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Predictors of Clinical Improvement in a Randomized Effectiveness Trial for Primary Care Patients with Panic Disorder

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Abstract

Objective—To prospectively examine demographic, clinical, and attitudinal variables that impact improvement among patients with panic disorder.

Methods—Subjects were 232 primary care patients meeting criteria for DSM-IV panic disorder. Eligible patients were randomly assigned to a collaborative care intervention or to treatment as usual. Assessments occurred at 3 month intervals during the course of 1 year.

Results—In final multivariate logistic regression models, patients with higher anxiety sensitivity and higher neuroticism scores at baseline were less likely to show clinical improvement (using a criterion of 20 or less on the Anxiety Sensitivity Index) at 3 months. Those who were non-Caucasian, had higher anxiety sensitivity, and higher overall phobic avoidance at baseline were less likely to show clinical improvement at 12 months.

Conclusion—A greater understanding of these predictors may help clinicians identify who is at greatest risk for persistent panic related symptoms and to plan the intensity of interventions accordingly.

Keywords

Panic Disorder; Predictors; Primary Care; Effectiveness Trial

Panic disorder is a common and disabling condition. According to the National Comorbidity Survey Replication (NCS-R), lifetime and 12-month prevalence rates in the general population are 4.7% and 2.7%, respectively (Kessler et al., 2005a; 2005b). In a recent study conducted in the primary care setting, the point prevalence of panic disorder was 6.8%

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(Kroenke et al., 2007). Prospective, naturalistic studies of panic disorder patients reveal that the clinical course of panic disorder is often chronic with some patients showing a more episodic pattern (Bruce et al., 2005). In both naturalistic and experimental studies, predictors of remission have typically included diagnostic and clinic severity factors (Chambless and Gracely, 1988; Keijsers et al., 1994; Sharp and Power, 1991).

In the Harvard Brown Anxiety Research Program naturalistic study, factors that were predictive of panic remission at 2 year follow up, included shorter duration of the disorder, less agoraphobic avoidance, social phobia, high socioeconomic status and good health status (Warshaw et al., 1997). At 12 year follow-up, patients with panic disorder without agoraphobia were most likely to have a recovery at all assessment points, however rates of recurrence were similar for both panic disorder with and without agoraphobia (Bruce et al., 2005). Additionally, the presence of comorbid major depressive disorder was associated with a less favorable outcome. In another prospective, naturalistic study of patients with panic disorder with or without agoraphobia (and no other non-anxiety psychiatric comorbidities), only duration of the disorder was related to recovery, remission, and relapse (Faravelli et al., 1995).

In pharmacological studies, diagnostic and clinical severity variables are frequent predictors of treatment response. In short-term pharmacotherapy studies (6–16 weeks), overall severity of illness, manifested variously as higher anxiety, higher phobic avoidance, higher panic, and comorbid personality disorders, are frequently cited predictors of poor treatment response. Demographic variables (e.g., gender, age, and marital status) were not reported as predictors in any of the studies, nor was a lower age of onset or the presence of comorbid anxiety disorders. Among patients who received long-term pharmacological treatment (1–7 years), many of the same illness variables (e.g., higher anxiety, higher phobic avoidance) and comorbid personality disorders were significant predictors (Slaap and den Boer, 2001). Longer duration of illness, comorbid anxiety and comorbid depressive disorders were also significant predictors of poor treatment response in more than half of the long-term treatment studies where it was assessed. Subsequent to the Slaap and den Boer review, findings from another study found that employed status and the lack of a recent emergency room visit were predictors of response to a collaborative care intervention delivered in primary care (Roy-Byrne et al., 2003).

