatment(s) (Fava *et al.*, 2003; Rush *et al.*, 2004).

Fourteen Regional Centers oversaw the STAR*D study, which was conducted at 18 primary and 23 psychiatric care settings. The STAR*D protocol was developed in accordance with the principles of the Declaration of Helsinki and was approved and monitored by the study’s National Coordinating Center (University of Texas Southwestern Medical Center, Dallas, TX), Data Coordinating Center (University of Pittsburgh Epidemiology Data Center, Pittsburgh, PA), the institutional review boards at each Clinical Site and Regional Center, and the Data Safety and Monitoring Board of the National Institute of Mental Health (NIMH; Bethesda, MD). Prior to enrollment, all potential risks, benefits, and adverse events associated with STAR*D participation were explained and a written informed consent was obtained from each participant.

Study population

STAR*D enrolled 4041 outpatients from across the United States, 18 to 75 years of age, who were diagnosed with non-psychotic MDD (based on the Mini-International Neuropsychiatric Interview (Sheehan *et al.*, 1998) and had a baseline HRSD₁₇ score ≥ 14 (moderate severity). Patients were excluded if they had schizophrenia, schizoaffective disorder, bipolar disorder, anorexia nervosa, a current primary diagnosis of bulimia nervosa or obsessive-compulsive disorder, psychiatric disorders or substance abuse that required immediate hospitalization, general medical conditions or concomitant medications that contraindicated the use of protocol treatments in the first two treatment steps, were using a targeted psychotherapy for depression, or had a well-documented history of non-response or intolerance (in the current major depressive episode) to one or more of the protocol treatments in the first two treatment steps. The study also excluded patients who were breastfeeding, pregnant, or trying to become pregnant.

Assessment measures

Sociodemographic and clinical data were collected at the screening/baseline visit. Participants completed the self-report Psychiatric Diagnostic Screening Questionnaire (PDSQ) (Zimmerman and Mattia, 1999) to identify the following concurrent anxiety disorders: Generalized Anxiety Disorder, Panic Disorder, Post-Traumatic Stress Disorder, Social Phobia, Obsessive-Compulsive Disorder, and Agoraphobia (Zimmerman and Mattia, 1999, 2001; Castel *et al.*, 2007; Gibbons *et al.*, 2009). The presence of each disorder was determined based on the specific PDSQ subscales (each PDSQ subscale has an 89% sensitivity and 97% negative predictive value), which have been found to be valid for assessing DSM Axis-I categories (Gibbons *et al.*, 2009; Rush *et al.*, 2005). Within 72 hours of the screening/baseline visit, trained Research Outcome Assessors (ROAs), who were masked to treatment and to the results of the PDSQ, conducted telephone interviews to complete the HRSD₁₇ and the IDS-C₃₀. A study by Rush *et al.* (2006a) found the telephone interview format of the HRSD₁₇ and the IDS-C₃₀ to be reliable and valid.

Defining anxious features

For this report, we defined the presence of anxious features as a minimum of one anxiety diagnosis based on the PDSQ (Zimmerman and Mattia, 1999). The HRSD_{ANX} was based on the analyses of Cleary and Guy (1977), while the IDS-C_{ANX} was based on prior analyses (Gullion and Rush, 1998; Bernstein *et al.*, 2006) and expert consensus.

Statistical analysis

Data for these analyses were obtained by the ROA at baseline and at exit from the first treatment trial with one antidepressant medication (citalopram) (Rush *et al.*, 2006b). Only those participants ($N = 3453$) who were not on any antidepressant medications at baseline were included in the analyses. Summary statistics were used to describe the sociodemographic and clinical characteristics of the sample. Means and standard deviations are presented for continuous variables; percentages are presented for discrete variables. The association between sociodemographic and clinical characteristics and the number of anxiety comorbidities was estimated using a Poisson regression model that was adjusted for dispersion. Results were interpreted based on standard guidelines for acceptable psychometric properties (Nunnally and Bernstein, 1994). A p -value of < 0.05 indicated a significant association.

To identify a possible threshold on the HRSD_{ANX} and IDS-C_{ANX} subscales for the identification of anxious features, sensitivity and specificity were calculated when comparing each subscale total to the presence of anxiety (yes/no). Receiver operating characteristic (ROC) curves were generated from the sensitivity and specificity estimates.

Similar to other investigations (Bernstein *et al.*, 2007, 2009), data were analyzed using both classical test theory (CTT) (Nunnally and Bernstein, 1994) and modern test theory (item response theory, IRT) (Embretson and Reise, 2000). CTT's key outputs are the item means, which define level of response, and item/total correlations (r_{it}), which define the strength of relation between the item and the scale, plus the scale mean, scale standard deviation and a measure of internal consistency reliability, usually Cronbach's alpha. CTT assumes the dimension to be assessed (anxiety in the present case) is the sum of the item scores, whereas IRT views the dimension as a latent variable to be inferred. The two are complementary. Although CTT rests upon more familiar constructs so that its results are generally rather easily understood, IRT allows the sensitivity of the test in making discriminations at various levels of the latent variable, focusing on the reliabilities instead of treating it as a constant (the internal consistency, i.e. coefficient alpha) and focusing on the scores as is done in CTT. This analysis involves the test information function (TIF). The Samejima graded

response model (Samejima, 1997) was employed for IRT analysis. IRT was also used to equate scores on the two tests being considered (Lord, 1980; Orlando *et al.*, 2000).

