Chapter 13

Combined Pharmacological and Psychological Treatment of Panic Disorder: Current Status and Future Directions

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Given the significant advances in both the pharmacological and psychological treatments for panic, it seems reasonable to consider the union of these two approaches. Do combined treatments yield greater benefits to panic disorder patients than either treatment administered alone?

The general enthusiasm generated for combination treatments is borne out by data suggesting that most panic disorder patients in treatment receive both medication and psychotherapy (Taylor et al. 1989). Although it is not clear that the particular singular treatments being combined in day-to-day clinical practice are those with established efficacy, there appears to be a pervasive attitude that combined drug-psychological treatments are superior to singular treatments. A question of central import is whether this attitude is consistent with the scientific evidence.

We organize our chapter around the following questions:

1. Why study combined treatments?
2. What is the current scientific knowledge base on combined treatments for panic disorder?
3. What is the clinical efficacy of combined treatments?
4. What implications do the research findings have for clinical practice?

5. What are the research priorities for advancing our understanding of combined treatments?

Rationales for Combined Treatments

The rationales for using a combined drug-psychological approach in treating panic disorder are inextricably linked to how one conceptualizes the disorder and the presumed efficacy and mechanisms of action of the singular treatments being combined. In this chapter, we do not review research on either the efficacy or mechanisms of action for psychological or pharmacological treatments, as that task is undertaken successfully in several other chapters. Rather, we briefly review a few of the most frequently discussed rationales for combining psychological treatment and medications. These include 1) treatment specificity, 2) facilitation of psychological treatment through pharmacotherapy, and 3) facilitation of pharmacotherapy through psychological treatment.

Treatment Specificity

The assumption that medications and psychological treatments exert their primary effect on different loci or facets of a disorder has been the subject of considerable debate. Originally, Klein (1980) stressed the specific action of certain classes of medications in blocking spontaneous panic. It was assumed that psychotherapies and benzodiazepines were ineffective for the spontaneous panic feature of the disorder, but that both could be helpful in treating the psychological complications of spontaneous panic, namely anticipatory anxiety and phobic avoidance. The assumption of treatment specificity for tricyclic antidepressants and the monoamine oxidase inhibitors (MAOIs), along with the recognition that panic disorder is a multifaceted syndrome, led to the recommendation of administering panic-blocking medication in conjunction with psychological treatment that encouraged patients to confront fear-provoking cues (Klein 1980). To the extent that medication and psychological treatments affect different symptom clusters within the panic syndrome, their combined use offers the advantage of treating multiple loci concurrently, and hence they may be more effective.

Facilitation of Psychological Treatment Through Pharmacotherapy

A second rationale for a combined treatment approach is the facilitation of psychological treatment through pharmacotherapy. Even when a psychological ap-

proach is being used as the primary treatment for panic, there may be circumstances in which the addition of medication may be indicated. For example, panic disorder patients displaying marked depression while undergoing psychological treatment may possess insufficient energy or motivation to participate in an intensive cognitive-behavior treatment for panic. In such cases, the addition of an antidepressant may be desirable.

Another example of the potential facilitation of psychological treatment through pharmacotherapy is when the patient's extreme anxiety interferes with the psychological treatment. In these cases, short-term administration of benzodiazepines or some other anxiolytic may allow the patient to calm down sufficiently so that psychological treatment may be initiated.

Facilitation of Pharmacotherapy Through Psychological Treatment

A third rationale for combining medication and psychological treatments involves the potential facilitative effects that psychological interventions may have for patients undergoing drug treatments for panic. One such facilitative function may be increased compliance with medication. As noted in previous reviews of pharmacological treatments, many panic disorder patients display a fear of taking medications (Telch 1988; Telch et al. 1983). Although reassurance by the physician may be sufficient for some, psychological treatment specifically targeting medication fears may be needed for the more severely phobic patient.

Psychological treatments may also serve a facilitative role in assisting patients during medication withdrawal. Patients who are provided with psychological strategies aimed at enhancing their sense of mastery and control may be more likely to withdraw from medications successfully. Moreover, there is now evidence to suggest that patients displaying comorbid personality disorders may show a less favorable response to pharmacological treatment (Noyes et al. 1990; Reich and Green 1991) or have a higher probability of relapse (Green and Curtis 1988). Consequently, concurrent psychological intervention specifically addressing spheres such as personality dysfunction may help to reduce relapse.

Current Scientific Knowledge Base on Combined Treatments

The present review is limited to those controlled studies that have compared one or more drug-psychotherapy combination treatments with one or more singular

treatments (drug or psychotherapy). Comparative studies of two or more singular treatments, whether drug or psychological, have been omitted because they do not directly address the issue of combined treatments. A total of 13 studies (11 published, 2 currently under editorial review) met the criteria for inclusion. Table 13–1 gives a breakdown of the types of combination treatments studied to date.

As seen in Table 13–1, the majority of combined drug-psychological treatment studies (8 of 13) used imipramine as the pharmacological treatment (Agras et al. 1991; Marks et al. 1983; Mavissakalian and Michelson 1986a, 1986b; Mavissakalian and Perel 1985; Sheehan et al. 1980; Telch et al. 1985; Zitrin et al. 1980, 1983). MAOIs were used in 3 of the combined studies (Lipsedge et al. 1973; Sheehan et al. 1980; Solyom et al. 1981), diazepam was used in one early study (Hafner and Marks 1976), and the high-potency benzodiazepine alprazolam was examined in one recently completed multicenter study (Marks and Swinson 1993). Finally, one study (Sheehan et al. 1980) included two separate combination treatments—imipramine plus supportive psychotherapy, and phenelzine plus supportive psychotherapy.

