

The Effect of Patient's Choice of Cognitive Behavioural or Psychodynamic Therapy on Outcomes for Panic Disorder: A Doubly Randomised Controlled Preference Trial

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Keywords

Doubly randomised controlled preference trial · Panic disorder · Cognitive behavioural therapy · Psychodynamic therapy

Abstract

Introduction: It remains unclear whether offering psychiatric patients their preferred treatment influences outcomes at the symptom level. **Objective:** To assess whether offering patients with panic disorder with/without agoraphobia (PD/A) a choice between 2 psychotherapies yields superior outcomes to random assignment. **Methods:** In a doubly randomised, controlled preference trial (DRCPT), 221 adults with PD/A were randomly assigned to: choosing panic-focused psychodynamic therapy (PFPP) or panic control treatment (PCT; a form of cognitive behavioural therapy); random assignment to PFPP or PCT; or waiting list control. Primary outcomes were PD/A severity, work status and work absences at post-treatment assessment. Outcomes at post-treatment assessment, 6-, 12-, and 24-month follow-ups were assessed using segmented multilevel linear growth models. **Results:** At post-treatment assessment, the choice and random conditions were superior to the control for panic severity but not work status/absences. The choice and random

conditions did not differ during treatment or follow-up for the primary outcomes. For panic severity, PCT was superior to PFPP during treatment (standardised mean difference, SMD, -0.64 ; 95% confidence interval, CI, -1.02 to -0.25); PFPP was superior to PCT during follow-up (SMD 0.62 ; 95% CI 0.27 – 0.98). There was no allocation by treatment type interaction (SMD -0.57 ; 95% CI -1.31 to 0.17). **Conclusions:** Previous studies have found that offering patients their preferred treatment yields small to moderate effects but have not employed designs that could rigorously test preference effects. In this first DRCPT of 2 evidence-based psychotherapies, allowing patients with PD/A to choose their preferred treatment was not associated with improved outcomes. Further DRCPTs are needed.

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Published by S. Karger AG, Basel

Introduction

Shared decision-making (SDM) is part of an overall strategy to improve health outcomes [1]. An important aspect of SDM is providing patients with information

M.S. and T.N. have contributed equally to the study and the paper. Trial registration: ClinicalTrials.gov identifier NCT01606592.

about the available treatments and encouraging them to choose the treatment they prefer. Although there is evidence that SDM improves patient knowledge about treatment options and increases their sense of involvement in their health care, the effects of SDM on health outcomes at the symptom/syndrome level remain unclear [1]. Across studies where patients with psychiatric disorders are offered a choice between 2 or more treatments, meta-analyses have found that a majority express a preference for psychotherapy over pharmacotherapy, with those receiving their preferred treatment being less likely to drop out, reporting higher treatment satisfaction, and experiencing marginally better clinical outcomes [2–4]. Of note, the majority of studies included in these meta-analyses compared pharmacotherapy to psychotherapy for depression, and the conclusions that could be drawn were significantly limited by heterogeneity across the included studies [5]. The effect size attributable to receiving one's preferred treatment has been estimated at Cohen's $d = 0.15$ – 0.31 [2, 3, 6, 7], and $d = 0.49$ for anxiety disorders specifically [7].

Panic disorder with or without agoraphobia (PD/A) is a commonly occurring condition with a lifetime prevalence of 1.7–4%; associated with high rates of comorbidity, an increased risk of morbidity and mortality, diminished work capacity, and increased health care utilization [8]. Meta-analyses by the Cochrane organization find that pharmacotherapies and psychotherapies (mostly antidepressants and cognitive behavioural therapies – CBT), either alone or in combination, yield moderate to large effect sizes relative to no/minimal treatment, and small to medium effect sizes relative to placebo or other psychological treatments, in terms of short-term remission [9–11]. However, the use of pharmacotherapy is associated with a significantly increased risk of attrition during treatment and relapse when treatment is discontinued [11]. A recent network meta-analysis of psychological therapies for PD/A failed to find unequivocal evidence of the superiority of any treatment, although CBT, followed by psychodynamic therapy (PDT), had the best evidence of short-term efficacy, with the latter showing slightly better tolerability [10]. Of further importance in the treatment of PD/A is the stability of change after treatment termination. A recent meta-analysis of long-term outcomes in CBT for anxiety disorders found significant further improvement up to 12 months after treatment with PD patients [12]. The longer-term efficacy of PDT for anxiety disorders, and PD/A specifically, remains unclear [13].

In view of the research on patient preferences, offering adults with PD/A their preferred treatment may be associated with improved outcomes. A doubly randomised controlled preference (DRCPT) design [14], in which participants are randomised to self-selection or random assignment to treatment conditions, would test this hypothesis. To date, no DRCPTs have been conducted to examine preference effects for any form of PD/A treatment, or indeed between any 2 forms of psychotherapy for any psychiatric disorder.

Using a DRCPT design, the primary aim of the present study was to evaluate short- and long-term change for participants with PD/A treated with CBT or PDT under self-selected versus randomised allocation to treatment conditions. The treatment alternatives were panic control treatment (PCT) [15, 16], the CBT approach with the largest evidence base for PD/A, and panic-focused psychodynamic therapy (PFPP) [16, 17], the PDT approach with the largest evidence base for PD/A. Our hypotheses were that for clinician-rated PD/A severity: (1) outcomes in the treatment groups would be superior to control at post-treatment assessment; (2) outcomes for participants who chose their treatment, irrespective of treatment type, would be superior to those of participants randomly assigned to treatment; and (3) PCT would yield superior outcomes to PFPP. Additional primary (occupational status, PD/A-related absences from work) and secondary outcomes (mobility, depression and functional impairment) were assessed but no a priori hypotheses tested. Finally, and in an exploratory way, we test whether there is an interaction effect between treatment allocation and treatment types on outcome.

Materials and Methods

Study Design and Participants

The Psychotherapy Outcome and Self-Selection Effects project (Project POSE) was a multicentre, DRCPT of PCT and PFPP for PD/A. Participants were randomly allocated to self-selection/choice of treatment (choice; C), random assignment to treatment (random; R), or to a waiting list control condition (control). Participants allocated to choice were provided written information about the 2 treatments and then asked to choose either PCT (CPCT) or PFPP (CPFPP). Participants allocated to random were randomly allocated to PCT (RPCT) or PFPP (RPFPP). Participants allocated to control were re-randomised to either the choice or random conditions at the end of the 3-month control period. Although waiting list controls have been found to be of limited value in trials evaluating the efficacy of a treatment [18], this was not strictly a waiting list group. The primary aim of this trial was to evaluate the relative efficacy of random assignment to 2 types of psychotherapy (random) versus the patients choosing their pre-

ferred option from the same 2 psychotherapies (choice). The waiting list condition was included to control for the possibility that both the randomly assigned and chosen treatments were equally ineffective in treating symptoms of PD/A. Further details of the study are presented in the published trial protocol [19].

