Panic Disorder: A Treatment Update

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This section of The Journal of Clinical Psychiatry *summarizes the highlights of a symposium entitled "Panic Disorder: A Treatment Update," held at the 8th Annual U.S. Psychiatric Congress in New York, N.Y. Individual presentations focused on the course and impact of panic disorder and pharmacologic, cognitive-behavioral, and integrated approaches to treatment of the disorder. Other participants were Mark H. Pollack, M.D., Director of the Anxiety Disorders Program, Massachusetts General Hospital and Associate Professor of Psychiatry, Harvard Medical School, Boston, Mass.; and Michael W. Otto, Ph.D., Director of the Cognitive-Behavioral Therapy Program, Massachusetts General Hospital and Assistant Professor of Psychology, Harvard Medical School, Boston, Mass. The program was sponsored by the Department of Psychiatry, University of Wisconsin-Madison Medical School, through an unrestricted educational grant from Roche Laboratories, a member of the Roche Group.*

The Course and Impact of Panic Disorder

In his opening remarks, John R. Marshall, M.D., described the "evolution" that has taken place in the diagnosis of panic disorder. "While panic attacks themselves have not changed, the diagnostic criteria for panic disorder have." As related by Dr. Marshall, the revisions in DSM-IV[1] recognize that panic attacks can occur outside of panic disorder. Thus, DSM-IV differentiates panic attacks according to whether they are unexpected or uncued (which is necessary for the diagnosis of panic disorder), situationally predisposed (which is often a feature of agoraphobia, posttraumatic stress disorder, or social phobia), or situationally bound or cued (a frequent occurrence in phobias).

Another change in DSM-IV discussed by Dr. Marshall is the replacement of a specific number of panic attacks (e.g., three attacks within 3 weeks or four attacks within 4 weeks) in the diagnostic criteria with the characteristics of recurrence and persistent anxiety about the attack(s).

Reviewing the prevalence of panic disorder, Dr. Marshall noted that the published data vary depending on the population studied and the inclusion criteria. For example, if agoraphobia is included, the prevalence figures are much higher. In the general community, the prevalence of panic disorder is about 1.6%. The prevalence figures are higher among high utilizers of medical care, particularly patients with a large number of complaints that are difficult to diagnose ("distressed high utilizers") (Table 1).[2–4]

Table 1. Prevalence of Panic Disorder*

General community	1.6%
Experience a panic attack	3%–10%
Among primary care patients	13.3%
"Distressed high utilizers"	12%
"Lifetime"	30.2%

*Data from references 2, 3, and 4.

Elaborating on the well-established pattern of high health care utilization among panic disorder patients, Dr. Marshall noted that most patients do not initially present to psychiatrists, but to other health care professionals, e.g., cardiologists, emergency room physicians, general practitioners, because of their diverse symptomatology. For example, studies indicate that one fifth of panic disorder patients presented with five or more medically unexplained symptoms during the past 6 months[5] and one third had seen three or more health care professionals within the past year.[6]

Further, patients with panic disorder account for 20% to 29% of emergency room visits[6,7] and are 12.6 times more likely to visit the emergency room than the general population.[8] These patients account for 15% of total medical visits, nearly three times the figure for the general population (5.8%), and they average 19.8 medical visits per year, a rate that is seven times higher than that of the general population.[9]

Because of the significant health care resources that are expended before panic disorder is appropriately diagnosed and treated, Dr. Marshall stressed the cost-effectiveness of accurate diagnosis upon initial presentation, particularly in managed care settings. However, many patients are still misdiagnosed when they present in the emergency room or other health care settings and are often told that "it's all in your head, there's nothing wrong with you, it's just stress."