What are the psychological treatments employed in the combined studies? As was the case with imipramine and pharmacotherapy, exposure-based therapies were overly represented compared with the other two categories of psychological treatments—cognitive-behavior therapy and insight-oriented or supportive therapy. As is shown in Table 13–1, 11 of the 13 studies examined a medication combined with an exposure-based treatment, two studies (Sheehan et al. 1980; Zitrin et al. 1983) combined medication with nonbehavioral supportive psychotherapy, and one study (Zitrin et al. 1983) included two separate combined treatments: imipramine plus supportive psychotherapy and imipramine plus imaginal desensitization.

Table 13–1 highlights the limitations in our current knowledge. Of the 12 possible psychological-pharmacological treatment combinations, 6 have yet to be examined and several others have limited coverage. Indeed, with the exception of the combined treatment of imipramine and exposure therapy, our knowledge base of combined drug-psychological treatments is quite limited. For example, despite the widespread use of high-potency benzodiazepines in the treatment of panic, only one study (Marks and Swinson 1993) examined their efficacy in combination with a psychological treatment. Of particular importance is the absence of data on the combined effects of pharmacotherapy and the new genre of cognitive-behavior treatments for panic (see Chapters 9 and 10, this volume).

A more detailed description of study characteristics is presented in Table 13–2. Due to space limitations, a full summary of this information is not given here. However, a few remarks about the studies deserve highlighting. First, as seen

in column 2, the patient samples are exclusively composed of agoraphobic patients. Patients with uncomplicated panic disorder or panic disorder with minimal avoidance are not represented. Only 4 of the studies (Agras et al. 1991; Mavissakalian et al. 1983; Solyom et al. 1981; Telch et al. 1985) included an active drug without psychological treatment as a comparison group. Moreover, none of the studies included a psychological treatment without placebo. As seen in the last column, 4 (Hafner and Marks 1976; Lipsedge et al. 1973; Sheehan et al. 1980; Solyom et al. 1981) of the 13 studies did not report outcome data for panic attacks. A discussion of these limitations and their implications for future research are presented later in this chapter.

Table 13–1. Combined treatment studies for panic disorder, classified by type of drug and type of psychological treatment

	Drug treatments			
Psychological treatments	Tricyclic antidepressants	Monoamine oxidase inhibitors	Low-potency benzodiazepines	High-potency benzodiazepines
Exposure-based therapy	Agras et al. 1991 Marks et al. 1983 Mavissakalian and Perel 1985 Mavissakalian et al. 1986a, 1986b Telch et al. 1985 Zitrin et al. 1980, 1983	Lipsedge et al. 1973 Solyom et al. 1981	Hafner and Marks 1976	Marks and Swinson 1993
Cognitive-behavior therapy	None	None	None	None
Insight-oriented/ supportive therapy	Sheehan et al. 1980 Zitrin et al. 1983	Sheehan et al. 1980		

Table 13–2. Studies of combined drug and psychological treatment for panic disorder

Study	Sample (no. of completers)	Design	No. per group	Assessment periods (weeks)	Duration of treatment (weeks)	Mean drug dosage (mg)	Assessment after drug withdrawal	Panic assessment
Agras et al. 1991	AG (87)	IM + EX	24	0, 8, 16, 24	Drug: 24 EX: 8	Week 8: 142 Week 16: 168	Yes	Prospective self-monitoring
		IM + AEX	23					
		PL + EX	20					
		PL + AEX	20					
Hafner and Marks 1976	AG (57)	GE + DZ (waning)	14	0, 2	2	0.1/kg body weight	No	None
		GE + DZ (peak)	13					
		GE + PL	14					
		IE (high anxiety)+ PL	6					
		IE (low anxiety)+ PL	6					
Lipsedge et al. 1973	AG (60)	MSD + IZ	10	0, 8	8	IP: 50 BR 1% IV solution	No	None
		SD + IZ	13					
		IZ	9					
		MSD + PL	10					
		SD + PL	8					
		PL	10					
Marks et al. 1983[a]	AG (45)	IM + EX or IM + RT	23	0, 14, 28, 35, 52, 104	Drug: 24 EX: 12	Week 14: 158 Week 26: 110	Yes	Rating scales
		PL + EX or PL + RT	22					
Marks and Swinson 1993	AG (129)	AZ + EX	34	0, 8, 18, 23, 43	18	Week 8: 6	Yes	Prospective self-monitoring
		AZ + RT	34					
		PL + EX	30					
		PL + RT	31					

