Next-Step Strategies for Panic Disorder Refractory to Initial Pharmacotherapy: A 3-Phase Randomized Clinical Trial

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Background: More data are needed to guide next-step interventions for panic disorder refractory to initial intervention.

Method: This 24-week randomized clinical trial (RCT) enrolled 46 patients with *DSM-IV*–defined panic disorder from November 2000 to April 2005 and consisted of 3 phases. Patients who failed to meet remission criteria were eligible for randomization in the next treatment phase. Phase 1 was a 6-week lead-in with open-label sertraline flexibly dosed to 100 mg (or escitalopram equivalent) to prospectively define treatment refractoriness (lack of remission). Phase 2 was a 6-week double-blind RCT of (1) increased-dose selective serotonin reuptake inhibitor (SSRI) versus (2) continued SSRI plus placebo. Phase 3 was a 12-week RCT of added cognitive-behavioral therapy (CBT) compared to "medication optimization" with SSRI plus clonazepam. Primary endpoints were remission and change in Panic Disorder Severity Scale (PDSS) score in the intent-to-treat sample in each phase.

Results: In phase 1, 20.5% (8/39) of the patients achieved remission, and only baseline severity predicted endpoint PDSS score (β [SE] = 1.04 [0.15], $t = 6.76$, $P < .001$). In phase 2, increasing the SSRI dose did not result in greater improvement or remission rates (placebo 15% [n = 2] vs increased dose 9% [n = 1]: Fisher exact test P = NS). In phase 3, remission was minimal (medication optimization = 11% [n = 1]; CBT = 10% [n = 1]), with a lack of group difference in PDSS score reduction ($t_{17} = 0.51$, $P > .60$) consistent with a small effect size ($d = 0.24$).

Conclusions: Although power was limited and larger studies are needed, we failed to find evidence for greater benefit of increased SSRI dose versus continuation of current dose for panic disorder symptomatic after 6 weeks at moderate dose. Further, augmentation with CBT or medication optimization with clonazepam augmentation in nonremitted panic after 12 weeks of an SSRI did not differ, suggesting that both are reasonable next-step options. However, low overall remission rates in this comorbid refractory population suggest that better predictors of response to specific treatments over time and additional interventions are needed.

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Panic disorder with or without agoraphobia is a common anxiety disorder, occurring in 4.7% of the population.[1] Although there have been a growing number of treatments with reported efficacy for panic disorder in clinical trials and practice in recent years, acute and longitudinal follow-up studies of patients with panic disorder suggest that many individuals remain symptomatic despite initial treatment.[2–5] Further, there remains a paucity of systematic data currently available to guide the treatment of patients with panic disorder who remain symptomatic after initial intervention.

The definition of responder status in acute panic disorder trials has varied across studies, with earlier focus on the frequency of panic attacks alone. However, this measure is not sensitive to the broad spectrum of symptoms that patients with panic disorder experience, and broader measures such as the Panic Disorder Severity Scale (PDSS), which includes ratings of panic attack frequency and severity, anticipatory anxiety, fear and avoidance, and functional impairment, are needed to assess treatment response.[6–12] The field has now recognized the importance of symptom-free status,[13] and when comprehensive assessments are applied, it is clear that many patients remain symptomatic with initial treatment and may require additional intervention to achieve remission; however, there are few data to guide clinicians in the "next step" for patients who respond incompletely or not at all to treatment.[14,15] Optimizing dose, adding cognitive-behavioral therapy (CBT) for panic disorder, augmenting with additional medication, or switching between agents are options for patients who remain symptomatic despite initial pharmacotherapy (eg, see Roy-Byrne et al[5]). However, more research is necessary to develop a data-based algorithm for the treatment of patients with panic disorder refractory to treatment.

The primary aims of this study were to examine 2 consecutive "next-step" options for patients with panic disorder with or without agoraphobia who remained symptomatic following initial treatment with standard panic pharmacotherapy, a selective serotonin reuptake inhibitor (SSRI) at

moderate dose for 6 weeks.[13] For the first step, we hypothesized that increasing the dose of the current SSRI would be more efficacious than adding placebo (or "more time at the initial dose") to the current dose of SSRI for an additional 6 weeks. In the second step, patients still not in remission were randomly assigned to continued SSRI pharmacotherapy with addition of a 12-week course of CBT or "best shot" medication optimization with the SSRI at optimized doses plus the addition of the benzodiazepine clonazepam. On the basis of the established efficacy of CBT as monotherapy and previous data in the literature specifically examining CBT as augmentation for incomplete response to initial pharmacotherapy for panic disorder,[16–23] we hypothesized that we would find preliminary support for the greater efficacy for the psychosocial relative to the pharmacologic "next-step" strategy.

