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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