Mavissakalian et al. 1983	AG (15)	IM IM + PR	7 8	0, 12	12	125	No	Rating scales
Mavissakalian and Perel 1985; Mavissakalian et al. 1986a, 1986b	AG (62)	IM + FL IM + PR PL + FL PL + PR	14 17 17 14	0, 4, 8, 12	12	Month 1: 80 Month 2: 125 Month 3: 123	Yes	Rating scales
Sheehan et al. 1980	EA (57)	PH + SG IM + SG PL + SG	17 18 22	0, 6, 12	12	PH: 45 IM:150	No	None
Solyom et al. 1981	AG (40)	PH + EX PH PL + EX PL	10 10 10 10	0, 8, 16	8	PH: 45	No	None
Telch et al. 1985	AG (29)	IM + EX IM + AEX PL + EX	10 10 9	0, 8, 26	Drug: 26 EX: 8	Week 8: 190 Week 26: 179	No	Prospective self-monitoring
Zitrin et al. 1980	AG (53)	IM + EX PL + EX	29 24	0, 14, 26	Drug: 26 EX: 10	200	No	Rating scales
Zitrin et al. 1983	AG, MP, SP (63)	IM + SD IM + ST PL + SD	18 24 21	0, 26	26	204	No	Rating scales

Note. **Treatment conditions:** IM = imipramine; EX = exposure therapy; AEX = anti-exposure instructions; PL = placebo; GE = group exposure; DZ = diazepam; IE = individual exposure; MSD = methohexitane-assisted systematic desensitization; IZ = iproniazid; SD = systematic desensitization; RT = relaxation training; AZ = alprazolam; PR = programmed practice; FL = flooding; PH = phenelzine; SG = support group; ST = supportive therapy. **Other:** AG = agoraphobic patients; EA = endogenous anxiety patients; MP = mixed phobic patients; SP = simple phobic patients; IV = intravenous.
[a]All groups received exposure homework.

Clinical Efficacy of Combined Treatments

Possible Outcomes When Evaluating Combined Treatments

In turning to the issue of efficacy, we should keep in mind that the combination of pharmacological and psychological treatments may result in one of several outcomes. These outcomes are illustrated in Figure 13–1. The first two outcomes, additivity and potentiation, are favorable in that the combination treatment outperforms either of the singular treatments. *Additivity* is displayed when the effects of the combined treatment resemble the sum of the effects of each singular treatment. *Potentiation* is demonstrated when the outcome of the combined treatment significantly surpasses the additive effects of the singular treatments.

Unfortunately, combining drug and psychological treatments does not always lead to additive or potentiation effects. Three additional outcomes are possible. *Inhibition* refers to a negative interaction between the treatments, resulting in a combined effect less than that from either treatment administered individually. Finally, two levels of *reciprocation*—combined treatment effects equivalent to the effects of either one or both of the singular treatments—are also possible.

Using real data from the panic disorder/agoraphobia literature, Figures 13–2 through 13–4 present a few possible outcomes. The figures show behavioral approach data at posttreatment from a recently completed treatment study of imipramine and exposure therapy (Agras et al. 1991). Note the additive effects of imipramine and exposure homework on the patient's behavioral approach test (BAT).

Figure 13–3 illustrates the potentiation of imipramine and exposure therapy reported by Telch et al. (1985). In this study the magnitude of change for the combination treatment exceeded the additive effects of the individual treatments. Agras et al. (1991) observed a significant negative interaction between imipramine and exposure therapy on agoraphobic patients' panic appraisals (Figure 13–4). Notice that imipramine appears to be inhibiting the effectiveness of exposure therapy on this measure of panic-related cognitions.

Short-Term Efficacy of Combined Treatments

How effective are combined treatments in the short term? To address this issue, we examined controlled studies comparing one or more combined treatments with one or more singular treatments. A series of meta-analyses were conducted to examine the relative efficacy of 1) combined treatments versus psychological treatments, and 2) combined treatments versus pharmacological treatments. Ef-

