Prognostic Subgroups for Remission and Response in the Coordinated Anxiety Learning and Management (CALM) Trial

J. MacLaren Kelly, MAPP; Ewgeni Jakubovski, MA; and Michael H. Bloch, MD, MS

ABSTRACT

Objective: Most patients with anxiety disorders receive treatment in primary care settings. Limited moderator data are available to inform clinicians of likely prognostic outcomes for individual patients. We identify baseline characteristics associated with outcome in adults seeking treatment for anxiety disorders.

Method: We conducted an exploratory moderator analysis from the Coordinated Anxiety Learning and Management (CALM) trial. In the CALM trial, 1,004 adults who met *DSM-IV* criteria for generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, and/or posttraumatic stress disorder (PTSD) were randomized to usual care (UC) or a collaborative care intervention (ITV) of cognitive-behavioral therapy and/or pharmacotherapy between June 2006 and April 2008. Logistic regression was used to examine baseline characteristics associated with remission and response overall and by treatment condition. Receiver operating curve (ROC) analyses identified subgroups associated with similar likelihood of response and remission of global anxiety symptoms. Remission was defined as score < 6 on the 12-item Brief Symptom Inventory (BSI-12) anxiety and somatization subscales. Response was defined as at least 50% reduction on BSI-12, or meeting remission criteria.

Results: Randomization to ITV over UC was often the strongest predictor of outcome. Several baseline patient characteristics were associated with poor treatment outcome including comorbid depression, increased severity of underlying anxiety disorder(s) ($P < .001$), low socioeconomic status (perceived [$P < .001$] and actual [$P < .05$]), and limited social support ($P < .001$). Patient characteristics associated with particular benefit from ITV were being female ($P < .05$), increased depression ($P < .01$)/GAD severity ($P < .05$), and low socioeconomic status ($P < .05$). ROC analysis demonstrated prognostic subgroups with large differences in response likelihood.

Conclusions: Further research should focus on the effectiveness of implementing the ITV intervention of CALM in community treatment centers where patients typically are of low socioeconomic status and may particularly benefit from ITV.

Trial Registration: ClinicalTrials.gov identifier: NCT00347269

J Clin Psychiatry 2015;76(3):267–278

Submitted: *December 6, 2013; accepted March 12, 2014.*
Online ahead of print: *December 9, 2014 (doi:10.4088/JCP.13m08922).*
Corresponding author: *Michael H. Bloch, MD, MS, Child Study Center, Yale University School of Medicine, PO Box 2070900, New Haven, CT 06520 (michael.bloch@yale.edu).*

Anxiety disorders[1] affect roughly 1 in 5 Americans[2] and are associated with significant disability, suicide risk, and poor quality of life.[3,4] Effective, evidence-based pharmacotherapies and psychotherapies have been developed, yet fewer than 1 in 4 adults with anxiety disorders receive treatment according to evidence-based care guidelines.[5]

Recognizing the gap in dissemination of evidence-based treatments and the predominant involvement of primary care providers in anxiety disorder treatment,[6] researchers conducted a large multisite, randomized controlled trial of a collaborative care intervention (ITV) versus usual care (UC) for treating anxiety disorders in primary care settings. The Coordinated Anxiety Learning and Management (CALM) trial demonstrated that the ITV intervention was superior to UC at 6 months on global anxiety and on principal anxiety disorder measures.[7,8] Patients randomized to ITV were given the choice of receiving pharmacotherapy, cognitive-behavioral therapy (CBT), or both for 10 to 12 weeks.

In addition to being a pivotal study demonstrating the effectiveness of a new treatment model, the CALM trial provided important data with the potential to yield prognostic information for managing anxiety disorders in primary care. Moderator analyses determine which patient characteristics are associated with treatment prognosis. Previous analyses in patients with anxiety disorders have associated anxiety disorder severity,[9] comorbid mood[10,11] and personality disorders,[12] socioeconomic status,[13] education level,[14] family dynamics,[15] and treatment duration[16] with poorer outcomes. However, these studies were comparatively underpowered to examine moderators of treatment efficacy and typically involved samples recruited through psychiatric settings rather than primary care samples.

We used traditional logistic regression techniques to examine baseline clinical characteristics associated with response and remission in patients seeking treatment for anxiety disorders in primary care settings. We specifically examined baseline characteristics associated with prognosis to treatment in the overall sample and by treatment condition. We additionally used logistic regression to identify patient characteristics that were associated with particular benefit from ITV as opposed to UC. We also used receiver operating curve (ROC) analysis to identify subgroups defined by the likelihood of treatment response/remission in each of these treatment groups.

METHOD

The rationale, design, and methods of the CALM trial (ClinicalTrials.gov identifier: NCT00347269) have been described in depth elsewhere.[17] The research protocol was approved by each site's institutional review board and by the

Clinical Points

- Patients with anxiety disorders randomized to the collaborative care intervention had better clinical outcomes than treatment as usual.
- Increased baseline depression and anxiety severity, low socioeconomic status, and less perceived social support were associated with poor treatment outcomes across treatment interventions.
- Female patients, patients with increased severity of baseline depression and generalized anxiety disorder, and those of low socioeconomic status derived particular benefit from the collaborative care intervention.
- Receiver operating curve analysis demonstrated prognostic subgroups with large differences in likelihood of treatment response.

RAND Survey Research Group. After describing the study to the participants, investigators at each site of the CALM study obtained written informed consent.

Subjects

Subjects recruited from 17 US primary care clinics were eligible if they were (1) aged 18 to 75 years; (2) met *DSM-IV* criteria for generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, and/or posttraumatic stress disorder (PTSD) (based on the Mini-International Neuropsychiatric Interview[18] [MINI]); and (3) presented with moderate and clinically significant anxiety symptoms (defined as Overall Anxiety Severity and Impairment Scale[19] [OASIS] score greater than 8).

Participants were excluded for (1) unstable/life-threatening medical conditions, (2) marked cognitive impairment, (3) active suicidal intent/plan, (4) psychosis, (5) bipolar I disorder, (6) active substance abuse/dependence (aside from alcohol or marijuana abuse), (7) existing cognitive-behavioral therapy (CBT) or ongoing medication management, and (8) inability to speak English or Spanish.

Assessment

The RAND Survey Research Group administered the assessment battery through a centralized telephone survey at baseline, 6, 12, and 18 months. Our data analysis utilized only the 6-month outcomes. The raters were blind to group assignment. The 12-item Brief Symptom Inventory [BSI-12] subscales for anxiety and somatization[20] were used as the primary outcome measure. Remission was defined as BSI-12 score < 6. Response was defined as at least 50% reduction on the BSI-12, or meeting the definition of remission.[21]

Every anxiety disorder was additionally assessed with disorder-specific scales at baseline. The Panic Disorder Severity Scale–Self-Report (PDSS-SR) assessed panic disorder.[22] GAD was measured with the 6-item Generalized Anxiety Disorder Severity Scale (GADSS).[23] The 17-item Social Phobia Inventory (SPIN) measured social anxiety disorder.[24] The 17-item PTSD Checklist–Civilian Version (PCL-C) measured PTSD.[25,26] Anxiety symptoms were continuously measured with the Overall Anxiety Severity and Impairment Scale (OASIS),[19] and depressive symptoms were measured with a 3-item version of the Patient Health Questionnaire-9 (PHQ-9).[27] The Alcohol Use Disorders Identification Test (AUDIT) was used to screen for alcohol dependence and simple queries were used to screen for drug use.[28]

Intervention

After a baseline interview, patients were randomized to ITV or UC using an automated computer program at RAND Corporation (Santa Monica, California). ITV participants received treatment involving pharmacotherapy, computer-assisted CBT delivered by study personnel, or both, depending on their preference, for up to 12 months. Participants who selected medication management alone or in combination with CBT had medication prescribed by their primary care provider. A local study psychiatrist provided initial single-session medication management training to study personnel at the start of the trial using a simple algorithm, and was available for as-needed medication consultation for the study duration. The treatment algorithm for all 4 disorders included first-line use of a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor antidepressant optimized for maximum tolerable dose. If response was not achieved after the first 10 to 12 weeks, a different antidepressant or CBT was used. If the switch did not result in significant improvement, either another antidepressant or a benzodiazepine (in select cases, except PTSD) was added as adjunctive treatment. More complex interventions were considered after consulting the local study psychiatrist. Further information on the study algorithm can be found elsewhere.[17] Patients randomized to UC were treated by their primary care provider in the usual fashion (ie, with medication, in-clinic counseling, or a referral to a mental health specialist). There was no prescribed intervention in terms of algorithm for medication or stepped care.

