A Clinical Application

We used ambulatory psychophysiological monitoring in the treatment of a patient with PDA (see Hofmann & Barlow, 1996, for a fuller account). Following successful treatment, the patient relapsed after a stressful life event and again became concerned that the panic attacks might reflect heart problems. Ambulatory physiological monitoring served two purposes. First, it demonstrated to the patient that she was in fact overestimating her actual heart rate. Second, because the increase in heart rate and respiration followed anxious thoughts, the patient was able to recognize that rather than coming from "out of the blue" as she had initially thought, the attacks were indeed precipitated by anxious thoughts and were therefore manageable. Although historically, ambulatory monitoring of heart rate and finger temperature have been most often used to corroborate self-reported panic attacks, this case example suggests the beneficial uses of psychophysiological assessment in the treatment of PDA. Although the costs associated with ambulatory monitoring are dropping, its utility in assessment and treatment planning needs to be balanced against the costs. Nevertheless, such physiological monitoring devices appear to hold promise for the future.

Issues of Medical Comorbidity and Evaluation

Whereas panic attacks are typically associated with anxiety disorders, similar attacks can be a sign of an underlying medical condition. Thus a key component of a diagnostic assessment includes obtaining a thorough medical history to ensure that potential medical causes for the panic symptoms are ruled out. Medical conditions may have a direct impact on the patient's somatic presentation or may actually be causally related to the incidence of panic attacks. As Zaubler and Katon (1996) have pointed out, it can be difficult to identify whether a medical condition is a cause, a correlate, or a complicating factor in panic disorder. Because the physical manifestations of panic attacks can mimic cardiorespiratory, gastrointestinal, and otoneurological illness, a large percentage of patients with panic disorder or PDA may initially seek care in the medical setting (cf. Zaubler & Katon, 1996). As we review below, a number of major physical disorders can be responsible for anxiety and panic-like symptoms; however, a medical etiology for the physical disorder does not necessarily rule out the coexistence of panic disorder or PDA, and thus the necessity of treating panic attacks directly.

Medical Conditions That May Mimic Panic Attacks

Specific disorders that may show panic-like symptoms and should be ruled out include endocrine disorders (e.g., hypoglycemia, hyperthyroidism, Cushing's syndrome, menopause, premenstrual dysphoric disorder, pheochromocytoma); cardiovascular disorders (e.g., mitral valve prolapse [MVP], cardiac arrhythmias, congestive heart failure, hypertension, myocardial infarction); respiratory disorders (e.g., chronic obstructive pulmonary disease, asthma); neurological disorders (e.g., epilepsy, Huntington's disease, vestibular disorders, multiple sclerosis); and substance-related anxiety following intoxication with drugs such as caffeine, cocaine, amphetamines, or withdrawal from drugs such as alcohol, barbiturates, or opiates. The effects of caffeine in provoking panic have been reviewed in Chapter 5. To illustrate the clinical overlap in symptomatology, hyperthyroidism results from excessive thyroid gland activity, and 95% of patients with this disorder report nervousness and episodic anxiety as their primary complaint. More than two-thirds of this group also report palpitations, tachycardia, and dyspnea (difficulty breathing)—all common panic attack symptoms. A years, and the disorder mentioned physical logical factors to ex comorbid physical c attacks directly.

The medical co ntion to possible org cardi ccondition a mitral valve of the h dyspnea, tachycard unusual and difficult relation of PDA to high percentage of (Crowe, Pauls, Szym Zitrin, & Zeldis, 19 be a biological mark ticated examinations high prevalence of A linking panic disorder concluded that the was due to biased sification of difference Fox, 1991). Indeed, card iologists cannot efficients below .20 and panic disorder Isaki, & Gejyo, 199 MVP has a ben on MVP and panic guishing patients wi There appears to be from around the US PDA to be no great Spacavento, Jacobsenence are quite varia from 4% to 7%, an age, peaking during Tsai, Hou, Chen, &e children with MVP anxiety than children reported in the litera appear to affect clin to be no clinical rea

Medical Comorbidity

In addition to anxiety coexist with genuine
attack symptoms. As for PDA, the age of onset for hyperthyroidism is between 20 and 40 years, and the disorder is more common among females. Importantly, any of the above-mentioned physical conditions may coexist with panic attacks and interact with psychological factors to exacerbate the effects of the panic attacks. Therefore, the diagnosis of a comorbid physical disorder should not rule out the potential necessity of treating the panic attacks directly.

The medical condition that has unquestionably received the greatest attention in relation to possible organic etiologies of panic is MVP. MVP is the most commonly occurring cardiac condition and results from an alteration (sagging) in the connective tissue of the mitral valve of the heart. It is characterized in its extreme form by chest pain, palpitations, dyspnea, tachycardia, lightheadedness, fatigue, and anxiety, and is accompanied by an unusual and difficult-to-characterize systolic murmur. The early excitement concerning the relation of PDA to MVP was caused by the fact that a series of early studies reported a high percentage of patients with recurrent panic attacks who also presented with MVP (Crowe, Pauls, Symen, & Noyes, 1980; Grunhaus, Gloger, Rein, & Lewis, 1982; Kantor, Zitlin, & Zeldis, 1980). These early data provoked a flurry of speculation that MVP might be a biological marker for panic in a substantial number of patients. However, more sophisticated examinations using echocardiogram procedures failed to confirm the earlier-reported high prevalence of MVP, and to date there is no firm evidence for a common genetic factor linking panic disorder and MVP (Rosenman & Swan, 1988). Researchers have generally concluded that the high prevalence of MVP in anxiety disorders found in earlier studies was due to biased screening, and sophisticated studies point to bias and erroneous classification of differences as reasons for early positive findings (cf. Shear, Deveeroux, & Kramer-Fox, 1991). Indeed, as pointed out by Dager, Comess, Saal, and Dumner (1986), even expert cardiologists cannot agree on the presence or absence of MVP, as reflected in kappa coefficients below .20. Follow-up studies have failed to find an association between MVP and panic disorder (e.g., Bowen, D'Arcy, & Orchard, 1991; Hamada, Koshino, Misawa, Isaki, & Gejyo, 1998; Toren et al., 1999).

MVP has a benign prognosis (Bouknight & O'Rourke, 2000), and current consensus on MVP and panic disorder holds that there is little if any clinical significance in distinguishing patients with both disorders from those with only panic disorder (Singh, 1996). There appears to be no increased risk for MVP in patients with PDA, based on studies from around the United States that have found the prevalence of MVP in patients with PDA to be no greater than that found in the normal population (e.g., Mazza, Martin, Spacavento, Jacobsen, & Gibbs, 1986; Toren et al., 1999). Current rates of MVP prevalence are quite variable, due to different diagnostic criteria. Conservative estimates range from 4% to 7%, and prevalence is higher among women and appears to be a function of age, peaking during the 30s. Panic attacks do not appear to exert any effect on MVP (Yang, Tsai, Hou, Chen, & Sim, 1997). Interestingly, Kearney and colleagues (1996) found that children with MVP who were aware of their medical diagnosis reported significantly more anxiety than children with other cardiac conditions and higher than normative values reported in the literature. Nevertheless, the presence of MVP comorbid with PDA does not appear to affect clinical course or response to treatment (Singh, 1996), and there appears to be no clinical reason to alter clinical strategies in patients with PDA who also have MVP.

Medical Comorbidity

In addition to anxiety disorders' mimicking physical complaints, anxiety disorders often coexist with genuine medical illness. Patients with PDA have an increased rate of medical
illnesses, including migraine (Stewart, Linet, & Centenano, 1989), hypertension, coronary artery disease, ulcer, and asthma (Katon et al., 1986; Rogers et al., 1994). The rate of panic disorder in patients with cardiac ailments is higher than the general population (9%, Goldberg et al., 1990; 23%, Katon et al., 1988; 16%, Yinglin, Wulsin, Arnold, & Rosenbaum, 1993). In addition, patients with PDA have an increased rate of respiratory illnesses such as asthma (Carr, Lehrer, Rausch, & Hochron, 1994; Perna, Caldirola, Arancio, Bellodi, 1997) and chronic obstructive pulmonary disease (Karaigi, Rifici, Dodd, & Kolli, 1990; Smoller, Pollack, Otto, Rosenbaum, & Kradin, 1996), as well as an increased rate of disability related to vestibular disease (Stein, Asmundson, Ireland, & Walker, 1994).

The presence of PDA may function to alter a medical disorder's presentation, course, and treatment outcome. PDA can worsen cardiac disease (Katon et al., 1992), and, as reviewed in Chapter 1, longitudinal studies have shown phobic anxiety to be associated with sudden cardiac death (Kawachi, Sparrow, Vokonas, & Weiss, 1994, 1995). Similarly, some medical conditions have been identified as risk factors for panic disorder. For instance, the development and severity of asthma may put an individual at risk for panic (Carr, 1998, 1999; Feldman, Giardino, & Lehrer, 2000). Substance abuse is also frequently considered a risk factor for development of panic (Cox et al., 1990), and caffeine, marijuana, and cocaine use have been associated with panic onset (e.g., Aronson & Craig, 1986; Geraci et al., 1991; Louie, Lannon, & Ketter, 1989; Schnell & Daghastani, 1986; Szuster, Pontius, & Campos, 1988).

Recognition of PDA in Medical Settings

Nearly 85% of patients with PDA initially seek medical attention for their symptoms (Katerdahl & Realini, 1995); however, PDA is poorly recognized in medical settings. Indeed, past studies have shown that the majority of patients with PDA (70%) saw an average of 10 physicians before finally being diagnosed (Sheehan, 1982). This finding is consistent with more recent studies describing high rates of physician nonrecognition of PDA (61% in primary care, Spitzer, Williams, Kroenke, et al., 1994; 98% in emergency departments, Fleet et al., 1996; and 80% in general medical patients referred for psychiatric evaluation, Roy-Byrne & Katon, 2000). Thus it is quite common for patients presenting to mental health clinics with PDA to have had a thorough battery of medical evaluations to rule out a medical etiology. Nevertheless, clinicians should be aware of the various physical disorders that can mimic panic attacks.

Roy-Byrne and Katon (2000) have cited several reasons for the nonrecognition of anxiety in medical settings, including patient barriers (e.g., stigma of mental illness, lack of knowledge of mind-body connection, cultural differences in clinical presentation), physician barriers (e.g., tendency to look for physical causes of somatic symptoms, overemphasize on nonmissing medical disorders in our litigious society, tendency to see anxious patients as "difficult") (Hahn et al., 1996), and system and process-of-care barriers (e.g., lack of adequate time for primary care physician diagnosis, overwhelmed medical system, need for health care reform). Compounding the lack of recognition of PDA in medical settings, a number of studies have shown that even when recognized, anxiety disorders are inadequately treated (Fifer et al., 1994; Mathias et al., 1994; Yelkin et al., 1996). As Higgins (1994) suggests, improved recognition alone is inadequate to increase identification and treatment of anxiety disorders in medical settings.

