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Long-Term Treatment Outcome and Prognostic Factors of Panic Disorder

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Panic disorder with or without agoraphobia seems to be a more chronic and relapsing form of anxiety disorder than was previously thought. There is considerable disagreement concerning the clinical course of this disorder. With respect to psychopharmacological treatments, the rates of recovery vary widely and patients showing improvement, although not severely disturbed, are still with some residual symptoms [1, 2]. A large follow-up study of 423 patients taking part in two multicenter drug trials, with alprazolam, imipramine and placebo, assessed 4 years later, revealed that 31% remained well during follow-up, and in 69% symptoms continued [3]. Preliminary findings from another study reported by Keller, [pers. commun., 146th Annual Meeting APA 1993] using data from an ongoing prospective, naturalistic, longitudinal study with 700 patients suffering from panic and other anxiety disorders (Harvard/Brown Anxiety Research Project – HARP) also showed that panic disorder is a recurrent condition with a worse prognosis than unipolar depression. The comorbidity of avoidance and depression exacerbate the course and severity of the disorder. These findings suggest that panic disorder could be a rather chronic and disabling condition, especially in complicated forms, and adequate treatment must encompass other alternatives.

A more optimistic view is held by behavior therapists about the course of panic disorder with agoraphobia after treatment with exposure therapy [4–6]. Several follow-up studies demonstrated the maintenance of the treatment results for periods of 4–9 years [7–11]. In spite of the good response to exposure therapy, the chronic nature of agoraphobia was acknowledged [6].

Although exposure treatments addressed avoidance behavior directly, treatment responders presented large reductions in nonphobic symptoms. However, only recently psychological treatments have been aimed directly at the reduction

of panic attacks. The reviews published so far attested also the efficacy of these treatments [12–16].

It seems that different therapeutic options available draw different prognostic pictures of the long-term course of panic disorder, even though most epidemiologists and clinicians agree on the chronic nature of this disorder. To improve the long-term course of panic disorder, we need accurate information about the treatment outcome, the predictors of the different treatments, knowledge about subtypes of patients that might respond to specific types of treatment and the optimal length of these treatments.

Pharmacological Treatments

A significant proportion of panic disorder patients with or without agoraphobia benefit from psychopharmacological treatments. The short-term efficacy of benzodiazepines, like alprazolam, of tricyclic antidepressants, as imipramine, clomipramine, or specific serotonin reuptake inhibitors, as fluvoxamine, was demonstrated in controlled studies [17–21]. Drug trials are generally designed to evaluate short-term efficacy and discontinuation effects, a long-term follow-up is generally not reported. There is a lack of information about long-term outcome or predictors in drug treatment of panic disorder. Few exceptions are found in the literature. An example is the study conducted by Schweizer et al. [22]. Assessment conducted at the 32nd week showed a differential effect of imipramine, alprazolam and placebo on the percentage of panic-free patients. Alprazolam had the highest percentage of panic-free patients, 62%, whereas imipramine and placebo had similar results, only 26% were panic free. A different result was obtained in a recent long-term outcome study done by Pollack et al. [23]. At a mean follow-up of 1.5 years, although there was no statistically significant difference between the groups in the percentage of panic-free subjects, the groups taking high-potency benzodiazepines and antidepressants had higher rates of panic-free patients, 57.1 and 58.3%, respectively, than the group without medication, 37.5%.

Rickles et al. [24] found in their 1-year follow-up that the clinical outcome of patients submitted to a maintenance drug treatment with alprazolam, imipramine or placebo was predicted by the completion of 8 months of study treatment, irrespective of the type of medication. In this study, baseline severity of generalized anxiety, but not panic frequency, was predictive of a presence of panic attacks at follow-up. Approximately 50% of patients were receiving drug therapy at 1 year follow-up. A history of treatment with antipanic medication before study, high phobia baseline score and noncompletion of the maintenance trial were the predictors of continued drug therapy during the follow-up period. Predictors of worse outcome at follow-up in the study of Pollack et al. [23] were the

total duration of the disorder, agoraphobic subtype and the presence of comorbid social phobia. An additional contribution comes from a follow-up involving 423 patients who had participated in the Cross-National Collaborative Panic Study [3]. It was found that the probability of the occurrence of a panic attack 4 years after the end of the drug trial was negatively related to the duration of initial treatment and positively related to the degree of social disability at baseline, also the probability of recurrence of panic attacks was lower in patients with uncomplicated panic disorder than in those with agoraphobia.