The trial was carried out in 4 regions in Sweden at outpatient psychiatry, primary health care, and youth guidance clinics. Inclusion criteria were: (1) aged 18–70¹ years; (2) current principal DSM-IV diagnosis of PD/A, including at least 1 panic attack per week during the 3 weeks preceding trial assessment; (3) if medicated, staying on a stable dose for at least 1 month prior to trial inclusion; (4) willing to keep medication dosage stable throughout the trial treatment phase; (5) not currently engaged in psychotherapy and willing to refrain from starting new treatments during the treatment phase; (6) ability to complete the treatment phase within 16 weeks; and (7) if participants actively avoided situations that caused them panic, they had to: (1) score ≥ 5 on an apprehension question about having a panic attack from the Anxiety Disorder Interview Schedule for DSM-IV [20] and (2) score ≥ 4 on at least 1 question from the Avoidance-Alone Subscale of the Mobility Inventory for Agoraphobia [21]. Exclusion criteria were: (1) a current substance abuse/dependence disorder (or in remission for ≤ 12 months prior to trial inclusion); (2) current psychosis, delusions, mania, or autism diagnosis; (3) acutely suicidal; (4) a history and current presentation of at least 1 clinically significant medical condition sufficient to cause cognitive or physical impairments that might prevent full participation in treatment; and (5) active involvement in a legal dispute related to their mental health.

Trial information was made available via a Project POSE website and advertisements. In addition, clinic staff provided trial information to patients who suffered from anxiety and panic. Interested individuals could also self-refer or be referred by their local mental health care provider. Individuals who expressed an interest were screened for eligibility by phone and, if suitable, invited to a face-to-face diagnostic interview. All results are reported according to CONSORT guidelines [22].

Randomisation and Masking

The allocation ratio to the choice, random, and control conditions was 4:4:1. At the end of the 3-month control condition, the re-allocation ratio to the choice and random conditions was 1:1. Participants were allocated to the choice, random, and control conditions at each clinic. For the random condition, a stratification procedure was used so that equal numbers of participants were allocated to PFPP and PCT at each clinic. Randomisation was done using the software Research Randomizer [23]. In the choice condition, participants were provided separate, 500-word written descriptions of the 2 treatments (PCT and PFPP) before indicating their treatment preference. The treatment descriptions were blinded (did not specify the name of the treatment), specific, well balanced, and easy-to-read presentations of PCT and PFPP that had been piloted before the study commenced. Each treatment description was comprised of 3 headed sections: (1) how is panic disorder viewed in treatment; (2) how do you work in treatment; and (3) what results can I expect. For PCT, the sections described:

(1) the role of fear of fear (bodily reactions) in the development of panic; (2) learning (with the therapist) how to change cognitions and behaviours in relation to panic triggers and exposure to situations that trigger panic; and (3) a better understanding of how to change cognitions/behaviours that increase the likelihood of panic attacks will be accompanied by a reduction in their frequency and greater functionality. For PFPP, the sections described: (1) the potential role of negative life events in the onset of panic attacks, and the effects of the latter on emotional functioning and relationships; (2) exploring (with the therapist) the causes of the panic attacks and their effects on emotions/relationships; and (3) a better understanding of the causes of panic attacks and their effects on emotions/relationships will be accompanied by reduced feelings of vulnerability, less frequent panic attacks, and greater functionality. The full treatment descriptions are available from the authors upon request.

Interventions

PCT [15] is a manualised, individual cognitive-behavioural treatment for adults with PD/A. In this trial, PCT comprised 12–14 sessions, completed in 10–16 weeks, with weeks 1 and 2 including 2 sessions and subsequent weeks 1 session each. Sessions were 60 min in length and extended to 90–120 min for sessions involving therapist-led exposure. Between 2 and 5 sessions include therapist-assisted exposure (total treatment duration = 780–1,140 min). PCT involves: psychoeducation about the nature of PD/A and training in self-monitoring of symptoms (sessions 1–2); building a hierarchy of agoraphobic situations (session 3); cognitive restructuring techniques and breathing retraining (sessions 4–6); in vivo and interoceptive exposure (sessions 6–13); and relapse prevention (session 14). Between-session homework assignments, done throughout treatment, involved symptom self-monitoring and after the first session, involved planned therapist-led and patient-led exposures.

PFPP [17] is a manualised, individual psychodynamic treatment for adults with PD/A. In this trial, PFPP comprised 19–24 sessions completed in 10–16 weeks, with 2 sessions per week. Individual sessions were 45 min in length (total treatment duration = 855–1,080 min). PFPP proceeds in 3 phases. Phase I is focused on identifying the content and meaning of panic episodes, and any links between these episodes and experiences with caregivers, difficulty expressing/managing feelings/fantasies, and any prior experiences of trauma/loss. Phase II addresses difficulties managing anger, abandonment fears, and separation situations, with links to panic episodes, through discussion of the patient's feelings/fantasies about past/present relationships and in the transference relationship with the therapist. Phase III is focused on increasing emotional expression and assertiveness around conflicts that arise in the context of panic episodes and treatment termination.

Control participants were contacted by phone by a trial assessor every second week for a brief conversation about their general well-being and panic symptoms during the past week. No advice/intervention was provided during these conversations; the purpose was to provide a minimal level of support that would help the participant remain in the condition/trial until re-randomisation.

Therapists

Treatment was delivered by 45 therapists: PCT = 20 (12 women, 8 men); PFPP = 25 (17 women, 8 men). Their basic professional training was: clinical psychology ($n = 22$; PCT = 10, PFPP =

¹ At CONSORT registration, an inclusion criterion was “aged 18–60 years.” However, before inclusion commencement this inclusion criterion was changed in order not to exclude individuals who were still actively working between 60 and 70 years of age.

12), social work ($n = 16$; PCT = 4; PFPP = 12), nursing ($n = 2$; PCT = 2), and other (social scientist, psychiatric health care) professional training ($n = 5$; PCT = 4, PFPP = 1). All therapists had completed a 3-year, state-regulated/approved, postgraduate training course in either CBT or PDT, with 18 of the 45 being further trained and licensed as psychotherapists by the National Board of Health and Welfare (PCT = 4, PFPP = 14). Therapists had no affiliation to the authors or their employer. Compared to PCT therapists, the PFPP therapists had longer experience providing psychotherapy (PFPP = 15.4 years (SD = 9.1) vs. PCT = 8.7 years (SD = 4.4), $p = 0.004$), but PFPP and PCT therapists did not differ in the average number of PD/A patients treated before study participation (PCT = 3.4 (SD = 1.0) vs. PFPP = 3.2 (SD = 1.3), $p = 0.670$).

