Psychotherapies for Panic Disorder: A Tale of Two Sites

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ABSTRACT

Objective: To compare cognitive-behavioral therapy (CBT), panic-focused psychodynamic psychotherapy (PFPP), and applied relaxation training (ART) for primary *DSM-IV* panic disorder with and without agoraphobia in a 2-site randomized controlled trial.

Method: 201 patients were stratified for site and *DSM-IV* agoraphobia and depression and were randomized to CBT, PFPP, or ART (19–24 sessions) over 12 weeks in a 2:2:1 ratio at Weill Cornell Medical College (New York, New York) and University of Pennsylvania ("Penn"; Philadelphia, Pennsylvania). Any medication was held constant.

Results: Attrition rates were ART, 41%; CBT, 25%; and PFPP, 22%. The most symptomatic patients were more likely to drop out of ART than CBT or PFPP ($P = .013$). Outcome analyses revealed site-by-treatment interactions in speed of Panic Disorder Severity Scale (PDSS) change over time ($P = .013$). At Cornell, no differences emerged on improvement on the primary outcome, estimated speed of change over time on the PDSS; at Penn, ART ($P = .025$) and CBT ($P = .009$) showed greater improvement at treatment termination than PFPP. A site-by-treatment interaction ($P = .016$) for a priori–defined response (40% PDSS reduction) showed significant differences at Cornell: ART 30%, CBT 65%, PFPP 71% ($P = .007$), but not at Penn: ART 63%, CBT 60%, PFPP 48% ($P = .37$). Penn patients were more symptomatic, differed demographically from Cornell patients, had a 7.2-fold greater likelihood of taking medication, and had a 28-fold greater likelihood of taking benzodiazepines. However, these differences did not explain site-by-treatment interactions.

Conclusions: All treatments substantially improved panic disorder with or without agoraphobia, but patients, particularly the most severely ill, found ART less acceptable. CBT showed the most consistent performance across sites; however, the results for PFPP showed the promise of psychodynamic psychotherapy for this disorder.

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Prevalent, debilitating, and costly,[1] panic disorder is associated with poor emotional and physical health, comorbid substance abuse, and suicide.[2] Efficacious treatment for panic disorder with or without agoraphobia typically involves cognitive-behavioral therapy (CBT)[3,4] or pharmacotherapy. Alternatives to pharmacotherapy are important, as panic patients in general prefer psychotherapy to medication,[5] and panic disorder is common among women of childbearing age. The research dominance of CBT in anxiety disorders makes testing non–CBT-based psychotherapies challenging.[6] Nonetheless, randomized controlled trials (RCTs) indicate that psychodynamic psychotherapies have efficacy for some anxiety disorders,[7] and panic-focused psychodynamic psychotherapy (PFPP)[8,9] has demonstrated efficacy compared with applied relaxation training (ART), itself a beneficial antipanic treatment.[10,11]

The present study is the first large panic disorder study to compare CBT and PFPP, 2 disparate psychotherapies. Highly structured, CBT assigns homework and provides interoceptive and in vivo exposure to patients' fears and physical anxieties. Far less structured, PFPP lacks homework and never undertakes exposure, attending instead to decoding emotional significance of panic symptoms and avoidance, attachment relationships, and ambivalence about separations, via articulating the transference.[9] We compared CBT and PFPP with ART, a credible, efficacious psychotherapy for panic disorder of lower potency than CBT and PFPP.[4,10] To minimize ART attrition, a problem in past studies,[10] we bolstered in vivo exposures and relapse prevention and informed all patients of the availability of crossover alternative study treatment should they not have respond by termination. Our primary a priori hypothesis was that CBT and PFPP would show greater improvement at treatment termination than ART on the Panic Disorder Severity Scale (PDSS).

METHOD

Two hundred one patients ages 18–70 years, with primary *DSM-IV* panic disorder with or without agoraphobia, recruited at Weill Cornell Medical College (hereafter, "Cornell") and University of Pennsylvania (hereafter, "Penn"), gave informed written consent; both sites' institutional review boards approved the protocol. Participants received study treatment gratis. The study is registered with ClinicalTrials.gov (identifier: NCT00353470).

The inclusion criterion was occurrence of ≥ 1 spontaneous weekly panic attack for the month before entry. Ongoing psychotherapy was prohibited. Medications, permitted if stable for ≥ 2 months at presentation, were recorded, held constant, and monitored. Exclusion criteria were active substance dependence (< 6 months' remission), history of psychosis or bipolar disorder, acute suicidality, and organic mental syndrome.

Therapists/Investigators

Thirty therapists (17 female) participated, with a mean of 13 years of postdegree experience (SD = 8.1, range [2–26]), 7 years performing time-limited therapy (SD = 7.0, range [0–22]), and ≥ 1 year's experience treating panic disorder.

Each therapist delivered 1 modality after receiving training. We attempted to equate CBT and PFPP on common factors with therapist comparability in experience and exposure to respective models.[12] ART therapists were CBT trained and experienced with relaxation, but did not usually practice ART alone. Six therapists conducted ART, 8 conducted CBT, and 16 conducted PFPP. Eleven therapists were MDs, 17 PhDs, 1 MSW, and 1 PsyD. There were no significant between-site therapist demographic differences. Therapist training did not significantly differ, aside from more psychiatrists delivering PFPP (11/16, 69%) than ART (0/6, 0%; $\chi^2_1 = 8.25$, $P < .004$) and CBT (0/8, 0%; $\chi^2_1 = 10.15$, $P < .002$).

Therapists received monthly group supervision and regular individual supervision from senior clinicians expert in their modality. CBT had strong allegiance at both sites: Dr Chambless at Penn and Baruch Fishman, PhD, at Cornell supervised CBT therapists. Highly experienced in relaxation therapies, Drs Chambless and Schwalberg supervised ART at Penn and Cornell, respectively.

