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Research report

Predicting relapse in major depressive disorder using patient-reported outcomes of depressive symptom severity, functioning, and quality of life in the individual burden of illness index for depression (IBI-D)

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ABSTRACT

Background: Patients with Major Depressive Disorder (MDD) often experience unexpected relapses, despite achieving remission. This study examines the utility of a single multidimensional measure that captures variance in patient-reported Depressive Symptom Severity, Functioning, and Quality of Life (QOL), in predicting MDD relapse.
Methods: Complete data from remitted patients at the completion of 12 weeks of citalopram in the STAR*D study were used to calculate the Individual Burden of Illness index for Depression (IBI-D), and predict subsequent relapse at six ($n=956$), nine ($n=778$), and twelve months ($n=479$) using generalized linear models.
Results: Depressive Symptom Severity, Functioning, and QOL were all predictors of subsequent relapse. Using Akaike information criteria (AIC), the IBI-D provided a good model for relapse even when Depressive Symptom Severity, Functioning, and QOL were combined in a single model. Specifically, an increase of one in the IBI-D increased the odds ratio of relapse by 2.5 at 6 months ($\beta=0.921\pm0.194$, $z=4.76$, $p<2\times10^{-6}$), by 2.84 at 9 months ($\beta=1.045\pm0.22$, $z=4.74$, $p<2.2\times10^{-6}$), and by 4.1 at 12 months ($\beta=1.41\pm0.29$, $z=4.79$, $p<1.7\times10^{-6}$).
Limitations: Self-report poses a risk to measurement precision. Using highly valid and reliable measures could mitigate this risk. The IBI-D requires time and effort for filling out the scales and index calculation. Technological solutions could help ease these burdens. The sample suffered from attrition. Separate analysis of dropouts would be helpful.
Conclusions: Incorporating patient-reported outcomes of Functioning and QOL in addition to Depressive Symptom Severity in the IBI-D is useful in assessing the full burden of illness and in adequately predicting relapse, in MDD.

1. Introduction

Depression affects 350 million people worldwide according to the latest statistics from the World Health Organization (WHO, 2012). Patients with Major depressive disorder (MDD) not only suffer from symptoms of depression, but also from impairments in quality of life (QOL) and function that lead to increased suffering with negative consequences for families as well as for society at large (Mathers and Loncar, 2006; IsHak et al., 2011; Rupp et al., 1997). In prior work, the concept of an MDD patient's individual burden of illness was introduced to accurately capture this suffering by incorporating symptom severity (intensity, frequency, duration), impairment in functioning (occupational, social, and leisure activities), and reduction in quality of life (QOL) (satisfaction with health, occupational, social, and leisure activities), as depicted in Fig. 1.

The Individual Burden of Illness Index for Depression (IBI-D) was developed and validated as a means of providing a single measure that would accurately reflect the degree to which an individual patient is suffering from depression (IsHak et al., 2013). Following on the above conceptualization, the IBI-D was the name given to the first and only statistically significant principal component obtained from a principal component analysis (PCA) of well-validated patient-reported outcomes of depressive symptom

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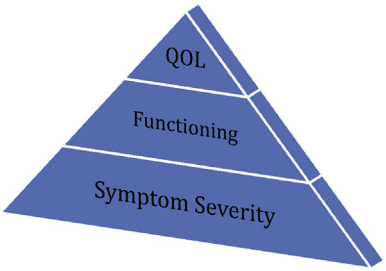

Fig. 1. The burden of illness components.

severity, functioning, and QOL: the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Rush et al., 2003), the Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002), and the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q) (Endicott et al., 1993), respectively. The initial exploratory PCA was based on the patient-reported measures from MDD patients in the Cedars-Sinai Psychiatric Treatment Outcome Registry (IsHak et al., 2013) and the confirmatory analysis was based on the patient-reported measures of patients enrolled in Level 1 of the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial study at their time of entry (Rush et al., 2004; Fava et al., 2003). More recently the single IBI-D number was shown to provide an accurate accounting of the multidimensional impact of antidepressant treatment (Cohen et al., 2013).

In the present study we examined whether this multidimensional measure of depression offers advantages over the more traditional one-dimensional measures that emphasize symptom severity. The evaluation rests on the examination of the relapse rates of STAR*D Level 1 citalopram treated remitted patients (QIDS-SR score of 5 or less) after 6, 9, and 12 months. We hypothesized that remitted patients with higher IBI-D scores, i.e., higher burden of illness, would be more likely to relapse over the ensuing 12 months. As all remitted patients have relatively low and similar symptom severity ratings, higher IBI-D values primarily reflect residual impairments in QOL and/or functioning. Finding such a relationship would provide strong support for (1) The need to focus on improvements in QOL and function in addition to reductions in symptom severity if we are to provide adequate treatment to MDD patients and, (2) The usefulness of the IBI-D as a clinical indicator in the assessment of antidepressant treatments and relapse potential.