There is also evidence that personality disorders negatively influence the treatment outcome of panic patients. In some patients the personality disorder remits with successful treatment, but in the majority it is a factor associated with a worse outcome [25]. Personality disorders may be a predictor of relapse after termination of antipanic medication [26]. In a 3-year follow-up of 89 panic disorder patients naturalistically treated was observed that panic subtypes according to the degree of avoidance were predictive of symptoms and social distress [27]. In this study abnormal personality was, in fact, the strongest predictor of long-term social maladjustment.

The proportion of patients still taking antipanic drugs after 1–4 years of follow-up ranged from 47 to 70% [24, 28–30]. This continued use of drugs in a subgroup of patients was reported with clonazepam, alprazolam and imipramine. For some patients the maintenance of intake could be related to the appearance of withdrawal symptoms during discontinuation. At least for some drugs, like benzodiazepines, the rates of recurrence of panic attacks during discontinuation is high, 52–74% [24, 31, 32]. For a subsample of these patients it is difficult to stop taking the drugs. Mavissakalian and Perel [33] reported that approximately 75% of patients with panic disorder and agoraphobia who had shown a marked and stable response to 6 months of treatment with imipramine relapsed within 6 months of discontinuing the drug. In marked contrast, none of the patients from a similarly treated sample with imipramine and who had received a half-dose maintenance therapy for 12 additional months relapsed or had a sustained worsening of panic or phobic symptoms throughout the maintenance period.

With respect to benzodiazepines, the rate of drug taper is an important variable to predict severity and intolerability of discontinuation. Other predictors of withdrawal symptoms in panic disorder patients treated with alprazolam during 8 months were studied by Rickles et al. [24]. They reported that 33% of the patients of a alprazolam group were unable to discontinue the drug successfully. These authors also found that frequency of pretreatment panic attacks and duration of illness both predicted severity of withdrawal and unsuccessful taper outcome. Other authors [32] have also found that pretreatment levels of anxiety were predictive of both rebound and relapse of symptoms during alprazolam taper in panic disorder patients.

Psychological Treatments

Panic Disorder with Agoraphobia

Reviews of behavioral treatments have shown that the in vivo exposure modality produced clinically significant changes in 60–75% of patients who completed treatment [5, 34–37]. The changes induced by the treatment are not restricted to avoidance behavior but also affect nonphobic anxiety, panic, depression and somatization, and these changes are maintained in follow-up. Research conducted by one of the authors at the Behavioral Psychotherapy Department showed this pattern of changes induced by exposure therapy, programmed practice, in 47 PDA patients during a 12-week treatment period and in 39 PDA patients who completed a 6-month follow-up (fig. 1). The effect sizes from before treatment to the follow-up assessments ranged from 0.61 in anger-hostility to 2.99 in agoraphobic avoidance, with a mean effect size of 1.15 across the 12 dependent variables [38].