Several researchers (e.g., Ballenger, 1997; Roy-Byrne & Katon, 2000) have proposed solutions to improve identification of PDA in medical settings. Roy-Byrne and Katon (2000) cite interventions that strengthen and support self-management by promoting physician-
patient collaboration focused on patient education and activation, development and implementation of expert systems, and process-of-care changes (i.e., increased integration of mental health professionals into primary care). To improve diagnostic screening of PDA, Ballenger (1997) has recommended a thorough workup, including (1) evaluation of medical, psychiatric, and social history; (2) physical and neurological examination; (3) family history assessment; (4) medication and drug use history; (5) an electrocardiogram (in patients over 40 years of age); and (6) laboratory tests (i.e., blood chemistry panel, thyroid function test).

In summary, there is little question that the various physical disorders described above can produce symptoms that mimic panic attacks, and as we have seen, it is not uncommon for a medical disorder to coexist with PDA. The complicating factor is that it is clear that individuals with PDA are overly sensitive to and vigilant for patterns of internal physical changes. Patients who develop learned alarms to these somatic events through the process of interoceptive conditioning are more likely to experience anxiety and panic than if the sensations produced by the physical disorder are not present. Similarly, those patients without PDA who present with one or more of these physical problems generally do not experience anxiety or panic once the underlying reasons for the physiological sensations have been thoroughly explained by a health care professional. The ultimate test is whether the symptoms of panic disorder diminish or disappear once the disorder is properly diagnosed and treated. If not, the panic disorder requires treatment in its own right.

OVERVIEW OF TREATMENT COMPONENTS

Treatments for PDA generally fall into one of two categories: (1) techniques targeting agoraphobia and related avoidance behaviors; and (2) techniques targeting panic attacks (i.e., frequency, intensity, and duration of panic attacks) and anxiety focused on panic attacks.

Treating Agoraphobia and Related Avoidance Behaviors

The Discovery of Exposure

As late as the 1960s, there were no proven effective treatments for agoraphobia or panic. Donald Klein had begun his work with imipramine, but only preliminary results were available. At about the same time, pioneering behavioral investigators were experimenting with possible behavior therapy approaches to agoraphobia. For example, Meyer and Gelder (1963) began encouraging patients with agoraphobia to venture away from their homes or the clinic along routes that were very difficult for them. However, they cautioned their patients to avoid experiencing any anxiety and to turn back if this occurred. This resulted in very limited improvement in a few patients, at an excruciatingly slow rate of progress (Matthews et al., 1981). This procedure was soon given up in favor of the predominant behavioral treatment for phobia in those days, systematic desensitization in imagination. Evidence began to accumulate at that time that systematic desensitization was effective with patients with specific and mixed phobias, at least some of whom also had agoraphobia, when compared to psychotherapy (Gelder & Marks, 1968; Gelder, Marks, & Wolff, 1967). Nevertheless, in studies confined to patients with severe agoraphobia, systematic desensitization did not provide a significant advantage over psychotherapy, and
overall improvements were small with both treatments (Emmelkamp, 1982; Gelder & Marks, 1966; Marks, 1971).

In the late 1960s, we experimented with the possibility of strongly encouraging patients with agoraphobia to expose themselves to real-life frightening situations (e.g., Agras et al., 1968). A course was set up that led from the clinic to an increasingly busy downtown area about 1 mile away. As patients walked further along this course (and therefore began to experience and tolerate greater anticipatory anxiety and panic), the value of this exercise was discussed with them, and they were effusively praised. If they were unable to make progress on a given trial, very little was said, although they were encouraged to try harder next time. Although these patients were told to return if they experienced what was vaguely defined as "undue anxiety," in fact the demands of the situation produced Herculean efforts on the part of many of these patients.

According to behavioral observations of distance walked along this course, the initial three patients in this series did extremely well in a relatively short period of time (Agras et al., 1968). But a surprising finding began to emerge, which we were to isolate experimentally only in later years. Although we were betting on the therapeutic value of praise and encouragement from a therapist with whom a patient had a good relationship, many of these patients began improving in a "baseline" phase before this encouragement was even introduced. That is, the opportunity to practice by walking further along this difficult course seemed therapeutic in and of itself. These results are graphically demonstrated in Figure 10.6 for one of the patients in this early series. As one can see, this patient was already improving in terms of distance walked and time away from a safe place during baseline. The slope of this improvement was not substantially affected by the introduction of social reinforcement, although removal of this reinforcement in a systematic way at a later date did exert some control over agoraphobic behavior. In fact, later studies in this series indicated quite clearly that the opportunity to practice in a systematic way by exposing oneself to feared situations accounted for the largest part of therapeutic benefit (e.g., Leitenberg, Agras, Edwards, Thompson, & Wincze, 1970; Mavissakalian & Barlow, 1981).

By the mid-1980s, positive outcomes for exposure-based treatments were found fairly consistently over a number of different studies conducted by clinicians in various parts of the world. If dropouts were excluded, the best estimates of outcome indicated that from 60% to 70% of those individuals with agoraphobia completing treatment showed some clinical benefit. Follow-up studies revealed that these effects were maintained, on the average, for periods of 4 years or more (Burns, Thorpe, & Cavallaro, 1986; Cohen, Monteiro, & Marks, 1984; Emmelkamp & Kuipers, 1979; Jansson, Jerremalm, & Öst, 1986; Jansson & Öst, 1982; McPherson, Brougham, & McLaren, 1980; Mynby & Johnston, 1980). The effectiveness of this approach was demonstrated repeatedly in controlled experimentation when exposure was compared to no treatment or some good placebo (e.g., Matthews, 1978; Mavissakalian & Barlow, 1981; O'Brien & Barlow, 1984).

The Administration of Exposure-Based Procedures: A Current Perspective

In vivo exposure involves systematic, repeated contact with the avoided situation. The approach to exposure can vary from graded or hierarchical to intense exposure, from therapist-directed to self-directed exposure, from massed to spaced exposure, from endurance to controlled-escape exposure, and from attention-based to distraction-based exposure. Choice of strategy generally depends on the patient's motivation and willingness to engage in exposures, and these may be strongly influenced by a patient's degree of avoidance.

FIGURE 10.6. The effect of exposure therapy on the fears of a patient with agoraphobia by the American Medical Association.
MASSED VERSUS SPACED EXPOSURE AND THE NEW THEORY OF DISLISE. Long, continuous exposure sessions would seem generally more effective than shorter, interrupted sessions on the face of it (Chaplin & Levine, 1981; Marshall, 1985; Stern & Marks, 1973), but the optimal rate for repeated exposure is not clear. For many years we thought that spaced exposures were generally preferable, because dropout rates (Emmelkamp & Ultee, 1974; Emmelkamp & Wessels, 1975) and relapse rates (Hafner, 1976; Jansson & Öst, 1982) were higher following massed exposure. Also, it seemed that rapid changes resulting from massed exposure made family adjustments to the change more difficult (Barlow, O'Brien, & Last, 1984). In contrast, Chambless (1990) did not find such detrimental outcomes, and in fact found massed exposure to be equal in effectiveness to graded exposure after treatment and at a 6-month follow-up with no differential relapse rates. However, a selection bias was operating in the massed-exposure group, since a number of potential patients were unwilling to participate (as is often the case to some extent, if the proposed schedule for exposure is too intense).

It may be that we have been attending to the wrong segment of treatment in deciding between massed and spaced sessions. In 1992, Bjork and Bjork proposed that an expanding-spaced schedule, once initial learning has occurred, is the most beneficial for long-term retention (Lang, Craske, & Bjork, 1999). As applied to PDA and other phobias treated with exposure, sessions could be relatively massed initially, since the theory predicts that some difficulty in learning results in better retention (Schmidt & Bjork, 1992). But as progress is made, and perhaps fear and anxiety have diminished considerably, sessions should be scheduled at increasingly spaced intervals to prevent return of fear. Bjork and
Bjork (1992) refer to this notion as the “new theory of disuse.” Craske and her colleagues have begun to test this notion with volunteers with nonclinical fears, as well as some patients with specific phobias, with promising results (e.g., Lang & Craske, 2000; Rowe & Craske, 1998a; Tsao & Craske, 2000). To date, studies have not examined this arrangement with PDA, but its success with specific phobias and its grounding in solid principles of learning should make this evaluation a priority.

**GRADUATED VERSUS INTENSE EXPOSURE.** In a related procedural strategy, exposure can be conducted in a graduated format, progressing from least to most difficult situations, or in an intensive format, beginning with most feared items on a hierarchy. An impressive series of studies examining a particularly aggressive and intensive form of exposure therapy with patients with PDA has been reported by Wolfgang Feigenbaum and his associates in Germany (Ehlers, Feigenbaum, Florin, & Margraf, 1995; Feigenbaum, 1988). This strategy involves intense, therapist-accompanied, ungraded, massed exposure. For example, in a comparison study of graduated (n = 23) versus intensive exposure (n = 25) in patients with severe agoraphobia, Feigenbaum (1988) found both treatment conditions to be equally effective at posttreatment and 8-month follow-up, but ungraded (intensive) exposure was clearly superior at 3-year follow-up (76% patients receiving intensive exposure vs. 35% from the graded condition were symptom-free). Interestingly, the patients receiving graded exposure reported the treatment to be more distressing than those in the intensive condition reported! After this finding, the next 104 subjects were treated with the intensive strategy. Results remained promising, with 78% remaining of the entire group symptom-free at 3-year follow-up. Moreover, these authors (Ehlers et al., 1995) found low attrition rates and comparable response rates to other studies at 2-year follow-up (e.g., Fava, Zielczyn, Savron, & Grandi, 1995).