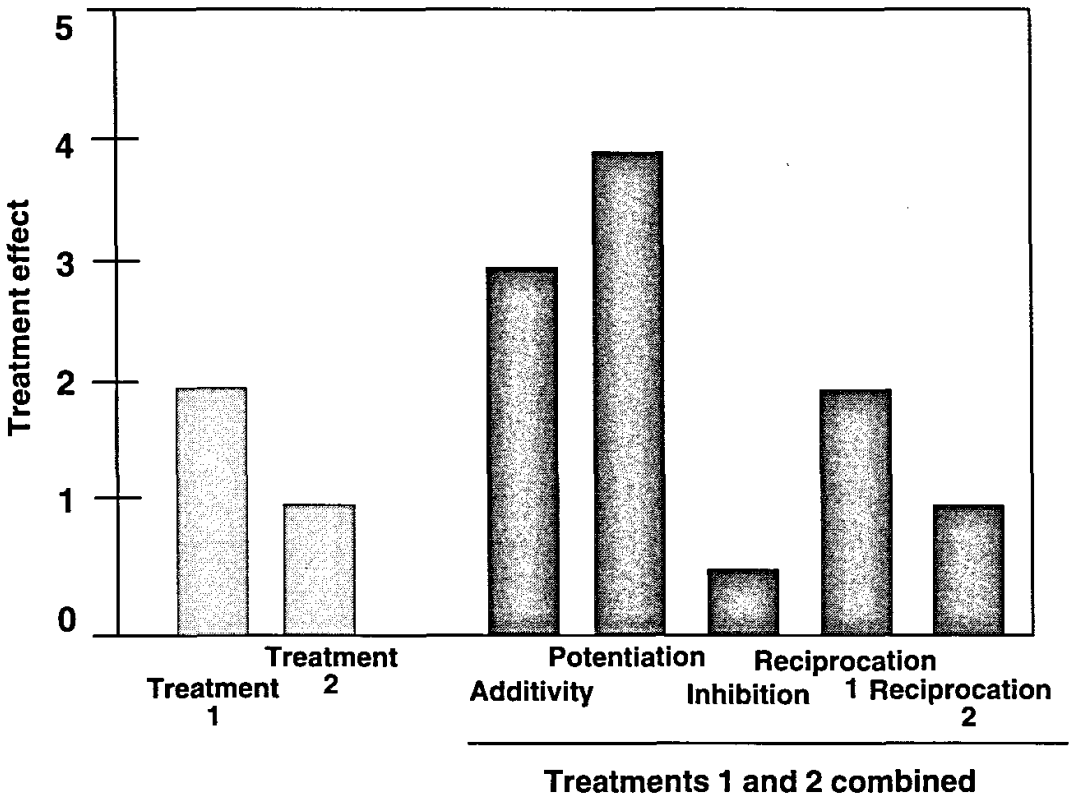

Figure 13–1. Possible drug-psychotherapy interactions. *Source.* Adapted from Uhlenhuth et al. 1969.

fect sizes for these two major sets of comparisons were calculated separately for each of the following five domains: 1) panic, 2) phobic anxiety, 3) phobic avoidance, 4) depression, and 5) global functioning or level of disability.

▮ **Combined versus psychological treatments.** Results of the eight studies (Agras et al. 1991; Marks and Swinson 1993; Marks et al. 1983; Mavissakalian and Perel 1985; Mavissakalian et al. 1986a, 1986b; Sheehan et al. 1980; Telch et al. 1985; Zitrin et al. 1980, 1983) that directly compared a combined treatment with a psychological treatment are presented in Table 13–3. Several studies were excluded from the meta-analysis for failing to report group means and standard deviations. The Sheehan et al. (1980) study is listed twice because it contributed two separate combined versus psychological comparisons to the analysis (imipramine plus supportive psychotherapy and phenelzine plus supportive psychotherapy). The row summaries represent the pooled effect size across the five assessment domains for each study, whereas the column summaries represent the average effect size for a particular assessment domain pooled across studies. Positive effect sizes signify an advantage for the combined treatment.

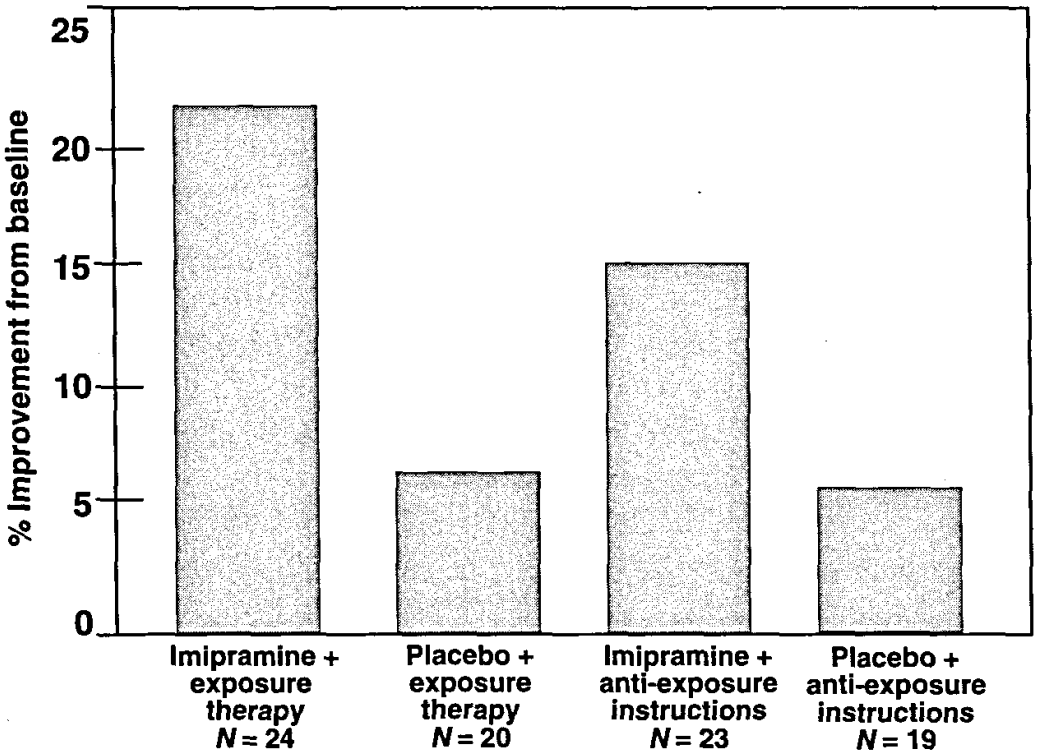

Figure 13–2. Improvement in Behavioral Approach Test (BAT) scores from pre- to posttreatment. *Source.* Data from Agras et al. 1991.

Results of this analysis reveal a significant overall advantage for the combined treatment for most of the studies. Moreover, inspection of the column summaries indicates that the short-term superiority of combined treatment was consistent across the five major assessment domains rather than being limited to one domain, such as panic. As seen in Table 13–3, a modest but significant overall advantage for combined treatments over psychological treatment alone was observed at posttreatment (overall pooled effect size = .45).

The data are at odds with a review by Clum (1989) in which he concluded that combined treatments were less effective than behavior therapies alone. It should be noted that Clum based this conclusion on comparisons of author-defined success rates for individual studies. Unfortunately, this analytical approach is flawed when one considers that the differences in success rates may simply reflect between-study differences in the criteria used to define successful outcome.