In a landmark paper Barlow and Wolfe [39] drew attention, some years ago, to treatment failures, dropouts and relapses. Taking into account these subjects, the ‘actual rate is closer to 49 than the oft quoted 75% of success’. It has also been recognized that treatment responders are left with residual symptomatology. We have analyzed these questions of individual response to treatment in a study with 37 patients with panic disorder, 26 with extensive avoidance/panic disorder with agoraphobia, and 11 without extensive avoidance/panic disorder, during a 12-week cognitive behavioral treatment [40]. One panic disorder patient with agoraphobia refused treatment, 2.7%, and 9 dropped out of treatment, 24.3%, 8 panic disorder patients with and 1 without agoraphobia. The treatment induced statistically significant changes in avoidance, panic, anxiety, depression, somatization and fear of fear. But when the results were also analyzed according to a 5-point Global Assessment of Severity Scale rated consensually by the therapists, we saw a different picture. Four patients were considered treatment nonresponders, 10.8%, 2 with and 2 without agoraphobia did not improve during the treatment and only 8 were considered completely symptom free at the end, 21.6%, 3 with and 5 without agoraphobia. So the majority of the patients at the end of treatment were in between these two conditions, they achieved some improvement but they were not completely recovered. We concluded that ‘approximately 80% of the patients could have improved more than they actually did’. It seems that despite the demonstrated efficacy of behavioral treatments there is definitely room for improvements regarding these treatments.

Several attempts have been made to enhance the effects of the standard exposure therapy with other psychological treatments [41–54]. With few exceptions, the addition of these components to exposure has produced small or few differences between the diverse treatment packages at the end of treatment or at the follow-up.

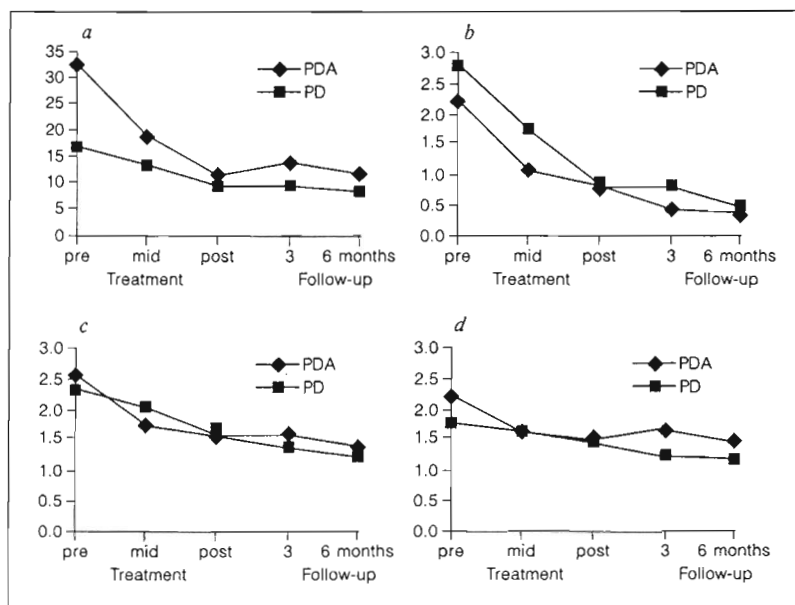


Fig. 1. Changes during a 12-week treatment period in panic disorder patients with ($n = 47$) and without agoraphobia ($n = 34$), and in a 6-month follow-up period (39 patients with agoraphobia and 21 without). PD = Panic disorder; PDA = panic disorder with agoraphobia. *a* Agoraphobic avoidance. *b* Panic frequency. *c* Anxiety. *d* Depression.

As far as psychological treatments are concerned, the best choice available for the treatment for a panic disorder patient with agoraphobia seems to be an exposure program using a group format with a manual-directed exposure [55]. The addition of a maneuver that gives a sense of personal control over panic attacks, cognitive therapy or applied relaxation might not improve the treatment effects but helps the patient to comply with exposure homework tasks. A gentle and supporting environment that encourages the continuous exposure of the patient to the feared situations could be one of the important factors in the long-term outcome of these patients [51, 56, 57].