**LEVEL OF ANXIETY REDUCTION DURING EXPOSURE.** Based on extinction models of fear reduction, it has long been assumed that exposure should continue until anxiety decreases substantially (Marks, 1978). Newer emotional processing models of fear reduction also assume that long-term fear reduction is generally dependent on activation of fear arousal during the session, as well as on within-session and between-session habituation or fear reduction (Foë & Kozak, 1986; Rachman, 1980). But research in this area has produced inconsistent results, and it is far from clear whether high levels of fear arousal followed by substantial reductions in fear and anxiety during exposure sessions are prerequisites for long-term fear reduction. For example, we found benefits of exposure without endurance of high levels of anxiety when we instructed patients to terminate the exposure session when they experienced “undue levels of anxiety” (Agras et al., 1982; see also Emmelkamp, 1982). On the other hand, Marshall (1985) observed substantial benefit from longer periods of exposure with time allowed for complete anxiety reduction. Others have found equally effective results, whether escape or endurance paradigms were used (de Silva & Rachman, 1984; Rachman, Craske, Tallman, & Solyom, 1986). Interestingly, Rachman et al. (1986) found patients in the escape condition to report more perceived control and less fear during the exposure than patients in the endurance condition, suggesting that maximal fear elicitation and subsequent habituation are not essential for therapeutic benefit. As suggested in previous chapters and in the first edition of this book (Barlow, 1988), reinforcing a sense of control, and preventing emotionally driven escapist action tendencies (also perceived to be out of volitional control by the patient), more accurately represent the process of emotional change and fear reduction—an idea that has similarities to Bandura’s self-efficacy model (Bandura, 1977, 1988).

**DISTRACTION DU**

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DISTRACTION DURING EXPOSURE. It seems common sense that distraction procedures during exposure exercises are basically avoidant strategies and should be counterproductive (e.g., counting to 100, saying a prayer, snapping a rubber band on a wrist, etc.). Thus it is standard procedure to make all attempts to eliminate distraction strategies during exposure. However, we are aware of only one study that has investigated this assumption with patients with PDA (Craske, Street, & Barlow, 1989). In this study, we administered therapist-directed and self-directed exposure in small groups for 11 sessions. In one condition (n = 16), patients were instructed to monitor bodily sensations and thoughts objectively throughout in vivo exposure and to use thought stopping and focusing self-statements to interrupt distraction; patients in the other condition (n = 14) were taught to use specific distraction tasks during in vivo exposures (e.g., word rhymes, spelling, etc.), and to use thought stopping and distracting self-statements to interrupt focusing attention on feared bodily sensations and images. Treatment groups did not differ at posttreatment; however, consistent with previous research in obsessive-compulsive disorder (Grayson, Fon, & Steketee, 1982), the focused-exposure group improved significantly from posttreatment to follow-up, in contrast to slight deterioration in the distracted-exposure group.

ELIMINATING SAFETY SIGNALS. An often overlooked treatment target is the elimination of safety signals—the “talismans” that are such prominent features in the lives of patients with PDA, as described earlier (Craske et al., 2000; Rachman, 1983, 1984). Although few therapists would ignore the necessity of attending to the functional impairment that results from requiring the presence of a safe person such as a spouse on ventures out, other safety signals receive less attention. As noted in Table 10.2, more subtle safety behaviors (e.g., empty pill bottles, sheets of paper containing coping self-statements, or even pets) may be unobtrusive companions. Therefore, an individual cannot be considered “recovered” with a continuing dependence on these items—a dependence that is readily acknowledged to be irrational.

The difficulty with ignoring this residue of extensive avoidance lies in the danger of the individual’s misplacing or otherwise forgetting the item after treatment is over. This of course may result in anxiety, a return of avoidance, or even relapse. At the very least, it will bring the patient to a realization that he or she has not recovered and that loss of control and panic may be just around the corner, depending on the presence or absence of a small piece of paper or an empty pill bottle. Since it is a rather small matter, in our experience, to wean patients from the variety of safety signals as part of their structured exposure exercises, there seems little reason not to do it. We consistently and carefully examine for the presence of safety signals, which on occasion have become so integrated with patients’ routines that they may not report their presence. Once identified, all safety signals are removed prior to the beginning of exposure exercises.

PARTNER-ASSISTED EXPOSURE. Agoraphobia is a problem that invariably impinges on the social system of the patient. For this reason, family members are important possible sources of support for patients with PDA. Over the years, several groups of investigators have included significant others or partners in the treatment of PDA, with the notion that involving a motivated partner would initially support a patient during exposure practices in the home environment, which is the social system in which a patient exists on a day-to-day basis. The first investigators to examine this issue were Hand, Lamontagne, and Marks (1974). They noted that patients with agoraphobia who were treated in what became a cohesive group stayed in touch with one another and supported each other after treatment, and this evidently resulted in further improvement after completion of treatment. Mathews
et al. (1977), in an uncontrolled clinical trial, included spouses of patients with agoraphobia as cotherapists and noted that over 90% of these patients were much improved at the end of treatment, with improvement continuing at follow-up. Munby and Johnston (1983) followed up a series of studies carried out by the same group of investigators. They concluded that the treatment in which spouses were directly included produced continued improvement. The results were superior at a 4- to 9-year follow-up to the results of treatments where patients with agoraphobia were treated in separate clinical trials, but more intensively and without spouses. Sinnott, Jones, Scott-Fordham, and Woodward (1981) noted that patients with agoraphobia selected from the same neighborhood and treated as a group had superior outcomes on many measures to those of patients from diverse geographical regions (who presumably did not meet, socialize, or generally support each other during or after therapy). It seems likely that the reason for greater improvement in these experiments lay in support and motivation for continued “practice” in facing feared situations between sessions and after treatment was over. We have also found that attending to a patient’s social support system may enhance the effects of exposure. Specifically, in the feasibility and benefit of including patients’ spouses directly in treatment (Barlow, O’Brien, & Last, 1984; Barlow, O’Brien, Last, & Holden, 1983). Results indicated an advantage for the spouse-assisted group compared with the non-assisted group. These posttreatment differences actually increased in favor of the spouse-assisted group at 1- and 2-year follow-ups (Cerny, Barlow, Craske, & Himadi, 1987). On the other hand, evidence from one of our studies (Barlow, O’Brien, Last, & Holden, 1984) indicated that in a well-adjusted marriage, the formal inclusion of the spouse in the treatment process made little difference. However, in a more poorly adjusted marriage, inclusion of the spouse seemed to override the influence of a poor relationship. Indeed, Arrow, Taylor, Agras, and Telch (1985) found that in marriages that were well adjusted at baseline, communication training further improved the effectiveness of treatment. These experiments underline the importance of considering the social system that provides the context for the treatment of agoraphobia, and highlights the role families may play in treatment. Moreover, as discussed above, educating family members on subtle reinforcement of agoraphobic behaviors (e.g., their role as potential safe persons) and the importance of modifying their behavior in response to the patients as they progress in treatment would seem to be important in maintaining success. Of course, the best “partner” may not always be a patient’s spouse. We have often utilized adult children or even close friends and neighbors to assist with treatment. This literature has been updated over the years (Carter, Turovsky, & Barlow, 1994; Daiuto, Baucum, Epstein, & Dutton, 1998; Marten & Barlow, 1993). Although some investigators have not found support for the importance of including significant others in treatment (e.g., Emmelkamp et al., 1992), the majority of studies generally support attending to a patient’s social system and enlisted that social system in a supportive manner while treating agoraphobia. Unfortunately, there has been little systematic research on this as it relates to long-term improvement. Daiuto et al. (1998) point to the need for considerably more effort in this area, and the importance of targeting both agoraphobic behavior and the structure of relationships with significant others, particularly the spouse.

Recent Results of Exposure-Based Treatment

Since the 1980s and the development of psychological treatments for PDA, fewer studies have appeared evaluating exposure-based procedures in isolation from a CBT package. One notable exception is a study by Fava et al. (1995), who reported on long-term follow-up of 90 patients who received treatment. These treatments were effective for the kind of expanding (Lang et al., 1999). A much larger number of patients also remained improved. More specifically, respondents to treatments that 96% remained improved in the following treatment, and 90% were the presence of until agoraphobia is

Exposure Combined

During the 1980s an emphasis on the efficacy of treatments for patients with antidepressants (TCP) and in this area. The treatment approach of Perel, 1989; Telch et al. disappeared. At first Mavissakalian & Miller, 1995 that a combined treatment. In vivo exposure was alone. But patients who had been months after discontinuation were less than with exposure, de Beurs, van B et al. fluvoxamine to explore naturalistic follow-up. Two groups were equivalent to the other treatments. Cottraux et al. (1999) showed the short term (16 w over the CBT condition.

Briefier Cost-Effectiveness

Investigators have compared the efficacy of exposure-based treatments, for a directed exposure treatment and text-instructed, load studies. Significant differences were found in clinical effectiveness of similar study with patients where exposure and cognitive-behavioral treatment. Cox, and Wickwire, 1999, compared to a showed treatment continued for traditional in-pa
up of 90 patients who had received 12 sessions of graduated self-paced exposure-based treatment. These treatments were administered biweekly over a 6-month period, approximating the kind of expanding-spaced schedule derived from the new theory of disuse described above (Lang et al., 1999). At the end of treatment, 87% were free of panic and were considered much improved. More importantly, using survival analysis to estimate the probability that responders to treatment would successfully remain in remission, Fava et al. (1995) reported that 96% remained in remission for the first 2 years, 77% throughout the first 5 years following treatment, and 67% after the first 7 years. The most important predictors of relapse were the presence of residual agoraphobia (suggesting the need to continue with treatment until agoraphobia is eliminated) and the presence of a personality disorder.

**Exposure Combined with Drug Treatments**

During the 1980s and early 1990s, prior to the new emphasis on CBT for panic, research on the efficacy of combined treatments focused on adding drugs to exposure-based treatments for patients with agoraphobia. Most of these studies examined the benefits of tricyclic antidepressants (TCAs) such as imipramine, with Matig Mavissakalian the leading investigator in this area. These studies, for the most part, reported evidence for superior results for combined treatment at the conclusion of therapy (Mavissakalian, 1996a; Mavissakalian & Perel, 1989; Telch, Agras, Taylor, Roth, & Gallen, 1985). However, the benefits generally disappeared at follow-up after discontinuation of the drug (e.g., Mavissakalian, 1993; Mavissakalian & Michelson, 1986; Telch & Lucas, 1994). Marks et al. (1993) also found that a combined treatment consisting of alprazolam, a high-potency benzodiazepine, and in vivo exposure was similar in its efficacy to either alprazolam or exposure administered alone. But patients receiving combination treatment also experienced a high relapse rate 6 months after discontinuation of the alprazolam, to the point that overall therapeutic gains were less than with exposure alone. In other studies combining antidepressants with exposure, de Beurs, van Balkom, Lange, Koel, and van Dyke (1995) found that the addition of fluvoxamine to exposure was superior to exposure alone in reducing avoidance. Long-term naturalistic follow-up of this study 2 years later, however, showed that the effects in the two groups were equivalent (i.e., the fluvoxamine-plus-exposure group was no longer superior to the other treatment groups) (de Beurs, van Dyke, Lange, & van Balkom, 1999). Cottraux et al. (1995) found that the combination of CBT and buspirone was superior in the short term (16 weeks), but that the addition of the medication provided no advantage over the CBT condition alone at 1 year posttreatment.