▮ **Combined versus pharmacological treatments.** A second set of analyses were conducted to examine the relative efficacy of combined versus pharmacological

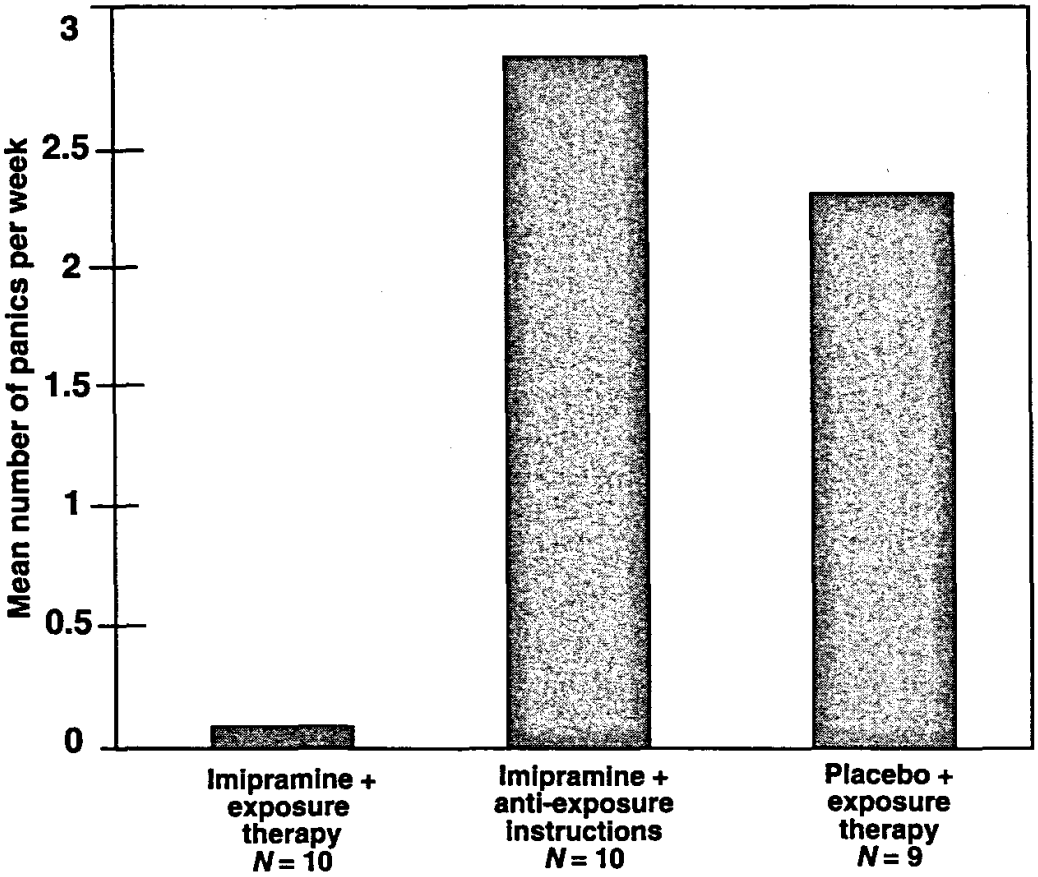

Figure 13–3. Mean number of panic attacks at 26 weeks posttreatment. *Source.* Data from Telch et al. 1985

treatments. Only three studies (Agras et al. 1991; Mavissakalian et al. 1983; Telch et al. 1985) included a direct comparison of a combined treatment with pharmacotherapy alone. In all three studies, the combined treatment was imipramine plus exposure-based therapy. These results are presented in Table 13–4.

Although limited by the small number of studies, this set of results reveals a clear short-term advantage for combined treatment over pharmacological treatment alone. As in the previous comparison, the advantage of the combined treatment over drug treatment alone was present across each of the major assessment domains, with the exception of panic (overall effect size = .39).

Long-Term Efficacy of Combined Treatments

Few studies have included an evaluation of the longer term effects of combined treatments. In a follow-up study of the patients originally treated in the Marks et al. (1983) study, Cohen et al. (1984) reported that approximately two-thirds of the patients interviewed (90% of the original cohort) at 2-year follow-up were im-

