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Assessment and Management of Treatment-Resistance in Panic Disorder

Abstract: Panic disorder (PD) is a severe, persistant and potentially disabling anxiety disorder which affects 3.5 to 5% of individuals at some point. PD is characterized by one or more unexpected panic attacks followed by worry about additional attacks and/or the implications of the attacks. If attacks are sufficiently severe or frequent, they can promote marked, sometimes debilitating behavioral changes and avoidance (agoraphobia). We know from clinical experience and clinical trial outcomes that many PD sufferers are incompletely responsive to the initial treatment. Based on accruing evidence in the literature and clinical experience, inadequate treatment appears an important factor in treatment failure. In this article, strategies for optimizing PD treatment—including sufficient intensity of treatment—will be presented. A differential diagnostic approach for clinical evaluation of unsatisfactory response of PD treatment will be outlined. Finally, potential next-step treatments for unsatisfactory PD treatment outcome will be presented.

Panic disorder (PD) is a severe and potentially disabling anxiety disorder that affects 3.5%–5% of individuals in the United States during their lives (1, 2). Panic attacks are characterized by a sudden surge of intense fear or discomfort, with at least four symptoms that occur abruptly and peak within 10 minutes (Table 1).

To meet diagnostic criteria for PD, the individual must experience recurrent unexpected panic attacks (Table 2), at least one of which is followed by ≥1 month of one or more of the following: 1) concern over having more attacks, 2) worrying about the implications of the attacks (e.g., having a heart attack, losing control or "going crazy"), and 3) significant change in behavior related to the attacks (help-seeking, fearful avoidance) (1). PD most frequently appears in the late teens or early twenties and affects women twice as often as men. A significant percentage of affected individuals exhibit fear and avoidance of situations in which they may be unable to escape or be embarrassed should another attack occur (agoraphobia) (1). The avoidance behavior can interfere with work, social, and family functioning (or all of these) and can range from mild to completely disabling. PD rarely occurs alone, but typically co-occurs with other anxiety disorders, depression and alcohol/substance abuse disorders (2–5).

Comorbid agoraphobia and other psychiatric disorders represent a significant treatment challenge and appear to contribute to increasingly poor outcome as they accrue (6, 7). In the published treatment research literature, patients with comorbid disorders were typically excluded, thus limiting extrapolation of many research findings to clinical practice. Findings from the National Comorbidity Study indicated that although 96.1% of individuals with PD with agoraphobia and 61.1% of individuals with panic attacks sought treatment within the past year, a significant percentage received inadequate treatment (2).

This review will focus on the assessment and management of inadequate treatment outcome in PD. The term "treatment resistance" for PD has not been operationalized. Consequently, much of the extant literature consists of reports including small groups of patients with PD with "unsatisfactory" response to one or several treatments, often without defining the degree of improvement or the treatments received. Likewise, there has been no consensus on what constitutes "adequate treatment" with medications or psychosocial treatment

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Table 1. DSM-IV-TR Diagnostic Criteria for Panic Attacks

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes:

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, light-headed, or faint
9. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
10. Fear of losing control or going crazy
11. Fear of dying
12. Paresthesias (numbness or tingling sensations)
13. Chills or hot flushes

such as cognitive behavior therapy (CBT), although some suggestions have been offered (8).

General Principles for Optimizing Treatment of Panic Disorder

The Initial Evaluation

The initial assessment should include a thorough psychiatric history to confirm the diagnosis of PD as well as screening for comorbid psychiatric disorders (other anxiety disorders, depression, and alcohol or substance abuse). Prior treatment (if any) and outcome should be reviewed. Psychosocial and developmental history including childhood adversity, family psychiatric history, and general review of symptoms should be included. Patient safety, including suicidal behaviors' current protective factors, family history of suicide, and current psychosocial stressors should be assessed (8).

Table 2. DSM-IV TR Diagnostic Criteria for Panic Disorder

1. Recurrent unexpected panic attacks
2. At least one of the attacks has been followed by 1 month (or more) of 1 or more of the following:
   Persistent concern about having additional attacks
   Worry about the implication of the attack or its consequences
   A significant change in behavior related to the attacks
3. The panic attacks are not due to the direct physiological effects of a substance or a general medical condition.
4. The panic attacks are not better accounted for by another mental disorder, such as social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, or separation anxiety disorder.