With the high utilization of medical care and frequent misdiagnosis, Dr. Marshall noted, it is not surprising that panic disorder patients typically rate their quality of life lower than controls do. In fact, the quality of life ratings in panic disorder are similar to those in major depression. Twenty-three percent to 35% rate their physical health as "fair" or "poor," and 38% to 71% rate their emotional health as "fair" or "poor."[8,10]

Another trend reported by Dr. Marshall is the apparent relationship between panic disorder and cardiovascular/cerebrovascular morbidity and mortality. In a community survey conducted by Weissman et al.,[11] the presence of panic disorder increased the risk of hypertension, myocardial infarction, and stroke (the adjusted odds ratios were 1.91, 4.54, and 11.95, respectively). Dr. Marshall noted that panic disorder, particularly if it is untreated, is associated with a significant degree of disability as well.

There is a growing body of data showing that impairment in the workplace is another consequence of this disorder. As related by Dr. Marshall, a recent study by Massion et al.[10] documented that more than one third of panic disorder patients (38%) had missed more than 1 week of work and only 53% to 58% were able to work full-time (compared with the national average of 91% working full-time). Further, 25% of those with panic disorder were fully unemployed, compared with the national unemployment average of 6%. Finally, in a recent study by Capital Outcomes Research, Inc. (Washington, D.C.; unpublished data, 1995), patients suffering from panic disorder rated their productivity in the workplace at 56%. In other words, they considered themselves approximately half as productive as when they were well. Not surprisingly, because of impaired work performance and reduced productivity, panic disorder is also associated with high rates of financial dependency[8] and participation in public assistance programs.[10]

Dr. Marshall underscored the chronic, relapsing nature of panic disorder, "a disorder that has extreme ramifications throughout our society beyond the health care systems." Reviewing a panic disorder follow-up study conducted by Katon et al.,[12] Dr. Marshall noted that 50% of patients continued to suffer from some type of disability, and 73% to 93% were symptomatic when followed for up to 20 years. Defining full remission as 2 months without a panic attack, Keller et al.[13] found that only 37% of their patients were in full remission in the first 12 months of follow-up, even though 80% of patients were receiving pharmacologic treatment. In panic disorder with agoraphobia, the chances of full remission are lower and the risk of relapse is higher. Further, these patients are 2½ times more likely to remain in an episode than are panic disorder patients without agoraphobia.[13]

Further evidence of the chronicity of panic disorder was provided by a recent outcomes study conducted by Roy-Byrne and Cowley.[14] This study, which surveyed the panic disorder literature and analyzed the outcomes of 16 studies involving more than 25 patients, found that most patients improve but few are "cured." Factors that predicted poorer outcome include the presence of agoraphobia, major depression, or personality disorder. Interestingly, the frequency of attacks was unrelated to panic disorder outcome.[14] Additional factors that were found to contribute to the severity and persistence of panic disorder in research conducted by Pollack et al.[15] include comorbid anxiety disorders and "anxiety sensitivity" (fear of having anxiety symptoms) (Table 2).

Table 2. Factors Predictive of Poorer Outcome in Panic Disorder*

• Agoraphobia
• Major depression
• Personality disorders
• Comorbid anxiety disorders
• "Anxiety sensitivity"

*Data from references 14 and 15.

In his concluding remarks, Dr. Marshall underscored the chronic nature of panic disorder, likening its longitudinal course to that of chronic dysthymia with major depressive episodes. Because panic disorder is a chronic condition marked by periods of remissions and relapses, Dr. Marshall urged awareness of the need for long-term and perhaps even lifelong treatment.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1995
2. Katon W, VonKorff M, Lin E, et al. Distressed high utilizers of medical care: DSM-IV diagnosis and treatment needs. Gen Hosp Psychiatry 1990;12:355–362
3. Katon WJ, VonKorff M, Lin E. Panic disorder: relationship to high medical utilization. Am J Med 1992;92(suppl 1A):75–115
4. Klerman GL, Weissman MM, Quellette R, et al. Panic attacks in the community: social morbidity and health care utilization. JAMA 1991;265:742–746
5. Simon G, VonKorff M. Somatization and psychiatric disorders in the NIMH Epidemiologic Catchment Area Study. Am J Psychiatry 1991;148:1494–1500
6. Swenson RP, Cox BJ, Woszezy CB. Use of medical services and treatment for panic disorder with agoraphobia and for social phobia. Can Med Assoc J 1992;147:878–883
7. Weissman MM, Klerman GL, Urankowitz J. Suicidal ideation and suicide attempts in panic disorder and attacks. N Engl J Med 1989;321:1209–1216