IRT models can use a wide array of response formats (e.g. binary, multiple choice), but the Samejima model specifically assumes a graded response format. Thus, for the purpose of these analyses, we chose the Samejima model as it was designed for tests that employ an ordered series of responses, such as the 0–3 scale of the IDS-C30. It is assumed that the probability of a participant choosing the higher of two response categories is a logistic (S-shaped) function of the latent trait (symbolized “ Θ ”), which for this study represents depression. In this analysis, there are three possible categorizations (0 versus 1, 2, or 3 – normal versus pathological; 0 or 1 versus 2 or 3 – normal and mildly pathological versus moderately or severely pathological; and 0, 1, or 2 versus 3 – normal, mildly pathological, and moderately pathological versus severely pathological). The three categorizations are assumed to produce a common slope but different locations along the anxiety axis. Collectively, these categorizations form category response functions. The slope that is common to the three functions is designated “ a ”. The three locations along the depression axis are designated “ b_1 ”, “ b_2 ”, and “ b_3 ” (“ b ” collectively). A steeper slope indicates a more discriminating item. The higher the values of b , the less likely the more pathological category is chosen, yielding four parameter estimations per item. In view of the six HRSD_{ANX} items and five IDS-C_{ANX} items, the item analysis generates 24 parameter estimates for the former measure and 20 for the latter. These a and b_i parameters are of central interest when groups are being compared to investigate what is known as differential item functioning. However, they are of lesser interest in this one-group design, so they have been omitted. They can be obtained upon request from the first author. The computation of TIF is described in Nunnally and Bernstein (1994) and Embretson and Reise (2000).

The Samejima model does assume that the items define a unidimensional scale. Scale dimensionality was inferred by parallel analysis (Horn, 1965; Humphreys and Ilgen, 1969; Humphreys and Montanelli, 1975; Montanelli and Humphreys, 1976). This involves generating matrices of random normal deviates with the same number of variables and observations as the obtained data. The random data are then factored. In the present case, 50 such random matrices were generated, and the results averaged. The dimensionality of the obtained data is the number of eigenvalues greater than in the randomly generated factors. Specifically, a series of variables is unidimensional if the first eigenvalue it generates is larger than the first eigenvalue of the randomly-generated data but the reverse is true of the second eigenvalue.

Statistical software packages used included SAS (Version 9.1.3, SAS Institute, Cary, NC) for CTT and factor analyses, and MULTILOG (Version 7, Scientific Software International, Lincolnwood, IL) for IRT analyses.

Results

Sociodemographic and clinical characteristics

In our study sample ($N = 3453$), most participants were female and the racial composition was comparable to the US population (US Census Bureau, 2000) (Table 1). Although statistically significant associations were found in sociodemographic and clinical characteristics, many were not clinically meaningful (Tables 1 and 2). Of clinical relevance, participants with anxiety comorbidities had higher rates of unemployment, correspondingly lower monthly household incomes, greater depression severity on both clinician-rated and self-report measures, and were more likely to have attempted suicide.

CTT analysis

Given their brevity, both the HRSD_{ANX} (Cronbach's alpha = 0.48) and the IDS-C_{ANX} (Cronbach's alpha = 0.58) demonstrated modest internal consistency (Table 3). The HRSD17 and the IDS-C30 were highly correlated ($r = 0.89$). The HRSD_{ANX} and the IDS-C_{ANX} were also highly correlated ($r = 0.75$), indicating that they tend to measure the same general construct. One negative feature of the HRSD_{ANX} was that the correlation between item 17 (loss of insight) and the total score was essentially zero at both baseline and exit ($r_s = -0.07$ and -0.15 , respectively), suggesting it is irrelevant to the scale. Disattenuation (correction for unreliability) suggested that virtually all of the systematic variance in each respective test is shared with the other.

The values of item-total correlation (r_{it}), and thus the overall coefficients alpha, increased from baseline to exit for both subscales (Table 3), which is expected given the greater variation among individual items at exit. At baseline, somatic anxiety, somatic symptoms-general and hypochondriasis all contributed to the HRSD_{ANX} scale total, and were joined by psychic anxiety at exit. In fact, the baseline and exit values of r_{it} have a very high correlation of 0.96. The most discriminating IDS-C_{ANX} item at baseline was sympathetic arousal, followed by the nearly equal contribution of panic/phobic symptoms and anxious mood. At exit, the five items were closer to equal, with anxious mood and sympathetic arousal being the two most discriminating items. In general, the correlation between baseline and exit values of r_{it} for the two subscales was relatively similar.

Table 3 shows the change in each item's mean score from baseline to exit (effect sizes), effect sizes in terms of Cohen's $d = \text{mean change}/\text{SD}$, the corresponding values of t testing the null hypothesis that the mean change was zero, and the total HRSD_{ANX} and IDS-C_{ANX} scale scores. Overall, the two scales were similar in effect size (HRSD_{ANX} = 0.81 versus IDS-C_{ANX} = 0.57) and the largest effect size was seen in psychic anxiety and general somatic symptoms on the HRSD_{ANX} and anxious mood on the IDS-C_{ANX}.

All correlations of the HRSD_{ANX} and the IDS-C_{ANX} with the anxiety dimensions of the PDSQ were significant ($p < 0.0001$) (Table 4). Although the correlations between the IDS-C_{ANX} and PDSQ anxiety dimensions were slightly higher than those between HRSD_{ANX} and PDSQ, these differences were modest.

Sensitivity and specificity

Approximately 48% of participants had at least one PDSQ-defined anxiety disorder. ROC curve analyses were estimated for the PDSQ anxiety diagnoses in each subscale (Figure 1) to examine the sensitivity and specificity estimates. The area under the ROC curve (AUC) for the HRSD_{ANX} was 0.656 for 1–5 PDSQ anxiety diagnoses, 0.702 for 2–5 PDSQ anxiety diagnoses, 0.740 for 3–5 PDSQ anxiety diagnoses, and 0.809 for 4–5 PDSQ anxiety diagnoses. For the IDS-C_{ANX}, the AUC was 0.701 for 1–5 PDSQ anxiety diagnoses, 0.758 for 2–5 PDSQ anxiety diagnoses, 0.808 for 3–5 PDSQ anxiety diagnoses, and 0.849 for 4–5 PDSQ anxiety diagnoses. The AUC was greatest when all five anxiety diagnoses of the PDSQ were examined in relation to the HRSD_{ANX} (AUC = 0.833) and IDS-C_{ANX} (AUC = 0.860) range of cut-off scores. The greater area under the curve that is above the line of discrimination, the more valid is the classification system. Sensitivity and specificity in distinguishing depressed participants with and without at least one concurrent anxiety disorder were maximized with a cut-off score of eight or nine for the HRSD_{ANX}, and seven or eight for the IDS-C_{ANX}.

