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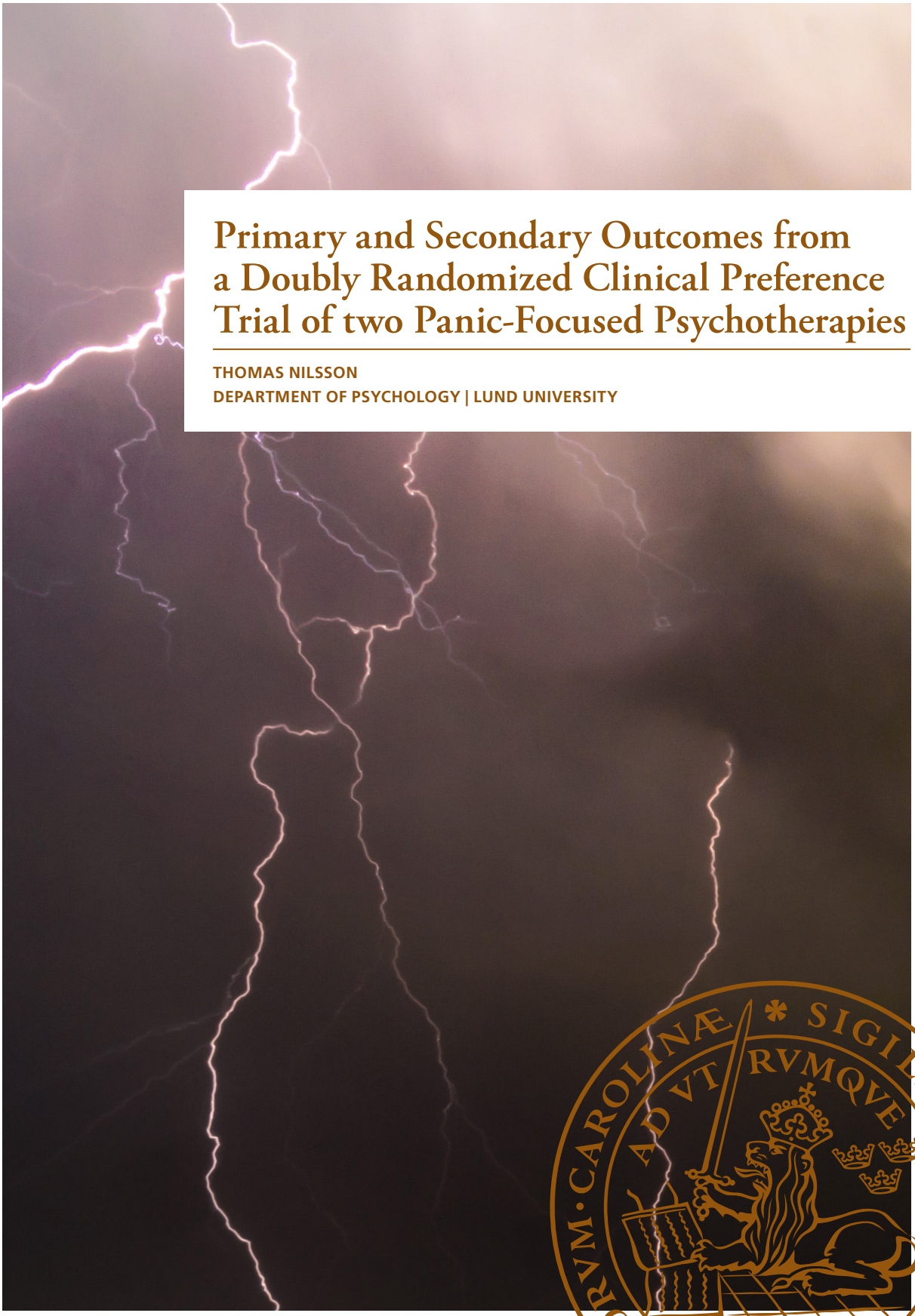

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Thomas Nilsson

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Project POSE (Psychotherapy outcome and Self-selection Effects) was a doubly randomized clinical preference trial (DRCPT) designed to test whether patient preferences for either PCT or PFPP, delivered in routine care, influenced outcomes for the two treatments. Adults (n=221) with primary PD/A were randomly allocated to: 1) to choose either PCT or PFPP; 2) to be randomly allocated to PCT or PFPP; or 3) to a treatment Waitlist. The primary outcome measures were the Panic Disorder Severity Scale (PDSS), work status and sick leave, assessed together with secondary outcomes, at post-treatment, 6-, 12-, and 24-month follow-ups. Treatment was delivered by 45 therapists trained in either PFPP or PCT. This thesis uses data from Project POSE to address three aims: 1) the relative efficacy of PCT and PFPP at post-treatment and during a two-year follow-up; 2) to explore apparent differences in the trajectory of weekly, self-reported panic symptoms in PCT and PFPP during the treatment phase; and 3) to investigate the effects of PCT and PFPP on Work ability and its relations with improvements in PD/A.

Study I was the trial protocol and presented the theoretical and empirical justifications for a DRCPT of two psychotherapies for PD/A. Study II presents the primary and secondary outcomes for Project POSE at post-treatment and all follow-ups. Study III presents the results of an exploratory investigation of a resurgence of self-reported panic symptoms in the termination phase of PFPP (Termination Setback – TS) and patient characteristics that might help to explain the TS. Study IV presents the findings for the self-report Work Ability Index (WAI) and its relation to symptom severity and occupational status at post-treatment and during follow-up.

Irrespective of assignment to the Choice or Random conditions, both treatments yielded clinically significant improvements for the primary and secondary outcomes, comparable to those found in previous trials of the two therapies. PCT was significantly superior to PFPP at post-treatment, possibly owing to a TS that occurred for patients in the PFPP treatment. Individuals with less avoidant attachment and less severe interpersonal problems were more likely to experience a TS during PFPP. However, PFPP was significantly superior to PCT during follow-up, so that the two treatments were equally effective at the 24-month follow-up for both the primary and secondary outcomes. Both treatments were well tolerated with no differences in drop-out rates. Further gains during the follow-up phase did not appear to be associated with further treatment seeking. High rates of employment were present at every assessment point, but significant improvement were observed for Work Ability at post-treatment and follow-up, apparently mediated by a reduction in self-reported panic symptoms during the treatment phase. Thus, it appears that a clinically meaningful reduction in panic symptoms is associated with significant improvements in the patient's beliefs about their capacity in meeting current and future work demands.

Key words

Panic Disorder, Cognitive Behavioural Therapy, Psychodynamic Therapy, Work Ability, Termination Setback

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Lund, oktober 2022

Thomas Nilsson

Abstract

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Summary in Swedish

I Sverige kommer ungefär 2-3 % av befolkningen någon gång att drabbas av paniksyndrom med eller utan agorafobi (PS/A), ett tillstånd som består av plötsliga, oväntade panikattacker som följs av ihållande rädsla för nya attacker och/eller betydande livsstilsförändringar. PS/A debuterar oftast i slutet av tonåren eller i tidig vuxenålder och ger om den förblir obehandlad ofta kroniska psykiska besvär, sociala svårigheter, nedsatt studie- och arbetsförmåga, generella hälsoproblem samt ökad risk för förtidig död. Kognitiv beteendeterapi (KBT), däribland Panic Control Treatment (PCT), är den mest utvärderade och rekommenderade psykologiska behandlingen, men långt ifrån alla patienter vill gå i eller blir hjälpta av denna behandling. En lovande psykologisk korttidsbehandling för PD/A är Panic Focused Psychodynamic Psychotherapy (PFPP). Tre randomiserade kontrollerade studier (RCT) på PFPP har visat på jämförbara resultat med KBT för paniksyndrom upp till 12 månader efter behandling. Väldesignade studier, genomförda i den reguljära vården av för terapierna oberoende forskare, där PFPP och KBT jämförs med långa uppföljningar av psykiatriska symtom och funktionsnivå behövs.

Projekt POSE (Psychotherapy outcome and Self-selection Effects) genomfördes med patienter och behandlare från primärvård, psykiatri och ungdomsmottagningar under åren 2010 till 2019. Studien hade en dubbelrandomiserad forskningsdesign (Doubly Randomized Clinical Preference Study, DRCPT) för att testa om patientpreferenser för antingen PCT eller PFPP påverkade behandlingarnas effektivitet. Vuxna (n=221) med PD/A som huvuddiagnos fördelades slumpmässigt till någon av följande: 1) att få välja antingen PCT eller PFPP (Självval); 2) att slumpmässigt fördelas till PCT eller PFPP (Randomisering); eller 3) till en 3-månaders väntelista inför behandling. De primära utfallsmåtten var Panic Disorder Severity Scale (PDSS), arbetsstatus och sjukfrånvaro. Utöver detta undersöktes ett antal sekundära utfallsmått. Deltagarna i studien bedömdes före behandling och följdes sedan upp vid avslutad behandling samt vid 6-, 12- och 24-månader. Behandlingarna utfördes av 45 terapeuter utbildade i antingen PFPP eller PCT. Denna avhandling använder data från Project POSE för att belysa tre syften: 1) den relativa effekten av PCT och PFPP vid avslut och under två års uppföljning; 2) att utforska de skillnader som veckovisa, självrapporterade paniksymptom i PCT och PFPP under behandlingsfasen visade på; samt 3) att undersöka effekterna av PCT och PFPP på arbetsförmåga vid avslut och under uppföljningsperioden samt arbetsförmågans eventuella samband med förbättringar i PD/A under behandling.

Studie I är projektets studieprotokoll och presenterade de teoretiska och empiriska motiven för en DRCPT på PD/A med långtidsuppföljningar av psykiatriskt mående och funktionsnivå. Studie II presenterar de primära och sekundära resultaten för Projekt POSE vid avslutad behandling samt under uppföljningarna. Studie III är en explorativ undersökning av en försämring i paniksymptom under avslutningsfasen av PFPP (Termination Setback – TS) och de behandlings- och patientegenskaper som kan hjälpa till att förklara denna TS. Studie IV presenterar resultaten för självrapporterad arbetsförmåga (Work Ability Index, WAI) och dess relation till symptomförändring under behandlingen samt arbetsstatus och sjukfrånvaro under uppföljningen.

Vid avslut och under uppföljning var det, mot förväntan, inga signifikanta skillnader för de som fick välja sin behandling jämfört med de som slumpmässigt fördelats till en av de två behandlingarna. För vidare analys och diskussion av preferensfrågan i projektet se Martin Svensson avhandling Preference Effects in the Treatment of Panic Disorder från 2021.

Både PCT och PFPP visade på kliniskt signifikanta förbättringar för primära och sekundära utfallsmått vid avslut, jämförbara med resultaten från tidigare studier av de två terapierna. För paniksymptom var PCT signifikant överlägsen PFPP vid behandlingarnas avslut, möjligen på grund av den TS som inträffade för patienter i PFPP. De deltagare som hade mindre av undvikande anknytning och mindre av allvarliga interpersonella problem var mer benägna att få en TS under PFPP. Under den två år långa uppföljningen efter behandling var PFPP signifikant bättre än PCT vad gäller förbättring i paniksymptom så att de båda behandlingar var lika effektiva vid 24-månadersuppföljningen. Båda behandlingarna tolererades väl och det fanns inga skillnader i avhopp under behandlingarna. Förbättring under uppföljningsfasen berodde inte på ytterligare behandling. Även om sysselsättningsnivån var hög, d.v.s. att de flesta hade arbete eller var i studier, vid samtliga bedömningar, förbättrades deltagarnas upplevda arbetsförmåga tydligt av behandlingarna. Denna förbättring medierades av självrapporterade paniksymptom under behandlingsfasen. Det verkar som att en kliniskt meningsfull minskning av paniksymptom är förknippad med betydande förbättringar i patientens upplevda förmåga att möta nuvarande och framtida arbetskrav.

List of Studies

I. Sandell, R., Svensson, M., Nilsson, T., Johansson, H., Viborg, G., & Perrin, S. (2015). The POSE study - panic control treatment versus panic-focused psychodynamic psychotherapy under randomized and self-selection conditions: study protocol for a randomized controlled trial. *Trials*, *16*(130). DOI: 10.1186/s13063-015-0656-7

II. Svensson, M., Nilsson, T., Perrin, S., Johansson, H., Viborg, G., Falkenström, F., & Sandell, R. (2021) The effect of patient's choice of cognitive behavioural or psychodynamic therapy on outcomes for panic disorder: A doubly randomised controlled preference trial. *Psychotherapy and Psychosomatics*, *90*(2), 107-118. DOI: 10.1159/000511469

III. Nilsson, T., Falkenström, F., Perrin, S., Svensson, M., Johansson, H. & Sandell, R. (2021). Exploring termination setback in a psychodynamic therapy for panic disorder. *Journal of Consulting and Clinical Psychology*, *89*(9), 762–772, DOI: 10.1037/ccp0000678

IV. Nilsson, T., Svensson, M., Falkenström, F., Perrin, S., Johansson, H., Viborg, G. & Sandell, R. (Unpublished). Effects of Two Brief Panic-Focused Psychotherapies on Work Ability in a Doubly Randomized Clinical Trial

Abbreviations

AS = Anxiety Sensitivity
BDP = Brief Dynamic Psychotherapy
CBT = Cognitive Behavioural Therapy
DIT = Dynamic Interpersonal Therapy
DRCPT = Doubly Randomized Clinical Preference Trial
DSM = Diagnostic and Statistical Manual
ECR-R = Experiences in Close relations – Revised
ES = Employment Status
IIP = Inventory of Interpersonal Problems
MADRS-S = Montgomery Åsberg Depression Rating Scale, Self-Report Version
MI = Mobility Inventory for agoraphobia
PCT = Panic Control Treatment
PD = Panic Disorder
PD/A = Panic Disorder with or without Agoraphobia
PDSS = Panic Disorder Severity Scale
PDSS-SR = Panic Disorder Severity Scale – Self Report
PDT = Psychodynamic Therapy
PFPP = Panic Focused Psychodynamic Psychotherapy
POSE = Psychotherapy Outcome and Self-selection Effects
PROMs = Patient Reported Outcome Measures
RCT = Randomized Controlled Trial
RTW = Return to Work
SCID = Structured Clinical Interview for DSM-IV
SDS = Sheehan Disability Scale
SMD = Standardized Mean Difference
TS = Termination Setback
WA = Work Ability
WAI = Work Ability Index
WAI-SR = Working Alliance Inventory – Short Revised

Introduction

Panic Disorder with and without Agoraphobia

Anxiety as a clinical phenomenon and subject of research, separate from depression, began to draw the attention of medical doctors and the emerging field of psychiatry in the second half of the nineteenth century. In 1879, Henry Maudsley, a pioneering English psychiatrist, described a "melancholic panic" and this is the first time the term panic is used in psychiatry (Nardi & Freire, 2016). Toward the end of the 19th century Sigmund Freud described the "angstneurose" (anxiety neurosis). Later in *Inhibitions, Symptoms and Anxiety* 1926 he described traumatic anxiety as "an experience of helplessness on the part of the ego in the face of an accumulation of excitation, whether of external or of internal origin, which cannot be dealt with" (Freud, p. 81), a description that, according to Nardi and Freire (2016), broadly captures the experience of what we today term a panic attack. Starting with Pavlov and Watson in the 1920s and forward, experimental and clinical studies, drawing on associative learning theory models, demonstrated the acquisition and extinction of fearfulness in response to specific (non-dangerous) stimuli in animals and humans, leading to the development of Cognitive Behavioural Treatments (CBT) for anxiety disorders (Mineka & Zinbarg, 2006). In the late 1950's, Donald Klein found that depressive patients treated with imipramine, a tricyclic antidepressant, became less acutely anxious and made fewer visits to the nursing station due to feelings of being sick and dying (Nardi & Freire, 2016). These and similar observations led to the first trials of imipramine of panic attacks (instead of anxiety attacks) and to the introduction of Panic Disorder (PD) in the third edition of the Diagnostic and Statistical Manual (DSM-III; American Psychiatric Association, 1980) published in 1980 (Nardi & Freire, 2016).

