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Research report

Rate of improvement during and across three treatments for panic disorder with or without agoraphobia: Cognitive behavioral therapy, selective serotonin reuptake inhibitor or both combined

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ABSTRACT

Background: Existing literature on panic disorder (PD) yields no data regarding the differential rates of improvement during Cognitive Behavioral Therapy (CBT), Selective Serotonin Reuptake Inhibitor (SSRI) or both combined (CBT+SSRI).
Method: Patients were randomized to CBT, SSRI or CBT+SSRI which each lasted one year including three months of medication taper. Participating patients kept record of the frequency of panic attacks throughout the full year of treatment. Rate of improvement on panic frequency and the relationship between rate of improvement and baseline agoraphobia (AG) were examined.
Results: A significant decline in frequency of panic attacks was observed for each treatment modality. SSRI and CBT+SSRI were associated with a significant faster rate of improvement as compared to CBT. Gains were maintained after tapering medication. For patients with moderate or severe AG, CBT+SSRI was associated with a more rapid improvement on panic frequency as compared to patients receiving either mono-treatment.
Limitations: Frequency of panic attacks was not assessed beyond the full year of treatment. Second, only one process variable was used.
Conclusions: Patients with PD respond well to each treatment as indicated by a significant decline in panic attacks. CBT is associated with a slower rate of improvement as compared to SSRI and CBT+SSRI. Discontinuation of SSRI treatment does not result in a revival of frequency of panic attacks. Our data suggest that for patients without or with only mild AG, SSRI-only will suffice. For patients with moderate or severe AG, the combined CBT+SSRI treatment is recommended.

1. Introduction

Cognitive Behavioral Therapy (CBT) and Serotonin Selective Reuptake Inhibitors (SSRIs) are now widely accepted as the gold standard for the treatment of panic disorder (PD) (Roshanaei-Moghaddam et al., 2011). In naturalistic settings, many patients receive a combination of these two treatment modalities. A handful of randomized trials have performed head-to-head comparisons between CBT and antidepressants for PD (Bakker et al., 1999; Barlow et al., 2000; Black et al., 1993; Van Apeldoorn et al., 2010; Van Apeldoorn et al., 2008; Sharp et al., 1996; Clark et al., 1994) but only three of these studies compared both mono treatments (CBT-only and antidepressants-only) with the combination of both within a single design allowing for an optimal comparison (Barlow et al., 2000; Van Apeldoorn et al., 2008; Sharp et al., 1996).

We previously reported on the differential long-term effectiveness of CBT, SSRI, and the combination of both (CBT+SSRI) in the treatment of PD with or without AG (Van Apeldoorn et al., 2010). Patients were treated at both academic and non-academic clinical sites in the Netherlands. Patients received one year of treatment, including medication taper in case of SSRI use. Results from pre-, and posttest outcome measures suggested that gains produced by CBT were slower to emerge than those produced by the other treatment modalities. Follow-up results revealed no fall-off in gains for either treatment modality after treatment discontinuation. However, to obtain a detailed insight into symptom changes in the course of therapy and relate those changes to treatment modalities, intensive measurement across time is needed. Surprisingly, the existing literature on PD yields no actual data regarding

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the differential rates of improvement during CBT-only, SSRI-only and the combination of both. There is some evidence from treatment outcome studies (e.g., Sharp et al., 1996) suggesting a more rapid improvement for a combined CBT and SSRI treatment but rate of improvement was not fully investigated in these studies. Rate of improvement is however considered to be a critical clinical variable as rapid improvement not only diminishes ongoing suffering, but may also prevent attrition (Penava et al., 1998).

The primary goal of the present study is to gain insight into the rate of improvement both during and across the currently most effective treatments for panic disorder. As primary measure that reflects symptom change during treatment and that can be measured intensively, we choose frequency of panic attacks. The occurrence of panic attacks is a core symptom of PD and contributes greatly to the suffering of PD patients. PD patients are thought to reliably indicate the presence or absence of panic attacks (de Beurs et al., 1992). Panic attack frequency was examined for the period of one year in which treatment was delivered including medication taper.

