Journal of Psychiatric Research 114 (2019) 34–40

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Treatment of anxiety and mood comorbidities in cognitive-behavioral and psychodynamic therapies for panic disorder

John R. Keefe[a,c,*], Dianne L. Chambless[a], Jacques P. Barber[b], Barbara L. Milrod[c]

[a] University of Pennsylvania, Department of Psychology, 425 S. University Avenue, Levin Building, 4th Floor, Philadelphia, PA, 19104, USA
[b] Adelphi University, Gordon F. Derner School of Psychology, Garden City, NY, USA
[c] Weill Cornell Medical College, Department of Psychiatry, New York, NY, USA

ARTICLE INFO

Keywords:
Panic disorder
Comorbidity
Clinical trials
Psychodynamic/psychoanalytic
CBT
Treatment trial

ABSTRACT

Background: It is not known whether common anxiety/mood comorbidities of panic disorder (PD) improve with panic-focused psychological treatment, nor whether there is differential efficacy between therapies in treating comorbidities.

Methods: In a randomized controlled trial for PD with and without agoraphobia comparing Cognitive-Behavioral Therapy (CBT) and Panic-Focused Psychodynamic Psychotherapy (PFPP), symptomatic comorbidities of agoraphobia, MDD, GAD, and social anxiety disorder (SAD) were assessed pre-to-post treatment with the Anxiety Disorders Interview Schedule (ADIS). Comparative efficacy of CBT versus PFPP for treating comorbid disorders was tested at termination and 1 year's follow-up. Covariance between panic and comorbidity improvements was also analyzed.

Results: Most treatment completers ($n = 120$) evidenced diagnostic remission of their comorbidity (range = 54–69%), which typically reflected a subclinical score on the ADIS (mean range = 1.3 to 1.8). These improvements were generally retained at follow-up. However, patients with MDD dropped out significantly more often (HR = 2.79). No significant symptom change or remission differences emerged between CBT and PFPP for any comorbidity at termination or at follow-up. Panic change was strongly related to improvements in agoraphobia ($r = 0.70$) and MDD ($r = 0.53$), moderately related for GAD ($r = 0.31$), and not significantly related for SAD ($r = 0.20$).

Discussion: Patients completing panic-focused psychotherapies often experience meaningful remission for diagnoses of agoraphobia, MDD, GAD, and SAD, with no detectable differences between treatments, although sample sizes for the MDD and SAD comparisons were small. In addition, additional efforts may be needed to keep MDD-comorbid patients in treatment.

Patients with panic disorder (PD), especially those with agoraphobia, commonly present with psychiatric comorbidities (Kessler et al., 2006). Some of the most common symptomatic/Axis-I co-morbidities in PD with agoraphobia are major depressive disorder (MDD; 38.5%), social anxiety disorder (SAD; 23.5%), and generalized anxiety disorder (GAD; 15.0%).

Symptomatic comorbidities pose an important clinical question: must multiple approaches be applied to treat each comorbid disorder, or does focused treatment for one presenting disorder often lead to improvements in comorbidities? For instance, comorbid personality disorder, which is diagnosable in 33%–50% of patients with PD (Friborg et al., 2013), does *not* appear to be adequately treated by short-term panic-focused psychological treatment (Keefe et al., 2018), as indicated by a low rate of personality disorder remission (37%) or recovery (17%).

There are relatively few data available about whether improvements made in a disorder-specific psychotherapy for PD generalize to conditions that are not the focus of that therapy. In the treatment of PD, clinical trial data (reviewed in Cuijpers et al., 2016; Pompoli et al., 2016) demonstrate that self- and observer-reported depressive symptoms often improve in cognitive-behavioral therapy for panic (CBT; e.g. Clark et al., 1999) and panic-focused psychodynamic psychotherapy (PFPP; e.g. Milrod et al., 2007), relative to inactive or active control groups.

It is possible that elements of effective treatment for one disorder mobilize mechanisms of change that help ameliorate other

* Corresponding author. University of Pennsylvania, Department of Psychology, 425 S. University Avenue, Levin Building, 4th Floor, Philadelphia, PA, 19104, USA.&.

E-mail addresses: jack.keefe@gmail.com, jok9134@nyp.org (J.R. Keefe).

https://doi.org/10.1016/j.jpsychires.2019.04.009
Received 21 October 2018; Received in revised form 8 March 2019; Accepted 11 April 2019

symptomatic conditions. Results from a randomized trial comparing the transdiagnostic CBT Unified Protocol (UP) with single-disorder CBT protocols support this possibility. This trial found that the two treatment types had equivalent outcomes in the treatment of comorbid SAD, GAD, and MDD among anxiety disorder patients at up to 12-months of post-treatment follow-up (Steele et al., 2018). On the other hand, if focused therapy for one disorder does not address important treatment targets that would be the aim of focused therapy for another disorder, we might not expect such cross-disorder improvements in non-transdiagnostic treatments. For instance, CBT for panic disorder does not explicitly entail exposure to social situations that are embarrassing to the patient (Craske et al., 2000), considered a key intervention in CBTs for SAD for the purposes of cognitive reappraisal and behavioral extinction (Heimberg, 2002).

Moreover, if two different evidence-based treatments for a disorder have differential effects on certain symptomatic comorbidities, this may influence treatment selection decisions. For example, panic patients with more severe personality disorder (defined by number of SCID-II criteria met) may have superior improvement in their personality disorder in PFPP as compared to CBT (Keefe et al., 2018). Psychodynamic approaches have exhibited similar efficacy to CBTs in the treatment of MDD (Driessen et al., 2013, 2015) and SAD (Bogels et al., 2014; Keefe et al., 2014; Leichsenring et al., 2014; Salzer et al., 2018). However, both non-manualized psychodynamic approaches and supportive-expressive therapy may be somewhat less effective in the treatment of GAD, particularly concerning core worry symptoms (Keefe et al., 2014; Salzer et al., 2011). In addition, to our knowledge, outcomes for agoraphobia, an extremely common, impairing, etiologically linked comorbidity of panic disorder (Roy-Byrne et al., 2006), have never been compared for patients receiving PFPP versus CBT.