A reasonable number of panic disorder patients with agoraphobia respond well to exposure treatments. On a clinical basis, it would be useful to know in advance what type of patients would benefit most or what type of patients do not improve with this kind of therapy. Three studies examined directly the predictive factors in the treatment of these patients [9, 58, 59]. In the Chambless and Grace-

ly study [58], higher frequency of panic attacks in the pretreatment assessment and unassertiveness posttreatment presented a tendency for worse long-term outcome. A measure of fear of fear, the Agoraphobic Cognitions Questionnaire, at the pretest presented also a tendency for poor end of treatment results. Whereas in this study the pretreatment scores were not related to the long-term outcome, a different pattern of results were obtained by Fisher et al. [9]. In their study initial higher levels of phobic anxiety and treatment nonresponse in depression and social anxiety were clearly associated with a worse long-term outcome. However, initial higher scores in psychopathology might not always be associated with a worse outcome. In the study of Janssen et al. [59] higher scores of anxiety at a behavioral avoidance test were predictors of improvement, whereas higher scores on a measure of perception of autonomic sensations were associated with a worse outcome at follow-up.

Panic Disorder without Extensive Agoraphobic Avoidance

Behavior therapy is not the treatment of choice for the disorders which are not related to an evoking stimulus, like the anxiety states [60]. Even though this assertion is not without its critics [61], it was with the cognitive model of anxiety disorders in general [62] and with the cognitive model of panic [63] that a theoretical support for the empirical procedures for treating panic attacks became available. Four studies using diverse forms of cognitive therapy with other psychological maneuvers, relaxation training, biofeedback and respiratory control, demonstrated the efficacy of psychological procedures to achieve large reductions of symptoms in patients whose main complaints were panic attacks [64–67]. Three of these studies reported follow-up periods from 5 to 24 months which demonstrated that the changes during treatment of 9–15 sessions were reliably maintained [64, 65, 67]. Only one of these studies reported the percentage of panic-free subjects at the follow-up which was an encouraging 90.9%.

After these studies, nine other psychological treatment trials for panic disorder patients were reported, and six of them had follow-up periods ranging from 6 to 24 months (table 1).

Of the studies without follow-up, two were comparisons between cognitive behavioral therapy and pharmacological treatment, alprazolam [68] and fluvoxamine [69], and one a report of the effects of 12 sessions of cognitive behavioral therapy on several dimensions of panic attacks, verbal-cognitive, physiological and behavioral [70]. As we are concerned here with long-term effects these studies will not be further analyzed.

The other six studies reported follow-up periods ranging from 6 to 24 months [38, 71–75]. One hundred and twenty patients completed these follow-ups in purely cognitive behavioral treatment, and treatment duration ranged from 9 to 18 sessions, with a mean of 13 sessions. This relative brief period induced marked

Table 1. Panic disorder treatment studies

Study	Year	n	Treatment duration weeks	Follow-up months	Panic-free patients %	Type of treatment
Baptista [38]	1994	21	12	6	80	PAAMT
Beck et al. [71]	1992	29	12	12	83	FCT
Black et al. [69]	1993	—	8	—	—	CT
Craske et al. [72]	1991	16	15	24	81.3	PCT
Klosko et al. [68]	1990	—	15	—	—	PCT
Michelson et al. [41]	1990	—	12	—	—	CBT (CT + AR)
Ost [73]	1988	7	14	19	100	AR
Sokol et al. [74]	1989	17	18	12	100	FCT
Telch et al. [75]	1993	30	9	6	83.3	PCT

PAAMT = Panic anxiety and avoidance management training; FCT = focused cognitive therapy; CT = cognitive therapy; PCT = panic control treatment; CBT = cognitive behavioral therapy; AR = applied relaxation.

changes in the frequency of panic attacks that were maintained at the last assessment of the follow-up. Using the criteria of the percentage of panic-free subjects, these six studies had a mean of 87.9% subjects without panic attacks at follow-up. However, the efficacy of cognitive behavioral treatment for panic disorder is not restricted to panic frequency. Our research as well as data reported in other treatment studies showed that this treatment also affects the other important dimensions of panic disorder, avoidance, anxiety and depression (fig. 1). The effect sizes from pretreatment to the 6-month follow-up in 21 panic disorder patients ranged from 0.78 in anger hostility to 1.60 in anxiety, with a mean effect size across 12 measures of panic symptomatology of 1.07. Beyond the importance of this generalized treatment effect and its maintenance is the fact that this new cognitive behavioral approach to panic disorder produces a large effect size, very similar to the one induced by the more empirically tested and scientifically respected exposure treatment to agoraphobia.