Medical history, current prescriptions and over-the-counter medications, usual caffeine intake (including soft drinks, energy drinks, tea, and coffee), and any alternative or herbal treatments that can cause anxiety should be reviewed (9, 10). The medical workup should include a complete physical examination, complete blood count, thyroid function tests, urinalysis, electrolytes, liver function tests, ECG, and, if indicated, a urine screen for abused drugs. For patients with onset of PD after age 45 or those with true vertigo, timing of anxiety clearly related to meals, loss of consciousness, amnestic episodes or panic attacks without fear, a more thorough assessment is indicated (10).

The Therapeutic Alliance

Establishing and maintaining credibility with the patient is a key strategy for successful treatment. Reviewing evidence that risk for PD can be inherited may help reduce the patient's sense of failure to manage symptoms on his or her own. Being available and encouraging questions will help foster a sense of trust. Available treatment options, including the pros and cons of each should be reviewed, noting that more than one treatment or treatment modality may be required to find the best "fit" for that individual. Significant others should be included in the education exchange whenever possible.

Assessment Tools

Many clinicians rely on clinical assessment of patients in treatment. Using validated rating tools that provide systematic assessment of PD to document severity of the illness and the clinical improvement is essential (8). For example, early treatment studies used panic attack frequency as the primary outcome variable. However, panic attack frequency is affected by many variables. For example, if one patient in treatment remained at home and had no panic attacks, while another actively entered previously avoided situations and had more panic attacks, panic attack frequency would provide a poor assessment of actual clinical progress. It has been shown that reduction in panic attack frequency correlated poorly with global outcome assessments (11). The Panic Disorder Severity Scale (PDSS) (12) is a clinically useful, validated rating scale for assessment of the status of patients with

PD (13). The PDSS domains include panic attack frequency, distress related to the attacks, degree of anticipatory anxiety, phobic avoidance, and PD impairment of work and social functioning. Effective use of the PDSS and other assessments includes educating the patient about reporting of symptoms, which will enhance the assessment process. To this end, weekly visits for the first several weeks is ideal for helping patients become more "tuned in" to symptoms and reporting them more reliably. Use of validated self-rating scales for depression such as the Hospital Anxiety and Depression Scale (HADS) (14) or the Quick Inventory of Depressive Symptomatology (QUIDS) (15) can likewise supplement the clinical interview in documenting progress in treatment. Such assessments can easily be incorporated into the clinical interview without detracting from the doctor-patient relationship and can provide valuable information for patients who do not respond well to initial treatment.

INITIAL CHOICE OF TREATMENT

PATIENT FACTORS

The goal of treatment is to reduce symptoms associated with PD (panic attacks, phobic avoidance, anticipatory anxiety, depression, and cognitive distortion) and comorbid conditions such as depression or other anxiety disorders). This includes not only reducing symptom severity with treatment but also attention to identifying the importance of progress made (such as driving a car, shopping for groceries, and attending social functions) as important steps in the journey to recovery of full functioning. The choice of the initial treatment is guided by patient factors (preference, treatment history, and psychiatric and medical status), the orientation and expertise of the clinician, and illness severity. Either pharmacotherapy or CBT is recommended as an effective first-line monotherapy (8). Theoretically, pharmacotherapy exerts therapeutic effects by normalizing the reactivity of the amygdala and brainstem areas within the fear network to suppress panic attacks, followed in turn by decreased anticipatory anxiety and reduction in conditioned fear behaviors. CBT is predicted to work "upstream" by normalizing distorted cognitions, enhancing the ability of the higher cortical structures to exert inhibitory effects on lower brain structures, and reducing panic attacks and related learned fear responses (16) (Figure 1). Choice of initial treatment may be influenced by the most distressing panic symptoms (e.g., predominantly somatic versus cognitive symptoms). There is insufficient evidence to recommend initial treatment with combined medication and CBT versus initial monotherapy (8) or to recommend one treatment modality over another.