Research goals for the present study are: 1. To examine the rate of improvement in panic attack frequency during treatment. We expect patients to improve significantly as indicated by a decline in the number of panic attacks in all three treatment modalities. 2. To determine possible differential effects in rate of improvement across treatment modalities. Based on previous results regarding differential treatment effectiveness, analyzing pre- and post-outcome data (Van Apeldoorn et al., 2010; Van Apeldoorn et al., 2008), we expect patients receiving an SSRI (either as mono treatment or in combination with CBT) to show a faster rate of improvement as compared to patients receiving CBT-only. 3. To examine the effect of tapering medication across treatment modalities. From week 40, patients receiving an SSRI, either as mono-treatment or combined with CBT, tapered their medication. Several authors suggest that patients are more prone to relapse following medication discontinuation due to a shift in context (Bouton, 2000; Otto et al., 2005; Craske et al., 2008). We previously referred to this theoretical frame-work as the 'context-safety hypothesis' (Van Apeldoorn et al., 2010) but our previous findings could not confirm this hypothesis. In the present study, we further examine this issue. In accordance to former hypothesis, an increase in number of reported panic attacks following medication taper is expected for patients who received either CBT+SSRI or SSRI. 4. To examine the relationship between rate of improvement in panic frequency and baseline severity of agoraphobia. In most clinical outcome studies, the proportion of PD patients with AG exceeds those of PD without AG (Grant et al., 2006), whereas some clinical trials excluded patients with agoraphobia altogether (Barlow et al., 2000). PD patients with AG are associated with a greater disability as compared to PD patients without AG (Grant et al., 2006). The question whether treatment for PD patients should differ depending on the presence or severity of AG has been subject of debate. Results from a recent meta-analysis support the contemporary view that there is no reason to offer PD patients with AG a different kind of treatment than patients without AG (Furukawa et al., 2006).

2. Method

Randomized patients met DSM-IV criteria for PD with or without AG as primary diagnosis.

Patients were not required a minimum number of panic attacks during baseline. Inclusion was restricted to patients between 18 and 65 years of age. Patients who were pregnant, lactating, suicidal, psychotic, or severely depressed were ineligible to participate in the study. Patients were treated in 11 treatment facilities located throughout the Netherlands. Three kinds of sites participated: 1. university training and research centers ($N=2$); 2. university research clinics ($N=2$); 3. regular mental health clinics ($N=7$). Previous analyses (Van Apeldoorn et al., 2010) revealed no site or interaction effects. The study was approved by the institutional review boards of all sites and written informed consent was obtained prior to randomization. Participating patients in each treatment condition received one year of treatment. Patients received either CBT, SSRI, or CBT+SSRI. CBT consisted of interoceptive exposure, cognitive therapy, and exposure-in-vivo. CBT patients received up to 21 treatment sessions of approximately 50 min each. The CBT treatment manual was intended to satisfy as closely as possible "care as usual" requirements and was based on the work of Clark, Craske, and Barlow (Craske and Barlow, 1993; Clark, 1986). Following each treatment session (in each modality), all therapists completed a detailed form regarding the content of that session. These forms were evaluated by the research team in order to check treatment adherence. Patients receiving an SSRI visited their therapist 9 times, with weekly sessions during the first month and the remaining sessions distributed evenly over the treatment period. Each visit lasted approximately 20 min. Clinicians treating patients assigned to SSRI or CBT+SSRI, were free to choose between five SSRIs currently marketed in the Netherlands: fluoxetine, paroxetine, sertraline, citalopram, and fluvoxamine. SSRI prescriptions were in conformance with the pharmacotherapeutical guidelines as formulated by the Dutch Psychiatry Association (Van Balkom et al., 1998). During the first month of treatment, patients were administered a minimum dosage which was titrated upward up to the effective range and was adjusted according to clinical response and tolerability. Patients were not allowed to use psychotropic drugs except small doses of benzodiazepines (maximum the equivalent of 20 mg oxazepam per day). Patients receiving an SSRI started tapering from week 40. In this period (weeks 40–52), three additional sessions were scheduled resulting in up to 12 SSRI sessions. For patients randomized to CBT +SSRI, the two treatments started simultaneously and were delivered parallel. AG level was assessed, after inclusion, by the first author based on chart review and a structured interview (Sheehan et al., 1998). Patients were classified as not suffering from AG, or suffering from mild, moderate or severe AG following DSM-III-R definitions. Presence of panic attacks was assessed prospectively (i.e., using event-contingent recording): participating patients were asked to color a box in a panic plot each time a panic attack occurred. From those panic plots, we derived the frequency of panic attacks. Patients kept this panic plot throughout treatment and brought it to each treatment session: it was then showed to the therapist who copied the information to the therapist version of the panic plot. For analyses, scores were added up into weekly frequency scores.