We examined outcomes and their correlation to panic improvement for four Axis-I comorbidities present in at least 20% of the patient sample (agoraphobia; MDD; GAD; SAD) in a two-site randomized trial comparing CBT, PFPP, and applied relaxation training (ART) (Milrod et al., 2016). We analyzed these outcomes for CBT and PFPP[1] across two spans: from baseline to termination, and from termination to one-year post-treatment follow-up. We hypothesized that we would observe that PFPP and CBT would have similar outcomes in treating agoraphobia, MDD, and SAD, while CBT would evidence superior GAD outcomes, following the available RCT evidence on PDTs for these disorders (Keefe et al., 2014). We also examined the degree to which panic improvements covaried with improvements in symptomatic comorbidities.

1. Methods

1.1. Patients

201 patients (aged 18–70 years) were recruited at Weill Cornell Medical College and the University of Pennsylvania and randomized to treatment: PFPP, CBT or ART in a 2:2:1 ratio. Of these, 161 were randomized to PFPP or CBT; 120 completed either treatment and are the focus of this manuscript, as the primary outcome measure for comorbidities was only administered pre- and post-treatment. All patients provided informed, written consent. Both sites' institutional review boards approved the protocol (ClinicalTrials.gov identifier: NCT00353470).

Patients were included in the trial if they experienced one or more spontaneous panic attacks for the month before trial entry, and qualified for a DSM-IV PD diagnosis with or without agoraphobia determined as per the ADIS-IV version (DiNardo et al., 1995). Cross-site agreement on ADIS PD diagnosis was excellent (κ = 1.00). Assessors from both sites rated two cases together annually to prevent drift, in addition to within-site reliability meetings.

Non-study psychotherapy was prohibited. Medications were permitted if stable for at least 2 months at presentation, and were recorded, held constant, and monitored during the trial. Exclusion criteria were: active substance dependence (less than 6 month's remission), history of psychosis or bipolar disorder, acute suicidality, or organic mental syndrome (Milrod et al., 2016).

1.2. Treatments

Twenty-four therapists (8 CBT; 16 PFPP) treated an average of 5 patients each. PFPP is based on the central assumption that panic symptoms have a partly unconscious psychological meaning. It explores feelings and subjective content of panic episodes, so the patient can begin to address these meanings rather than experiencing conflicts physically as somatic anxiety leading to panic (Milrod et al., 1997). The therapy helps patients understand and alter core conflicts (e.g., regarding attachment and dependency) to avert future panic vulnerability. CBT for PD followed a modified version of the Panic Control Therapy protocol (Craske et al., 2000), entailing education about panic, correction of maladaptive thoughts about anxiety and body sensations, and both in-session and homework interoceptive exposures to bodily sensations designed to mimic those experienced during panic (Craske et al., 2000). For patients with comorbid agoraphobia, the protocol also involved cognitive restructuring around agoraphobic cognitions and exposure exercises in the latter third of therapy to specifically treat these symptoms. Both psychotherapies comprised 24 sessions delivered twice weekly (12 weeks). Up to three booster sessions were allowable during the one-year follow-up period. Additional information on treatments, including training, supervision, and adherence monitoring, can be found in Milrod et al. (2016).

1.3. Measures

Anxiety Disorders Interview Schedule (DiNardo et al., 1995**).** ADIS scores were collected at baseline, treatment termination, 6 months post-treatment, and 1 year post-treatment. For the analysis of continuous outcomes, ADIS severity scores were employed. Inter-rater reliability was excellent for agoraphobia (ICC = 0.95), good for MDD (ICC = 0.86) and SAD (ICC = 0.87), and fair for GAD (ICC = 0.64).[2] In addition, we examined agoraphobia, MDD, SAD, and GAD diagnoses at termination and 1-year follow-up, as indicated by a score of "4" or more on the ADIS. Inter-rater reliability for presence/absence of an ADIS-defined disorder was excellent for agoraphobia (κ = 0.94), and good for MDD (κ = 0.79), SAD (κ = 0.70), and GAD (κ = 0.78).

Panic Disorder Severity Scale (PDSS) (Shear et al., 1997**).** The PDSS is a diagnosis-based, composite, global rating of PD severity, with acceptable psychometric properties, which was the primary outcome measure of the study (Shear et al., 1997). Inter-rater reliability was excellent (*ICC* = 0.95).

[1] We did not include the ART group in these analyses, as comorbidity outcomes were collected pre- and post-treatment, and ART had significantly higher dropout than CBT/PFPP patients, wherein patients dropping out of treatment earlier tended to have worse trajectories of panic improvement. Moreover, patients with more severe baseline panic disorder were specifically more likely to drop out of ART, further indicating that completer ART patients were perhaps unrepresentative (Milrod et al., 2016).

[2] For the reliability study, clinical interviews (including the ADIS) from 28 patients (18 Cornell, 10 Penn) were rated by an additional diagnostician from the other site at 3 time points (intake, termination, and 12-month follow-up if present) using video tapes of the assessment. Thirteen diagnosticians (4 Cornell, 9 Penn) participated in the study.

Table 1
Descriptive data for completer patients with different ADIS-IV symptomatic comorbidities.

	Agoraphobia + (n = 94)	GAD (n = 60)	SAD (n = 32)	MDD (n = 20)
Baseline PDSS	14.5 (3.3)***	14.0 (3.8)	14.3 (3.4)	13.9 (4.5)
Baseline SDS	15.8 (7.3)*	17.4 (6.7)**	16.6 (6.1)	19.2 (6.8)*
Baseline ADIS Agoraphobia Severity	5.2 (1.0)***	4.5 (2.0)	4.5 (2.0)	4.6 (2.0)
Baseline ADIS GAD Severity	2.7 (2.4)	4.8 (0.8)***	3.3 (2.0)	4.1 (2.0)
Baseline ADIS SAD Severity	1.3 (2.1)	1.5 (2.2)	4.6 (0.7)***	1.8 (2.3)
Baseline ADIS MDD Severity	1.2 (2.0)	1.6 (2.3)	1.6 (2.4)	5.1 (0.8)***
Baseline # SCID-II Personality Disorder Criteria	8.2 (6.5)	9.9 (5.9)***	10.0 (6.3)*	11.6 (6.2)*
Age	39.3 (13.3)	38.6 (13.2)	40.0 (13.3)	37.4 (11.9)
Gender (female)	58 (61.7%)	40 (66.7%)	21 (65.6%)	12 (60.0%)
Concurrent psychopharmacology (yes)	25 (26.6%)	16 (26.7%)	11 (34.4%)	5 (25%)
Age of first panic onset	26.0 (12.7)	27.2 (12.2)	26.7 (13.1)	29.5 (12.4)