PHARMACOTHERAPY

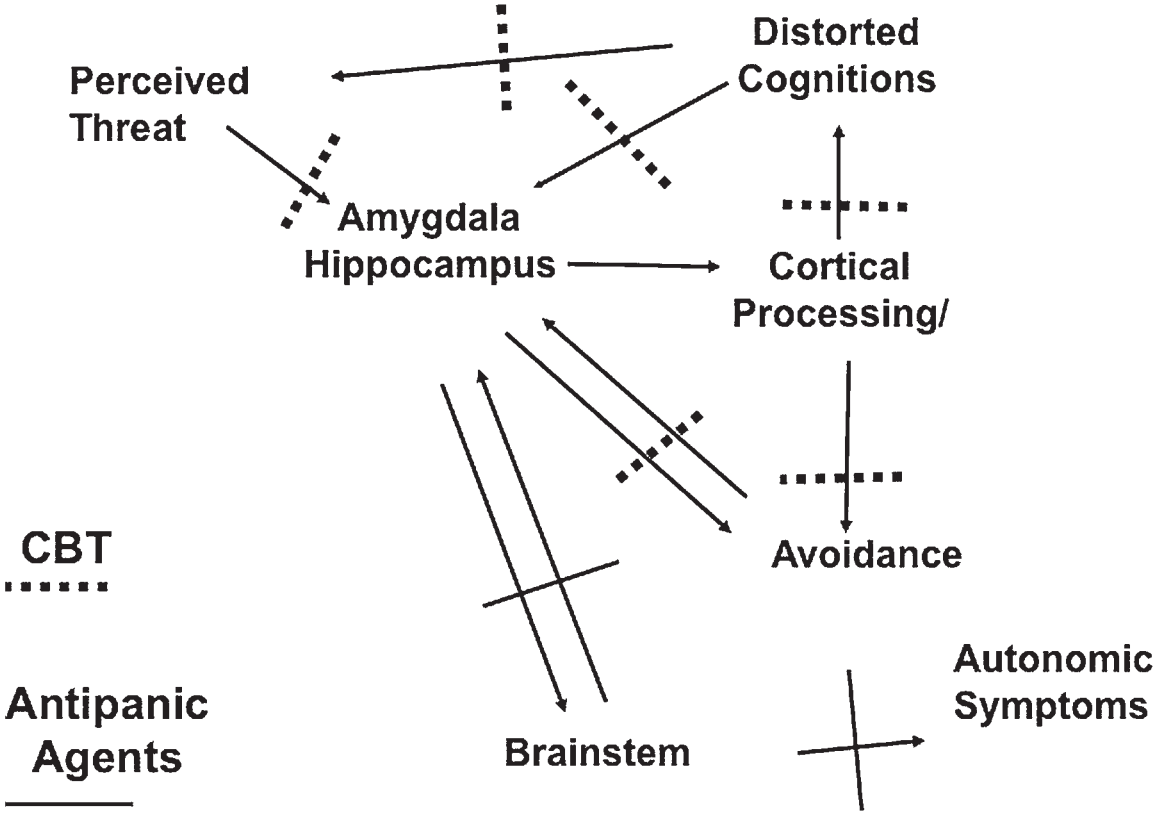
The selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), traditional monoamine oxidase inhibitors (MAOIs), and benzodiazepines (BZDs) are approximately equally efficacious in the treatment of PD (8, 17). Antidepressant monotherapy with an SSRI or SNRI is the recommended first-line treatment.

Antidepressants. On the basis of their breadth of efficacy, tolerability, ease of administration, and safety in overdose, the SSRIs and SNRIs are recommended as the first-line treatment for PD with or without agoraphobia (8, 17). Sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram, and escitalopram have been empirically shown to be effective for PD (17), as has the SNRI venlafaxine. Fluoxetine, sertraline, paroxetine, and venlafaxine are considered to be equivalent in efficacy for the treatment of PD and have received U.S. Food and Drug Administration (FDA) approval.

Tricyclic antidepressants (TCAs). Imipramine (IMI) is the most well-studied TCA (18). Its desmethyl metabolite desmethylimipramine has also been shown to be effective for PD (19). Clomipramine, a TCA that is a potent inhibitor of serotonin reuptake, is effective in the treatment of PD and has a greater breadth of efficacy against other anxiety disorders than the other TCAs (20, 21). Although TCAs are as effective as SSRIs for PD, the predictable side effect burden (anticholinergic and cardiovascular) and danger in overdose limits enthusiasm for their use unless at least two first-line treatments fail.