2.1. Statistical analyses

To investigate and compare the rate of improvement in frequency of panic attacks over time, two multilevel poisson models were build (Snijders and Bosker, 2000; Verbeke and Molenberghs, 2000). We used poisson regression to adequately model the counts (i.e., the discrete non-negative responses (0,1, ….)). The statistical significance of the regression effects was tested using the approximate t-test, and alpha was set at 0.05. The modeling strategy to examine the rate of improvement, the effect of tapering medication and possible differential effects across treatments (research goals 1 to 3), resulting in Model I, was as follows: firstly, an adequate representation of the variance structure of the repeated assessments was found using the following predictors (and its meaning in brackets): Intercept (week

0), Week (long-term changes), Lnweek (logarithm of week; short-term changes), Dcondition (dummy; differential effect of conditions at week 0), interactions of week with Dcondition, and Lnweek with Dcondition (differential effects of conditions in long-term and short-term changes, respectively), Dweek40 (dummy, change in effect at week 40), interactions of Dweek40 with Dcondition (differential effects of conditions in effect at week 40), interactions of Dweek40 with Dcondition and lnweek (differential recovery effects of conditions of change at week 40). Secondly, we retained the following effects (and their justification for not expecting) only when significant: Dcondition (due to random assignment, no initial differences expected), interaction Lnweek with Dcondition (if any, differential effects of conditions in long-term changes expected to suffice), Dweek40 (due to dummy coding, effect refers to CBT group, for which no tapering takes place).

To examine the relationship between rate of improvement of panic frequency and baseline severity of agoraphobia, we first removed from Model I non-significant effects to avoid instabilities of model estimates. Subsequently, we included the following effects: AG status (dummy; differential effect of AG status at week 0), interactions of AG status with Week (differential effect of AG status in long-term changes), and interactions of AG status with Week with Dcondition (differential change effects of conditions and AG status), resulting in Model II.

All models were built using the program MlwinN (Multilevel Models Project, 1995). In order to obtain a proper comparison between treatments, we distinguished three types of patients: dropouts, no-tapers, and completers. Dropouts were lost during the first treatment year because of various reasons such as non-compliance or needing other treatment. No-tapers failed to taper medication and used an SSRI throughout the entire study period. Patients were defined completers when treatment had ended with therapist consent. Also, completer patients received a minimum of 15 out of 21 CBT sessions and/or 8 out of 12 SSRI sessions. For the present analysis, only completer patients were included because the other groups were too small (regarding both numbers of patients and of available time points) to obtain reliable results (total panic logs available: for drop-outs: CBT $N=17$, SSRI $N=9$, CBT+SSRI $N=11$; for no-tapers: SSRI $N=6$, CBT+SSRI $N=5$). Further, data from one (CBT completer) patient was excluded from analyses, because the extremely high reported panic attack frequency (i.e., about 20 attacks per week) casted doubt on the score reliability. The number of panic logs present for analyses varied somewhat from week to week. Table 1 summarizes the number of available panic logs, as the mean number per treatment group for three time periods. To further evaluate differences between treatment groups per week, we used univariate analyses of variance (ANOVAs) and post-hoc pair wise comparisons, with bonferroni correction. Tests were two-tailed and alpha was set at 0.05.