METHOD

This 24-week randomized clinical trial consisted of 3 phases (see Figure 1). Patients who failed to meet remission criteria were eligible for randomization in the next treatment phase. Remission status (ie, a patient requiring no further intervention) was defined as zero panic attacks for at least 1 week and a Clinical Global Impressions-Severity of Illness (CGI-S) score of 1 or 2: "normal, not at all ill" or "borderline ill." Phase 1 was a 6-week open treatment phase with a moderate dose of an SSRI to prospectively assess failure to achieve remission. The primary SSRI was sertraline flexibly dosed to 100 mg, but patients with a prior history of intolerance or lack of response to sertraline were allowed an equivalently dosed SSRI, escitalopram. Sertraline was initiated at 25 mg/d (or 5 mg/d of escitalopram) and then increased to 50 mg/d (or 10 mg/d of escitalopram) at week 1 and 100 mg/d (or 15 mg/d of escitalopram) at week 3. Upward dose titration could be slowed if necessary due to side effects, but those unable to tolerate 100 mg/d of sertraline or 15 mg/d of escitalopram by week 6 were not eligible for randomization to phase 2 and were instead referred for appropriate clinical care.

Phase 2 examined the effect of increased dose on outcome for those with continued panic symptoms: individuals who did not meet remission criteria at week 6 were randomly assigned in double-blind fashion to 6 weeks of either continued moderate-dose SSRI plus placebo or increased-dose SSRI. Dosing was increased by sertraline 50 mg (or escitalopram 5 mg) at week 6 and again by sertraline 50 mg (or escitalopram 10 mg) at week 8 if side effects allowed. The maximum dose at week 8 was sertraline 200 mg/d (or escitalopram 30 mg/d), although titration could be slowed with the last allowed dose increase at week 10. To improve generalizability and recruitment, study entry at phase 2 was allowed for patients already initiated on treatment with an SSRI up to phase 1 endpoint dosing (ie, sertraline 100 mg/d for at least 6 weeks).

Phase 3 examined the relative efficacy of randomization to 2 next-step interventions for those who remained symptomatic on SSRI at week 12: (1) the addition of CBT or (2) "medication optimization" (MO) with combined clonazepam and SSRI treatment. Patients assigned to MO were titrated as tolerated to clonazepam flexibly dosed to 1.0 mg bid by week 18, and sertraline was raised, in a blinded fashion, to 200 mg/d (or escitalopram 30 mg/d) for those not receiving an increased dose in phase 2. Patients remaining symptomatic on this regimen at week 18 had clonazepam flexibly titrated by 0.5 mg per week up to week 23 as tolerated for a maximum of 4 mg/d. The treating study pharmacotherapist performed symptom ratings at each visit. In addition, for this phase, even though medication remained blinded, independent evaluators were utilized at randomization and endpoint as secondary raters to confirm that blinded ratings did not differ with the primary assessments performed by the study clinician.

Patients randomly assigned to CBT maintained their week 12 SSRI dose with the addition of weekly CBT. Patients received 12 weekly 50-minute individual CBT sessions for a total of 12 weeks. A standard protocol of CBT for panic disorder adapted from an 11-session treatment manual,[20] but without a focus on medication discontinuation, was employed. Treatment included information about the nature of panic disorder and emphasis on interoceptive exposure, cognitive restructuring, and situational exposure. Relaxation and diaphragmatic breathing skills were applied in select cases. All study therapists were trained and supervised by a senior cognitive-behavioral therapist (M.W.O.).

The Institutional Review Board of Massachusetts General Hospital approved this study, and all subjects received and signed an informed consent statement prior to participation. Participants were enrolled in the study from November 2000 to April 2005. Participants were recruited by advertisement and referral to research at the Center for Anxiety and Traumatic Stress Disorders at Massachusetts General Hospital. Eligible participants were men or women 18 to 65 years of age with a primary diagnosis of panic disorder with or without agoraphobia, as diagnosed by a psychiatrist with the Structured Clinical Interview for *DSM-IV* (SCID-IV),[24] and with a panic disorder–specific CGI-S score of at least 4 ("moderately ill") at baseline. Comorbid past or present *DSM-IV* major depressive disorder, dysthymia, generalized anxiety disorder, social phobia, or specific phobia as diagnosed by *DSM-IV* criteria was permitted as long as panic disorder was primary (the disorder most distressing to the patient), in order to accrue a clinically relevant patient population.