8. Markowitz JS, Weissman MM, Ouellette R, et al. Quality of life in panic disorder. Arch Gen Psychiatry 1989;46:984–992
9. Siegel L, Jones WC, Wilson JO. Economic and life consequences experienced by a group of individuals with panic disorder. Journal of Anxiety Disorders 1990;4: 201–211
10. Massion AO, Warshaw MG, Keller MB. Quality of life and psychiatric comorbidity in panic disorder and generalized anxiety disorder. Am J Psychiatry 1993;150: 600–607
11. Weissman MM, Markowitz JS, Ouellette R, et al. Panic disorder and cardiovascular/ cerebrovascular problems: results from a community survey. Am J Psychiatry 1990;147:1504–1508
12. Katon W, Vitaliano PP, Russo J, et al. Panic disorder spectrum of severity and somatization. J Nerv Ment Dis 1987;175:12–19
13. Keller MB, Yonkers KA, Warshaw MG, et al. Remission and relapse in subjects with panic disorder and panic with agoraphobia: a prospective short-interval naturalistic follow-up. J Nerv Ment Dis 1994;182: 290–296
14. Roy-Byrne PP, Cowley DS. Course and outcome in panic disorder: a review of follow-up studies (1994/1995). Anxiety 1995;1:151–160
15. Pollack MH, Otto MW, Rosenbaum JF, et al. Longitudinal course of panic disorder: findings from the Massachusetts General Hospital Naturalistic Study. J Clin Psychiatry 1990;51(12, suppl A):12–16

Table 3. Pharmacotherapy for Panic Disorder

Class	Agents	Starting and Maintenance Doses
SSRIs	Fluoxetine	5–10 mg/d; 20–80 mg/d
	Sertraline	25–50 mg/d; 50–200 mg/d
	Paroxetine	10 mg/d; 20–50 mg/d
	Fluvoxamine	25 mg/d; 50–300 mg/d
Tricyclic antidepressants	Imipramine	10 mg/d "test dose"
	Nortriptyline	Recommended dosage for all TCAs:
	Desipramine	2.25 mg/kg/d (imipramine equivalents)
	Amitriptyline	
	Doxepin	
Atypical antidepressants	Venlafaxine	18.75 mg b.i.d.
	Nefazodone	50 mg b.i.d.
MAOIs	Phenelzine	45–90 mg/d; 100–300 mg/d
	Tranylcypromine	30–60 mg/d; 300–500 mg/d
High-potency benzodiazepines	Clonazepam	1–5 mg/d
	Alprazolam	2–10 mg/d

Psychopharmacology Update

In his opening remarks, Mark H. Pollack, M.D., noted the variety of effective psychopharmacologic agents that are now available for treating panic and other anxiety disorders (Table 3). In some cases, he observed, clinical practice has "jumped ahead of the data." For example, serotonin selective reuptake inhibitors (SSRIs) are now widely used for treating panic disorder, despite the relative paucity of published controlled data documenting their efficacy in panic disorder. However, SSRIs represent a major advance over the older tricyclic antidepressants (TCAs) because of the more favorable safety profile of these agents.

Dr. Pollack reviewed the SSRIs currently available in the United States (fluoxetine, sertraline, paroxetine, and fluvoxamine) and stressed that "starting low" is an important consideration in the use of these agents to minimize the increased anxiety associated with the initiation of treatment. Adjunctive use of benzodiazepines and/or β-blockers may also be beneficial to reduce patients' anxiety early in treatment. According to Dr. Pollack, typical initial daily doses of SSRIs for panic disorder are 5 to 10 mg of fluoxetine, 25 to 50 mg of sertraline, 10 mg of paroxetine, and 25 mg of fluvoxamine. Patients are maintained on these low dosages for the first 1 or 2 weeks and then gradually titrated up to full doses. While the SSRIs tend to be better tolerated than the older TCAs, Dr. Pollack noted, these agents may be associated with a variety of side effects that may complicate treatment.