Psychodynamic psychotherapy had strong allegiance at Cornell (Dr Milrod) and Penn (Dr Barber), although Cornell had more PFPP experience. Site ombudsmen determined need for nonstudy treatments.

Patient Protocol Violations

Five patients (Penn, 3; Cornell, 2) were removed for using nonstudy treatments (new medications ± psychotherapies) and deemed protocol failures. Blinded evaluators attempted to assess dropped subjects per intention-to-treat [ITT] strategy.

Diagnostician Training and Reliability

Masters- or doctoral-level independent evaluators blinded to treatment and therapist conducted a standardized assessment battery.[13] Independent evaluators received ≥ 35 hours of training to criterion on the Anxiety Disorders Interview Schedule for *DSM-IV* (ADIS-IV)[14] and ≥ 12 hours on the PDSS.[15] ADIS raters across sites corated 2 patients twice annually to prevent drift. ADIS reliability ranged from moderate (social phobia, intraclass correlation coefficient [ICC] = 0.70) to excellent (panic disorder, ICC = 1.0). Interrater PDSS reliability, monitored regularly, proved excellent (ICC = 0.95) based on a sample of 40 patients at both sites (2–3 raters/site).

Measures

The ADIS-IV Lifetime version[14] determined inclusion. Response[3,13] was defined a priori as ≥ 40% reduction from baseline PDSS total score,[15] the primary outcome measure. The 7-item PDSS,[15] the primary dependent variable, provides a diagnosis-based, composite, global rating of panic disorder severity. PDSS has acceptable psychometric properties.[15] Internal consistency in this sample was acceptable. The PDSS was administered 5 times at monthly intervals: before, during (at weeks 1, 5, and 9 of treatment), and at termination of treatment. The Sheehan Disability Scale (SDS)[16,17] measured psychosocial impairment.

Clinical Points

- Brief psychodynamic psychotherapy for panic disorder with or without agoraphobia had never been tested in a large, multisite randomized controlled trial compared with cognitive-behavioral therapy (CBT). This is important because patients with panic prefer psychotherapy to pharmacotherapy.
- Patients who completed their 3-month course of therapy, regardless of modality, improved more than those who dropped out. Patients randomized to applied relaxation training were more likely to drop out than those assigned to CBT or panic-focused psychodynamic psychotherapy (PFPP), particularly among the most symptomatic patients.
- CBT performed most consistently across sites; PFPP was less effective at the University of Pennsylvania relative to the other 2 treatment conditions than it was at Cornell, although it showed promise.

Therapist Training

PFPP training encompassed a 2-day, 10-hour course delivered at both sites by Dr Milrod; CBT training was a 2-day, 8-hour course delivered at both sites by Dr Schwalberg; ART training was a 6-hour course delivered at both sites by Drs Schwalberg and Klass.

Treatments

Treatments were delivered individually in twice-weekly 45- to 50-minute sessions. Nineteen to 24 sessions were provided within 16 weeks.

Cognitive-behavioral therapy. CBT followed the Panic Control Therapy (PCT) protocol,[18] modified by Drs Chambless and Schwalberg to fit the 24-session format of the trial. CBT has the following features: education about anxiety and panic; identification and correction of maladaptive thoughts about anxiety and panic; training in slow, diaphragmatic breathing; and exposure to bodily sensations designed to mimic those experienced during panic. In vivo exposure via homework assignments was introduced at session 17 for those patients with significant agoraphobic avoidance, whereas session 24 focused on review and relapse prevention.

Panic-focused psychodynamic psychotherapy. PFPP[9] is divided into 3 phases: Treatment of Acute Panic, Treatment of Panic Vulnerability, and Termination. The strategy assumes that panic symptoms have a psychological meaning, and PFPP works to uncover their unconscious meanings to achieve relief. Elucidating the meaning of symptoms involves viewing them in a more complex way, a process that raises reflective function.[19] To this end, exploration of circumstances and feelings surrounding panic onset, exploration of personal meanings of panic symptoms, and complex exploration of feelings and content of panic episodes are pursued. Common psychodynamic conflicts in panic disorder are (1) separation

and autonomy; (2) anger recognition, management, and coping with expression; and (3) panic symptoms occur as an expression of guilt. PFPP aims to lessen vulnerability to panic by helping patients understand and alter core unconscious conflicts. These conflicts are often identified and understood through their emergence in the transference. Termination permits patients to reexperience conflicts directly with the therapist so that underlying feelings can be articulated and rendered less frightening. Patient reaction to termination is aggressively addressed for a minimum of the final third (ie, 1 month) of treatment.

Applied relaxation training. Drs Chambless and Schwalberg adapted Cerny's ART manual (J. A. Cerny, B. B. Vermilyea, D. H. Barlow, et al; 1980; available from the authors on request) to a 24-session format. Progressive muscle relaxation training involves focusing of attention onto particular muscle groups, tensing the muscle group for 5–10 seconds, attending to the sensations of tension, relaxing of the muscle group, attending to the difference between the sensations of tension and relaxation, and suggestions of deepening relaxation. The number of muscle groups is gradually reduced from 16 to 4. Discrimination training, generalization, relaxation by recall, and cue-controlled relaxation (pairing the relaxed state to the word "relax") follow. Home practice is required twice per day. At session 11, patients are encouraged to begin applying relaxation skills whenever they notice tension in their bodies, and beginning at session 17 they are asked to deliberately enter mildly, then moderately anxiety-provoking situations for practice of their skills. ART involved no cognitive restructuring or interoceptive exposure.

Adherence Measures

Modality-specific, discrete adherence raters for each condition, graduate clinical psychology students and senior psychotherapists, were trained on treatment-specific scales. Patients were randomly selected for adherence rating: for each selected patient, 1 session was randomly selected for rating from the first 8 sessions, the second 8, and final 8. For each condition, 10% of session tapes were corated for reliabilities (ICCs). The 3 scales used to measure adherence are described below.