Statistical Analysis

We conducted an exploratory moderator analysis on data from the National Institute of Mental Health (NIMH)–supported CALM public access database, Version 1. Data preparation was conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) and Microsoft Excel (Microsoft, Redmond, Washington). Both logistic regression models and signal detection methodology were used to find the best prediction model. SAS was used for simple and multiple logistic regression models. The ROC analysis was performed using free software available online (http://www.stanford.edu/~yesavage/ROC.html).

Logistic regression models assessed the association of demographic, social, and clinical characteristics with remission and response at 6 months. Simple logistic regression was calculated with the following predictor variables:

- Demographic predictors: age, race, ethnicity, and gender;
- Socioeconomic predictors: high school completion, employment status, disability income, insurance status, personal income, family income, marital status;
- Subjective ratings: lack of money, step on socioeconomic or community ladder in comparison to others, patient's belief in efficacy of psychotherapy or medication, self-efficacy expectancy—subjective likelihood of own ability to benefit from treatment, outcome expectancy—subjective likelihood of treatment success, satisfaction with treatment;
- Health-related behaviors and treatment: help-seeking behaviors—readiness, comfort and embarrassment associated with treatment; alcohol use frequency during the past 6 months; smoking (number of cigarettes per day); exercise; social support; previous therapist used CBT techniques; previous medication use for depression; previous antidepressant or benzodiazepine treatment for at least 2 months;
- Clinical predictors: principal disorder (social anxiety disorder, GAD, PTSD, panic disorder), suicidality in the past month, PHQ-9 score, OASIS score, and comorbid axis I psychiatric disorders (MDD, past alcohol dependence, current alcohol abuse, obsessive-compulsive disorder). We intended also to examine the influence of past substance use disorders but sample frequencies were too low to provide reliable data for moderator analysis.
- Treatment assignment: ITV vs UC.

All predictor variables were tested for main effects and interaction with treatment assignment. Significant predictors ($P < .05$) from the simple regression models were entered into a backward step-wise multiple logistic regression model to assess the unique and independent contribution of these variables to remission and response rates. The analysis was repeated in the UC and ITV subgroups. GADSS, PCL-C, PDSS, and SPIN scales needed to be excluded from multiple regression analysis due to a large number of missing values.

ROC analysis was used as an alternative prediction model. ROC analysis is a nonparametric method that operates via recursive partitioning. It aims at identifying subgroups of individuals who have a higher or lower probability of achieving a particular binary outcome.[29] Remission and response at the end of the first 6 months of treatment were utilized as the binary outcomes for ROC analysis. For each measured potential predictor, cutoff points are generated at all values observed in the variable. The quality of a cutoff point is defined by its ability to divide the sample into 2 subsamples maximally distinct in the specified binary outcome. The cutoff point that yields the best prediction is identified across all values of all variables. That cutoff point is then used to divide the total sample into 2 subsamples. The same procedure is repeated systematically in each of the 2 subsamples. This iterative process continues until a stopping criterion is reached. The traditional stopping criterion for ROC analysis is either a subgroup size of less than 10 individuals or a failure to reach a significant group difference at $P < .05$ for any candidate cutoff value.[29] With a sample as large as the CALM trial, following these common stopping rules would result in a large number of high order interaction terms, which would be difficult to interpret. Therefore, we decided a priori to introduce additional stopping rules, namely stopping the analysis once the 3-way interaction level or a minimal subgroup size of less than 20 is reached. After the last step of the ROC analysis was reached, we calculated the probability of response and remission and presented results as hierarchical decision tree diagrams. Models were calculated for response and remission at 6 months as the outcome variable. The model was calculated using the same predictors as previous regression models (with the addition of rating score for all anxiety disorders—which were excluded from the regression analysis because of a large number of missing values). Separate ROC analyses were calculated for the UC and ITV subgroups.

RESULTS

Subjects

Demographic and clinical characteristics for the subjects were published previously.[7,8] The sample size for all models was 1,004.

Predictors of Treatment Outcome

Table 1A depicts baseline characteristics associated with response and remission in the CALM trial within the overall sample in simple logistic regression. There were a large number of factors associated with treatment remission in CALM. Baseline characteristics associated with response to treatment were similar to those associated with remission and are also depicted in Table 1A. Table 1A also depicts the baseline characteristics associated with response and remission within ITV and UC separately.

Baseline Characteristics Associated With Differential Outcome by Treatment Assignment

Figure 1 displays baseline characteristics that demonstrated significant interactions with treatment assignment in predicting treatment outcome. These interactions identify baseline patient characteristics that were associated with a particular benefit of ITV as opposed to UC. Gender, satisfaction with previous treatment, baseline depression, and GAD severity as well as reported personal and family income displayed significant interactions with treatment assignment. Female gender was associated with lower likelihood of treatment response and remission in UC but had an improved outcome in ITV. Low patient satisfaction with previous treatment was associated with worse treatment response and remission in UC but had little effect on treatment outcome in ITV. Low personal and family income was associated with a lower likelihood of treatment response in UC but had no association with outcome in ITV. Greater severity of depression and GAD symptoms was associated

Table 1. Moderators of Treatment Response and Remission Using Regression Analysis