These adverse events include gastrointestinal distress, jitteriness, headaches, sleep disturbance, and sexual dysfunction. Management strategies have been utilized to minimize the occurrence of these adverse events. For example, the use of adjunctive agents such as yohimbine or dopaminergic agonists such as amantadine has been proven effective in treating sexual dysfunction associated with the use of SSRIs.

Turning his attention to some of the newer atypical antidepressants, e.g., venlafaxine and nefazodone, Dr. Pollack noted that, while these agents appear effective in treating panic disorder and social phobia, there are few data yet to support their use, although positive clinical experience is starting to accumulate. Like the SSRIs, venlafaxine and nefazodone should be initiated at low doses (e.g., 18.75 mg b.i.d. and 50 mg b.i.d., respectively) to minimize increased anxiety and titrated up over time. Bupropion and trazodone appear to be unique among antidepressants in their relative lack of efficacy in treating panic disorder and other anxiety conditions in contrast to most of the other antidepressants.

One of the oldest and most well-known groups of antidepressants, the tricyclics, e.g., imipramine, nortriptyline, desipramine, amitriptyline, and doxepin, has documented efficacy in panic disorder with or without comorbid depression. As related by Dr. Pollack, recent research conducted by Mavissakalian and Perel[1] suggests that a new dosing strategy for using tricyclics to treat panic disorder may be appropriate. The traditional dosing strategy has been to start patients at a low dose and then titrate the dose up as high as necessary to produce relief, the

same way depression is treated. However, the data by Mavissakalian and Perel provide evidence of a therapeutic window for tricyclics and suggest that the optimal dose for patients may be 2.25 mg/kg/day (imipramine equivalents). Translating this dosing guideline into mg/day, Dr. Pollack suggested that the optimal dose of tricyclics in panic disorder may be in the range of 100 to 200 mg/day of imipramine equivalents, with blood levels of approximately 100 to 150 ng/day. Dr. Pollack recommended checking blood levels in patients who have not responded to tricyclics, to determine if the optimal therapeutic blood level has not been reached or has been exceeded.

As with the SSRIs, starting doses of TCAs are usually low (e.g., 10 mg of imipramine, 25 mg of nortriptyline) to minimize initial worsening of anxiety. The typical side effects of tricyclics (anticholinergic effects, orthostatic hypotension, cardiac conduction disturbance, weight gain, and sexual dysfunction) limit their usefulness in treating panic disorder. In fact, a study by Noyes et al.[2] found that weight gain was the most common reason why panic disorder patients discontinued maintenance treatment with tricyclics. Close to half of patients followed for 1 to 2 years while taking TCAs discontinued treatment because of side effects. Although tricyclics are effective for treating panic disorder, generalized anxiety syndrome, and posttraumatic stress disorder, they are increasingly being replaced by the newer and more tolerable antidepressants and benzodiazepines.

Monoamine oxidase inhibitors (MAOIs) are broadly effective for a variety of anxiety and depressive conditions, e.g., panic disorder, agoraphobia, atypical depression, obsessive-compulsive disorder (OCD), posttraumatic stress disorder, and social phobia. According to Dr. Pollack, however, the most critical issues that limit the use of MAOIs are concerns about their adverse effects, in particular, dietary restrictions and the induction of hypertensive reactions. Thus, MAOIs are rarely used as first-line therapy, but, rather, are reserved for patients who have failed easier and safer treatments. While it was hoped that the newer types of MAOIs, called reversible MAOIs, or RIMAs, would incorporate the efficacy of the older MAOIs with improved tolerability, it is unlikely that these newer MAOIs will be available in the United States for several years.

Dr. Pollack then turned his attention to the benzodiazepines, noting that, while all agents in this class are effective for blocking generalized and anticipatory anxiety and inducing sleep, potency appears to be a critical determinant of their efficacy in panic disorder. For example, the higher potency benzodiazepines, clonazepam and alprazolam, block panic attacks more effectively than lower potency agents, e.g., diazepam, chlordiazepoxide, and oxazepam. In reviewing the benefits of high-potency benzodiazepines in treating panic disorder, Dr. Pollack stated that a primary advantage of these agents and the reason for their increased use in this disorder is their rapid onset of clinical effect in nondepressed panic patients (Table 4). Their clinical effectiveness is often apparent within the first week of treatment.