CBT. Adherence Ratings for PCT (CBT) (D.L.C., B.A.S.; available from the authors on request) is session-specific, including 3–9 items rated on 1–7 Likert-type scales. Mean scores of 4 indicate adherence (ICC = 0.83; mean CBT adherence 5.3 [1.7]).

PFPP. On the PFPP Adherence Scale (F.N.B., B.M.; available from the authors on request), the cutoff for acceptable adherence is ≥ 4/6 on ≥ 5/7 items (ICC = 0.92; mean 5.4 [1.6]).

ART. The ART Adherence Scale (M.S., D.L.C.; available from the authors on request) comprises session-specific forms with 3–4 items/session scored on 1–7 Likert-type scales. A mean score of 4 was defined as adequate adherence (ICC = 0.86; mean 5.5 [1.4]). We found no evidence of contamination (employing competing treatments) in sampling 10–37 sessions/treatment.

Data Analytic Procedures

We note that the results of initial analyses of the primary outcome measure, the PDSS, surprised us because they contradicted both prior findings in the literature and our clinical observations during the trial. We then double-checked the PDSS data and found 11 transcription errors (scores from PDSS interview forms were transcribed onto a single summary sheet before data entry) and 4 additional PDSS forms that had inadvertently not been submitted for data entry. With the approval of our Data Safety and Monitoring Board, we corrected these transcription errors and omissions and used the corrected PDSS for the data reported in this manuscript. The original locked data sets were used for all other measures.

Statistical analyses. We implemented multilevel models (MLM), a form of mixed-effect regression models, to assess change over time and between-group differences.[20] Ordinary MLM assumes data are missing at random, but they were not in this study. Accordingly, we used a shared parameters model,[21,22] an analytic approach accommodating data not missing at random.* Each individual was simultaneously modeled for change over time (using MLM) and attrition (using a survival model). The 2 processes share a common random effect inducing a quantifiable correlation between outcome and dropout processes. The MLM model for investigating change models both within-subject (Level 1) and between-subjects (Level 2) effects. At Level 1, outcome varies within subjects over time (weeks from baseline). Level 2 views person-specific change parameters as varying randomly across subjects as a function of treatment assignment. The attrition process is captured with a discrete time survival model[25] in which at each time point an individual is classified as "active," "completer," or "dropout." Jointly modeling outcome and attrition processes evaluates effects of interest on each portion of the model (outcome and attrition) while adjusting for the association between the outcome and attrition models. Analyses were conducted using SAS Version 9.3.[26] Kenward-Roger approximation, accommodating small sample inferences, estimated degrees of freedom.[27] Psychosocial function (SDS) (normalized with square root transformation) analysis of covariance using the last observation carried forward (LOCF),[28] including a covariate of propensity scores predicting attrition derived from clinical/demographic variables adjusted for nonignorable missing data† (baseline [n = 193], termination [n = 138]) were used in this calculation.

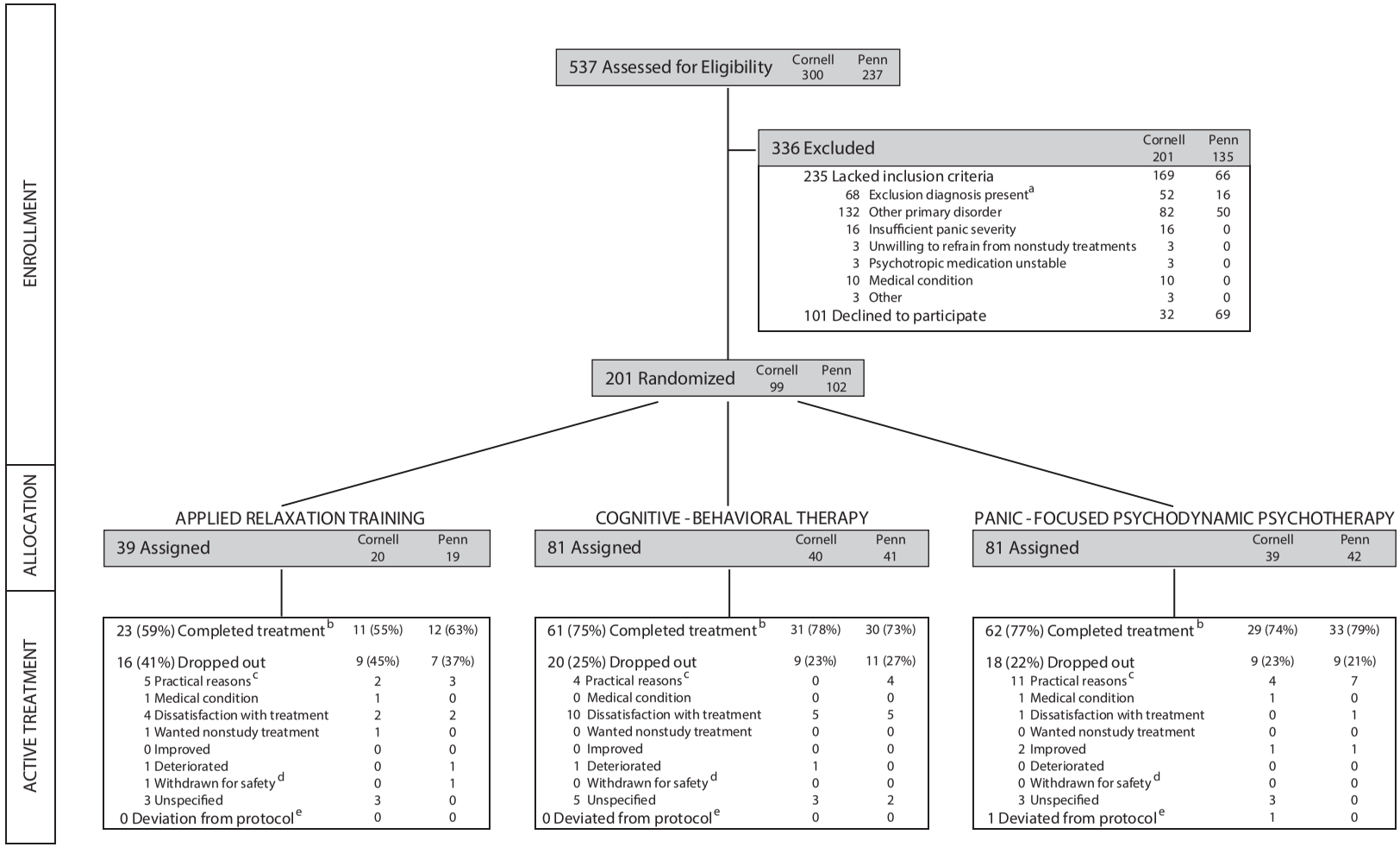
Power. To detect a between-group effect size of 0.45, for statistical power of 0.80, 56 patients for PFPP or CBT vs 28 for ART were required.

