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Does the addition of cognitive behavioral therapy improve panic disorder treatment outcome relative to medication alone in the primary-care setting?

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ABSTRACT

Background. Randomized clinical trials indicate a benefit from combining medications with cognitive behavioral therapy (CBT) relative to medication alone for panic disorder. Using an as-treated analysis, we evaluated whether the addition of CBT enhanced outcomes for panic disorder relative to medications alone in the primary-care setting.

Method. Primary-care patients with panic disorder reported on their receipt of CBT and medications over the 3 months following baseline assessment. The degree to which outcomes for those who used anti-panic medications were enhanced by the receipt of at least one component of CBT was analyzed using a propensity score model that took into account observable baseline patient characteristics influencing both treatment selection and outcomes.

Results. The addition of CBT resulted in statistically and clinically significant improvements at 3 months on anxiety sensitivity, social avoidance, and disability. Also, patients receiving CBT in the first 3 months of the study were more improved at 12 months than patients who took medications only during the first 3 months of the study.

Conclusions. The clinical utility of the findings are discussed in terms of the importance of primary-care physicians encouraging their panic disorder patients to receive CBT as well as medications.

INTRODUCTION

The relative efficacies of cognitive behavioral therapy (CBT) and medications for panic disorder have been compared via randomized controlled trials (e.g. Barlow *et al.* 2000) and meta-analyses of independent and combined studies of each treatment approach (e.g. van Balkom *et al.* 1997). In general, the results indicate that each approach is more effective than waitlist or placebo conditions, and an advantage exists for a combined treatment approach whilst medication is continued (Telch & Lucas, 1994; de Beurs *et al.* 1995; Barlow *et al.* 2000). Also, CBT tends to yield more durable effects than medications once they are discontinued (Marks *et al.* 1993; Barlow & Lehman, 1996; Barlow *et al.* 2000; Nadiga *et al.* 2003).

However, these results derive mostly from samples of patients who actively seek treatment in specialized mental health settings or are part of clinical research trials. Hence, they possess limited generalizability to primary-care practices, where the majority of individuals with

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anxiety disorders seek treatment (e.g. Goisman *et al.* 1994; Kessler *et al.* 1998, 1999; Roy-Byrne *et al.* 1999; Young *et al.* 2001; Harman *et al.* 2002).

Previously, we reported the effects of random assignment to a collaborative care treatment, involving resources for cognitive behavioral therapy and expert based guidelines for psychotropic medication, compared to treatment as usual, all conducted in the primary-care setting (Craske *et al.* 2002; Roy-Byrne *et al.* 2003). Patients randomized to collaborative care were offered six in-person CBT visits with a behavioral health specialist over a 3-month interval, and recommendations for appropriate anti-panic medication. Overall, we found that patients randomized to collaborative care achieved lower symptom severity and higher functioning that was sustained for 12 months than participants randomized to treatment as usual (Roy-Byrne *et al.* 2005). A unique aspect of our design was flexibility in terms of treatment received. That is, although patients were randomized to receive a combination of CBT and medication (or treatment-as-usual, which generally consisted of medication only, though they were free to access other community resources available to them), they were not dropped if they were non-compliant with either or both treatment modalities. We tracked the receipt of anti-panic medication and CBT in our entire sample, whether randomized to collaborative care or treatment as usual. Thus, in this report, we evaluate the effect of receiving CBT and medications in comparison to receiving medications only. This particular comparison was selected because the majority of the sample was taking medication, as would be expected since it is the most common treatment modality for panic and anxiety disorders within primary-care settings (Roy-Byrne *et al.* 1999, 2002).

Without the benefit of random assignment to CBT and medications *versus* medications only, it is necessary to control for patients characteristics that are associated with treatment selection and outcomes. This can be done using a propensity score adjustment method that models the probability of selecting the 'medications only' treatment based on a set of patient characteristics (Rosenbaum & Rubin, 1983). Propensity scores eliminate the bias induced by differences in observed characteristics, although they cannot eliminate the potential bias due to differences in unmeasured characteristics. This methodology has been used previously in the psychiatric outcomes literature. Leon *et al.* (2003), using a propensity for treatment adjustment, found that Collaborative Depression participants who received higher levels of antidepressant medication were nearly twice as likely to recover from their depressive episodes as those who received no medication treatment. In contrast, those who received lower levels of medications were no more likely to recover than those who were untreated. After controlling for similar 'sickness bias' variables via instrumental analyses, Schoenbaum *et al.* (2002) found that 'appropriate care' for depression among primary-care patients was related to improved symptom outcomes and employment status relative to 'no care' or 'inappropriate care'.