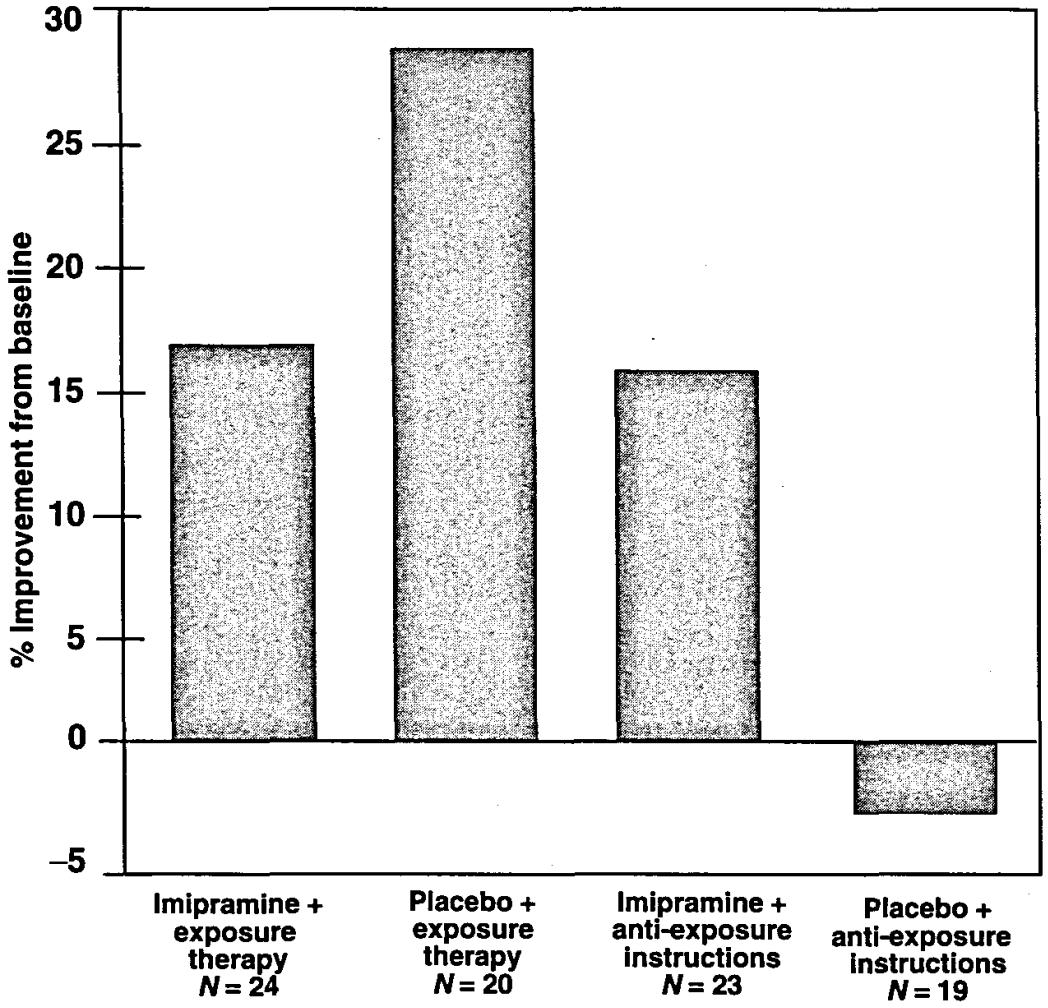

Figure 13–4. Improvement in panic appraisals from pre- to posttreatment. *Source.* Agras et al. 1991.

proved or much improved from their pretreatment level of functioning. No significant advantage of the combined treatment was observed on any of the major clinical outcome measures. Mavissakalian and Michelson (1986b) conducted a 2-year follow-up of agoraphobic patients treated in their original study, comparing the singular and combined efficacy of imipramine and therapist-assisted exposure therapy. All subjects received a systematic program of self-directed exposure therapy. Seventy-six percent of the original cohort were interviewed. The overall improvement was maintained throughout follow-up. However, the superiority of the combined treatment over exposure therapy alone, which was present at week 12, was no longer present at follow-up because of higher relapse among the imipramine-treated patients and the continued improvement for patients in the self-directed exposure therapy control group. Consistent with the follow-up find-

Table 13–3. Posttreatment effect sizes for combined treatment versus psychological treatment

Study	Weeks	Assessment domain					Pooled effect sizes across assessment domains
		Panic	Phobic anxiety	Phobic avoidance	Depression	Functioning/ disability	
Agras et al. 1991	8	.30 (.10)	−.22 (.03)	.38 (.05)*	.18 (.09)	.10 (.05)	−.08 (.01)
Marks et al. 1983	14	NR	NR	.13 (.04)	.01 (.09)	.39 (.09)	.16 (.02)
Marks and Swinson 1993	8	.41 (.06)	.37 (.06)	0.00 (.06)	.37 (.06)	.36 (.03)*	.31 (.01)**
Mavissakalian and Perel 1985; Mavissakalian et al. 1986a, 1986b	12	.30 (.07)	.52 (.01)**	.05 (.03)	.23 (.06)	.36 (.03)*	.36 (.01)**
Sheehan et al. 1980 (imipramine)	12	NR	.81 (.04)**	.76 (.11)**	.97 (.06)**	.55 (.10)*	.81 (.02)**
Sheehan et al. 1980 (phenelzine)	12	NR	1.10 (.04)**	1.19 (.12)**	1.26 (.06)**	1.30 (.13)**	1.19 (.02)**
Telch et al. 1985	8	.18 (.21)	.67 (.11)*	.83 (.06)**	.04 (.07)	NR	.48 (.02)**
Zitrin et al. 1980	14	.65 (.05)**	NR	.66 (.04)**	NR	.65 (.03)**	.65 (.01)**
Zitrin et al. 1983	26	.48 (.02)**	.56 (.04)**	.53 (.03)**	.41 (.11)	.51 (.03)**	.51 (.01)**
Pooled effect sizes across studies	—	.45 (.01)**	.52 (.01)**	.34 (.001)**	.48 (.01)**	.47 (.01)**	.45 (.001)**

Note. Numbers in parentheses refer to the variance of the effect size. Positive effect sizes signify an advantage for the combined treatment. NR = no means reported for this domain.
*$P \leq .05$. **$P \leq .01$.