Pregnant or lactating women and those of childbearing potential who were not using a medically acceptable means of birth control, as well as patients with severe unstable medical illness, were ineligible for study participation. Other exclusion criteria included clinically significant baseline laboratory, electrocardiogram, or physical examination

findings; unstable medical illness; lifetime history of *DSM-IV* schizophrenia, psychotic disorders, bipolar disorder, mental disorder due to a medical condition or substance, or obsessive-compulsive disorder; history of posttraumatic stress disorder within the past 6 months; a 17-item Hamilton Depression Rating Scale (HDRS) score greater than 21 or greater than 2 on item 1; alcohol or substance abuse or dependence within the past 6 months; and positive toxicology screen at baseline consistent with current substance abuse or dependence as determined by clinical interview. Additionally excluded were patients who had known hypersensitivity to sertraline, escitalopram, or clonazepam; those receiving concurrent psychotropic medications including buspirone, antidepressants, benzodiazepines, or β-blockers; and those receiving concurrent cognitive-behavioral psychotherapy. Participants were required to be free of benzodiazepine therapy and antidepressant therapy for at least 2 weeks prior (with fluoxetine at least 4 weeks) to be eligible for entry into phase 1.

Primary outcomes were the proportion of patients successfully achieving remission status and the change in the PDSS[25] score in each treatment study phase. The PDSS is a 7-item scale with each item rated from 0 (none) to 4 (extreme), for a total score range of 0 to 28 and an established interrater reliability of 0.87.[10] Remission status, as noted, was defined as zero panic attacks for at least 1 week and a CGI-S score of 1 or 2. The CGI-S is a standard, single-item, clinician-rated scale ranging from 1 to 7 ("extremely ill")[26]; we utilized a previously adapted version of the CGI-S with specific anchor points for number and frequency of panic attacks, intensity of anticipatory anxiety, degree of phobic avoidance, and impairment of function[27] and for which we established an interrater reliability of 0.89. Patients kept a weekly panic diary; this was reviewed with the clinician at each visit, and the clinician then completed a panic attack inventory that recorded number of full and partial triggered and nontriggered panic attacks in the past week.

Secondary outcome measures included the 14-item Hamilton Anxiety Rating Scale (HARS),[28] the 17-item HDRS,[29] the Reiss-Epstein-Gursky Anxiety Sensitivity Index (ASI: a 16-item self-report instrument designed to assess fear of anxiety),[30] and the Sheehan Disability Scale (SDS: a 3-item scale covering 3 areas of functioning—work, family/home life, and social life/leisure).[31]

Statistical Analysis

Analyses in each study phase were for a modified intent-to-treat (ITT) sample, defined as all participants who had at least 1 on-treatment assessment during that phase. Primary univariate analyses consisted of *t* tests for continuous outcome variables (eg, PDSS score) and Fisher exact test for binary variables (eg, remission status). Predictors of response in phase 1 were examined in a linear regression model examining change in PDSS score. Follow-up longitudinal mixed-effects regression models (xtmixed in Stata version 9.1; StataCorp; College Station, Texas) were employed for both phase 2 and phase 3 PDSS scores to examine examining slope of change over time.

Table 1. Demographic Characteristics and Psychiatric Comorbidity in 42 Patients With Panic Disorder

Characteristic	Mean ± SD	
Age, y	37.7 ± 11.2	
Age at onset, y	28.0 ± 9.5	
Duration, y	9.7 ± 9.9	
	N (%)	
Sex, female	24 (57.1)	
Race		
White	37 (88.1)	
Hispanic	3 (7.1)	
Asian	2 (4.8)	
Comorbidity	Lifetime	Current
Social anxiety disorder	13 (31.0)	13 (31.0)
Posttraumatic stress disorder	5 (11.9)	NA
Generalized anxiety disorder	NA	11 (26.2)
Major depressive disorder	24 (57.1)	15 (35.7)
Alcohol abuse/dependence	10 (23.8)	NA[a]
Substance abuse/dependence	3 (7.1)	NA[a]
Eating disorder	1 (2.4)	0
Any anxiety disorder	28 (66.7)	27 (64.3)
Any comorbid disorder	35 (83.3)	30 (71.4)

[a]Not applicable; patients with alcohol or substance abuse or dependence within the last 6 months were not eligible for the study.