Covariates. All statistical analyses included a priori antidepressant use, anxiolytic use, site, treatment condition, and site-by-treatment interactions in the model. Among

*Gottfredson et al[23] suggested that 10 data points are needed to successfully use the shared parameters approach, but elsewhere we show successful application of the model with 5 data points.[24] Analyzing data using the more familiar MLM approach yielded similar findings.

†Analyses using multiple imputation yielded similar findings.

Figure 1. Study Flowchart



[a]Met criteria for substance dependence in the past 6 months, a lifetime history of psychotic disorder or bipolar disorder, or panic symptoms due to a general medical condition.
[b]At the Penn site, 4 patients (1 applied relaxation training, 2 cognitive-behavioral therapy, 1 panic-focused psychodynamic psychotherapy) attended only 15 sessions before their participation in the study elapsed (16 weeks).
[c]Reasons involving distance from site, personal finances, and time commitment.
[d]Investigators withdrew the patient from the study due to behaviors with a potential for harm (emergent psychotic symptoms).
[e]Patient did not disclose exclusionary symptoms at intake (psychosis).

Table 1. Descriptive Statistics and Differences at Baseline by Site and Condition

Variable	Entire Sample (N = 200)	Cornell (n = 98)			Penn (n = 102)			Effect (*P*)		
		ART (n = 20)	CBT (n = 40)	PFPP (n = 38)	ART (n = 19)	CBT (n = 41)	PFPP (n = 42)	Site	Condition	Site-by-Condition
Female, n (%)	136 (68)	18 (90)	27 (68)	25 (66)	14 (74)	19 (46)	33 (79)	.31	.011	.051
Age, median (SD), y	38.8 (13.2)	40.9 (14.3)	39.4 (14.0)	44.0 (12.5)	31.0 (9.6)	39.2 (11.4)	35.5 (13.9)	.004	.37	.06
Race, n (%)								.036	.38	.40
Asian	8 (4.0)	1 (5.0)	4 (10.0)	0 (0)	0 (0)	1 (2.4)	2 (4.8)			
Black/African American	39 (19.5)	4 (20.0)	13 (32.5)	9 (23.7)	3 (15.8)	6 (14.6)	4 (9.5)			
Native American/ Indian	1 (0.5)	0 (0)	0 (0)	1 (2.6)	0 (0)	0 (0)	0 (0)			
White/Caucasian	148 (74.0)	15 (75.0)	23 (57.5)	28 (73.7)	14 (73.7)	33 (8.5)	35 (83.3)			
Other	4 (2.0)	0 (0)	0 (0)	0 (0)	2 (1.5)	1 (2.4)	1 (2.4)			
Hispanic, n (%)	28 (14.0)	3 (15.0)	12 (30.0)	7 (8.4)	1 (5.3)	2 (4.9)	3 (7.1)	.0007	.51	.60
Employment, n (%)	152 (72.0)	17 (85.0)	35 (87.5)	28 (73.7)	12 (63.2)	28 (68.3)	32 (76.2)	.068	.89	.17
Education, n (%)[a]								.028	.80	.87
Some high school	5 (2.5)	0 (0)	1 (2.6)	0 (0)	1 (5.3)	2 (4.9)	1 (2.4)			
High school	17 (8.5)	0 (0)	1 (2.6)	2 (5.3)	3 (15.8)	5 (12.2)	6 (14.3)			
Some college	37 (18.6)	2 (10.0)	6 (15.4)	7 (18.4)	6 (31.6)	4 (9.8)	12 (28.6)			
Two-year college	16 (8.0)	1 (5.0)	3 (7.7)	4 (10.5)	0 (0)	5 (12.2)	3 (7.1)			
Four-year college	57 (28.6)	9 (45.0)	10 (25.6)	11 (29.0)	4 (21.1)	14 (34.2)	9 (21.4)			
Some graduate school	13 (6.5)	1 (5.0)	5 (12.8)	2 (5.3)	1 (5.3)	0 (0)	4 (9.5)			
Master's degree	37 (18.6)	5 (25.0)	9 (23.1)	7 (18.4)	3 (15.8)	9 (22.0)	4 (9.5)			
Professional degree	17 (8.5)	2 (10.0)	4 (10.3)	5 (13.2)	1 (5.3)	2 (4.9)	3 (7.1)			
Anxiety Disorders Interview Schedule for *DSM-IV* rating, median (SD)	5.64 (0.79)	5.45 (0.65)	5.89 (0.78)	5.84 (0.59)	5.53 (1.07)	5.46 (.81)	5.52 (0.77)	.011	.41	.25
Comorbidity, n (%)										
Agoraphobia	158 (79.0)	16 (80.0)	31 (77.5)	32 (84.2)	15 (79.0)	31 (75.6)	33 (78.6)	.58	.76	.87
Any anxiety disorder[b]	135 (67.5)	14 (70.0)	24 (60.0)	29 (76.3)	10 (52.6)	28 (68.3)	30 (71.4)	.80	.29	.37
Any depressive disorder[c]	51 (25.5)	5 (25.0)	12 (30.0)	13 (34.2)	3 (15.8)	9 (21.9)	9 (21.4)	.10	.71	.95
Any Axis I disorder[d]	145 (72.5)	15 (75.0)	27 (67.5)	31 (81.6)	11 (57.9)	30 (73.2)	31 (73.8)	.54	.40	.40
> 1 Axis I disorders[d]	84 (42.0)	8 (40.0)	20 (50.0)	18 (47.4)	6 (31.6)	17 (41.5)	15 (35.7)	.17	.59	.98
Any Axis II disorder[e]	96 (48.0)	11 (55.0)	17 (42.5)	21 (55.3)	9 (47.4)	20 (48.8)	18 (42.9)	.57	.84	.48