Since its inclusion in DSM-III, the core features of PD have remained largely unchanged. When this PhD research program began, the latest version was the fourth, text revised edition (DSM-IV-TR; American Psychiatric Association, 2000), in which PD was defined as recurrent unexpected panic attacks followed by fear of future attacks, and causing marked impairment in functioning. In DSM-IV-TR (APA, 2000) a panic attack is a defined as a discrete period of intense fear or discomfort in which at least four of 13 possible symptoms develops rapidly and peak within 10 minutes: palpitation, sweating, trembling, sensations of shortness of breath, feeling of choking, chest pain, nausea or abdominal distress, dizziness or

lightheaded, de-realization or depersonalization, fear of losing control, fear of dying, numbness and finally chills or hot flashes.

Individuals with PD were categorized as having PD with Agoraphobia (PD/A) or without Agoraphobia (PD), the former involving an intense fear and avoidance of, or enduring with extreme distress, places where panic attacks are more likely to occur, and from which escape will be either difficult or embarrassing (APA, 2000). Agoraphobia also existed as a separate diagnostic category in DSM-IV-TR. This tri-fold division (PD, PD/A, Agoraphobia) was changed in DSM-5 (American Psychiatric Association, 2013) to two diagnoses: Panic Disorder and Agoraphobia. The criteria for the two diagnoses however remained unchanged from the previous edition. Throughout this thesis the acronym PD/A is used to refer to PD with or without Agoraphobia as defined in DSM-IV-TR, as these were the diagnostic criteria used when participants were originally recruited to the research program, and for the sake of continuity, used at post-treatment and the follow-up assessments.

PD/A is common in the general population, with a lifetime prevalence of approximately 2-5% (Bandelow & Michaelis, 2015; Goodwin et al., 2005). In clinical samples the prevalence is substantially higher, for example 10% in individuals referred for a mental health consultation and 60% in those attending a cardiology clinic have PD/A (APA, 2000). PD/A tends to onset between late adolescence and 35 years of age, a period in life with expectancies of independency, work, higher education, and self-sufficiency. Onset in childhood and after 45 are unusual but do occur (APA, 2000). The course is known to be waxing, waning and often chronic with great demands on health service resources, especially if the condition is untreated (Durham et al., 2012). PD occurs about twice as frequently in women as men, while women are three times more likely to be affected by PD with Agoraphobia (APA, 2000). The presence of Agoraphobia is associated with increased PD severity and poorer outcomes than PD alone (Kessler et al., 2006).

PD/A rarely occurs alone with estimates of some form of psychiatric comorbidity as high as 80%, most often depression or another anxiety disorder (de Jonge et al, 2016). For example, Breilmann et al. (2019) 68% suffer (concurrently) with Generalized Anxiety Disorder and 50% with Major Depression. When PD/A is comorbid with any other mental illness the risk for unnatural death (accidents, suicide and homicide) is increased and if comorbid with substance abuse the risk further increases (Chang et al., 2022). The presence of depression is associated with more severe and frequent panic attacks and depressive episodes, and involve a substantially higher risk of suicide attempts compared to with those with depression or panic alone (Martini et al., 2011). In a systematic review Navinés (2016) found that 44.3% of adults with PD/A had a comorbid personality disorder diagnosis, most frequently disorders from cluster C (Avoidant, Dependent, Obsessive-Compulsive), then from clusters B (Antisocial, Borderline, Histrionic, Narcissistic) and finally from cluster A (Paranoid, Schizoid, Schizotypal). The author found that the prevalence of personality disorders was highest (61.8%) when the individual had

both PD/A and another anxiety disorder or major depression, once again with disorders from cluster C being most common.

Anxiety disorders (including PD/A) are now recognized as one of the leading causes of disability globally (Yang et al., 2021) with excessive costs for the society (Kessler et al., 2010). Findings from the longitudinal Netherlands Study of Depression and Anxiety (NESDA; Penninx et al., 2021) suggest that the type of anxiety disorder appears to be of less importance in terms of disability than are the number of anxiety disorders, their severity and chronicity. Nevertheless, studies find that individuals affected by PD, and particularly those with PD and Agoraphobia, experience high levels of social/marital difficulties, diminished work ability (WA), financial instability, and are at elevated risk of substance use, general health problems and, early mortality (de Jonge et al., 2016; Goodwin et al., 2005; Markowitz et al., 1989).

Assessment of PD/A

Following the *National Institutes of Health Consensus Development Conference on the Treatment of Panic Disorder,* Shear and Maser (1994) published a guideline for assessment of PD/A in clinical trials that has defined this area for more than two decades. The authors recommended the Structured Clinical Interview for DSM-IV to establish the presence or absence of PD/A and diagnostic comorbidity (SCID-I; First et al., 1996) and the 7-item, clinician-rated Panic Disorder Severity Scale to assess PD severity (PDSS; Shear et al., 1997). The conference could not agree on how to define response to treatment and remission (irrespective of treatment), or whether remission was at all possible (Shear & Maser, 1994). Later, Furukawa et al. (2009) proposed that response should be defined as a ≥40% pre-to-post-treatment reduction in total PDSS scores, and remission as a total score on PDSS ≤ 5.

Shear and Maser (1994) recommended the 26-item self-report Mobility Inventory for Agoraphobia (MI; Chambless et al., 1985); for general functioning, the three-item self-report Sheehan Disability Scale (SDS; Sheehan, 1983). It has long been recognized that individuals with PD/A often have a heightened awareness of, and a tendency to catastrophize, normal bodily sensations and functions, termed Anxiety Sensitivity (AS), with changes in AS being important to treatment outcome (McNally, 2002). Two commonly used self-report measures of AS are the 17-item Body Sensations Questionnaire (BSQ; Chambless et al., 1984) and the 16-item Anxiety Sensitivity Index (ASI; Arnau et al., 2009).

Finally, as there was little available evidence about the long-term course of PD/A and the effects of panic-focused interventions, the conference recommended that all panic-focused treatment trials should include at least a12-month follow-up assessment including the above recommended measures, and efforts to monitor and

identify the impacts of further treatment seeking during the follow-up period (Shear & Maser, 1994)

General etiological models of PD/A

PD/A may have multiple etiologies and likely arises from interactions between genetic, epigenetic, somatic (including neural), environmental (including negative life events/trauma), and psychosocial risk factors (Breilmann et al., 2019). A further complication arises when trying to identify specific etiological factors, like genetics, in that such a high proportion of PD/A sufferers have another psychiatric or physical condition (see above) (Ask et al., 2021; Kim & Kim, 2018). In general, twin studies find heritability estimates in the range of 40%, with approximately 60% owing to shared and non-shared environmental effects (Roy-Byrne et al., 2006), but again these contributions are not unique to PD/A (Ask et al., 2021).

Brain studies have identified irregularities in the structure, functioning, and communication in the limbic system and frontal cortex region (among others), but again these are not unique to PD/A because of the high rates of comorbidity in individuals with PD/A (Dresler et al., 2013; Sobanski & Wagner, 2017). Researchers have long posited a diathesis-stress model involving a heightened and inborn sensitivity to physiological cues and challenges, possibly reflecting a false suffocation alarm from owing to hypersensitivity to carbon dioxide (Breilmann et al., 2019; Klein, 1993), potentially indexed by an anxious temperament early in childhood or anxious sensitivity and neuroticism in adulthood (Roy-Byrne et al., 2006). The stressors may include exposure to extremely stressful life events, such as loss/separation, physical/sexual abuse and other maltreatment, or persistent and upsetting stress from any number of current factors (health, interpersonal, work), all of which may contribute to elevated levels of physiological arousal and vulnerability to the occurrence of panic attacks and the development of PD/A (Busch et al., 2012; Roy-Byrne et al., 2006).

Overview of treatments for PD/A

Medication

Short-acting but potent benzodiazepines have long been prescribed to individuals with anxiety disorders, including PD/A, but are now recognized as having potentially serious side-effects including addiction and post-withdrawal rebound effects for some individuals (Wick, 2013). Today, antidepressant medications are recommended as the first-line pharmaceutical treatments for PD/A by healthcare bodies around the world, including the American Psychiatric Association (2009) and the UK National Institute for Health and Care Excellence (NICE, 2011). These antidepressants include serotonin and norepinephrine reuptake inhibitors (SSRIs/SNRIs) as well as older tricyclic antidepressants (TCAs) (APA, 2009; Baldwin et al., 2014; Breilmann et al., 2019).

As for the evidence for pharmacological interventions for PD/A, a Cochrane Collaboration review by Imai et al. (2016) found no differences between psychotherapy and antidepressants or benzodiazepines, in terms of short-term remission, short-term response or drop-out. However, the number of identified studies were small (K: 16) and no study in the review reported on follow-ups after immediate termination or other outcome indicators such as incidence of dependence and withdrawal symptoms. Another Cochrane review found evidence to support the use of combined therapy (antidepressants plus psychotherapy) or psychotherapy alone, but not medication alone, as a first-line treatment for PD/A (Furukawa et al., 2007). However, subsequent meta-analytic reviews (Bighelli et al., 2016; Watanabe et al., 2009) have not found this superiority and no treatment guidelines advocate combined treatments as a first choice (APA, 2009; NICE, 2011). According to the recommendations from the British Association of Pharmacology (BAP) medical treatments for PD/A have side-effects, are not considered to be definitive, and should merely be seen as a symptomatic treatment (Baldwin et al., 2014). However, somewhat contradicted in a meta-analysis of follow-up studies by Bandelow et al. (2018) that found enduring effects for CBT and other psychotherapies as well as for medication and pill and psychological placebo.

While antidepressant medicines (and benzodiazepines) are effective treatments for PD/A, many affected individuals refuse to take them, or discontinue their use once prescribed because of concerns about side effects and dependency (Farach et al., 2012; Furukawa et al., 2007). For example, one third of 308 eligible patients refused to participate in a large RCT comparing CBT to imipramine (a tricyclic antidepressant) because they were unwilling to take imipramine, whereas only one eligible patient refused because of the possibility of being randomized to CBT (Hofmann et al., 1998).

Pharmacotherapy remains an important treatment option, especially when there are no other treatment options available, but pre- and post-treatment attrition, adverse effects and the durability off the effects of pharmacotherapy remains a significant understudied concern (e.g. Baldwin et al., 2014; Bighelli et al., 2016; Breilmann et al., 2019; Imai et al., 2016).

Psychological treatments for PD/A

Since 2007, there have been six systematic reviews of psychological treatments for PD/A carried out by the Cochrane Collaboration. The latest (Pompoli et al., 2016) identified 54 RCTs: CBT, 32 studies), Behaviour Therapy (BT, 12 studies), Physiological Therapies (PT, 10 studies), Cognitive Therapy (CT, 3 studies), Supportive Psychotherapy (SP, 3 studies), Psychodynamic Therapy (PDT, 2 studies), Interpersonal Psychotherapy (IPT, 2 studies), Eye Movement Desensitization Reprocessing Therapy (EMDR, 2 studies). There was considerable heterogeneity across trials, particularly for therapies with fewer RCTs, as well as evidence of researcher allegiance effects. While there was some evidence in favour of CBT and PDT for remission and response 12-24 months post-treatment, the authors concluded: a) that no "unequivocal" evidence exists to support the superiority of one form of psychological treatment over another; and b) that further comparative trials, including non-CBT interventions, are needed before firm conclusions can be drawn. A later network meta-analyses on psychotherapies for PD/A by Papola et al. (2021) found that panic-focused CBT and Panic Focused Psychodynamic Psychotherapy (PFPP) had the best quality evidence of efficacy, were acceptable to patients, and recommended both to be offered as first line psychotherapies for PD/A.

Cognitive Behavioural Therapy for Panic Disorder

CBT is the most well-studied treatment for PD/A and has been a first-line, recommended, treatment for PD/A for over 30 years (APA, American Psychiatric Association, 2009; National Institute for Health and Care Excellence, 2011; 2016). Within an overall CBT framework, two models have tended to dominate the literature and they differ primarily in the extent to which they assert a "causal" role for panic-specific beliefs and the prioritization/use of standard cognitive restructuring techniques in therapy. The cognitive model developed by the British researcher David Clark (1986) emphasizes a causal role for panic-specific catastrophic beliefs that arise from a tendency to misinterpret benign bodily sensations as threatening. The origin of these tendencies and panic-specific beliefs is not a central focus of the model and are thought to be acquired through a range of social learning processes during childhood and adolescence (e.g., observation/modelling, direct experience) or as a consequence of single traumatic-

like experience of illness or loss at any time of life (Clark (1986)). These panic-specific beliefs produce idiosyncratic “safety behaviors” (e.g., vigilant monitoring of bodily sensations, avoidance of activities/situations believed to trigger panic, reassurance seeking) that have the unintended consequence of an increased sense of physical vulnerability and the likelihood of further panic attacks, resulting in a vicious cycle of fear and safety behaviors and the development of PD/A. Psychoeducation about PD/A and the model is followed by therapist-led exposures (often termed “behavioral experiments”) and standard cognitive restructuring techniques to elicit and modify panic-specific beliefs and safety behaviors (Clark, 1996).