Factor analyses

The obtained first and second eigenvalues were 1.80 and 0.99 for the baseline HRSD_{ANX}, 2.37 and 0.97 for the exit HRSD_{ANX}, 1.99 and 1.018 for the baseline IDS-C_{ANX} and 2.25 and 0.95 for the exit IDS-C_{ANX}. The corresponding simulated eigenvalues were 1.05 and 1.05, 1.06 and 1.03, 1.05 and 1.021, and 1.06 and 1.01. Thus, the obtained first eigenvalue exceeded the simulated first eigenvalue, but the reverse was true for the second eigenvalue. This means that the two measures were unidimensional at both baseline and exit, fulfilling the requirements of the IRT analysis.

IRT analyses

The HRSD_{ANX} was better able to resolve differences in anxiety up to Θ of about 1.0 (Figure 2), which represents the bottom 84% of the sample (in reference to level of anxiety) since the scale for Y is the normal distribution. Beyond this point, the IDS-C_{ANX} was the more sensitive to anxious features. Thus, the HRSD_{ANX} was more sensitive to anxious features in participants with low depression severity, whereas the IDS-C_{ANX} was more sensitive to anxious features in participants with moderate to high depression severity.

Test equating

Test equating involves associating total test scores on each test with values of the dimension under investigation, commonly denoted " Θ ". Total scores on each test that have similar values of Θ derived from the same sample are considered matched. Table 5 contains the matching scores on the HRSD_{ANX} and the IDS-C_{ANX} with their estimated values of Θ .

Discussion

Both the HRSD_{ANX} and IDS-C_{ANX} subscales were found to have adequate psychometric properties and were moderately sensitive indicators of anxious features in depressed outpatients. IDS-C_{ANX} demonstrated a moderate level of internal consistency. The lack of redundancy in the IDS-C_{ANX} items suggests that all are valuable. The high correlation between the subscales supported their concurrent validity, and both showed discriminant ability in identifying patients with anxious features. Factor analytic methods indicated that both scales were unidimensional. The IDS-C_{ANX} had greater sensitivity to anxious features in patients with moderate to severe depression, while the HRSD_{ANX} had greater sensitivity to anxious features in patients with mild depression severity.

CTT and IRT analyses indicated that HRSD_{ANX} item 17 (loss of insight) may be problematic. Its removal improved the measure's Cronbach's alpha coefficient (increased to 0.54), suggesting greater internal consistency among the remaining five items (removal of any of these items lowered alpha between 0.37 and 0.49). Item 17 has been found to have variable internal reliability and poor inter-rater reliability (Bagby *et al.*, 2004). Other investigations of factors on the HRSD₁₇ have also reported mixed results (Fleck *et al.*, 1995; Pancheri *et al.*, 2002). Recent research (Pancheri *et al.*, 2002) suggests that the HRSD₁₇ contains two independent anxiety factors: somatic anxiety (including somatic anxiety, hypochondriasis, somatic energy, appetite, and insomnia symptoms) and psychic anxiety (including psychic anxiety, psychomotor agitation, insight, and guilt). This dispute, however, does not bear upon what we found to be a unidimensional structure of the six anxiety items.

The IDS-C₃₀ has been well validated as a comprehensive measure of depression severity (Rush *et al.*, 1996; Trivedi *et al.*, 2004) with demonstrated significant strengths (e.g. excellent psychometric properties, structured gradient metric, sensitivity to change, and availability of self-report). Bernstein *et al.* (2006) found that the IDS-C₃₀ had two

dimensions, a depressive dimension that consists mainly of core depressive items, and a second dimension containing somatic and anxiety items (e.g. somatic complaints, sympathetic arousal, gastrointestinal complaints). Our investigation confirms that certain items contribute to a somatic/ anxiety domain.

The threshold total score by which to identify anxious features with either subscale depends on the desired ratio between sensitivity (i.e. correctly identifying depressed patients with anxious features) and specificity (i.e. correctly identifying depressed patients without anxious features). Ideally, the threshold should maximize both sensitivity and specificity (Loong, 2003). Based on this paradigm, the thresholds that maximized sensitivity and specificity in this study (based on 69 participants with five or more anxiety disorders) were 8–9 for the HRSD_{ANX} and 7–8 for the IDS-C_{ANX}. The cut-off score previously recommended for the HRSD_{ANX} (Cleary and Guy, 1977) and used in clinical trials was seven (Fava *et al.*, 2004, 2008), which the present study indicates would result in high sensitivity (94.2) but moderate specificity (55.5). This could result in some over-identification of patients with anxious features.