3. Results

3.1. Sample information

After screening and randomization, 150 patients started treatment (see Fig. 1 for flowchart). According to our definition, 83 out of 150 patients who started treatment were completers of which CBT+SSRI: $N=27$, CBT: $N=32$, SSRI: $N=24$ (total $N=83$). In the completer sample, 56.6% was female. Mean age was 36.6 years (SD 10.7). On average, patients had suffered from PD for 7.4 (SD 7.9) years at pretest. About half of the patients did not suffer from AG or suffered from only mild AG (48.2%, $N=40$ of which $N=7$ no AG, and $N=33$ mild) while the other half suffered from moderate or severe AG (51.8%, $N=43$ of which $N=32$ moderate, and $N=11$ severe).

CBT completers received a mean of 19.0 (SD 4.0, range 7–25)[1] sessions. SSRI completers received a mean of 11.6 (SD 1.3, range 9–15) sessions. CBT+SSRI completers received a mean of 18.6 (SD 3.01, range 11–22) CBT sessions and a mean of 11.8 (SD 1.3, range 9–14) SSRI sessions.

Table 1
Mean numbers of available panic logs per week (min–max) at weeks 1–17, 18–35, and 36–52. *N* indicates total number of patients in sample.

Weeks	CBT ($N=32$)	SSRI ($N=24$)	CBT+SSRI ($N=27$)
1–17	26.94 (25–29)	20.88 (20–21)	22.94 (22–23)
18–35	23.50 (22–25)	19.55 (19–20)	20.66 (20–23)
36–52	15.18 (7–21)	18.10 (17–19)	15.88 (8–20)

3.2. Rate of improvement

Parameter estimates of Model I are presented in Table 2. As can be seen in Table 2 and Fig. 2, patients in all three treatment modalities improved significantly (effect of Week and Lnweek) on the frequency of panic attacks during treatment. As can be seen in Fig. 2, the expected frequency of panic attacks declined fastest after starting treatment and then levels off, resulting in virtually no panic attacks at all by the end of the year.

3.3. Treatment differences in rate of improvement

Model I revealed that the number of panic attacks in both SSRI and CBT+SSRI dropped significantly faster in time as compared to CBT (as indicated in Table 2 by the significant interactions between Week and SSRI, and Week and CBT+SSRI, respectively), whereas the difference in rate of improvement between SSRI and CBT+SSRI appeared to be non-significant (not shown explicitly in Table 2).

Additional analyses per week revealed significant differences in panic frequency between treatment groups at weeks 6, 7, 10, 11, 27–31, 33–37 and week 40 (all $p\leq 0.03$). Subsequent pair wise analyses revealed that in all these weeks CBT was outperformed by SSRI (weeks 11 and 33), or by CBT+SSRI (weeks 6 and 29), or by both CBT+SSRI and SSRI (the remaining weeks).

3.4. The effect of tapering medication on frequency of panic attacks

From week 40, patients receiving an SSRI started to taper medication. For CBT+SSRI and SSRI, Model I revealed no significant changes in panic attack frequency from week 40 (start tapering) up to week 52 (tapering completed) (indicated by non-significant two-way interaction effects of Dweek40 by SSRI and CBT+SSRI, respectively) implying that gains were maintained throughout medication taper. Also, no differential effects between SSRI and CBT+SSRI were found from week 40 up to week 52 (indicated by non-significant three-way interaction effects of Dweek40 and Lnweek by SSRI and CBT+SSRI, respectively).