Two other recent reviews [13, 15] describe ongoing treatments that attest to the efficacy of cognitive behavioral treatment for panic disorder. However, none of these studies looked for predictive factors for this type of treatments. In our study [38] we pooled the treatment data from the treatment of 39 panic disorder patients with and 21 without agoraphobia and we found that a global measure of improvement assessed at the 6-month follow-up was predicted by the end of treat-

ment depression and by the end of treatment score on a measure of catastrophic misinterpretation, the Agoraphobic Cognitions Questionnaire. None of the pre-treatment measures predicted the follow-up status. It seems that a failure to reduce depression and demoralization feelings associated with panic, or the belief about the personal dangerousness of the panic symptoms during treatment is associated with poorer long-term outcome.

Psychological and Pharmacological Treatments Combined

The available data from clinical trials with drugs – benzodiazepines and antidepressants – and with cognitive-behavioral treatment showed both treatments equally efficacious in reducing panic symptomatology with a group of patients without a complete recovery or with residual symptoms. The wisest way to proceed seems to study the interactions of both treatments in order to look for addition or potentiation effects.

Low potency benzodiazepines reduced the effect of exposure therapy as it is already known from animal learning experimentation. Outcome data from the Cross-National Collaborative Panic Study [76] might suggest that alprazolam and exposure therapy might potentiate each other. Research studying this association, however, produced negative results. Marks et al. [77] found that alprazolam interfered with long-term gains from exposure. In a commentary, other researchers reply that the study showed only how not to combine alprazolam with exposure [78].

In relation to antidepressants the studies were mainly focused on imipramine. Interactions between imipramine and exposure generally found that their short-term effects are synergistic. Six controlled studies [10, 79–83] addressed this question and only one reported negative results [10]. Data from follow-up conducted in these patients showed that this difference between treatments was maintained only in one study [81]. Telch et al. [81] found that patients assigned to the combined treatment (imipramine and exposure) demonstrated superior improvement at 6 months in several panic measures, avoidance, anticipatory anxiety and depression. Nevertheless, longer follow-up periods failed to demonstrate this differential treatment effect. Zitrin et al. [80], Mavissakalian and Michelson [82], Lelliott et al. [10] and Nagy et al. [83] reported follow-up periods from 2 to 5 years. The follow-up reported by Lelliott et al. [10] was based in the Marks' study where no improvements were found by the association of imipramine with exposure. The long-term effects of this association in panic and avoidance measures showed the same pattern. Contrary to the results obtained on a short term, the follow-ups reported by Zitrin et al. [80], Mavissakalian and Michelson [82] and Nagy et al. [83] did not show an effect of imipramine associat-

ed with exposure. However, a sustained improvement was found in all studies irrespective of the medication status during follow-up.

This might imply that a combined intervention that addresses several components of the disorder has a superior therapeutic efficacy on a short term than each of its components. As this effect is not maintained on a long term, it seems that when the basic aspects of panic disorder, panic attacks and avoidance, are changed or reduced by any treatment, these changes are likely to endure and to generalize to the secondary symptoms, for instance somatization or demoralization.

In spite of the studies reviewed, it seems that we have several potent therapeutic options to change the course of a chronic condition, panic disorder, and that there is a definite room for integration of these treatments. Future research should aim first at identifying subtypes of panic patients, for instance those with comorbid depression, avoidance or personality disorders, and then study which treatment packages are most effective in changing the specific response profiles of these patients. The most adequate treatment should encompass the available strategies aimed at the specific problems presented by the different subtypes of panic disorder.

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