Prior to delivering treatment in the trial, all therapists underwent group-based trainings in either PCT or PFPP, and then completed a supervised treatment case using the per-protocol manual with an adequate level of adherence. As therapists were recruited throughout the trial, 4 separate 2-day PCT/PFPP trainings were carried out. The first was delivered by Professors Barbara Milrod (PFPP) and Michelle Craske (PCT), who also provided training to the trial supervisors (who worked throughout the length of the trial). Three further training courses in PFPP and PCT were carried out by H.J., G.V., and S.P. Approximately 120 therapists were trained, but only 45 agreed to participate and were subsequently approved on at least 1 case per trial protocol and supervised during the entire trial.

Treatment Adherence

Two groups of graduate clinical psychology students (PCT = 5, PFPP = 3), trained to rate treatment adherence, rated one therapy session drawn from the beginning, middle, and termination phase of treatment for every participant. PCT adherence was evaluated using a session-specific rating scale approved by Prof. Craske, including 3–9 items (varying between sessions), each rated on a 7-point Likert scale. A mean score ≥ 4 indicates satisfactory adherence. The interrater reliability coefficient (ICC) between the PCT adherence raters was ICC(2, 1) = 0.89. The mean adherence rating across all items and participants was 4.55 (SD = 0.73). PFPP adherence was rated using a session nonspecific scale approved by Prof. Milrod, including 7 items, each rated on a 7-point Likert scale. A score ≥ 4 on at least 5 items indicates adequate levels of adherence. For PFPP raters the ICC(2, 1) was 0.67. The mean adherence rating across all items and participants for PFPP was 4.88 (SD = 0.87).

Outcome Assessor Training

Given the widely dispersed geographical locations of the treatment sites, the number and length of the inclusion/outcome assessments, and the overall length of the trial, it was decided prior to the trial that it would be difficult to recruit and maintain blinded assessors who were external to the research group for the duration of the trial. It was also assumed that participants would be more willing to complete all assessments if they had the same assessor throughout the trial. Accordingly, all assessments were conducted by M.S. and T.N. Both were trained to conduct diagnostic assessments and met regularly throughout the trial to maintain the quality and similarity of the assessment procedure across participants and sites. As the assessors were responsible for all inclusion and outcome assessments, they were not blinded to condition. To control for possible rating bias, 3 masters-level clinical psychology students, external to

the trial, were trained to assess the primary outcome variable using videotapes of trial assessments. For the post-treatment/control and follow-up assessments, the internal assessor's videotaped assessments did not include discussion of allocation or treatment status. From all 5 assessments points (trial inclusion, post-treatment assessment, 6-, 12-, and 24-month follow-up) a random sample of 264 videotapes of Panic Disorder Severity Scale (PDSS) interviews were selected (representing $>25\%$ of all interviews) and rated by the external assessors who were blinded to condition. The ICC(2, 1) for total scores on the primary outcome measure between the internal and external assessors was 0.98.

Measures

Primary and secondary outcome measures were administered at trial inclusion, after treatment, and at the 6-, 12-, and 24-month follow-up assessments. Diagnostic status (PD/A and comorbidity) was assessed via the Structured Clinical Interviews for DSM-IV [SCID-I and SCID-II; 24, 25]. Reliability for a PD/A diagnosis between M.S. and T.N. was computed as κ -coefficient = 1.00 for agreement, based on 10 videotaped SCID interviews.

Primary Outcome Measures. Consistent with recommendations for the evaluation of outcomes in treatment trials for PD/A, the clinician-rated PDSS was chosen as the primary outcome measure [26]. The PDSS is a 7-item measure of the severity of the core features of PD over the past month [27]. Items are rated on a 5-point scale (from 0 to 4) with higher scores indicating greater severity. The PDSS has excellent psychometric properties [28]. Responder status after treatment and at follow-up was calculated as a $\geq 40\%$ reduction (relative to pre-treatment) on the PDSS [25]. Occupational status (work) and the number of self-reported absences due to sickness (absences) were included as additional primary outcomes owing to the explicit targets/outcomes identified as important by the government agency who funded part of this trial. Work was a dichotomised categorisation of the participant's self-reported employment status. Absences was a dichotomised categorisation (0 weeks or ≥ 1 week of absence from work during the last 3 months).

Secondary Outcome Measures. The PDSS Self-Report version (PDSS-SR)² contains the same 7 items and scoring system as the PDSS and possesses excellent psychometric properties [27]. In the present study, the correlation between the PDSS-SR and PDSS across treatment and follow-up was $r = 0.86$. The Mobility Inventory for Agoraphobia is a 4-item self-report measure of the degree of agoraphobic avoidance (1 = never, 5 = always) across 27 different situations, rated for when the individual is alone or accompanied [21]. A single, item-level average is computed. The Sheehan Disability Scale is a 3-item self-report measure of the degree of functional impairment (0 = not all, 10 = extremely) in work, social life, and the family over the past week [29]. A single total score (0–30) is computed. The 9-item self-report version of the Montgomery-Åsberg Depression Rating Scale assesses the severity (0–6) of depressive symptoms over the past 3 days, with a single total score computed [30]. For adverse events, we recorded severe medical or psychiatric conditions, deaths from whatever cause, all self-harm and suicide attempts, and reliable worsening of symptoms as measured by the PDSS. All scales had acceptable internal consistency in the present sample (Cronbach's $\alpha > 0.72$).

² In the protocol paper, PDSS-SR was, in contradiction to the Clinical Trials registration, erroneously labelled as a primary outcome.

Table 1. Baseline characteristics by condition

	Total (n = 221)	After re-randomisation				Control ¹ (n = 21)
		randomised condition		choice condition		
		RPCT (n = 53)	RPFPP (n = 55)	CPCT (n = 49)	CPFPP (n = 60)	
<i>Demographics, n (%)</i>						
Female	165 (74.7)	40 (75.5)	40 (72.7)	34 (69.4)	49 (81.7)	14 (66.7)
Basic level education	23 (10.4)	6 (11.5)	7 (12.7)	3 (6.1)	5 (8.5)	2 (9.5)
High school	114 (51.6)	28 (53.8)	31 (56.4)	27 (55.1)	27 (45.8)	11 (52.4)
University education	82 (37.1)	18 (34.6)	17 (30.9)	19 (38.8)	27 (45.8)	8 (38.1)
Employed	193 (87.3)	43 (82.7)	49 (89.1)	43 (89.6)	54 (90.0)	14 (66.7)
Mean age at entry (SD), years	34.9 (12.6)	34.4 (13.9)	35.3 (13.1)	36.8 (13)	33 (10.4)	36.7 (13.6)
<i>Current psychiatric conditions, n (%)</i>						
PD with agoraphobia	184 (83.3)	41 (77.4)	45 (81.1)	43 (87.8)	51 (85.0)	18 (85.7)
PD without agoraphobia	37 (16.7)	12 (22.6)	10 (18.2)	6 (12.2)	9 (15.0)	3 (14.3)
Any axis I diagnosis besides PD/A	156 (70.6)	30 (56.6)	40 (72.7)	37 (75.5)	48 (80.0)	13 (61.9)
Any personality disorder	52 (23.5)	10 (18.9)	15 (27.3)	11 (22.4)	16 (26.7)	3 (14.3)
Mean number of axis I diagnoses besides PD/A (SD)	1.7 (1.7)	1.2 (1.4)	2.1 (2.1)	1.6 (1.4)	1.8 (1.5)	1.6 (2.2)
<i>Clinical characteristics</i>						
Median panic debut (IQR), months	72 (144)	48 (84)	96 (204)	96 (143)	74 (113)	120 (198)
Median panic episode (IQR), months	10 (29)	6 (18)	9 (34)	18 (80)	12 (26)	6 (21)
Mean PDSS (SD)	15.6 (4.1)	14.9 (3.8)	15.9 (3.8)	16.1 (4.7)	15.5 (4.1)	16.8 (4.7)
Previous psychotherapy, n (%)	136 (61.5)	32 (64.0)	39 (70.9)	28 (59.6)	35 (58.3)	14 (66.7)
Psychotropic medication use, n (%)	117 (53.4)	27 (50.9)	29 (51.7)	31 (63.3)	27 (45.0)	14 (66.7)