Notations designate comorbid groups significantly different from patients without that comorbidity, considered in a linear regression framework including all 4 comorbidities dummy-coded; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.
ADIS = Anxiety Disorders Interview Schedule; PDSS = Panic Disorder Severity Scale; SCID-II = Structured Clinical Interview for the Diagnosis of Axis-II Disorders; SDS = Sheehan Disability Scale.

1.4. Analyses

Statistical analyses were conducted in the *R* statistical computing language (R Core Team, 2017). All CBT and PFPP patients completing treatment were potentially included in analyses of termination outcome data (n = 120). 88 of these patients evidencing a panic treatment response (PDSS improvement ≥40%) were assessed into follow-up (McCarthy et al., 2018) and had ADIS assessments through the 1-year period. To be included in an analysis for a given comorbid disorder, a patient had to meet diagnostic criteria at baseline for that disorder as determined through the ADIS (see Supplementary Analyses and Footnotes 1 and 2).

All analyses of between-treatment group continuous outcomes were conducted in a linear mixed model framework, using the *R* packages "lme4" (Bates et al., 2017) and "lmerTest" (Kuznetsova et al., 2017). Acute treatment outcome analyses examined a fixed effect of time (pre-to-post treatment) with a random patient intercept. Treatment effects were represented as an interaction between treatment group and time. Follow-up treatment outcome analyses similarly examined a fixed effect of time (termination-to-follow-up) and a random patient intercept, using all available ADIS assessments at both 6- and 12-months of follow-up and controlling for baseline ADIS clinical severity. We also performed sensitivity analyses controlling in the follow-up model for patient use of both booster sessions and non-study psychotherapy or medication changes.

Covariance between improvements in ADIS clinical severity and PDSS panic symptoms using termination scores were examined using partial correlations controlling for baseline PDSS and the relevant baseline ADIS clinical severity.

Between-group differences in ADIS diagnostic status at termination and 1-year follow-up were examined in logistic models controlling for baseline ADIS clinical severity.

Finally, we analyzed the influence of comorbidities on dropout, using the entire PFPP and CBT samples (n = 161). Survival analyses using Cox proportional hazards models with right censoring were applied to examine predictors of dropout, using the core *R* package "survival." Time of dropout was defined as the session at which a patient dropped out (between 0 and 24).

We also examined whether any significant site by treatment interactions emerged in our analyses (at least $p < 0.10$), following site-by-treatment differences detected in panic outcomes in the primary trial (Milrod et al., 2016).

Between-group differences on continuous outcomes are described by Cohen's *d*, such that positively-signed *d* values indicate a superiority for CBT over PFPP, and vice versa. Differences in remission rates are described by odds ratios (OR), such that ORs greater than 1 reflect a higher remission rate in CBT as compared to PFPP.

Due to the number of statistical tests being conducted, we corrected our *p*-values using the Benjamini-Hochberg method for controlling the false discovery rate (Benjamini and Hochberg, 1995). We corrected within each family of analyses—acute outcomes, acute covariation between panic and comorbidity symptom change, and follow-up outcomes. These *p*-values are reported as adjusted *p*-values.

2. Results

2.1. Description of sample

Among patients completing therapy (n = 120), agoraphobia was the most common Axis-I comorbidity (n = 94; 78.3%), followed by GAD (n = 60; 50.0%), SAD (n = 32, 26.7%), and MDD (n = 20, 16.7%). The average patient in the trial had 1.7 comorbid Axis-I disorders, including agoraphobia, in addition to their panic diagnosis (see Table 2). Out of the 120 patients with analyzed outcome data, 18 of those patients (11 CBT, 7 PFPP; difference *ns*) used at least one booster session, with an average of 2.1 out of 3 possible booster sessions used among these patients. In addition, among these patients, 30 (17 CBT, 13 PFPP; difference *ns*) sought extra treatment during long-term follow-up (psychotherapy or a medication change). Additional demographic and clinical information on treatment completers in our sample on a per-comorbidity basis can be found in Table 1.

2.2. Dropout rates

To help contextualize the representativeness of any obtained findings regarding improvements in symptomatic comorbidities, we examined the degree to which patients with different comorbidities dropped out of treatment. Patients with comorbid MDD were significantly more likely to drop out of treatment as compared to patients without MDD (HR = 2.79 [95% CI: 1.44, 5.37], z = 3.04, p = 0.002;

Table 2
Combinations of patient comorbid symptom diagnoses.

	Agoraphobia (n = 94)	GAD (n = 60)	SAD (n = 32)	MDD (n = 20)
Agoraphobia (n = 94)	34	49	25	17
GAD (n = 60)		6	19	16
SAD (n = 32)			4	8
MDD (n = 20)				0

A given combination indicates the number of patients who share a given comorbidity. The diagonal indicates patients who have only that comorbidity and no others. Rows/columns do not add up to the number of patients, as patients may have no additional comorbidities or multiple.

Table 3
Pre-treatment, post-treatment, and follow-up ADIS clinical severity scores for patients with a given comorbid diagnosis.