Differences between the HRSD_{ANX} and IDS-C_{ANX}

The HRSD_{ANX} and the IDS-C_{ANX} are unitary measures of anxious features, but these subscales differ in terms of item content (i.e. face validity) and rating metric. The face validity of these scales is different based on their respective item content. Both measure physical and psychic anxious symptoms, but the HRSD_{ANX} includes items related to appetite, energy, and insight, all core depressive features in the DSM-IV-TR (American Psychiatric Association, 2000). Also, Gullion and Rush (1998) reported HRSD₁₇ item 13 (somatic symptoms: general) loaded on the “hedonic capacity” factor, and item 17 (loss of insight) was excluded from their analyses as it was endorsed by less than 25% of the participant sample and could have obscured factor construction. Other studies have also suggested that item 17 does not contribute to the HRSD₁₇ (Bech, 1981; Bech *et al.*, 1981). The present study further suggests that item 17 was poor in discriminating between the presence and absence of anxious features. Thus, the HRSD_{ANX} may have poor face validity, as only two of the six items are related to anxiety. The IDS-C_{ANX} items, however, are representative of symptoms included in DSM-IV-TR anxiety spectrum disorders. These items are germane to anxiety, somatic and phobic symptoms, and demonstrate good discriminatory ability (e.g. the removal of any one item from the subscale did not result in a significant change in the Cronbach’s alpha, which indicates its relative importance in the IDS-C_{ANX}).

The HRSD₁₇ and the HRSD_{ANX} weigh items disproportionately by assigning greater weight to psychic anxiety, somatic anxiety and hypochondriacal symptoms. This could be problematic as there is no theoretical or empirical basis for the HRSD_{ANX} item metric-rating assignments. In contrast, the IDS-C_{ANX} assigns equal weight to all items with the rationale that all contribute equally to the total score.

Utility of the HRSD_{ANX} and IDS-C_{ANX}

Both the HRSD_{ANX} and the IDS-C_{ANX} would be useful for systematically monitoring anxious features in clinical practice and research studies. Depressed patients with comorbid anxiety may have increased levels of clinical impairment and functional impairment (Fava *et al.*, 2004), and may be less likely to achieve remission with antidepressant medications than depressed patients without anxiety (Fava *et al.*, 1997, 2008). Thus, the monitoring and treatment of anxiety symptoms can enhance clinical practice by optimizing antidepressant therapy and overall clinical outcome (Zimmerman and McGlinchey, 2008). Further, the monitoring of anxiety symptoms is warranted for research studies to address their effects on

therapeutic outcome. Use of the HRSD_{ANX} and IDS-C_{ANX} by clinicians or trained interviewers is feasible (Duffy *et al.*, 2008) and may enhance time management and office-visit efficiency because they are subscales of the HRSD₁₇ and the IDS-C₃₀, respectively, and thus enable depression and anxiety symptoms to be monitored with a single instrument. Both of these psychometrically sound instruments can play a vital role for psychiatric practitioners and researchers with the advent of measurement-based care (Trivedi and Daly, 2007; Rush *et al.*, 2009). Indeed, recommendations from international studies suggest that many clinicians and clinical practices could maximize efficiency and increase quality of care through the use of depression and anxiety rating instruments (Gibody *et al.*, 2002; Pancheri *et al.*, 2002; Laugharne 2009; Zimmerman *et al.*, 2010).

Limitations

The study sample comprised patients who did and did not remit with citalopram, which could introduce a treatment bias as alternative therapeutic interventions (e.g. psychotherapy) may have resulted in different change scores on the HRSD_{ANX} and the IDS-C_{ANX}. However, these measures will be useful in assessing anxious features in depressed patients regardless of treatment intervention. This study used the self-report PDSQ to diagnose anxiety disorders, an instrument designed to compliment, not replace, clinical interview strategies (e.g. SCID-I [First *et al.*, 1997]) for diagnoses (Zimmerman and Chelminski, 2006). It may be possible that the sensitivity and specificity of the HRSD₁₇ and IDS-C₃₀ anxiety subscales could be different if they were validated by the SCID-I. However, the STAR*D trial benefited from the moderate to strong sensitivity and negative predictive value of the PDSQ anxiety disorder subscales (Rush *et al.*, 2005; Zimmerman and Chelminski, 2006). Further, the PDSQ has been shown to be a valid instrument for assessing DSM diagnostic categories (Gibbons *et al.*, 2009). Nonetheless, a structured clinical interview such as the SCID-I would be helpful in future validation studies. A second limitation was not comparing either subscale to pure anxiety rating measures such as the State Trait Anxiety Inventory (Spielberger, 2005) or the Hamilton Rating Scale for Anxiety (HRSA) (Hamilton, 1959), which would have improved the reliability and validity of the psychometric analyses. However, we did compare the HRSD_{ANX} and IDS-C_{ANX} to the PDSQ anxiety dimensions and found convergent validity for both subscales. Although not a limitation of the present study, both subscales had modest alpha levels, which were likely related to the small number of items (Nunnally and Bernstein, 1994) that constitute the respective scales. In future investigations, these subscales may benefit from the addition of newer items that measure anxiety spectrum symptoms. One approach to optimize the item content would be to combine these psychometric data with the clinimetric method (Bech, 2004; Emmelkamp, 2004). Clinimetrics principally focuses on the sensitivity of the rating scale to discriminate between cohorts and has been used to evaluate and develop other depression and anxiety rating scales (Sirri *et al.*, 2008; Bech, 2009). Lastly, the high correlation between the HRSD_{ANX} and the IDS-C_{ANX} could have been due to their administration by the same trained ROA.

Conclusion

Both the HRSD_{ANX} and the IDS-C_{ANX} have adequate psychometric properties and reliably identify anxious features in depressed patients. Thus, both may be useful for clinical and research work by systematically monitoring both depressive symptoms and anxious features in order to optimize therapeutic outcome. Given the validity and utility of self-report measures of depression and anxiety (Prusoff *et al.*, 1972; Fava *et al.*, 1986), future research to evaluate the anxiety subscale of the patient self-report version of the IDS is warranted. Further, future studies should examine the HRSD_{ANX} and the IDS-C_{ANX} for sensitivity to change with antidepressant therapies as well as their predictive validity. In future studies, the

utility of the HRSD_{ANX} to identify anxious features may benefit from the removal of item 17 (loss of insight).

