

Panic Disorder: Making Clinical Sense of the Latest Research

Chairperson: Jerrold F. Rosenbaum, M.D., Director, Outpatient Psychiatry Division and Chief, Clinical Psychopharmacology Unit, Massachusetts General Hospital; Associate Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts.

This section of The Journal of Clinical Psychiatry summarizes the highlights of a symposium entitled "Panic Disorder: Making Clinical Sense of the Latest Research" held on March 29, 1996, in Orlando, Florida. Individual presentations focused on the impact of panic disorder on quality of life, new data concerning the selection and optimization of pharmacotherapy, and the integration of cognitive-behavioral approaches to pharmacotherapy in the treatment of panic disorder. Other participants were Jonathan R. T. Davidson, M.D., Professor of Psychiatry and Director, Anxiety and Traumatic Stress Disorders Program, Duke University Medical Center, Durham, North Carolina, and David H. Barlow, Ph.D., Distinguished Professor of Psychology, University at Albany, State University of New York and Director, Phobia and Anxiety Disorders Clinic, Albany, New York. The program was sponsored by the Department of Psychiatry, Harvard Medical School, through an unrestricted educational grant from Roche Laboratories, a member of the Roche Group.

Quality of Life in Panic Disorder

In his opening remarks, Jonathan R. T. Davidson, M.D., noted that the concept of quality of life—"the impact of illnesses on everyday life, everyday functioning, personal contentment, and health-seeking behaviors"—has only recently received recognition as an important consideration in the treatment of all anxiety disorders, including panic disorder.

According to Dr. Davidson, quality of life is generally measured in three separate domains: personal happiness, which may be assessed in part by examining the patient's relationships and tendencies toward substance abuse and suicide attempts; role functioning, which includes work and family adjustment and the pursuit of social and leisure activities; and health status, which encompasses the patient's use of medical resources and limitations on functioning. He stressed that all three domains must be addressed when evaluating the impact of treatment on quality of life in panic disorder.

The disorder affects a significant proportion of the population and, if untreated, remains a chronic illness. Dr. Davidson noted that the prevalence of panic disorder in the community continues to grow, from the 1.5%

demonstrated in the epidemiologic catchment area (ECA) study¹ conducted nearly 10 years ago to the more recent estimate of 3.5% from the National Comorbidity Study.² Thus, appropriate diagnosis and treatment of panic disorder are urgent priorities, to avoid the pervasive effects of the disorder on the lives of both its sufferers and those surrounding them. Even when panic disorder is treated, Dr. Davidson pointed out, only about 49% of patients achieve full remission.³ This rate drops even further with comorbid agoraphobia.

As related by Dr. Davidson, Markowitz et al.⁴ were the first to draw attention to quality of life issues in the treatment of panic disorder. Their study, conducted as part of the ECA survey, demonstrated significant impairment in the interpersonal, work/leisure, and health status domains. For example, over 25% of panic disorder patients were receiving welfare or disability benefits, a rate that is twice that of the general population. Marital and social functioning was impaired, as was emotional and physical health status. Thus, Dr. Davidson noted, it is no surprise that an increase in health care utilization has been repeatedly demonstrated among patients with panic disorder. In the Markowitz et al. study, 43% of panic disorder patients sought medical and psychiatric care, compared with only 4% of controls.

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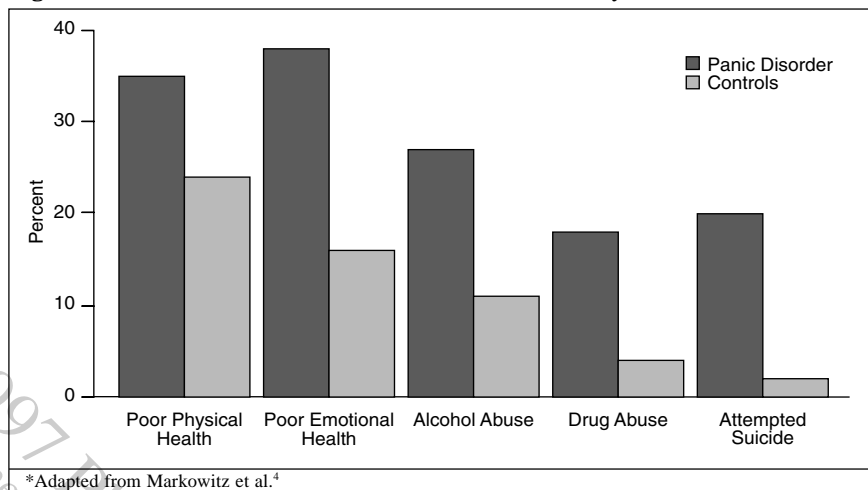
Other indicators of the pervasive physical and emotional impairment associated with panic disorder include increased emergency room visits,⁴ increased rates of medication consumption,⁴ and increased rates of attempted suicide⁵ (Figure 1).