	Agoraphobia (M/SD)	GAD (M/SD)	SAD (M/SD)	MDD (M/SD)
CBT	Pre (n = 62): 5.3 (1.1)	Pre (n = 33): 4.9 (0.9)	Pre (n = 25): 4.6 (0.7)	Pre (n = 14): 5.1 (0.8)
	Post (n = 45): 2.9 (1.7)	Post (n = 27): 3.4 (1.7)	Post (n = 17): 1.8 (1.9)	Post (n = 9): 3.2 (1.9)
	1-year (n = 34): 2.5 (2.3)	1-year (n = 23): 3.1 (2.1)	1-year (n = 15): 1.6 (1.8)	1-year (n = 6): 3.2 (1.7)
PFPP	Pre (n = 65): 5.2 (1.0)	Pre (n = 42): 4.9 (0.8)	Pre (n = 19): 4.8 (0.7)	Pre (n = 19): 5.1 (0.7)
	Post (n = 49): 3.1 (1.7)	Post (n = 33): 2.4 (2.0)	Post (n = 15): 2.8 (1.7)	Post (n = 11): 3.1 (2.2)
	1-year (n = 30): 3.0 (2.0)	1-year (n = 21): 2.5 (2.0)	1-year (n = 11): 2.4 (2.2)	1-year (n = 9): 2.9 (2.5)

42.4% dropout MDD vs. 18.8% dropout no-MDD). By contrast, there were no effects on dropout of comorbid diagnoses of agoraphobia, GAD, or SAD (ps = 0.400–0.880). Patients with a higher count of comorbid symptom diagnoses were not significantly more likely to drop out of treatment compared to other patients (HR = 1.30 [95% CI: 0.95, 1.78], z = 1.63, p = 0.103). Furthermore, there were no significant interactions between these comorbidities (ps = 0.200 to p = 0.706) or the number of comorbidities (p = 0.910) and treatment condition in predicting dropout.

2.3. Acute treatment outcomes

Continuous scores. Overall, the average patient with Axis-I comorbidities experienced significant pre-post improvement in the severity of his/her comorbidity (see Table 3 for pretreatment, termination, and follow-up scores for CBT and PFPP patients). Clinically relevant improvements on ADIS-rated severity were observed for agoraphobia (B = −2.20 [95% CI: 2.52, −1.87], t [121.1] = −13.2, p < 0.001, d = 1.93), MDD (B = −1.93 [95% CI: 2.66, −1.19], t [32.9] = −5.20, p < 0.001, d = 1.64), SAD (B = −2.44 [95% CI: 3.04, −1.84], t [74.0] = −8.01, p < 0.001, d = 1.85), and GAD (B = −2.03 [95% CI: 2.46, −1.61], t [70.7] = −9.46, p < 0.001, d = 1.73).

No significant differences between PFPP and CBT were observed in pre-to-post treatment improvement in ADIS clinical severity for any comorbid diagnosis (see Fig. 1 for illustration; Table 3 for raw observed scores). Differential efficacy was not observed for agoraphobia (B = 0.32 [95% CI: 0.30, 1.04], t [120.1] = 0.973, p = 0.333, adjusted p = 0.621, d = 0.18), MDD (B = 0.01 [95% CI: 1.43, 1.49], t [31.5] = −0.01, p = 0.989, adjusted p = 0.989, d < 0.01), SAD (B = 0.86 [95% CI: 0.29, 2.02], t [72.0] = −1.45, p = 0.151, adjusted p = 0.604, d = 0.34), or GAD (B = −0.81 [95% CI: 1.66, 0.05], t [69.3] = −1.89, p = 0.062, adjusted p = 0.496, d = −0.46).[3]

Diagnostic remission. We examined the degree to which patients met remission criteria for their Axis-I comorbidities. Among patients with comorbidities who completed treatment, 54.2% (n remitting = 51) with agoraphobia, 59.1% (n = 13) with MDD, 68.6% (n = 24) with SAD, and 64.2% (n = 45) with GAD experienced an ADIS-defined remission of their disorder. Out of 109 patients with at least one comorbidity, 50 (45.9%) patients experienced a remission of all their baseline comorbidities. Meeting an ADIS-defined remission for a comorbidity generally reflected having only a mild to absent level of symptoms for that comorbidity by treatment termination (mean agoraphobia = 1.8; mean MDD = 1.7; mean SAD = 1.3; mean GAD = 1.6). Thus, remission typically did not reflect falling just under diagnostic threshold on the ADIS for one's comorbid disorder, but rather experiencing a meaningful level of comorbid symptom relief.

There were no significant differences between treatments in remission rates for comorbid diagnoses of agoraphobia (OR = 1.11 [95% CI: 0.48, 2.58], z = 0.25, p = 0.808, adjusted p = 0.989), MDD (OR = 0.95 [95% CI: 0.15, 2.57], z = −0.06, p = 0.956, adjusted p = 0.989), SAD (OR = 1.98 [95% CI: 0.43, 10.06], z = 0.86, p = 0.388, adjusted p = 0.621), or GAD (OR = 0.57 [95% CI: 0.19, 1.70], z = −1.01, p = 0.314, adjusted p = 0.621), controlling for baseline severity of each disorder. Patients were similarly likely to experience remission in all baseline diagnoses in either treatment (OR = 1.33 [95% CI: 0.61, 2.89], z = 0.72, p = 0.470), controlling for the combined baseline severity across disorders.

2.4. Covariation of acute treatment outcomes with panic improvement

We examined whether, among patients with a given comorbid diagnosis, there was a link between their change in panic symptoms and change in symptoms of the comorbid diagnosis, examining the partial correlation between termination scores for each controlling for both baseline scores. Effect sizes of the correlation between improvements in PDSS symptoms and ADIS-defined changes comorbid disorder clinical severity were large and significant for agoraphobia (r = 0.70, p < 0.001, adjusted p < 0.001) and MDD (r = 0.53, p = 0.005, adjusted p = 0.010), and medium for GAD (r = 0.31, p = 0.010, adjusted p = 0.013). However, improvements in SAD severity did not