Monoamine oxidase inhibitors (MAOIs). The traditional nonselective MAOIs such as phenelzine and tranylcypromine have not been studied in DSM-defined PD but are effective in individuals with phobic avoidance with panic attacks (22, 23). These agents are rarely used because of their side effects, potential danger after tyramine ingestion or overdose, and dietary restrictions. For the rare patient whose PD is unresponsive to other treatments, judicious use by an experienced psychopharmacologist may be beneficial (17, 24). The selective MAO-A selegiline has not been studied in PD; moclobemide (unavailable in the United States) is of questionable use as a treatment for PD (17).

Figure 1. Theoretical Sites of Action of CBT and Antipanic Agents.



Other antidepressants. There are insufficient data to recommend mirtazapine or nefazodone (which also has a small risk for hepatic damage) (17). Mixed results were seen in open-label studies of bupropion, and it is not recommended (25, 26) as a first-line treatment. Bupropion may be coprescribed to address depression or sexual side effects of antidepressant treatment (27).

Benzodiazepines. The most well-studied BZDs are alprazolam and clonazepam (18, 28). Other less well-studied BZDs including lorazepam and diazepam are also effective for PD (8, 29). Alprazolam is effective and well-tolerated, reducing panic attack frequency and severity within the first several days of treatment. A practical disadvantage is that several daily doses are necessary and "interdose rebound" between doses can be bothersome for some patients (30). Clonazepam is more potent, has a longer elimination half-life and efficacy equal to alprazolam (28), and is also FDA-approved. It has the clinical advantage of requiring only one or two daily doses, and its slow elimination reduces discontinuation effects.

Daily administration of BZDs invariably results in the development of physiological dependence and the appearance of withdrawal upon discontinuation. It is important to distinguish between "addiction" (nonmedical use) and physiological dependence (iatrogenic). This confusion promotes the largely unfounded concern over the abuse potential of BZDs (31). In anxious patients without a history of substance abuse, it is rare (32). The evidence indicates that long-term use is associated with a decrease in daily dosage (33, 34). Unwanted effects of BZDs include sedation, ataxia, fatigue, and subjective memory difficulty. The latter concern—memory disruption—remains controversial (35) despite evidence to the contrary (31, 36).

Anticonvulsants. The evidence for efficacy of anticonvulsants in the treatment of PD is limited to one multicenter, placebo-controlled study of gabapentin, in which secondary but not primary outcome measures provided some support for a benefit in PD (37). The use of sodium valproate (VPA) is limited to open studies (38) and has been reported to be helpful for patients with comorbid bipolar disorder and PD (39) and those with the additional complication of alcohol abuse (40, 41). Evidence for use of other anticonvulsants such as tiagabine, vigabatrin, and levetiracetam is limited to open-label reports for PD (8, 42).

Other agents. Buspirone, a nonbenzodiazepine anxiolytic, is ineffective as monotherapy for PD (43). Standard neuroleptics have no role in the

treatment of PD. There are reports suggesting beneficial effects from the second-generation antipsychotics olanzapine (44, 45) and risperidone (46) in treatment-resistant PD. There is no evidence to support long-term treatment (47).

CBT

CBT is as effective as pharmacotherapy for PD in acute treatment (48). The standard components of CBT for PD include cognitive-restructuring interventions, exposure, and arousal reduction. CBT has been shown to significantly increase the likelihood of successful BZD discontinuation (49). It is generally provided in 12–16 weekly sessions (48). Some studies have reported that patients with PD with comorbidity respond well to PD-focused CBT (50, 51), although others reported less benefit in patients with comorbid conditions (52).

ADEQUATE INTENSITY OF TREATMENT

ANTIDEPRESSANTS

Approximately three-quarters of apparent PD treatment failures are due to inadequate dosage and/or duration of treatment with antipanic medication (53–55). The "recommended" dosage for antipanic medications is derived from fixed-dose studies completed during the process of obtaining FDA approval. For example, the "target dose" listed for paroxetine is 40 mg daily, even though many patients receiving lower doses benefitted. For sertraline, there is a range of recommended therapeutic doses of 50–200 mg daily. This was based on the *lack* of statistical differences between drug groups (50, 100, or 200 mg daily) in pivotal clinical trials. Because there is no information about dosages higher than those studied during drug development, there are no official recommendations for higher doses. Clinical experience indicates that the optimal dose for some patients with PD can be higher than the "recommended" dose or range and must be determined by gradually advancing the dose until a full therapeutic effect or limiting side effects occur.