The goal of the current study was to evaluate the relative effectiveness of medication and CBT *versus* medications alone for panic disorder in the primary-care setting, controlling for observed sources of bias that influence the propensity to use either type of treatment and outcomes. The combination of CBT and medications was hypothesized to yield superior outcomes compared to medications alone in this primary-care sample.

METHOD

Setting and participants

Participants for the larger, intent-to-treat randomized trial (Roy-Byrne *et al.* 2005) were recruited from university-affiliated primary-care clinics in Seattle, San Diego, and Los Angeles. Eligible subjects (*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). Psychiatric and medical co-morbidities were not reasons for exclusion, 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

Table 1. *Endorsement of components of cognitive behavioral therapy (CBT) received*

CBT components	Collaborative care ($n=90$)*	Treatment as usual ($n=89$)	Total sample ($n=179$)
Relaxation	66 (73·3%)	11 (12·4%)	77 (43·0%)
Exposure to feared situations	64 (71·1%)	11 (12·4%)	75 (41·9%)
Homework	67 (74·4%)	10 (11·2%)	77 (43·0%)
Change behavioral responses to feared bodily sensations	65 (72·2%)	12 (13·5%)	77 (43·0%)
Information about panic attacks	66 (73·3%)	13 (14·6%)	79 (49·7%)
Identify cognitive errors	71 (78·9%)	18 (16·9%)	89 (49·7%)
Challenge cognitive errors	67 (74·4%)	15 (16·9%)	82 (45·8%)

* Missing data for one participant.

seeing a psychiatrist or cognitive behavioral therapist were excluded. Subjects were recruited in clinic waiting rooms using a validated two-question PD screener (Stein *et al.* 1999). Referrals from clinic physicians also were actively solicited. All positive screened or referred patients were administered the Composite International Diagnostic Interview (CIDI; WHO, 1997) over the phone by a research assistant to determine eligibility. The study was approved by the Institutional Review Boards of all three universities (University of Washington, University of California, Los Angeles, and University of California, San Diego).

Treatment received

Participants in the larger trial were randomized to Collaborative Care, (i.e. they were offered CBT and expert medication recommendations) or to Treatment as Usual (which typically entailed no treatment or pharmacotherapy alone, provided by the primary-care provider). Of interest herein was the comparison of participants who received CBT and medications *versus* medications alone, regardless of the initial random assignment. Treatment received during the prior 3 months was assessed for all participants at the 3-month outcome assessment.

For receipt of CBT, each participant was asked to indicate whether they had received the following seven CBT therapeutic strategies over the last 3 months (see Table 1): relaxation practice, such as breathing retraining or meditation; exposure to feared situations rather than avoiding such situations; homework assignments; practice of new behaviors in session (e.g. management of uncomfortable bodily sensations); detailed information about panic attacks; identification of distortions in thinking and beliefs; and restructuring of distortions. A liberal criterion of endorsement of at least one CBT item was used to dichotomize the sample, so as to maintain adequate cell sizes and statistical power for analyses. Notably, the majority of patients endorsed more than one CBT item (mean = 6).

For receipt of medications, participants were asked about medications they had taken over the last 3 months. A liberal criterion of anti-panic pharmacotherapy (see Stein *et al.* 2004) was used to dichotomize the sample as having received pharmacotherapy or not so as to maintain adequate cells sizes and statistical power. Notably, 72·1% of those receiving anti-panic pharmacotherapy reported having done so at an appropriate dose (according to our medication algorithm; Roy-Byrne *et al.* 1998) for at least 6 weeks.