3.5. The relationship between rate of improvement and baseline severity of agoraphobia

The parameter estimates of Model II are also presented in Table 2. The expected frequencies, on the basis of Model II, as a function of week and AG status (no/mild vs. moderate/severe) are depicted in Fig. 3, for each treatment modality separately. As can be seen in Table 2, no significant main effect of AG status (no/mild

[1] In four CBT-only cases, therapist and patient both agreed that more treatment sessions were not applicable because of early treatment success. These CBT completer patients received less than 15 CBT sessions (7, 11, 12 and 14 CBT sessions respectively).

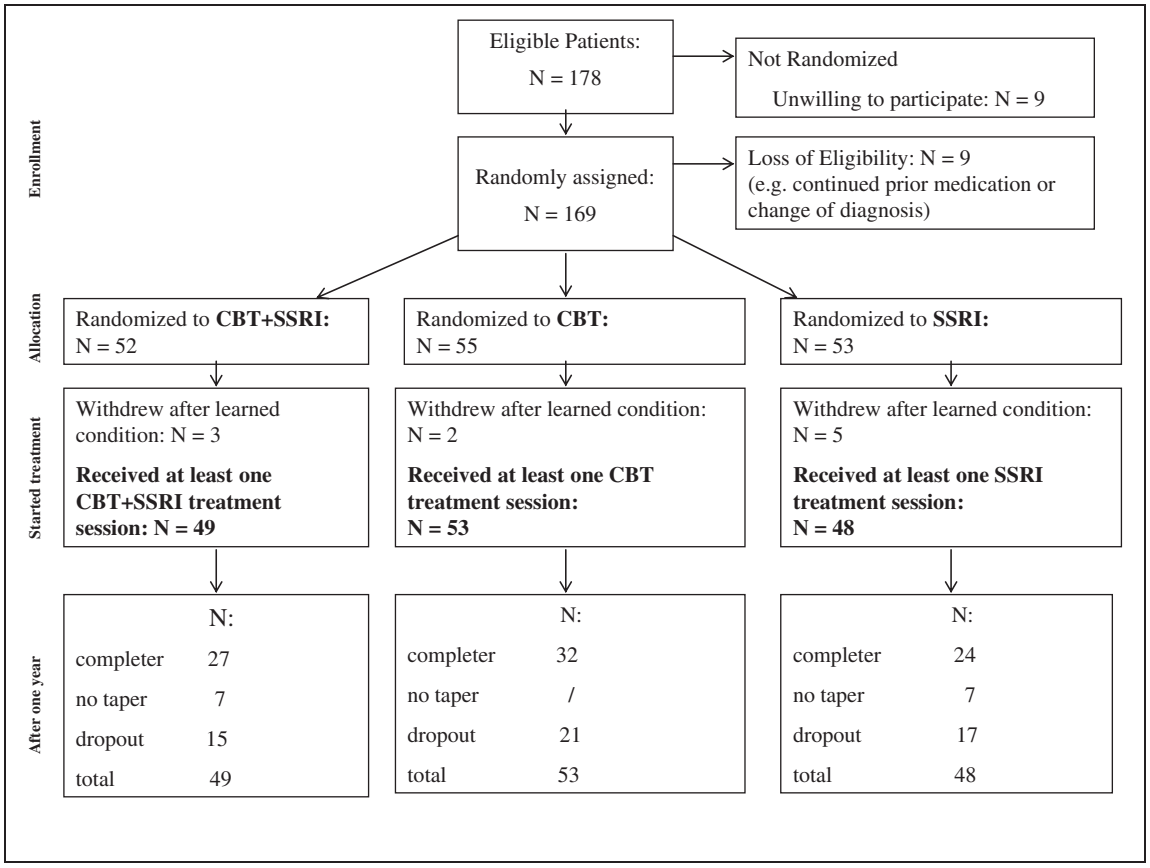

Fig. 1. Flowchart of study enrollment, allocation, and treatment end-point.