**Briefer Cost-Effective Modifications to Exposure-Based Procedures**

Investigators have examined the effectiveness of more self-directed treatments for agoraphobic avoidance. First, Ghosh and Marks (1987) examined three combinations of self-directed exposure treatment over 10 weeks (i.e., therapist-instructed, computer-instructed, and text-instructed). These researchers found support for all three conditions, with no significant differences between conditions. As such, this study provides sound support for clinically effective and cost-effective treatment for agoraphobic avoidance. Second, in a similar study with patients suffering from moderate or severe agoraphobia, Swinson, Fergus, Cox, and Wickwire (1995) found support for a telephone-administered exposure treatment compared to a wait-list control group—and follow-up assessments at 3 and 6 months showed continued gains. Moreover, the gains made were reportedly comparable to those for traditional in-person treatment sessions. It is important to note, however, that some of
our past research did not find support for bibliotherapy with patients who had more severe agoraphobia (Holden, O'Brien, Barlow, Stetson, & Infantino, 1983). Third, Côté, Gauthier, Lapierge, Cormier, and Plamondon (1994) examined standard CBT with standard therapist contact (approx. 20 hours) compared with reduced therapist contact (approx. 10 hours). They found comparable results for both treatment conditions, and fully 73% of patients reported panic-free status and clinical improvement at 6-month follow-up. Finally, Lidren et al. (1994) found self-directed bibliotherapy to be as effective as group CBT when both were compared with a wait-list control condition, and gains were maintained at 3- and 6-month follow-ups.

**Treating Panic and Associated Anxiety**

**Pharmacological Treatments and Their Effectiveness**

Pharmacological approaches to the treatment of PDA have been the focus of an increasing number of controlled clinical trials during the last decade. The recent explosion of public marketing campaigns and research attention devoted to evaluating these drug treatments has led to an array of available medicinal agents with varying efficacy data. These medications are associated with a host of individual advantages and disadvantages for each patient, and appropriate treatment is often complicated by patients seeking treatment from multiple caregivers (Sanderson & Wetzler, 1993) and combination treatments for the same problems (Rapaport et al., 1996; Waikar, Bystritsky, Craske, & Murphy, 1994–1995). Below we review the pharmacological management of PDA. We begin with a brief discussion of the historical evolution of pharmacological therapies, followed by a review of meta-analyses and efficacy data documented in recent clinical trials.

Following some historic clinical observations by Donald Klein (discussed at some length in Chapter 3; Klein, 1964; Klein & Fink, 1962), early pharmacological management of PDA emphasized the suppression of panic attacks. The expectation was that control of panic attacks would naturally result in reduced anticipatory anxiety and agoraphobic avoidance. In this way, Klein "pharmacologically dissected" panic attacks from more generalized anticipatory anxiety—an observation that had a profound impact on our conception of the nature of anxiety and panic, and led to the creation of the diagnosis of panic disorder. Pharmacotherapies and their efficacy in the treatment of PDA have evolved considerably over the past several decades (Spiegel, Wiegell, Baker, & Greene, 2000). The drug discovered by Klein as potentially effective was a TCA, imipramine. Beginning at that time and into the 1970s, TCAs, monoamine oxidase inhibitors (MAOIs), and barbiturates established the foundation of pharmacological treatments for PDA. In the 1980s, high-potency benzodiazepines were introduced as a safer and better-tolerated alternative to barbiturates. More recent pharmacological treatments include the use of selective serotonin reuptake inhibitors (SSRIs) and related agents. In Table 10.3 we present a list of medications with empirically established efficacy for PDA and their recommended dosages for healthy adults.

**TRICYCLIC ANTIDEPRESSANTS.** Since the early reports from Klein, over 15 controlled clinical trials have demonstrated the efficacy of the TCAs with panic disorder (APA, 1998), and the TCAs are still considered by many to be the "gold standard" for pharmacotherapeutic efficacy with this disorder (Spiegel et al., 2000). The TCAs have demonstrated both short-term and long-term effectiveness (Mavissakalian, 1996b; Mavissakalian & Perel, 1989, 1992a, 1992b, 1995, 1999); as such, they are the most studied of the medications used in the treatment Collaborative Pa to placebo and alprazolam exert vestigating the t & Woods, 2000 (3 months after the end of maint less well studied, et al., 1988; Moc 1993), and nortriptyline, the TCAs a reuptake of nore by Mavissakalian tic window for p noted above, a hance suggests th after attrition is .
TABLE 10.1. Typical Doses for Medications with Empirically Supported Efficacy for the Treatment of PDA in Healthy Adults with No Concurrent Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual starting dose (mg/day)</th>
<th>Initial target dose (mg/day)</th>
<th>Maximum rec'd dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam+++</td>
<td>0.75</td>
<td>2-3</td>
<td>10</td>
</tr>
<tr>
<td>Clonazepam+++</td>
<td>0.25-0.50</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Lorazepam+++</td>
<td>0.50</td>
<td>1-3</td>
<td>10</td>
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<tr>
<td>TCAs</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Imipramine+++</td>
<td>10</td>
<td>100-150</td>
<td>300</td>
</tr>
<tr>
<td>Clomipramine+++</td>
<td>2.5</td>
<td>50-100</td>
<td>250</td>
</tr>
<tr>
<td>SSRIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine+++</td>
<td>10</td>
<td>40</td>
<td>60</td>
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<tr>
<td>Sertraline+++</td>
<td>2.5</td>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td>Fluoxetine+++</td>
<td>5-10</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Fluvoxamine+++</td>
<td>25</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>Citalopram+++</td>
<td>10</td>
<td>20</td>
<td>60</td>
</tr>
</tbody>
</table>

Note. Combine medication with exposure instructions for patients with significant agoraphobia. ++, probably effective (efficacy demonstrated in at least one large, well-designed, double-blind trial or in several uncontrolled trials by different investigators). +, effective (efficacy demonstrated in at least two large, well-designed, double-blind trials conducted at multiple sites or by different investigators comparing the drug with placebo or to another drug with established efficacy). TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors. Adapted from Spiegel, Wiegel, Baker, and Greene (2000). Copyright 2000 by Allyn & Bacon. Adapted by permission. *Alprazolam is usually taken in divided doses 3-4 times daily to avoid between-dose symptoms. This medication is usually taken in divided doses 2-3 times daily.

There may be a therapeutic window for imipramine for overall response.

Low starting doses may be required to avoid initial hyperstimulation. If one SSRI is effective, others are likely to be as well.

used in the treatment of panic disorder and PDA. One large clinical trial (Cross-National Collaborative Panic Study, 1992; Klerman, 1992) found that imipramine was superior to placebo and comparable to the high-potency benzodiazepine alprazolam, although alprazolam exerted its effects sooner. In addition, in the large multicenter clinical trial investigating the treatment of panic disorder reported below (Barlow, Gorman, Shear, & Woods, 2000), imipramine was clearly superior to placebo after acute treatment (3 months after the beginning of the study), with drug-placebo differences even larger at the end of maintenance treatment (9 months after the beginning of the study). Although less well studied, other TCAs have shown similar efficacy, including clomipramine (Cassano et al., 1988; Modigh, Westburg, & Eriksson, 1992), desipramine (Lydiard, Morton, et al., 1993), and nortriptyline (Roy-Byrne, Wingerson, Cowley, & Dager, 1993). Pharmacologically, the TCAs are thought to exhibit their effects through the inhibition of the postrelease reuptake of norepinephrine or serotonin into presynaptic nerve terminals. A notable study by Mavissakalian and Perel (1995) found that imipramine may have an optimal therapeutic window for phobic anxiety, with preferred dosages at approximately 130 mg/day. As noted above, a far less specific dose-response relationship was found for panic. The evidence suggests that TCAs, particularly imipramine, are as effective as the newer SSRIs even after attrition is considered, clinical impressions notwithstanding.
Despite their effectiveness, the TCAs are often accompanied by troublesome side effects (e.g., blurred vision, weight gain, constipation) that are difficult for many patients to tolerate (Papp et al., 1997). Perhaps more importantly, the TCAs have been shown to cause central nervous system (CNS) activation and a side effect called “jitteriness syndrome” characterized by anxiety, panic, shakiness, insomnia, and irritability (Pohl, Wolkow, & Clary, 1998). This effect is reported in a substantial minority of patients with panic disorder. Generally, this side effect is time-limited; it often occurs at the outset of treatment; and it can be minimized by starting at low doses with slow titration. Nevertheless, it is a common case of treatment discontinuation. Similar to the benzodiazepines, termination of TCA use is linked with high relapse rates (D. M. Clark et al., 1994; Katschnig et al., 1995; Wiborg & Dahl, 1996). One nonrandomized comparison, however, suggested that relapse was significantly lower in patients treated with imipramine for 18 months versus only 6 months (Mavissakalian & Perel, 1992a).

It is interesting to note that imipramine does potentiate exposure-based treatments, but, despite Klein’s (1964) provocative hypotheses, very little evidence has accumulated over the last decades that imipramine directly affects panic attacks. Despite a few suggestions to the contrary (Uhlenhuth, Matuzas, Warner, & Thompson, 1997), the weight of the evidence strongly suggests that imipramine has its effects on more generalized (or anticipatory) anxiety. This conclusion is buttressed by general findings that imipramine potentiates exposure treatments in which the focus is not on reducing anxiety and panic, but rather on increasing anxiety in the service of changing behavior, at least in the short term. On the other hand, imipramine does not seem to potentiate CBT for panic and associated anxiety. This may be because CBT focuses directly on anxiety and panic, via perhaps a different mechanism than imipramine and other antidepressants. Thus imipramine and related anxiolytics, such as the high-potency benzodiazepines (see below), not only do not potentiate therapeutic effects of CBT; they may well interfere with their effects by dampening the provocation of anxiety under controlled circumstances, which is an integral part of all forms of CBT (Barlow et al., 2000; Spiegel & Bruce, 1997; Spiegel et al., 2000).