Outcome variables

Assessments were derived from telephone-interviewer-administered questionnaires, queried by interviewers blind to intervention status (collaborative care *versus* treatment as usual), at baseline and at 3-month and 12-month follow-ups. The interview included portions of the CIDI interview (WHO, 1997) at baseline only; a battery of scales and individual items to dimensionally measure severity of symptoms, disability and quality of life (see below); and questions regarding treatment received (described above) and health care utilization.

Measures of interest for the current report are described below.

Symptom measures included the Anxiety Sensitivity Index (ASI; Reiss *et al.* 1986), which measures discomfort with anxiety-related symptoms, with good psychometric properties (McNally, 1989; Peterson & Reiss, 1992; Rapee & Medoro, 1994; Zinbarg *et al.* 1997; Zinbarg *et al.* 1999). The ASI was our primary outcome measure. The Fear Questionnaire (FQ; Marks & Mathews, 1979) measures phobic avoidance of agoraphobia, and social and blood/injury/injection situations, with adequate to good reliability and good validity (e.g. Cox *et al.* 1993). We evaluated the agoraphobia and social phobia subscales of the Fear Questionnaire as well as the total (agoraphobia plus social phobia) avoidance score. Depressive symptoms were measured using the Center for Epidemiological Studies – Depression Scale (CES-D), a 20-item scale with good internal consistency and excellent convergent and discriminative validity (Radloff, 1977).

To measure functional status and health-related quality of life, we used five items selected from the larger WHO Disability Scale (WHO, 2001) and the global physical and mental health scales of the short-form health survey SF-12 (PCS12, MCS12; Ware *et al.* 1996) which reproduces SF-36 summary measures with an accuracy of over 90% and has demonstrated good validity (Ware *et al.* 1995). The five WHO items possessed high internal consistency in our sample (alpha = 0·78) and correlated moderately ($r = -0{\cdot}48$) to strongly ($r = -0{\cdot}61$) with the emotional well-being and physical functioning subscales, respectively, of the SF-12.

The current analyses focus primarily on outcomes at 3 months. Secondarily, we assessed whether the addition of CBT during the first 3 months was associated with different outcomes at the 12-month assessment in comparison with medications only during the first 3 months.

Propensity variables

Baseline values for the following measures were considered to model the probability of selecting the medications-only treatment (*versus* the medications and CBT treatment option): study site (Seattle, Los Angeles, San Diego), insurance status (uninsured or not), marital status (yes/no), employed full-time (yes/no), years of education, gender (female/male), minority status (white, non-white), age, number of chronic medical diseases, ASI, CES-D, FQ, WHO Disability, PCS12, MCS12, frequency of limited symptom and full panic attacks over the last week and over the last month, and number of other psychiatric diagnoses. Only those variables that were significantly different between the groups under comparison were retained for the propensity score model.

Statistical approach

As stated, the comparison between combined CBT and medications *versus* medications alone was of primary interest to test the hypothesis that CBT enhances outcomes when added to the standard treatment modality for panic disorder in the primary-care setting (i.e. medications). We elected not to compare patients who received CBT with those who did not receive CBT because the estimated CBT effect would be confounded with the medications effect, as the two groups differed in the proportion taking medications: (67% of the patients receiving CBT also received medications, whereas 56% of the patients not receiving CBT received medications).

RESULTS

Attrition

Baseline variables that were predictive of non-response at the 3-month follow-up were limited to site and frequency of full panic attacks in the past week. Analyses of the 3-month outcomes were weighted for non-response to correct for biases due to attrition. Similarly the 12-month outcomes were weighted by non-response, since 16 patients [CBT + medications (MEDS) = 9; MEDS only = 7] dropped out of the study between the 3-month and 12-month assessments.

Sample characteristics

Over one-third of subjects were of non-Caucasian ethnicity, with a wide range of ages (mean = 41·2) and income levels. Seventy-six per cent had 12 or more years of education and 67% were female. Almost two-thirds had a co-morbid medical condition and over 70% had at least one co-morbid mood or anxiety disorder; 39% reported clinically significant levels of agoraphobia as defined by a score of 10 or

higher on the Agoraphobia subscale of the Fear Questionnaire.

Treatment characteristics

The endorsement rates for the seven CBT items are shown in Table 1, and the number who reported receiving anti-panic medication and/or at least one CBT item, or neither, is shown in Table 2.