Table 13–4. Posttreatment effect sizes for combined treatment versus drug treatment

Study	Weeks	Assessment domain					Pooled effect sizes across assessment domains
		Panic	Phobic anxiety	Phobic avoidance	Depression	Functioning/ disability	
Agras et al. 1991	8	−.37 (.09)	.12 (.03)	.19 (.04)	.23 (.09)	.40 (.04)	.16 (.01)
Mavissakalian et al. 1983	12	.30 (.09)	.45 (.27)	.87 (.15)*	.93 (.15)**	1.05 (.30)*	.65 (.03)**
Telch et al. 1985	8	.14 (.20)	.94 (.11)**	1.23 (.06)**	.17 (.07)	NR	.71 (.02)**
Pooled effect sizes across studies		−.003 (.04)	.30 (.02)*	.66 (.02)**	.35 (.03)*	.48 (.04)**	.39 (.006)**

Note. Numbers in parentheses refer to the variance of the effect size. Positive effect sizes signify an advantage for the combined treatment. NR = no means reported for this domain.
*$P \leq .05$; **$P \leq .01$.

ings from the Marks et al. (1983) study, approximately two-thirds of the patients assessed cross-sectionally at the 2-year follow-up were markedly improved.

Preliminary data on the long-term effects of combined alprazolam and exposure therapy are now available from the recently completed multicenter trial conducted in London and Toronto (Marks and Swinson 1993). These data are of particular interest because they represent the only available information on the efficacy of a combined alprazolam plus exposure treatment. Our effect size analyses presented earlier suggested a slight advantage of the combined alprazolam-exposure treatment over exposure therapy plus placebo at the posttreatment assessment. In contrast to the short-term results, data on the combined treatment's long-term efficacy after medication withdrawal revealed that patients receiving the combination treatment evidenced a significantly poorer outcome at follow-up, compared with those patients treated with exposure therapy plus placebo. The poorer long-term outcome for the combined alprazolam-exposure group was due to a markedly higher relapse rate among those treated with alprazolam, rather than further gains made by the placebo plus exposure therapy group. These findings are consistent with early reports suggesting that tranquilizing medication may interfere with the therapeutic effects of exposure therapy (Chambless et al. 1979).

Conclusions Regarding the Efficacy of Combined Treatments

▮ **Short-term efficacy.** From the data just presented, several conclusions about the short-term efficacy of combined treatments seem warranted:

1. Approximately 66%–75% of patients displaying panic disorder with agoraphobia achieved marked improvement when treated with a combination of imipramine plus exposure therapy or alprazolam plus exposure therapy.
2. For patients displaying panic disorder with agoraphobia, the combination of imipramine and exposure therapy offers a short-term advantage over either imipramine alone or exposure therapy alone.
3. For patients displaying panic disorder with agoraphobia, the combination of alprazolam and exposure therapy offers a slight short-term advantage over exposure therapy alone, and a marked short-term advantage over alprazolam alone.

▮ **Long-term efficacy.** Based on the limited data available, conclusions concerning the long-term effects of combined treatments are as follows:

1. Between one-half and two-thirds of agoraphobic patients treated with exposure therapy and imipramine will evidence marked improvement at follow-ups ranging from 12 to 24 months.
2. For patients displaying panic disorder with agoraphobia, the combination of imipramine and exposure therapy is no more effective than exposure therapy alone.
3. For patients displaying panic disorder with agoraphobia, the use of alprazolam in combination with exposure therapy results in higher relapse and poorer long-term outcome than exposure therapy treatment without alprazolam.

Recommendations for Clinical Practice

What are our recommendations for clinical practice with respect to combining treatment of panic disorder using a combined pharmacological and psychological approach? The gaps in the current knowledge base severely limit prescriptions for clinical practice. Despite our conclusion that the combination of imipramine and exposure therapy confers a short-term advantage over either treatment administered individually, the failure of the combined treatment to show an advantage in the long term argues against its routine use as a first-line treatment. Similarly, the combined use of exposure therapy plus alprazolam cannot be recommended, given the recent findings from the London-Toronto multicenter study (Marks and Swinson 1993) showing that alprazolam plus exposure therapy was less effective in the long term than placebo plus exposure therapy.

Considering the current state of knowledge on combined treatments and the recent data supporting the efficacy of cognitive-behavior therapy administered without medications (see Chapters 12 and 16, this volume), we cannot recommend any combined treatment as the first line of attack for the panic disorder patient. Rather, we recommend that either an antidepressant (such as imipramine) or a high-potency benzodiazepine (such as alprazolam) be administered in conjunction with a psychological treatment that includes a systematic program of self-directed exposure to feared cues under the following conditions:

1. When an 8- to 12-week trial of cognitive-behavior therapy is either unavailable or unacceptable to the patient
2. When an adequate trial of cognitive-behavior therapy has proved unsuccessful
3. When other clinical considerations (e.g., the presence of severe depression or substance abuse) suggest that the patient may be unsuitable for cognitive-behavior therapy

Critique and Future Directions

Despite the interest in combined treatments for panic disorder, research on them has lagged behind that for single treatments. Previous reviews of the combined treatment literature on panic disorder have enumerated many design and measurement deficiencies (Telch 1988; Telch et al. 1983). The more significant of these included 1) the confounding of drug and exposure therapy, 2) the inappropriate use of placebo plus psychotherapy to represent psychotherapy alone, 3) the measurement deficiencies in the assessment of panic, and 4) the failure to assess the long-term effects of combined treatments. Most of these deficiencies are still with us today, although there are some promising developments.