R, randomised condition; C, choice condition; PFPP, panic-focused psychodynamic psychotherapy; PCT, panic control treatment; control, control condition; PDSS, Panic Disorder Severity Scale; IQR, interquartile range. ¹ Re-randomised after completed control condition and re-assessment of eligibility.

Sample Size

Power calculations were performed using Power IN Two-level designs (PINT v. 2.12, September 2007) [31] for change scores on the PDSS. Based on previous research on preference effects on the severity of psychiatric symptoms [6, 7], we assumed that the effect of allocation (choice vs. randomisation) would have a standardised mean difference (SMD) = 0.40 on the PDSS at post-treatment assessment and during follow-up. Therefore, at $\alpha = 0.05$, power = 0.80, and SMD = 0.40, 200 participants were required, with a planned recruitment of 221 to allow for attrition.

Statistical Methods

All analyses and reported outcomes follow the intention-to-treat principle. Post-treatment differences for the PDSS for participants in each treatment arm versus control were compared using 1-way ANOVAs on unadjusted raw PDSS scores and post hoc analyses according to Dunnett's method. Trajectory differences between the treatments in the random (RPCT, RPFPP) and choice conditions (CPCT, CPFPP) were examined using segmented multilevel linear growth modelling to handle nested and missing data. Outcome measures were modelled as functions of the number of months from baseline (0) until the 24-month follow-up (27), with a breakpoint at post-treatment assessment (3). Linear, quadratic, and log-linear trajectory shapes were compared using Akaike's information criterion (AIC). For all outcome variables, the log-linear model yielded

the smallest AIC value. Random intercepts and slopes for both time segments (baseline to post-treatment assessment, post-treatment time to 24-month follow-up) were estimated at both participant and therapist levels. Change in medication and additional treatment during the post-treatment to follow-up segments were added as time-dependent covariates with $t - 1$ lags. Between-group differences on these variables were tested. The missing at random assumption was tested using pattern-mixture modelling [32] and revealed no violation of the missing at random assumption (AIC increased slightly for the pattern-mixture model). SMDs were calculated according to Feingold [33] as the difference between treatments in model-estimated change from baseline, divided by the observed SD at baseline across all groups. χ^2 tests were carried out for responder status and the 2 work-related variables. Data were analysed with SPSS (version 26) and Stata (version 16).

Results

Between November 2011 and May 2017, 604 adults were screened and 221 with a primary DSM-IV diagnosis of PD/A were included and randomised to the choice, random, or control conditions. Two participants ran-

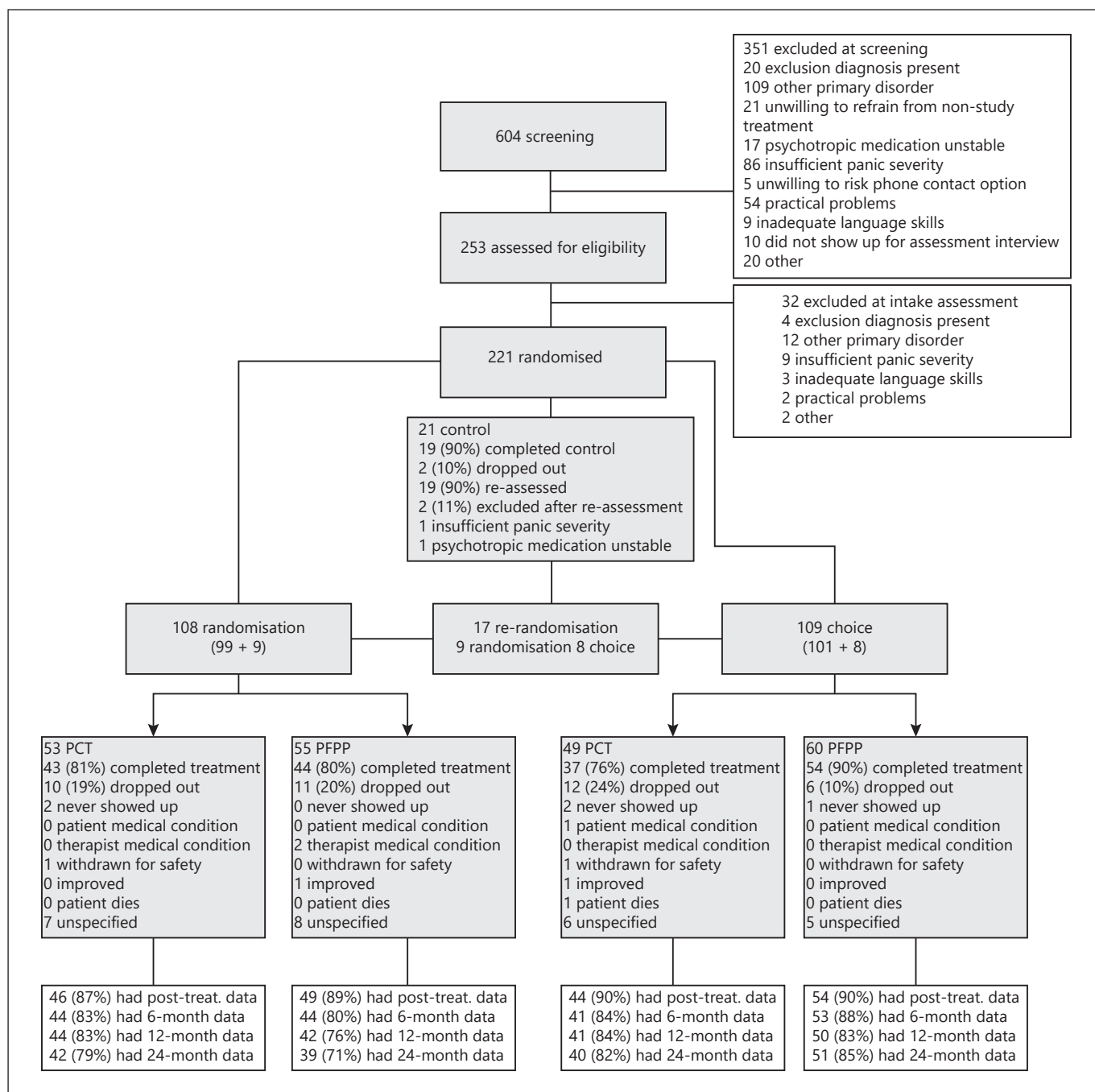


Fig. 1. Participant flow chart. PCT, panic control treatment; PFPP, panic-focused psychodynamic therapy.