Evidence on the anxiolytic versus panicolytic effects of antidepressants such as imipramine can also be found in the seeming lack of dose-response relationships in the Mavissakalian and Perel (1995) study reported above. In fact, this replicates important earlier studies by Mavissakalian and colleagues showing dose-response relationships for imipramine in the overall outcome of treatment for PDA, but no relationship whatsoever between drug dosage or plasma concentrations of drug on the one hand, and reductions in panic on the other. That is, PDA responded equally well to all dosages of imipramine in several important studies in the 1980s (Mavissakalian & Michelson, 1986; Marks et al., 1983). Drug relationships were found only for global response to treatment, and then only at posttreatment. The most likely possibility, in our view, is that imipramine may contribute to exposure-based procedures by directly reducing anxious apprehension (rather than panic). Thus the somatic sensations associated with anxiety that seem to serve as cues for panic would decrease, as well as levels of anxious self-preoccupation (self-focused attention). A sense of control would increase. Panic attacks would then decrease because the platform of anxious apprehension from which panic attacks emerge would be removed (see Chapters 5 and 7). Direct evidence for the anxiolytic effects of imipramine was obtained in other studies in the 1980s (e.g., Kahn et al., 1986). In the Kahn et al. study, imipramine produced substantial anxiolytic effects that were superior to those of a standard benzodiazepine on most measures. Furthermore, this effect was observed despite the exclusion of patients with clear panic and phobic components to their anxiety.

In addition, some occurring alarms or near-accidents in auto were not on drugs (N. Barlow, 1988; Barlow control, along with cl what may ultimately | All drug and behavio anxiety or anxious ap

BENZODIAZEPINE tration (FDA) for the c pivotal multicenter st Study, 1992; Lester et dose of 6 mg/day) was ability, panic attacks, dose trials have found 2 mg/day; Lydiard acute treatment impro tolerance to the med

Benzodiazepines effects than other dru logically, benzodiazep acid (GABA) on chlo ability (cf. Stahl, 1999) panic disorder and PD Chouinard, 1994; De (Schweizer et al., 1999 et al., 1996), lorazepa (C. S. Carter et al., 1996) Common concer Shader & Greenblatt benzodiazepines, few Wardle, & Higgitt, 1 and usually occurs in studies have found th escalation over time (1989; over 2 years’ u

The difficulty is evi dence that results in w when the drug is disct 1990). For example, (O’Sullivan et al a rapidly; as such, this discontinuation has b treatment (Ballenger, return to drug after p medication can overl be interpreted by pat
In addition, some evidence exists that drugs for panic disorder do not block naturally occurring alarms or fear. In one study, patients reported that “alarming” events such as near-accidents in automobiles provoked the same response as they did when the patients were not on drugs (Nesse, Cameron, Curtis, & Lee, 1986). In fact, we suggest elsewhere (Barlow, 1988; Barlow, Chorpita, & Turosky, 1996) that the development of a sense of control, along with changes in action tendencies and alterations in focus of attention, is what may ultimately be the target of all drug and behavioral treatments (see Chapter 3). All drug and behavioral treatments may be effective only to the extent that they reduce anxiety or anxious apprehension.

**Benzodiazepines.** The first medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of PDA was alprazolam. This approval was based on several pivotal multicenter studies (Ballenger et al., 1988; Cross-National Collaborative Panic Study, 1992; Lesser et al., 1988; Noyes et al., 1988) showing that alprazolam (at an average dose of 6 mg/day) was superior to placebo on critical clinical outcome measures (e.g., disability, panic attacks, panic-related phobias, and global improvement). Subsequent fixed-dose trials have found that patients may benefit from substantially smaller doses (i.e., 2 mg/day; Lydiard et al., 1992; Uhlenhuth, 1998). Additional studies have shown that the acute treatment improvements were maintained at 6-month follow-up with no demonstrable tolerance to the medication (Schweizer, Rickels, Weiss, & Zavodnick, 1993).

Benzodiazepines are generally considered to be safe and quick-acting, with fewer side effects than other drugs used to treat anxiety disorders (Spiegel et al., 2000). Pharmacologically, benzodiazepines are thought to enhance the natural effect of gamma-aminobutyric acid (GABA) on chloride conductance through cell membranes inhibiting cellular excitability (cf. Stahl, 1996). Other anxiolytics have shown similar results in the treatment of panic disorder and PDA, including clonazepam (Beaulier, Fontaine, Annable, Holobow, & Chouinard, 1994; Davidson & Moroz, 1998; Moroz & Rosenbaum, 1999), lorazepam (Schweizer et al., 1990), diazepam (Dunner, Ishiki, Avery, Wilson, & Hyde, 1986; Noyes et al., 1996), lorazepam (Charney & Woods, 1989; Schweizer et al., 1990), and adinazolam (C. S. Carter et al., 1993).

Common concerns about these agents focus on tolerance, abuse, and dependence (cf. Shader & Greenblatt, 1993). Although tolerance develops to the sedative side effects of benzodiazepines, few studies have found tolerance to the anxiolytic effects (Hayward, Wardle, & Higgit, 1989; Romach et al., 1992). In fact, abuse of benzodiazepines is rare and usually occurs in a pattern of poly-substance abuse (APA, 1998). Several longitudinal studies have found that treatment gains are maintained with no evidence of abuse or dose escalation over time (over 4 years’ use of alprazolam, Nagy, Krystal, Woods, & Charney, 1989; over 2 years’ use of clonazepam, Worthington et al., 1998).

The difficulty is that with prolonged use, most patients develop physiological dependence that results in withdrawal symptoms (e.g., nervousness, sleep disturbance, dizziness) when the drug is discontinued (Pecknold, Swinson, Kuch, & Lewis, 1988; Schweizer et al., 1990). For example, alprazolam has been shown to increase anxiety during discontinuation (O’Sullivan et al., 1996; Pecknold et al., 1988), particularly if the drug is tapered rapidly; as such, this effect renders the medication particularly addictive. Benzodiazepine discontinuation has been related to high rates of relapse (50–75%), even after 8 months of treatment (Ballenger, 1994; Spiegel, 1998a), and another study found increased rates of return to drug after prolonged use (Wardle et al., 1994). The withdrawal symptoms from medication can overlap considerably with panic attacks and anticipatory anxiety, and may be interpreted by patients as a return of the disorder, leading them to request additional
medication. However, Spiegel and Bruce (1997) report that this “rebound” effect can be avoided by a very slow, flexible drug taper. A series of systematic studies investigating the use of psychological strategies to overcome dependence on benzodiazepines is described below.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS. SSRIs are currently considered by many to be the state-of-the-art choice in medications for panic disorder and PDA. Numerous studies have demonstrated the efficacy of the SSRIs, including paroxetine (Ballenger, Wheeler, Steiner, Bushnell, & Gergel, 1998; Oehrberg et al., 1995), citalopram (Lydiard, Pollack, Judge, Michelson, & Tamura, 1997; Wade, Lepola, Koponen, Pedersen, & Pedersen, 1997), fluoxetine (Michelson et al., 1998), fluvoxamine (Bakish et al., 1996; Black, Wester, Bowers, Gabel, 1993), and sertraline (Pohl, Wolkow, & Clary, 1998; Pollack, Otto, Worthington, Manfro, & Wolkow, 1998). Paroxetine was the first FDA-approved SSRI in the treatment of PDA, and its efficacy has been shown in several multicenter clinical trials (Ballenger et al., 1998; Lecrubier et al., 1997; Oehrberg et al., 1995).

Comparative studies of SSRIs with each other, or with TCAs or benzodiazepines, have been generally inconclusive, with all treatments yielding similarly equivalent results in most analyses (van Balckom et al., 1997; Wilkinson, Balestrieri, Ruggeri, & Bellantuono, 1991). Whereas one meta-analysis by Boyer (1994) found the SSRIs to be superior to imipramine, others have concluded these medications to be equally effective (Bakish et al., 1996). In fact, in four different randomized studies, none found significant differences at the end of the study in intent-to-treat analyses, which included consideration of dropouts (Lecrubier et al., 1997; Bystritsky et al., 1994–1995; Nair et al., 1996; Wade et al., 1997). Although Lecrubier et al. (1997) did find evidence for a more rapid response for the SSRI, Nair et al. (1996) actually found that the TCA, but not the SSRI, was more effective than placebo. Although SSRIs tend to have a longer duration to response than TCAs, the optimal duration of treatment is not known. Ballenger et al. (1998), in an extension of a earlier trial of a fixed dose of paroxetine, crossed half of the responders to 22 weeks of placebo, resulting in a 30% relapse rate for the patients on placebo within 12 weeks. To date, rates of relapse following long-term treatment with paroxetine have not been reported.

Despite these inconclusive findings, the SSRIs are often preferred because they are better tolerated than the TCAs, are easier to dose than the TCAs and the MAOIs, lack the abuse and dependence potentials of benzodiazepines, and are considered safer. Moreover, the SSRIs have a broad band of therapeutic activity that may be especially helpful with comorbid disorders. Pharmacologically, SSRIs exert their action by inhibiting the postrelease reuptake of serotonin into presynaptic nerve terminals (similar to TCAs), but they have less affinity for the postsynaptic receptors associated with many of the adverse side effects of the TCAs. However, the SSRIs may cause side effects that include sexual impairment (in as many as 50–75% of patients), gastrointestinal symptoms, and CNS activation (including the jitters syndrome discussed above). As such, the SSRIs may require more informational support, slower titration, lower start doses, and possibly the time-limited use of a sleep medication early in treatment. Despite these advantages, some SSRIs have a varied profile with significant differences in drug interactions, functional half-lives, and use in older populations (Tollefsen & Rosenbaum, 1998), all of which require specific caution in their use.

OTHER PRESCRIPTION MEDICATIONS. Several less studied agents have demonstrated provisional but promising findings in the treatment of panic disorder, including the MAOIs (Bakish, Saxena, Bowden, & D’Souza, 1993; Buigues & Vallejo, 1987; Roy-Byrne et al., 1993) as well as other antidepressants. The latter include venlafaxine (Papp et al., 1998; Pollack, Worthington, & Zajecaka, 1996). Be careful, MAOIs are rare.

Psychological Treatments

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Pollack, Worthington, et al., 1996) and nefazodone, a related agent that has shown efficacy in depressed patients with panic attacks (DeMartinis, Schweizer, & Rickels, 1996; Zajecka, 1996). Because of their side effects and the strict dietary restrictions they necessitate, MAOIs are rarely prescribed.

**Psychological Treatments and Their Effectiveness**

The development of interoceptive exposure and "panic control treatment.

At the heart of the psychological treatment of panic are reproduction of and exposure to the somatic symptoms of panic. The reproduction-exposure process has been accomplished in a variety of different ways, accompanied by different explanations for its effectiveness. Nevertheless, all psychological treatments for panic with any demonstrated success have this process as a core ingredient.