Table 1A — **Simple Regression**

	Remission									Response								
	Overall			Collaborative Care			Usual Care			Overall			Collaborative Care			Usual Care		
Baseline Characteristics (categorical)	OR (95% CI)	*P*	Pseudo-R^2	OR (95% CI)	*P*	Pseudo-R^2	OR (95% CI)	*P*	Pseudo-R^2	OR (95% CI)	*P*	Pseudo-R^2	OR (95% CI)	*P*	Pseudo-R^2	OR (95% CI)	*P*	Pseudo-R^2
Intervention assignment	2.03 (1.53–2.69)	.0001***	0.0278							2.32 (1.77–3.04)	.0001***	0.0422						
Major depression (current)	0.53 (0.40–0.71)	.0001***	0.0211	0.66 (0.45–0.98)	.0371*	0.0097	0.38 (0.25–0.59)	.0001***	0.0431	0.67 (0.51–0.88)	.0045**	0.0092	0.73 (0.49–1.09)	.1225	0.01	0.57 (0.38–0.86)	.0065**	0.0171
Suicidality																		
"Better off dead"	0.52 (0.36–0.75)	.0005***	0.0145	0.60 (0.37–0.96)	.0343*	0.0103	0.41 (0.22–0.75)	.0039**	0.0219	0.56 (0.40–0.79)	.0008***	0.0132	0.61 (0.39–0.97)	.0364*	0.01	0.48 (0.28–0.81)	.0057**	0.0190
Primary diagnosis																		
Social phobia	0.43 (0.22–0.84)	.0137*	0.0079	0.56 (0.25–1.26)	.1593	0.0047	0.20 (0.05–0.88)	.0329*	0.0160	0.67 (0.38–1.18)	.1659	0.0022	1.06 (0.49–2.27)	.8910	0.00	0.30 (0.10–0.87)	.0274*	0.0142
Marital status																		
Married	1.26 (0.96–1.66)	.0995	0.0031	1.16 (0.79–1.68)	.4515	0.0013	1.44 (0.94–2.20)	.0924	0.0066	1.34 (1.03–1.75)	.0316*	0.0053	1.15 (0.79–1.68)	.4705	0.00	1.64 (1.10–2.43)	.0147*	0.0139
Divorced	0.63 (0.42–0.95)	.0268*	0.0059	0.69 (0.41–1.18)	.1740	0.004	0.56 (0.29–1.06)	.0745	0.008	0.68 (0.47–0.98)	.0393*	0.005	0.73 (0.43–1.22)	.2239	0.003	0.61 (0.35–1.08)	.0903	0.007
Employment status (1 = unemployed)	0.65 (0.45–0.94)	.0211*	0.0063	0.68 (0.41–1.11)	.1195	0.006	0.63 (0.35–1.10)	.1053	0.006	0.63 (0.45–0.89)	.0086**	0.008	0.59 (0.37–0.96)	.0323*	0.010	0.68 (0.41–1.13)	.1388	0.005
Disability	0.28 (0.16–0.48)	.0001***	0.0303	0.27 (0.14–0.54)	.0002***	0.036	0.28 (0.12–0.67)	.0041**	0.025	0.36 (0.23–0.56)	.0001***	0.026	0.36 (0.20–0.65)	.0006***	0.027	0.33 (0.16–0.68)	.0025**	0.025
Medical insurance																		
Medicare	0.53 (0.34–0.84)	.0071**	0.0089	0.39 (0.21–0.75)	.0043**	0.020	0.76 (0.39–1.47)	.4185	0.002	0.61 (0.41–0.92)	.0193*	0.006	0.44 (0.25–0.79)	.0058**	0.017	0.86 (0.48–1.56)	.6295	0.001
Medicaid	0.40 (0.23–0.69)	.0011**	0.0140	0.30 (0.14–0.63)	.0016**	0.026	0.57 (0.26–1.26)	.1631	0.005	0.59 (0.37–0.93)	.0227*	0.006	0.43 (0.23–0.81)	.0093**	0.016	0.81 (0.42–1.59)	.5410	0.001
Private insurance	1.90 (1.35–2.68)	.0003***	0.0161	1.97 (1.25–3.08)	.0033**	0.020	1.96 (1.13–3.39)	.0169*	0.014	1.43 (1.05–1.95)	.0249*	0.006	1.47 (0.96–2.26)	.0785	0.007	1.48 (0.92–2.39)	.1053	0.006
Gender (1 = male)	1.22 (0.90–1.66)	.1910	0.0019	0.89 (0.58–1.35)	.5730	0.001	1.85 (1.18–2.90)	.0072**	0.016	1.07 (0.80–1.43)	.6692	0.000	0.71 (0.47–1.07)	.0992	0.006	1.69 (1.11–2.59)	.0152*	0.014
High school	2.05 (0.97–4.35)	.0616	0.0045	3.91 (1.31–11.69)	.0147*	0.017	1.00 (0.00–1.00)	.9970	0.000	1.43 (0.75–2.71)	.2784	0.001	1.81 (0.78–4.21)	.1709	0.004	1.17 (0.43–3.19)	.7536	0.000
Medication																		
Benzodiazepines taken for 2 mo	0.47 (0.32–0.69)	.0001***	0.0183	0.51 (0.31–0.84)	.0082**	0.017	0.51 (0.31–0.84)	.0037**	0.023	0.58 (0.41–0.82)	.0022**	0.011	0.67 (0.42–1.07)	.0956	0.006	0.45 (0.26–0.79)	.0049**	0.020
Baseline Characteristics (continuous)	**OR (95% CI)**	***P***	**Pseudo-R^2**	**OR (95% CI)**	***P***	**Pseudo-R^2**	**OR (95% CI)**	***P***	**Pseudo-R^2**	**OR (95% CI)**	***P***	**Pseudo-R^2**	**OR (95% CI)**	***P***	**Pseudo-R^2**	**OR (95% CI)**	***P***	**Pseudo-R^2**
OASIS baseline score	0.89 (0.85–0.94)	.0001***	0.0217	0.88 (0.82–0.94)	.0002***	0.032	0.91 (0.84–0.98)	.0158*	0.014	0.97 (0.93–1.02)	.2648	0.001	0.96 (0.89–1.02)	.1869	0.004	0.99 (0.92–1.06)	.7647	0.000
GADSS baseline score	0.85 (0.81–0.89)	.0001***	0.0772	0.89 (0.84–0.94)	.0001***	0.047	0.79 (0.73–0.85)	.0001***	0.126	0.92 (0.88–0.96)	.0001***	0.026	0.94 (0.89–0.99)	.0262*	0.015	0.89 (0.83–0.95)	.0004***	0.042
PHQ-9 baseline score	0.65 (0.58–0.74)	.0001***	0.0638	0.73 (0.63–0.85)	.0001***	0.041	0.52 (0.43–0.64)	.0001***	0.108	0.80 (0.72–0.89)	.0001***	0.023	0.84 (0.73–0.98)	.0234*	0.016	0.73 (0.61–0.86)	.0002***	0.039
PCL-C baseline score	0.94 (0.91–0.98)	.0006***	0.0810	0.94 (0.90–0.98)	.0023**	0.127	0.95 (0.89–1.02)	.1425	0.029	0.98 (0.95–1.01)	.1074	0.017	0.97 (0.94–1.01)	.1471	0.027	0.99 (0.94–1.03)	.5668	0.004
PDSS baseline score	0.91 (0.87–0.94)	.0001***	0.0669	0.89 (0.85–0.94)	.0001***	0.089	0.92 (0.87–0.97)	.0036**	0.043	0.96 (0.93–1.00)	.0252*	0.012	0.95 (0.91–1.00)	.0420*	0.020	0.98 (0.93–1.03)	.3367	0.005
SPIN baseline score	0.97 (0.95–0.99)	.0005***	0.0355	0.96 (0.94–0.99)	.0029**	0.050	0.98 (0.95–1.00)	.0448*	0.024	0.98 (0.97–1.00)	.0222*	0.015	0.99 (0.97–1.01)	.2500	0.007	0.97 (0.95–1.00)	.0300*	0.028
Self-efficacy expectancy	1.11 (1.01–1.23)	.0369*	0.0051	1.06 (0.92–1.21)	.4140	0.002	1.19 (1.02–1.39)	.0304*	0.011	1.18 (1.07–1.30)	.0008***	0.013	1.17 (1.02–1.34)	.0267*	0.011	1.20 (1.04–1.39)	.0110*	0.016
Outcome expectancy	1.15 (1.06–1.26)	.0013**	0.0122	1.14 (1.01–1.29)	.0317*	0.011	1.16 (1.02–1.31)	.0268*	0.012	1.15 (1.06–1.25)	.0006***	0.014	1.13 (1.00–1.27)	.0438*	0.009	1.17 (1.04–1.32)	.0091**	0.016
Personal income (in 10,000)	1.03 (1.00–1.06)	.0416*	0.0074	1.01 (0.99–1.04)	.4050	0.002	1.08 (1.01–1.15)	.0206*	0.019	1.03 (1.00–1.07)	.0519	0.007	1.00 (0.98–1.02)	.9256	0.000	1.15 (1.08–1.23)	.0001***	0.049
Family income (in 10,000)	1.02 (1.00–1.04)	.0344*	0.0068	1.01 (0.99–1.04)	.3580	0.002	1.04 (1.00–1.08)	.0275*	0.015	1.02 (1.00–1.05)	.0462*	0.006	1.00 (0.98–1.02)	.8746	0.000	1.06 (1.02–1.10)	.0036**	0.027
Subjective measures																		
Perceived lack of money (1–3)	0.63 (0.51–0.79)	.0001***	0.0200	0.62 (0.46–0.84)	.0016**	0.023	0.60 (0.43–0.83)	.0020**	0.022	0.71 (0.58–0.88)	.0013**	0.012	0.70 (0.52–0.95)	.0202*	0.012	0.66 (0.49–0.90)	.0081**	0.016
Belief in therapy (1–5)	1.22 (1.00–1.48)	.0452*	0.0047	1.07 (0.82–1.38)	.6358	0.001	1.45 (1.07–1.98)	.0179*	0.014	1.29 (1.07–1.55)	.0072**	0.008	1.28 (0.99–1.66)	.0651	0.008	1.31 (0.99–1.72)	.0567	0.009
Step on socioeconomic ladder (1–10)	1.26 (1.16–1.37)	.0001***	0.0347	1.24 (1.11–1.38)	.0001***	0.034	1.31 (1.15–1.50)	.0001***	0.039	1.22 (1.13–1.32)	.0001***	0.029	1.20 (1.08–1.34)	.0009***	0.025	1.28 (1.13–1.44)	.0001***	0.037
Step on community ladder (1–10)	1.18 (1.10–1.26)	.0001***	0.0245	1.19 (1.08–1.30)	.0002***	0.031	1.17 (1.05–1.31)	.0064**	0.018	1.16 (1.09–1.24)	.0001***	0.023	1.19 (1.09–1.31)	.0001***	0.034	1.13 (1.02–1.26)	.0179*	0.013
Help-seeking behavior (3–12)	0.98 (0.91–1.05)	.5248	0.0005	0.97 (0.88–1.08)	.6054	0.001	0.97 (0.86–1.09)	.5679	0.001	0.93 (0.87–1.00)	.0580	0.004	0.89 (0.81–0.99)	.0314*	0.011	0.96 (0.86–1.07)	.4506	0.001
Smoking (cigarettes/day)	0.96 (0.94–0.99)	.0043*	0.0117	0.96 (0.92–0.99)	.0190*	0.015	0.97 (0.94–1.01)	.1305	0.007	0.98 (0.96–1.00)	.0307*	0.006	0.98 (0.95–1.01)	.1733	0.004	0.98 (0.95–1.01)	.1644	0.005
Patient satisfaction (2–10)	1.10 (1.02–1.18)	.0197*	0.0066	1.02 (0.92–1.14)	.6955	0.000	1.22 (1.08–1.38)	.0014**	0.026	1.08 (1.01–1.16)	.0364*	0.005	1.01 (0.91–1.12)	.8531	0.000	1.18 (1.06–1.32)	.0026**	0.023
CBT techniques used in previous treatment (6–24)	0.95 (0.90–1.00)	.0393*	0.0052	0.96 (0.89–1.02)	.1911	0.004	0.93 (0.86–1.01)	.1016	0.007	1.00 (0.95–1.04)	.8337	0.000	1.01 (0.95–1.08)	.7589	0.000	0.98 (0.92–1.05)	.5670	0.001
Social support (1–5)	1.38 (1.20–1.58)	.0001***	0.0254	1.25 (1.04–1.49)	.0162*	0.013	1.64 (1.33–2.03)	.0001***	0.051	1.34 (1.18–1.53)	.0001***	0.024	1.27 (1.06–1.52)	.0091**	0.015	1.51 (1.24–1.83)	.0001***	0.041