The dominant “behavioral” or CBT model is the vulnerability-stress model originally proposed by the American researchers Michelle Craske and David Barlow (Craske and Barlow (1988). According to this model, individuals may be born with higher levels of autonomic reactivity and over time develop a "sensitivity” to their autonomic responses, such that they are more aware of and monitor bodily activities than those with lower levels of what is termed “anxiety sensitivity” (Craske & Barlow, 2006). Through classical conditioning processes, fear/anxiety responses become associated with a range of benign physical sensations, either gradually or through one-off traumatic conditioning (e.g., becoming intensely physically sick, losing a loved-one), with exaggerated/catastrophic beliefs about the meaning of bodily sensations and one’s own fear arising from these experiences for some (Bouton et al., 2001; Roy-Byrne et al., 2006). As in the cognitive model, panic-specific beliefs may exacerbate the fear response but it is avoidance/escape behaviors that prevent extinction of the fear response to benign bodily sensations and increase the likelihood of developing PD/A.

The treatment developed by Craske and Barlow for PD/A, termed Panic Control Treatment (PCT; Craske & Barlow, 2006), is delivered over 12 weeks involving weekly individual sessions lasting 60 minutes, extended to 90-120 minutes when doing therapist-led exposures. Psychoeducation, also addressing beliefs and avoidance behaviors, is followed by brief training in controlled breathing [now largely de-prioritized in the model/treatment], therapist-led interoceptive exposures (gradual), and prescribed homework involving approaching feared situations while refraining from escape/neutralizing behaviors. This format, or variants of the PCT protocol, have been shown to be effective at post-treatment and 12-24-month follow-up, when compared to placebo and medicine, and when delivered in a variety of settings (Barlow et al., 2000; Fairholme et al., 2017; Furukawa et al., 2007; Pompoli et al., 2016).

As noted above, both cognitive and CBT approaches to PD/A involve psychoeducation about the nature of PD/A and the treatment model followed by therapist-led exposures to panic cues while refraining from all avoidance/escape/safety behaviors, in addition to efforts to identify and modify panic-specific beliefs that vary between the two approaches (Pompoli et al., 2016).

Nevertheless, the latter two interventions - *interoceptive exposure* and *cognitive restructuring* - delivered in *face-to-face therapy* were identified as the most important (treatment-active) components in successful CBT for PD/A in a dismantling study by Pompoli et al. (2018).

Psychodynamic Therapy for Panic Disorder

Two small studies have been done on Brief Dynamic Psychotherapy (BDP) for PD/A. The first study (Wiborg & Dahl, 1996) showed that clomipramine combined with BDP reduced the relapse rate in PD compared with clomipramine only. The second study by Martini et al. (2011) showed that BDP combined with antidepressant was superior to Brief Supportive Therapy combined with antidepressant for patients with PD/A with concurrent depressive symptoms. The BDP used in the two studies focused on enhancing the patient's insight of intrapsychic and interpersonal repetitive conflicts concerning autonomy and separation and associated affects, facilitated through therapist interpretation and clarification, and linking of these. A quite similar approach as in PFPP developed by Milrod and colleagues (Milrod et al., 1997). PFPP is a manualized, diagnose specific psychodynamic psychotherapy for adults with PD/A that consists of twice weekly 45 minute sessions and is delivered over 12 weeks (24 sessions). In the Cochrane review by Pompoli et al. (2016), the two studies on PDT were evaluations of PFPP (Beutel et al., 2013; Milrod et al., 2007). Since then one additional large RCT-studies on PFPP has been published by Milrod et al. (2016) and the treatment has shown positive results both for immediate outcome (Milrod et al., 2016; Milrod et al., 2007), and outcomes up to 12 month post treatment. (McCarthy et al., 2018).

The etiological model of PD/A in PFPP is similar to PCT, in the sense, that it draws on a vulnerability-stress model focused on neurophysiological vulnerability, temperamental characteristics, and childhood experiences (Busch et al., 2012). Specifically, vulnerable individuals will be easily frightened by (real or imagined) loss of love or protection, or separation from their caregivers, with the risk of developing a sense of fearful dependency on them. This tendency may arise from high levels of trait-based fear of the unfamiliar or from traumatic childhood experiences of loss, abandonment threats or abuse. This creates an ambivalent attachment conflict between excessive dependency (that is not met) and the need and urge for autonomy (also not met), with associated feelings of anger and disappointment towards the caregivers. As these hostile feelings are experienced as a treat to the relational bond with the caregiver the child will unconsciously use defence mechanism to change or get rid of them. However, these underlying emotional conflicts will persist and fuel the anxiety and the panic reactions when triggered in close relationships or by fears of autonomy. Avoidance of negative affect may also impact the development of mentalization as the ability to know the minds of self and others gets limited by avoidance of these "bad" but essential feelings and thoughts. Overall, these factors

contribute to the risk of getting panic attacks when later in life experiencing stressful life events, loss, or threat to an important relation.

Long-term outcomes of psychotherapies for PD/A

In the Cochrane review Pompoli et al. (2016) concluded that CBT and PDT had the highest rates of response and remission in the long term, suggesting that these two treatments has more stable effects than other psychological treatments for PD. In a systematic review and meta-analysis on long-term outcomes of CBT for anxiety disorders van Dis et al. (2020) found small effect sizes favouring CBT over control conditions for PD for follow-ups within 1 to 12 months, beyond 12 months no evidence of superiority for CBT was found. In the ambitious project with eight Scottish CBT trials for anxiety disorders by Durham et al. (2012), 40% of the patients stayed recovered, with no or little extra treatment, at the follow-ups commenced between two to eleven years after inclusion, in the four studies that were on PD/A. However, all patients in three of the four studies (359 of 454 participants with PD/A) were treated by the same single therapist, which questions the generalizability of these findings. Moreover, less than half of those originally enrolled could be reached and assessed, and Durham et al. (2012) suspects that their follow-up sample was biased towards a more positive picture of the overall outcome. In a large RCT by Gloster et al. (2013) on CBT the 24-month follow-up showed that outcomes on all panic-related measures were somewhat lower than 6 months after treatment, yet impressive 75% of the participants were still treatment responders at 24 months. Less is known of the long-term effects of PDT treatment for PD/A, as the only study, on PFPP, with a 12-month follow-up was restricted to post-treatment responders (McCarthy et al., 2018). Most responders in PFPP stayed responders at 12-month, and the same applied for the participants that got PCT.

In summary, CBT in general and PCT specifically are highly researched treatments that have showed robust effects for PD/A and are the form of treatment that most often is recommended as a first-line by international guidelines. (APA, 2009; National Institute for Health and Care Excellence, 2011; BAP, 2014). However, not all patients can tolerate this approach and approximately 30-40% fail to achieve a clinically meaningful reduction in symptoms in CBT (Pompoli et al., 2016). Other forms of psychotherapy are less well researched for PD/A, even though the available evidence suggests that they yield effect sizes comparable to CBT (Papola et al., 2021; Pompoli et al., 2016). Psychodynamic psychotherapy in the form of PFPP has shown evidence of efficacy for PD/A in: a pilot trial (Milrod et al., 2007), a subsequent large scale RCT (Milrod et al., 2016), when implemented in routine care (Beutel et al., 2013) and responders seems to stay improved at 12-month (McCarthy et al., 2018). Additional large scale RCTs involving different forms of psychotherapy for PD/A, including PFPP and other PDTs, are needed, especially with long-term follow-up.

Treatment preferences for psychiatric disorders

In the last decades healthcare professions have been encouraged and called upon to include patient preferences as an essential part of best-practice standard (American Psychological Association, 2006). The three key components in evidence-based practice (EBP) are best available research, clinical expertise and the patients' characteristics and preferences. APA (2006) states that treatment decisions should be made with the goal to maximize patient influence on the choice.

Swift et al. (2018) defines patients' preferences in psychotherapy as the specific conditions and activities wanted in their treatment experience. These can be grouped into three broad categories. First, *activity preferences*, the activities that the individual hope to be engaged in with their therapist throughout therapy. Second, *treatment preferences*, type of intervention preferred, this could be different forms of psychotherapy or psychotherapy versus medication or self-guided help or an individual or group format. Last, *therapist preferences*, the type of practitioner a patient wants to work with, based on demographic and personality characteristics.

Patient treatment preferences have been found to be positively associated with treatment outcomes in psychotherapy. In a meta-analysis Swift et al. (2011) found a positive effect for primary outcome and that significant fewer patients dropped out if the treatment matched the patients preference. The effect on outcome from preference were found to vary by psychiatric diagnoses; for anxiety disorders (k = 6) d = 0.49, for depression (k = 12) d = 0.35, and for substance abuse (k = 8) d = 0.34. However, they also found a lower effect size when comparing one psychotherapy with another form of psychotherapy, d = 0.21 as when comparing psychotherapy versus pharmacotherapy, d = 0.36. In contrast, Lindhiem et al. (2014) failed to find any significant moderators of preference effects, including study design and client diagnosis (mental health versus other). A later meta-analysis (Swift et al., 2018) confirmed the benefits of receiving one's preferred treatment (*d* = 28) and that preference had larger influence on outcome for anxiety or depression than those treated for behavioral health problems, substance use problems or psychotic disorder.

However, the beneficial effects of patient preferences for psychotherapy have often been evaluated in relation to pharmacotherapy or in relation to variations in same form of psychotherapy, most often CBT. With respect to PD/A, the three existing studies (Bakker et al., 2000; Perreault et al., 2014; Spinhoven & Van Dyck, 1997) provides very limited information about preference effects as all involved choice between different forms of CBT interventions or formats (one study also involved medicine) with designs that probably underestimate preference effects. In fine, very little is known about the effects of patient treatment preferences for any psychiatric disorder when the choice is between two distinct forms of psychotherapy as in this project.

Sudden losses in psychotherapy

Generally, outcome researchers in psychotherapy have assumed that progress is monotonic, following a dose-response-relationship. This assumption has been challenged or at least supplemented by studies investigating discontinuity of progress on the level of individuals using session reports (Barkham et al., 1993; Lutz et al., 2013; Schuler et al., 2021). For instance, in a sample of 1500 outpatients primarily suffering from anxiety and depression 23% of the patients experienced a sudden gain and 10% experienced a sudden loss (Lutz et al., 2013). The sudden gain and the sudden loss were defined to be a clinically meaningful and stable change from three sessions prior to three sessions following the sudden gain or loss. Sudden gains were more common early in therapy and sudden losses occurred over the course of treatment without any specific peak. They also found a lower probability for later sudden losses in patients with early sudden gains. (Lutz et al., 2013)

Termination of a psychological treatment, particularly if therapist-initiated, can for some patients be perceived as quite stressful and be accompanied by deterioration in symptoms among other reactions (Bostic et al., 1996). A therapist initiated termination is sometimes referred to as a forced termination as can often be the case in a RCT (Joyce et al., 2007). Quintana and Holahan (1992) showed that successful cases of counselling were less frequently terminated by external factors and more likely to end on a mutual decision when compared to unsuccessful cases. Successful cases were also associated with a greater therapeutic focus on the end phase and on the clients' earlier experience of loss. Such symptomatic impairment during the termination phase of psychotherapy is a phenomenon recognized as being of both theoretical and clinical importance and is a significant example of sudden loss. The occurrence and potential reasons for negative responses to termination have received the most attention in the psychodynamic literature (e.g., Busch et al., 2012; Joyce et al., 2007; Marx & Gelso, 1987; Nof et al., 2017; Safran & Muran, 2000; Strupp & Binder, 1984; Summers & Barber, 2010). As termination approaches, Strupp and Binder (1984) have suggested, patients through different actions try to dodge a possibly painful separation experiences. For example, they may bring up 'new' problems that 'urgently' require solutions and there may be a recurrence of the symptoms and problems that brought them to therapy. In regard to PFPP Busch et al. (2012) point to the same vicissitudes in the termination phase: "Termination permits reexperiencing of conflicts directly with the therapist…[with p]ossible temporary recrudescence of symptoms as feelings are experienced in therapy" (p. 60). Lemma et al. (2011a) have argued that patients in short-term PDT often develop intense feelings toward their therapist, partly driven by the present and unavoidable termination, and that these patients may experience intense feelings of separation that can contribute to strong negative anti-therapeutic and symptomatic reactions as termination approaches.

The occurrence of symptomatic deterioration during termination may negatively impact the process of continued recovery after termination. According to general psychodynamic theory, a mourning phase ensues after successful termination, which is suggested to result in the patient taking over important positive functions and objectives from the therapist and help the patient to continue on her/his own in a kind of self-therapy, (Falkenström et al., 2007; Lemma et al., 2011a), leading to recovery and further improvement (Milrod et al., 1997). But if this mourning process is halted due to strong and/or inflexible defences against feelings about the separation from the therapist, the post-treatment process may not be as successful.

The greater attention to the termination phase in PDT follows from the emphasis on the therapist-patient relationship as a therapeutic motor wherein the patient's feelings about the therapist and their relation are explored and clarified. Following from this emphasis, it is reasonable to consider that patients who have difficulties more generally with separation situations and interpersonal relationships may be at increased risk of experiencing a sudden loss or symptomatic setback during the termination of a PDT. Such vicissitudes are seen to play an important role in psychodynamic conceptualizations of PD/A (Milrod & Shear, 1991; Milrod et al., 1997; Shear, 1996). In partial support of these ideas, there is now a large body of evidence that finds an increased risk of PD/A among individuals who have suffered from childhood separation (Kossowsky et al., 2013) and/or have experienced interpersonal abuse or a significant loss at some time prior to the onset of PD/A (Klauke et al., 2010). Because few trials on PDT for PD/A have been carried out, the relationship between these interpersonal variables and therapy outcomes remains unclear, and the relationship of attachment and interpersonal difficulties to negative termination response in PDT or any form of therapy has not been examined.

We have found only one small study reporting symptomatic impairment during the final phase of therapy (Lemma et al., 2011b). For weekly measures of anxiety and depression the authors reported a clear decrease until a slight but significant tendency for increase in symptoms in the last few sessions of the treatment.

Work ability and mental health

Having a job, and the capacity to strive and succeed at it, are important factors in mental health. It offers the feeling of being needed and gives a daily structure, a working-role, relations, meaning, money and benefits – things that can contribute to a good life (Batic-Mujanovic et al., 2017; Ervasti & Venetoklis, 2010; Farré et al., 2018; Kessler et al., 2009). Contrariwise, as reported by Vågerö and Garcy (2016), unemployed are at higher risk for somatic and psychiatric illnesses and alcohol abuse, and the mortality rate increases due to higher risk of ill-health or suicide.

They also describe the "healthy worker effect", meaning that people with poorer somatic and mental health are less likely to be employed and more likely to lose their job if employed. Common mental disorders are highly prevalent in the working population and identified as a major cause of functional impairment, long-term work disability, and long-term absences from work (Hendriks et al., 2015; Iancu et al., 2013; Poulsen et al., 2017). If untreated, PD/A has many negative health and social consequences, including persistent occupational disability, especially if comorbid with other anxiety disorders or/and depression (Hendriks et al., 2015, 2016).