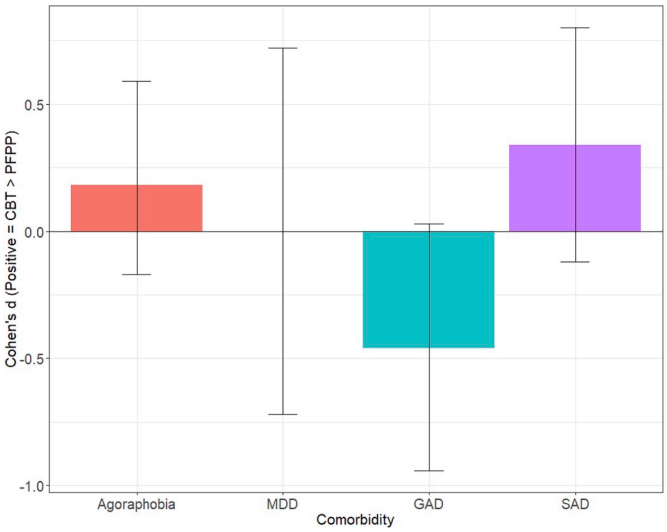

Fig. 1. Estimated between-groups effect sizes for CBT versus PFPP at treatment termination for each ADIS-defined comorbidity clinical severity score. Positive values reflect an advantage of CBT over PFPP, and vice versa. No differences were statistically significant with or without statistical correction for multiple comparisons.

[3] As a secondary check, we also examined declines in symptoms of each comorbid disorder among the full group of patients (i.e., including those who did not have a diagnosed comorbidity but who had any baseline clinical severity elevation for that disorder). In terms of differential treatment effects, the only difference from the primary results was that ADIS-rated GAD severity improved significantly more among patients receiving PFPP as compared to CBT, with a small to medium effect size (B = −0.76 [95% CI: 1.47, −0.04], t [125.2] = −2.15, p = 0.033, d = −0.34). Full results are reported in the Online Supplement.

significantly correlate with PDSS improvements ($r = 0.20$, $p = 0.206$, adjusted $p = 0.206$).[4]

2.5. One-year responders follow-up outcomes

Continuous scores. Of the 120 treatment completers, 88 patients who were treatment responders also had ADIS ratings through the 1-year follow-up. On average, patients maintained the level of agoraphobia, MDD, SAD, and GAD severity they were assessed as having at treatment termination. There were no reliable changes in the severity of agoraphobia ($B = -0.24$ [95% CI: 0.58, 0.09], t [140.4] $= -1.43$, $p = 0.156$), MDD ($B = -0.03$ [95% CI: 0.89, 0.84], t [20.1] $= -0.07$, $p = 0.944$), SAD ($B = -0.32$ [95% CI: 0.98, 0.34], t [46.8] $= -0.96$, $p = 0.341$), or GAD ($B = -0.03$ [95% CI: 0.57, 0.51], t [93.7] $= -0.11$, $p = 0.916$) across a year's follow-up.

Over the course of a year's follow-up, treatment condition did not predict a patient's level of clinical severity for their comorbidities. All significance values were nonsignificant, and the nonsignificant effect sizes ranged from medium to small ($ds = -0.47$ to 0.27, unadjusted $ps = 0.597$ to 0.305). No results notably changed statistical significance (i.e., becoming significant at $p < .10$) when controlling for use of booster sessions or non-study psychotherapy or medication changes during the follow-up period.

Diagnostic remission. Observed remission rates remained high for agoraphobia (60.5%, n remitting = 46), MDD (56.3%, $n = 9$), SAD (71.4%, $n = 20$), and GAD (64.2%, $n = 34$) comorbidities across one year's follow-up. In addition, remission rates remained statistically indistinguishable between treatment groups (ORs = 0.76 to 2.82, unadjusted $ps = 0.919$ to 0.280).

3. Discussion

Among patients completing a panic-focused psychotherapy, comorbid diagnoses of agoraphobia, MDD, SAD, and GAD often remit to sub-clinical levels. Moreover, patients responding to panic treatment tend to experience continued remission of symptomatic comorbidities across one year's follow-up. This pattern of findings is relevant to treatment planning in panic disorder, suggesting that patients receiving panic-focused psychotherapies often may not need additional therapy focusing on alleviating their symptomatic comorbidities. In addition, CBT and PFPP did not exhibit differential treatment effects for comorbid disorders, suggesting that there is no indication that patients should receive one treatment or the other based on the symptomatic comorbidities we examined. On the other hand, sample sizes for SAD ($n = 32$) and MDD ($n = 20$) were inadequate for reliably detecting treatment differences, which may be extant but undetectable in this small sample. Conversely, among the full sample ($n = 120$) rather than just patients meeting full diagnostic criteria, improvements in clinical severity for comorbidities was also not statistically distinguishable between treatments (see Online Supplement). Finally, patients experiencing significant panic improvements can be expected to similarly improve their symptomatic comorbidities, apart from patients with SAD, who nevertheless generally exhibited high remission (69%) even if their panic did not improve.

However, depression outcomes for patients with MDD were less clearly positive. While MDD-comorbid patients remaining in treatment often experienced depression remission across a year of follow-up, these patients dropped out significantly more than other patients. Thus, the observed rates of MDD remission could be inflated by the fact that MDD patients not experiencing symptom remission may have frequently dropped out of treatment, leaving only more successful MDD patients to be observed. Combined panic-MDD may represent an especially severe illness marked by unique psychological difficulties (Rudden et al., 2003)—for example, the combination of MDD and experiencing fears of dying during panic attack is especially predictive of suicide attempts (Yaseen et al., 2013).

Contrary to our hypotheses and the available RCT evidence base (Keefe et al., 2014), CBT was not superior to PFPP for comorbid GAD outcomes. In a past trial, supportive-expressive therapy (SET), the only manualized psychodynamic treatment for GAD, did not treat core worry symptoms as well as CBT (Salzer et al., 2011), although general anxiety as measured by the HAM-A did not show a differential treatment effect. PFPP is distinguishable in several key clinical features from SET. Compared to SET, PFPP has a strong focus on formative attachment relationships, developmental experiences, and the exploration of unconscious fantasy, in addition to interpretation of the transference, whereas SET therapy focuses on the core conflictual relationship theme (Milrod, 2009). These results may also differ because, in this study, GAD was a comorbid condition considered secondary to panic disorder, rather than a primary GAD. In addition, ADIS severity ratings for GAD symptoms had a relatively lower inter-rater reliability in this study. Overall, this finding suggests that GAD symptoms may not be a contraindication to receive PFPP, and that it may be worthwhile to test the PFPP model (Busch et al., 2012) to treat primary GAD.