Similar variables have been found to be important predictors of response for patients receiving cognitive behavior therapy (CBT). In a meta-regression of factors that may predict outcome (i.e., effect size), the inclusion of severe patients had a negative relationship with effect size and severity of symptoms at baseline was associated with a poorer treatment response (Haby et al., 2006). With regard to comorbidity, inconsistent findings were present for depressive disorders while personality psychopathology was found to more consistently exert a negative effect on treatment outcome (Heldt et al., 2003; Martinsen et al., 1998; Mennin and Heimberg, 2000; Prasko et al., 2005). In other studies, negative predictors of remission status in patients who received CBT or a combination of CBT and medication were comorbid dysthymia, social phobia, GAD (Berger et al., 2004; Heldt and Manfro, 2006; Heldt et al., 2006) and substance abuse and dependence (Martinsen et al., 1998). Less frequently studied are attitudinal variables such as expectations about therapy success, however in at least one study, positive expectations have been shown to be negatively correlated with post-treatment panic-anxiety (Clark et al., 1999).

In the current study, we build on the existing literature by examining patient variables that may be associated with clinical improvement including often cited demographic and clinical variables as well as less frequently examined attitudinal variables. We assess several baseline factors that may be predictive of clinical improvement at 3- and 12-month outcome,

regardless of the intervention provided. In this study, patients with panic disorder have been recruited from primary care settings, as opposed to specialty mental health and research clinics, which allows for a more representative sample. The sample size is larger than many of the previously mentioned studies and assessments occurred longitudinally at two time points (3-months and 12 months). Consistent with other studies, we expect clinical severity variables to be most influential however as suggested by the one study conducted in primary care, demographic factors such as socioeconomic status may also be important (Roy-Byrne et al., 2003).

Methods

Setting and Subjects

The settings for this study were university-affiliated primary care clinics in San Diego, Seattle, and Los Angeles. Clinics were mainly staffed by board-certified physicians with some care (between 15% and 30%) provided by residents-in-training under attending supervision. Insurance included both private (50–80%) and public coverage.

Eligible subjects were primary care patients who: (a) were between 18 and 70 years old, (b) met DSM IV criteria for panic disorder (PD) with at least one panic attack in the prior week, (c) were English speaking, (d) had access to a telephone, and (e) were “willing to accept” a combined treatment of anti-anxiety medication and cognitive behavioral therapy (CBT). Patients with psychiatric and medical co-morbidities were included, except those that were potentially life threatening (i.e., suicidal ideation, terminal medical illness) or those expected to severely limit patient participation or adherence (e.g., psychosis, current substance abuse, dementia, pregnancy). Patients receiving psychiatric disability benefits or those already seeing a psychiatrist or cognitive behavioral therapist were excluded.

Subjects were recruited in primary care clinic waiting rooms using a validated two-question PD screener Stein et al., 1999). Clinic physicians also provided referrals. All positive screened or referred patients were administered a telephone diagnostic interview (the Composite International Diagnostic Interview (CIDI) (Means-Christensen et al., 2003; World Health Organization) by a research assistant to determine eligibility. The study was approved by the Institutional Review Boards from all participating institutions.

Intervention

In the hybrid efficacy-effectiveness Collaborative Care for Anxiety and Panic Study (CCAP) (Roy-Byrne et al., 2005) patients randomized to the active intervention (i.e., collaborative care) were given the option of receiving pharmacotherapy, cognitive behavior therapy (CBT) or both. More specifically, patients randomized to collaborative care (CC) were offered a demonstration video, an educational workbook, six in person CBT sessions delivered by a behavioral health specialist, six follow-up phone contacts (15 minute booster sessions), and algorithm study based pharmacotherapy prescribed by the primary care provider and guided by the study psychiatrist. Patients were to complete the six CBT sessions within the first three months of the study. Throughout the intervention, the behavioral health specialist was in frequent contact with the primary care provider (PCP), often serving as a liaison between the psychiatrist and the provider.

Patients in usual care received treatment as usual (typically pharmacotherapy) from their PCP, who received the results of the initial diagnostic telephone assessment so that eventual outcomes were not attributable to non-recognition of panic disorder and associated disorders. Usual care subjects could also be referred or self-refer to mental health resources available to them in the community.