(continued)

Table 1 (continued). Moderators of Treatment Response and Remission Using Regression Analysis

Table 1B — **Multiple Regression**

	Remission						Response					
	Overall		Collaborative Care		Usual Care		Overall		Collaborative Care		Usual Care	
Independent Predictors	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Intervention assignment	2.34 (1.68–3.25)	.0001***					2.52 (1.85–3.44)	.0001***				
PHQ-9 score baseline	0.95 (0.92–0.97)	.0001***	0.96 (0.93–1.00)	.0243*	0.90 (0.86–0.94)	.0001***						
Patient satisfaction	1.12 (1.02–1.23)	.0215*			1.26 (1.08–1.46)	.0026**					1.18 (1.04–1.34)	.0118*
Step on socioeconomic ladder					1.26 (1.06–1.49)	.0085**	1.14 (1.03–1.26)	.0105*			1.19 (1.02–1.38)	.0275*
Step on community ladder	1.14 (1.05–1.25)	.0019**	1.14 (1.03–1.26)	.0093**			1.11 (1.02–1.21)	.0195*	1.18 (1.07–1.29)	.0006***		
Benzodiazepines taken for 2 mo	0.49 (0.31–0.76)	.0017**			0.30 (0.14–0.64)	.0019**					0.33 (0.17–0.63)	.0007***
Social support							1.24 (1.07–1.44)	.0053**				
Social phobia	0.42 (0.19–0.91)	.0286*										
Lack of money	0.72 (0.56–0.93)	.0119*										
Belief in therapy	1.31 (1.04–1.65)	.0216*										
CBT techniques used in previous treatment	0.94 (0.88–1.00)	.0394*					0.52 (0.35–0.76)	.0010***				
Self-efficacy expectancy							1.15 (1.03–1.28)	.0163*				
Gender (male)					2.29 (1.32–3.96)	.0032**					1.69 (1.01–2.84)	.0450*
Disability			0.37 (0.18–0.78)	.0086**					0.41 (0.23–0.75)	.0039**		
Personal income											1.00 (1.00–1.00)	.0171*
Smoking			0.96 (0.93–1.00)	.0480*								
High school			3.44 (1.11–10.67)	.0321*								
Pseudo-R^2	0.1419		0.096		0.181		0.116		0.052		0.141	

Table 1A depicts the results of simple logistic regression analysis examining baseline demographic, social, and clinical characteristics associated with remission and response at 6 months of treatment overall and by treatment condition.

Table 1B depicts the results of backward-stepwise multiple logistic regression models predicting remission and response rates at 6 months of treatment overall and by treatment condition. GADSS, PCL-C, PDSS, and SPIN scales needed to be excluded from multiple regression analysis due to a large number of missing values.

*$P < .05$. **$P < .01$. ***$P < .001$.

Abbreviations: GADSS = Generalized Anxiety Disorder Severity Scale, OASIS = Overall Anxiety Severity and Impairment Scale, PCL-C = PTSD Checklist–Civilian Version, PDSS = Panic Disorder Severity Scale, PHQ-9 = Patient Health Questionnaire-9, SPIN = Social Phobia Inventory.

with lower likelihood of remission across treatment assignments but had a greater association with outcome in UC.

Backward-Stepwise Multiple Logistic Regression Models Predicting Treatment Outcome

Table 1B depicts the results of the best fitting backward-stepwise models depicting treatment outcome in the overall sample and within UC and ITV separately. Stepwise logistic regression models were able to explain 12%–14% of the variance in treatment outcome (pseudo-R^2) in the overall sample, 14%–18% in UC, and only 5%–10% in ITV.

Overall ROC Analysis

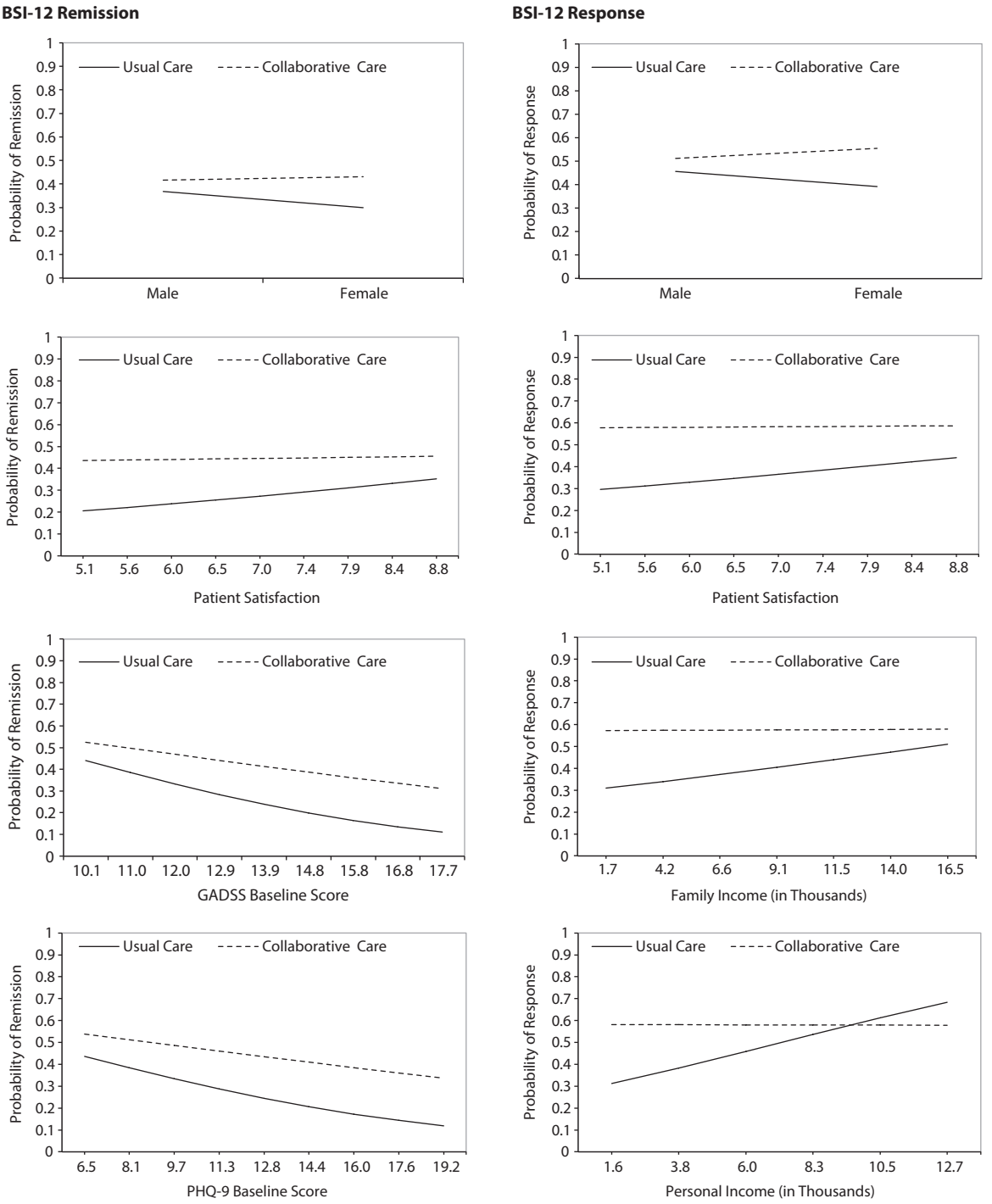
Figure 2A displays hierarchical prognostic subgroups for remission at 6 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as a 14.7% likelihood of remitting (moderate to severe depression severity [PHQ-9 ≥ 8], random assignment to UC, and personal income less than $50,000 per year) to as high as a 67.2% likelihood of remitting (low depression severity [PHQ-9 < 8] and higher perceived step on socioeconomic ladder [≥ 6]). The most discriminative predictor of remission was depression severity at baseline (PHQ-9 baseline score with a threshold of 8) ($\chi^2_{1,876} = 56.9$, $P < .001$).