Traumatic exposure or comorbid posttraumatic stress disorder (PTSD) significantly increases the level of impairment in panic and other anxiety disorders, Dr. Davidson noted. Earlier findings of increased rates of mortality among panic disorder patients by Coryell et al.⁶ have since been corroborated by data from the ECA study. The new data, published by Weissman et al.,⁷ demonstrated an increased risk of hypertension, stroke, myocardial infarction, and other cardiovascular/cerebrovascular problems that profoundly affect mortality.

Another measure of the impact of panic disorder on patients' lives—summary scores from the Short Form 36 Medical Outcomes Survey (SF36)—was recently assessed at various clinical trial sites (data on file, Hoffmann-LaRoche). These data demonstrated significantly greater impairment among panic patients relative to the U.S. population in many measures of physical and mental health status. Impairment at work was also documented: the rate of unemployment among panic disorder patients was 25% compared with a rate of 6% in the general population's labor force. According to Dr. Davidson, more severe cases of panic disorder (as measured by number of panic attacks or other severity measures) are associated with greater impairment in physical and mental health functioning and reduced quality of life.

Turning his attention to the impact of treatment on the impairment associated with panic disorder, Dr. Davidson reminded the audience that panic and other anxiety disorders account for 31% of all mental illness costs.⁸ This figure, nearly one third of every men-

Figure 1. Fellow Travelers With Panic Disorder: ECA Study*



tal illness health care dollar spent, is greater than the amount spent on mood disorders (22%) or schizophrenia (20%).⁹ Reviewing the evidence that appropriate diagnosis and treatment can help to reduce the financial, physical, and personal costs of panic disorder, Dr. Davidson cited data from a recent Spanish study by Salvador-Carulla et al.⁹ This study, which collected data on health service utilization and work adjustment among 61 Health Maintenance Organization (HMO) patients treated for panic disorder for 1 year, demonstrated marked improvement in many measures of productivity and well-being (e.g., global assessment scores, level of agoraphobia, number of medical visits). Treatment consisted of pharmacologic therapy (monotherapy or combination therapy with alprazolam and/or clomipramine) and supportive behavioral therapy.

After proper diagnosis and treatment were provided, there was a substantial reduction in the number of unproductive and costly visits to various specialists (e.g., neurologists, cardiologists, gastroenterologists). Of interest, Dr. Davidson noted, while the direct costs of treatment (i.e., the cost of tests,

medications, hospitalization, etc.) appeared to increase after 1 year of treatment, the indirect costs (i.e., the toll that unemployment and impairment take on the patient and his or her family and friends) were reduced. On a per patient basis, the average yearly costs were reduced from more than \$1500 in the year before treatment to less than \$990 after treatment. Dr. Davidson underscored the importance of accurate diagnosis and treatment for reducing the costs associated with panic disorder.

Another study discussed by Dr. Davidson focused on the effects of treatment with the benzodiazepine clonazepam versus placebo on quality of life measures. Using the SF36, this short-term study demonstrated significant improvement in mental and physical health after 6 weeks of clonazepam treatment (data on file, Hoffmann-LaRoche). Work productivity improved as well; an increase in performance and effectiveness from 71% to 88% was demonstrated on the work productivity and impairment scale. Dr. Davidson noted that these findings translate into clinically meaningful improvement, i.e., an additional 6 hours of productive work each week or an

additional 7 full-time productive work weeks each year. In addition, the proportion of patients who reported feeling happy increased from 18% to 37%, and those who reported increased energy increased from 7% to 36%.