[a]One participant at the Cornell site did not report education level.
[b]Consisting of generalized anxiety disorder, social phobia, obsessive-compulsive disorder, or specific phobia.
[c]Consisting of major depressive disorder or dysthymic disorder.
[d]Consisting of major depressive disorder, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, or dysthymic disorder.
[e]Consisting of paranoid, schizoid, schizotypal, obsessive-compulsive, histrionic, dependent, antisocial, narcissistic, avoidant, borderline, and not otherwise specified personality disorders.
Abbreviations: ART = applied relaxation training, CBT = cognitive-behavioral therapy, PFPP = panic-focused psychodynamic psychotherapy.

statistically significant site differences (see Table 1), Penn patients had higher PDSS baseline severity and reported less education. The Penn sample was significantly younger but less racially and ethnically diverse. Site-by-treatment interactions were marginally significant for gender and age. Accordingly, age and gender were added to the models as covariates. None of these site differences explained the site-by-treatment outcome differences to be reported, whether possibly confounding variables were tested singly, in a composite variable, or in propensity scores.

Response rate. Treatment differences in response rates were examined using χ^2 tests in the full ITT sample, based on observed data and, for missing data, carrying the last available PDSS observation forward (LOCF).

Table 2. Number of Psychotropic Medication Prescriptions by Site and Condition[a]

Condition	Cornell[b] (n = 98)		Penn (n = 102)				
	0	1	0	1	2	3	4
ART	15	5	11	5	3	0	0
CBT	33	7	20	14	5	2	0
PFPP	38	0	22	11	4	4	1
Total	86	12	53	30	12	6	1

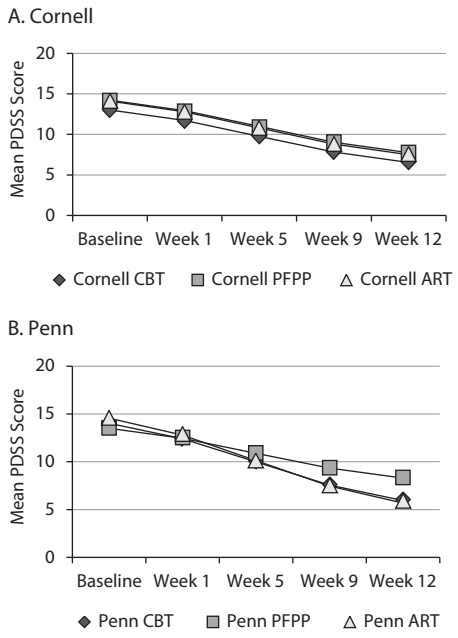
[a]As-needed anxiolytic use was counted as a medication prescription.
[b]No Cornell participant took more than 1 psychotropic medication.
Abbreviations: ART = applied relaxation training, CBT = cognitive-behavioral therapy, PFPP = panic-focused psychodynamic psychotherapy.

RESULTS

Patients

Using within-site stratification involving *DSM-IV* diagnoses of depression and agoraphobia, we randomized 201 patients (Figure 1). One psychotic participant was withdrawn postrandomization with consent of the Data Safety and Monitoring Board. Thirty-nine patients were randomized to ART, 81 apiece to CBT and PFPP. Table 1 shows that these primary panic disorder patients had high comorbidity: 80% had moderate to severe agoraphobia, 73% had ≥1 additional Axis I disorder(s), 68% had ≥ 1 additional anxiety disorder(s), and 48% had Axis II comorbidity.

Figure 2. Speed of PDSS Improvement by Assessment Point by Site



Abbreviations: ART = applied relaxation training, CBT = cognitive-behavioral therapy, PDSS = Panic Disorder Severity Scale, PFPP = panic-focused psychodynamic psychotherapy.

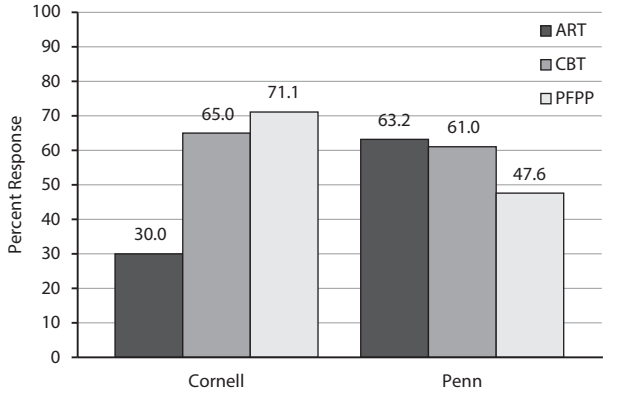
Psychotropic use. Fewer patients at Cornell (12%) than at Penn (48%) were on psychotropic medication (Table 2). Medication rates differed significantly by site (any vs no medication) (odds ratio = 7.196; CI, 3.504–14.776). No Cornell patients took prn anxiolytic medications; 28 at Penn did (5/19 ART [26.3%], 12/41 CBT [29.3%], 11/42 PFPP [26.2%]). Such anxiolytic use did not differ by condition ($\chi^2_2 = 0.11$, $P = .95$). An overall main effect of prn anxiolytics (increased apparent rate of change) on improvement speed ($P = .025$) did not affect site-by-treatment differences.