The concept of WA is inherently vague and may refer to several phenomena or indicators. Return to work (RTW) of people without a job or outside the labour force is one. Two recent meta-analytical reviews have found that RTW is difficult to achieve with mere clinical interventions (mostly CBT for depression) (Nieuwenhuijsen et al., 2020) or interventions (mostly CBT) specifically targeting RTW in common mental illness (Nigatu et al., 2016). A basic reason is probably that RTW is heavily influenced by societal and economic factors beyond the individual's personal resources (Brady et al., 2020; Elfering, 2006). Another aspect of WA is absenteeism, which is to be more than just occasionally absent from work due to illness according to Henderson et al. (2011), and the longer an individual is absent from their work, the less likely they are to return. For absenteeism Nigatu et al. (2016) found an effect in terms of decreased sick-leave days for the clinical interventions compared to control. A third aspect of WA is defined as an individual's physical and mental ability to meet the demands of their job (Ilmarinen, 2009). The most frequently used WA measure in occupational health science and in interventions studies today is the Work Ability Index (WAI; Brady et al., 2020; Ilmarinen, 2009). The WAI investigates a broad range of individual work-related factors like illnesses and other limiting conditions, sick listing, mental and physical demands, and resources. The WAI has been found to be a reliable and sensitive measure of WA and to predict a variety of both positive and negative work-related outcomes (Bokma et al., 2017; Brady et al., 2020; McGonagle et al., 2015).

Most intervention studies focusing on WA have focused on work-place-related interventions like increased employee control, physical exercise, stress and conflict management, or health promotion on the workplace (Joyce et al., 2016). Few manualized psychotherapy treatments have had WA as an explicit target. It is also rare to find studies with WA as a measured outcome of psychotherapy overall. Thus, little is known about the effects of psychotherapy on WA. The few RCTs that have been published on the subject were mainly done on CBT (Hallgren et al., 2015; Hange et al., 2017; Kaldo et al., 2017) or interpersonal psychotherapy (Niedermoser et al., 2020; Schramm et al., 2020) with depressed participants. PDT have been applied only in a comparison with solution focused therapy in a mixed depression and anxiety sample (Knekt et al., 2008).

When diagnosis-specific psychotherapies are concerned, such as PD/A-focused therapies like PCT and PFPP, little is known about their effectiveness on work-

related abilities and disabilities such as absences from work due to sickness, RTW and WA. Reducing symptoms per se does not necessarily improve these aspects of functioning. WA has seldom been investigated in trials of psychotherapy and no RCT has been found focusing on WA for PD/A.

General and Specific Aims

In sum, RCTs on PD/A with long-term follow-ups on all patients (Intention to treat, ITT) are rare when considering psychotherapy trials, and the generalizability of some of the studies done are questionable. There is a large amount of evidence that CBT treatments are effective up to 12 months after treatment. Little is known of the long-term effects of PDT treatment for PD/A. For WA we have found no study on psychotherapy for PD/A.

The overarching aim for this thesis is to contribute to the literature about psychiatric and work-related outcomes of two different forms of panic-specific psychotherapy. The specific aims are: 1) to investigate the relative efficacy of PCT and PFPP for PD/A post-treatment and in follow-ups to 24 months after treatment. The primary outcomes will be clinician rated panic severity, occupational status and sick leave, and the secondary outcomes: self-rated depression, and functional impairment; 2) to explore apparent differences in the trajectory of weekly, self-reported panic symptoms in PCT and PFPP during the treatment phase; 3) to investigate the effects of PCT and PFPP on WA as measured with WAI and its relations with improvements in PD/A.

A parallel PhD thesis by Svensson (2021) concerned itself with the first overarching aim in the Psychotherapy Outcome and Self-selection Effects project (POSE), namely self-choice and preference effects for the treatments. This doctoral thesis will therefore only briefly touch on that part of the project.

Study I: This is the published trial protocol that presents the theoretical background for, and design of, the study.

Study II: Presents the primary and secondary outcomes for Project POSE at post-treatment and all follow-ups for the study participants treated with PCT or PFPP under self-selected or randomized allocation to treatment conditions.

Study III: This study concerns itself with the resurgence of symptoms in PFPP towards the end of treatment and analyses the frequency and magnitude of such termination setbacks (TSs) and explores its possible predictors.

Study IV: This study evaluates the effects of PFPP and PCT on self-reported WA at post-treatment and follow-ups. The study also explores the relationship between WA and panic symptoms, employment, and sick leave.

Method

Design and Settings

Project POSE was a multicentre doubly randomized clinical preference trial (DRCPT) designed to test the effects of patient preference for one of two evidence-based psychotherapies for PD/A: PCT (Craske & Barlow, 2007) and PFPP (Milrod et al., 1997). Participants were randomly allocated to Choice of treatment, Random assignment to treatment, or to a low-frequency contact/wait-list Control condition. Participants allocated to Choice were provided well-balanced written information about the two treatments and then asked to choose either PCT or PFPP. The design thus included five groups, randomized to either PCT (RPCT) or PFPP (RPFPP), self-selected (Choice) to either PCT (CPCT) or PFPP (CPFPP), or to the Control group. The control condition was included to rule out the possibility that all conditions were equally ineffective in treating symptoms of PD/A. Participants allocated to Control were re-randomized to either the Choice or Random conditions after three months.

The trial was carried out between 2011 and 2019 in four regions in Sweden at outpatient psychiatry, primary health care, and youth counselling clinics. 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 self-refer on the projects website or be referred by their local mental health care provider. Individuals who expressed an interest were pre-screened for eligibility by phone and, if eligible, invited to a face-to-face diagnostic interview. All participants gave written informed consent to participate. Martin Svensson and Thomas Nilsson were responsible for running the sites and all assessments of patients from pre-treatment to the 24 month follow up.

Ethics and transparency

Project POSE was approved by the Regional Ethical Review Board in Lund (Ref: DNR-2010/88). Informed consent was obtained from every participant in the trial at intake assessment. The project was preregistered with ClinicalTrials.gov (NCT01606592)

Participants

Participants in the three empirical studies in this thesis were adults with PD/A recruited between November 2011 and May 2017. Studies II and IV used all available data from 221 patients randomized to Control, Choice or randomization condition from the five assessment points (pre- and post-treatment, 6-, 12-, and 24-month follow-up) collected between 2010 and 2019. Study III used data from the 217 treated patients from the five assessment points plus weekly in-treatment data.

Inclusion and Exclusion Criteria

Inclusion criteria were: 1) aged 18 to 70 years; 2) current principal DSM-IV diagnosis of PD/A, including at least one panic attack per week during the three weeks preceding trial assessment. 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 (Brown, 2004) and: 2) score ≥ 4 on at least one question from the Avoidance-Alone Subscale of the Mobility Inventory for Agoraphobia (Chambless et al., 1985) 3) if medicated, staying on a stable dose for at least one month prior to trial inclusion and willing to keep medication dosage stable throughout the trial treatment phase; 5) not being in psychotherapy and willing to refrain from starting any new treatment during the treatment phase; 6) ability to complete the treatment phase within 16 weeks. Exclusion criteria were: 1) a current substance abuse/dependence disorder (or in remission for at least 12 months prior to trial inclusion); 2) current psychosis, delusions, mania, or autism diagnosis; 3) acutely suicidal 4) a history or current presentation of a clinically significant medical condition (e.g. heart decease, dementia) sufficient to cause cognitive or physical impairments if participating in treatment.

Interventions

The two treatments compared in the study are both manualized, time limited, and of equal length (12 weeks) and duration (around 1000 minutes), but with different session frequency and length of sessions as is described below.

Panic Control Treatment

PCT (Craske & Barlow, 2007) is a manualized, individual cognitive-behavioral treatment for adults with PD/A. In this trial PCT comprised 12-14 sessions,

completed in 10-16 weeks, with the first two weeks including two sessions and subsequent weeks one session each. Sessions were 60 minutes in length and extended to 90-120 minutes for sessions involving therapist-led exposure (total treatment duration = 780-1140 minutes). PCT involved: psychoeducation about the nature of PD and agoraphobia and training in self-monitoring of symptoms (sessions 1-2); building a hierarchy of agoraphobic situations (session 3); breathing retraining (session 4); cognitive restructuring techniques (sessions 4-6); in vivo exposure and exposure to internal sensations (sessions 6-13); and relapse prevention (session 14). Between-session homework assignments, done throughout treatment, involved symptom self-monitoring and after the first session therapist-led exposure and planned patient-led exposures.

Panic Focused Psychodynamic Psychotherapy

PFPP (Milrod et al., 1997) is a manualized, individual psychodynamic treatment for adults with PD/A. In this trial, PFPP comprised 19-24 sessions completed in 10-16 weeks, with two sessions per week. Individual sessions were 45 minutes in length (total treatment duration = 855-1080 minutes). PFPP proceeds in three 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 exploration of the patient's feelings/fantasies about past/present relationships and the 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 in the control condition were contacted over phone by a trial assessor every second week for a brief conversation about their general wellbeing and assessment of 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-randomization. Participants in the control condition were re-randomized to the Random or Choice conditions after three months.

Power-calculation

For the straightforward comparisons between the two active treatments (PCT and PFPP) and control, 25 patients per group would be needed to establish an effect size (SMD) of 0.8 at alpha = 0.05 and power = 0.80. This was conservative compared to the average effect size for psychological treatment for PD/A (d = 1.02, 95% CI = 0.86 to 1.18) reported by Sanchez-Meca et al. (2010) For the more complex comparison involving the interaction between assignment type (Randomization or Choice) and treatment type (PCT or PFPP) power calculations were performed using Power IN Two-level designs (PINT v. 2.12, September 2007) (Bosker et al., 2003) for change scores on the PDSS. Based on previous research on preference effects (Swift & Callahan, 2009; Swift et al., 2011), we assumed that choice would enhance the effect of the treatments when compared to randomized assignment, with an extra effect of SMD d = 0.4, at alpha = 0.05, power = 0.80. Then a total of 200 patients were required, the targeted recruitment was set at 216 to allow for attrition.

Randomization and masking

The allocation ratio to the Choice, Random and Control conditions was 4:4:1. Participants were allocated to the Choice, Random, and Control conditions at each clinic. At the end of the three-month Control condition, the re-allocation ratio to the Choice and Random conditions was 1:1. For the Random condition, a stratification procedure was used so that equal numbers of participants were allocated to PFPP and PCT at each clinic. Randomization was done using the software Research Randomizer (Urbaniak & Plous, 2010). In the Choice condition, participants were provided separate, 500-word written descriptions of the two 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, and had been piloted in a master thesis before the study commenced (Hultman, 2010).

Measures

We followed the guideline (presented in the introduction of this thesis) by Shear and Maser (1994) on how to assess and evaluate PD/A in clinical trials. At each time point - baseline assessment, post-treatment, 6-, 12- and 24-month follow-up - participants were interviewed, asked about possible psychiatric medication and to complete the self-report measurements. Sociodemographic information were asked for at intake and a full assessment with DSM-IV SCID I and II was done at intake

and 6 months follow-up. At post-treatment, 12- and 24-months follow-up the diagnostic assessment was limited to PD/A. Panic severity, agoraphobic avoidance, fear of bodily sensations, depression, functional impairment, general psychological symptoms and functioning, adult attachment and interpersonal problems were assessed at all assessment points. The PDSS-SR was used in weekly assessments during treatment. During treatment therapeutic alliance, treatment credibility, alexithymia and fear of bodily sensations were assessed. The measurements used in this thesis is seen in table 1 and will be presented below.

Table 1. Measurements used in this thesis by timepoint in the trial

Instrument	Intake	Week 1-11	Week 12	Month 6	Month 12	Month 24
SCID-I	X		X	X	X	X
SCID-II	X			X		
PDSS	X		X	X	X	X
PDSS-SR	X	X	X	X	X	X
MADRS-S	X		X	X	X	X
MI	X		X	X	X	X
SDS	X		X	X	X	X
WAI	X		X	X	X	X
ECR-R	X		X	X	X	X
IIP	X		X	X	X	X
WAI-SR	X	X	X			

Structured Clinical Interview for DSM-IV (SCID-I & SCID II)

SCID-I and SCID-II; (First et al., 1996; First, 1997) was used in studies II and IV to establish a PD/A diagnosis and psychiatric comorbidities at intake. The SCID-I and II have been found to have good psychometric properties and to be valid measures of psychiatric symptoms and personality disorders (Lobbestael et al., 2011). Reliability for a PD/A diagnosis between Martin Svensson and Thomas Nilsson was computed as Kappa coefficient = 1.00 for agreement, based on 10 videotaped SCID interviews.

Panic Disorder Severity Scale (PDSS)

The clinician rated PDSS was used to assess severity of PD/A in study II. The PDSS is a 7-item measure of the severity of the core features of PD/A over the past month (Shear et al., 1997) assessing the frequency of panic attacks, distress during panic attacks, anticipatory anxiety, agoraphobic fear and avoidance, body-sensation fear and avoidance, and impairment in work and social functioning. Items are rated on a 5-point scale (0-4) with higher scores indicating greater severity. The Swedish version of PDSS has excellent psychometric properties (Svensson et al., 2019).

Panic Disorder Severity Scale – Self Report (PDSS-SR)

The self-report version of the PDSS (PDSS-SR; Houck et al., 2002) is a seven-item self-report measure of PD/A severity over the past week used in study II-IV. It contains the same seven items and scoring system as the clinician-rated PDSS (Shear et al., 1997). Items are rated on a 5-point scale (0-4) with higher scores indicating greater severity. The correlation between the PDSS-SR and PDSS across all assessments was $r = .86$. The Swedish version has been validated and found to have good psychometric properties (Svensson et al., 2019).

Montgomery Åsberg Depression Rating Scale (MADRS-S)

MADRS-S (Montgomery & Asberg, 1979) is a 9-item questionnaire used in study II to assess the severity of depressive symptoms over the past three days. Each item is rated on a seven-point (0-6) severity scale; higher scores indicate higher levels of depression. A total score (0-56) is calculated with depression (mild) starting at 11 points. The MADRS has been validated and found to have good psychometric properties (Montgomery & Asberg, 1979).

Mobility Inventory for agoraphobia (MI)

The MI (Chambless et al., 1985) is a self-report instrument used in study II to assess the degree of agoraphobic avoidance. Respondents rate their level of avoidance on a five-point scale (1-5) in 24 places/situations when accompanied (Avoidance Accompanied) and when alone (Avoidance Alone). Means are computed separately for the items on the two subscales, and these scores are used for research purposes.

Sheehan Disability Scale (SDS)

The SDS (Sheehan, 1983) is a 3-item self-report measure used in study II to assess the extent of functional impairment in work, social life, and at home/family life over the past week. Each item is rated on an 11-point scale (0-10). A total score is computed with higher scores indicate higher levels of panic-related dysfunction. A Swedish translation has been used in research in Sweden (Bergstrom et al., 2010).