Table 2
Estimated coefficients and standard errors of the multilevel Poisson models:.

	Model I		Model II	
	Estimate	S.E.	Estimate	S.E.
Fixed effects:				
Intercept	1.18*	0.16	1.20*	0.23
Week	−0.03*	0.00	−0.04*	0.01
Lnweek	−0.27*	0.05	−0.27*	0.05
Week*SSRI	−0.06*	0.01	−0.06*	0.01
Week*CBT+SSRI	−0.09*	0.01	−0.05*	0.01
Dweek40*SSRI	−4.45	27.82		
Dweek40*CBT+SSRI	−29.64	17.62		
Dweek40*SSRI*Lnweek	0.97	7.32		
Dweek40*CBT+SSRI*Lnweek	8.25	4.61		
AG status			−0.03	0.31
AG statu*Week			0.02*	0.01
AG status*Week*SSRI			0.00	0.01
AG status*Week*CBT+SSRI			−0.05*	0.01
Random effects:				
Intercept	1.18*	0.16	1.69*	0.29

Note: NA=Not Applicable, S.E.=Standard Error, CBT=Cognitive Behavioral Therapy, SSRI=Selective Serotonin Reuptake Inhibitors, CBT+SSRI=Combined CBT and SSRI treatment.

* $p < 0.05$.

vs. moderate/severe) was found indicating that the frequency of reported panic attacks appeared to be equal at week 0 among patients with moderate or severe AG and patients without or with only mild AG. We subsequently found a positive significant interaction effect of AG status with week (effect of AG status *Week) and no differential effect of SSRI (effect of AG status *Week *SSRI), suggesting that patients in the SSRI and CBT condition with moderate/severe AG showed less decrease in reported panic attacks during treatment as compared to patients with no/mild AG. Subsequently, we also found a negative significant interaction effect of AG status, week, and CBT+SSRI (effect of AG status *Week *CBT+SSRI), indicating that among patients with moderate or severe AG, rate of improvement was faster with CBT+SSRI as compared to SSRI and CBT.

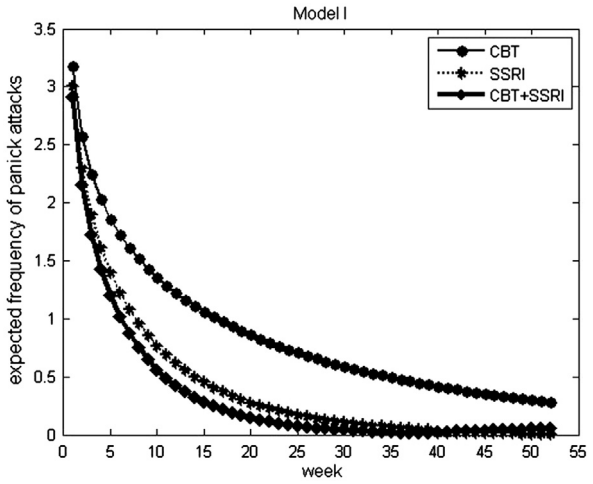

Fig. 2. Plot of expected frequency of panic attacks according to Model I for three groups: CBT, SSRI, and CBT+SSRI.