As with all new discoveries, some interesting early examples of this approach were either misinterpreted or ignored. In Wolpe’s classic early work, CO₂ inhalations were a common but largely overlooked component of his anxiety reduction procedures. Generally, inhaling CO₂ was conceptualized as facilitating relaxation, and therefore promoting the reciprocal inhibition of anxiety. In fact, this may have been a very effective procedure for systematically exposing panic-prone patients to their feared cues in the benign setting of the therapist’s office (Wolpe, 1958). Other early reports can also be similarly interpreted. Orwin (1973) treated eight patients who had agoraphobia with “the running treatment.” In his procedure, patients were instructed to sprint until breathless, and then to approach or enter a feared situation. Running, of course, produced many of the somatic signs of panic, resulting in systematic exposure to these cues. This recalls some of the early panic provocation work using exercise (e.g., Cohen & White, 1950; see Chapter 5). Watson and Marks (1971), in a study with patients with agoraphobia, reported the then-puzzling finding that imaginal flooding to relevant phobic cues (imagining an intensely vivid scene depicting phobic cues) was no more effective than irrelevant flooding (visualizing being eaten by tigers). In fact, irrelevant flooding produced significantly greater therapeutic effects on patients’ subjective anxiety while imagining a phobic scene! This is understandable if one considers that arousal cues produced by irrelevant flooding are the primary phobic cues.

One of the most interesting early reports along these lines was that of Bonn, Harrison, and Rees (1971). Following up on the origins of provoking panic in the laboratory with lactate (see Chapter 5), Bonn et al. (1971) carried this procedure to its logical conclusion from the point of view of treatment by administering it repeatedly to 33 patients. Although panic was not directly measured, this procedure seemed quite successful. Interestingly, this result was totally ignored. In another early series, Haslam (1974) treated 16 subjects, 10 of whom panicked following a sodium lactate challenge with repeated CO₂ inhalation. Of the 10 patients who panicked with lactate, 9 demonstrated marked improvement after 6 weeks of CO₂ inhalation treatment. Other early case reports or clinical series by Latimer (1977) and Lum (1976) reported on diverse procedures such as CO₂ inhalation or voluntary hyperventilation, which seemed to result in substantial improvement in cases of what we would now call panic disorder.

Independent of other treatment techniques, fear reduction via interoceptively induced physical sensations has found support in the research. Several classic studies have supported the role of interoceptive exposure in fear reduction—by utilizing repeated infusions of sodium lactate (a drug that produces panic-like bodily sensations; Bonn, Harrison, & Rees, 1971; Haslam, 1974), and still others have found graduated carbon dioxide inhalations to be superior to propranolol (a Beta blocker that suppresses panic-like sensations) in reduc-
ing fear of sensations (Griep & van den Hout, 1986). More recently, several studies have replicated this finding, that fear is reduced through repeated exposure to carbon dioxide inhalations (Beck & Shipherd, 1997) and that panic attacks and panic-related fears are significantly reduced following six sessions of CO2 inhalation (Beck, Shipherd, & Zebb, 1997). Similarly, some recent research examining physical exercise, a type of interoceptive exposure, in comparison to medication (clomipramine) and pill placebo, found exercise to be superior to the pill placebo but inferior to the drug in the treatment of panic disorder (Broocks et al., 1998).

Cognizant of this early work, in the mid-1980s we developed a CBT approach to treating panic attacks and related anxiety called “panic control treatment” (PCT; Barlow, Cohen, et al., 1984; Barlow, Craske, Cerny, & Kloos, 1989), which has achieved wide acceptance (Barlow & Craske, 2000). Contemporaneously and independently, David M. Clark and colleagues were developing an approach similar in practice, but with greater theoretical emphasis on cognitive changes (Clark, 1986; D. M. Clark et al., 1994). PCT begins with a focus on the panic attacks themselves and anxiety focused on panic, which is then followed by techniques that target agoraphobic avoidance. Specifically, the goals of PCT are to directly influence catastrophic misappraisal of panic and anxiety, hyperventilatory response, and conditioned fear reactions to physical cues.

The first step in this process is psychoeducation to impart knowledge to the patient on the nature of the fight-or-flight response and the physiology of the anxiety system. Via this information, patients are taught that they experience “sensations” rather than “panics,” and that these sensations are normal and harmless. See Barlow and Craske (2000) for detailed and verbatim instructions provided to the patient. The second aim of treatment is to identify and challenge anxious thoughts and beliefs through cognitive restructuring. Next, specific information concerning the effects of hyperventilation and its role in panic attacks is provided. This information is commonly combined with extensive practice of breathing retraining—a somewhat controversial technique (see below). Historically, breathing retraining has played a key role in treatments for panic disorder because patients often describe symptoms of hyperventilation as similar to panic attack symptoms, and this procedure is still included in our protocols. Interoceptive exposure exercises are the last component; in these exercises, patients are instructed to repeatedly expose themselves to anxiety-provoking internal cues and sensations to lessen fear, and to provide an occasion to practice cognitive restructuring strategies. Manuals describing the treatment in some detail are available for the patient (Barlow & Craske, 2000; Craske et al., 2000).

RECONCEPTUALIZATION OF BREATHING RETRAINING. Breathing retraining seems to provide some symptomatic relief for patients with PDA (Clark, Salkovskis, & Chalkley, 1985; Bonn, Readhead, & Timmons, 1984). But treatment studies have generally examined breathing retraining as one component of multicomponent treatments, so it is difficult to attribute positive findings solely to breathing retraining. Garssen, de Ruiter, and van Dyck (1992) concluded from a review of its mechanisms of action and efficacy that breathing retraining probably effects change through distraction or imparting a sense of control, rather than through modulation of breathing per se. As such, breathing retraining has been the focus of recent controversy; investigators have questioned its theoretical compatibility and its incremental benefit over other cognitive and behavioral components of treatment (Schmidt et al., 2000; de Ruiter, Rijken, Garssen, & Kraaimaat, 1989). Using a dismantling design, Schmidt et al. (2000) concluded that breathing retraining did not add any clear benefits to a treatment package consisting of education, cognitive restructuring, and

Panic Disorder and exposure-based tech was subject to low retraining showed measures (Schmidt may put a patient at An important limits true use of each tree. Such an evaluative technique we have been used. We are aware that has d components of CBT)

In our view, an distraction from the behavior because it symptoms, high an could be conceptual to the goals of treat exposure practices

In light of this with using breathing breathing is concep the patient experi procedure in the PC duce the anxiety se strong evidence that standable, predicta conclusion, contro ramination to counter a encouraged as a m anxiety focused on tions of overbreath

EFFICACY OF PS panic disorder and controlled clinical trials evaluating native treatments.
agoraphobia, althor presents results from all levels of agorap were 43 controlled largest effect sizes e ments or to approa treatments utilizing although many of avoidance. It is also increase in quality 1995).
exposure-based techniques (both *in vivo* and interoceptive). In addition, although this study was subject to low power, their data showed a trend that patients who received breathing retraining showed lower end-state functioning on both self-report and clinician-rated measures (Schmidt et al., 2000). Thus these authors speculated that breathing retraining may put a patient at greater risk for relapse or decrease the chances for complete recovery. An important limitation of this study, however, is the lack of assessment of each patient's true use of each treatment component—an important question that needs to be examined. Such an evaluation would benefit from a thorough assessment that identifies what treatment techniques were used or not used by the patients, and what nonstudy techniques may have been used. Nevertheless, the Schmidt et al. (2000) study is the only one of which we are aware that has directly evaluated the addition of breathing retraining to the other main components of CBT interventions.

In our view, any behavior that minimizes panic symptoms or enables avoidance of or distraction from the panic sensations is maladaptive. Such avoidance is considered a safety behavior because it is an attempt to keep a patient “safe” from a false threat (i.e., panic symptoms, high anxiety). As such, teaching the skill of breathing retraining in this context could be conceptualized as teaching avoidance as a coping technique—a concept antithetical to the goals of treatment! Thus we instruct patients that use of breathing retraining during exposure practices is discouraged and is maladaptive.

In light of this potential theoretical incompatibility, we are currently experimenting with using breathing retraining in a very different way. In this new approach, controlled breathing is conceptualized as a means of testing whether some of the anxiety symptoms the patient experiences may be due to overbreathing; thus it is used as an experimental procedure in the PCT protocol. The rationale is presented that if the patient is able to reduce the anxiety sensations simply by changing the way he or she breathes, then this is strong evidence that the sensations are the result of overbreathing—and are therefore understandable, predictable, manageable, and harmless. Once the patient correctly draws this conclusion, controlled breathing is faded out, and the emphasis is shifted to using this information to counter anxious thoughts about the sensations. Thus controlled breathing is not encouraged as a means to reduce physical sensations; its use in this way could maintain anxiety focused on panic attacks, because the patient never learns that even strong sensations of overbreathing, though uncomfortable, are not dangerous.

**Efficacy of Psychological Treatments.** The efficacy of various forms of CBT for panic disorder and PDA is strongly supported by more than 25 independently conducted controlled clinical trials. Table 10.4 summarizes results from several of the major clinical trials evaluating the efficacy of different versions of CBT, compared to credible alternative treatments. In most studies patients suffered from no more than mild to moderate agoraphobia, although interoceptive avoidance was substantial in some studies. Table 10.5 presents results from a comprehensive meta-analysis of treatment outcome for PDA with all levels of agoraphobic avoidance (Gould et al., 1995). Included in the meta-analysis were 43 controlled studies. As is evident in Table 10.5, CBT was associated with the largest effect sizes and the smallest rate of patient attrition when compared to drug treatments or to approaches that combined psychological and drug treatments. Importantly, treatments utilizing interoceptive exposure were associated with the largest effect sizes, although many of these studies included patients with no more than mild agoraphobic avoidance. It is also important to note that these versions of CBT produce a incremental increase in quality of life for patients (Telch, Schmidt, Jaimez, Jacquin, & Harrington, 1995).
### TABLE 10.4: Clinical Trials of Cognitive-Behavioral Treatments for Panic Disorder: Intent-to-Treat Analysis