Propensity score methodology

Because patients were not randomized to MEDS only *versus* MEDS + CBT, but instead were permitted to make use of one or both of these treatments as they desired, the groups may have differed in important ways. For example, more severely distressed patients may be more likely to choose MEDS + CBT compared with MEDS alone. We used a propensity score method (Rosenbaum & Rubin, 1983) to eliminate the bias induced by differences of the baseline characteristics between the two treatment groups.

In this analysis, the propensity score is defined as the probability that a patient with a given set of baseline characteristics x is in the MEDS-only group selects the treatment MEDS only. This probability is used to build weights (Hirano *et al*. 2003; McCaffrey *et al*. 2004) for patients in the MEDS + CBT group. Patients in the MEDS + CBT group who have similar characteristics to patients in the MEDS-only group have a larger propensity score and therefore are 'upweighted' when computing the treatment effect. Patients in the MEDS + CBT group with characteristics dissimilar to the MEDS-only group are down-weighted when computing the treatment effect. The ultimate result of this weighting is to eliminate the imbalance at baseline between MEDS only and MEDS + CBT.

The propensity score was estimated using a generalized boosted model (GBM) (Ridgeway, 1999; Friedman, 2001) instead of a logistic linear regression. GBM is a non-parametric regression technique and a general, automated, data-adaptive modeling algorithm that can estimate non-linear relationships between the outcome of interest and many covariates. Some of the advantages of GBM are: the ability to capture non-linear effects and interaction terms; handling continuous, nominal, ordinal, and missing variables (or covariates); being invariant to one-to-one transformations of the covariates; and handling large numbers of correlated variables. To fit such a model we used the GBM package (Ridgeway, 2004), which is available as an R-project library (www.r-project.org).

Table 2. *Distribution of as-treated groups across randomized groups*

	Collaborative care	Treatment as usual		
Randomization status	119	113		
Responder status at 3 months				
Non-responders	28	24		
Responders	91	89		
As-treated status for responders				
MEDS only	11	38	$n=49$	As-treated analyses
CBT only	23	7		
CBT + MEDS	48	14	$n=62$	
None	9	30		

MEDS, Any anti-panic agent; CBT, endorsed at least one CBT component.

Main analyses

Patients who received MEDS + CBT ($n=62$) were compared with those who received MEDS only ($n=49$), regardless of whether they were randomized to Collaborative Care or Treatment as Usual. Table 3 shows the means of baseline variables used in the propensity score and the associated p value for group differences for all covariates (except Site), both before and after weighting adjustment. For example, columns 5 and 6 in Table 3 show the means for each covariate in the MEDS + CBT group after the propensity score weighting adjustment and the p value for the test comparing the weighted mean of MEDS + CBT *versus* MEDS only. The MEDS-only group tended to be 'healthier' than MEDS + CBT group at baseline, and the propensity score weights effectively eliminated imbalances in the observed characteristics.

Table 4 shows the 3-month outcomes (i.e. the difference in mean outcomes for MEDS only *versus* MEDS + CBT) before and after the propensity score adjustment. After the propensity adjustment, patients who received MEDS + CBT generally were less symptomatic at 3 months than patients who received MEDS

Table 3. *Baseline covariate values before and after propensity-weighting*

Covariate	MEDS mean	MEDS + CBT mean	*p* value* before weighting	Propensity-score-weighted MEDS + CBT mean	*p* value* after weighting
ASI (0–64)	31	36	0·01	34	0·24
Panic frequency†	1·25	1·66	0·01	1·49	0·18
MCS12 (0–100)	38	33	0·03	36	0·44
No. of medical conditions (0–7)	0·13	0·85	0·01	0·34	0·26
Anti-panic medication at baseline (yes/no)	0·81	0·63	0·04	0·77	0·64

MEDS, Any anti-panic agent; CBT, endorsed at least one CBT component; ASI, Anxiety Sensitivity Index; MCS12, Mental health Subscale of SF-12.

* Test of difference in covariate between MEDS and MEDS + CBT.

† Panic frequency (0–4; 0 = none, 4 = full panic attacks more than once per day, more days than not over last month).

only. The groups differed statistically on ASI, FQ-Social subscale, and WHO disability.