In his concluding remarks, Dr. Davidson stressed the importance of appropriate diagnosis and treatment of panic disorder, to increase productivity at work and improve the mental and physical quality of life. Effective treatment can help to reduce the profound effects of panic disorder on personal happiness, role functioning, quality of life, and the costly and inappropriate use of health services.

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Panic Disorder: Sorting Through the Psychopharmacology

Dr. Rosenbaum opened his presentation with a personal anecdote, recounting his "conversion" to psychopharmacology when early evidence of the benefits of drug therapy on panic disorder patients and their families began to emerge. "In view of the pervasive impact of this disorder on patients' lives," he noted, "we need to optimize therapeutic strategies. In spite of the extensive array of available agents, we are still far from eliminating the impact of panic disorder as a factor in patients' lives."

Reviewing the goals of pharmacotherapy, Dr. Rosenbaum stressed the importance of blocking panic attacks as the primary objective since recurrence of panic attacks is responsible for the significant morbidity associated with the disorder. According to Dr. Rosenbaum, "If we can shut down panic attacks entirely, we hope that

some of the secondary complications might yield either spontaneously or to additional therapeutic efforts over time."

A second goal of pharmacotherapy is to treat comorbid conditions. Dr. Rosenbaum estimated that up to 40% of panic disorder patients have social phobic symptoms, 10% have obsessive-compulsive symptomatology, and at least 50% suffer from comorbid depressive disorder. Thus, he stressed the importance of addressing these comorbid conditions, so as not to limit the outcome of treatment.

Achieving remission is a third goal, as residual symptoms and residual impairment may persist in spite of initial improvement. Dr. Rosenbaum noted that even if the initial treatment is effective, the response may be suboptimal if achieving remission is not included as a therapeutic goal. Facili-

tating adjunctive therapies, e.g., exposure or other psychotherapies, is another important goal, particularly for patients whose responses to pharmacotherapy have been suboptimal. According to Dr. Rosenbaum, the recurrent and chronic nature of panic disorder necessitates ongoing treatment for the majority of patients. Thus, another goal of pharmacotherapy is to establish an acceptable regimen for long-term treatment of the disorder.

Dr. Rosenbaum then turned his attention to the extensive pharmacopoeia for panic disorder, emphasizing that no treatment is optimal for all patients. The currently available categories of drugs include high-potency benzodiazepines, antidepressants (e.g., tricyclic antidepressants [TCAs], monoamine oxidase inhibitors [MAOIs], serotonin selective reuptake inhibitors [SSRIs], and newer agents), antiadrenergic agents, and anticonvulsants. Combination strategies, e.g., polypharmacy and integrated pharmacologic and psychosocial therapy, are also increasingly important for the optimal treatment of this disorder.

According to Dr. Rosenbaum, while the principles of panic prescribing are quite straightforward (Table 1), the selection of appropriate treatment(s) for each patient is not. The presence of comorbid conditions is an important consideration in prescribing pharmacotherapy for panic disorder. For example, antidepressants are generally first-line agents if the patient suffers from comorbid depression. Benzodiazepines are more rapidly effective for the anticipatory anxiety component of panic disorder. Clinical experience and accumulating data suggest that spontaneous symptoms, e.g., spontaneous or nocturnal panic attacks, may respond more favorably to pharmacologic therapy than situationally cued symptoms.

Many patients require combination treatment, Dr. Rosenbaum noted, because of residual symptoms and the

Table 1. Principles of Panic Prescribing by Drug Category

High-potency benzodiazepines

- Minimize sedation and ataxia by starting low and titrating dose
- Reduce interdose rebound anxiety by using longer-acting agents
- Increase dose (to ensure adequate dosing) in nonresponsive or poorly controlled patients
- Use adjunctive antidepressants if necessary
- Discontinue with slow taper and consider adjunctive cognitive-behavioral strategies

Antidepressants

- Allow adequate dosing and time to achieve therapeutic response
- Select an agent that minimizes side effects over the short and long term
- Start low to minimize jitteriness; consider use of adjunctive β -blocker or benzodiazepine at initiation of treatment
- Employ combination or augmentation strategies for treatment-resistant patients
- Consider trial of MAOIs in patients nonresponsive to other agents

relative drawbacks of each class of medication. For example, antidepressants may effectively control depression and spontaneous panic attacks, but anticipatory anxiety may require the addition of a high-potency benzodiazepine. For patients started on a high-potency benzodiazepine to control their panic and anticipatory anxiety, an antidepressant is often added to control mood symptoms.