domised to the control condition dropped out and 2 were excluded after completing it, leaving 217 participants available for randomisation to the choice or random conditions. Of the 109 participants randomised to choice, 49 (45%) chose PCT and 60 (55%) chose PFPP ($p = 0.341$). The only significant difference between any of the groups

at baseline was a higher mean number of axis I diagnoses (besides PD) in RPFPP than in RPCT ($p = 0.028$, corrected for family-wise error rate; see Table 1).

As shown in the CONSORT flow chart (Fig. 1), 178 of the 217 participants (82%) randomised to the choice and random conditions completed treatment in accordance

with the protocol. Five (2.3%) did not show up for treatment, 26 (11.8%) terminated prematurely on their own initiative, and 3 (1.4%) were withdrawn for reasons of safety (see serious adverse events below). The number of drop-out/withdrawn cases did not vary by allocation (choice vs. random; $p = 0.38$) or treatment type (PCT vs. PFPP; $p = 0.93$). PCT averaged 11.7 sessions, ranging between 60 and 120 min. PFPP averaged 20.3 sessions, with a constant session length of 45 min. There was no association between PDSS outcome and number of sessions completed ($p = 0.45$). There were no significant differences in the number of completers in the choice and random conditions, or between treatment types.

Serious Adverse Events

Serious adverse events during treatment were as follows: 1 participant (CPCT) suffered a non-trial-related death; 1 participant (CPCT) experienced the onset of a severe medical illness, 2 participants were withdrawn for reasons of safety, one (CPCT) of them attempting suicide and the other (RPCT) experiencing a significant increase in symptoms of major depression. In addition, 2 participants (RPCT and CPFPP) experienced significant worsening (>5.94) of panic symptoms according to the PDSS.

Primary Outcome Measures

Table 2 presents the mean raw scores for the PDSS at baseline and after treatment for participants initially randomised to choice, random, and control conditions. Outcome differences between participants in the control versus the choice or random conditions were both large and significant ($p < 0.001$). Choice: SMD 1.74 (95% confidence interval, CI, 1.20–2.28); random: SMD 1.71 (95% CI 1.17–2.26). Not reported in Table 2, the differences between treatment types within the choice and random conditions (CPCT, CPFPP, RPCT, and RPPP) and the control condition were all large and highly significant. Table 3 presents the mean raw scores for the primary (PDSS only) and secondary outcome measures at baseline, after treatment, and at follow-ups, by condition (choice vs. random) and treatment within condition (PCT vs. PFPP).

Table 4 presents the SMDs between the choice and random conditions, between PCT and PFPP, and the allocation by treatment type interaction, based on the rate of change coefficients (b). Figure 2 presents the modelled trajectories on the PDSS and secondary outcome measures for the treatment types within the choice and random conditions. Irrespective of choice versus random assignment to treatment or treatment type, steep

Table 2. Raw scores for control, randomised and choice conditions

Mean PDSS (SD)	Control	<i>n</i>	Random	<i>n</i>	Choice	<i>n</i>
Baseline	16.8 (4.7)	21	15.5 (3.9)	99	15.5 (4.2)	101
Post-treatment	16.4 (5.0)	19	9.2 (5.6)	87	9.1 (4.6)	93

decreases for the estimated scores on the PDSS occurred during treatment (mean $b = -6.32$, $p < 0.001$; 95% CI -7.12 to -5.52 ; SMD -1.53 ; 95% CI -1.72 to -1.34) and continued to decrease during the follow-up (mean $b = -3.06$, $p < 0.001$; 95% CI -3.91 to -2.21 ; SMD -0.74 ; 95% CI -0.95 to -0.54). Accordingly, PDSS change from intake to follow-up 27 months later was SMD = -2.27 (95% CI -2.52 to -2.02). There was no significant effect of allocation (choice vs. random) during treatment or follow-up. Consistent with expectation, significantly larger reductions on the PDSS occurred for those receiving PCT than PFPP during treatment, but during follow-up the pattern was significantly reversed so that from baseline to the 24-month follow-up, the 2 treatment types yielded similar outcomes. The allocation by treatment type by time interaction was not significant during treatment or follow-up. Not reported in Table 4, all comparisons for work or absences were nonsignificant during treatment or follow-up (all p values >0.485 for work and >0.327 for absences). Neither change in medication nor additional treatment differed significantly between the treatment groups at any time (p values = 0.107–0.939).

Secondary Outcome Measures

For clinician-rated outcomes, the percentage of participants achieving a clinically significant response on the PDSS (i.e., $\geq 40\%$ reduction from pre-treatment scores) [26] at post-treatment assessment and by the 24-month follow-up were as follows: RPCT = 63.0 and 69.6%; RPFPP = 32.7 and 65.3%; CPCT = 56.8 and 61.4%; and CPFPP = 46.3 and 75.9%. The p value for between-group differences at post-treatment assessment was $p = 0.018$, and at ensuing follow-ups all between-group p values were >0.413 . The proportion of participants who fell into the normal or borderline level of severity on the PDSS (total score ≤ 5) [26] by the 24-month follow-up was as follows: RPCT = 49.1%; RPFPP = 38.2%; CPCT = 40.8%; and CPFPP = 55.0% ($p = 0.416$).