SSRI/SNRI- and TCA-induced activation is common during initiation of treatment. This should be explained before initiation of treatment. Advising the patient that this reaction is not dangerous and may even suggest that the diagnosis of panic disorder is correct may help shift the perception of this side effect to a more positive experience. For patients who experience activation from even small initial doses, reducing the dose by dissolving capsules in fruit juice to administer a tolerable dose of a few milligrams can be accomplished, with very gradual dose adjustments as tolerated.

TCAs should be reserved for patients with a poor response to at least two first-line agents. Empirical data for the TCAs is limited to imipramine. Mavissakalian and Perel (56) reported that patients whose daily oral IMI dose was at or above a threshold of approximately 150 mg orally showed better rates of response than those taking lower doses. These investigators also reported that patients who achieved steady-state plasma concentrations of (IMI + desipramine combined) in the 125–150 ng/ml range experienced an optimal balance between benefits and side effects reported at higher doses (57). For more severely ill patients with comorbid depression, higher doses or levels may be necessary. In addition to targeting plasma levels, TCA levels can also be useful in confirming compliance.

BENZODIAZEPINES

For most patients, doses of alprazolam in the range of 1.5 to 6 mg daily are sufficient, but clinical experience suggests that some may require higher doses (8–10 mg) (58, 59). A dose-finding study in patients with uncomplicated PD comparing several dosages of clonazepam versus placebo suggested that the "optimal" dose for clonazepam is approximately 2–4 mg daily (again, higher doses may be required by some patients). For clinical use, clonazepam is about twice as potent as alprazolam (28).

When there is inadequate response, compliance with treatment is unclear, or if an individual patient appears to require much higher levels than expected, plasma levels of BZDs may be clinically useful. Fixed-dose studies of alprazolam show that each oral dose of 1 mg is associated with 10 ng/ml at steady-state plasma levels. Maximal clinical improvement with a tolerable side effect burden appeared to be in the 20–60 ng/ml range (correlating with a 2–6 mg daily alprazolam dose) (58).

Adequately intense treatment also requires an appropriate duration of treatment at an effective dose. The available information from the published literature indicates that for uncomplicated PD, improvement in panic attack frequency is usually observable within 4–6 weeks for antidepressants and for BZDs often within the first week but may take several weeks for some patients. For more patients with comorbid conditions, the response may be slower, and the observation for response should be accordingly longer (8–12 weeks).

Table 3. Dosage Ranges for Antipanic Medications*

Agent	$T_{1/2}$ (hr)	Suggested Dosage Range (mg/day)	Initial Dose (mg/day)
SSRIs/SNRIs			
Fluoxetine	24–72	20–40	5–10
Citalopram	35	20–40	5
Sertraline	24	100–200	12.5–25
Paroxetine	21	20–40	5–10
Escitalopram	27–32	10–20	5
Fluvoxamine	15	100–200	25
Venlafaxine	5–11	150–225	12.5
Benzodiazepines			
Alprazolam†‡	6–12	2–6	0.5–1
Lorazepam†	8–12	2–8	1.5–2
Clonazepam	18–50	1–4	0.25–0.5
Tricyclic antidepressants			
Imipramine‡	12–24	150–300	10
Clomipramine	11–20	50–150	10
Desipramine	28–36	100–200	10
MAOIs			
Phenelzine		45–60	15
Tranylcypromine		30–40	10

* Some patients will require higher doses than recommended range.
† Multiple divided doses necessary.
‡ Plasma levels can guide treatment.