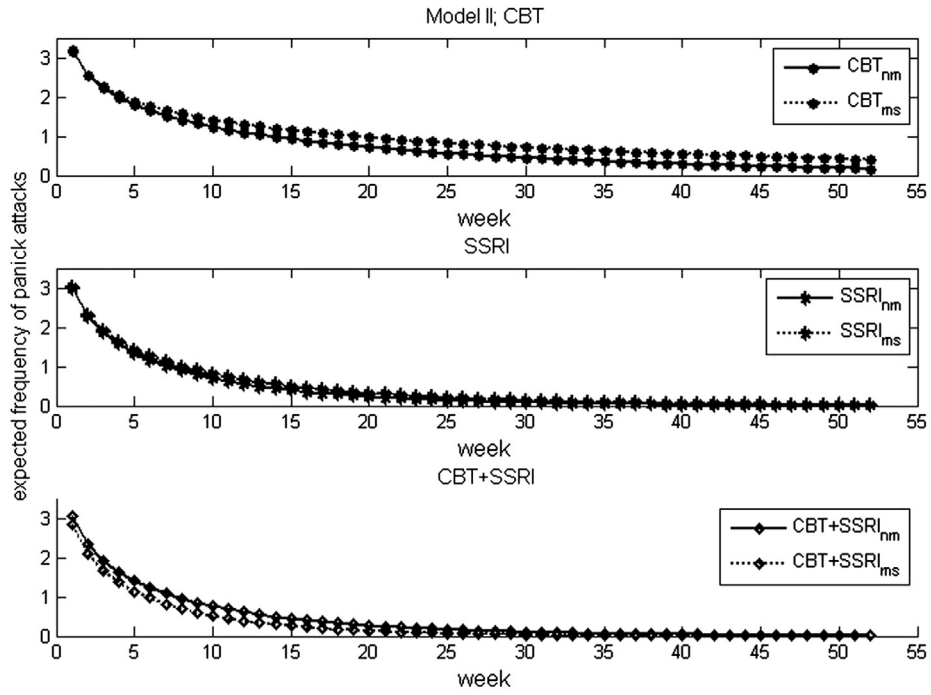

Fig. 3. Plot of expected frequency of panic attacks according to Model II for CBT (nm/ms), SSRI (nm/ms), and CBT+SSRI (nm/ms) in which nm=no AG or mild AG and ms=moderate or severe AG.

4. Discussion

To our knowledge, this is the first study to analyze the differential rate of improvement in panic frequency in a randomized trial evaluating CBT, SSRI and the combination of both for PD with or without AG. As expected, randomized patients who completed treatment showed a decline in number of panic attacks during treatment, resulting in virtually no panic attacks at the end of treatment. Thus, all three treatments tended to lead to improvement on the key symptom of PD, namely panic attacks. Although it was expected that patients who received CBT would need more time to reach the same rate of improvement as patients who were assigned to SSRI and CBT+SSRI, we were surprised to find that patients who received CBT reported relatively more panic attacks not only in the first phase of treatment but throughout the entire year. Furthermore, the difference in frequency of panic attacks reached statistical significance even up to week 40. A treatment with SSRI-only appeared equally effective in diminishing the frequency of panic attacks as the combined treatment implying that no additive value of CBT to SSRI-only was observed.

Clinical studies reveal that SSRIs need about four to six weeks of treatment before becoming effective (Bandelow et al., 2008). Visual inspection of Fig. 2 suggests that frequency of panic attacks started to decline from week 1 in each treatment modality. Subsequent analyses revealed that there were no significant differences between treatment modalities up to week 6 suggesting that SSRIs indeed started to become effective from week 6, resulting in significant differences in weeks 6–12, while CBT treatment needed more time to become equally effective. This would be in agreement with current understanding of the neurobiology of PD (Gorman et al., 2000; Ninan and Dunlop, 2005). It is thought that CBT and SSRI may operate through different pathways in the brain leading to a different pattern of response over time. Following this, it might be expected that when using an SSRI, effects will first be observed on the level of somatic symptoms resulting in a more rapid decline of panic attacks as compared to CBT. It could be presumed that CBT would reveal its therapeutic effect in the early phase of treatment on different process measures (e.g. belief in catastrophic cognitions) but up to date, no data is available to corroborate this.