For the treatment of agoraphobia, it is notable that CBT did not show a strong superiority to PFPP despite the absence of an exposure component in PFPP, while exposure homework targeted to agoraphobia was assigned in CBT. While some psychodynamic therapy protocols have integrated secondary exposure components into the treatment (Leichsenring et al., 2007), a meta-analysis of psychodynamic therapies for anxiety did not find any advantage for these protocols compared to other psychodynamic treatments (Keefe et al., 2014). Similarly, in CBT treatment of anxiety, a meta-analysis found that outcomes for exposure-focused treatments were statistically indistinguishable from to exclusively cognitive therapies (Lorenzo-Luaces et al., 2016). These findings add to the growing literature that therapist-directed exposure, while efficacious, may not be necessary to treat anxiety disorders (Markowitz et al., 2014; Markowitz et al., 2015). However, this interpretation should be tempered by the fact that these findings are in the context of treating agoraphobia in the context of a primary panic disorder.

Like recent findings demonstrating cross-disorder improvements using both the Unified Protocol and single-disorder protocol CBT for anxiety and mood disorders (Steele et al., 2018), both CBT for panic and PFPP may potentially have transdiagnostic effects on other disorders. Specific therapies may have such transdiagnostic effects to the extent that they treat psychopathological vulnerabilities underlying many specific symptom profiles (Kotov et al., 2017). CBT for panic may teach skills to challenge and restructure cognitions generally (Strunk et al., 2007), alter maladaptive beliefs and conditioning contributing to anxiety sensitivity (Naragon-Gainey, 2010), and bolster self-efficacy to approach avoided situations and accomplish behavioral goals (Gallagher et al., 2013); PFPP seeks to improve patient mentalization (Katznelson, 2014; Rudden et al., 2006), insight into psychological dynamics (Jennissen et al., 2018), attachment insecurity (Mikulincer and Shaver, 2012), and ability to tolerate and experience difficult affects and meanings without resorting rigidly to defenses (Perry and Bond, 2012). Future work may examine how putative mediators for specific symptoms (e.g., improvements in catastrophic cognitions and mentalization ameliorating panic; Barber et al., 2018) may instantiate treatment effects for presenting symptoms more generally. Identifying effective transdiagnostic approaches to psychopathology from cognitive-behavioral (Steele et al., 2018) and psychodynamic (Busch et al., 2012; Leichsenring and Steinert, 2018) perspectives may represent a pragmatic way to disseminate evidence-based treatment for common

[4] We examined these patterns employing *all* patients with symptom elevations, rather than just patients meeting full diagnostic criteria. In this instance, there were no notable changes in effect size (r + -0.05) or statistical significance when examining the full sample as compared to the diagnostic sample.

mental disorders.

Limitations. The ADIS was only administered twice during acute treatment, and we would have had better statistical power for our analyses if we had more ADIS measurements. On the other hand, we did examine outcomes at 1-year follow-up for responders and found that trends observed at termination were maintained up to a year later. We also could not incorporate dropout participants because of the lack of multiple measurements, combined with the not missing at random dropout pattern (i.e., those who improved the least were more likely to drop out) observed in the trial (Milrod et al., 2016). In response to concerns about using a completer sample in the context of outcome-dependent dropout for panic symptom improvement, we examined whether treatment influenced dropout among patients with particular symptom disorders or among patients with more versus fewer co-morbidities. While we did not find any such relationships, it is possible that there are weaker but undetectable relationships between treatment and dropout—and thus some degree of estimating bias for treatment effects *per se*.

Because the trial was powered to detect differences between groups on primary panic outcomes and not for symptomatic comorbidities, it may be that medium-to-small effect size but undetected treatment differences exist for SAD and MDD. At termination, nonsignificant effect sizes ranged from small (agoraphobia, SAD, MDD) to medium (GAD). Treatment decisions between CBT and psychodynamic therapies regarding primary diagnoses of SAD, GAD, and MDD should be informed by the research base for those disorders *per se*.

4. Conclusions

Patients typically experience sustained (1-year) remission of agoraphobia, SAD, GAD, and MDD after completing treatment with panic-focused psychotherapies, although these conclusions are tentative as concerns MDD due to its high dropout rate. No differential effects between CBT and PFPP were found in treatment of comorbidities, although power was inadequate to detect differences for SAD and MDD.

Financial Support

This work was supported by Grant NIH R01-MH070664, R01MH070918 from the National Institute of Mental Health, awarded to Barbara L. Milrod and Jacques P. Barber, respectively. The opinions and assertions contained in this article should not be construed as reflecting the views of the sponsors.

Disclosures

Barbara L. Milrod is a developer of the panic-focused psychodynamic psychotherapy treatment. She is also a co-author of the published treatment manual, the current edition of which is “Manual of Panic Focused Psychodynamic Psychotherapy – eXtended Range,” published by Routledge. No other authors report conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.04.009.

References

Barber, J.P., Milrod, B., Gallop, R., Solomonov, N., Rudden, M., McCarthy, K., Chambless, D., 2018. Mechanisms of Change in CBT and Dynamic Therapy for Panic Disorder. Paper presented at the Society for Psychotherapy Research, Amsterdam, the Netherlands.

Bates, D., Maechler, M., Bolker, B., Walker, S., Christensen, R.H.B., Singmann, H., ... Green, P., 2017. lme4: Linear Mixed-Effects Models Using 'Eigen' and S4 (Version 1.1-13). Comprehensive R Archive Network Retrieved from. https://cran.r-project.org/web/packages/lme4/index.html.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B 57 (1), 289–300.

Bogels, S.M., Wijts, P., Oort, F.J., Sallaerts, S.J., 2014. Psychodynamic psychotherapy versus cognitive behavior therapy for social anxiety disorder: an efficacy and partial effectiveness trial. Depress. Anxiety 31 (5), 363–373. https://doi.org/10.1002/da.22246.

Busch, F.N., Milrod, B.L., Singer, M.B., Aronson, A.C., 2012. Manual of Panic Focused Psychodynamic Psychotherapy - Extended Range, vol. 36 Routledge, New York, NY.