Figure 2B displays hierarchical prognostic subgroups for response at 6 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as 25.2% likelihood of responding (UC, social support some of the time or less, PHQ-9 ≥ 7) to as high as 70.4% likelihood of responding (ITV, step on the community ladder ≥ 5, age < 50 years). Random treatment assignment was the most discriminative predictor of treatment outcome ($\chi^2_{1,876} = 37.5$, $P < .001$).

ROC Analysis Within ITV Intervention

Figure 3A displays hierarchical prognostic subgroups for remission of anxiety symptoms at 6 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as 20.2% likelihood of remitting (low perceived step on socioeconomic ladder [< 6], high severity of GAD symptoms [GADSS ≥ 12], and previous medication use for depression) to as high as 62.9% likelihood of remitting (high perceived step on socioeconomic ladder [≥ 6],

Figure 1. Baseline Characteristics Associated With Differential Outcome by Treatment Assignment[a]

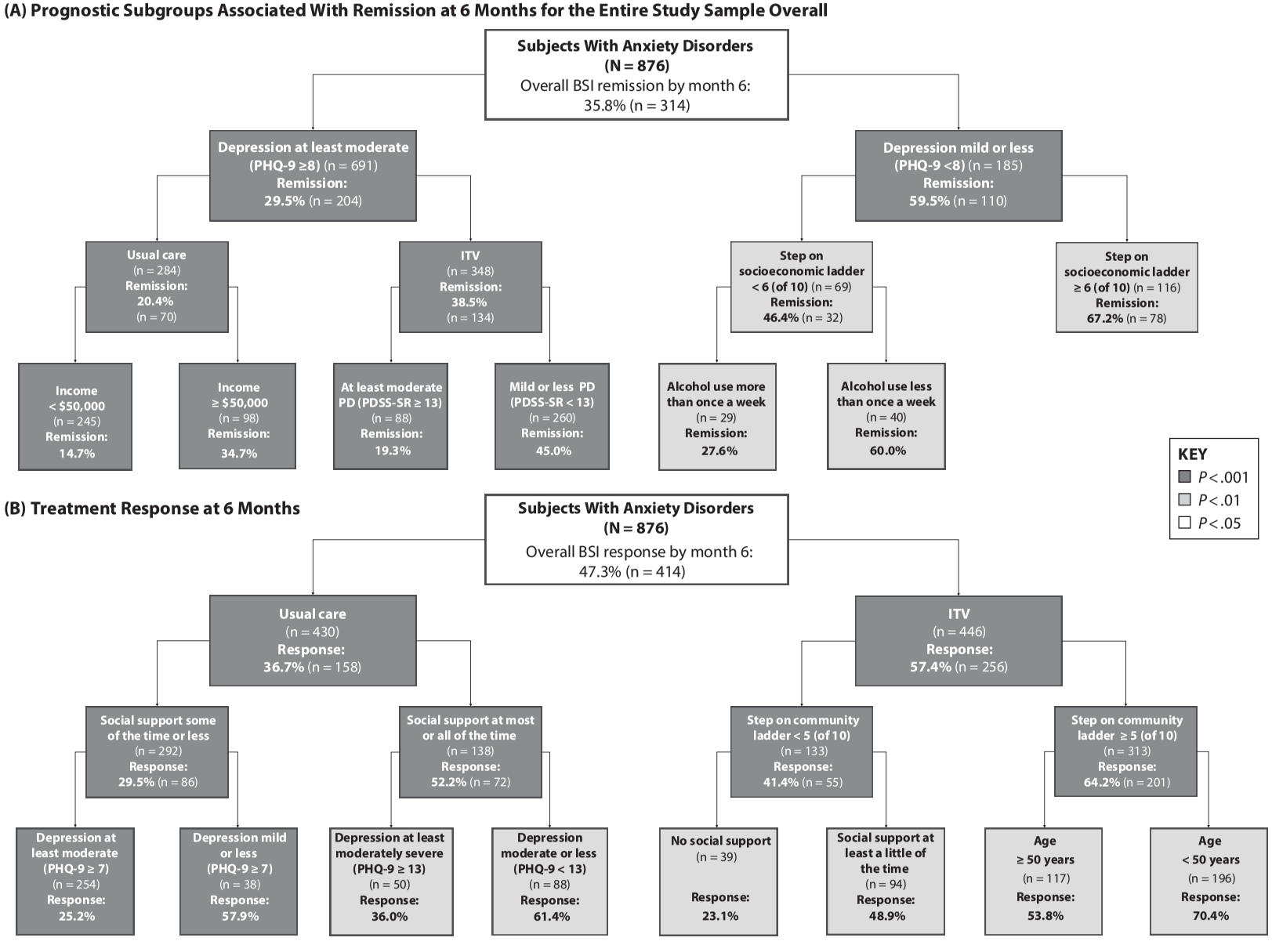


[a]Remission = score of < 6 on BSI-12; response = at least 50% reduction on BSI-12 or meeting remission criteria.
Abbreviations: BSI-12 = 12-item Brief Symptom Inventory, GADSS = Generalized Anxiety Disorder Severity Scale, PHQ-9 = Patient Health Questionnaire-9.

high perceived step on community ladder [≥ 7]). The most discriminative predictor of remission was perceived step on socioeconomic ladder at threshold of 6 ($\chi^2_{1,446} = 16.1$, $P < .001$).