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Length of follow-up (months)</th>
<th>Treatment (% panic-free)</th>
<th>Treatment comparisons (% panic-free)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barlow et al. (2000)</td>
<td>12</td>
<td>PCT (n = 77), 41%</td>
<td>Yes: PCT + PL (n = 63), 31.9%,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes: PL (n = 24), 13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes: IMI (n = 83), 19.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes: PCT + IMI (n = 65), 26.3%</td>
</tr>
<tr>
<td>Black, Wesner, et al. (1993)</td>
<td>PT</td>
<td>CT (n = 25), 32%</td>
<td>Yes: FL = 68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes: PL = 20%</td>
</tr>
<tr>
<td>Beck et al. (1992)</td>
<td>PT</td>
<td>CT (n = 17), 94%</td>
<td>Yes: ST = 25%</td>
</tr>
<tr>
<td>Craske et al. (1991)</td>
<td>24</td>
<td>PCT (n = 15), 81%</td>
<td>Yes: AR = 36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes: PCT &amp; AR = 43%</td>
</tr>
<tr>
<td>Craske, Maidenberg, &amp; Bystriksky (1995)</td>
<td>PT</td>
<td>CBT (n = 16), 53%</td>
<td>Yes: NPT = 8%</td>
</tr>
<tr>
<td>D. M. Clark et al. (1994)</td>
<td>12</td>
<td>CT (n = 17), 76%</td>
<td>Yes: AR = 43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes: IMI = 48%</td>
</tr>
<tr>
<td>Côté et al. (1994)</td>
<td>12</td>
<td>CBTM (n = 13), 92%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBTNM (n = 8), 100%</td>
<td></td>
</tr>
<tr>
<td>Klosko et al. (1990)</td>
<td>PT</td>
<td>PCT (n = 15), 87%</td>
<td>No: AL = 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes: FL = 36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes: WL = 33%</td>
</tr>
<tr>
<td>Margraf &amp; Schneider (1991)</td>
<td>1</td>
<td>CT (n = 22), 91%</td>
<td>Yes: WL = 3%</td>
</tr>
<tr>
<td>Newman et al. (1990)</td>
<td>12</td>
<td>CTM (n = 24), 87%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CTNM (n = 19), 87%</td>
<td></td>
</tr>
<tr>
<td>Öst et al. (1993)</td>
<td>12</td>
<td>CT (n = 19), 89%</td>
<td>No: AR = 74%</td>
</tr>
<tr>
<td>Shear et al. (1994)</td>
<td>6</td>
<td>CBT (n = 23), 45%</td>
<td>No: NPT = 43%</td>
</tr>
<tr>
<td>Telch et al. (1993)</td>
<td>PT</td>
<td>PCT (n = 34), 85%</td>
<td>Yes: WL = 30%</td>
</tr>
</tbody>
</table>

Note: Abbreviations: AL, alprazolam; AR, applied relaxation; CBT, cognitive-behavioral therapy; CBTM, cognitive-behavioral therapy without medication; CBTNM, cognitive-behavioral therapy without medications; CT, cognitive therapy; CTM, cognitive therapy and medication; CTNM, cognitive therapy without medications; FL, fluoxetine; IMI, imipramine; NPT, non-prescriptive treatment; PL, pill placebo; PCT, panic control treatment (exposure and cognitive restructuring); PT, posttreatment; ST, supportive therapy; WL, wait list. Adapted from Barlow and Lehman (1996). Copyright 1996 by the American Medical Association. Adapted by permission.

- Yes, comparison was significant; No, comparison was not significant; —, comparison was not made.
- Follow-up study of Barlow et al. (1989).
- Percentage of patients who were panic-free at follow-up and who had received no additional treatment during the follow-up period.
- At 8 weeks (the end of supportive therapy), 71% of patients receiving CT were panic-free.
- Patients meeting criteria for "responder" status.

A noteworthy finding from the above-described studies is that forms of CBT for panic disorder have consistently proven more efficacious than credible alternative psychosocial treatments, largely eliminating interpretations related to nonspecific factors (expectancy, therapist relationship issues, etc.). This finding is best illustrated in a program of research first reported by Katherine Shear and colleagues (Shear, Pilkonis, Cloitre, & Leon, 1994), who developed a new approach to panic disorder called "emotion-focused therapy" (EFT). This approach focuses on explicating and treating interpersonal triggers for panic attacks rather than interoceptive ones.
TABLE 10.5. Findings from a Meta-Analysis of 43 Controlled Studies of Treatment of PDA

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive-behavioral therapy</td>
<td>0.68</td>
<td>5.6%</td>
</tr>
<tr>
<td>Cognitive therapy and interoceptive exposure</td>
<td>0.88</td>
<td>NR</td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td>0.47</td>
<td>19.8%</td>
</tr>
<tr>
<td>Combination treatment</td>
<td>0.56</td>
<td>22.0%</td>
</tr>
</tbody>
</table>


rather than interoceptive cues. Attrition was high in the first study, but preliminary results were promising. Further evaluation by Shear, Houck, Greeno, and Masters (in press) is now complete. In this study, patients were randomly assigned to receive either EFT, CBT, imipramine, or placebo. Since EFT was evaluated in parallel to the multicenter study reported below, these comparison conditions were drawn from that study. EFT was less effective than either CBT or imipramine. In fact, results of EFT at the end of treatment, and 6 months later after maintenance treatment, were no different from those for placebo. At follow-up, after all treatments were discontinued, EFT fared better than placebo, but was significantly less effective than CBT or imipramine (see Figure 10.7). The fact that this study was carried out by an investigator with allegiance to EFT illustrates the strength of the study, the power of new psychosocial treatments designed for specific patterns of psychopathology, and the growing sophistication of psychotherapy research in elucidating these differences.

THE MULTICENTER STUDY. We have recently reported results from a multicenter clinical trial for panic disorder, the largest combined treatment study to date (Barlow et al., 2009). In this study, we compared the combination of PCT (Barlow & Craske, 2000) and imipramine to each treatment alone, a pill placebo, and PCT plus placebo in 312 patients with mild to moderate agoraphobia. Patients were seen at four different sites: the Departments of Psychiatry at Yale University, Columbia University/Hillside Hospital, and University of Pittsburgh/Western Psychiatric Institute and Clinic, and the Center for Anxiety and Related Disorders at Boston University. All patients were treated weekly for 3 months (12 sessions for the acute phase), and “responders” were then seen monthly for 6 months (maintenance phase). All patients were followed up 6 months after treatment ended; thus the overall duration of the study was 15 months.

Results indicated that both imipramine and PCT were significantly superior to placebo after the acute phase of treatment, as were the two combined treatments in terms of total number of patients meeting a response criterion based on scores on the PDSS. However, the PCT-imipramine combination was not significantly better than the PCT-placebo combination or either of the individual treatments. Notably, among those who responded to treatment (for the moment, excluding those who didn’t respond or dropped out), imipramine evidenced a somewhat broader therapeutic effect, since patients were also less depressed and had slightly better results on some self-report measures (see Figure 10.8). At the end of the maintenance phase, all treatments remained significantly better than placebo; most remaining patients in the placebo condition who had done well initially had deteriorated substantially, resulting in even more dramatic treatment-placebo differences. Also, the PCT-imipramine combined treatment proved to be slightly better at this 9-month follow-up data
Panic Disorder and/or while advantage to c appears to be more
treatment relapse rate
and patients who co logical treatment (i.e.
Although the st
treatments (Boston st
treatments (Yale an "allegiance" effects
to a particular appr
the study indicated
hold income) were r
undergoing further

THE COMBINAT
diazepines do not cr
viewed earlier the s
alprazolam seemed b
in our multicenter st
of imipramine and c
1996a). Reports that
are more consistent

Some innovati
approaches and possi
found that a modifi
taper over 10 weeks
taper condition disc
only condition. A s
nearly all patients v
portive medical ma
Importantly, howe

FIGURE 10.7. Response rates among acute treatment completers for cognitive-behavioral therapy (CBT), imipramine (IMI), emotion-focused therapy (EFT), and placebo (PLA). PDSS, Panic Disorder Severity Scale; CGI, Clinical Global Improvement. *p < .05. **p < .001. From Shear, Houck, Greeno, and Masters (in press). Reprinted by permission of the authors.

point than even PCT plus placebo, although probably not to the point of clinical signi
ificance, particularly considering the extra cost associated with this combined treatment.
No other differences among treatments were noted at this point (see Figure 10.8). At the
15-month point in the study, 6 months after all treatments were discontinued, patients who
had responded to imipramine (either as a single treatment or in combination with PCT)
lost any gains they had made, making PCT (either alone or in combination with placebo)
significantly more effective than the other conditions (see Figure 10.8). The results suggest
that both individual treatments are clearly effective; that there appears to be no worth-


6
5
4
3
2
1

% Relapsed within 6 months

FIGURE 10.9. Postr
intent-to-follow and
while advantage to combining treatments; and that the psychological treatment (i.e., PCT) appears to be more durable in its effects. Indeed, data comparisons of the 6-month post-treatment relapse rate based on the Clinical Global Improvement Scale for intent-to-follow and patients who completed treatment provide some support for the durability of psychological treatment (i.e., PCT) (see Figure 10.9).

Although the study was conducted at two sites known for expertise in psychological treatments (Boston and Pittsburgh) and two sites known for expertise in pharmacological treatments (Yale and Columbia), no site differences were observed in outcome. Thus any “allegiance” effects (in which treatments do better at sites where therapists are adherents to a particular approach) did not seem to contribute to outcome. Attrition analyses from the study indicated that life stressors and lower education level (as a function of household income) were most strongly related to attrition (Grilo et al., 1998). These results are undergoing further analyses.

THE COMBINATION OF CBT AND BENZODIAZEPINES. Most evidence suggests that benzodiazepines do not combine well with CBT or other psychosocial treatments. We have reviewed earlier the study by Marks et al. (1993) in which concurrent administration of alprazolam seemed to detract from long-term effects of exposure, paralleling the effects noted in our multicenter study with PCT and imipramine. But others have noted synergistic effects of imipramine and exposure-based treatments under certain conditions (e.g., Mavissakalian, 1996a). Reports that high-potency benzodiazepines may interfere with and detract from CBT are more consistent (Brown & Barlow, 1995; Otto, Pollack, & Sabatino, 1996).

Some innovative research provides insight into the future of combined treatment approaches and possible success of sequential treatment strategies. First, Otto et al. (1993) found that a modified PCT protocol conducted in combination with a slow alprazolam taper over 10 weeks resulted in excellent outcomes. Fully 75% of the patients in the PCT-taper condition discontinued medication, compared with only 25% of those in the taper-only condition. A similar study (Spiegel, Bruce, Gregg, & Nazzarelli, 1994) found that nearly all patients were able to discontinue alprazolam use (80% of those receiving supportive medical management plus taper, and 90% of those receiving PCT plus taper). Importantly, however, at the 6-month follow-up, half of the patients receiving support-

![Figure 10.9](image-url)
ive medical management plus taper had relapsed, compared to none receiving PCT plus taper. A 3-year follow-up found that one-third of those receiving PCT plus taper had suffered a relapse in the 6–18 months following treatment, compared with 70% in the supportive condition (Spiegel et al., 1994). Taken together, these findings provide support for the potential use of combination treatments that include benzodiazepines (initially to provide immediate relief and/or to treat those who desire medication) followed by or used in conjunction with CBT protocols. The future of these sequential treatment approaches as opposed to comparative or simultaneous approaches awaits further investigation.