There is wide variation in the dosage required for successful treatment of PD, especially for patients with considerable comorbidity. When it appears that further benefit at a given dose is unlikely, a systematic dose increase with observation at appropriate (8- to 12-week) intervals can avoid adverse effects and optimize benefit. Table 3 shows recommendations based on the published literature (8). In this author's experience, higher dosages may be necessary. If the upper limit of the dosage range shown is reached and there is a clinically significant partial response with tolerable side effects and no evidence of toxicity or misuse of the medication, gradual increases in the dose and observation for further improvement and continued tolerability of side effects is a reasonable strategy. For example, doses of alprazolam up to 10 mg may be required for some patients. The psychiatrist can address medico-legal concerns by documenting (when possible with rating scales) the rationale for prescribing higher dosages and the fact that risks and benefits have been discussed and the patient understands and agrees. If the psychiatrist or patient has significant concerns about higher dosages, referral for consultation to a psychiatrist with expertise in anxiety disorders can help reassure the patient and the clinician.

CBT

Although manualized treatments have substantially standardized CBT, treatment "dose" is less easily defined and would depend on the number of sessions, the specific CBT protocol, and the skill of the individual therapist. The number of CBT sessions suggested by experts as adequate should be at least 12 weekly sessions (60). Effective CBT in some published studies can be accomplished in as few as 5 sessions (61).

Differential Diagnosis for Inadequate Response to Initial Treatment

Attention to the domain(s) of PD that remain inadequately improved offers a systematic method for assessing unsatisfactory outcome of the initial PD treatment. Attention to potential contributors to persistent panic attacks, nonpanic anxiety, comorbid anxiety or mood disorders, residual phobia and other factors that may interfere with improvement, as shown in Table 4, is helpful for planning the next step in treatment.

Persistent Panic Attacks

If unexpected panic attacks have diminished but still persist, and pharmacotherapy has been optimized in dose and duration, adding a BZD or CBT is a reasonable next step. For attacks that are stimulus-bound, consider other anxiety disorders such social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), or obsessive-compulsive disorder (OCD), each of which can be associated with panic attacks (62, 63). Disorder-specific CBT with exposure for the specific disorder(s) should be added to treatment. If there has been no change in unexpected attacks, switching to a different SSRI or SNRI is suggested.

Persistent Nonpanic Anxiety

Antidepressant intolerance is sometimes overlooked by the clinician, and should be considered in the differential diagnosis as a potential cause of persistent anxiety. Comorbid anxiety disorders such as SAD, generalized anxiety disorder, or PTSD can contribute to persistent nonpanic. If the

patient is receiving an intermediate half-life BZD such as alprazolam or lorazepam, and anxiety worsens before the next scheduled dose or in the morning several hours after the bedtime dose, gradually changing to a longer-acting agent such as clonazepam may be effective. Review current medications and any new medications, including alternative or herbal remedies that the patient may not have reported. Previously undetected alcohol and/or substance abuse can worsen PD and interfere with treatment (64, 65). A controlled study that combined CBT and an SSRI plus relapse prevention for individuals with PD and alcohol dependence reduced anxiety symptoms. However, there was no apparent advantage over psychosocial treatment alone on subsequent relapse rates (66).

COMORBID MOOD DISORDER

Unrecognized depression should be considered in the initial evaluation of inadequate response to treatment. When depression and PD coexist, both disorders are more severe, more persistent, and less likely to respond to standard treatments (6, 67, 68). If there is a partial response to the initial antidepressant treatment, increased treatment intensity is indicated.

For patients with depression that does not respond to aggressive pharmacotherapy with at least two first-line antidepressants or CBT, using imipramine with targeted plasma levels is a reasonable consideration. For some patients, improvement can subsequently be maintained with gradual switching to an SSRI or SNRI and tapering imipramine.

There is significant co-occurrence of PD and bipolar disorder (9, 69–71). The coexistence of PD and bipolar disorder predicts poor prognosis for both conditions (72, 73). Comorbid bipolar II disorder can be overlooked during the initial evaluation, as these patients often fail to identify and report periods of hypomania as problematic. In addition, a positive family history for cyclic mood changes can help increase the index of suspicion. Because antidepressant treatment may cause mood instability, reduction or discontinuation of antidepressant treatment should be considered, and a mood stabilizer should be added. Limited data suggest that VPA treatment (38) may be a good choice. VPA has been reported to be beneficial in patients with comorbid PD and bipolar disorder, including a subgroup further complicated by alcohol abuse (40, 41, 74). Short-term atypical neuroleptics have been reported to be beneficial for some patients (75, 76). The risk of treatment must be considered in the context of the severity of illness and functional impairment of the individual patient.