Subjects were 232 primary care patients meeting DSM-IV criteria for panic disorder. Approximately two-thirds of subjects were Caucasian and female. The majority had 12 or more years of education (75%), and the mean age was 41.2 years. Almost two-thirds of the subjects had a co-morbid medical condition and over 70% had at least one co-morbid mood or anxiety disorder. Intervention and usual care groups were comparable at baseline on all measures (details presented in Roy-Byrne et al., 2005).

Assessments

Assessments were derived from telephone interviewer-administered questionnaires, delivered by interviewers blind to subject intervention status, at baseline and every 3 months during the course of the study. The interview included sociodemographic information; portions of the CIDI interview (World Health Organization, 1997) covering panic, generalized anxiety, social anxiety, post traumatic stress and major depressive disorders (baseline only); scales and individual items to dimensionally measure severity of symptoms, disability and quality of life; and questions about service utilization (Wells, 1999). Severity of anxiety symptoms was assessed with the Anxiety Sensitivity Index (ASI) (Reiss et al., 1986) the Fear Questionnaire (FQ) (Marks and Mathews, 1979), and a separate measure of panic attack frequency. To measure functional status and health-related quality of life, we used five items selected from the larger WHO Disability Scale (Epping-Jordan and Ustun, 2000). A separate assessment of patient beliefs and attitudes about medication and psychotherapy was also included (Bystritsky et al., 2005). Patients were categorized as demonstrating clinical improvement (the outcome of interest in this study), using as a criterion a score of 20 or less on the ASI, a scale which measures the cognitions that underlie panic-related somatic sensations and is also sensitive to the frequency of recent panic attacks (Otto and Reilly-Harrington, 1999; Schmidt et al., 2000).

Statistical Analyses

Of the initial sample of 232 enrolled patients, 180 were assessed at month 3 and 179 were assessed at month 12. Of the 179 patients who were assessed at month 12, 153 were also assessed at month 3. To correct for the bias induced by the missing assessments for some of the patients at month 3 and month 12 and essentially in order to make the analyses at month 3 and 12 comparable, non-response weights were built (Brick and Kalton, 1996). The non-response weights are computed as the inverse of the probability of response of having an assessment. Such probability is estimated via a logistic regression that compares the patients that have and do not have the assessment at month 3 and 12 with respect to patients' characteristics collected at baseline. All the analyses incorporated these weights and were conducted in R: A Language and Environment for Statistical Computing (R Development Core Team, 2007).

Logistic regression models were used to determine which patients' characteristics, beyond or in addition to the intervention status, were predictive of clinical improvement (using the binomial ASI as the dependent variable) at month 3 and month 12. Initially, bivariate logistic regressions were used to examine the relationships between individual patient characteristics and clinical improvement, after having accounted for intervention status. Next, multivariate stepwise logistic regression analyses were conducted using a backward-forward entry method. In these analyses, all patient characteristics had a chance to be in the final model, with the exception of intervention status, which was always included in the model. The Aikaike Information Criterion (AIC) (Akaike, 1974) was used to determine the variables to be added to or deleted from the model. Only the set of variables that minimized the AIC was retained in the final model, which explains why some of the variables retained in the final model are not significantly related to the outcome. The AIC is used since it combines the two most important aspects of selecting a model: goodness of fit (equivalent to

maximizing the likelihood) and model complexity. The model that minimizes AIC is an optimal compromise between model fit and model complexity.

Results

As shown in Table 1, potential predictors of clinical improvement as measured by the binomial ASI were categorized as clinical, sociodemographic and attitudinal variables. Bivariate logistic regression analyses, adjusting for intervention status, revealed significant relationships between clinical variables and clinical improvement at both 3 months and 12 months among patients recruited from primary care settings. More specifically, comorbid DSM disorders, severity of panic related symptoms (as measured by ASI), severity of fears (overall phobic avoidance as measured by FQ), neuroticism, and overall disability (as measured by the WHO) all had negative relationships with clinical improvement at both 3 month and 12 month time points. Clinical variables which were not significant at either time point were major depression and age of onset of panic disorder.