Outcomes

Attrition. Attrition rates were 41% in ART, 25% in CBT, and 22% in PFPP. Attrition did not differ by site ($P = .66$), but varied significantly among treatments: ART patients completed significantly fewer sessions than PFPP patients ($P = .037$) and marginally fewer than CBT patients ($P = .057$). The shared parameters model quantified correlation between outcome and attrition as $r = -0.56$ (SE = 0.29), indicating that patients who improved more slowly would be less likely to reach the next outcome assessment. Dropout was not random but correlated with lack of improvement, supporting use of the shared-parameters model. To better understand attrition, we divided patients into terciles by baseline PDSS severity. Attrition rates differed among the most symptomatic patients (baseline PDSS score ≥ 16): 69% in ART dropped out, versus 26% in CBT and 29% in PFPP ($\chi^2_2 = 8.62$, $P = .013$).

Serious adverse events. Two Penn ART patients required hospitalization, 1 for posttraumatic stress disorder and depression and 1 for psychotic depression.

Figure 3. Observed Response Rates by Site



Abbreviations: ART = applied relaxation training, CBT = cognitive-behavioral therapy, PFPP = panic-focused psychodynamic psychotherapy.

Effects of Psychotherapies

Primary outcome. A linear time form of the shared-parameters model revealed a significant site-by-treatment interaction in speed of PDSS change over time ($F_{2,198} = 4.41$, $P = .013$; Figure 2). Cornell patients improved at similar rates across treatments: 0.32 (SE = 0.029) PDSS units/week, 0.32 (SE = 0.030), and 0.33 (SE = 0.053), respectively, for CBT, PFPP, and ART. However, at Penn, CBT patients (0.40 [SE = 0.028] units/week; $t_{198} = 3.74$, $P = .0002$) and ART patients (0.45 [SE = 0.049] units/week; $t_{198} = 3.32$, $P = .001$) improved significantly faster than PFPP patients (0.26 [SE = 0.027] units/week). At termination, CBT ($P = .009$) and ART ($P = .025$) were both superior to PFPP at Penn, whereas at Cornell no significant differences emerged among treatments (all P values > .16). Greater attrition in the ART group, along with a smaller subsample, contributed to greater error in imputed ART improvement rates as time elapsed.

Because of differential site medication use (Table 2), we conducted further analysis, covarying number of medications within the shared parameters model. Controlling for this variable reduced the variance of the site-by-treatment interaction by 0.6%, but the interaction remained statistically significant ($P = .013$ changed to $P = .039$).[29] We additionally created a composite potential site-by-treatment moderator variable per Kraemer,[29] including number of medications, gender, age, psychotropic medication, and anxiolytics. Controlling for this composite variable reduced the variance of the site-by-treatment interaction by 1.1%, but the interaction remained statistically significant ($P = .013$ changed to $P = .048$).

Response rates. Overall response rates were ART, 46%; CBT, 63%; and PFPP, 59%. Site-by-treatment differences in response rate ($\chi^2_2 = 8.24$, $P = .016$) showed a significant difference among interventions at Cornell ($\chi^2_2 = 9.87$, $P = .007$) but not at Penn ($\chi^2_2 = 2.00$, $P = .37$). Driving this effect were lower Cornell response rates for ART than CBT ($\chi^2_1 = 6.56$, $P = .01$) and PFPP ($\chi^2_1 = 9.00$, $P = .003$) (Figure 3). Most patients were responders, with those who completed

treatment (defined as >16 sessions) being significantly more likely to respond ($P = .04$).

Sheehan Disability Scale. The site-by-treatment interaction was also obtained in analyses of psychosocial function as captured by the SDS ($F_{2,183} = 3.18$, $P = .045$). Although no significant differences were observed among treatments at Cornell ($P \geq .41$), Penn ART ($P = .036$) and CBT ($P = .026$) patients improved more than PFPP patients. Therapist effects on PDSS[30] did not approach significance for the outcome ($\chi^2_{0:1} = 0.40$, $P = .34$) or attrition ($\chi^2_{0:1} = 0.16$, $P = .67$) portions of the shared parameters model. Accordingly, this factor was not included further.

DISCUSSION

This first large randomized controlled comparison of PFPP and CBT for panic disorder had site-by-treatment interactions that complicated interpretation of results. Site-by-treatment interactions appeared despite regular meetings and telephone conferences by site principal investigators (PIs) and project coordinators, carefully maintained cross-site assessment measure reliability, balanced therapy delivery, attempts to balance investigator allegiance across sites, meticulously tracked patients, and blinded independent evaluators. Although site differences emerged on variables such as initial severity and medication, controlling for these did not eliminate the interaction.

Could differences in treatment implementation explain the site-by-treatment interaction? CBT did well at both sites. This finding and the adherence data suggest CBT was well conducted at both sites, despite a PCT protocol novel for all CBT therapists. CBT response rates were 61%–65%, comparing favorably to 49% in the Multicenter Collaborative Study for the Treatment of Panic Disorder,[3] in which patients were less agoraphobic than ours. Comparisons across trials are fraught, but possibly our longer course of treatment (24 sessions vs 12 in the Multicenter Collaborative Study) increased our response rate despite the greater difficulty of our sample. In sum, PCT appears readily transportable to practicing CBT therapists. Adherence ratings indicate that ART was conducted adequately. In the primary outcome analysis, our revised ART protocol performed well in this trial, relative to our earlier study,[10] particularly at Penn. A PI closely supervised ART only at Penn and encouraged therapists' positive expectancy of outcomes in that condition, whereas at Cornell, ART therapists were experienced from previous studies and were supervised at frequencies used for experienced therapists in the other 2 conditions. These factors may have improved ART's performance relative to the other treatments at Penn. Unfortunately, we do not have measures of therapists' expectancy to test this hypothesis. However, attrition continued to be a problem in ART, especially for the most severe patients, of whom 69% dropped out. Given this dropout rate, it is unsurprising that the secondary analysis of responder rates yielded a different pattern of results.