RESULTS

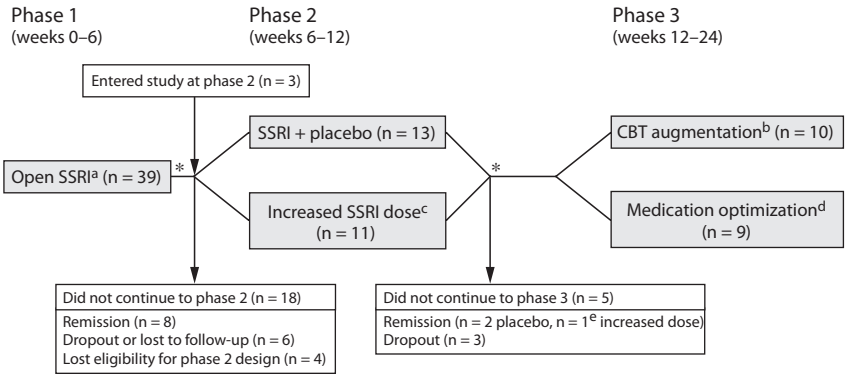
Subject Flow and Description

One hundred thirteen individuals were screened, and 46 met entry criteria and were enrolled in the study (43 entered at phase 1, and 3 who were already at phase 1 endpoint doses of sertraline or escitalopram entered at phase 2). Two participants were lost to follow-up prior to the first phase 1 on-medication visit, and 2 were removed after discovery of current alcohol abuse, leaving 42 patients available for overall analyses (n = 40 sertraline, n = 2 escitalopram), with n = 39 in phase 1. Phase 2 analyses included 24 individuals, with 19 continuing on to phase 3 of the study. See Table 1 for patient demographics and Figure 1 for patient flow. Agoraphobia was present in 83% of the patients; additional psychiatric comorbidity was high, with 64% having a current comorbid anxiety disorder and 36% having current major depressive disorder (see Table 1).

Phase 1: Six Weeks of Open-Label Pharmacotherapy With Moderately Dosed SSRI

In phase 1, 5/39 patients in the ITT sample discontinued treatment prior to week 6 (1 due to adverse events including nausea, vomiting, and headache; 2 due to time constraints; and 2 lost to follow-up). Baseline scores on symptom ratings were as follows (mean ± SD): PDSS = 16.3 ± 4.5, CGI-S = 4.8 ± 0.8, HARS = 23.2 ± 8.4, HDRS = 11.6 ± 4.5, ASI = 34.3 ± 10.5. There was a significant reduction at

Figure 1. Study Design Schematic and Patient Flow



[a]Sertraline to 100 mg/d or escitalopram to 15 mg/d.
[b]CBT added to phase 2 pharmacotherapy.
[c]SSRI to sertraline 200 mg/d or escitalopram 30 mg/d.
[d]SSRI to sertraline 200 mg/d or escitalopram 30 mg/d plus clonazepam flexibly dosed up to 4 mg/d.
[e]Also included in dropout group.
Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitor.
Symbol: * = point of randomization.

phase 1 endpoint for the primary continuous measure, the PDSS (mean ± SD reduction of 4.3 ± 4.3 points, $t_{38} = 6.3$, $P < .001$), with a mean ± SD endpoint CGI-S score of 3.9 ± 1.2. Remission status at phase 1 endpoint was achieved by 20.5% (8/39) of the patients, who were thus not eligible to enter phase 2 (see Figure 1).

We examined potential predictors of phase 1 outcome, adjusting for PDSS score at baseline. Baseline severity alone was significantly predictive of endpoint PDSS score (β [SE] = 1.04 [0.15], $t = 6.76$, $P < .001$), as was early reduction (in the first 2 weeks) in PDSS score (β [SE] = 0.65 [0.21], $t = 3.00$, $P < .005$). Age, gender, duration of illness, current agoraphobia, current anxiety or depression comorbidity, and current psychiatric comorbidity were not significantly associated with endpoint PDSS score. Patients with a younger age at panic onset had modestly poorer outcomes at the level of a statistical trend (β [SE] = −0.03 [0.15], $t = 1.89$, $P = .067$).