Reviewing the use of TCAs in panic disorder, Dr. Rosenbaum noted that imipramine, one of the most studied TCAs, was first reported effective in panic disorder in 1964. Other TCAs, e.g., desipramine, nortriptyline, and clomipramine, have also been shown to decrease panic attack frequency and intensity within a few weeks of initiating treatment in most patients. Dr. Rosenbaum recommended starting the TCAs at low doses, noting that the optimal dose will vary considerably from patient to patient. New evidence suggests that doses of imipramine may be reduced over the long term, a finding at odds with conventional thinking on the maintenance treatment of depression. Two potential problems with the use of TCAs in panic disorder are relapse upon discontinuation (as with "almost all classes of pharmacotherapy") and discontinuation secondary to side effects. Dr. Rosenbaum

noted that recent data and clinical experience suggest that clomipramine may be the most effective TCA for treating panic disorder.

Turning his attention to the use of MAOIs, Dr. Rosenbaum noted that these agents, e.g., phenelzine and tranylcypromine, may be the most comprehensively effective agents, particularly with comorbid conditions such as obsessive-compulsive disorder, atypical depression, and social phobia. However, these agents are often reserved as a last choice because of their side effects profile, particularly in a patient population that is "vigilant about bodily symptoms and signs of bodily danger." There is a potential for sudden catastrophic medical events when MAOIs are combined with the wrong medication or the wrong food. As with other agents, abrupt discontinuation of MAOIs can produce adverse effects. Reversible inhibitors of MAO-A have shown promise and are currently under investigation.

The SSRIs have become the consensus first-line agents for panic disorder. Compared with the older antidepressants, i.e., TCAs, the SSRIs offer a more favorable safety and side effects profile. Accumulated data from controlled trials are now available to support the observations from clinical practice on the efficacy of these agents

in panic disorder. However, data that compare the various SSRIs against each other are not yet available, since most studies compared the agents with placebo. Generally, since the response to SSRIs varies, it is reasonable to try another SSRI if the patient is unable to initiate treatment with a particular agent. As with other pharmacologic therapies, initiating treatment with low doses (e.g., 10 mg of paroxetine, 25 mg of sertraline, 10 mg of fluoxetine) is recommended. Dr. Rosenbaum indicated that paroxetine will be the first SSRI labeled for panic disorder in the United States, although fluvoxamine was the first well-studied SSRI used in panic disorder.

Another pharmacologic class, the high-potency benzodiazepines, can also be considered first-line treatment for panic disorder because of their efficacy and safety and rapid onset of clinical effect. Dr. Rosenbaum recommended low starting doses and dose titration, to minimize sedation and ataxia upon initiation of treatment. For patients experiencing interdose rebound anxiety with the use of a shorter-acting agent (e.g., alprazolam), increasing the dosing frequency, increasing the dose, or switching to a longer half-life agent are recommended. Generally, longer-acting agents, e.g., clonazepam, are preferred in the treatment of panic disorder.

Contrary to what many professionals may believe about the tendency for doses of high-potency benzodiazepines to increase over time, long-term studies have shown that many patients treated with these agents continue to suffer from residual symptoms because of doses that are too low. Dr. Rosenbaum recommended using adequate dosing with high-potency benzodiazepines just as with the antidepressants. To make a difference in patients' quality of life and suppress symptoms, Dr. Rosenbaum stressed, a dose that is not effective should be raised.

While high-potency benzodiazepines rapidly reduce anticipatory anxiety and block panic attacks (within the first week or two), they do not protect against depression. Thus, these agents are often used in combination with antidepressants. Unlike the antidepressants, however, high-potency benzodiazepines offer the possibility of p.r.n. use for patients who prefer a pretreatment for potentially difficult situations rather than ongoing treatment. In patients without a history of prior substance abuse, the abuse risk is actually quite low.