Besides their rapid onset of therapeutic response, other advantages of high-potency benzodiazepines in the treatment of panic disorder include their more favorable side effect profile compared with antidepressants, as they lack the anticholinergic side effects of the tricyclics and the initial increase in anxiety associated with SSRI administration. In addition, dosages of high-potency benzodiazepines can be rapidly adjusted if necessary and administered on a p.r.n. basis. The concomitant use of high-potency benzodiazepines and antidepressants is increasing, Dr. Pollack noted, to provide rapid anxiolysis and more comprehensive relief of panic and depressive symptoms (since high-potency benzodiazepines are generally not as effective for significant comorbid depression). Some of the potential disadvantages of high-potency benzodiazepines discussed by Dr. Pollack include: initial sedation (which can be minimized by "starting low and going slow"), potential abuse in patients with a history of alcohol or substance abuse (although in clinical practice, he noted, this is not usually as significant a problem among panic disorder patients), and discontinuation-related difficulties (which can be minimized by gradually tapering the dosage).

Table 4. Benefits of High-Potency Benzodiazepines in Panic Disorder

- Comparable efficacy to antidepressants
- Shorter latency of therapeutic onset
- Lack of antidepressant side effects
- Allow rapid dose adjustment or p.r.n. dosing for panic or anxiety
- Ease of adjunctive use with antidepressants

Dr. Pollack cited studies by Clinthorne et al.[3] and Mellinger et al.[4] suggesting that the major problem with the use of benzodiazepines in the treatment of anxiety may be getting patients to take enough medication for comprehensive relief rather than too much. The recommended dose of alprazolam for treating panic disorder is 2 to 10 mg/day (dosed on a q.i.d. basis), although the usual effective dose is 4 to 6 mg/day. Some of the drawbacks associated with the use of alprazolam are related to its pharmacokinetic profile, e.g., its relatively short half-life necessitates more frequent dosing.

Clonazepam, another high-potency benzodiazepine with antipanic efficacy, has a longer half-life than alprazolam. Thus, clonazepam can be dosed on a b.i.d. rather than a q.i.d. basis. In addition to its more gradual onset of

clinical effect, its use is associated with a lower incidence of inter-dose rebound anxiety (patients' jitteriness or anxiety as blood levels drop off) than that associated with agents with a shorter half-life. Another potential benefit of agents with a longer half-life like clonazepam often seen in clinical practice, and beginning to be investigated in clinical trials, is the greater ease with which patients may tolerate drug tapering or withdrawal. In addition, the more gradual onset of clinical effect seems to reduce the potential for abuse in predisposed individuals. Thus, it may be a safer drug for patients with a history of substance abuse in cases where benzodiazepine therapy is indicated.

Dr. Pollack reviewed the early evidence supporting the use of clonazepam in patients who had failed antidepressant and other interventions and in those who were intolerant of antidepressant side effects.[5] He cited a report by Herman et al.[6] documenting the benefits of clonazepam in patients who were having difficulty with the shorter half-life associated with alprazolam therapy. Dr. Pollack also discussed the results of studies[7] conducted at Massachusetts General Hospital, which demonstrated that the antipanic effectiveness of clonazepam was comparable to that of alprazolam (and was maintained on a long-term basis in patients followed for 1 to 5 years of treatment). Additional large-scale multicenter randomized trials of clonazepam have confirmed the earlier observations of its antipanic effectiveness and rapid onset of clinical effect (Roche Laboratories. Data on file).

A growing trend discussed by Dr. Pollack is the concomitant use of different psychopharmacologic agents, e.g., antidepressants and benzodiazepines, tricyclics, and SSRIs. Adjunctive use of buspirone (for generalized anxiety), β-blockers (for somatic symptoms and performance anxiety), and anticonvulsants (because panic attacks may be partial seizures) is also increasing.