Phase 2: Increased-Dose SSRI or Continued-Dose SSRI (placebo augmentation)

See Figure 1 for summary of patient flow. Of the 26 phase 1 completers eligible for randomization in phase 2, 1 was lost to follow-up after the week 6 assessments (bringing total to n = 6 from phase 1). Three individuals entered phase 2 already on treatment with an SSRI for a mean ± SD duration of 11.7 ± 7.2 weeks prior to entry (1 escitalopram 15 mg, 2 sertraline 100 mg). Four individuals included in phase 1 were excluded from phase 2 and phase 3 analyses because of design changes made to phase 2 (eliminating a third arm with the addition of benzodiazepine at week 6 to enhance sample size in the primary SSRI dose comparison) after their participation. Thus, 24 patients were included in phase 2 group analyses: 13 randomly assigned to adjunctive placebo and 11 to increased SSRI doses.

There were no significant differences in phase 2 baseline severity between groups on the PDSS, CGI-S, HARS, HDRS, ASI, or SDS (all P values = NS). Patients taking increased SSRI doses had a mean ± SD endpoint dose of 195.5 ± 15.1 mg of sertraline or equivalent. Three patients (27%) receiving increased-dose SSRI discontinued (n = 1 due to adverse events of jitteriness, tremor, and diarrhea, and n = 2 lost to follow-up). No patients receiving placebo augmentation discontinued.

Although there was further significant reduction in the PDSS score overall (mean ± SD decrease = 2.33 ± 3.84, paired $t = 2.98$, $P < .007$), increasing the SSRI dose relative to the addition of placebo did not result in greater improvement according to significance testing or estimation of effect size (Cohen $d = 0.01$: see Table 2). Further, increased dose did not result in significant differences in remission at phase 2 endpoint (placebo augmentation 15% [n = 2], increased SSRI dose 9% [n = 1]: FET P = NS), with the 1 remitter receiving an increased dose also dropping out prior to week 12. During phase 2, there was no overall reduction in any of the secondary measures including the HARS, HDRS, ASI, and SDS at endpoint (all P values > .25), with no significant differences between the placebo and increased-dose groups (see Table 2) and with mean ± SD scores of 10.7 ± 5.8 on the PDSS and 4.0 ± 1.1 on the CGI-S at phase 2 endpoint.

We performed follow-up longitudinal regression analyses to examine whether there were differences in the slope of symptomatic change over time as measured by PDSS scores at each visit, adjusting for severity (PDSS score) at week 6 randomization. While there was a significant reduction in PDSS score over time overall during phase 2

Table 2. Phase 2 and Phase 3 Change in Symptom Scale Scores by Randomized Treatment Assignment

Scale	Phase 2 Reduction, Mean ± SD (n)					Phase 3 Reduction, Mean ± SD (n)				
	Placebo	SSRI	*t* (*df*)	*P*	Cohen *d*	Medication Optimization	CBT	*t* (*df*)	*P*	Cohen *d*
PDSS	2.31 ± 4.29 (13)	2.36 ± 3.44 (11)	−0.03 (22)	.97	0.01	3.78 ± 3.80 (9)	2.90 ± 3.63 (10)	0.51 (17)	.61	0.24
CGI-S	0.31 ± 1.03 (13)	0.45 ± 0.69 (11)	−0.40 (22)	.69	0.16	1.00 ± 1.00 (9)	0.90 ± 0.89 (10)	0.23 (17)	.82	0.11
HARS	2.08 ± 6.78 (13)	1.13 ± 6.83 (8)	0.31 (19)	.76	0.13	3.78 ± 6.61 (9)	1.90 ± 5.82 (10)	0.66 (17)	.52	0.30
HDRS	0.00 ± 3.51 (13)	0.00 ± 3.46 (9)	0.00 (20)	1.00	0.00	1.67 ± 4.42 (9)	0.70 ± 2.83 (10)	0.57 (17)	.57	0.26
SDS	0.62 ± 5.87 (13)	2.00 ± 8.15 (6)	−0.42 (17)	.68	0.19	3.63 ± 5.58 (8)	4.88 ± 5.36 (8)	−0.46 (14)	.65	0.23
ASI	2.00 ± 7.07 (13)	0.57 ± 8.81 (7)	0.40 (18)	.70	0.18	3.00 ± 3.63 (8)	6.29 ± 14.14 (7)	−0.64 (13)	.54	0.32

Abbreviations: ASI = Anxiety Sensitivity Index, CBT = cognitive-behavioral therapy, CGI-S = Clinical Global Impressions-Severity of Illness scale, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, MO = medication optimization, PDSS = Panic Disorder Severity Scale, SDS = Sheehan Disability Scale, SSRI=selective serotonin reuptake inhibitor.