According to Dr. Rosenbaum, it is particularly important to discontinue these agents with a slow taper. The addition of cognitive-behavioral therapy (CBT) can significantly increase the rate of successful discontinuation, compared with slow taper alone. One study, conducted by Otto et al.¹ at Massachusetts General Hospital demonstrated a threefold increase in the percentage of patients who successfully discontinued high-potency benzodiazepines when CBT was incorporated into the discontinuation process. Dr. Rosenbaum stressed the benefits of longer half-life agents such as clonazepam, to avoid "clock watching" between doses. He summarized the results of earlier studies demonstrating the efficacy of clonazepam and alprazolam in panic disorder compared with placebo. More recent controlled trials² have established the efficacy of clonazepam versus placebo in improving the quality of life in patients who are moderately to severely ill.

Combination treatment, e.g., combining an SSRI with a high-potency benzodiazepine, offers the advantages of rapid anxiolysis during the antidepressant therapeutic lag, decreased anxiety during the initiation of antidepressant therapy, control of residual anxiety, and management of depression in benzodiazepine-treated patients. Dr. Rosenbaum noted that, while patients who start on this combi-

nation tend to require it over time, the combination is necessary in many cases to control initial and residual symptoms.

Reviewing the array of other agents available to treat panic disorder, Dr. Rosenbaum noted that β -blockers are useful for managing peripheral symptoms such as tremor and tachycardia. Clonidine, another antiadrenergic agent, has shown transient benefits. Buspirone has been used adjunctively with SSRIs and high-potency benzodiazepines, since it has little efficacy in panic disorder by itself. For patients who have not responded to other treatments, valproic acid may be effective for typical and atypical panic disorder. Newer agents, e.g., venlafaxine and nefazodone, have shown promise but require further investigation. Agents reported to be ineffective for panic disorder include bupropion, trazodone, and amoxapine.

In spite of the growing number of psychopharmacologic options for acute effective treatment of panic disorder, 30% to 75% of patients remain symptomatic after treatment. In follow-up studies ranging from 1.6 to 6 years, 50% to 80% of patients were symptomatic and 40% continued to have panic attacks.³ Of those patients who remitted, the length of remission averaged 9 months and 58% of patients relapsed. According to Dr. Rosenbaum, the risk factors for chronicity and recurrence include: comorbid depression, agoraphobia, other anxiety or personality disorders, and increased sensitivity to bodily symptoms.

Thus, Dr. Rosenbaum concluded his presentation by stressing that to optimize pharmacologic therapy, combination treatment is often indicated. Combination regimens may include a high-potency benzodiazepine and an antidepressant; combinations of antidepressants, e.g., SSRI and low doses of a TCA; CBT and pharmacotherapy; as well as other psychosocial treatments. He stressed the importance of

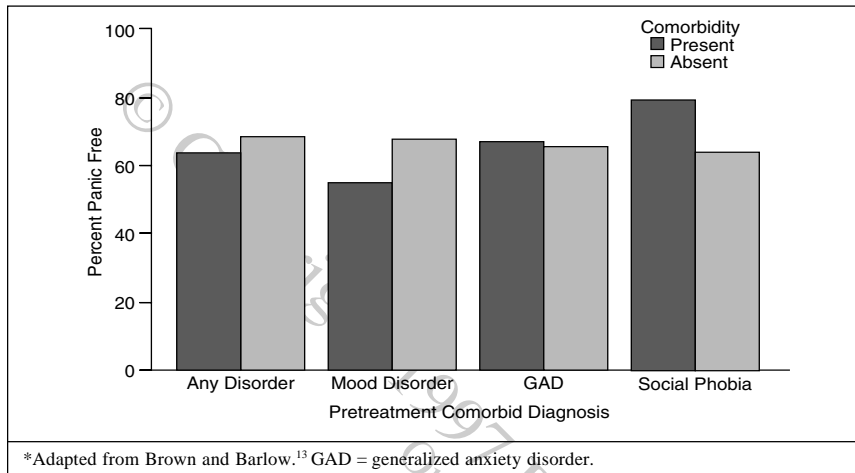
seeking incremental gains even if patients appear to have had adequate treatment. Finally, he called for further research to develop well-tolerated, broad-spectrum therapies to add to our armamentarium.