Priorities for Future Research on Combined Treatments

Where do we go from here? The gaps in our current knowledge base and the conceptual and methodological limitations in the research to date suggest a tentative listing of recommended research. (The order of the following listing in no way implies a ranking of importance.)

1. *Clinical trials examining the efficacy of pharmacotherapy in conjunction with the new genre of psychological treatments.* As discussed in Chapters 9 and 10 (this volume), there are now compelling data that support the effectiveness of a new genre of cognitive-behavior treatments that target panic directly. However, as seen in Table 13–1, there are as yet no data on the efficacy of cognitive-behavior therapy plus pharmacotherapy. Efficacy studies are clearly indicated.
2. *Clinical trials evaluating the efficacy of combined treatments for patients displaying panic disorder without agoraphobia.* As noted in Table 13–2, research on the efficacy of combined treatments for panic disorder have been restricted to patients displaying agoraphobia. The generalizability of these findings to uncomplicated panic disorder has not been examined. This is a particular concern given that approximately two-thirds of panic disorder patients in the general population have little or no agoraphobia (see Chapter 3, this volume).
3. *Use of experimental designs that correct for 1) the confounding of drug effects and psychological treatment effects and 2) the inappropriate use of placebo plus psychotherapy to represent psychotherapy alone.* We need to move beyond the 2×2 factorial study in which active drug versus placebo is crossed with the presence or absence of an active psychological treatment. None of the studies reviewed included a "pure" psychological treatment without pill placebo. The problems associated with using pill placebo plus psychotherapy to represent

psychotherapy alone have been cogently discussed (Hollon and Beck 1978; Hollon and DeRubeis 1981). In short, designs that rely on placebo-plus-psychotherapy comparisons, although useful in illuminating the mechanisms governing the interaction of medication and psychotherapy, are inadequate for drawing valid inferences about differential outcome. The scant empirical evidence directly comparing placebo plus psychotherapy with psychotherapy alone suggests it is misguided to assume equivalence. For example, Klerman et al. (1974) found that depressed patients receiving placebo plus interpersonal psychotherapy had twice the relapse rate (i.e., 28% versus 14%) of a similar group receiving interpersonal psychotherapy alone.

4. *Research aimed at identifying optimal sequencing and dosing of combined treatments.* We have yet to scratch the surface in understanding how best to sequence combination treatments. Systematic examination of sequencing variations is needed to deliver combined treatment in an optimal fashion. In addition to sequencing, the dosing of psychological treatments deserves study. For instance, it is not uncommon for pharmacological studies to continue medication for 6 months, yet the dosing of psychological treatments in the combined treatment studies has been relatively low.
5. *Research aimed at identifying patient subtypes for whom combined treatments are indicated and those for whom combined treatments are contraindicated.* Moderator analyses aimed at identifying patient variables that predict response to combined treatment are critical for attaining an effective system of matching treatment modality and patient characteristics. The presence of severe depression, Axis II psychopathology, or obsessive-compulsive symptomatology are just a few of the factors that deserve careful study and that may assist the clinician in determining whether a combination treatment is indicated. To assist in meeting the sample size requirements for moderator analyses, outcome data from several research centers might be pooled and reanalyzed.
6. *The development of a standardized panic assessment battery to facilitate cross-study comparisons.* Panic researchers continue to employ idiosyncratic methods for assessing panic attacks. Moreover, recent data (Telch et al. 1989) point to the importance of moving beyond panic attack and symptom counts and toward a more comprehensive assessment of the meaning that patients give to their attacks. Panic appraisal dimensions, including 1) beliefs in the likelihood of panic, 2) beliefs in the negative consequences of panic, and 3) the perceived capacity to cope with panic, should be routinely assessed in treatment outcome studies.
7. *Need for a broader assessment of treatment utility that integrates information along several evaluative dimensions.* The evaluation of treatments for panic,

whether singular or combined, has been too limited in scope. We need to move beyond unitary indices of treatment effectiveness (e.g., percentage panic-free) to a more multidimensional mapping of treatment utility that integrates information from several evaluative dimensions, such as 1) degree of symptom improvement, 2) clinical significance of improvements, 3) quickness of action, 4) attrition, 5) adverse effects, and 6) treatment durability. The development of evaluative algorithms for integrating diverse information into a composite index of treatment utility would be a major advance. Preliminary work along these lines has recently appeared (see Chapter 16, this volume).

Concluding Remarks

Research and clinical management of panic disorder have been plagued by a biology-versus-psychology polarization (Middleton 1991; Telch 1991). This polarization impedes advancement of the field by fostering a defensive posture among investigators and consequently inhibiting the disconfirmatory process so important in the practice of good science. Can this sundered state of affairs be improved? As with the integration of disparate psychosocial treatments (Goldfried 1982), the integration of biological and psychological perspectives can occur at several levels of analysis, including the study of common change mechanisms and integration at the procedural level. The National Institute of Mental Health has recently funded a four-site multicenter panic treatment study to investigate the singular and combined effects of imipramine and cognitive-behavior therapy for panic disorder. In addition to its methodological advances (e.g., inclusion of a psychological treatment without placebo, the long-term follow-up of patients following medication withdrawal), the study is noteworthy because it attests to the feasibility of collaborative research between biologically and psychologically minded investigators. Demonstration of such cooperation provides hope that in the years to come depolarization between the two disciplines will occur and with it a deeper understanding of combined treatments.

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