(β [SE] = −2.12 [0.32], $P < .001$), and panic severity at randomization predicted slope of response (β [SE] = 0.13 [0.01], $P < .001$), there was no randomization group–by-week interaction (β [SE] = 0.14 [0.45], $P = .98$), supporting that slope of change in PDSS score in phase 2 did not vary for the placebo augmentation versus increased-dose SSRI groups.

Phase 3: Cognitive-Behavioral Therapy Augmentation Versus Medication Optimization With SSRI and Clonazepam

In phase 3, 19 patients were randomly assigned to treatment and eligible for analysis (CBT: n = 10 and MO: n = 9). At initial entry into phase 3, sertraline dosing was 100 mg/d for n = 6 in CBT and n = 5 for MO, and 200 mg/d for n = 4 in CBT and n = 4 in MO. Pharmacotherapy at endpoint in the MO group consisted of 200 mg SSRI equivalent for all and a mean ± SD dose of clonazepam of 2.5 ± 0.8 mg/d (range, 1.0–3.5 mg/d). Only 1 patient discontinued in phase 3 from each group (both lost to follow-up). Nonetheless, only 1 additional patient in each group achieved remission status by phase 3 endpoint (MO = 11%; CBT = 10%). Although there was significant overall reduction on the PDSS (mean ± SD decrease = 3.32 ± 3.64, paired $t = 3.97$, $P < .000$), there was no group difference in PDSS score reduction, consistent with evidence of only a small effect size favoring pharmacotherapy ($d = 0.24$; Table 2). Overall in phase 3, there was a reduction from a mean ± SD PDSS score of 11.6 ± 5.2 at baseline to 8.3 ± 5.8 at endpoint on the PDSS and a reduction from 4.2 ± 0.8 at baseline to 3.2 ± 1.2 at endpoint on the CGI-S. Confirmatory analyses using the independent evaluator assessments also demonstrated no significant difference in reduction in PDSS scores (mean ± SD reduction 3.3 ± 3.3 CBT vs 1.8 ± 4.3 MO, $t_{17} = 0.9$, $P > .39$) or CGI-S scores (1.1 ± 0.99 CBT vs 0.78 ± 0.83 MO, $t_{17} = 0.76$, $P > .45$). Further, independent evaluator ratings and clinician PDSS ratings were highly correlated ($r = 0.91$ week 12, $r = 0.96$ endpoint).

Consistent with the primary analyses, there were no significant differences between the MO and CBT groups on any secondary measures, and effect sizes were all small (Table 2). Secondary measures demonstrated overall (n = 19) improvement on the SDS (mean ± SD decrease = 4.25 ± 5.32, paired $t_{15} = 3.19$, $P < .01$) and a statistical trend toward improvement on the HARS (mean ± SD decrease = 2.79 ± 6.11, paired $t_{18} = 1.99$, $P < .07$) and ASI (mean ± SD decrease = 4.53 ± 9.75, paired $t_{14} = 1.80$, $P < .10$), but not the HDRS (paired $t_{32} = 3.42$, $P > .17$).

Although there was no significant difference in baseline severity by treatment group, the mean ± SD PDSS score at baseline was somewhat higher (13.67 ± 6.12) in the MO group compared to the CBT group (9.70 ± 3.65: $P = .101$). To examine potential differences in the slope of response over time adjusting for baseline score, we performed mixed-effects longitudinal regression analyses including terms for week 12 (baseline) PDSS score and phase 2 randomization group by week. While there was a significant reduction in the PDSS score over time (β [SE] = −0.54 [0.89], $P < .001$), and baseline score predicted slope of response (β [SE] = 0.03 [0.00], $P < .001$), there was no randomization group–by-week interaction (β [SE] = 0.10 [0.10], $P = .31$), supporting a lack of difference in slope of PDSS change over time for the CBT versus MO groups.