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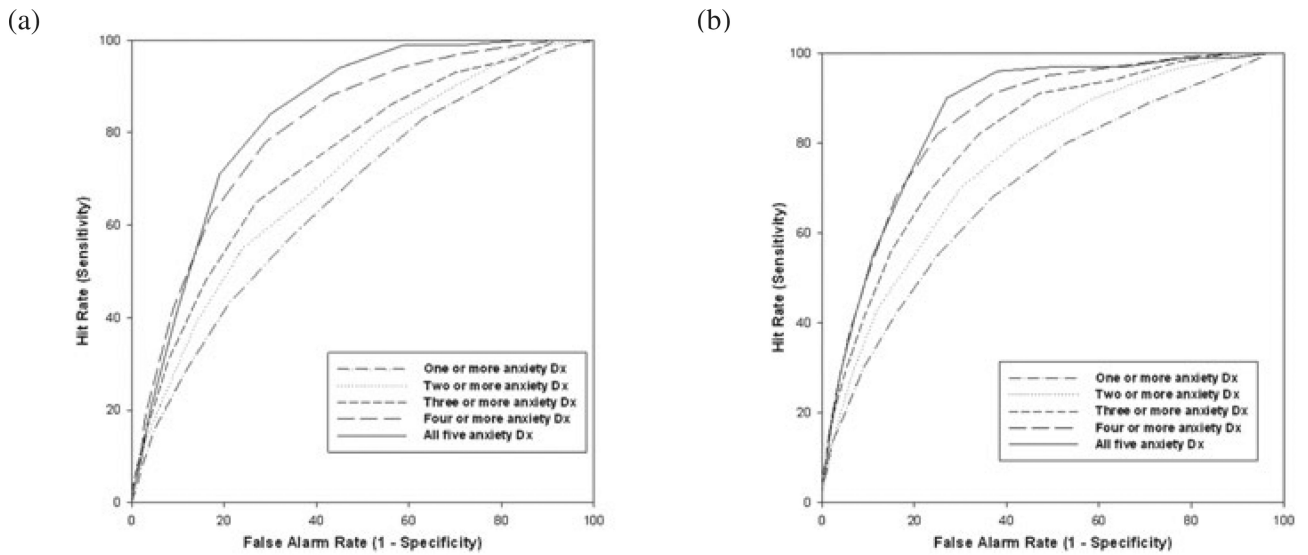
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HRSD _{ANK} subscale		N anxiety disorders assessed by the PDSQ ¹									
Score	1 or more		2 or more		3 or more		4 or more		All 5		
	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	
1	100	0	100	1	100	1	100	0	100	0	
2	99	5	100	4	100	3	100	3	100	3	
3	97	11	99	9	100	8	100	8	100	8	
4	91	22	96	19	96	17	99	16	100	16	
5	83	37	89	32	93	30	97	29	99	28	
6	71	51	80	47	86	44	94	42	99	41	
7	57	66	67	61	76	58	88	57	94	55	
8	43	79	55	76	65	73	78	71	84	70	
9	29	88	39	86	48	84	62	83	71	81	
10	16	95	23	93	31	92	42	91	42	90	
11	7	98	11	98	15	97	19	97	20	96	
12	3	99	5	99	7	99	10	98	9	98	
13	0	100	1	100	2	100	3	100	1	100	
14	0	100	0	100	0	100	1	100	1	100	
15	0	100	0	100	0	100	1	100	1	100	

¹The numbers in the figure refer to the number of anxiety disorders (based on PDSQ) that had to be present for the patient to be considered as "anxious." For example, the category 1-5 means that someone with one to five positive PDSQ anxiety disorders was considered to be "anxious" while the category 4-5 means only those with four or five positive PDSQ anxiety disorders were considered to be "anxious".