Similarly, the effectiveness of psychosocial treatments for those patients who do not show full response to pharmacotherapies has begun to receive attention. Pollack et al. (1994) examined the addition of 12 weeks of CBT for patients who were “medication nonresponders” (i.e., patients who had previously exhibited an incomplete response to pharmacotherapy). Compared to a prior nonresponse to medication, these patients showed marked improvement following the CBT—both improved global functioning and reduced panic attack frequency. It is possible that these patients may represent a unique sample who were nonresponsive to medication and who showed improvement from psychosocial treatments. It is also possible that providing medication for patients who do not respond to CBT (i.e., the reverse sequence) may have comparable outcomes.

EFFECTS OF TREATMENT ON COMORBID CONDITIONS. Effective treatments for panic disorder have been shown to have a positive impact on comorbid conditions of anxiety and depression (T. A. Brown, Antony, & Barlow, 1995; Laberge, Gauthier, Côté, Plamondon, & Cormier, 1993; Tsao, Lewin, & Craske, 1998). That is, following CBT of panic disorder, co-occurring symptoms of depression and other anxiety disorders also show improvement. Moreover, in a recent exploratory single-case design with three patients who reported current alcohol abuse, the alcohol abuse subsided in all three patients after successful treatment with PCT (although one patient later relapsed; Lehman, Brown, & Barlow, 1998). This result is very preliminary and requires extensive investigation before clinicians begin reversing the usual order of treating substance abuse before comorbid anxiety disorders. But it may be a useful strategy, since the onset of anxiety often precedes substance abuse, as described in some detail in Chapter 1. Still other research has found that some personality traits may subside following CBT for panic (Hoffart, 1997; Hoffart & Hedley, 1997; Hofmann et al., 1998; Rathus, Sanderson, Miller, & Wetzler, 1995).

In a recent study (Hofmann et al., 1998), we examined the comparative effects of CBT and pharmacotherapy for panic disorder on personality disorder characteristics in a sample of 93 patients with panic disorder with mild or no agoraphobia. Results of this study showed that both treatments had a positive impact on nearly all personality disorder characteristics, independent of type of treatment and response to the particular treatment. In fact, with some exceptions (i.e., scores on the Schizoid Personality Disorder Scale), all personality disorder characteristics showed significant change from baseline to posttreatment for both treatment groups. Notably, however, personality disorder characteristics did not predict treatment outcome with either CBT or imipramine—a finding consistent with other studies (Dreessen, Amrntz, Luttels, & Sallaets, 1994). A study examining benefits of CBT (T. A. Brown, Antony, & Barlow, 1995) found that the beneficial effects of CBT for panic disorder on comorbid conditions may lessen over time. As such, if the comorbid condition is not completely remitted, both the comorbid condition and the panic disorder may return to pretreatment levels by follow-up. However, other researchers (Woody, McLean,
Panic Disorder and Agoraphobia

Taylor, & Koch, 1999) found that reductions in co-occurring diagnoses of depression were no greater after treatment for panic than after a wait-list period. Indeed, these findings raise important questions regarding the mechanisms of action of the treatments and the overlap in treatment components for related anxiety and mood disorders, as well as the nature of psychopathology in anxiety and mood disorders.

SEVERAL CAVEATS. Despite the positive findings reviewed above, research on CBT for panic disorder must be interpreted with only cautious optimism and with several caveats in mind. First, and as noted above, many studies of CBT for panic have excluded patients with severe agoraphobia, and thus findings may overestimate the effectiveness of CBT. Controlled studies including patients with the full range of agoraphobic avoidance have found more attrition and fewer patients showing clinical improvement at posttreatment and follow-up.

Second, methodological rigor and outcome measures are often quite variable across studies and may account for inconsistent outcome findings. Such methodological differences may misrepresent true longitudinal outcome. For example, using very stringent criteria (e.g., recurrence of panic attacks, help-seeking behavior), we (Brown & Barlow, 1995) found that more than one-third of patients with panic who were classified as “panic-free” at 24 months posttreatment had experienced a panic attack in the preceding year. Moreover, we found that a large minority (27%) of this sample had obtained further treatment for panic during the follow-up interval. Such findings highlight the importance of obtaining consistent, longitudinal follow-up on patients, in order to evaluate their clinical status most reliably and validly.

The third caveat concerns the generality of findings from studies reviewed above to clinical settings. Whereas most treatment outcome studies are conducted in highly controlled clinical research settings with thoroughly trained therapists, and are thus designed to maximize both internal validity and the specificity of causal mechanisms of treatment, such controlled conditions are rarely found in the real-world settings to which the treatment is ultimately transported. Researchers have only recently begun to demonstrate the transportability of empirically supported treatments. Fortunately, the early results are encouraging. Wade, Treat, and Stuart (1998), using a benchmarking strategy to compare results from a large community mental health center (CMHC) with those of clinical trial results, found that panic-free status and the percentage of patients achieving normative levels of functioning were comparable across the two settings. These researchers examined 110 patients with PDA or panic disorder without agoraphobia—and patients were not excluded on the bases of age, medication use or medication instability, severity of panic, or the presence or absence of agoraphobia. Patients who completed a 15-session CBT protocol in the CMHC were compared with patients from two controlled clinical trials. This transportability study involved extensively trained therapists (both psychologists and master’s-level clinicians) and included patients who used concomitant pharmacotherapy when appropriate. Over half (56%) of the CMHC sample reported using anxiolytic medication, compared with somewhat lower percentages in the controlled clinical trial samples (40%, Barlow et al., 1989; 47%, Telch et al., 1993). Moreover, and importantly, the CMHC sample reported having significantly fewer years of education than the clinical trial samples, and a large percentage of the CMHC sample was described as suffering moderate to severe agoraphobia (47%). Findings for the CMHC treatment completers indicated that 87% were panic-free at the end of treatment, and that these patients also exhibited less anticipatory anxiety, less agoraphobic avoidance, less general anxiety, and fewer symptoms of depres-
sion. At a 1-year follow-up, these results were maintained with 89% of the CMHC treatment completers free of panic and with a substantial proportion having discontinued any prior benzodiazepine use (Stuart, Treat, & Wade, 2000). The findings from this transportability study are promising indeed and await replication.

Despite these optimistic findings, naturalistic studies examining the likelihood of patients’ actually receiving empirically supported treatments outside research settings have had disappointing results (Barlow, Levison, & Bufka, 1999). For example, Goisman et al. (1993) and Goisman, Warshaw, and Keller (1999) studied patients, many with PDA, presenting to leading clinical centers in New England as part of the Harvard-Brown study. Specifically, 362 patients were interviewed in 1991, and then again in 1995–1996. Only 22% of patients were receiving an empirically supported treatment, and this percentage had not increased over the follow-up period.

**Brief Cost-Effective Treatments for Panic and Associated Anxiety**

With their efficacy established, investigations have begun to examine brief and more cost-effective alternatives to CBT for panic disorder and PDA. Efforts to examine the efficacy of intensive, briefer, or self-directed formats have shown promise. Côte et al. (1994) conducted a study in which patients were randomly assigned to receive CBT with either a standard amount of therapist contact (weekly hour-long sessions) or reduced therapist contact (bi-monthly hour-long sessions with bi-monthly 10-minute telephone contacts). Results of this study demonstrated that both treatment modalities were equally effective; over 73% of the patients in both groups were both panic-free and clinically improved at the 6-month follow-up assessment. It should be noted that therapist time in the reduced therapist contact condition was still considerable, amounting to approximately 10 hours of contact, as compared with approximately 20 hours of contact in the standard condition.

Several others have examined the efficacy of briefer alternatives. First, Lidren et al. (1994) examined the effectiveness of self-directed treatment utilizing a manual (bibliotherapy) for panic attacks. They found bibliotherapy to be as effective as CBT administered in a group therapy setting. Patients in both conditions were treated for 8 weeks and were compared with patients in a wait-list control condition. The patients in both of the active treatment conditions showed evidence of significant clinical improvement at posttreatment assessments, while the patients in the wait-list control did not. Moreover, patients in the bibliotherapy and group therapy conditions maintained their treatment gains at the 3- and 6-month follow-up assessments. In addition, an attrition rate of 0 was reported for this study, pointing to the desirability of these interventions for patients suffering from panic attacks. In another study, Craske, Maidenberg, and Bystritsky (1995) examined the effectiveness of a brief form of CBT; A four-session PCT protocol was compared to a four-session nondirective supportive therapy protocol. The brief PCT was found to be significantly more effective than the nondirective supportive therapy; the patients’ clinical statuses were assessed by noting the frequency of their panic attacks, their degree of worry about panic attacks, and their level of phobic fear. Finally, Clark et al. (1999) randomly assigned 43 patients with panic disorder to either standard cognitive therapy (consisting of up to 12 sessions lasting 1 hour each in the first 3 months) or brief cognitive therapy (where patients attended 5 sessions in addition to using between-session self-study modules). Both treatments produced significantly better results than a wait-list control group.
New Developments: Integrating Treatment for Panic and Avoidance in an Intensive Treatment Format

A promising treatment approach we have been developing and investigating is an intensive treatment program for PDA that combines treatments for panic and avoidance, called "sensation-focused intensive treatment" (SFIT). For a full description of this program and protocol, see Heinrichs, Spiegel, and Hofmann (in press). Inspired by the work of Feigenbaum (1988), this program differs from PCT in several ways. First, the program was designed for patients with PDA whose agoraphobia is moderate to severe. Second, it is conducted intensively in a CBT self-study format (with therapist review) over 8 consecutive days. Third, rather than a hierarchically based exposure plan, treatment involves interoceptive and situational exposures conducted in ungraded massed fashion. That is, patients are exposed to their most feared agoraphobic situations while simultaneously inducing feared somatic sensations. This aspect of the SFIT approach is unique, in that it emphasizes the deliberate provocation and maximal intensification of anxious symptoms without teaching any arousal reduction procedures. Although therapists often accompany patients during the initial exposure trials to insure that the patients conduct the exposure effectively, the therapists are then rapidly removed from the exposure practices. Despite these differences, the program has a number of similarities to our PCT protocol, including education, cognitive restructuring, symptom inductions, and interoceptive and situational exposure practices.

Initial findings for this program appear promising, and long-term outcome evaluations are ongoing. To date (winter 2001), 23 patients with PDA whose agoraphobia is moderate to severe have completed the SFIT protocol, and follow-up data are available on 15 patients (see Spiegel & Barlow, 2000a, 2000b). Following treatment, patients were significantly improved on nearly all self-reported and clinician-rated measures, and the gains have been maintained at follow-up (mean follow-up = 5 months). At posttreatment, the majority (87%) were much or very much improved at posttreatment. Notably, 2 patients evidenced worsening symptoms at follow-up (compared with posttreatment). Of course these results are preliminary, but they are promising enough to warrant replication and comparison with "gold standard" PCT and/or pharmacotherapy.