The relationships between sociodemographic characteristics and clinical improvement were less consistent across time points. At 3 months, having a college education and being insured were associated with clinical improvement while low income was associated with the absence of clinical improvement. At 12 months, having a college education continued to be significant of clinical improvement; however at this endpoint, being Caucasian and employed were also significant predictors. Demographic variables such as being female, age, and marital status were not significant at either time point. Lastly, attitudinal characteristics which included patient beliefs about psychotherapy and patient beliefs about medication were not significant at either 3 or 12 month time points.

As shown in Tables 2 and 3, when stepwise logistic regression analyses were conducted, including all patient characteristics and adjusting for intervention status, few variables remained significant within the final models predicting clinical improvement. For 3 month outcomes, lower anxiety sensitivity and neuroticism at baseline were associated with clinical improvement. For the 12 month outcomes, lower anxiety sensitivity and overall fear severity as well as being Caucasian were all associated with clinical improvement.

Discussion

Consistent with previous findings, various diagnostic and clinical severity variables at baseline emerged as being predictive of short term and long term clinical improvement. More specifically, the presence of comorbid social phobia and PTSD was associated with less clinical improvement at both 3 and 12 months. Both social phobia and PTSD have a chronic and unremitting course (Bruce et al., 2005; Davidson et al., 2004; Yonkers et al., 2003) and it is likely that additive presence of these disorder specific symptoms, (e.g., social avoidance, concerns about embarrassment, and heightened physiological arousal) exacerbate the course of panic related symptoms. Similarly, greater severity of panic related symptoms, and phobic avoidance (including agoraphobic severity and overall fears) predicted poorer improvement at both time points. Greater disability at baseline, or impaired functioning in daily life, was also a stable predictor of poorer clinical improvement. As suggested by previous studies, anxiety disorders are often associated with work disability and impairment in daily routine activities (Carerra et al., 2006; Sareen et al., 2006; Stein et al., 2005). The other variable that was associated with greater clinical improvement at both time points was having a college education. Education may be a proxy for income however it may also be a proxy for access, more access to information about anxiety related symptoms as well as access to resources. Demographic variables such as being female, age, and marital status were not significant at either time point. Lastly, attitudinal characteristics which included

patient beliefs about psychotherapy and patient beliefs about medication were not significant at either 3 or 12 month time points.

In the final models predicting clinical improvement, few variables remained significant. As expected, intervention status was significant in all models, and consistent with previous studies and current bivariate findings, severity of symptoms and personality traits were the most important predictors of clinical improvement in this randomized effectiveness trial for panic disorder in primary care. More specifically, a higher level of anxiety sensitivity at baseline was related to a less favorable outcome at both 3 month and 12 month end points. Anxiety sensitivity (AS) has been defined as an excessive fear of anxiety-related sensations, and beliefs that these sensations are harmful (Reiss et al., 1986; Reiss et al., 1991). In other studies, measures of anxiety sensitivity (i.e., the ASI) have been useful in prospectively identifying individuals who may develop panic attacks as well as those who many have persistent panic attacks in longitudinal studies (Li and Zinbarg, 2007; Schmidt et al., 2006). The severity score on the Fear Questionnaire is an overall index of phobic avoidance (which included avoidance related to agoraphobia, social phobia, and other specific phobic situations) and consistent with previous studies (Slaap and den Boer, 2001) greater overall severity was also predictive of less clinical improvement at longer term follow-up in this study.

The personality domain, neuroticism, also was found to be a predictor of clinical improvement at 3 months; that is, lower neuroticism scores at baseline were related to clinical improvement. Neuroticism, a core factor in many personality models, has been defined as a predisposition toward negative affective states such as depression, anxiety, anger, and shame (Costa and McCrae, 1985). In both clinical and general population studies alike, neuroticism has been identified as a risk factor for Axis I and Axis II disorders (Hettema et al., 2004; Jylha and Isometsa, 2006; Miller and Pilkonis, 2006). In a recent study, neuroticism was significantly correlated with four of the 10 personality disorders (paranoid, borderline, avoidant and dependent personality disorder) and it was prospectively (12 months after initial intake) shown to be a predictor of depression and anxiety scores, occupational impairment and lower overall functioning (Miller and Pilkonis, 2006). In general, personality styles involving avoidance and overdependence on others may seriously curtail clinical improvement as well as constrain the efficacy of various behavioral exposure tasks.