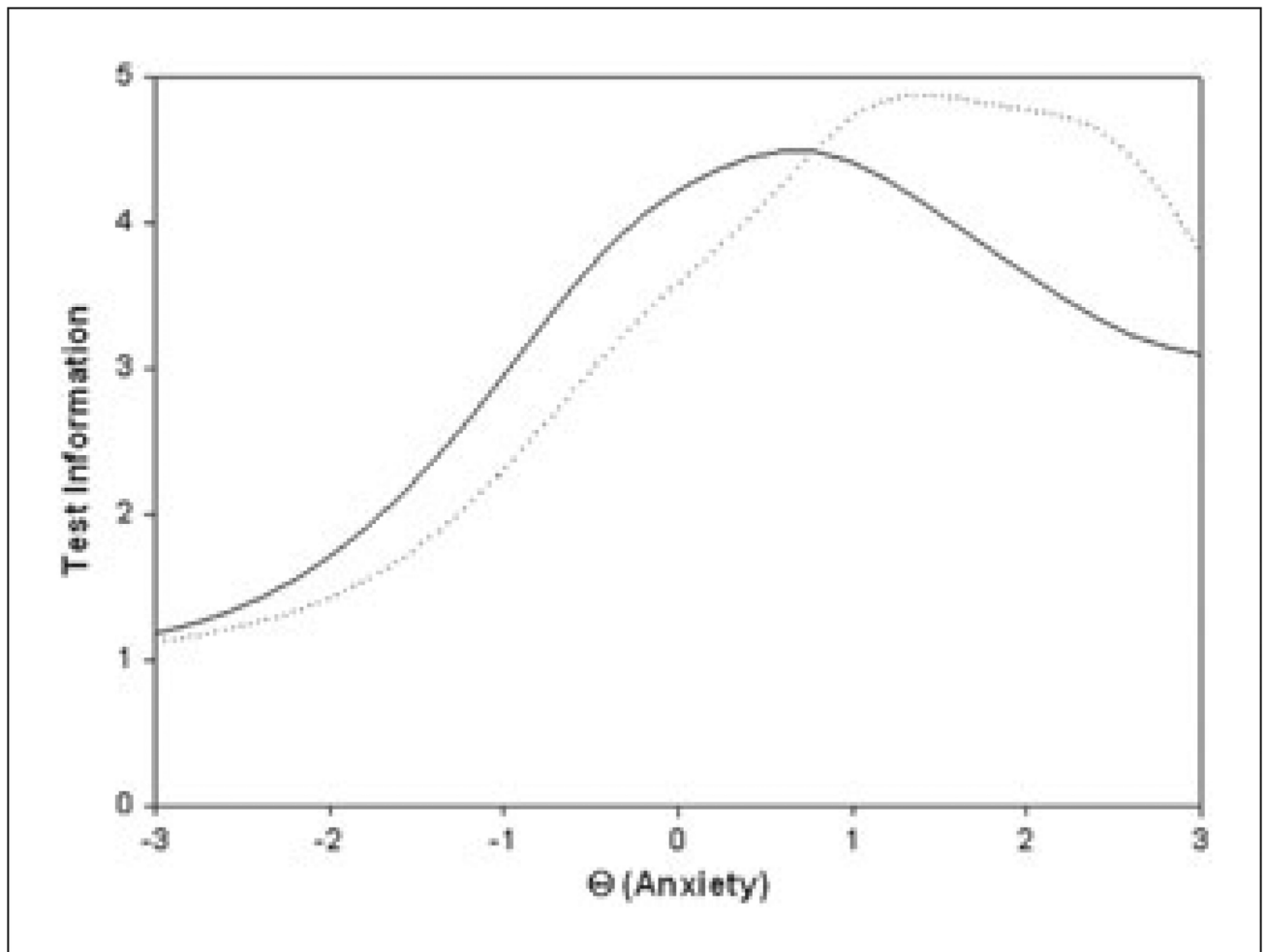
Note: ROC, receiver operating characteristic; HRSD_{ANK}, Hamilton Rating Scale for Depression Anxiety/Somatization Factor; IDS-C_{ANK}, Inventory of Depressive Symptomatology Anxiety Factor; Sens, Sensitivity; Spec, Specificity.

IDS-C _{ANK} subscale		N anxiety disorders assessed by the PDSQ ¹									
Score	1 or more		2 or more		3 or more		4 or more		All 5		
	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	
1	99	5	100	4	100	3	100	3	100	3	
2	95	14	99	12	100	11	100	10	99	10	
3	89	29	96	25	98	23	99	22	99	21	
4	80	47	90	41	94	37	97	36	97	34	
5	68	63	81	57	91	53	95	51	97	49	
6	55	75	70	70	82	66	91	63	96	62	
7	42	84	55	80	69	77	82	75	90	73	
8	30	91	43	88	56	85	68	84	71	82	
9	20	95	30	93	41	91	51	90	55	89	
10	13	98	20	96	29	95	38	94	41	93	
11	7	99	12	98	18	98	24	97	29	96	
12	4	100	6	9	9	99	12	99	17	98	
13	2	100	2	100	4	100	7	99	10	99	
14	1	100	1	100	2	100	4	100	6	100	
15	0	100	0	100	1	100	1	100	2	100	

¹The numbers in the figure refer to the number of anxiety disorders (based on PDSQ) that had to be present for the patient to be considered as "anxious." For example, the category 1-5 means that someone with one to five positive PDSQ anxiety disorders was considered to be "anxious" while the category 4-5 means only those with four or five positive PDSQ anxiety disorders were considered to be "anxious".

Note: IDS-C_{ANK}, Inventory of Depressive Symptomatology Anxiety Factor; ROC, receiver operating characteristic; PDSQ, Psychiatric Diagnostic Screening Questionnaire; Sens, Sensitivity; Spec, Specificity.

Figure 1. ROC curve for the HRSD_{ANK} and IDS-C_{ANK} factors: (a) HRSD_{ANK} ROC curve; (b) IDS-C_{ANK} ROC curve.



HRSD_{ANX}— solid line
 IDS-C_{ANX}— dotted line

This test information function (TIF) figure shows the HRSD_{ANX} is a better measure of anxious symptoms in patients with less anxious severity (see how the peak of the curve is before Θ of one) whereas the IDS-C_{ANX} is a better measure of anxious symptoms in patients with high anxious severity (see how the peak of the curve is after Θ of one).

Note: HRSD_{ANX}, Hamilton Rating Scale for Depression Anxiety/Somatization Factor; IDS-C_{ANX}, Inventory of Depressive Symptomatology Anxiety Factor.

Figure 2.
 Test information function for the HRSD_{ANX} and the IDS-C_{ANX}.

Table 1
Sociodemographic and clinical characteristics of participants by number of anxiety-related disorders