In addition, the group differences were clinically meaningful in size. A secondary representation of the clinical significance of the group differences is the percentage of each group that fell below established cut-offs on the outcome indices for which such cut-offs exist (ASI, FQ-Social). Although these statistics are *not* propensity-weighted, and thereby are likely biased, they nonetheless indicate superior rates of normative functioning within the CBT + MEDS *versus* MEDS only groups: ASI less than 20, CBT + MEDS = 35%, MEDS only = 29%; and FQ-Social less than 10, CBT + MEDS = 55%, MEDS only = 33%.

We examined 12-month outcomes as well. These analyses control for observed baseline differences that influenced which treatment participants selected in the first 3 months of the study, but do not control for variables that may have influenced their choice of treatments in the subsequent 9 months. As seen in Table 5, significant differences were maintained for ASI, FQ-Social subscale, and WHO disability. In addition, two outcomes which were not significant at the 3-month outcome became significant at 12 months (CES-D and FQ-Total Avoidance).

DISCUSSION

As hypothesized, primary-care patients with panic disorder who received at least one component of CBT in addition to anti-panic medication achieved significantly better outcomes at 3 months on some measures than those treated with MEDS alone. Moreover, the results were sustained and even enhanced when outcomes were evaluated at 12 months, although, as noted below, the reasons for this long-term pattern are unclear. The propensity adjustments effectively eliminated the baseline differences between the two groups in the observed characteristics, thus allowing comparison between the two as-treated groups even though participants were self-selected rather than randomized. It was interesting to note, however, that participants who elected MEDS only were less severe at baseline than those who elected both CBT + MEDS, in terms of panic-related symptomatology (Anxiety Sensitivity), general mental health (MCS-12), and number of comorbid medical conditions. On the other hand, they were also more likely to be already receiving an anti-panic medication at baseline. While this could account for their lowered severity and may have contributed to their choice to refrain from an additional treatment modality (i.e. CBT), we cannot rule out the possibility that they were relatively treatment-resistant, and hence, despite already being medicated, chose to enter a treatment trial for panic disorder. Those who additionally received CBT did not differ on sociodemographic variables from those who did not receive CBT, which is consistent with our earlier findings that sociodemographic variables did not relate to willingness to receive CBT

Table 4. *Three-month outcomes for groups before and after propensity weighting* ($n=111$)

Outcome variable	MEDS mean − MEDS + CBT mean (before propensity score weighting)	MEDS mean − MEDS + CBT mean (after propensity score weighting)
CES-D (0–60)	25–22 = 2·7 S.D. = 14·2 ES = 0·20 ($p=0·3$)	25–21 = 4·1 S.D. = 14·2 ES = 0·29 ($p=0·17$)
Panic frequency*	1·19–1·31 = −0·12 S.D. = 0·88 ES = 0·13 ($p=0·54$)	1·19–1·28 = −0·09 S.D. = 0·88 ES = 0·10 ($p=0·65$)
Social avoidance (0–40)†	20–16 = 3·6 S.D. = 10·0 ES = 0·36 ($p=0·08$)	20–15 = 5·0 S.D. = 10·0 ES = 0·50 ($p=0·02$)
Agoraphobia avoidance (0–40)‡	16–13 = 2·7 S.D. = 10·7 ES = 0·25 ($p=0·23$)	16–14 = 1·7 S.D. = 10·7 ES = 0·16 ($p=0·57$)
Total avoidance (0–80)§	35–29 = 6·0 S.D. = 19 ES = 0·33 ($p=0·11$)	35–28 = 6·7 S.D. = 19 ES = 0·35 ($p=0·16$)
WHO (0–25)	13–11 = 1·7 S.D. = 5·2 ES = 0·33 ($p=0·06$)	13–11 = 2·1 S.D. = 5·2 ES = 0·40 ($p=0·03$)
MCS12 (0–100)	40–42 = −1·72 S.D. = 11·15 ES = −0·15 ($p=0·43$)	40–42 = −2·19 S.D. = 11·15 ES = −0·20 ($p=0·39$)
PCS12 (01–00)	40–44 = −3·4 S.D. = 13·6 ES = −0·25 ($p=0·17$)	40–44 = −3·6 S.D. = 13·6 ES = −0·26 ($p=0·23$)
ASI (0–64)	28–25 = 2·8 S.D. = 14 ES = 0·20 ($p=0·30$)	28–21 = 6·8 S.D. = 14 ES = 0·49 ($p=0·02$)