Work ability Index (WAI)

The WAI (Tuomi et al., 1998) is a self-report 10-item questionnaire used in study IV. The WAI covers various aspects of capacity for work: current WA compared with one's lifetime best (range 0-10); WA in relation to demands of the job (2-10); number of diagnosed illnesses or limiting conditions (1-7); impairment owing to diseases/illnesses or limiting conditions (1-6); number days on sick leave last year

(1-5); own prognosis of WA in 2 years' time (1-7); mental resources (1-4). Ratings are summed to an index varying between 7 and 49. Scores 7-27 are taken to indicate poor WA, 28-36 moderate, 37-43 adequate (or good), and 44-49 excellent WA. The WAI has been used extensively internationally in studies in various types of workplaces and has been found to predict a variety of work capacity indicators (Brady et al., 2020).

Experiences in Close Relationships-Revised (ECR-R)

The ECR-R (Fraley et al., 2000) is a 36-item questionnaire about adult romantic attachment style used in study III. The questionnaire has two subscales measuring attachment anxiety and avoidance in intimate relations. All items are rated on a 7-point scale (1-7). Higher scores on the two subscales indicate higher levels of anxious and avoidant attachment, respectively.

Inventory of Interpersonal Problems (IIP)

The IIP (Horowitz et al., 2000) is a 64-item self-rating scale used in Study III to asses relational problems. The questionnaire identifies a person's most salient interpersonal difficulties through eight subscales (Domineering, Vindictive, Cold, Socially avoidant, Non-assertive, Exploitable, Overly nurturant, and Intrusive). Each item is rated on 5-point (0-4) scale and higher scores indicates more interpersonal distress. The Swedish version of this scale has been validated and found to have good psychometric properties (Weinryb et al., 1996).

Working Alliance Inventory – Short Revised (WAI-SR)

The WAI-SR (Hatcher & Gillaspy, 2006) is a 12-item measure of three components of therapeutic alliance (task, goal, and bond) and was assessed by the patients at week 2, 6, and 12. Each item is rated on 7-point (1-7) with higher scores indicating better alliance. WAI-SR was used in study III.

Employment status and Absence

At every assessment point patients were asked to fill in their employment status (ES) and their amount of absences due to sickness the last three months (Absences).

Self-selection material in POSE

In the Choice condition, participants were provided separate, 500-word written descriptions of the two treatments. The treatment descriptions were composed with

the aim to be specific, well balanced, and easy-to-read presentations of PCT and PFPP. Each treatment description was comprised of three headed sections: 1) How is PD/A viewed in treatment; 2) How do you work in treatment; and 3) What results can you expect. For more information on this material see Svensson (2021).

Data Analysis

Study I

This study presents the background and the overview of the design and planned analysis for Project POSE. This paper also includes planned studies beyond the focus of this thesis; and some of these were presented in the PhD thesis by Martin Svensson (2021).

Study II

Post-treatment differences for the PDSS for participants in each treatment arm versus control were tested using one-way ANOVAs on unadjusted raw PDSS scores and post hoc analyses according to Dunnett's method. Change rate differences between the treatments in the random and choice conditions were examined using multilevel linear growth modelling to handle nested and missing data. All analyses were done using piecewise models, in which the overall trajectory was split up into two phases (during and after treatment). Linear, quadratic, and log-linear trajectory shapes were compared using Akaike's information criterion (AIC). Change in medication and additional treatment post-treatment were analysed. SMD for each segment was calculated according to Feingold (2015) as the difference between treatments in model-estimated change, divided by the observed SD at baseline across all groups. For the categorical variables: responder status, ES and Absence χ^2 tests were carried out. Data was analysed with SPSS (version 26) and Stata (version 16). All analyses were performed using all available data and no data points were excluded. The analyses of reported outcomes follow the intention-to-treat principle.

Study III

The occurrence of a sudden loss (in this study called a termination setback, TS) was assessed using Latent Growth Curve Modeling (LGCM; e.g., Bollen & Curran, 2005), a form of Structural Equation Modeling (SEM). As recommended in growth curve modeling (e.g., Singer & Willett, 2003) the trajectories of change in PCT and PFPP were first visually graphed. As a second step, the Bilinear Spline Model

(Kohli & Harring, 2013; Preacher & Hancock, 2015) was applied to identify the time-point for a potential break in the growth curves. To test mean differences in slopes between treatment phases (and treatments), a piecewise/segmented growth curve model with fixed loadings for two phases was specified, based on the breakpoint identified. Predictors of TS were entered to predict all three random effects for the treatment period (i.e., intercept and slopes for the two segments). To explore the relationship between TS and panic symptoms during follow-up the post-treatment measurements were included as distal outcomes. Analyses were conducted using Mplus 8th edition (Muthén & Muthén, 1998-2017). All analyses were performed using all available data. No data points were excluded. Sensitivity analyses were performed for therapist effects, missing data, and by analyzing only patients who were randomized to the respective treatment methods.

Study IV

Multilevel growth modeling (Singer & Willett, 2003) was used. All analyses were done using piecewise models, in which the overall trajectory was split up into two phases (during and after treatment). Nesting due to therapists was tested by adding random effects for therapists as a post-hoc sensitivity test. The growth models were estimated in Stata v.16 (StataCorp, 2019) using Restricted Maximum Likelihood. We also tested if changes in panic severity during treatment mediated changes in WAI. Test of mediation was performed using the PATHj module from the jamovi software, v. 2.0 (Gallucci, 2020). Finally, we assessed the relationships between WAI scores and self-reported ES and absences from work through logistic regression. All analyses were performed using all available data and no data points were excluded.

Research Studies

Study I – The POSE study – panic control treatment versus panic-focused psychodynamic psychotherapy under randomized and self-selection conditions: study protocol for a randomized controlled trial

Introduction

This study presents the trial protocol for the project. The prevalence of PD/A in Sweden is 2-3%, and the condition is one of the most frequent and debilitating causes of illness among Swedes aged 15 to 44 years (Swedish agency for health technology assessment and assessment of social services, 2005). Allowing patients to choose their treatment has been reported to have positive effects on outcome and dropout (Swift & Callahan, 2009; Swift et al., 2011), but this has seldom been tested in a rigorous controlled fashion. For the preference part of project POSE, see Svensson (2021). Another aim is to compare PCT, a CBT-treatment with a large evidence base for PD/A, and PFPP. These treatments have never been tested in a RCT in a Sweden and psychotherapy trials with long-term follow-ups are needed. Little is known about the impact of these evidence-based approaches on the functional disability that usually accompany PD/A such as WA, absences from work and difficulties returning to work.

Method

The project is a multicenter randomized clinical trial with PFPP (Milrod et al., 1997) and PCT (Craske & Barlow, 2007) for adult patients (aged 18-70 years) diagnosed with PD/A. The DRCPT, with a planned recruitment of 216 patients, will evaluate the effects of two methods of treatment assignment on PCT and PFPP at the end of treatment and at 6, 12 and 24 months after termination. At each clinic (outpatient psychiatry, primary health care, and youth guidance clinics) participants are randomized to either PCT or PFPP, choice between the two or to a low-frequency contact/wait-list control. Primary outcomes are changes in panic symptom severity as measured by the PDSS (Shear et al., 1997), ES, and sickness-related absences.

Secondary outcomes include changes in agoraphobic avoidance, depression, functional disability, and self-rated WA. As the assessor reveals the result of the randomization to the patient at baseline, the assessments after treatment will not be carried out blind to treatment condition. Therefore, all assessments will be recorded, and a substantial proportion of these assessments will be evaluated by independent, blinded raters. These ratings will be reported.

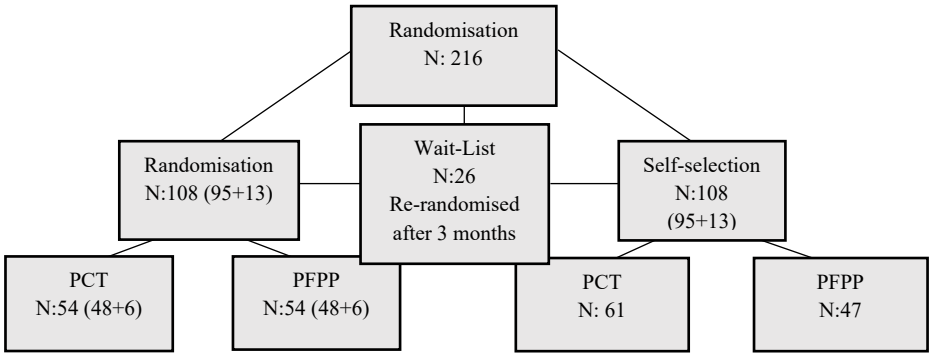

Figure 1. Participant flowchart. The number of participants in PCT and PFPP in the self-selection condition are estimations based on previous studies.

Discussion

Well-controlled trials, comparing different forms of psychotherapies in a real-world setting, with long term follow-ups, are needed for PD/A. Little is known about the effectiveness of PCT and PFPP on WA.

Study II – The effect of patient´s choice of either cognitive behavioural or psychodynamic therapy on outcomes for panic disorder: A doubly randomised controlled preference trial

Introduction

The present study will evaluate short- and long-term change for participants diagnosed with PD/A under self-selected or randomized allocation to PCT (Barlow & Craske, 1994) or PFPP (Milrod et al., 1997) compared with a low-contact control condition. Primary hypotheses were that for clinician-rated PD/A severity: 1) outcomes in the treatment groups would be superior to Control at post-treatment; 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 outcomes (ES and Absences) and secondary outcomes (mobility, depression and functional impairment) were assessed but not a priori hypotheses tested.

Method

221 adults with PD/A were included and randomly assigned to: random assignment to PFPP or PCT a choice between PFPP or PCT; or a Control condition. Outcomes were assessed at post-treatment, 6-, 12- and 24-month follow-ups. Clinically assessed PDSS was the studies primary psychiatric outcome measure, however ES and Absences were included as additional primary functional outcomes. Secondary outcome measures were PDSS-SR, MI, MADRS-S and SDS.

Results

Most participants (82%) completed treatment in accordance with the protocol. Irrespective of treatment type, steep decreases for the estimated scores on the PDSS occurred during treatment. Larger reductions on the PDSS occurred for those receiving PCT than PFPP during treatment (SMD, –0.64; 95% CI, –1.02, –0.25), but during follow-up the pattern was reversed (SMD 0.62; 95% CI, 0.27–0.98) so that from baseline to the 24-month follow-up, the two treatments yielded similar large outcomes (SMD 2.27; 95% CI, –2.52, 2.02). There was no effect of self-choice over randomized treatment allocation. Despite a moderate effect there was no allocation by treatment type interaction (SMD –0.57; 95% CI, –1.31, 0.17). There were no effects on ES or Absences during treatment or follow-up. The secondary, self-reported outcomes showed the same pattern of effects as the clinician rated PDSS, albeit of varying sizes.

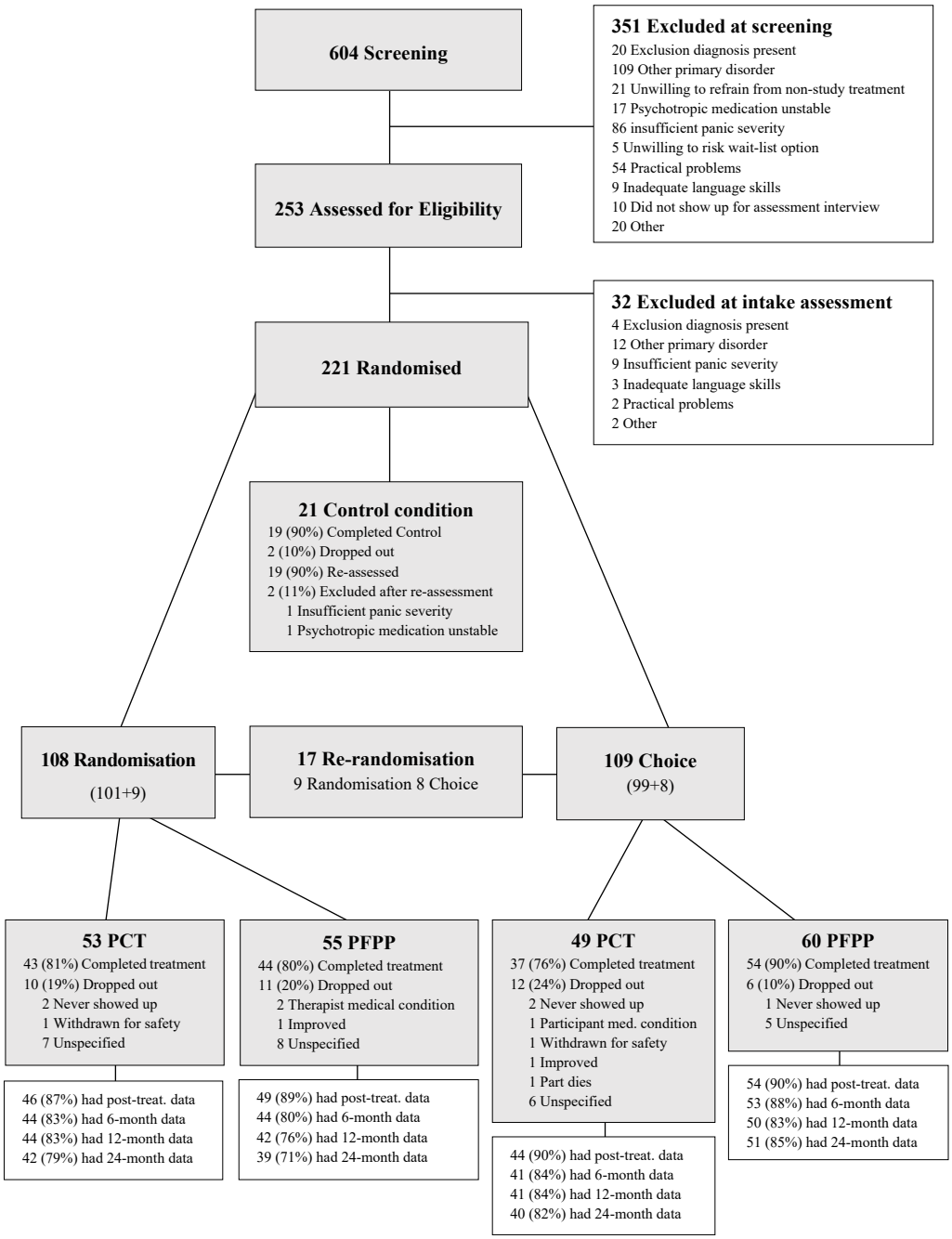

Figure 2. Participant Flowchart.
Abbreviations: PCT = Panic Control Treatment; PFPP = Panic-Focused Psychodynamic Psychotherapy