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The Role of Cognitive-Behavioral Therapy in an Integrated Treatment

David H. Barlow, Ph.D., opened his presentation by noting that he was drawn to the cognitive-behavioral approaches to panic disorder early in his career because of "the possibility of having a rather immediate, direct, and substantial impact on a group of patients who were clearly severely disabled." However, exposure therapy and other psychosocial treatments for panic disorder have only recently been accepted by the psychiatric community. As late as the 1960s, Dr. Barlow explained, using exposure therapy to help the patient "emotionally reprocess anxiety and all that goes with it" was contraindicated in anxiety disorders because of the universal belief that patients would be at risk for "some kind of a psychotic break." Since then, effective psychosocial treatments have been developed and accepted by the psychiatric community. Today, systematic exposure through carefully

Figure 2. Pretreatment Comorbidity and Treatment Outcome: 3-Month Follow-Up*

conducted exposure therapy under therapeutic supervision is now the mainstay of cognitive-behavioral therapy for panic disorder. Typically, exposure therapy also includes calming techniques such as relaxation and breathing retraining and cognitive restructuring to teach patients to experience and process their anxiety in a different way.

According to Dr. Barlow, a new addition to cognitive-behavioral treatment for panic disorder is “interoceptive exposure.” This technique exposes patients to the somatic sensations or daily activities that might signal the beginning of a panic attack, e.g., drinking coffee, getting angry and other strong emotional events, watching horror movies or sports events. Interoceptive exposure is now considered as important in the treatment of panic disorder as exposure to agoraphobic situations.

In reviewing the growing body of data demonstrating the effectiveness of cognitive-behavioral therapy for panic disorder, Dr. Barlow cited a recent meta-analysis¹ of 43 controlled studies conducted by Gould, Otto, and Pollack at Massachusetts General Hospital. This meta-analysis (or summary statistics of 43 studies that met the neces-

sary scientific criteria) demonstrated a notably strong effect size for cognitive-based exposure treatments. The meta-analysis also documented an impressively low dropout rate. The inclusion of interoceptive exposure to CBT increased the effect size even further, confirming the benefits of including interoceptive exposure in the treatment of panic disorder with or without agoraphobia, Dr. Barlow noted.

In more recent studies,¹⁻¹² utilizing some of the newer techniques that focus directly on the panic attacks rather than on agoraphobic avoidance, e.g., panic control or cognitive therapy, more than 80% of patients were panic-free after treatment. However, panic-free does not mean high end-state functioning, nor does it mean cured, Dr. Barlow noted. Nevertheless, a substantial proportion of patients stop having panic attacks. This outcome is significantly better than what would be achieved either with no treatment or with a psychosocial alternative that patients believe to be effective, e.g., applied relaxation or supportive psychotherapy. In the occasional studies that found lower percentages of patients to be panic-free after treatment, the investigators usually shortened or altered the cognitive-behavioral procedure.

For example, Craske et al.¹¹ shortened the treatment period from 10 or 12 sessions to only 4 sessions.

According to Dr. Barlow, studies such as the above indicate that “cognitive-behavioral treatments are not necessarily easily abbreviated.” He noted that one of the disadvantages of psychosocial treatments, in comparison to pharmacotherapy, is that therapists need to learn the techniques for administering psychosocial treatments. Proper administration requires considerable effort, continuing education, and the opportunity for the therapist to learn the techniques. When these factors are not available, Dr. Barlow suggested, there is evidence that patients will not do as well. Thus, he noted the need to make these treatments more cost-effective, more accessible, and briefer.

Turning his attention to the impact of comorbidity on the outcome of treatment in panic disorder, Dr. Barlow reviewed recent findings¹³ suggesting that the presence of comorbidity does not generally affect outcome immediately after treatment. In fact, the presence of comorbid social phobia is associated with *greater* improvement (i.e., percentage of patients who are panic-free) than is the absence of comorbid social phobia prior to treatment. However, patients with a pretreatment diagnosis of comorbid depression showed less improvement than those without this diagnosis when assessed immediately after treatment, although these differences largely disappeared by 3 months (Figure 2).

Nevertheless, Dr. Barlow noted, over the following 2 years, patients with remaining comorbid disorders after treatment for panic disorder was completed were more likely to seek treatment in general and treatment for their panic disorder. Thus, there are negative predictive implications for the presence of residual comorbidity.