Measure	Number of anxiety related disorders ^a										Analyses												
	All (N = 3435)	0 (N = 1799)	1 (N = 852)	2 (N = 415)	3 (N = 203)	4 (N = 117)	5 (N = 67)	n	%	β	SE	χ ²	df	P									
Male gender	1291	37.4	718	39.9	324	38.0	136	32.8	59	29.1	34	29.1	20	29.9	-0.0977	0.0259	14.2	1	0.0002				
Race																				24.8	2	<0.0001	
White	2622	76.0	1414	78.7	645	75.8	301	72.7	143	70.4	79	67.5	40	59.7									
Black	586	17.0	259	14.4	151	17.7	75	18.1	51	25.1	28	23.9	22	32.8	0.1595	0.0316	25.5	1	<0.0001				
Other	241	7.0	124	6.9	55	6.5	38	9.2	9	4.4	10	8.5	5	7.5	0.0475	0.0486	0.95	1	0.3285				
Hispanic ethnicity	426	12.3	186	10.3	103	12.1	68	16.4	38	18.7	22	18.8	9	13.4	0.1398	0.0357	15.3	1	<0.0001				
Employment status																							
Employed	2001	58.0	1095	60.9	518	60.9	219	52.8	97	47.8	44	37.6	28	41.8									
Unemployed	1250	36.2	591	32.9	285	33.5	173	41.7	97	47.8	66	56.4	38	56.7	0.1651	0.0257	41.2	1	<0.0001				
Retired	200	5.8	113	6.3	47	5.5	23	5.5	9	4.4	7	6.0	1	1.5	-0.0091	0.0558	0.03	1	0.8707				
Medical insurance																							
Any private	1762	52.6	997	57.1	435	52.6	187	47.1	82	41.2	35	30.7	26	41.3									
Public only	447	13.4	190	10.9	106	12.8	66	16.6	44	22.1	32	28.1	9	14.3	0.2344	0.0365	41.2	1	<0.0001				
None	1138	34.0	560	32.1	286	34.6	144	36.3	73	36.7	47	41.2	28	44.4	0.1249	0.0277	20.3	1	<0.0001				
Marital status																							
Never married	1036	30.0	525	29.2	278	32.7	131	31.6	55	27.1	31	26.5	16	23.9	0.0091	0.0298							
Married/cohabiting	1448	41.9	781	43.4	348	40.9	158	38.1	88	43.3	47	40.2	26	38.8									
Divorced/separated	870	25.2	444	24.7	200	23.5	114	27.5	53	26.1	37	31.6	22	32.8	0.0578	0.0309							
Widowed	98	2.8	49	2.7	25	2.9	12	2.9	7	3.4	2	1.7	3	4.5	0.0465	0.0749							
Age at first episode <18	1280	37.4	603	33.8	340	40.3	185	44.9	76	38.0	50	43.9	26	40.0	0.0827	0.0254	10.6	1	0.0011				
At least one prior episode	2373	74.0	1221	72.3	594	75.4	284	74.7	146	79.8	80	75.5	48	80.0	0.0625	0.0298	4.4	1	0.0362				
Ever attempted suicide	574	16.6	248	13.8	144	16.9	88	21.2	43	21.3	34	29.3	17	25.4	0.1633	0.0315	26.9	1	<0.0001				
Family history of depression	1887	55.1	974	54.6	464	54.9	232	56.3	117	57.9	63	54.3	37	56.1	0.0160	0.0250	0.41	1	0.5226				
Months since index onset	24	853	24.9	410	23.0	191	22.7	138	33.6	56	28.0	37	31.6	21	31.8	0.1003	0.0280	12.8	1	0.0003			
Psychiatric care	2115	61.3	1086	60.4	536	62.9	262	63.1	129	63.5	61	52.1	41	61.2	0.0006	0.0254	<0.01	1	0.9820				

^a Assessed by the Psychiatric Diagnostic Screening Questionnaire.

Table 2
Sociodemographic and clinical characteristics of participants by number of anxiety-related disorders

	Number of anxiety related disorders ^c															Analyses			
	All (N = 3435)		0 (N = 1799)		1 (N = 852)		2 (N = 415)		3 (N = 203)		4 (N = 117)		5 (N = 67)		SE	χ^2	df	P	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	β				
Age	40.3	13.2	41.7	13.6	38.8	12.7	38.3	12.9	39.5	12.4	39.4	12.0	40.4	11.5	-0.0035	0.0009	13.5	1	0.0002
Education (years)	13.5	3.2	14.0	3.3	13.4	3.1	12.9	3.3	12.3	3.0	11.7	2.6	12.5	2.4	-0.0362	0.0038	93.1	1	<0.0001
Monthly household income ^b	2440	3191	2768	3735	2346	2569	2117	2582	1587	1788	1371	1744	1342	1323	-0.0322	0.0049	42.6	1	<0.0001
Age at first episode	25.3	14.3	27.0	15.0	24.2	13.5	22.6	13.2	22.7	12.3	22.6	12.5	21.6	12.4	-0.0056	0.0009	38.6	1	<0.0001
Years since first episode	15.1	13.1	14.7	13.5	14.6	12.4	15.6	12.8	17.0	12.9	16.9	12.7	18.8	12.8	0.0029	0.0009	9.4	1	0.0021
N/Episodes	5.4	9.2	4.9	8.6	5.8	9.8	5.6	9.2	6.7	10.6	5.7	10.3	8.4	11.7	0.0038	0.0013	8.3	1	0.0040
Months since index onset	24.2	51.6	21.2	45.3	23.5	53.7	32.3	60.5	21.8	32.8	42.3	82.7	42.0	80.4	0.0009	0.0002	20.4	1	<0.0001
N/Moderate to severe GMC ^{s,c}	1.0	1.3	1.0	1.3	1.0	1.2	1.0	1.3	1.2	1.4	1.5	1.5	1.6	1.3	0.0481	0.0093	26.6	1	<0.0001
HRS _{D17}	19.9	6.5	17.9	6.1	20.3	6.0	22.5	5.9	23.4	6.0	26.8	5.5	28.2	4.1	0.0386	0.0019	410	1	<0.0001
IDS-C ₃₀	35.5	11.5	31.7	10.6	36.5	10.4	40.4	10.4	42.7	10.2	47.8	10.1	50.8	7.1	0.0233	0.0011	467	1	<0.0001
QIDS-SR ₁₆	15.4	4.3	14.1	4.1	15.8	4.0	17.4	3.6	17.9	3.9	19.0	3.6	19.8	3.6	0.0561	0.0030	361	1	<0.0001
Q-LES-Q	41.8	15.2	45.6	14.2	40.6	14.2	37.5	14.8	32.5	14.7	30.9	16.7	27.4	15.6	-0.0131	0.0008	246	1	<0.0001
SF ₁₂ Mental	26.5	8.6	27.7	9.0	25.5	8.1	24.4	7.6	25.1	7.1	26.8	9.1	23.4	7.4	-0.0092	0.0015	36.8	1	<0.0001
SF ₁₂ Physical	49.8	11.8	51.5	11.6	50.0	11.4	48.1	11.4	44.4	11.7	41.7	12.0	40.0	10.4	-0.0118	0.0010	127	1	<0.0001
WSAS	23.4	9.3	21.0	9.1	24.3	8.9	26.4	8.2	29.2	7.7	29.5	8.5	30.9	7.8	0.0219	0.0014	235	1	<0.0001