Response rates at Cornell for both CBT and PFPP significantly exceeded ART, supporting the study's hypothesis. Penn response rates did not differ across treatments. In this case, therapists' experience is unlikely to explain the better performance of ART relative to PFPP at Penn, as Cornell therapists had previous experience with ART,[10] whereas Penn therapists did not. We conclude that ART may well be helpful for those patients who accept it, but this will be a limited sample relative to PFPP and CBT.

The difference in findings across sites in PFPP is striking. Whereas Cornell treatments did not show differential speed of response, PFPP patients at Penn improved more slowly than CBT or ART patients and ended treatment more symptomatic. Nonetheless, the responder analysis indicated that, consistent with a recent meta-analysis pointing to the promise of psychodynamic therapies for anxiety disorders,[7] PFPP was successful in treating 48%–71% of the patients. PFPP's underperformance relative to CBT and ART at Penn might reflect its novelty for the Penn dynamic therapists. Although Penn therapists were experienced in time-limited dynamic therapy, several had a background in supportive expressive therapy (SET),[31] which differs from PFPP in a number of ways. SET identifies a central, focal "Core Conflictual Relationship Theme" (CCRT), which forms an organizing focus for treatment. The CCRT is related to but differs from the transference. PFPP is more symptom-focused than most dynamic therapies and requires a shift in focus particularly for some experienced dynamic therapists. PFPP focuses specifically on decoding underlying emotional meanings of symptoms and agoraphobic fantasies and highlights separation and autonomy difficulties, partly interpreted through the transference. Moreover, PFPP supervision was often conducted by telephone at Penn, and group supervisions that were so helpful for therapists were difficult to schedule there as frequently.

Limitations. Large site differences, particularly in psychotropic use, do not entirely explain differential treatment response across sites. ART, included as an active control treatment, showed the highest response rate at Penn. Strengthening ART with in vivo exposure and homework practice to limit dropout may have succeeded too well. Although Öst and Westling[32] describe such interventions as standard ART, ART clinical trials do not always include them. These changes made ART more active, albeit not for the sickest patients. Moreover, inclusion of in vivo exposure in ART blurred distinctions between ART and CBT.

This study raises important research questions. Investigators often fail to examine and address site-by-treatment interactions in RCTs. However, these do occur. For example, DeRubeis et al[33] found differential effects for medication and CBT across their 2-site RCT of cognitive therapy vs pharmacotherapy for major depression. In this trial, differences were in part accounted for by differential rates of Axis I comorbidity. The authors also suggest that CBT performed better at one site, relative to pharmacotherapy, than at the other because therapists at the first site were more experienced in CBT than at the

second. In our study, differences in comorbidity did not affect site differences in treatment outcome, but it is the case that PFPP therapists at Cornell were more experienced with this particular protocol than were Penn therapists. Exporting a psychotherapy has lowered response rates at new sites,[33,34] and between-site supervision differences can affect outcomes.[34] Both of these factors may help explain the less robust PFPP improvements at Penn, in that CBT and ART were closely supervised by a local supervisor, whereas PFPP was supervised more often remotely (eg, via telephone supervision) even though overall therapist experience did not differ. When multisite studies find site-by-treatment differences, they inevitably raise questions of researcher allegiance,[34–36] which has correlated with outcomes in psychotherapy trials.[34,35] However, allegiance is unlikely to explain PFPP results in our trial, as both sites featured psychodynamic PIs.

CONCLUSIONS

Most patients who completed treatment in each condition responded, but no treatment intervention benefits all patients with panic disorder. A critical question is whether prescriptive variables can guide optimal treatment selection for particular patients. We plan moderator analyses that may provide prescriptive recommendations.[37,38] Further, mediation analyses may elucidate common and distinct mechanisms associated with change across treatments.

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Author contributions: **Dr Milrod** was site principal investigator (PI) at the Cornell site and was trainer, supervisor of PFPP at both sites, and therapist for 2 subjects at Cornell. **Dr Busch** served as PFPP trainer, supervisor at both sites, and therapist at Cornell. **Mr Gross** was project coordinator at Cornell, maintained and cleaned the Cornell dataset, and trained research assistants and maintained reliability on all study instruments from the Cornell side. **Dr Leon** was the project biostatistician who helped with the design and implementation of this study, he maintained close contact with the Data Safety and Monitoring Board (DSMB), provided randomization algorithms, and interfaced with the data management team. **Dr Chambless** was site PI after Dr Barber's departure from Penn and was site supervisor of CBT and ART at Penn. **Dr McCarthy** maintained and unscrambled the database after Dr Leon's death and served as research assistant and project coordinator at Penn. **Dr Gallop** was the project biostatistician after Dr Leon's death. **Dr Schwalberg** trained clinicians at both sites in both CBT and ART, developed adherence instruments with Dr Chambless in CBT and ART, and provided supervision in ART at Cornell. **Dr Sharpless** was Program Coordinator at the Penn site for years 1–3 of the study. **Dr Barber** was the original site PI at the Penn site for the first 4 years of the study until his move to Adelphi. He remains a co-PI from Penn.