Side Effects

The majority of participants experienced at least 1 side effect in each phase, with 85% (33/39) in phase 1, 88% in phase 2 (21/24), and 79% in phase 3 (15/19). Side effects were generally tolerable and mild to moderate in severity. Two patients withdrew due to intolerable side effects: 1 in phase 1 due to nausea and headache and 1 receiving increased-dose SSRI in phase 2 due to jitteriness.

In phase 1, the most commonly reported side effects were gastrointestinal distress (48.7%), headache (41.0%), nausea or vomiting (38.5%), jitteriness or restlessness (30.8%), and insomnia (28.2%). In phase 2, the most common were gastrointestinal distress (36.4% SSRI, 23.1% placebo), headache (36.4% SSRI, 23.1% placebo), sedation (27.3% SSRI, 23.1% placebo), insomnia (27.3% SSRI, 7.7% placebo), and jitteriness or restlessness (27.3% SSRI, 7.7% placebo). In phase 3, the most common side effects were gastrointestinal distress (44.4% MO, 20.0% CBT), headache (22.2% MO, 40.0% CBT), sedation (33.3% MO, 10.0% CBT), and dizziness (33.3% MO, 0% CBT).

Naturalistic Follow-Up

Participants were followed naturalistically and reassessed 3 months after study endpoint. An additional 6/17 (35%) of completers achieved remission at 3-month follow-up (3 from MO and 3 from CBT), while the 2 completers who had achieved remission at phase 3 endpoint maintained remission status 3 months later. All but 1 of these remitters remained on the same pharmacotherapy treatment that they were on in the study, with minor fluctuations in dosage; this individual continued taking sertraline but initiated augmentation with amitriptyline and clonazepam.

DISCUSSION

Although power was limited to detection of a large effect size in phase 2 and larger studies are needed before definitive conclusions may be drawn, we failed to find any supportive evidence (Cohen $d = 0.01$) in a rigorous, randomized controlled prospective design for greater benefit of increased SSRI (92% sertraline, 8% escitalopram) dose versus continuation of current dose for panic disorder not in remission after 6 weeks at moderate dose of an SSRI. Further, although sample sizes were too small for significance testing, 3 of 11 (27%) of participants dropped out of the increased-dose arm, while all with placebo augmentation completed phase 2, suggesting that tolerability may have been poorer with the increased dose.

These findings may be interpreted in light of conflicting data regarding optimal dosing with the SSRIs for panic disorder in the literature in general. For example, in a fixed-dose study[32] of paroxetine in 425 patients with panic disorder, the minimum dose found to separate drug from placebo (and the highest dose in the trial) was 40 mg/d. A fixed-dose study[33] of fluoxetine in 243 patients with panic disorder found some improvement with both 10 mg/d and 20 mg/d, but suggested greater efficacy with the higher dose. In contrast, a fixed-dose, multicenter study[34] of sertraline in 178 patients with panic disorder found equal efficacy for 50 mg, 100 mg, and 200 mg, while a study[35] of citalopram with doses fixed in ranges of 10 to 15 mg, 20 to 30 mg, or 40 to 60 mg found greater efficacy for the 20- to 30-mg range. It is thus possible that the results of this study may have been different had other agents been employed.

In general, the dose response relationship in clinical trials refers to doses that show statistically significant effects compared to placebo, and not necessarily optimal clinical effect; these studies do not generally address whether raising the dose improves response for refractory patients. Data from the flexible-dose multicenter sertraline trial[36] suggested that dose escalation may have improved response for 16% of patients who would have otherwise remained symptomatic at initial dose levels. This multicenter study also suggested that remission status at 12 weeks can be predicted on the basis of early response: 73% of patients with a panic frequency reduction of greater than 50% by week 4 met responder status by week 12 versus 10% of patients with minimal response at week 4,[37] supporting intervening by 6 weeks as we did in our protocol and consistent with our finding that PDSS score reduction by week 2 was significantly associated with improvement at week 6 with SSRI pharmacotherapy.