Table 2. Raw Scores by Treatment Conditions and Time of Assessment

		RPCT	N	RPFPP	n	CPCT	n	CPFPP	n
PDSS, M, 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 m follow-up	6.4 (5.4)	44	8.4 (5.5)	44	8.4 (5.5)	41	7.8 (5.3)	53
	12 m follow-up	5.9 (4.7)	44	8.5 (6.1)	42	8.3 (5.9)	41	6.4 (5.2)	50
	24 m 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 m follow-up	11.4	44	11.9	42	14.6	41	5.7	53
	12 m follow-up	9.5	42	17.1	41	12.5	40	4.0	50
	24 m 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 m follow-up	9.3	43	19.5	41	14.6	41	22.6	53
	12 m follow-up	10.0	40	25.6	39	10.3	39	12.0	50
	24 m follow-up	10.8	37	17.6	34	15.8	38	19.1	47
PDSS-SR, M, 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 m follow-up	3.2 (4.0)	44	5.4 (4.6)	42	4.9 (5.1)	41	5.6 (5.3)	53
	12 m follow-up	3.1 (3.5)	42	5.8 (5.6)	41	4.8 (4.7)	40	4.4 (4.5)	50
	24 m follow-up	3.0 (3.8)	39	4.2 (5.1)	37	3.5 (5.3)	38	3.3 (4.0)	47
SDS, M, 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 m follow-up	5.3 (7.2)	44	7.7 (6.9)	42	5.6 (7.1)	41	6.9 (6.4)	53
	12 m follow-up	4.3 (5.3)	42	6.5 (7.5)	41	6.2 (7.6)	40	5.1 (6.6)	50
	24 m follow-up	3.7 (5.8)	39	5.7 (6.9)	37	5.2 (7.1)	38	4.7 (6.6)	47
MI, M, 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 m follow-up	1.6 (0.7)	44	1.8 (0.8)	42	1.7 (0.6)	41	1.6 (0.7)	53
	12 m follow-up	1.5 (0.7)	42	1.7 (0.7)	41	1.6 (0.6)	40	1.5 (0.6)	50
	24 m follow-up	1.5 (0.6)	39	1.8 (0.9)	37	1.5 (0.5)	38	1.4 (0.5)	47
MADRS-S, M, 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 m follow-up	9.7 (8.8)	44	11.7 (8.8)	42	10.2 (6.7)	41	10.2 (7.7)	53
	12 m follow-up	8.6 (8.3)	42	10.5 (8.2)	41	9.9 (7.9)	40	9.2 (7.1)	50
	24 m follow-up	8.7 (8.5)	39	8.9 (8.5)	37	10.4 (8.2)	38	8.5 (7.4)	47

Note. 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 Asberg Depression Rating Scale

*Re-randomised after completed Control condition and re-assessment of eligibility

Table 3. Effect Sizes (SMDs) of Differential Change, by Treatment Contrasts and Time Segments (Confidence Intervals in brackets)

Outcome Measure	Segment/Months	C-R	PFPP- PCT	(RPFPP - CPFPP) – (RPCT - CPCT)	RPFPP - RPCT
PDSS	Baseline to Post-treat.	0.03 [-0.26, 0.33]	-0.64 [-1.02, -0.25]	-0.29 [-0.88, 0.30]	-0.78 [-1.27, -0.30]
	Post-treatment to 24 m	0.08 [-0.26, 0.42]	0.62 [0.27, 0.98]	-0.28 [-0.96, 0.41]	0.48 [-0.02, 0.98]
	Baseline to 24 m	0.11 [-0.26, 0.48]	-0.01 [-0.47, 0.44]	-0.57 [-1.31, 0.17]	-0.30 [-0.89, 0.29]
PDSS-SR	Baseline to Post-treat.	0.00 [-0.32, 0.32]	-0.56 [-0.89, -0.22]	-0.22 [-0.86, 0.42]	-0.67 [-1.13, -0.20]
	Post-treatment to 24 m	0.04 [-0.25, 0.33]	0.40 [0.11, 0.69]	-0.12 [-0.70, 0.46]	0.34 [-0.07, 0.76]
	Baseline to 24 m	0.04 [-0.27, 0.34]	-0.15 [-0.48, 0.17]	-0.34 [-0.95, 0.27]	-0.32 [-0.77, 0.13]
SDS	Baseline to Post-treat.	0.08 [-0.19, 0.36]	-0.53 [-0.80, -0.25]	-0.01 [-0.56, 0.54]	-0.54 [-0.93, -0.14]
	Post-treatment to 24 m	-0.09 [-0.37, 0.19]	0.37 [0.09, 0.65]	-0.36 [-0.92, 0.20]	0.19 [-0.22, 0.59]
	Baseline to 24 m	-0.01 [-0.29, 0.27]	-0.16 [-0.44, 0.11]	-0.37 [-0.93, 0.18]	-0.35 [-0.75, 0.05]
MI	Baseline to Post-treat.	0.03 [-0.27, 0.22]	-0.49 [-0.73, -0.25]	0.24 [-0.24, 0.72]	-0.37 [-0.71, -0.03]
	Post-treatment to 24 m	0.11 [-0.12, 0.33]	0.27 [0.02, 0.51]	-0.24 [-0.68, 0.20]	0.15 [-0.18, 0.48]
	Baseline to 24 m	0.08 [-0.21, 0.37]	-0.22 [-0.53, 0.09]	-0.00 [-0.59, 0.58]	-0.22 [-0.65, 0.21]
MADRS-S	Baseline to Post-treat.	0.11 [-0.18, 0.40]	-0.26 [-0.55, 0.02]	-0.19 [-0.7, 0.38]	-0.36 [-0.7, 0.05]
	Post-treatment to 24 m	-0.14 [-0.44, 0.15]	0.29 [-0.01, 0.58]	-0.33 [-0.92, 0.26]	0.13 [-0.30, 0.55]
	Baseline to 24 m	-0.03 [-0.32, 0.25]	0.03 [-0.26, 0.31]	-0.52 [-1.10, 0.05]	-0.24 [-0.65, 0.18]

Note. 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 Asberg Depression Rating Scale; 24 mos = 24 month follow-up

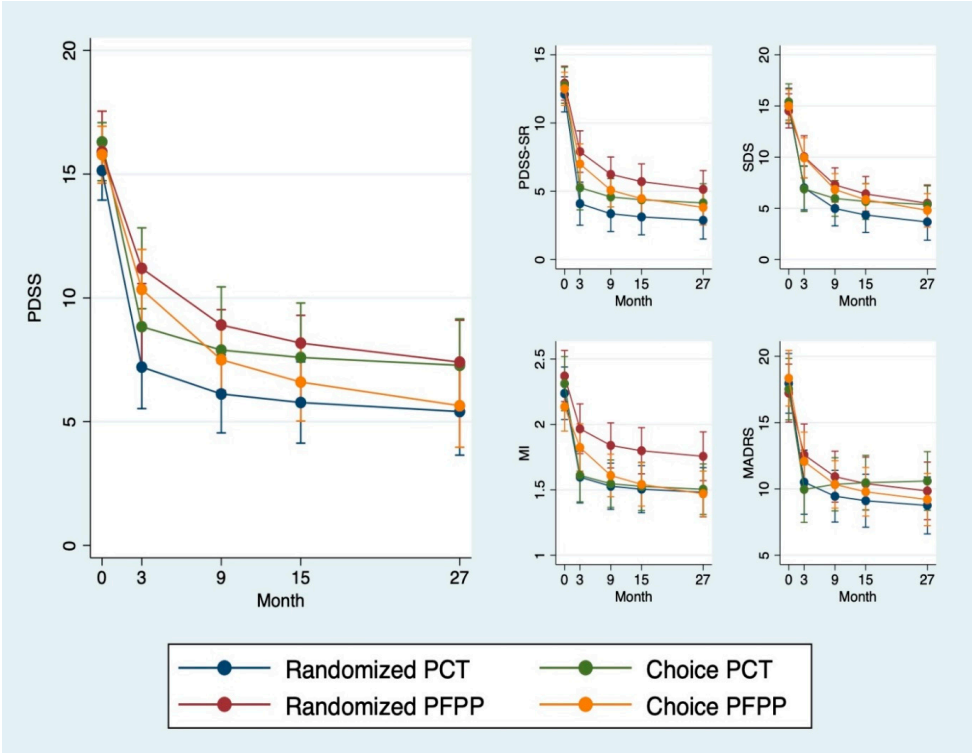

Figure 3. Modelled trajectories, with 95% confidence intervals, on the PDSS and the secondary outcome measures for the therapy types within the Choice and Random conditions
Abbreviations: 0 = Baseline; 3 = Post-treatment; 9 = 6 months follow-up; 15 = 12 months follow-up; 27 = 24 months follow-up.

Discussion

Consistent with hypotheses, treated participants experienced significantly greater reductions than controls at post-treatment. PCT was superior to PFPP during treatment, but during the follow-up period, participants who received PFPP improved significantly more than PCT so that the two treatments at 24-month follow-up were equally successful in treating panic symptoms. This result demonstrates the importance of long-term follow-ups in PD/A trials. There was a tendency for PCT to do better than PFPP when randomized and for PFPP to do better than PCT in the choice allocation. This unsuspected disordinal interaction effect was statistically insignificant but still moderate in SMDs, for both panic symptoms (d = 0. 57) and depressive symptoms (d = 0.52), between baseline and the 24 month follow-up.

Study III - Exploring termination setback in a psychodynamic therapy for panic disorder

Introduction

Termination of a psychological treatment, particularly if therapist-initiated (or limited by a RCT-protocol), can be painful and signifying real loss for patients and be followed by marked increases in symptoms among other reactions (Bostic et al., 1996). The occurrence of symptomatic increases during the termination phase of psychotherapy have received most attention in psychodynamic oriented clinical literature. The risk of TSs occurring in PDT has been associated particularly with the patient's attachment to, and separation difficulties from, the therapist, and if the therapy has dealt effectively enough with this issues approaching the termination (e.g., Busch et al., 2012; Joyce et al., 2007; Marx & Gelso, 1987; Nof et al., 2017; Safran & Muran, 2000; Strupp & Binder, 1984; Summers & Barber, 2010). However, few empirical investigations have been carried out to assess their occurrence and what may predict them. The present study will explore if there was a termination setback (TS) in PFPP.

Method

In the present study all 217 treated patients were included. The trajectories of change in PCT and PFPP according to the PDSS-SR were visually graphed and then statistically analysed. The rate of change of the weekly self-reported panic symptoms during treatment was estimated separately for PFPP and PCT participants from the pooled Choice and Random conditions. Based on the Bilinear Spline Model (Kohli & Harring, 2013; Preacher & Hancock, 2015) the treatment phase in PFPP was divided in two segments, pre-TS and TS and change estimated for each segment. Predictors tested were therapeutic Alliance, Inventory of Interpersonal problems, Personality Disorder, patients' Adult Attachment style and therapists' adherence to the treatment protocol during the termination phase. Finally, as it is possible that the superiority of PFPP during the follow-up period (Svensson et al., 2021) reflects the recovery of patients having had a temporary TS during the treatment end-phase, we examined the relationship between the TS magnitude and outcomes from termination to follow-up until 24 months after treatment termination.

Results

Figure 4 shows the mean trajectories of observed PDSS-SR scores across weeks. Consistent with the visual inspection of the weekly panic symptom reports during the treatment phase, piecewise modelling provided evidence of a sudden increase in

self-reported panic severity during the last three weeks (10-12) in PFPP, whereas PCT participants continued to improve. Indeed, nearly half (or one-sixth when using the stricter definition) of those receiving PFPP experienced a TS, as indicated by deterioration in self-reported panic symptoms from weeks 10 to 12 of a 12-week treatment. Importantly, the TS occurred despite the change in panic symptoms in the PFPP group being the same as in PCT up to week 10. Analyses also indicated that those who were making the fastest recovery up to week 10 in PFPP were most likely to experience a TS. Less avoidant attachment and less severe interpersonal problems predicted more severe TS. Patients who reacted with a TS rated the working alliance as weaker than other patients in weeks 2, 6, and 12. During the follow-up period, these patients (with a TS) improved, but nevertheless continued to stay behind in terms of symptom levels for the first year. At the 24-month follow-up there was no longer any differences. There was no association between having a TS and psychotropic medication during the treatment phase.

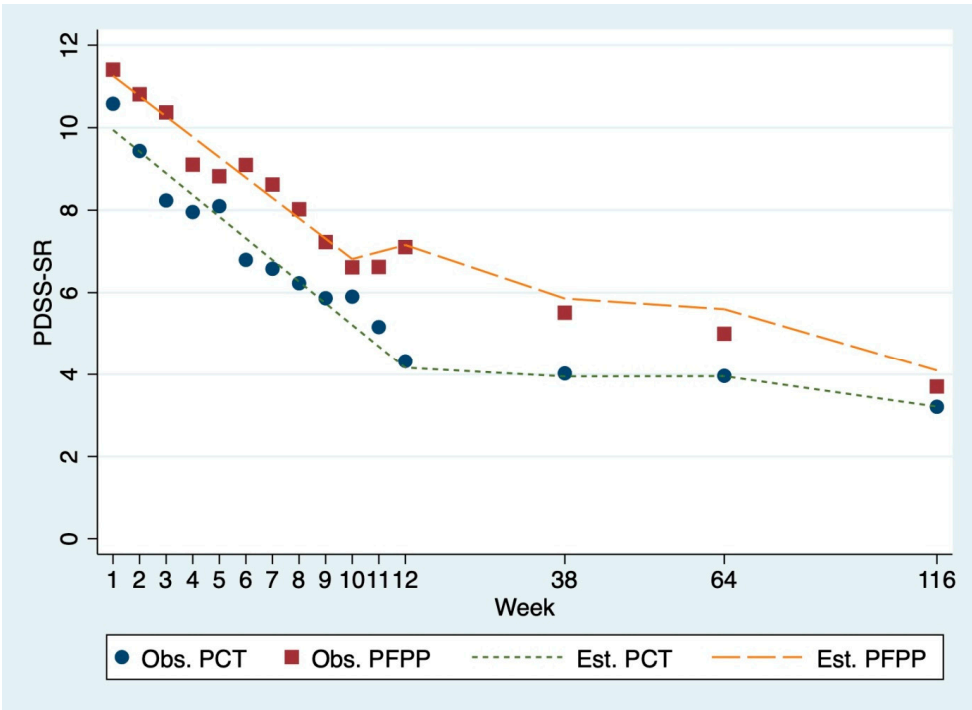

Figure 4. Estimated PDSS-SR trajectories and observed scores across weeks in treatments. PCT = Panic Control Treatment; PFPP = Panic-Focused Psychodynamic Psychotherapy. Lines show estimated trajectories, while circles show observed means.