RESIDUAL PHOBIC AVOIDANCE

The differential diagnosis for residual avoidance includes evaluation of whether there was insufficient exposure for agoraphobia or if there may be a concurrent anxiety disorder with related avoidance (SAD, PTSD, or OCD). If avoidance is being driven by a comorbid anxiety disorder, disorder-specific CBT should be added. If social avoidance due to demoralization or social withdrawal due to depressed mood appears to be promoting avoidance, more aggressive treatment of depression is indicated.

OTHER FACTORS

New onset or worsening of preexisting psychosocial stress can exacerbate PD and interfere with treatment. Reassessment should include asking about new problems, interpersonal difficulties, and occupational or family stressors. Noncompliance with treatment is not infrequent and can result from lack of sufficient patient understanding of the principles of treatment, including compliance with medication administration or behavioral changes prescribed is not frequent. Some patients or significant others may require refresher information sessions about the nature of the illness and/or the requirements for adequate treatment.

Practical strategies that make clinical sense to be considered include other interventions, which may also contribute to clinical progress for many patients. One such strategy is to increase the frequency of patient visits, which may strengthen the doctor-patient relationship, provide more confidence in the clinician and promote a sense of caring for and dedication to the progress of the patient. Another strategy that may be useful is a recommendation to initiate or return to a regular exercise regimen, which is known to improve stress tolerance. Yoga or meditation exercises may be useful. Such activities can both promote a sense of well-being and enhance the patient's sense of mastery and confidence.

THE NEXT STEP: AFTER THE FIRST TREATMENT FAILS

If the issues of diagnosis, treatment intensity, and other factors noted above have been addressed, and an unsatisfactory response is apparent, it makes sense to modify the treatment. The options are to augment the initial treatment or switch to a different treatment. The empirical literature in this area is very limited. The majority of published studies reporting beneficial effects from treatment changes included patient samples that have not been care-

Table 4. Differential Diagnosis for Inadequate Treatment Response in Panic Disorder

Persistent Symptom(s)	Differential Diagnosis	Suggested Approach
Persistent panic attacks	Unexpected	Inadequate treatment intensity: Adjust accordingly
		Partial response:
		Increase dose and observe
		Augment with second agent
		CBT/exposure
		Imipramine with plasma levels
		No response:
		Reconsider diagnosis
		Switch to different agent or CBT
	Situationally bound	Agoraphobia: Add CBT/exposure
	Situationally bound	Related to PTSD, social anxiety, OCD
		Disorder-specific CBT
		Increase antidepressant dose
		Add BZD
	Medical condition or treatment	Address as indicated
	Caffeine excess	
Persistent non-panic anxiety	Residual anticipatory anxiety	Add/increase dose of BZD
		Add CBT
	Antidepressant-related activation	Adjust dosage; add BZD, β-blocker
	Interdose BZD rebound	Long-acting BZD
	Psychosocial stress	Patient education
		Environmental hygiene
		Adjust treatment plan as needed
	Alcohol/substance abuse	Assess, treat, or refer
	Generalized anxiety disorder	Increase antidepressant dose
		Add or increase BZD
		Disorder-specific CBT
Residual avoidance	Agoraphobia	CBT/exposure
	Social anxiety, PTSD, OCD	Disorder-specific CBT/exposure
Other psychiatric disorders	Depression	Increase antidepressant treatment
		Add CBT
	Bipolar disorder	Mood stabilizer ± BZD
		Discontinue antidepressant if possible
Nonadherence	Inadequate patient or family understanding	Education
		Information resources
	Sexual dysfunction or weight gain	Bupropion, sildenafil, switch agents

fully characterized. There is only one published study to date that prospectively studied SSRI treatment resistance and used state-of-the-art methods. Unfortunately, the results of the study were inconclusive because of a small sample size (77). However, it did support the concept that increasing the dose of the initial treatment, supplementing pharmacotherapy with CBT, or augmenting with a BZD provided similar but small increases in remission. Although not as illuminating as would be hoped, the study is a model for future research, which includes a sufficiently large sample size and adequate statistical power.