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REFERENCES

1. Greenberg PE, Sisitsky T, Kessler RC, et al. The economic burden of anxiety disorders in the 1990s. *J Clin Psychiatry*. 1999;60(7):427–435.
2. Katon W. Panic disorder: relationship to high medical utilization, unexplained physical symptoms, and medical costs. *J Clin Psychiatry*. 1996;57(suppl 10):11–18, discussion 19–22.
3. Barlow DH, Gorman JM, Shear MK, et al. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA*. 2000;283(19):2529–2536.
4. Siev J, Chambless DL. Specificity of treatment effects: cognitive therapy and relaxation for generalized anxiety and panic disorders. *J Consult Clin Psychol*. 2007;75(4):513–522.
5. Hofmann SG, Barlow DH, Papp LA, et al. Pretreatment attrition in a comparative treatment outcome study on panic disorder. *Am J Psychiatry*. 1998;155(1):43–47.
6. Markowitz JC, Lipsitz J, Milrod BL. Critical review of outcome research on interpersonal psychotherapy for anxiety disorders. *Depress Anxiety*. 2014;31(4):316–325.
7. Keefe JR, McCarthy KS, Dinger U, et al. A meta-analytic review of psychodynamic therapies for anxiety disorders. *Clin Psychol Rev*. 2014;34(4):309–323.
8. Beutel ME, Scheurich V, Knebel A, et al. Implementing panic-focused psychodynamic psychotherapy into clinical practice. *Can J Psychiatry*. 2013;58(6):326–334.
9. Milrod B, Busch F. Cooper, A, et al. *Manual of Panic-Focused Psychodynamic Psychotherapy*. Washington, DC: APA Press; 1997.
10. Milrod B, Leon AC, Busch F, et al. A randomized controlled clinical trial of psychoanalytic psychotherapy for panic disorder. *Am J Psychiatry*. 2007;164(2):265–272.
11. Öst LG. Applied relaxation vs progressive relaxation in the treatment of panic disorder. *Behav Res Ther*. 1988;26(1):13–22.
12. Frank JD, Frank JB. *Persuasion and Healing*. 3rd ed. Baltimore, MD: Johns Hopkins University Press; 1991.
13. Shear MK, Maser JD. Standardized assessment for panic disorder research: a conference report. *Arch Gen Psychiatry*. 1994;51(5):346–354.
14. DiNardo PA, Brown TA, Barlow DH. *Anxiety Disorders Interview Schedule for DSM-IV: Current Version (ADIS-IV)*. New York, NY: Graywinds Publications; 1995.
15. Shear MK, Brown TA, Barlow DH, et al. Multicenter collaborative panic disorder severity scale. *Am J Psychiatry*. 1997;154(11):1571–1575.
16. Sheehan DV. The Sheehan disability scales. *The Anxiety Disease*. New York, NY: Charles Scribner and Sons; 1983:151.
17. Leon AC, Shear MK, Portera L, et al. The relationship of symptomatology to impairment in patients with panic disorder. *J Psychiatr Res*. 1993;27(4):361–367.
18. Craske MG, Barlow DH, Meadows E. *Master Your Own Anxiety and Panic: Therapist Guide for Anxiety, Panic, and Agoraphobia (MAP-3)*. San Antonio, TX: Graywind/Psychological Corporation; 2000.
19. Fonagy P, Target M. Attachment and reflective function: their role in self-organization. *Dev Psychopathol*. 1997;9(4):679–700.
20. Raudenbush SW, Bryk AS. *Hierarchical Linear Models*. 2nd ed. London, UK: Sage; 2002.
21. Little RJA. Modelling the drop-out mechanism in repeated-measures studies. *J Am Stat Assoc*. 1995;90(431):1112–1121.
22. Ten Have TR, Kunselman AR, Pulkstenis EP, et al. Mixed effects logistic regression models for longitudinal binary response data with informative drop-out. *Biometrics*. 1998;54(1):367–383.
23. Gottfredson NC, Bauer DJ, Baldwin SA, et al.

Using a shared parameter mixture model to estimate change during treatment when termination is related to recovery speed. *J Consult Clin Psychol*. 2014;82(5):813–827.
24. Gallop RJ, Ten Have TR, Crits-Christoph P. A mixed effects Markov model for repeated binary outcomes with non-ignorable dropout. *Stat Med*. 2006;25(14):2398–2426.
25. Willett JB, Singer JD. Investigating onset, cessation, relapse, and recovery: why you should, and how you can, use discrete-time survival analysis to examine event occurrence. *J Consult Clin Psychol*. 1993;61(6):952–965.
26. SAS Institute Inc. *Base SAS 9.3 Procedures Guide*. Cary, NC: SAS Institute Inc; 2011.
27. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics*. 1997;53(3):983–997.
28. Leon AC, Mallinckrodt CH, Chuang-Stein C, et al. Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. *Biol Psychiatry*. 2006;59(11):1001–1005.
29. Kraemer HC. Discovering, comparing, and combining moderators of treatment on outcome after randomized clinical trials: a parametric approach. *Stat Med*. 2013;32(11):1964–1973.
30. Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data*. New York, NY: Springer-Verlag; 2000.
31. Milrod B. Psychodynamic psychotherapy outcome for generalized anxiety disorder. *Am J Psychiatry*. 2009;166(8):841–844.
32. Öst LG, Westling BE. Applied relaxation vs cognitive behavior therapy in the treatment of panic disorder. *Behav Res Ther*. 1995;33(2):145–158.
33. DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry*. 2005;62(4):409–416.
34. Luborsky L, Diguer L, Selgman DA, et al. The researcher's own therapy allegiances: a "wild card" in comparisons of treatment efficacy. *Clin Psychol Sci Pract*. 1999;6(1):95–106.
35. Falkenström F, Markowitz JC, Jonker H, et al. Can psychotherapists function as their own controls? meta-analysis of the crossed therapist design in comparative psychotherapy trials. *J Clin Psychiatry*. 2013;74(5):482–491.
36. Munder T, Flückiger C, Gerger H, et al. Is the allegiance effect an epiphenomenon of true efficacy differences between treatments? a meta-analysis. *J Couns Psychol*. 2012;59(4):631–637.
37. Milrod BL, Leon AC, Barber JP, et al. Do comorbid personality disorders moderate panic-focused psychotherapy? an exploratory examination of the American Psychiatric Association practice guideline. *J Clin Psychiatry*. 2007;68(6):885–891.
38. Barber JP, Muenz LR. The role of avoidance and obsessiveness in matching patients to cognitive and interpersonal psychotherapy: empirical findings from the Treatment for Depression Collaborative Research Program. *J Consult Clin Psychol*. 1996;64(5):951–958.