MEDS, Any anti-panic agent; CBT, endorsed at least one CBT component; CES-D, Center for Epidemiological Studies – Depression Scale; S.D., standard deviation; ES, effect size; WHO, World Health Organization Disability Scale; MCS12, mental health subscale of SF-12; PCS12, physical health subscale of SF-12; ASI, Anxiety Sensitivity Index.

* Panic frequency (0–4; 0 = none, 4 = full panic attacks more than once per day, more days than not over last month).

† Social avoidance = Social subscale of Fear Questionnaire.

‡ Agoraphobia avoidance = Agoraphobic subscale of Fear Questionnaire.

§ Total Avoidance = sum of Social and Agoraphobia subscales of Fear Questionnaire.

Table 5. *Twelve-month outcomes for groups before and after propensity weighting* ($n=95$)

Outcome variable	MEDS mean − MEDS + CBT mean (no propensity score weighting)	MEDS mean − MEDS + CBT mean (after propensity score weighting)
CES-D (0–60)	23–18 = 4·86 S.D. = 14·3 ES = 0·34 ($p=0·1$)	23–17 = 6·5 S.D. = 14·3 ES = 0·45 ($p=0·03$)
Panic frequency*	1·11–0·98 = 0·13 S.D. = 0·79 ES = 0·16 ($p=0·46$)	1·11–0·97 = 0·14 S.D. = 0·79 ES = 0·18 ($p=0·57$)
Social avoidance (0–40)†	19–15 = 4·8 S.D. = 11·0 ES = 0·44 ($p=0·03$)	19–12 = 7 S.D. = 11·0 ES = 0·64 ($p<0·01$)
Agoraphobia avoidance (0–40)‡	14–11 = 3·12 S.D. = 10·9 ES = 0·29 ($p=0·16$)	14–11 = 3·34 S.D. = 10·9 ES = 0·31 ($p=0·16$)
Total avoidance (0–80)§	34–26 = 8·0 S.D. = 19·95 ES = 0·40 ($p=0·05$)	34–23 = 10·4 S.D. = 19·95 ES = 0·52 ($p=0·01$)
WHO (0–25)	12–10 = 2·5 S.D. = 5·4 ES = 0·45 ($p=0·02$)	12–9 = 2·7 S.D. = 5·4 ES = 0·51 ($p=0·01$)
MCS12 (0–100)	42–45 = −2·6 S.D. = 11·4 ES = −0·23 ($p=0·30$)	42–44 = −2·15 S.D. = 11·4 ES = −0·19 ($p=0·44$)
PCS12 (01–00)	38–43 = −5·3 S.D. = 13·0 ES = −0·41 ($p=0·05$)	38–43 = −5·5 S.D. = 13·0 ES = −0·42 ($p.=0·08$)
ASI (0–64)	23–20 = 3·2 S.D. = 13·5 ES = 0·24 ($p=0·26$)	23–15 = 7·8 S.D. = 13·5 ES = 0·58 ($p<0·01$)

MEDS, Any anti-panic agent; CBT, endorsed at least one CBT component; CES-D, Center for Epidemiological Studies – Depression Scale; S.D., standard deviation; ES, effect size; WHO, World Health Organization Disability Scale; MCS12, mental health subscale of SF-12; PCS12, physical health subscale of SF-12; ASI, Anxiety Sensitivity Index.

* Panic frequency (0–4; 0 = none, 4 = full panic attacks more than once per day, more days than not over last month).

† Social avoidance = Social subscale of Fear Questionnaire.

‡ Agoraphobia avoidance = Agoraphobic subscale of Fear Questionnaire.

§ Total Avoidance = sum of Social and Agoraphobia subscales of Fear Questionnaire.