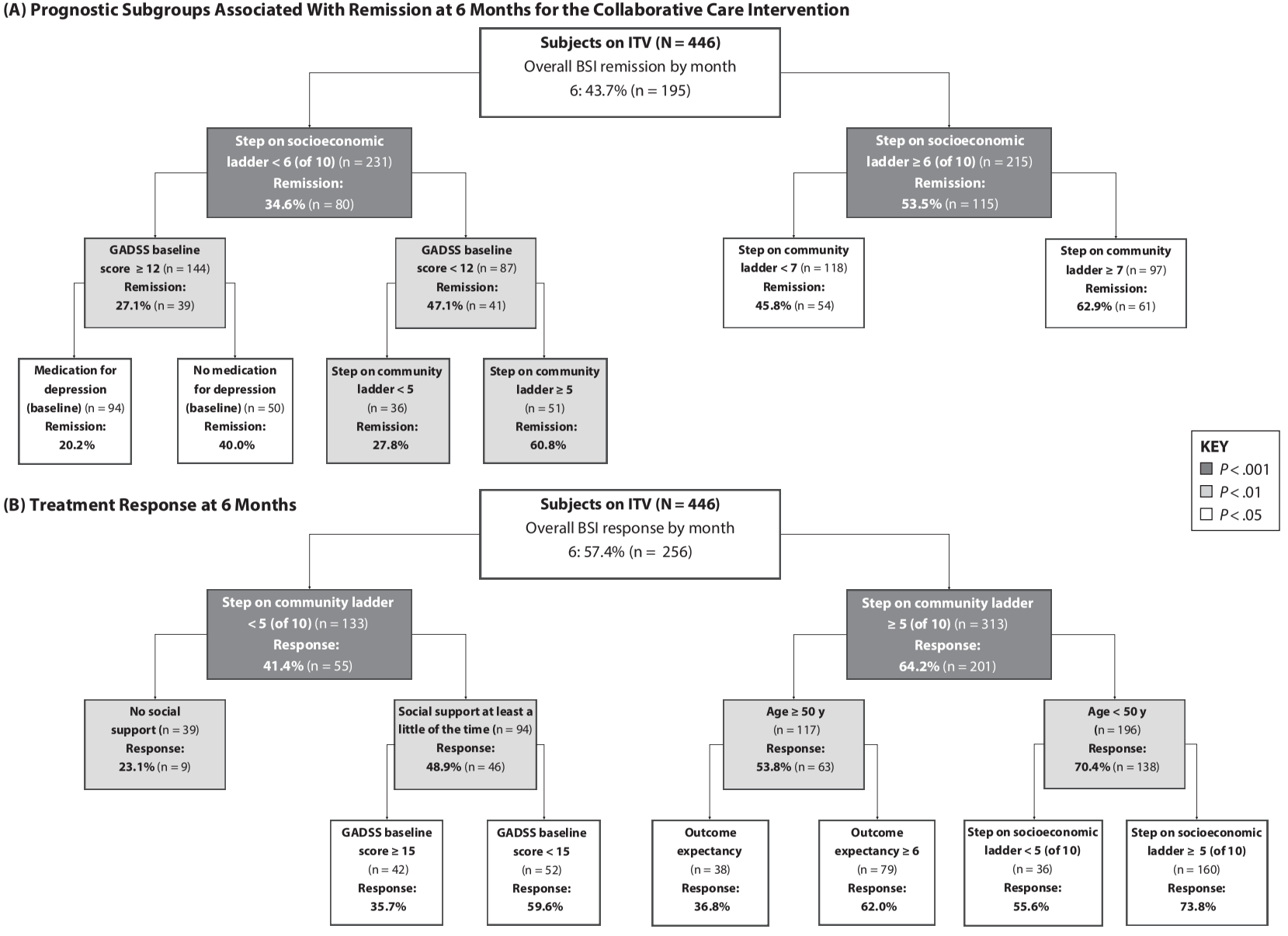
Figure 3B displays hierarchical prognostic subgroups for response at 6 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as 23.1% likelihood of responding (low perceived step on community ladder [< 5] and perceived lack of social support) to as high as 73.8% likelihood of responding (high perceived step on community ladder [≥ 5], age < 50 years, and high perceived step on socioeconomic ladder [≥ 5]). The most discriminative predictor of response was perceived step on community ladder at threshold of 5 ($\chi^2_{1,446} = 20.0$, $P < .001$).

Figure 2. Overall Treatment Outcome at 6 Months: Receiver Operating Curve (ROC) Analysis



Abbreviations: BSI = Brief Symptom Inventory, ITV =Collaborative Care Intervention, PD = panic disorder, PDSS-SR = Panic Disorder Severity Scale–Self-Report, PHQ-9 = Patient Health Questionnaire-9.

Figure 3. Collaborative Care Intervention at 6 Months: Receiver Operating Curve (ROC) Analysis



Abbreviations: BSI = Brief Symptom Inventory, GADSS = Generalized Anxiety Disorder Severity Scale, ITV = Collaborative Care Intervention.

ROC Analysis Within Usual Care

Figure 4A displays hierarchical prognostic subgroups for remission at 6 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as 13.6% likelihood of remitting (PHQ-9 ≥ 9, income < $50,000) to as high as 60.3% likelihood of remitting (PHQ-9 < 7). The most discriminative predictor of remission was PHQ-9 with threshold of 9 [$\chi^2_{1,430} = 43.5$, $P < .001$].

Figure 4B displays hierarchical prognostic subgroups for response at 6 months of treatment. Baseline clinical characteristics were able to identify subgroups with as low as 20.7% likelihood of responding (social support some of the time or less, PHQ-9 ≥ 7, income < $50,000) to as high as 73.5% likelihood of responding (social support most of the time, PHQ-9 < 13, OASIS ≥ 10). The most discriminative predictor was social support with threshold of most versus some of the time ($\chi^2_{1,430} = 20.8$, $P < .001$).

DISCUSSION

Moderator analyses of the CALM trial yielded several types of patient characteristics strongly and consistently associated with treatment outcome. Presence and severity of comorbid depressive symptoms were strongly associated with poorer outcomes to the anxiety disorder treatment. Overall severity of anxiety disorder symptoms was negatively associated with likelihood of both remission and response. Beyond clinical characteristics, several measures indicating poor socioeconomic status were also strongly associated with poor treatment response, including unemployment, personal income, and current receipt of disability payment. Additionally, patients' self-ratings of socioeconomic variables such as perceived ranking on community and socioeconomic ladder, perceived lack of money, and perceived degree of social supports were all strongly negatively associated with likelihood of treatment response.

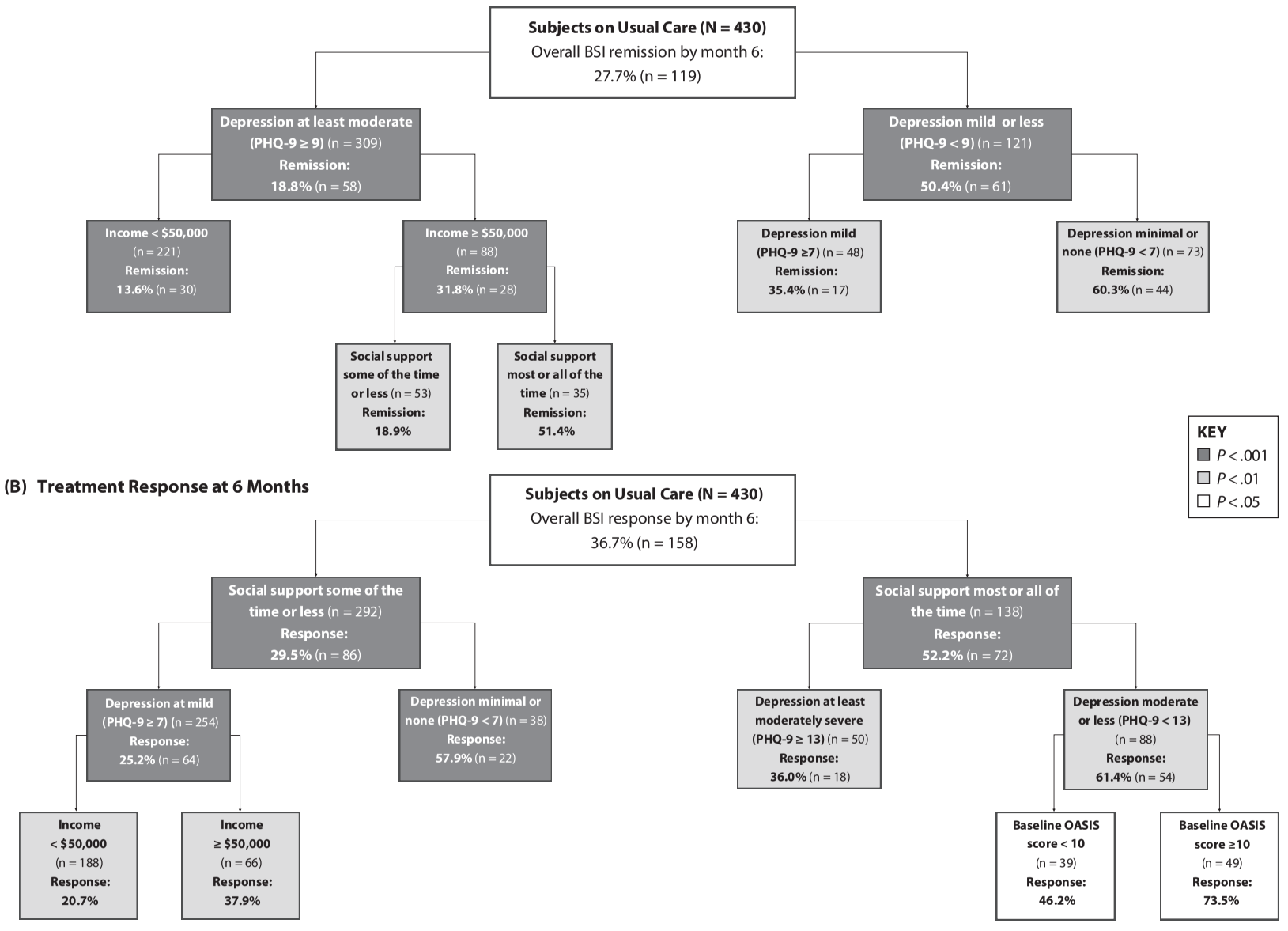
The ITV model in the CALM trial involving pharmacotherapy, computer-assisted CBT, or both was demonstrated to be highly effective compared to UC.[8] Consistent with its overall efficacy, random assignment to ITV was typically the most or one of the most discriminant predictors of treatment outcome in the trial. Moderator analysis demonstrated characteristics of patients who may particularly benefit from ITV. Those patients who were female, who had an anxiety disorder with greater severity of GAD or comorbid depression, who had low personal and family income, and who had low treatment satisfaction with previous treatment appear to particularly benefit from ITV compared to UC.