Clark, D.M., Salkovskis, P.M., Hackmann, A., Wells, A., Ludgate, J., Gelder, M., 1999. Brief cognitive therapy for panic disorder: a randomized controlled trial. J. Consult. Clin. Psychol. 67 (4), 583–589. https://doi.org/10.1037/0022-006X.67.4.583.

Craske, M.G., Barlow, D.H., Meadows, E., 2000. Master Your Own Anxiety and Panic: Therapist Guide for Anxiety, Panic, and Agoraphobia (MAP-3). Graywind/Psychological Corporation, San Antonio, TX.

Cuijpers, P., Cristea, I.A., Weitz, E., Gentili, C., Berking, M., 2016. The effects of cognitive and behavioural therapies for anxiety disorders on depression: a meta-analysis. Psychol. Med. 46 (16), 3451–3462. https://doi.org/10.1017/s0033291716002348.

DiNardo, P.A., Brown, T.A., Barlow, D.H., 1995. Anxiety Disorders Interview Schedule for DSM-IV: Current Version (ADIS-IV). Graywinds Publications, New York, NY.

Driessen, E., Hegelmaier, L.M., Abbass, A.A., Barber, J.P., Dekker, J.J.M., Van, H.L., ... Cuijpers, P., 2015. The efficacy of short-term psychodynamic psychotherapy for depression: a meta-analysis update. Clin. Psychol. Rev. 42, 1–15. https://doi.org/10.1016/j.cpr.2015.07.004.

Driessen, E., Van, H.L., Don, F.J., Peen, J., Kool, S., Westra, D., ... Dekker, J.J., 2013. The efficacy of cognitive-behavioral therapy and psychodynamic therapy in the outpatient treatment of major depression: a randomized clinical trial. Am. J. Psychiatry 170 (9), 1041–1050. https://doi.org/10.1176/appi.ajp.2013.12070899.

Friborg, O., Martinussen, M., Kaiser, S., Øvergård, K.T., Rosenvinge, J.H., 2013. Comorbidity of personality disorders in anxiety disorders: a meta-analysis of 30 years of research. J. Affect. Disord. 145 (2), 143–155. https://doi.org/10.1016/j.jad.2012.07.004.

Gallagher, M.W., Payne, L.A., White, K.S., Shear, K.M., Woods, S.W., Gorman, J.M., Barlow, D.H., 2013. Mechanisms of change in cognitive behavioral therapy for panic disorder: the unique effects of self-efficacy and anxiety sensitivity. Behav. Res. Ther. 51 (11), 767–777. https://doi.org/10.1016/j.brat.2013.09.001.

Heimberg, R.G., 2002. Cognitive-behavioral therapy for social anxiety disorder: current status and future directions. Biol. Psychiatry 51 (1), 101–108. https://doi.org/10.1016/S0006-3223(01)01183-0.

Jennissen, S., Huber, J., Ehrenthal, J.C., Schauenburg, H., Dinger, U., 2018. Association between insight and outcome of psychotherapy: systematic review and meta-analysis. Am. J. Psychiatry 175 (10), 961–969. https://doi.org/10.1176/appi.ajp.2018.17080847.

Katznelson, H., 2014. Reflective functioning: a review. Clin. Psychol. Rev. 34 (2), 107–117. https://doi.org/10.1016/j.cpr.2013.12.003.

Keefe, J.R., McCarthy, K.S., Dinger, U., Zilcha-Mano, S., Barber, J.P., 2014. A meta-analytic review of psychodynamic therapies for anxiety disorders. Clin. Psychol. Rev. 34 (4), 309–323. https://doi.org/10.1016/j.cpr.2014.03.004.

Keefe, J.R., Milrod, B.L., Gallop, R., Barber, J.P., Chambless, D.L., 2018. What is the effect on comorbid personality disorder of brief panic-focused psychotherapy in patients with panic disorder? Depress. Anxiety 35 (3), 239–247. https://doi.org/10.1002/da.22708.

Kessler, R.C., Chiu, W.T., Jin, R., Ruscio, A.M., Shear, K., Walters, E.E., 2006. The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. Arch. Gen. Psychiatr. 63 (4), 415–424. https://doi.org/10.1001/archpsyc.63.4.415.

Kotov, R., Krueger, R.F., Watson, D., Achenbach, T.M., Althoff, R.R., Bagby, R.M., ... Zimmerman, M., 2017. The Hierarchical Taxonomy of Psychopathology (HiTOP): a dimensional alternative to traditional nosologies. J. Abnorm. Psychol. 126 (4), 454–477. https://doi.org/10.1037/abn0000258.

Kuznetsova, A., Brockhoff, P.B., Christensen, R.H.B., 2017. lmerTest package: tests in linear mixed. Effects Models 82 (13), 26. https://doi.org/10.18637/jss.v082.i13. 2017.

Leichsenring, F., Beutel, M., Leibing, E., 2007. Psychodynamic psychotherapy for social phobia: a treatment manual based on supportive-expressive therapy. Bull. Menn. Clin. 71 (1), 56–83. https://doi.org/10.1521/bumc.2007.71.1.56.

Leichsenring, F., Salzer, S., Beutel, M.E., Herpertz, S., Hiller, W., Hoyer, J., ... Leibing, E., 2014. Long-term outcome of psychodynamic therapy and cognitive-behavioral therapy in social anxiety disorder. Am. J. Psychiatry 171 (10), 1074–1082. https://doi.org/10.1176/appi.ajp.2014.13111514.

Leichsenring, F., Steinert, C., 2018. Towards an evidence-based unified psychodynamic protocol for emotional disorders. J. Affect. Disord. 232, 400–416. https://doi.org/10.1016/j.jad.2017.11.036.

Lorenzo-Luaces, L., Keefe, J.R., DeRubeis, R.J., 2016. Cognitive-behavioral therapy: nature and relation to non-cognitive behavioral therapy. Behav. Ther. 47 (6), 785–803. https://doi.org/10.1016/j.beth.2016.02.012.