Lastly, being Caucasian (versus not being Caucasian) was associated with a more favorable clinical outcome at long-term follow-up (i.e., at 12 months). There are several possible explanations for this finding. In general, differential patterns of service utilization and treatment adherence may lead to disparities in quality of care and mental health outcomes (Alvidrez, 1999; Schraufnagel et al., 2006). Such patterns may be influenced by unfavorable attitudes and expectations about mental health treatment among ethnic minorities (Alvidrez, 1999). In the current sample, ethnic minorities reported less favorable attitudes toward both medication and psychotherapy (Hazlett-Stevens et al., 2002); however for the total sample (including Caucasians) patient beliefs were not associated with clinical improvement. Other variables which may differentially influence clinical outcomes include difficulties with language (Sleath et al., 2003), logistic barriers (Barron et al., 2004; Alvidrez and Azocar, 1999), beliefs about causes (Barron et al., 2004), stigma associated with mental health treatment (Alvidrez, 1999; Barron et al., 2004; Alvidrez and Azocar, 1999) and the potential influence of social networks (Wynaden et al., 2005).

In the final logistic regression models, demographic variables such as marital status, age, and gender were not predictors of clinical improvement at either time point. Also, attitudinal variables, (i.e., attitudes and beliefs about medication and psychotherapy) were not

associated with clinical outcome which is somewhat inconsistent with a previous study including attitudinal variables (Clark et al., 1999). Important to note, previous findings from the CCAP project (Hazlett-Stevens et al., 2002) support differences in attitudes across ethnic groups, therefore attitudes may have a greater influence on clinical improvement in samples with greater ethnic minority representation. While bivariate relationships existed for other variables such as specific DSM-IV diagnoses (social phobia, agoraphobia, PTSD), as well as indices of health functioning and disability, these relationships were no longer significant in the presence of other clinical variables (i.e., anxiety sensitivity, fear severity and neuroticism).

Limitations

This study has a number of limitations. First of all, treatment was delivered in university-affiliated clinics on the West coast which limits the generalizability of the findings. Second, while our list of potential predictors was rather comprehensive, some important possible predictors such as Axis II personality disorders were not formally assessed. Third, assessments were conducted by telephone rather than in-person which may have affected the psychometric properties of the interview and self-report assessments. Fourth, the majority of the patients were Caucasians and small sample sizes of each respective ethnic group did not allow for comparisons extending beyond Caucasian versus non-Caucasian categories.

Conclusions

In this study, we identified several baseline factors that predicted of 3- and/or 12-month clinical improvement, irrespective of the intervention provided (i.e., intervention status was adjusted for in the model). Data are consistent with previous studies which have found that severity at baseline is a predictor of clinical improvement and treatment response however, in this study it was a significant predictor for both short and longer term clinical outcomes. The personality domain, neuroticism was also an important predictor. Neuroticism may be a proxy for severity of psychiatric symptoms, but it is important to note that studies have also linked neuroticism to certain candidate genes (Schinka et al., 2004; Sen et al., 2004; Stein et al., 2004), suggesting the importance of possible genetic factors in clinical outcomes. Lastly, the significance of ethnicity as a predictor for longer-term clinical improvement, underscores the need for additional studies with larger samples of ethnic minorities to adequately explain these relationships and address potential disparities in care.

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Table 1

Bivariate logistic regressions for 3 and 12 month outcome while controlling for intervention status.