2. Methods

2.1. Population

The patient sample for this study was derived from the STAR*D trial. STAR*D is an NIMH-funded study, conducted at 18 primary care settings and 23 psychiatric care settings in the United States, from 2001 to 2007, that enrolled 4041 treatment-seeking outpatients from 18 to 75 years old who had a primary diagnosis of MDD, for the purpose of evaluating response and remission using a sequential approach of medication regimens: Level 1 through 4. The full details of the study are described elsewhere (Fava et al., 2003; Rush et al., 2004). The authors obtained NIMH Data Use Certificate to use the STAR*D dataset (STAR*D Pub Ver3). This analysis focused on patients with complete severity, functioning, and QOL data, collected by the Interactive Voice Response system, at six ($n=956$), nine ($n=778$), and twelve ($n=479$) months of the follow-up phase of the study who met criteria for remission at exit after completing Level 1 treatment as defined by QIDS-SR of 5 or less. Follow-up patients were instructed to stay on the same medication at the same dose of the acute treatment and have follow-up visits every two months.

2.2. Outcome measures

The measures used to calculate the IBI-D consisted of the following three instruments: (a) Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Rush et al., 2003) for depressive symptom severity, (b) Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002) for functioning, and (c) Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q) (Endicott et al., 1993) for QOL.

The QIDS-SR measures depressive symptom severity with scores ranging from 0 (not depressed) to 27 (most depressed). Remission is defined as a score of 5 or less, which is equivalent to a score of 7 or less on the Hamilton Rating Scale for Depression. Scores of 6–10 are used for mild, 11–15 for moderate, 16–20 for severe, and >20 for very severe depression (Rush et al., 2003).

The WSAS was used to measure functioning, with scores ranging from 0 (no impairment) to 40 (severe impairment). Scores above 20 indicate moderate to severe impairment, 10–20 for significant impairment, and <10 for subclinical impairment. The WSAS has fairly strong psychometric properties, with a Cronbach's alpha ranging from 0.70 to 0.94, and a test–retest reliability of $r=0.73$ (Mundt et al., 2002).

QOL was assessed using the Q-LES-Q; with a score range of 0–100 where 0 is the lowest QOL score and 100 is the highest. Community norm samples have an average Q-LES-Q score of 78.3 (SD=11.3) and scores within 10% of this value are considered within-normal (Q-LES-Q $>=70.47$), whereas Q-LES-Q scores greater than 2 SD below the community norm indicate severe impairment, i.e., Q-LES-Q scores less than or equal to 55.7 are considered severely impaired. The Q-LES-Q also enjoys strong psychometric properties, with a Cronbach's alpha of 0.90 and a test–retest reliability of 0.74 (Endicott et al., 1993).

2.3. Calculation of IBI-D index

Each scale is converted to a z-score according to the development and validation study (5). For the QIDS-SR: zQIDS-SR=(QIDS-SR−15.6)/5.1, for the WSAS: zWSAS=(WSAS−23.9)/9.3, and for the Q-LES-Q: zInvQ-LES-Q=(41.4−Q-LES-Q)/15.3. The IBI-D index is calculated using the following formula:

IBI-D index=[0.57(zQIDS-SR)+0.58(zWSAS)+0.59(zInvQ-LES-Q)]/1.51.

2.4. Defining remission and relapse

Remission was defined as QIDS-SR= <5 at exit after completing Level 1 treatment. Relapse was defined as QIDS-SR equal or more than three standard deviations above the mean for remitters, i.e., QIDS-SR >7 at each follow-up point of 6, 9, and 12 months. Although QIDS-SR $>=11$ was used in examination of relapse in some STAR*D analyses, 11 seems to be a relatively high score (equivalent to moderate depression) that would encompass a variety of patients who are well into full blown depressive episodes, so we opted to a definition that include patients experiencing even mild depressive symptoms.

2.5. Statistical analyses

Summary values are expressed as means (SD) for continuous variables, and frequencies (%) for categorical variables. χ^2 Analysis was used to compare the percentage of patients who relapsed to those who maintained remission at 6, 9, and 12 months. P values