In his concluding remarks, Dr. Pollack stressed that the critical issue in treating patients with panic disorder is the high rate of relapse with discontinuation of antipanic medication (whether it is an antidepressant and/or a benzodiazepine). He estimated that more than 50% of panic disorder patients will need to be maintained on antipanic pharmacotherapy indefinitely and suggested that "the dose that gets you well acutely may be the dose that's necessary to keep you well over time" to help prevent relapse. According to Dr. Pollack, the focus of pharmacotherapy should shift from "being in a hurry to get people off medication to the idea that we need to have people on long-term treatments that they can tolerate over time and live with." Dr. Pollack urged professionals to consider panic disorder a chronic condition requiring chronic treatment and predicted that the use of high-potency benzodiazepines (in combination with antidepressants and as monotherapy) will increase because of the long-term tolerability and effectiveness of these agents.

References

1. Mavissakalian MR, Perel JM. Imipramine treatment of panic disorder with agoraphobia: dose ranging and plasma level–response relationships. Am J Psychiatry 1995;152:673–682
2. Noyes R, Garvey M, Cook B. Follow-up study of patients with panic attacks treated with tricyclic antidepressants. J Affect Disord 1989;16:247–257
3. Clinthorne JK, Cisin IH, Balter MB, et al. Changes in popular attitudes and beliefs about tranquilizers. Arch Gen Psychiatry 1986;43:527–532
4. Mellinger GD, Balter MB, Uhlenhuth EH. Prevalence and correlates of the long-term regular use of anxiolytics. JAMA 1984;251:375–379
5. Tesar GE, Rosenbaum JF. Successful use of clonazepam in patients with treatment-resistant panic disorder. J Nerv Ment Dis 1986;174:477–482
6. Herman JB, Rosenbaum JF, Brotman AW. The alprazolam to clonazepam switch for the treatment of panic disorder. J Clin Psychopharmacol 1987;7:175–178
7. Pollack MH, Otto MW, Tesar GE, et al. Long-term outcome after acute treatment with clonazepam and alprazolam for panic disorder. J Clin Psychopharmacol 1993;13:257–263

Integrated Treatment of Panic Disorder

Michael W. Otto, Ph.D., began his presentation by reviewing the findings of controlled trials conducted over the past 20 years, which evaluated the relative efficacy and tolerability of various treatments for panic disorder. The results of this meta-analysis[1] (based on 43 studies and 78 separate comparisons) indicated that pharmacotherapy (the average of all treatments in the literature with control groups) was associated with an overall effect size of about .47, while the effect size with cognitive-behavior therapy (CBT) was .63 (Table 5). While there were no significant differences within the pharmacologic or CBT groups, Dr. Otto noted that newer CBT techniques, e.g., interoceptive exposure plus cognitive restructuring, were associated with higher effect sizes. CBT overall was found to be highly tolerable, with the lowest percent dropout (6%). Benzodiazepines were more tolerable than antidepressants (13% dropout vs. 25%, respectively), which may reflect the wide use of TCAs for panic disorder before the introduction of SSRIs.

This meta-analysis also revealed that slippage of treatment effect (from the end of the acute trial through follow-up periods) was greatest in patients treated exclusively with pharmacotherapy. However, when exposure therapy was added to pharmacotherapy, some of the slippage was reduced. The least slippage of treatment effects occurred with cognitive-behavioral therapy. Thus, while short-term outcome is comparable with pharmacologic therapy or CBT, there is evidence of greater treatment retention with CBT. However, Dr. Otto pointed

Table 5. Meta-Analysis of Panic Disorder*

Acute treatment effects 43 studies; 78 separate comparisons Treatment Strategy	Effect Size[a]	Panic Free (%)
Pharmacotherapy	.47	
Antidepressants	.55	58
Benzodiazepines	.40	61
Cognitive-behavior therapy	.63	70
Interoceptive exposure + cognitive restructuring	.88	

*Data from reference 1.
[a]Relative to controls (1974–January 1994).

out that there is self-selection by panic disorder patients as to which therapy they want, e.g., some patients will not go to CBT because they do not like the outlay of time necessary at the beginning of treatment. Similarly, there are patients who will not go through pharmacotherapy because they are uncomfortable with taking medications.