The secondary, self-reported outcomes showed the same pattern of effects as the clinician-rated PDSS, albeit of varying sizes (Table 3). Again, the allocation effects

Table 3. Raw scores by treatment conditions and time of assessment

	RPCT	<i>n</i>	RPFPF	<i>n</i>	CPCT	<i>n</i>	CPFPP	<i>n</i>
Mean PDSS (SD)								
Baseline	14.9 (3.8)	53	15.7 (4.1)	55	16.0 (4.6)	49	15.5 (4.1)	60
Post-treatment	7.5 (4.8)	46	10.8 (5.9)	49	8.6 (4.1)	44	9.7 (5.5)	54
6-month follow-up	6.4 (5.4)	44	8.4 (5.5)	44	8.4 (5.5)	41	7.8 (5.3)	53
12-month follow-up	5.9 (4.7)	44	8.5 (6.1)	42	8.3 (5.9)	41	6.4 (5.2)	50
24-month follow-up	6.2 (5.3)	42	7.5 (5.6)	39	7.1 (5.9)	40	5.1 (5.1)	51
Work, %								
Baseline	17.3	52	12.7	55	8.3	48	12.1	60
Post-treatment	11.4	44	10.2	49	11.9	42	9.4	53
6-month follow-up	11.4	44	11.9	42	14.6	41	5.7	53
12-month follow-up	9.5	42	17.1	41	12.5	40	4.0	50
24-month follow-up	13.2	38	14.3	35	15.8	38	6.4	47
Absence, %								
Baseline	13.5	52	23.6	55	24.5	49	19.0	58
Post-treatment	13.6	44	21.3	47	16.7	42	23.1	52
6-month follow-up	9.3	43	19.5	41	14.6	41	22.6	53
12-month follow-up	10.0	40	25.6	39	10.3	39	12.0	50
24-month follow-up	10.8	37	17.6	34	15.8	38	19.1	47
Mean PDSS-SR (SD)								
Baseline	11.9 (4.5)	52	12.8 (4.6)	55	12.6 (4.9)	49	12.4 (4.2)	60
Post-treatment	4.1 (4.2)	44	7.6 (5.9)	49	4.5 (4.3)	42	6.7 (5.6)	54
6-month follow-up	3.2 (4.0)	44	5.4 (4.6)	42	4.9 (5.1)	41	5.6 (5.3)	53
12-month follow-up	3.1 (3.5)	42	5.8 (5.6)	41	4.8 (4.7)	40	4.4 (4.5)	50
24-month follow-up	3.0 (3.8)	39	4.2 (5.1)	37	3.5 (5.3)	38	3.3 (4.0)	47
Mean SDS (SD)								
Baseline	14.6 (6.5)	52	14.1 (6.3)	55	15.0 (6.3)	49	14.6 (6.1)	60
Post-treatment	6.7 (6.6)	44	9.7 (7.7)	49	6.0 (6.9)	42	9.3 (8.0)	54
6-month follow-up	5.3 (7.2)	44	7.7 (6.9)	42	5.6 (7.1)	41	6.9 (6.4)	53
12-month follow-up	4.3 (5.3)	42	6.5 (7.5)	41	6.2 (7.6)	40	5.1 (6.6)	50
24-month follow-up	3.7 (5.8)	39	5.7 (6.9)	37	5.2 (7.1)	38	4.7 (6.6)	47
Mean MI (SD)								
Baseline	2.2 (0.8)	52	2.4 (0.8)	55	2.3 (0.7)	49	2.1 (0.7)	60
Post-treatment	1.6 (0.6)	44	2.0 (0.8)	49	1.6 (0.5)	42	1.8 (0.7)	54
6-month follow-up	1.6 (0.7)	44	1.8 (0.8)	42	1.7 (0.6)	41	1.6 (0.7)	53
12-month follow-up	1.5 (0.7)	42	1.7 (0.7)	41	1.6 (0.6)	40	1.5 (0.6)	50
24-month follow-up	1.5 (0.6)	39	1.8 (0.9)	37	1.5 (0.5)	38	1.4 (0.5)	47
Mean MADRS-S (SD)								
Baseline	17.7 (8.1)	52	17.0 (8.0)	55	17.3 (9.2)	49	18.0 (7.7)	60
Post-treatment	10.4 (8.8)	44	12.0 (8.7)	49	9.2 (7.6)	42	11.8 (8.5)	54
6-month follow-up	9.7 (8.8)	44	11.7 (8.8)	42	10.2 (6.7)	41	10.2 (7.7)	53
12-month follow-up	8.6 (8.3)	42	10.5 (8.2)	41	9.9 (7.9)	40	9.2 (7.1)	50
24-month follow-up	8.7 (8.5)	39	8.9 (8.5)	37	10.4 (8.2)	38	8.5 (7.4)	47

R, randomised condition; C, choice condition; PFPP, panic-focused psychodynamic psychotherapy; PCT, panic control treatment; PDSS, Panic Disorder Severity Scale; PDSS-SR, Panic Disorder Severity Scale, Self-Rating; MI, Mobility Inventory for Agoraphobia; SDS, Sheehan Disability Scale; MADRS-S, Montgomery-Åsberg Depression Rating Scale.

(choice vs. random) were nonsignificant throughout. PCT produced steeper changes than PFPP during the treatment phase while the reverse was true during the follow-up phase. There were no significant allocation by treatment type by time interactions.

Discussion

Both theory and previous preference studies suggest that psychotherapy patients who receive their preferred treatment may experience better outcomes than either

Table 4. Effect sizes (SMDs) of differential change, by treatment contrasts and time segments (CI in parentheses)

Outcome measure	Segment/months	C-R	PFPP-PCT	(RPFPP-CPFPP) – (RPCT-CPCT)	RPFPP-RPCT
PDSS	Baseline to post-treatment	0.03 (–0.26 to 0.33)	–0.64 (–1.02 to –0.25)	–0.29 (–0.88 to 0.30)	–0.78 (–1.27 to –0.30)
	Post-treatment to 24 months	0.08 (–0.26 to 0.42)	0.62 (0.27 to 0.98)	–0.28 (–0.96 to 0.41)	0.48 (–0.02 to 0.98)
	Baseline to 24 months	0.11 (–0.26 to 0.48)	–0.01 (–0.47 to 0.44)	–0.57 (–1.31 to 0.17)	–0.30 (–0.89 to 0.29)
PDSS-SR	Baseline to post-treatment	0.00 (–0.32 to 0.32)	–0.56 (–0.89 to –0.22)	–0.22 (–0.86 to 0.42)	–0.67 (–1.13 to –0.20)
	Post-treatment to 24 months	0.04 (–0.25 to 0.33)	0.40 (0.11 to 0.69)	–0.12 (–0.70 to 0.46)	0.34 (–0.07 to 0.76)
	Baseline to 24 months	0.04 (–0.27 to 0.34)	–0.15 (–0.48 to 0.17)	–0.34 (–0.95 to 0.27)	–0.32 (–0.77 to 0.13)
SDS	Baseline to post-treatment	0.08 (–0.19 to 0.36)	–0.53 (–0.80 to –0.25)	–0.01 (–0.56 to 0.54)	–0.54 (–0.93 to –0.14)
	Post-treatment to 24 months	–0.09 (–0.37 to 0.19)	0.37 (0.09 to 0.65)	–0.36 (–0.92 to 0.20)	0.19 (–0.22 to 0.59)
	Baseline to 24 months	–0.01 (–0.29 to 0.27)	–0.16 (–0.44 to 0.11)	–0.37 (–0.93 to 0.18)	–0.35 (–0.75 to 0.05)
MI	Baseline to post-treatment	0.03 (–0.27 to 0.22)	–0.49 (–0.73 to –0.25)	0.24 (–0.24 to 0.72)	–0.37 (–0.71 to –0.03)
	Post-treatment to 24 months	0.11 (–0.12 to 0.33)	0.27 (0.02 to 0.51)	–0.24 (–0.68 to 0.20)	0.15 (–0.18 to 0.48)
	Baseline to 24 months	0.08 (–0.21 to 0.37)	–0.22 (–0.53 to 0.09)	–0.00 (–0.59 to 0.58)	–0.22 (–0.65 to 0.21)
MADRS-S	Baseline to post-treatment	0.11 (–0.18 to 0.40)	–0.26 (–0.55 to 0.02)	–0.19 (–0.77 to 0.38)	–0.36 (–0.77 to 0.05)
	Post-treatment to 24 months	–0.14 (–0.44 to 0.15)	0.29 (–0.01 to 0.58)	–0.33 (–0.92 to 0.26)	0.13 (–0.30 to 0.55)
	Baseline to 24 months	–0.03 (–0.32 to 0.25)	0.03 (–0.26 to 0.31)	–0.52 (–1.10 to 0.05)	–0.24 (–0.65 to 0.18)