	3 month Outcome OR	CI	12 month Outcome OR	CI
Intervention	**2.2** *	1.1–4.1	**2.4** *	1.3–4.4
Clinical variables				
CIDI-SP diagnosis	**.42** *	.22–.82	**.43** *	.23–.83
CIDI PTSD diagnosis	**.40** *	.19–.82	**.45** *	.23–.90
CIDI MDD diagnosis	.60	.32–1.1	.65	.35–1.2
ASI total score	**.91** *	.87–.94	**.91** *	.89–.94
Agoraphobia severity	**.94** *	.91–.97	**.96** *	.93–.98
Overall fear severity	**.96** *	.94–.98	**.96** *	.95–.98
Panic frequency	.78 (p=.09)	.59–1.04	**.81** *	.68–.97
Panic age of onset	1.01	.98–1.03	.98	.96–1.0
WHO disability scale	**.92** *	.86–.99	**.93** *	.87–.99
Neuroticism	**.89** *	.84–.95	**.90** *	.86–.96
Sociodemographics				
Female	.73	.38–1.4	.77	.41–1.4
Caucasian	1.7	.89–3.4	**2.2** *	1.1–4.2
Low income	**.51** *	.26–1.00	.71	.37–1.3
Age	1.0	.97–1.03	.98	.95–1.01
Insurance	**2.7** *	1.16–6.4	1.4	.57–3.2
College	**2.5** *	1.1–5.5	**3.1** *	1.4–6.5
Married	1.2	.60–2.5	.80	.39–1.6
Employed	1.7	.89–3.1	**2.7** *	1.5–5.1
Attitudes				
Therapy beliefs	1.04	.97–1.1	.99	.93–1.06
Medication beliefs	.95	.87–1.03	.97	.90–1.05

Note: Outcome = no clinical improvement vs. clinical improvement (no improvement =0 and clinical improvement =1)

OR = odds ratio; CI = confidence interval; CIDI = (Composite International Diagnostic Interview); SP = social phobia; PTSD = post traumatic stress disorder; MDD= major depressive disorder; ASI = anxiety sensitivity index; WHO = World Health Organization.

* $p < .05$

Table 2

Predictors of clinical improvement at 3 months using stepwise (forward and backward) logistic regression analyses.

	coefficient	p-value	3 month OR	95% CI
Intervention	**1.64**	**.001** ***	**5.15**	**(2.18, 12.18)**
Neuroticism	**−0.10**	.03*	**0.90**	**(0.82, 0.99)**
Panic Attack Frequency	−0.12	.27	0.88	(0.71, 1.10)
ASI	**−0.10**	**.001** ***	**0.91**	**(0.87, 0.94)**
Agoraphobia Severity	−0.04	.11	0.96	(0.91, 1.01)
WHO Disability Scale	0.09	.08	1.10	(0.99, 1.22)

Outcome = no clinical improvement vs. clinical improvement (no improvement =0 and clinical improvement =1).

OR = Odds ratio; CI=Confidence interval; ASI = anxiety sensitivity index; WHO = World Health Organization.

*** $p < .001$

* $p < .05$

Table 3

Predictors of clinical improvement at 12 months using (forward and backward) stepwise logistic regression analyses.

	coefficient	p-value	12 month OR	95% CI
Intervention	**1.67**	**.002** **	**5.29**	**(1.85, 15.13)**
Panic onset age	−0.03	.07	0.97	(0.94, 1.00)
ASI	**−0.09**	**.001** ***	**0.91**	**(0.86, 0.96)**
Agoraphobia Severity	0.07	.10	1.08	(0.98, 1.17)
Overall Fear Severity	**−0.07**	**.04** *	**0.94**	**(0.88, 0.99)**
WHO Disability Scale	0.09	.16	1.10	(0.96, 1.24)
Beliefs about Psychotherapy	−0.07	.15	0.94	(0.85, 1.02)
Married	−0.77	.09	0.47	(0.19, 1.12)
Employed	0.82	.08	2.26	(0.91, 5.63)
Caucasian	**0.91**	**.04** *	**2.49**	**(1.06, 5.83)**

Outcome = no clinical improvement vs. clinical improvement (no improvement =0 and clinical improvement =1).

OR = Odds ratio; CI=Confidence interval; ASI = anxiety sensitivity index; WHO = World Health Organization.

*** $p < .001$

** $p < .01$

* $p < .05$