Note: GMC, general medical comorbidity; HRS_{D17}, 17-item Hamilton Rating Scale for Depression; IDS-C₃₀, 30-item Inventory of Depressive Symptomatology – Clinician-rated; QIDS-SR₁₆, 16-item Quick Inventory of Depressive Symptomatology – Self-rated; Q-LES-Q, Quality of Life and Enjoyment Satisfaction Questionnaire; SF₁₂, 12-item short-form health survey; WSAS, Work and Social Adjustment Scale.

^a Assessed by the Psychiatric Diagnostic Screening Questionnaire.

^b Beta based on units of \$1000.

^c Assessed by the Cumulative Illness Rating Scale.

Table 3

Comparison of HRSD_{ANX} and IDS-C_{ANX}

#	Item	Baseline			Exit			Change ^d			Analyses		
		M	SD	r _{it}	M	SD	r _{it}	M	SD	t	df	p	ES
HRSD _{ANX}													
		$\alpha = 0.48$											
10	Anxiety, psychic	1.64	0.98	0.23	0.89	0.98	0.50	0.74	0.98	26.6	4924	<0.0001	0.76
11	Anxiety, somatic	1.60	0.90	0.39	1.27	0.97	0.49	0.33	0.94	12.5	4894	<0.0001	0.36
12	Somatic symptoms, gastrointestinal	0.67	0.83	0.18	0.31	0.63	0.36	0.36	0.74	17.3	4577	<0.0001	0.49
13	Somatic symptoms, general	1.41	0.74	0.31	0.85	0.84	0.52	0.56	0.79	24.9	4845	<0.0001	0.71
15	Hypochondriasis	0.69	0.87	0.30	0.49	0.76	0.43	0.20	0.82	8.4	4844	<0.0001	0.24
17	Insight	0.03	0.20	-0.07	0.06	0.31	-0.15	-0.03	0.26	3.5	4274	0.0004	0.10
	Total	6.03	2.52		3.86	2.84		2.17	2.69	28.4	4853	<0.0001	0.81
IDS-C _{ANX}													
		$\alpha = 0.58$											
7	Mood (anxious)	1.37	0.88	0.36	0.75	0.86	0.49	0.62	0.87	25.1	4924	<0.0001	0.72
25	Somatic complaints	1.31	1.00	0.28	0.94	1.01	0.43	0.36	1.01	12.7	4924	<0.0001	0.36
26	Sympathetic arousal	0.91	0.80	0.45	0.72	0.78	0.49	0.19	0.79	8.6	4924	<0.0001	0.25
27	Panic	0.62	0.94	0.37	0.30	0.71	0.44	0.33	0.83	13.7	4598	<0.0001	0.39
28	Gastrointestinal	0.63	0.87	0.24	0.54	0.84	0.36	0.09	0.85	3.6	4924	0.0003	0.10
	Total	4.85	2.75		3.25	2.81		1.60	2.78	20.2	4924	<0.0001	0.57

Note: HRSD_{ANX}: Hamilton Rating Scale for Depression anxiety subscale; IDS-C_{ANX}: Inventory of Depressive Symptomatology – Clinician-rated anxiety subscale; r_{it}: item-total correlation coefficient.

^aChange from baseline (entry into STAR*D Level 1) to exit (end of STAR*D Level 1).

Table 4Correlations between the PDSQ anxiety subscales, HRSD_{ANX} and IDS-C_{ANX}^a (*N* = 3453)

PDSQ anxiety subscale	HRSD _{ANX}	IDS-C _{ANX}
Post traumatic stress	0.31	0.41
Panic	0.34	0.42
Agorophobia	0.42	0.51
Social phobia	0.25	0.31
Generalized anxiety	0.16	0.24

Note: HRSD_{ANX}, Hamilton Rating Scale for Depression Anxiety/Somatization Factor; IDS-C_{ANX}, Inventory of Depressive Symptomatology Anxiety Factor; PDSQ, Psychiatric Diagnostic Screening Questionnaire.

^aAll correlations were significant at $p < 0.0001$.

Table 5Equated scores on the HRSD_{ANX} and IDS-C_{ANX}^a

HRSD _{ANX}		IDS-C _{ANX}	
Raw score	Θ	Raw score	Θ
0	-1.40	0	-1.20
1	-0.84	1	-0.63
2	-0.48	2	-
3	-0.17	3	-0.27
4	0.11	4	0.01
5	0.36	5	0.29
6	0.60	6	0.54
7	0.84	7	0.78
8	1.10	8	1.00
9	1.30	9	1.20
10	1.50	10	1.50
11	1.80	11	1.70
12	2.00	12	1.90
13	2.30	13	2.10
14	2.50	14	2.40
15	2.70	15	2.70
16	2.90	—	—
17	3.30	—	—

Note: HRSD_{ANX}, Hamilton Rating Scale for Depression Anxiety/Somatization Factor ($N=2697$); IDS-C_{ANX}, Inventory of Depressive Symptomatology Anxiety Factor ($N=2698$).

^aTest equating involves associating raw scores on each test with values of the dimension under investigation denoted Θ , which in this case are anxious symptom features. The total range for the HRSD_{ANX} is 0–18 and the total range for the IDS-C_{ANX} is 0–15.