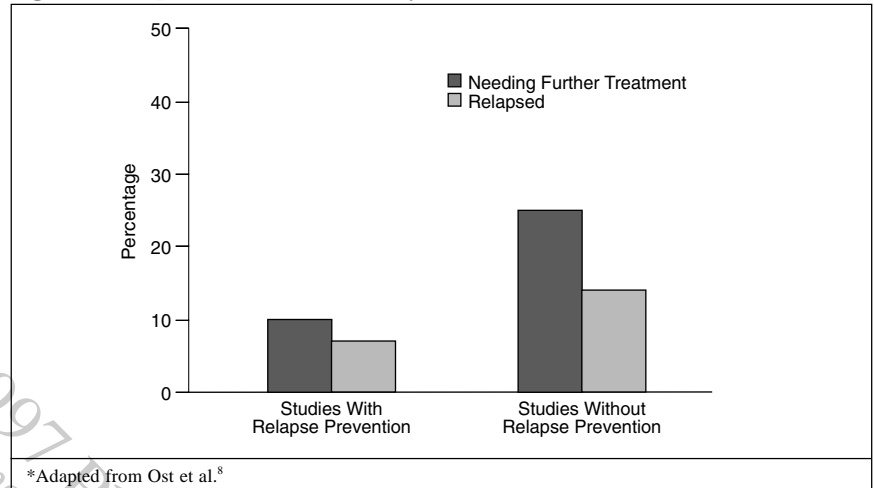
Among patients followed for 2 years after treatment, approximately 80%

were panic-free and 55% to 60% met high end-state criteria.^{11,13} However, a closer look at these patients reveals a more pessimistic picture. Many of the high end-state functioning patients have periods of exacerbations and remissions when they are followed longitudinally rather than cross-sectionally. Very few patients become symptom-free and stay symptom-free, Dr. Barlow noted.

Thus, relapse prevention techniques are increasingly incorporated into cognitive-behavioral treatments, as one or more sessions added after the end of treatment or as periodic interventions over a longer period of time. Dr. Barlow likened relapse prevention to maintenance of weight loss; in both cases, the original goals must be maintained through continuous practice. Research conducted by Ost et al.⁸ in Sweden indicates the effectiveness of relapse prevention in anxiety disorder treatment, findings which have been corroborated by Hiss et al.¹⁴ in relapse prevention in OCD. In studies where relapse prevention procedures were incorporated, significantly fewer patients needed further treatment or relapsed compared with cases where these procedures were not implemented (Figure 3). Dr. Barlow stressed that patients must be taught to avoid interpreting a panic attack as total relapse and failure and to distinguish a setback from a relapse.

A variety of coping procedures are introduced to help patients respond appropriately to setbacks, including organizing patients' coping procedures, helping patients reenter the stressful situation which produced the initial panic attack, and teaching them how to cope with it, calling the therapist, etc. Dr. Barlow underscored the importance of ongoing support groups, even in patients who have been "seemingly successfully treated." Intervening in the interpersonal system of the client can also substantially contribute to the success

Figure 3. Relapse Prevention in Anxiety Disorder Treatment*



of relapse prevention procedures, he noted.

Combining cognitive-behavioral therapy with pharmacologic approaches is another incremental approach undergoing investigation. Dr. Barlow summarized the preliminary results of a large-scale, multicenter study involving patients with panic disorder and mild or no agoraphobia. These results indicate that patients treated with combination treatment plus imipramine improved more than those treated with either treatment alone or with placebo. Another combination strategy discussed by Dr. Barlow is a sequential combination of cognitive-behavioral treatments with high-potency benzodiazepines. The cognitive-behavioral treatment is designed to help patients manage drug discontinuation. The sequential aspect involves introducing a fast-acting and effective drug first, followed by a clear contract to discontinue the drug, with cognitive-behavioral therapy to help in this effort. Preliminary results from Spiegel et al.¹⁵ support the benefits of this combination: at the 3-year follow-up, patients in whom cognitive-behavioral therapy was added to the drug discontinuation process (alprazolam) were more than

twice as likely to be doing well, compared to those without cognitive-behavioral therapy.

Dr. Barlow concluded by underscoring the importance of developing creative strategies for integrating powerful treatments for panic disorder, "given the serious nature of this disorder and the necessity of using every incremental tool at our disposal."

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