McCarthy, K.S., Chambless, D.L., Solomonov, N., Milrod, B., Barber, J.P., 2018. Twelve-month outcomes following successful panic-focused psychodynamic psychotherapy, cognitive-behavioral therapy, or applied relaxation training for panic disorder. J Clin Psychiatry 79 (5). https://doi.org/10.4088/jcp.17m11807.

Markowitz, J.C., Lipsitz, J., Milrod, B.L., 2014. Critical review of outcome research on interpersonal psychotherapy for anxiety disorders. Depress. Anxiety 31 (4), 316–325. https://doi.org/10.1002/da.22238.

Markowitz, J.C., Petkova, E., Neria, Y., Van Meter, P.E., Zhao, Y., Hembree, E., ... Marshall, R.D., 2015. Is exposure necessary? A randomized clinical trial of interpersonal psychotherapy for PTSD. Am. J. Psychiatry 172 (5), 430–440. https://doi.org/10.1176/appi.ajp.2014.14070908.

Mikulincer, M., Shaver, P.R., 2012. An attachment perspective on psychopathology. World Psychiatr. 11 (1), 11–15. https://doi.org/10.1016/j.wpsyc.2012.01.003.
Milrod, B., 2009. Psychodynamic psychotherapy outcome for generalized anxiety disorder. Am. J. Psychiatry 166 (8), 841–844. https://doi.org/10.1176/appi.ajp.2009.09060810.
Milrod, B., Busch, F., Cooper, A., Shapiro, T., 1997. Manual of Panic-Focused Psychodynamic Psychotherapy. APA Press, Washington, DC.
Milrod, B., Chambless, D.L., Gallop, R., Busch, F.N., Schwalberg, M., McCarthy, K.S., ... Barber, J.P., 2016. Psychotherapies for panic disorder: a tale of two sites. J. Clin. Psychiatry 77 (7), 927–935. https://doi.org/10.4088/JCP.14m09507.
Milrod, B., Leon, A.C., Busch, F., Rudden, M., Schwalberg, M., Clarkin, J., ... Shear, M.K., 2007. A randomized controlled clinical trial of psychoanalytic psychotherapy for panic disorder. Am. J. Psychiatry 164 (2), 265–272. https://doi.org/10.1176/ajp.2007.164.2.265.
Naragon-Gainey, K., 2010. Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. Psychol. Bull. 136 (1), 128–150. https://doi.org/10.1037/a0018055.
Perry, J.C., Bond, M., 2012. Change in defense mechanisms during long-term dynamic psychotherapy and five-year outcome. Am. J. Psychiatry 169 (9), 916–925. https://doi.org/10.1176/appi.ajp.2012.11091403.
Pompoli, A., Furukawa, T.A., Imai, H., Tajika, A., Efthimiou, O., Salanti, G., 2016. Psychological therapies for panic disorder with or without agoraphobia in adults: a network meta-analysis. Cochrane Database Syst. Rev. 4, Cd011004. https://doi.org/10.1002/14651858.CD011004.pub2.
R Core Team, 2017. R: A Language and Environment for Statistical Computing (Version 3.4.3). R Foundation for Statistical Computing, Vienna, Austria Retrieved from. https://www.R-project.org/.
Roy-Byrne, P.P., Craske, M.G., Stein, M.B., 2006. Panic disorder. Lancet 368 (9540), 1023–1032. https://doi.org/10.1016/S0140-6736(06)69418-X.
Rudden, M., Busch, F.N., Milrod, B., Singer, M., Aronson, A., Roiphe, J., Shapiro, T., 2003. Panic disorder and depression: a psychodynamic exploration of comorbidity. Int. J. Psychoanal. 84 (Pt 4), 997–1015.
Rudden, M., Milrod, B., Target, M., Ackerman, S., Graf, E., 2006. Reflective functioning in panic disorder patients: a pilot study. J. Am. Psychoanal. Assoc. 54 (4), 1339–1343. https://doi.org/10.1177/00030651060540040109.
Salzer, S., Stefini, A., Kronmuller, K.T., Leibing, E., Leichsenring, F., Henningsen, P., ... Steil, R., 2018. Cognitive-behavioral and psychodynamic therapy in adolescents with social anxiety disorder: a multicenter randomized controlled trial. Psychother. Psychosom. 1–11. https://doi.org/10.1159/000488990.
Salzer, S., Winkelbach, C., Leweke, F., Leibing, E., Leichsenring, F., 2011. Long-term effects of short-term psychodynamic psychotherapy and cognitive-behavioural therapy in generalized anxiety disorder: 12-month follow-up. Can. J. Psychiatr. 56 (8), 503–508. https://doi.org/10.1177/070674371105600809.
Shear, M.K., Brown, T.A., Barlow, D.H., Money, R., Sholomskas, D.E., Woods, S.W., ... Papp, L.A., 1997. Multicenter collaborative panic disorder severity scale. Am. J. Psychiatry 154 (11), 1571–1575. https://doi.org/10.1176/ajp.154.11.1571.
Steele, S.J., Farchione, T.J., Cassiello-Robbins, C., Ametaj, A., Sbi, S., Sauer-Zavala, S., Barlow, D.H., 2018. Efficacy of the Unified Protocol for transdiagnostic treatment of comorbid psychopathology accompanying emotional disorders compared to treatments targeting single disorders. J. Psychiatr. Res. 104, 211–216. https://doi.org/10.1016/j.jpsychires.2018.08.005.
Strunk, D.R., DeRubeis, R.J., Chiu, A.W., Alvarez, J., 2007. Patients' competence in and performance of cognitive therapy skills: relation to the reduction of relapse risk following treatment for depression. J. Consult. Clin. Psychol. 75 (4), 523–530. https://doi.org/10.1037/0022-006x.75.4.523.
Yaseen, Z.S., Chartrand, H., Mojtabai, R., Bolton, J., Galynker II., , 2013. Fear of dying in panic attacks predicts suicide attempt in comorbid depressive illness: prospective evidence from the National Epidemiological Survey on Alcohol and Related Conditions. Depress. Anxiety 30 (10), 930–939. https://doi.org/10.1002/da.22039.