According to Dr. Otto, CBT usually includes the following components: informational intervention; somatic management skills, including breathing retraining and relaxation skills, and of more importance, cognitive restructuring, which helps patients change their catastrophic responses and fears concerning the somatic sensations; interoceptive exposure (for example, exposing patients to rapid heartbeat, numbness and tingling, and showing them that these sensations do not have to drive them toward a panic attack); and situational exposure, to help agoraphobic patients overcome their fear of having panic attacks in certain situations or settings. Dr. Otto underscored the importance of interoceptive exposure, which, he believes, is the most important component of CBT.

Turning his attention to CBT "dosing," Dr. Otto stressed that adequate dosing is as important for CBT as it is for pharmacologic therapy. "Just as it's not fair to consider a patient who has tried a quarter milligram of a benzodiazepine as having tried pharmacologic treatment, neither is it fair for a patient who has gotten some relaxation treatment, stress management, or breathing retraining alone, to be considered to have received an adequate dose of cognitive-behavioral therapy." As related by Dr. Otto, a sufficient dose of CBT would include a minimum of 12 to 15 sessions (individual or group) stressing exposure and cognitive restructuring. Homework between each session is also part of dosing, so that patients can learn on their own not to fear the sensations that are the target of interoceptive exposure.

The long-term efficacy of pharmacotherapy versus CBT, particularly when therapy is discontinued, is an important issue given the chronic nature of panic disorder. Dr. Otto reviewed the results of long-term studies that followed patients treated with pharmacotherapy.[2–4] These follow-up assessments, which ranged from 1.5 to 6 years, indicated that significant loss of treatment effects occurs with discontinuation of pharmacotherapy: 40% of patients continued to have panic attacks and 50% to 80% remained symptomatic. With CBT, on the other hand, follow-up studies[5–9] conducted from 1 to 3 years indicate that treatment effects with CBT are maintained for a longer period of time.

Dr. Otto suggested reasons why CBT appears to be associated with a greater retention of treatment effects: it targets behavioral patterns that maintain panic disorder, provides instruction in the reapplication of skills in the future, and continues when treatment ends by establishing new habits. "We don't really have to discontinue treatment. We just give away the therapy to the patients and have them continue doing it as part of new habits." Thus, exposure therapy continues for the rest of the patient's life, as it teaches patients to stop avoiding situations that produce anxiety. An implication of the extended efficacy of CBT is the potential for combining CBT with pharmacotherapy to improve the treatment outcome of patients initially treated with pharmacotherapy.

Reviewing various strategies for combining CBT and pharmacotherapy, Dr. Otto noted that one common integrated approach is to encourage patients on pharmacotherapy to try new situations (which can be considered a low level of exposure treatment). Pollack and Otto[10] demonstrated that the sequential application of CBT in pharmacologic treatment-resistant patients improves patients' overall functioning, panic-free rates, and treatment outcomes. Dr. Otto cited three studies[11–13] that demonstrated improved maintenance of treatment effects in patients initially treated with pharmacotherapy who underwent CBT before and during drug discontinuation.

The opposite approach, i.e., adding pharmacotherapy to CBT, provides short-term treatment gains but may reduce the long-term benefits of CBT. Thus, Dr. Otto cautioned that "adding the two together does not always mean you get the gains of both, except in the short-term." Research also suggests that if pharmacotherapy is added to CBT, CBT must be reinstated at the time of medication discontinuation. Some of the effectiveness of CBT may be lost unless patients are allowed to rehearse their behavioral skills at the time of drug discontinuation. This teaches them how to handle a panic attack and "shut down the entire panic cycle" without medication.