R, randomised condition; C, choice condition; PFPP, panic-focused psychodynamic psychotherapy; PCT, panic control treatment; PDSS, Panic Disorder Severity Scale; PDSS-SR, Panic Disorder Severity Scale, Self-Rating; MI, Mobility Inventory for Agoraphobia; SDS, Sheehan Disability Scale; MADRS-S, Montgomery-Åsberg Depression Rating Scale; post-treatment, assessment just after treatment; 24 months, 24-month follow-up; SMDs, standardized mean differences.

those not offered a treatment choice or who receive their nonpreferred treatment. However, these studies have not employed designs that permit a rigorous test of this preference/choice-outcome relationship. The present study is the first DRCPT to address these questions. The specific aim was to test whether giving patients with PD/A a choice between 2 evidence-based psychotherapies conferred an advantage over randomisation to these same treatments for PD/A severity, employment status, and absences from work. Contrary to expectation, and the small to moderate effects on symptoms of receiving one's preferred treatment found in previous studies [2, 3, 7], no such advantage was observed for clinician-rated PD/A severity in this study. In addition, there was no added benefit of choosing one's preferred treatment on employment status or work absences. We also note that participants randomised to treatment were no less likely to drop out of treatment than those who chose their treatment, in direct contrast to one of the reported benefits of providing patients a choice of their treatment. While further DRCPTs are needed before firm conclusions can be drawn, in the context of the extant literature, the present findings suggest that treatment preference effects may be limited when the choice is between 2 evidence-based psychotherapies when compared to psychotherapy versus medication.

It is also possible that our failure to find any beneficial effect of choice versus random allocation to treatment lies in the choice of psychotherapies (PCT and PFPP) and the unexpected disordinal interaction between allocation and treatment type, the presence of which mitigates any main effect. Specifically, the positive RPFPP-CPFPP and the negative RPCT-CPCT differences tended to cancel one another out leaving the choice-random difference close to zero. A different set of findings may have emerged if the choice had been between 2 other forms of evidence-based psychotherapy for PD/A. Importantly, this type of interaction (e.g., allocation by treatment type), which did not reach significance in this trial, requires significantly larger samples than used here [34]. The assumption at study planning was that the effect of choice would be in the same direction for both treatment types, and the trial was powered to detect the main effect of choosing versus random allocation to treatment.

Consistent with hypotheses, treated participants experienced significantly greater reductions than controls after treatment, with PCT being superior to PFPP, but only during treatment. During the follow-up period, participants who received PFPP continued to improve more than those who received PCT, and this difference was not explained by receipt of additional treatments during the