Discussion

To our knowledge, this is the first study to explore a possible increase in symptoms towards the end of treatment, which we have referred to as a TS. Somewhat confusing is the fact that those patients who reacted with a TS, was making the fastest recovery up to the TS and had less of interpersonal and attachment difficulties, also rated the working alliance during treatment as weaker. One tentative explanation may be that the TS came as a result of a strained patient-therapist relationship due to a too strong treatment focus on symptoms. There remains a gap in the literature as to the prevalence of termination setbacks in psychotherapy, because so few trials measure symptoms at sufficiently frequent intervals (weekly or more often) during the treatment phase. More research on TS is needed and the two definitions of TS applied in this study are only provisional.

Study IV - Effects of two brief panic-focused psychotherapies on work ability in a doubly randomized clinical trial

Introduction

The present study assesses whether PFPP or PCT for PD/A are associated with improvements in self-reported WA. There is a large body of evidence indicating a bi-directional relationship between mental health and work. Poor mental health often negatively impacts work productivity and employment, whereas being employed in good work is protective against mental health difficulties (Bokma et al., 2017; Brady et al., 2020; Modini et al., 2016; van der Noordt et al., 2014). Anxiety disorders are identified as a major cause of functional impairment, work disability and sick leave, and Iancu et al. (2013) argues that treatments of anxiety disorders need to focus much more on the wider functional impacts of anxiety, including occupational functioning. We have found no studies evaluating the effectiveness of diagnosis-specific psychotherapies for PD/A on WA.

Method

Participants were 221 adults with a primary diagnosis of PD/A (female = 165; mean age = 34.9 (SD = 12.6)) randomized to wait-list (with low-frequency contact) or the active treatments PFPP or PCT, or to the choice between the two treatments. Participants completed the WAI at baseline, post-treatment, and 6, 12 and 24-month follow-ups. Changes in WAI scores were assessed using segmented multilevel linear growth models, and mediation was explored through path analysis. We also assessed the relationships between WAI scores and self-reported ES and Absence.

Results

Treated participant's WAI scores, irrespective of the type of treatment, changed from the "not so good" to the "good" category between baseline and post-treatment, with no such change for wait-listed participants (SMD = 0.45; 95% CI, 0.33, 0.57) These gains continued to increase during the follow-up period (SMD = 0.16, 95% CI, 0.03, 0.28), with no differences between treatment types or assignment (random or choice). Pre- to post-treatment changes on the WAI were mediated by reductions in self-reported panic symptoms during treatment (measured week 6). WAI scores significantly predicted employment status and absences with one assessment wave lag.

Discussion

To our knowledge, this is the first study to examine the effects of a disorder-specific psychotherapy, and patient preferences for type of psychotherapy, on WA in adults with a primary anxiety disorder. The study adds new information to the literature with respect to the impact of anxiety-focused treatments on WA, and particularly treatments designed to target PD/A. Given the relatively small evidence base for PFPP, improvements in WA were the same in this treatment as for the most-frequently evaluated, and widely disseminated, treatment for PD/A (i.e., PCT). This is promising findings, for PCT and PFFF, as increased WA appears to be protective against future work disability, work leave and early retirement.

Discussion

The primary aim of this thesis was to expand the knowledge about short and long-term effects of two forms of psychotherapies for PD/A on panic symptoms and WA. Data for Articles II-IV were drawn from participants recruited to Project POSE, a large DRCPT, comparing outcomes for PCT and PFPP under randomization and self-selection conditions at post-treatment, and at 6-, 12-, and 24-month follow-ups. Article I summarised the literature on the treatment of PD/A, how treatment preference influence outcomes in mental health, and described the DRCPT protocol for the project. Article II presented the main findings from the trial. Article III explored the resurgence of self-reported panic symptoms towards the end of the PFPP treatment. Article IV explored the impact of PCT and PFPP on WA as measured by WAI.

Complicating comparison between PCT and PFPP is the choice condition. Visual inspection of the PDSS trajectories suggested that there was a disordinal interaction, indicating that choice was moderated by treatment type. Specifically, patients who chose PFPP improved more compared to the randomized patients, and patients who were randomized to PCT improved more than those who chose PCT. This disordinal interaction, although not statistically significant, was in fact moderate in size (SMD = –0.57), and this was the main reason why the main effect of allocation was essentially nil. In view of this moderate-sized interaction it might mask important differences by pooling the randomized and choice participants into the two treatment groups (PCT and PFPP) for the purposes of subsequent comparisons. Nevertheless, from a statistical point of view, as the interaction was not significant, and as Articles II, III and IV found no effects of the method of allocation on the investigated hypotheses, the choice was made to present PCT and PFPP as two instead of four groups throughout in this discussion. So that a clearer examination could be made to understand why and how the PCT and PFPP groups differed at post-treatment, and the effect of this difference on long-term outcomes. The within-group effects sizes for self-reported depression (MADR-S) and overall disability (SDS) for PCT and PFPP were calculated and presented for this discussion.

General Discussion

Psychiatric outcomes

There were no differences in dropout rates between PCT and PFPP or self-selection and randomization and overall, the trial had very low attrition throughout; 82% completed treatment in accordance with the treatment protocol, and 89% of the intent-to-treat sample provided post-treatment data and 79% provided data at the 24-month follow-up data. This lends robustness to the statistical analyses and their results. Both treatments yielded large reductions in symptoms of panic and depression and improved functioning. Consistent with hypotheses, treated participants experienced significantly greater reductions than waitlist controls at post-treatment. On clinically assessed panic symptom severity (PDSS), the primary outcome measure, PCT and PFPP from baseline to 24-month follow-up yielded comparable improvements, with an SMD of 2.27 for the whole period. At post-treatment, PCT was superior to PFPP for panic symptoms but gains during the follow-up period were greater in those treated with PFPP than PCT. The between-group difference at treatment termination was indirectly investigated in Study III by examining the trajectory of weekly self-reported panic symptoms in the PCT and PFPP during the treatment phase of the trial. Up to weeks 10 of the 12-week treatment phase, the trajectory of weekly panic symptoms (declining) was the same in PCT and PFPP. Then in the last three weeks of PFFP, almost half of the participants experienced an increase in panic symptoms. We described this end-of-treatment increase in panic symptoms a *termination setback (TS)*. Few participants in PCT experienced a TS, which may explain the superiority of this treatment over PFPP at post-treatment. The longer-term impact of the TS was also examined. Compared to those who did not suffer a TS in PFPP, those who had a TS had worse outcomes at the 6- and 12-month follow-ups but continued to improve so that the two groups were equivalent by the 24-month follow-up. However, most of the setback, i.e., increase in symptoms, was restituted already at the 6 months follow-up. It would have been beneficial for the understanding of the TS post-treatment if the trial had had an assessment point for PDSS and other measurements one- or two-months post-treatment.

The evidence-based guidelines for interpretation of the PDSS (Furukawa et al., 2009) describe a clinically significant treatment response as a $\geq$ 40% reduction in pre- to post-treatment scores on the PDSS, and remission as a total PDSS score of $\leq$ 5 at post-treatment or follow-up. The proportion of participants who experienced a clinically significant response at post-treatment and 24-month follow-up in the two groups were as follows: PFPP = 43% and 72%; PCT = 60% and 67%, respectively. Remission rates at post-treatment and 24-month follow-up were as follows: PFPP = 21% and 52%; PCT = 32% and 52%, respectively. More participants in PCT than PFPP achieved a clinically significant response at post-

treatment ($p < .05$), otherwise there were no differences between the groups for clinically significant response or remission.

Response rates for PCT at post-treatment in this trial (60%) were comparable to that reported by Milrod et al. (2016) in their trial comparing PCT (62%). Milrod et al. (2016) achieved higher rates of recovery for PFPP in their trial versus this one (59% vs 43%, respectively). The inferences that can be drawn from these between-trial differences are limited by the fact that the two trials were carried out in different countries, in different clinical settings and that the TS found in this trial, lowered the acute outcome, for PFPP. It is important to note that the investigative team responsible for this trial (Project POSE) were not the originators of either PCT or PFPP. Further trials involving PCT and PFPP, carried out by researchers independent of the treatment originators are warranted.

It is worth noting that, even though PFPP participants experienced a statistically significant larger decrease on the PDSS during the 24-month follow-up period, participants who received PCT also improved during the follow-up period although not as much as PFPP. When looking at remission, there is a fairly large proportion of patients moving into remission during the 24-month follow-up period in both treatments. The finding that roughly twice as many patients achieved remission during follow-up than during the treatment phase, and that 52% of the patients in both treatments achieved remission at the 24-month follow-up is of clinical significance, as these patients are the ones that benefitted the most from treatment. But also suggest that future studies should look at factors that might help explain this variability in PCT and PFPP and over time. (e.g., utilizing information/techniques vs. intrapsychic/relational insights gained during treatment in everyday life, partner/family/friend involvement in the patient's recovery efforts, etc).

Overall, these results suggest that two brief psychological treatments for PD/A yield improvements in panic, comorbid difficulties, and overall functioning, with further clinically significant improvements occurring up to 24 months after these treatments are withdrawn. Also, the results of Article II suggest that the durability of gains achieved at post-treatment, and the continued gains achieved during follow-up, were not owing to further or new treatment during the follow-up phase. As one of few RCTs to include a 24-month follow-up, with unusually low rates of attrition during treatment and follow-up, and with the trial being led by researchers independent of the treatment originators, and patients recruited from and treated in routine care by therapists employed in the community clinics, these findings add important information to the literature on the long-term effectiveness of PCT and PFPP for PD/A.

Article II found that self-reported depression (MADRS-S) followed a similar pattern of improvement, albeit with smaller effect sizes, as panic severity (PDSS), during the pre- to post-treatment and post-treatment to follow-up phase. As seen in Table

3, and again similar to the findings for panic, participants in PCT experienced greater reductions in depression symptoms during treatment than those in PFPP, and those receiving PFPP experienced greater reductions in depression during follow-up than those receiving PCT, although these between-treatment differences were non-significant in both time segments. The within-group effect sizes (SMDs) from baseline to post-treatment were in the large range with further improvements from post-treatment to 24-month follow-up for the two treatments: PCT = –0.94, 95% CI, –1.15, –0.73 and –0.04, 95% CI, –0.26, 0.18; PFPP = –0.76, 95% CI, –0,95 –0.57 and –0.39, 95% CI, –0.60, –0.17. This is important, because as noted in the introduction, comorbid depression is associated with higher PD/A severity, poorer response to PD/A focused treatment, and greater impairments in overall functioning and health.

While reductions in panic and depressive symptoms are important, so are improvements in day-to-day functioning (work, social life, and home/family life). As recommended in the literature for PD/A trials, overall functioning was measured with the Sheehan Disability Scale (SDS). As shown in Table 3 participants in PCT achieved greater improvements in overall functioning during treatment than participants in PFPP, with functional improvements being greater during the follow-up period in the PFPP groups, with significant between-treatment differences for both time segments. Again, the within-group effect sizes (SMDs) from baseline to post-treatment were in the large range with further improvements from post-treatment to 24-month follow-up for the two treatments: PCT = –1.39, 95% CI, –1.60, –1.18 and –0.32, 95% CI, –0.55, –0.09; PFPP = –0.84, 95% CI, –1,03 –0.65 and –0.62, 95% CI, –0.83, –0.40.

Looking at outcomes for the two treatments across the wide range of psychiatric measures (Article II), where the measure of agoraphobic avoidance (MI) also improved with a similar pattern (i.e. steeper change for PCT during treatment while the reverse was true for PFPP during the follow-up period), suggest that these two disorder-specific treatments yielded positive transdiagnostic effects. Further studies involving sophisticated tests of mediation are warranted. However, it has been suggested that mental health treatments (pharmacotherapy and psychotherapy) that yield positive transdiagnostic effects may be acting upon a so-called “p-factor” of psychopathology or mental vulnerability (Caspi et al., 2014; Gluschkoff et al., 2019; Selzam et al., 2018). In essence the p- factor is based on research that argues that a single mental vulnerability dimension or continuum best explains a person’s liability for having mental disorders, comorbidity among disorders and over time, and the persistence and severity of the disorders (Caspi & Moffitt, 2018). According to Caspi and Moffitt (2018) there is a strong relationship between higher scores on the p-factor with a family history of psychiatric illness, childhood developmental problems, and adult life impairment. They also argue that this one-dimensional p-factor may explain why multiple disorders share the same etiological risk factors and often respond to the same psychological or medical treatments. The p-factor

may help explain the apparent transdiagnostic effects of the two disorder-specific treatments under test in this trial (PCT and PFPP).

Understanding the relative efficacy of PCT vs PFPP during the treatment phase

Two of the key elements used in PCT, *interoceptive exposure* and *cognitive restructuring*, were found to be the most "active" components in successful CBT for PD/A in a dismantling study by Pompoli et al. (2018). *In vivo exposure* (done by patients between therapy sessions) and *breathing retraining* (practiced very briefly in, and then between session), were associated with treatment acceptability but not outcomes.

A main technical component of PCT (as in CBT in general) is the use of patient-and-therapist-agreed homework assignments, which involves patient-led symptom monitoring (awareness training), exposures (in vivo), and avoidance/safety behaviour change strategies. Every session starts with a review of the previous week's homework, and the basic idea is to encourage the patient to use strategies/information between sessions that they acquire in-session with the help of their therapist. To help guide this process, the patient completes and the therapist and patient review brief, Patient-Reported Outcome Measures (PROMs) to monitor panic/mood symptoms and progress over the past week. The use of PROMS as a tool for feedback-informed treatment modifications is associated with improved outcomes in psychotherapy irrespective of treatment type, and Lambert et al. (2018) especially found it to reduce deterioration rates and particularly improve the response rates in patients who were predicted to have a poor outcome. It is interesting to contemplate whether outcomes in PFPP would have yielded similar outcomes to PCT during the treatment phase if the PFPP manual had required the therapist to collect and use weekly PROMs and to adjust treatment based on this data.

Termination Setback (TS)

As the TS in fact decisively affected the PFPP patients' outcome negatively and the between-treatment comparison during the treatment phase, it is important to try to understand it – and possibly counteract it. Was the TS connected to the implementation and use of the PFPP-manual in this study? Was there an insufficient therapeutic focus on separation and termination issues that triggered the late-treatment difficulties in PFPP? Or could it be that a too strong and one-sided focus on the separation provoked a TS in some patients? Neither of these two contradictory speculations found support in our analyses, as there was no relationship between independently rated level of adherence to the PFPP-manual

during the final part of the therapy and having or not having a TS. It is worth pointing out that the adherence measure is quite crude and does not capture qualitative or competence differences in how PFPP was delivered or how termination difficulties were handled.