Dr. Otto reviewed the potential obstacles to combining CBT with pharmacotherapy and presented strategies for overcoming these obstacles. An ini-

tial obstacle is the delivery of a strong biological model of panic disorder, which may discourage patients from fully engaging in psychosocial treatment. This problem can be overcome by helping patients understand that panic disorder is multidetermined and can be helped by pharmacotherapy and/or behavior therapy. A second obstacle is the p.r.n. use of medication (benzodiazepine) rather than CBT skills to cope acutely with an anxiety episode. This can be avoided by encouraging patients to apply their new behavioral skills to coping with an anxiety episode and keeping patients maintained on steady-state doses of pharmacotherapy. State-dependent learning (or attributing any therapeutic gain to some other source, e.g., a pill in their pocket or mouth, a safety cue, charm, significant other) can lessen the efficacy of exposure and other effects of CBT. Dr. Otto suggested that this problem can be addressed by having the patient practice all skills independent of "safety cues," while asking the patient to self-monitor to confirm the effects of treatment. He also stressed that independent rehearsal of skills is also important in preparation for drug discontinuation.

Dr. Otto concluded by summarizing the applications of CBT for panic disorder (Table 6), stressing the importance of CBT in the longitudinal course of treatment—including the use of exposure as a regular adjunct to all medication treatments, the application of bibliotherapy or other self-help methods as an adjunctive treatment, and the application of a full CBT package as an alternative, adjunct, or replacement for pharmacotherapy.

Table 6. Summary of Applications of CBT for Panic Disorder

- Exposure instruction
- Bibliotherapy, i.e., providing patients with self-help guides
- Individual or group treatment
- Adjunctive treatment for medication nonresponders
- Medication discontinuation programs

References

1. Gould RA, Otto MW, Pollack MH. A meta-analysis of treatment outcome for panic disorder. Clinical Psychology Review 1995;15:819–844
2. Nagy LM, Krystal JH, Woods SW, et al. Clinical and medication outcome after short-term alprazolam and behavioral group treatment of panic disorder. Arch Gen Psychiatry 1989;46:993–999
3. Noyes R, Garvey MJ, Cook BL, et al. Problems with tricyclic antidepressant use in patients with panic disorder or agoraphobia: results of a naturalistic follow-up study. J Clin Psychiatry 1989;50:163–169
4. Pollack MH, Otto MW, Kaspi SP, et al. Cognitive behavior therapy for treatment-refractory panic disorder. J Clin Psychiatry 1994;55:200–205
5. Beck AT, Sokol L, Clark DA, et al. A crossover study of focused cognitive therapy for panic disorder. Am J Psychiatry 1992;149:778–783
6. Clark DM, Salkovskis PM, Hackman A, et al. A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. Br J Psychiatry 1994;164:759–769
7. Cote G, Bouchard S, Gauthier G, et al. Reduced therapist contact cognitive behavioral treatment for panic disorder: effectiveness of three-year follow-up. Paper presented at the 28th annual meeting of the Association for Advancement of Behavior Therapy; November 10–13, 1994; San Diego, Calif
8. Craske MG, Brown TA, Barlow DH. Behavioral treatment of panic: a two year follow-up. Behavior Therapy 1991;22: 289–304
9. Hulbert D, Polk D, Casey A, et al. Cognitive-behavioral treatment for panic disorder: a one-year follow up study. Paper presented at the 28th annual meeting of the Association for Advancement of Behavior Therapy; November 10–13, 1994; San Diego, Calif
10. Pollack MH, Otto MW. Long-term pharmacologic treatment of panic disorder. Psychiatric Annals 1994;24:291–298
11. Otto MW, Pollack MH, Sachs GS, et al. Discontinuation of benzodiazepine treatment: efficacy of cognitive-behavioral therapy for patients with panic disorder. Am J Psychiatry 1993;150:1485–1490
12. Hegel MT, Ravaris CL, Ahles TA. Combined cognitive-behavioral and time-limited alprazolam treatment of panic disorder. Behavior Therapy 1994;25:183–195
13. Spiegel DA, Bruce TJ, Gregg SF, et al. Does cognitive behavior therapy assist slow-taper alprazolam discontinuation on panic disorder? Am J Psychiatry 1994;151:876–881

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