Depression is a particularly common comorbidity in patients with anxiety disorders. More than half of CALM trial participants were at least moderately depressed; this subgroup was half as likely to remit at 6 months compared to those with mild or no depression. These findings are consistent with previous research illustrating that comorbid depression leads to poorer outcomes among those with anxiety disorders[30–32]; however, results have been mixed.[33,34] CALM authors found that in the ITV group, twice the percentage of depressed patients achieved remission at 6 months compared to those in the UC group, although results did not reach significance at their a priori threshold of $P < .01$.[35] In our analysis, ITV led to relatively improved treatment outcomes in those with more severe depression. In the context of comorbid depression, enhanced interventions such as the collaborative care model may be particularly necessary. Our analysis also suggested that overall severity of principal anxiety disorders and comorbid GAD are associated with poorer outcomes. This result converges with some past literature,[9,36,37] but stands in contrast to others.[38–40] Aaronson et al[41] actually found that greater baseline severity of panic disorder led to increased response rates and that comorbidity of GAD and of depression did not predict outcome. Perhaps disorder-specific outcome predictors and degree of baseline symptom improvement, independent of remission/response cutpoints, should be explored as well.

Low socioeconomic status (perceived or actual) was highly predictive of poor treatment response and remission across the entire sample in both our logistic regression and ROC analyses. These results alone are not surprising, given the robust associations between lower socioeconomic status and poor mental health.[13,42–45] More broadly, researchers have been studying the relationship between physical health and associated indices of socioeconomic status (eg, employment status, education level, household income) for decades.[46,47] Findings have indicated that lower socioeconomic status increases risk and contributes to poor outcomes for a wide range of health conditions such as type II diabetes, cardiovascular diseases, cancer, cystic fibrosis, and mortality.[48–52] Underlying explanations for poorer outcomes remain unclear, although some point to factors such as decreased utilization of services, lack of insurance, reduced care quality, financial strain, and ongoing chronic stress.[46,53–56] In the CALM trial, some of the barriers, such as service utilization, were accounted for, yet low socioeconomic status still seemed to be associated with poorer outcomes. In the context of such a stable finding, it is especially encouraging that ITV treatment dampened the impact of low socioeconomic status on treatment outcome as compared to UC.

These findings should be considered in the context of several limitations to our methodological approach. Our logistic regression and ROC analyses were exploratory in nature rather than hypothesis-driven, and therefore require independent replication. It is likely, given the number of independent logistic regression analyses performed, that some of the reported findings are false-positives. However, the statistical advantages of ROC analysis allowed for exploration of higher-order interactions between clinical variables and identification of homogenous prognostic subgroups based on easily measurable clinical characteristics. Second, generalizability of the collaborative care model requires significant engagement on the part of the physicians, care managers, and patients. Nonetheless, the CALM study is critical in demonstrating definitive efficacy of the ITV treatment when implemented correctly across multiple sites. On the other hand, the study design does not allow a

Figure 4. Usual Care Treatment Arm at 6 Months: Receiver Operating Curve (ROC) Analysis



Abbreviations: BSI = Brief Symptom Inventory, PHQ-9 = Patient Health Questionnaire-9, OASIS = Overall Anxiety Severity and Impairment Scale.

closer examination of differential effectiveness of individual medications and therapies within each treatment assignment.

CONCLUSION

This secondary analysis of the CALM trial demonstrated: (1) particular characteristics of patients with anxiety disorders associated with poor treatment outcome—comorbid depression, increased severity of underlying anxiety disorder(s), low socioeconomic status (perceived and actual), and limited social support; (2) particular patient characteristics associated with particular benefit from the ITV intervention—female, increased depression and GAD severity, and low socioeconomic status; and (3) prognostic subgroup identifying likelihood of treatment response of individual patients with anxiety disorders. Based on these findings, future treatment research and practice should focus on implementing the ITV model within community care centers where it appears it may particularly benefit patients.

Author affiliations: Yale OCD Research Clinic and Department of Psychiatry, Yale University, New Haven (Dr Bloch and Mr Kelly) and the Connecticut Mental Health Center and the Yale Child Study Center in New Haven, Connecticut (Dr Bloch and Mr Jakubovski).
Author contributions: Messrs Kelly and Jakubovski contributed equally to the production of this manuscript.
Potential conflicts of interest: None reported.
Funding/support: The authors acknowledge the support of the US National Institutes of Health (NIH) grant 1K23MH091240 (Dr Bloch), the APIRE/Eli Lilly Psychiatric Research Fellowship (Dr Bloch), the Rembrandt Foundation (Dr Bloch), and grant UL1 RR024139 from the National Center for Research Resources, a component of the National Institutes of Health, and NIH Roadmap for Medical Research (Dr Bloch). Data used in the preparation of this article were obtained from the limited access datasets distributed from the NIH-supported "Coordinated Anxiety Learning and Management" (CALM). CALM focused on anxiety disorders adults seen in primary care settings.
Additional information: The Limited Access Dataset from the CALM Trial can be requested by investigators at http://www.nimh.nih.gov/funding/clinical-trials-for-researchers/datasets/nimh-procedures-for-requesting-data-sets.shtml.