Before further studies and a deeper understanding of the processes behind the TS one can only speculate about what caused it and what could have prevented it. From a PDT perspective, a TS may be due to the patient not fully internalizing the therapist's therapeutic functions and objectives, leading to symptom instability rather than stability towards the end of treatment. A solution in accordance with the PFPP-manual would be to address the time-limited nature of PFPP and termination issues earlier in treatment and more thoroughly. In PFPP (Bush et al., 2007) the working-through in the termination phase should be guided by the patient's awareness of and increased ability to manage situations and relations where conflicts concerning loss, separation and autonomy arise. In the termination phase these conflicts are intensified, often with anger or withdrawal out of feelings stemming from fantasies of being abandoned or mistreated by the therapist or other important persons in the patient's life. According to the manual, by tuning in on these feelings, and interpreting them, repeatedly, the therapist helps the patient gain a deepening understanding of the conflicts underlying the symptoms of panic. Helping the patient to tolerate having and expressing feelings of anger, dissatisfaction, love, sadness etc. towards important others is, from a PFPP point of view, crucial for remaining panic free in the long run. This final separation-work is obviously not an easy operation to manage and adhere to for the therapist in a time-limited therapy.

Another solution may be to broaden the psychodynamic technique in the termination phase by stabilizing the patient's gains through empathic understanding, summarizing advances, and previewing how to handle lapses, thus bringing a smoother closure to the treatment. In Brief Dynamic Interpersonal Therapy (DIT) (Lemma et al., 2011a), the patient is prepared for termination through the therapist's formulation of a summarizing "goodbye letter" focused on which problems have been worked on, which have changed and which remain. Lemma et al. (2011a) argue that such letters may be helpful because: 1) the pace and rate of learning are inevitably faster in brief than in longer-term PDT, and the scope for consolidating gains is also much shorter; 2) the letter provides a record of the therapeutic work done; and 3) it can be seen and used as a therapeutic transitional object – that may aid the internalization of a helping attachment figure – offering reassurance at the point of separation and beyond. Yet another possible solution would be to schedule booster sessions to mitigate the experience of definitive separation and reduce the likelihood of post-treatment relapse. Booster sessions are recommended if needed (Busch et al., 2012) and were actually offered during the 12 month follow-up period of responders (from PFPP, PCT or ART) in the Cornell-Penn study (McCarthy et al., 2018).

Could PFPP be updated?

It seems reasonable to assume that, like any "new" treatment, PFPP could be modified to improve its efficacy. One suggestion is to introduce the supportive and stabilizing interventions, presented above, that could be used when needed and would widening the psychodynamic techniques in the termination phase. Our own experience with PFPP, while clearly positive, suggests also that outcomes could be further improved if the therapist were to introduce the patient quickly and transparently into the psychodynamic model of how PD/A develops and how it is treated in PFPP, preferably in both oral and an easy-to-read written format. For example, the therapist might make clear in the first sessions that ambivalent attachments are likely at the root of the patient's panic experience, driving a cycle of fearful 'clinging' and angry attacks when she or he perceives or experiences important others pulling away in times of distress, and that her or his panic attacks probably emerge from and are driven by the attachment system. Such a modified PDT-specific form of psychoeducation early in treatment might help to create, a more secure therapeutic alliance, greater levels of understanding and insight, and perhaps help resolving early therapeutic relationship challenges; all processes that could enhance stable symptom changes.

There is a growing evidence base indicating that marked (noticeable) symptom reductions early in psychotherapy (often within 4 weeks) for anxiety, irrespective of treatment type, are associated with improved outcomes at post-treatment, with the effect sizes for those with early treatment gains being in the very large range relative to the absence of such gains (Beard & Delgadillo, 2019; Stiles et al., 2003). However, this is somewhat contradicted by our findings that patients in PFPP who had improved most in the first 10 weeks were more likely to experience a TS. Again, it is interesting to speculate whether PFPP could have been helped by the use of weekly PROMs to adjust the treatments. Especially as PROMs has been found to reduce deterioration rates and particularly improve the response rates in patients who are predicted to have a poor outcome. Maybe the PROMS could have detected instability or fluctuation in symptoms between sessions that would have been helpful to stabilize or captured disagreement about how therapy was done or its progress.

It is possible that a TS, while a negative outcome during the treatment phase, provided an opportunity to the PD/A patients, known to have extreme difficulty with separations and confronting intense emotions without the presence of individuals associated with security, to work through this aspect of their anxiety, with their therapist, or on their own and with loved ones in the first few weeks/months after treatment is ended. Such an explanation/opportunity seems less likely if the TS arose out of a therapeutic avoidance of the patient's separation and termination issues. It is important to underline that the patients who suffered a TS did not stay impaired, that most of the reaction was transient and that they did improve throughout the

follow-up period. Thus, positive long-term outcome for some PFPP patients may partly depend on the experience of a TS, if the TS arose from the patient's confronting their separation issues, and while this produced an increase in panic symptoms, their understanding of their symptoms and/or the way they managed them changed in the ways that PFPP intends. Future process studies focusing on the TS and changes in beliefs about the symptoms, the therapeutic relationship, the implementation of the PFPP method, and relationships more broadly may help to further our understanding of the TS and how termination more broadly impacts individuals with PD/A. Analysis of data from the 6-month qualitative follow-up interview carried out in this trial may help to elucidate change mechanisms associated with the TS and PFPP.

Outcomes for Work Ability

The final article (IV) in this thesis broadens the evidence for PCT and PFPP as this was the first trial to report improvements in WA as measured with a validated and widely used measure (WAI). It is important to note there were no changes in employment status at post-treatment or follow-up for any treatments (Article II). Possibly due to the fact that 89% of the participants already were employed or in education at the start of the trial and that this proportion remained stable throughout the treatment and follow-up phases with 88 – 90% of the participants reporting being employed or in education at every assessment point. Similar to employment status, there were no changes in sick leave associated with treatment in this trial (Article II).

Even though most of the participants were employed at intake, our experience from the interviews at baseline assessment, were that many found their symptoms of PD/A causing them extreme difficulties in work, education, and other activities. Traveling back and forth from home to work/school, attending meetings or lectures, seeing colleagues and customers over a lunch or cup of coffee, or going away in business were difficult or impossible due to their PD/A. Importantly, both PCT and PFPP yielded significant increases on the WAI from pre- to post-treatment and during the two-year follow-up. Essentially, participants moved from 'a not so good' WAI score to a 'good' WAI score during treatment, and during follow up this ability further increased; an improvement that may be protective against future work difficulties and exacerbation of, or relapse, of mental health difficulties. Pre- to post-treatment changes on the WAI were mediated by reductions in panic symptoms during the treatment phase. Thus, it appears that a clinically meaningful reduction in panic symptoms is associated with significant improvements in the patient's beliefs about their capacity and confidence in meeting current and future work demands.

For explorative reasons the model was re-run in a two-group analysis, for PCT and PFPP separately. Although the two models did not differ significantly, it is worth mentioning that mediation was confirmed for PFPP but not for PCT. Awaiting

replication one can only speculate about these findings. But one tentative suggestion could be that the therapeutic focus on intrapsychic conflicts surrounding interpersonal closeness, separation, and autonomy in PFPP first must be successful, thus lowering the panic symptoms, for the WA to increase. Whereas in PCT the core elements of practice on tolerating having panic symptoms and exposure of feared situations (e.g., daily travels to work, be at meetings, lectures and in other public venues) also yield a more direct result on an individual's WA.

It would have been interesting to connect this increase in WA with some actual day to day work-related measures capturing, e.g. task completion, engagement, satisfaction or creativity at the workplace. The latest review on treatments for anxiety disorders by SBU from 2005 (Swedish agency for health technology assessment and assessment of social services) concluded that as PD/A is accompanied by significant functional impairment, the goal of treatments can not only be to reduce panic symptoms, but also to improve the patient's functional capacity. Therefore, as most treatment studies on PD/A and on other diagnoses, still mainly have focused on symptomatic outcomes, it is an encouraging result that two symptom-focused, disorder-specific therapies (PCT and PFPP) yielded significant improvements in WA.

Clinical Implications

The results of Article II add to the large literature indicating that PCT is an efficacious treatment for PD/A when delivered in routine care. The results also add to a growing literature of the efficacy of PFPP, and importantly, for the efficacy of PFPP delivered in routine care. Specifically, participants were recruited from routine, community-based, outpatient psychiatric and primary care services and via advertising, with the majority having significant psychiatric comorbidity in addition to PD/A, and with a large proportion being medicated and/or having a prior history of psychiatric treatment. Further extending the real-world context of the trial, the 45 therapists (PFPP = 25; PCT = 20) who provided the treatments were from the same clinics as the patients and recruited based on their interest in participating in the trial, as long as they had the basic psychotherapy training stipulated by law in Sweden to be allowed to deliver psychotherapy. The therapists also had different basic professional training and years of experience of delivering psychotherapy. After a two-day training course in PCT or PFPP and completion of one approved supervised training case, they were accepted to treat patients in the trial. Finally, the investigators were not the original developers of the treatments under study and included a mix of PDT and CBT researchers. Thus, the results from Articles II and IV suggest that both PCT and PFPP yield disorder-specific and transdiagnostic effects, including improvements in WA, that are present after 12 weeks of treatment and 24-months after treatment is withdrawn, irrespective of continued/further

treatment during the follow-up phase, in a large sample of PD/A patient recruited from routine mental healthcare in Sweden.

Joyce et al. (2007) conclude that forced terminated treatment relations in psychotherapy (and medicine) probably are much more common and cause more damage than recognized. If the TS in study III partly was a result of a forced termination initiated by the therapist on the basis of the protocol this problem may also apply more generally to the Swedish health care system, that has been criticised for, and stands out internationally for its health care discontinuity, affecting patients' health and recovery negatively. (Statens Beredning för medicinsk Utvärdering, 2021).

Of course, it is important to acknowledge that these treatments were evaluated in the context of a randomized controlled trial and the quality controls and added cost entailed in such trials. Therapists in the trial had to devote some portion of their work time to training in the use of the PCT and PFPP manuals and then received supervision from experienced clinicians closely monitoring adherence to the treatment protocol. It remains a subject for further enquiry whether these treatments will retain their levels of efficacy when delivered in routine care without such training, regular supervision, and adherence monitoring.

Limitations

This treatment outcome study conforms to the main recommendations for trial design (Guidi et al., 2018) with two exceptions: the use of a waiting list control group and non-blinded outcome assessments. Although a waiting list control group was used, which involves some limitations in evaluating the efficacy of an active treatment, the design involved comparisons between two active therapy types (PCT vs. PFPP) that both have successfully been compared with active placebo treatments. Also, while outcomes were not blindly assessed, three external judges blindly rated a large sample of outcome interviews and obtained very high levels of agreement with the non-blinded assessors. A very similar pattern of results was also obtained for the self-report version (PDSS-SR) of our primary outcome measure and other secondary, patient-reported outcomes.

In this thesis some inferences are based on a pooling of data from participants randomized to or self-selecting PCT or PFPP, which strictly speaking, prevents causal interpretation of between-group differences. However, Articles II, III and IV found no effects of the method of allocation on the investigated hypotheses.

As with outcomes in any RCT, other unidentified variables may have interacted with treatment conditions to influence or moderate outcomes. Of specific relevance are the potential contributions of comorbidities and medication usage. 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. However, our analyses found no evidence that medication usage influenced outcomes in this trial. It is also important to point out that the findings and results in this study were based on mean scores for the different treatment groups and that there likely are important variations in outcomes for individuals and for subgroups not considered. Future quantitative investigations of predictors and moderators and qualitative studies will investigate this.

Although the majority having significant psychiatric comorbidity and with a large proportion also being medicated and/or having a prior history of psychiatric treatment a possible limitation is that the participants in this study are a bit more well educated, and with 87% employed or in education one can also assume that the participants were reasonably well functioning compared with the larger PD/A population in Sweden.

Concerning the termination setback (TS), our findings may not extend to other forms of PDT or CBT, or if delivered outside the context of a treatment trial. The predictor analyses were constrained by the measures administered in the trial; other unmeasured variables might have better explained the occurrence of a TS in the PFPP condition. And in addition to assessment of adherence, ratings of competence of delivery might have illuminated how the therapists handled terminations issues. Indeed, our implementation of the PFPP-manual may not have been optimal, despite adequate adherence ratings.

Implications for Future Research

Psychotherapy trials with long-term follow-ups, i.e., beyond 6-months follow up, are needed to improve our knowledge of what happens after termination of treatment (Pompoli et al., 2016; van Dis et al., 2020). In this trial long-term follow-ups changed the conclusion that would have been drawn post-treatment. More research is needed on functional outcomes such as WA in psychotherapy.

There is a need for more research on termination setback in psychotherapy. As this was the first large trial to report a TS, we do not know how common or uncommon the phenomenon is, as reported weekly assessment during treatment has been infrequent in psychotherapy trials. The present study adds to a growing consensus that weekly or every session assessment during treatment is needed to properly identify symptom changes throughout the treatment and change mechanisms in treatment. Future studies are needed with measures that address the breadth of the patient's experience of termination in psychotherapy. These should include some

measure of traumatic loss and separation anxiety to contribute to the understanding of the dynamics of TS. There is yet no consensus on a definition of TS, and the two definitions applied in this study are only provisional. However, our definition of the strict TS, that it should be clinically significant, was in that sense similar with the definition of sudden losses by Lutz et al. (2013). Further discussion and research are needed to arrive at the best definition.

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Primary and Secondary Outcomes from a Doubly Randomized Clinical Preference Trial of two Panic-Focused Psychotherapies

Photo: Kristoffer Nilsson

Thomas Nilsson

Panic Disorder with or without Agoraphobia (PD/A) has a lifetime prevalence of 2-3%. The disorder is too often chronic especially if untreated with affected individuals experiencing high levels of psychological and social suffering, diminished abilities for studies and work, and elevated risk for substance use, health problems, and early mortality.

In the Project Psychotherapy Outcome and Self-selection Effects (Project POSE) a total of 221 adults with primary PD/A were randomly allocated to Panic Control Treatment (PCT) or Panic Focused Psychodynamic Psychotherapy (PFPP) or to a choice between these two treatments. Irrespective of assignment to the Choice or Random conditions, both treatments yielded clinically significant improvements for both panic and depressive symptoms. PCT was significantly superior to PFPP at post-treatment. However, during the follow-up period PFPP was significantly superior to PCT, so that the two treatments were equally effective in treating PD/A at the 24-month follow-up. Both treatments were well tolerated with no differences in drop-out rates. Significant improvements, with no differences between PFPP and PCT, were observed for Work Ability at post-treatment and during the follow-up period.

The treatments were delivered by 45 therapists in primary health care, psychiatry, and youth counseling clinics. The researchers responsible for Project POSE were Rolf Sandell, Sean Perrin, Håkan Johansson, Gardar Viborg, Fredrik Falkenström, Martin Svensson and Thomas Nilsson, all licensed psychologists.

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