Regarding the context–safety hypothesis, we found no evidence for the assumption that patients having discontinued the SSRI subsequently relapse due to a shift in context. In the ten weeks following tapering medication, patients in SSRI and CBT+SSRI maintained achieved gains regarding panic frequency. It can be argued that for patients receiving both CBT and SSRI, CBT enhances patient's confidence in coping with possible withdrawal effects during tapering. Interestingly however, patients receiving SSRI-only also maintained their gains following medication taper, questioning the additive value of CBT. Possibly, the adequate information and guidance of clinicians through-out the tapering process contributed to the prevention of relapse but more research is clearly needed on relapse factors.

Present findings support the notion that patients with PD and moderate or severe AG at baseline are more seriously impaired in daily functioning as compared to patients with PD without AG (Grant et al., 2006). Although it is suggested that there is no reason to offer PD patients with AG a different kind of treatment than patients without AG (Furukawa et al., 2006), present findings suggest that specifically for patients with moderate to severe AG, a combined CBT and SSRI treatment offers a surplus value to both mono-treatments. This is in line with the notion that especially exposure-based techniques are considered to be important in the treatment of moderate to severe AG.

Strengths of the present study include the advanced statistical techniques applied, which resulted in a sound model of rate of improvement in panic frequency during and across the different treatment modalities. Also, results can be considered highly externally valid with respect to type of patients, type of treatments, and type of treatment centers (Van Apeldoorn et al., 2008) which allows practitioners to draw inferences regarding clinical practice.

The fact that frequency of panic attacks was not assessed beyond the full year of treatment can be considered a limitation

of this study. Panic frequency data was collected for one year (albeit long as compared to other studies), until ten weeks following medication taper. We cannot rule out the possibility that relapse occurred in the weeks after that, although follow-up assessments, six and twelve months after medication taper, again revealed no relapse on several outcome measures (Van Apeldoorn et al., 2010). A second factor that possibly limits the reliability of our findings is the fact that patients' compliance to accurate and immediate completing the panic plot is not assessed in this study. However, every session the panic plots were checked upon receipt for the accuracy of completion by the therapist. In general, event-contingent recording has been particularly suitable for data collection in the domain of psychopathology, when the clinical symptoms are sudden and have acute onset (Moskowitz and Sadikaj, 2011). A third limitation is that we did not collect another process variable, next to panic frequency, to supplement present findings. Although irrefutable a core symptom of PD, other important aspects of the disorder would have been interesting regarding rate of improvement as well. A suggestion for future research might be adapting a more process-oriented approach in which timing and sequencing of changes regarding different aspects of PD within and across treatments is the focus (for examples of such a process-oriented approach, see Stanley et al., 1996; Polman et al., 2011). This might lead to a better understanding of processes involved in recovery from PD as a result from different treatment modalities.

In the treatment guidelines for PD we have seen a development from a more psychopharmacological approach to a more psychological approach. What can we suggest the practitioner facing the decision how to treat his PD patients, based on present findings? From a cost-effectiveness perspective, SSRI seems first choice because it results in a rapid decline in the number of panic attacks and leads to no relapse following medication taper. For patients with moderate or severe AG however, the combined CBT+SSRI treatment may be recommended because for this patient group, a combined package was associated with the most rapid decline in the number of panic attacks and again, no relapse after medication taper was observed. The latter finding is especially important considering the hesitancy that clinicians tend to feel toward tapering, which can result in ongoing, perhaps even unnecessary, SSRI treatment.

We emphasize the need to integrate insights from contemporary learning theory in clinical studies under real life conditions with real life PD patients. The present study contributes to this endeavor as no stringent inclusion criteria were applied, clinical practice sites joined and treatments were delivered according to care as usual. In this way, we may come to understand how phenomena observed in the laboratory (such as context dependency in the extinction of fear), emerge into the clinical practice of treating PD patients. Future studies are required to examine the effects of SSRI, CBT, and CBT+SSRI on other process measures than panic attack frequency.

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Conflict of interest

No financial or commercial involvements that might present a conflict of interest in connection with the present study are present.

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