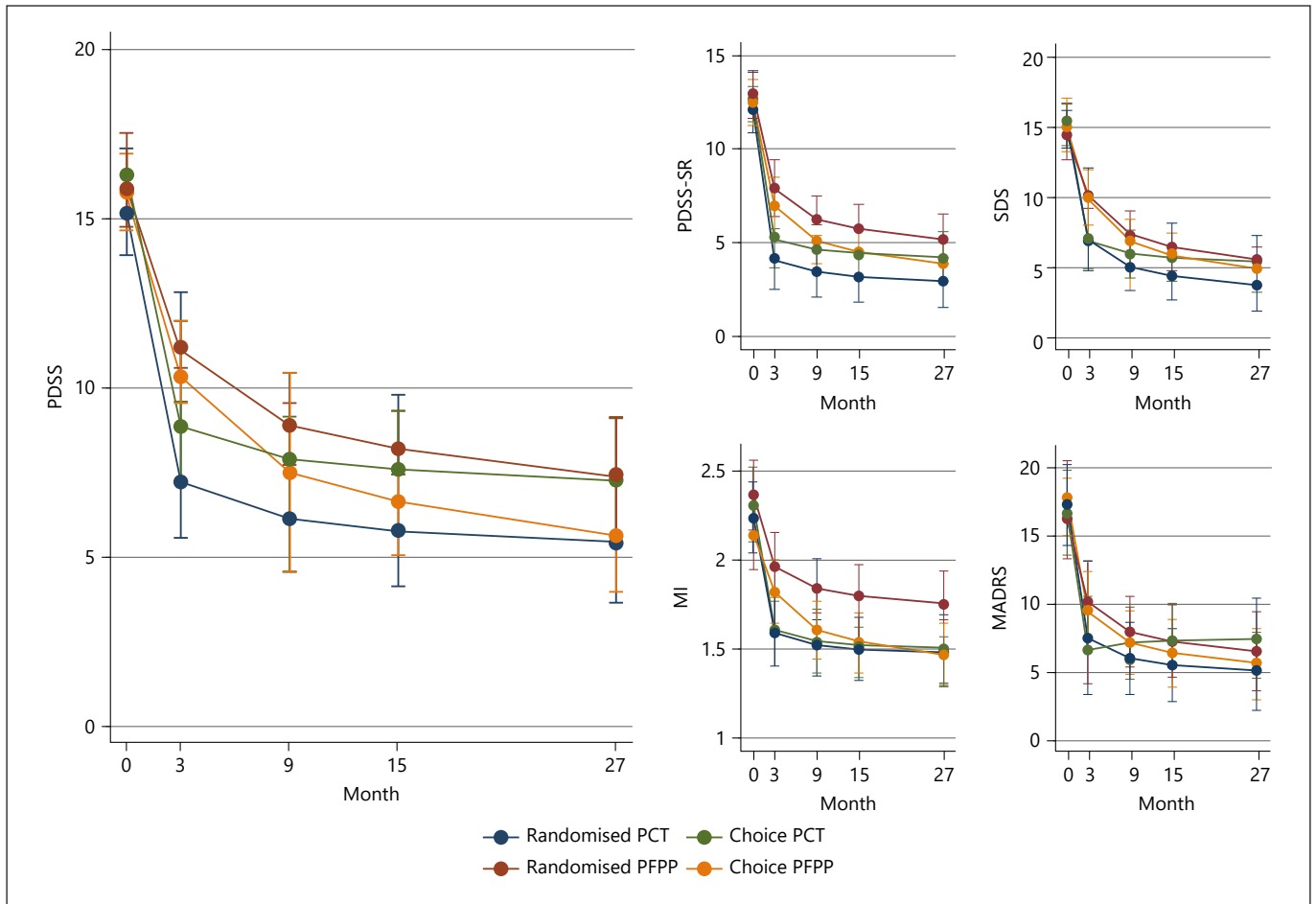


Fig. 2. Modelled trajectories, with 95% confidence intervals, on the Panic Disorder Severity Scale (PDSS) and the secondary outcome measures for the therapy types within the choice and random conditions. PDSS, Panic Disorder Severity Scale; PDSS-SR, PDSS self-

report version; SDS, Sheehan Disability Scale; MI, Mobility Inventory for Agoraphobia; MADRS-S, Montgomery-Åsberg Depression Rating Scale; PCT, panic control treatment; PFPP, panic-focused psychodynamic therapy.

follow-up period, whether pharmaceutical or psychological. In addition, therapists delivering PFPP and PCT did not differ in terms of their prior experience of treating PD/A before the trial or in relation to treatment adherence during the trial, the latter being high for both treatment types. This finding provides a demonstration of the importance of long-term follow-ups in PD/A trials. The secondary outcomes (proportion of responders, self-reported PD severity, agoraphobia, depression, and disability) tended to show the same pattern of results as the primary outcome variable (clinician-rated PD/A severity). A meta-analysis suggested that treatment preferences may exert stronger effects on non-targeted than targeted symptoms [2]. The present findings for depression, employment status, and work absences do not appear to support such a conclusion.

In addition to the literature on treatment preferences, the current trial adds important information to the broader literature on the effectiveness of psychological treatments for PD/A. The trial was carried out in routine psychiatric care clinics, by therapists working in these services, and with patients who had a prior history of treatment for PD/A, and high levels of comorbidity. The investigators are not the original developers of the treatments under study and included a mix of PDT and CBT researchers. While response rates for PCT were comparable to those reported in meta-analyses [10], those for PFPP were somewhat lower than in the 2 randomised controlled trials (RCTs) carried out by the developers of that treatment [15, 17]. However, and in contrast to a previous trial comparing PFPP to PCT [35], participants receiving PFPP in this trial continued to improve for up to 2 years after treatment ter-

mination. This is only the fourth RCT to evaluate the efficacy of PDT for PD/A specifically and provides further support for PFPP as a treatment for PD/A.

With respect to limitations, this treatment outcome study conforms to the main recommendations for trial design by Guidi et al. [19] with 2 exceptions: the use of a waiting list control group and non-blinded outcome assessments. While the present trial involved a waiting list control group, which is of limited utility for evaluating the efficacy of a particular treatment, the design involved comparisons between 2 active treatment conditions (random vs. choice) and therapy types (PCT vs. PFPP). Also, while outcomes were not blindly assessed, 3 external judges blindly rated a large sample of outcome interviews and obtained very high levels of agreement with the non-blinded assessors. A similar pattern of results was also obtained for the secondary, patient-reported outcomes. Consistent with prior preference studies, written information sheets about the treatments were used to elicit choice. As noted above, we endeavoured to make the written presentations comparable in terms of detail, and this may have made the 2 treatments appear too similar or elicited unintended biases. The present trial involved the choice between PCT and PFPP, as representatives of CBT and PDT, because CBT and PDT are the 2 most widely used approaches in routine care facilities throughout Sweden, and because they draw upon distinct theories of change and ways of working. A different set of findings may have emerged had we chosen 2 other forms of psychotherapy, or indeed different forms of CBT [36] and PDT (however, there are no other panic-specific forms of PDT). It is also important to point out that the findings from this paper are based on mean scores for groups and there are likely important variations in outcomes for individuals. Outcome analysis at the individual level, for instance by multilevel latent class regression analysis, was beyond the scope of this paper and is the subject of future investigations.

Finally, as with outcomes in any RCT, other variables may interact with allocation to influence (predict or moderate) outcomes. Of particular relevance are the potential contribution of comorbidity (e.g., personality disorders) and medication usage [37]. In routine clinical practice, patients with PD/A are often assisted in tapering or withdrawing from medication during psychotherapy to facilitate emotional expression and symptom change, while in RCTs medication is usually held constant during the immediate pre-treatment and treatment phases to isolate the effects of allocation to the trial conditions. Preliminary analyses found no evidence that medication usage influenced outcomes in this trial. A full multivariate in-

vestigation of how patient variables influence both the choice of treatment and outcomes is the subject of separate papers.

This was the first DRCPT comparing 2 forms of psychotherapy for PD/A, and indeed any psychiatric condition. Giving patients with PD/A the opportunity to choose 1 of 2 evidence-based treatments (psychotherapies) was not associated with improved outcomes over randomisation to these same treatments. The effect of choice of treatment appeared to be moderated by treatment type, but only in a positive direction for PFPP. Further DRCPTs, employing larger sample sizes, different treatments, and similarly long-term follow-ups are warranted.

Statement of Ethics

All participants gave written informed consent to participate. The study was approved by the Regional Ethical Review Board in Lund, Sweden.

Conflict of Interest Statement

All authors report no financial relationships with commercial interests.

Funding Sources

The study was funded by the Swedish Research Council for Health, Working Life, and Welfare, Swedish Social Insurance Agency, Regions Skåne and Halland, Lindhaga Foundation, B. Gadelius Foundation and L.J. Boëthius Foundation. The funders of the study had no role in study design, data analysis, interpretation of data, or writing of the paper. The views expressed in this publication are those of the authors and do not necessarily reflect those of the funders.

Author Contributions

M.S., T.N., H.J., G.V., R.S., and S.P. were all members of the Project POSE trial management group, which was responsible for study design, securing funding, overseeing, and administering the trial, data interpretation, and manuscript preparation. R.S. was the chief investigator with overall responsibility for the management of the study. M.S. and T.N. had responsibility for the trial sites (recruitment, assessment, and data collection). G.V., H.J., and S.P. provided therapist-training workshops, and G.V. and H.J. provided ongoing clinical supervision to the trial therapists. Treatment adherence was monitored by H.J./M.S. (PFPP) and G.V./T.N. (PCT). The regional clinical trials unit assisted in an initial evaluation of primary outcomes. Further statistical analyses were carried out by F.F. and R.S. All authors contributed to, and approved, the final paper.

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