AUGMENTATION OF PHARMACOTHERAPY

Several augmentation strategies have been reported to improve inadequate response in PD, but none has been intensively studied. There is substantial clinical experience that addition of a BZD at this point can be beneficial. Pindolol, a β-adrenergic agonist with $5HT_{1a}$ agonist properties, which was useful as an augmenting agent in resistant depression, has been shown in one small controlled study to benefit patients who had not responded to 20 mg of fluoxetine for 8 weeks (78) although the initial dose (79) and duration of SSRI treatment in

that study may have been inadequate. One case series reported that combining an SSRI with TCAs was helpful for patients with PD that was unresponsive to either an SSRI or a TCA (80). There are limited uncontrolled data supporting the utility of mirtazapine for PD as an augmenting strategy (8, 81). Uncontrolled reports have suggested the utility of addition of atypical neuroleptics in treatment-resistant PD (44, 46). However, this practice should be considered only for very severely ill patients and those with treatment-resistant PD. Repetitive transcranial magnetic stimulation as an augmentation treatment was shown to be beneficial in a small group of patients with PD that was unresponsive to SSRIs (82), although this approach is probably not practical or widely available. Finally, addition of CBT to augment inadequately effective drug treatment for PD has been shown to be an effective strategy (83–85).

AUGMENTATION OF CBT

There are only limited data regarding the addition of pharmacotherapy for partial responders to CBT. Clomipramine augmentation of unsuccessful behavioral treatment for hospitalized patients has been reported to be effective (20). For outpatients who were inadequately responsive to CBT, adding the SSRI paroxetine has been shown to be an effective strategy (86).

The literature on combined treatments has generally suggested a slight advantage for combined medication and psychotherapy over either monotherapy alone so long as medication is continued. After treatment discontinuation, combined treatments were comparable to psychotherapy alone and slightly better than medication alone (87, 88). A few studies in which clonazepam was combined initially with an SSRI and then tapered after a few weeks showed faster onset of the combination (89, 90).

SWITCHING TREATMENT

If the initial treatment fails to show clinically significant benefit, switching treatments is indicated. For pharmacotherapy, switching to a different first-line treatment (a different SSRI or an SNRI) is recommended. After two SSRIs or an SSRI and an SNRI, second-line pharmacotherapy such as TCAs or benzodiazepines is a reasonable next step (8). When treatment is switched from one SSRI or SNRI antidepressant to another, it is common practice to add the second agent and increase the dose with gradual up-titration to a moderate dose treatment and then gradual down-titration of the initial agent. Careful additional upward titration during or after the process of cross-titration can avoid SSRI discontinuation symptoms. The process usually takes several weeks and requires careful observation.

For patients who are considered appropriate and willing to follow a low tyramine diet, the older MAOIs may be beneficial. There is no empirical basis beyond the older published literature, but one recent report suggested benefits from phenelzine after other treatments were unhelpful (24). Use of these older MAOIs should be completed by psychiatrists who are familiar with them and the management their side effects. Introducing these agents requires tapering and discontinuation of other antidepressants for at least 2 weeks before initiation of treatment.

With the exception of one controlled study of psychodynamic psychotherapy for PD (91), there is no alternative to individual or group CBT that has been empirically shown to be effective for PD. Other approaches that enhance treatment adherence, provide more information, or otherwise support the individual should be made on the basis of the psychiatrist's knowledge of the patient.

CONCLUSIONS

Treatment of PD has evolved and improved substantially as our understanding of the neurobiology and neurobiological substrates of anxiety have expanded. The optimal treatment must still be individualized for each patient. A systematic, differential diagnostic approach to the evaluation and optimal treatment of PD has been presented. As research provides more information on optimizing treatment, additional advances in providing relief for the many individuals who experience PD will be made. Undertreatment of PD remains a major problem. The most important of the identified factors for promoting adequate treatment of PD is insufficient intensity of treatment.

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INFORMATION RESOURCES FOR PANIC DISORDER AND OTHER PSYCHIATRIC DISORDERS

Anxiety Disorders Association of America: http://www.adaa.org
National Institute of Mental Health (NIMH): http://www.nimh.nih.gov
American Psychiatric Association; http://www.psych.org
American Academy of Child and Adolescent Psychiatry: http://www.aacap.org
Association for Behavioral and Cognitive Therapies: http://www.abct.org
National Alliance on Mental Illness (NAMI): http://www.nami.org
National Mental Health Association: http://www.nmha.org

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