(Hazlett-Stevens *et al*. 2002). As an aside, it is noteworthy that twice as many patients randomized to collaborative care received CBT alone than MEDS alone, indicating a general preference for CBT. That the most common treatment received in those randomized to treatment as usual was MEDS likely reflects standard practice for treating panic disorder in primary care – which, according to our findings, may be inconsistent with patient preferences for non-pharmacologic treatments such as CBT.

Patients receiving at least one component of CBT during the first 3 months of the study maintained their positive outcomes at month 12. Although positive long-term effects of CBT are well established in intent-to-treat analyses, it

is more difficult to assign long-term outcomes to CBT (or any given treatment modality) with as-treated analyses. That is, whereas propensity score weights adjust for differences in the baseline covariates that might have influenced the selection of MEDS + CBT *versus* MEDS alone during the first 3 months of the study, they do not control for differences that may have influenced the choice of different treatments in the subsequent 9 months of the study, and participants may have switched treatment modalities throughout that interval. Whereas alternative treatments during follow-up intervals are less of a threat to the integrity of intent-to-treat analyses of randomized samples, they pose a more serious threat to the integrity of as-treated analyses in which effects are statistically tied to the actual treatment received. Nevertheless, the pattern of continuing improvement in those who initially selected CBT is consistent with intent-to-treat analyses which indicate continuing improvement following CBT for panic disorder over longer-term follow-ups (e.g. Barlow *et al.* 2000).

The benefits from adding CBT were not only statistically but also clinically significant. For example, after propensity score weighting, the mean difference in Anxiety Sensitivity resembled the difference typically seen between clinical and non-clinical samples (Peterson & Reiss, 1992). Moreover, effect sizes were moderate and increased at 12 months.

On the surface, the size of the effects is somewhat surprising, given our liberal criterion for CBT. In other words, adding at least one component of CBT to medications had a measurable and meaningful effect on symptom status. However, the average number of CBT components endorsed was six; thus the observed effects were mostly attributable to more comprehensive CBT rather than just one component of CBT. By the same token, while using a liberal criterion for anti-panic medication, by far the majority (approximately three-quarters) of those dichotomized as 'medicated' were taking an appropriate dose for at least 6 weeks and therefore met our definition for adequate anti-panic medication as described elsewhere (Roy-Byrne *et al.* 1998, 2005; Stein *et al.* 2004).

In general, the results support conclusions from randomized controlled trials and meta-analyses, in which an initial and long-term benefit is observed from combining CBT with medications compared with medications alone. Limitations of the study include the restriction of propensity adjustments to observable group differences. Despite our thorough battery of sociodemographic and mental health variables at baseline, other, unobservable differences may have existed between participants who elected MEDS only *versus* MEDS + CBT. For example, unobserved treatment resistance factors may have characterized our MEDS-only group. In addition, our reliance on patient report to ascertain type of treatment received may have introduced some error, particularly in terms of CBT components. For example, even though interviewers aided in interpretation whenever possible, some confusion may have remained (e.g. 'Did their therapist help them identify problems or distortions in their thinking?'), and social desirability responding or other response biases may have introduced additional error. Finally, in the absence of a non-specific or alternative psychotherapy comparison group, the results cannot be attributed exclusively to CBT. That is, non-specific factors of the therapeutic relationship may have been more important than the therapeutic strategies of cognitive behavioral therapy. This limitation is tempered by the evidence for brief CBT to be more effective than non-directive supportive therapy for panic disorder (Craske *et al.* 1995) and for results from CBT, at least for depression, to be explained by therapist adherence to concrete symptom-focused methods rather than therapeutic alliance factors (DeRubeis & Feeley, 1990; Feeley *et al.* 1999). However, alternative psychosocial treatments may have yielded the same benefits and thus the results cannot be exclusively attributed to CBT.

Nonetheless, the current set of findings suggest that when primary-care providers prescribe anti-panic medications for their panic disorder patients, not only should they follow guidelines for effective medications and dosages, but they should also inform patients about cognitive behavioral approaches to management of their panic and anxiety, and encourage those patients who express an interest in CBT to initiate or continue in such a therapy. Finally, these findings highlight the importance of dissemination efforts to increase the availability of CBT to anxious patients in the primary-care setting.

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DECLARATION OF INTEREST

None.

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