REFERENCES

1. Kessler RC, Ruscio AM, Shear K, et al. Epidemiology of anxiety disorders. *Curr Top Behav Neurosci*. 2010;2:21–35.
2. Kessler RC, Petukhova M, Sampson NA, et al. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res*. 2012;21(3):169–184.
3. Sareen J, Cox BJ, Afifi TO, et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. *Arch Gen Psychiatry*. 2005;62(11):1249–1257.
4. Sareen J, Jacobi F, Cox BJ, et al. Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions. *Arch Intern Med*. 2006;166(19):2109–2116.
5. Wang PS, Berglund P, Kessler RC. Recent care of common mental disorders in the United States: prevalence and conformance with evidence-based recommendations. *J Gen Intern Med*. 2000;15(5):284–292.
6. Kessler RC, Demler O, Frank RG, et al. Prevalence and treatment of mental disorders, 1990 to 2003. *N Engl J Med*. 2005;352(24):2515–2523.
7. Craske MG, Stein MB, Sullivan G, et al. Disorder-specific impact of coordinated anxiety learning and management treatment for anxiety disorders in primary care. *Arch Gen Psychiatry*. 2011;68(4):378–388.
8. Roy-Byrne P, Craske MG, Sullivan G, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *JAMA*. 2010;303(19):1921–1928.
9. Brown TA, Barlow DH. Long-term outcome in cognitive-behavioral treatment of panic disorder: clinical predictors and alternative strategies for assessment. *J Consult Clin Psychol*. 1995;63(5):754–765.
10. Collimore KC, Rector NA. Symptom and cognitive predictors of treatment response in CBT for social anxiety disorder. *Int J Cogn Ther*. 2012;5(2):157–169.
11. van Balkom AJ, van Boeijen CA, Boeke AJ, et al. Comorbid depression, but not comorbid anxiety disorders, predicts poor outcome in anxiety disorders. *Depress Anxiety*. 2008;25(5):408–415.
12. Dreessen L, Arntz A. The impact of personality disorders on treatment outcome of anxiety disorders: best-evidence synthesis. *Behav Res Ther*. 1998;36(5):483–504.
13. Cohen A, Gilman SE, Houck PR, et al. Socioeconomic status and anxiety as predictors of antidepressant treatment response and suicidal ideation in older adults. *Soc Psychiatry Psychiatr Epidemiol*. 2009;44(4):272–277.
14. Ronalds C, Creed F, Stone K, et al. Outcome of anxiety and depressive disorders in primary care. *Br J Psychiatry*. 1997;171(5):427–433.
15. Southam-Gerow MA, Kendall PC, Weersing VR. Examining outcome variability: correlates of treatment response in a child and adolescent anxiety clinic. *J Clin Child Psychol*. 2001;30(3):422–436.
16. Stein DJ, Stein MB, Pitts CD, et al. Predictors of response to pharmacotherapy in social anxiety disorder: an analysis of 3 placebo-controlled paroxetine trials. *J Clin Psychiatry*. 2002;63(2):152–155.
17. Sullivan G, Craske MG, Sherbourne C, et al. Design of the Coordinated Anxiety Learning and Management (CALM) study: innovations in collaborative care for anxiety disorders. *Gen Hosp Psychiatry*. 2007;29(5):379–387.
18. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
19. Campbell-Sills L, Norman SB, Craske MG, et al. Validation of a brief measure of anxiety-related severity and impairment: the Overall Anxiety Severity and Impairment Scale (OASIS). *J Affect Disord*. 2009;112(1–3):92–101.
20. Derogatis LR. *BSI 18, Brief Symptom Inventory 18: Administration, Scoring and Procedures Manual*. Minneapolis, MN: NCS Pearson, Inc; 2001.
21. Simon GE, Katon WJ, VonKorff M, et al. Cost-effectiveness of a collaborative care program for primary care patients with persistent depression. *Am J Psychiatry*. 2001;158(10):1638–1644.
22. Houck PR, Spiegel DA, Shear MK, et al. Reliability of the self-report version of the panic disorder severity scale. *Depress Anxiety*. 2002;15(4):183–185.
23. Shear K, Belnap BH, Mazumdar S, et al. Generalized Anxiety Disorder Severity Scale (GADSS): a preliminary validation study. *Depress Anxiety*. 2006;23(2):77–82.
24. Connor KM, Davidson JR, Churchill LE, et al. Psychometric properties of the Social Phobia Inventory (SPIN): new self-rating scale. *Br J Psychiatry*. 2000;176(4):379–386.
25. Ruggiero KJ, Del Ben K, Scotti JR, et al. Psychometric properties of the PTSD Checklist-Civilian Version. *J Trauma Stress*. 2003;16(5):495–502.
26. Weathers F, Litz B, Huska I, et al. The PTSD Checklist-Civilian Version (PCL-C). Boston, MA: National Center for PTSD Boston VA Medical Center; 1994.
27. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–613.
28. Bohn MJ, Babor TF, Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. *J Stud Alcohol*. 1995;56(4):423–432.
29. Kraemer H. Evaluating Medical Tests: Objective and Quantitative Guidelines. Newbury Park, CA: Sage Publications, Inc; 1992.
30. Berman SL, Weems CF, Silverman WK, et al. Predictors of outcome in exposure-based cognitive and behavioral treatments for phobic and anxiety disorders in children. *Behav Ther*. 2000;31(4):713–731.
31. Bruce SE, Yonkers KA, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *Am J Psychiatry*. 2005;162(6):1179–1187.
32. Ledley DR, Huppert JD, Foa EB, et al. Impact of depressive symptoms on the treatment of generalized social anxiety disorder. *Depress Anxiety*. 2005;22(4):161–167.
33. Abramowitz JS. Treatment of obsessive-compulsive disorder in patients who have comorbid major depression. *J Clin Psychol*. 2004;60(11):1133–1141.
34. Chambless DL, Tran GQ, Glass CR. Predictors of response to cognitive-behavioral group therapy for social phobia. *J Anxiety Disord*. 1997;11(3):221–240.
35. Campbell-Sills L, Sherbourne CD, Roy-Byrne P, et al. Effects of co-occurring depression on treatment for anxiety disorders: analysis of outcomes from a large primary care effectiveness trial. *J Clin Psychiatry*. 2012;73(12):1509–1516.
36. Penninx BW, Nolen WA, Lamers F, et al. Two-year course of depressive and anxiety disorders: results from the Netherlands Study of Depression and Anxiety (NESDA). *J Affect Disord*. 2011;133(1–2):76–85.
37. Ramnerö J, Ost LG. Prediction of outcome in the behavioural treatment of

panic disorder with agoraphobia. *Cogn Behav Ther*. 2004;33(4):176–180.
38. Wolitzky-Taylor KB, Arch JJ, Rosenfield D, et al. Moderators and non-specific predictors of treatment outcome for anxiety disorders: a comparison of cognitive behavioral therapy to acceptance and commitment therapy. *J Consult Clin Psychol*. 2012;80(5):786–799.
39. Olatunji BO, Cisler JM, Tolin DF. A meta-analysis of the influence of comorbidity on treatment outcome in the anxiety disorders. *Clin Psychol Rev*. 2010;30(6):642–654.
40. Newman MG, Przeworski A, Fisher AJ, et al. Diagnostic comorbidity in adults with generalized anxiety disorder: impact of comorbidity on psychotherapy outcome and impact of psychotherapy on comorbid diagnoses. *Behav Ther*. 2010;41(1):59–72.
41. Aaronson CJ, Shear MK, Goetz RR, et al. Predictors and time course of response among panic disorder patients treated with cognitive-behavioral therapy. *J Clin Psychiatry*. 2008;69(3):418–424.
42. Dohrenwend BP, Levav I, Shrout PE, et al. Socioeconomic status and psychiatric disorders: the causation-selection issue. *Science*. 1992;255(5047):946–952.
43. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of *DSM-III-R* psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(1):8–19.
44. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month *DSM-IV* disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617–627.
45. Andrade L, Caraveo-Anduaga JJ, Bergland P; WHO International Consortium in Psychiatric Epidemiology. Cross-national comparisons of the prevalences and correlates of mental disorders. *Bull World Health Organ*. 2000;78(4):413–426.
46. Adler NE, Snibbe AC. The role of psychosocial processes in explaining the gradient between socioeconomic status and health. *Curr Dir Psychol Sci*. 2003;12(4):119–123.
47. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. *Ann N Y Acad Sci*. 1999;896(1):3–15.
48. Stringhini S, Batty GD, Bovet P, et al. Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: the Whitehall II prospective cohort study. *PLoS Med*. 2013;10(7):e1001479.
49. Kanjilal S, Gregg EW, Cheng YJ, et al. Socioeconomic status and trends in disparities in 4 major risk factors for cardiovascular disease among US adults, 1971–2002. *Arch Intern Med*. 2006;166(21):2348–2355.
50. Clegg LX, Reichman ME, Miller BA, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. *Cancer Causes Control*. 2009;20(4):417–435.
51. Schechter MS, Shelton BJ, Margolis PA, et al. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. *Am J Respir Crit Care Med*. 2001;163(6):1331–1337.
52. Marmot MG, Smith GD, Stansfeld S, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet*. 1991;337(8754):1387–1393.
53. Lorant V, Kampfl D, Seghers A, et al. Socio-economic differences in psychiatric in-patient care. *Acta Psychiatr Scand*. 2003;107(3):170–177.
54. McAlpine DD, Mechanic D. Utilization of specialty mental health care among persons with severe mental illness: the roles of demographics, need, insurance, and risk. *Health Serv Res*. 2000;35(1 pt 2):277–292.
55. Roy-Byrne PP, Joesch JM, Wang PS, et al. Low socioeconomic status and mental health care use among respondents with anxiety and depression in the NCS-R. *Psychiatr Serv*. 2009;60(9):1190–1197.
56. Young AS, Klap R, Sherbourne CD, et al. The quality of care for depressive and anxiety disorders in the United States. *Arch Gen Psychiatry*. 2001;58(1):55–61.