In phase 3, both augmentation with CBT and medication optimization with clonazepam augmentation were associated with significant additional reduction in panic disorder and associated symptoms for subjects remaining symptomatic after 12 weeks of an SSRI; however, there was no significant difference between groups. There were small differences in favor of CBT for primary panic and agoraphobia symptoms as measured by the PDSS ($d = 0.24$) and similarly small effects in favor of MO for improvement in generalized anxiety symptoms as measured by the HARS ($d = 0.30$), suggesting that both are reasonable next-step clinical options. Additional research is needed to confirm these preliminary findings, as phase 3 of this study was designed only to establish initial effect sizes. Though preliminary, these data are the first to our knowledge to prospectively examine the relative efficacy of CBT augmentation compared to any medication optimization for patients with panic disorder who do not remit following a carefully monitored SSRI antidepressant trial, and they suggest comparable benefit for adding CBT or adding clonazepam and optimizing the antidepressant dose. It should be noted, however, that only 1 additional subject in MO (11%) and in CBT (10%), respectively, achieved remission in phase 3, suggesting alternate interventions may be needed for individuals with panic disorder who do not achieve remission with antidepressant pharmacotherapy.

Although not addressing sequential treatment, the largest study[21] to date examining the combination of an antidepressant—in this case the tricyclic imipramine—with CBT versus either treatment alone found a slight but not statistically significant acute response rate benefit for the combined treatment (60%) compared with CBT (49%) or imipramine alone (46%); this difference became significant after 6 months of treatment maintenance, but did not persist after treatment discontinuation, with those receiving the combination faring worse than those receiving CBT alone, suggesting a mixed picture regarding the relative benefits of combined antidepressant and CBT in the long run. Of interest, a secondary analysis[38] from this study found greater tolerability and lesser severity of imipramine-related side effects in individuals in combination treatment with CBT compared to the pharmacotherapy alone. In phase 3 of our study, we similarly found somewhat greater side effects in the medication-only group after the addition of clonazepam (gastrointestinal distress, dizziness, and sedation) compared to the CBT augmentation group, with the exception of headaches, which were more common in the CBT augmentation group.

Other studies, however, provide stronger support that CBT combined with pharmacotherapy is of benefit

compared to pharmacotherapy alone, including one in a primary care setting in which 232 individuals with panic disorder were treated with an algorithm-based pharmacotherapy manual alone or with CBT as part of collaborative care, which found significant additional benefit for the combined treatment acutely and at 12 months.[19,39] In addition, a trial of SSRI plus CBT versus either treatment alone for 150 patients with panic reported superior benefit for combined treatment, although differences were modest, with statistical significance achieved for combined treatment versus SSRI alone only for study completers, with no difference in response rates.[40] Available meta-analytic studies examining combination treatment with CBT and antidepressants for panic support the notion that there may be greater efficacy for combination treatment over CBT alone[41] as well as over antidepressant alone acutely.[42]

More directly applicable to the case of the antidepressant-refractory patient are studies by Heldt and colleagues[22,43] that examined outcomes for the addition of CBT for individuals with panic historically resistant to treatment with long-term pharmacotherapy, including continuation of antidepressants for the vast majority and benzodiazepines for some; they found benefit for the addition of group CBT acutely and at 1 year, although there was no comparison group. Thus, our findings of continued reduction in panic symptoms with CBT augmentation for individuals with an incomplete response to an SSRI are consistent with prior work suggesting benefit for combined CBT and antidepressant treatment, and suggest a lack of significant difference in acute outcomes compared to medical optimization with clonazepam augmentation.

Additional limitations to conclusions from our study include a potential lack of generalizability to optimal next-step treatment decisions for individuals with panic disorder in the community. In clinical practice, decisions about next-step interventions also include patient-specific issues not assessed by a formal study that by definition enrolls individuals willing to consider medication as well as weekly CBT. For example, some individuals may not be willing to receive CBT due to logistical reasons or may not be willing to initiate exposures because of the severity of their anxiety and avoidance. Also, a switch to CBT may be conceptually difficult for some patients after undergoing 2 stages of an exclusively pharmacologic treatment with the same provider. Alternately, side effect sensitivity or concerns about substance abuse may limit the use of benzodiazepines as a next-step strategy. Finally, this study examined next-step interventions specifically for individuals initially treated with antidepressant pharmacotherapy and thus by design cannot provide any information about the effectiveness of adding a pharmacotherapy to initial CBT.

It is worth highlighting, however, that remission rates in this population were low overall (only 33% of patients prospectively initiating treatment with an SSRI in phase 1 achieved remission after even 2 phases of additional interventions), suggesting that better predictors of response to specific treatments over time, methods to further optimize care with available interventions, and the development of additional effective interventions are needed.

Drug names: buspirone (BuSpar and others), citalopram (Celexa and others), clonazepam (Klonopin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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