Pharmacologic Treatment of Panic Disorder

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Contents

Abstract Comprehensive management of panic disorder involves a wide array treatments and interventions to reduce symptoms and increase functionality. This chapter provides an overview of the pharmacologic treatment of panic disorder including aspects of assessment, treatment selection and the biologic mechanisms of the illness.

Keywords Anxiety · Benzodiazepine · Panic · Pharmacology · SNRI · SSRI · TCA · Treatment

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1 Introduction

The anxiety disorders are among the most common psychiatric syndromes affecting up to about 15% of the population (Robins et al. 1984; Kessler et al. 1994). Panic disorder (PD), one of the most severe anxiety syndromes, is characterized by recurrent unprovoked panic attacks. During these attacks, a variety of physical symptoms may occur accompanied by a sense of doom together with a strong desire to escape (Weissman et al. 1990). This need to escape may lead people to quit jobs, avoid friends and social activities, and can lead to significant withdrawal and isolation (Roy-Byrne et al. 2006). Comprehensive management of PD involves a wide array of treatments and interventions designed to reduce symptoms and increase functionality. This chapter provides an overview of the pharmacologic treatment of PD, including aspects of patient assessment, treatment selection, and a description of the biologic mechanisms of the illness. Each mechanism will be presented with a discussion of selection, efficacy, and implementation of the treatments presented.

2 Clinical Assessment Before Treatment

There are several key steps in the clinical assessment of the anxious patient that precede the formulation of a comprehensive treatment plan. In addition to diagnosis of the specific anxiety disorder affecting the patient, the clinician needs to have a high index of suspicion for co-morbid conditions such as other anxiety disorders, mood disorders, and substance use disorders (Royal Australian and New Zealand College of Psychiatrists 2003). Furthermore, an anxiety disorder due to a medical condition or substance use (e.g., thyrotoxicosis, caffeinism, alcohol withdrawal) and medical conditions that mimic clinical anxiety (e.g., cardiac arrhythmias, seizure disorders, asthma) need to be ruled out. Thus, a thorough work-up should include a full physical examination, urinalysis, urine toxicology, electrolytes, liver functions, thyroid function tests, a full blood count, and an EKG. For patients with atypical presentations, for example, panic attacks with syncope, it is important to refer them for a neurological evaluation. A central principle of pharmacological management of anxiety disorders is the need to guide treatment by focusing on key target symptoms, such as panic attacks, phobic anxiety, or generalized anxiety. The goal of pharmacotherapy then becomes suppression or eventual blockade of the target symptom. Not all features of anxiety syndromes are directly responsive to medical interventions (e.g., agoraphobic symptoms in a PD patient). Therefore, another general rule of medical treatment is to consider the inclusion of cognitive–behavioral therapy (CBT) or other psychotherapies in the overall treatment plan. Determination of the specific features of PD that characterize a given patient's experience is an essential element of assessment and treatment planning; it is also an opportunity to begin the process of building a strong therapeutic alliance with the patient (Royal Australian and New Zealand College of Psychiatrists 2003).

Careful counseling of the anxious patient concerning the short- and long-term risks and benefits of medications is the key to satisfactory compliance as these patients are extremely side-effect sensitive.

3 Treatment Selection

A variety of psychosocial and pharmacologic interventions have proven benefits in treating PD. Treatment selection is guided by a knowledge of the efficacy profile of a given agent and consideration of potential liabilities including side-effect burden, drug–drug interactions, safety in overdose, and other nonclinical factors such as cost and availability (Canadian Psychiatric Association 2006). There are no reliable clinical predictors of treatment responsivity excepting a previous history or family history of such a response. Furthermore, despite the extensive database of neurobiological studies in PD, there are, as yet, no clinically useful biological markers of treatment responsiveness. In patients with uncomplicated PD, as well as in patients with co-morbidity, the SSRIs are now considered the first-line medications (American Psychiatric 2009). Their ease of administration and favorable toxicity/side-effect profile in comparison with older-generation agents [tricyclic and monoamine oxidase inhibitors (MAOIs)] has contributed to this trend. As mentioned earlier, there is now some evidence that SSRIs might have superior antipanic efficacy compared to other standard agents. In addition, the data from some efficacy trials suggest that SSRIs may have an earlier onset of action compared to the older generation 5-HT/NE anxiolytics (Royal Australian and New Zealand College of Psychiatrists 2003). Taken together, these characteristics strongly argue in favor of the selection of an SSRI as the first-line agent in PD. Imipramine and other tricyclics should now be considered the second-line agents for panic. Benzodiazepines are third-line, anticonvulsant the fourth-line, and the classical MAOIs would be considered fifth-line antipanic agents due to their side-effect profile and safety issues. Indeed, there appear to be few contraindications to SSRI treatment for panic. One caveat is the potential for drug–drug interactions due to hepatic P450 enzyme inhibition. For example, paroxetine and fluoxetine, in regular clinical doses, substantially inhibit the P450 IID6 isoenzyme (American Psychiatric 2009). A number of medication classes, including tricyclics, some neuroleptics, β-blockers, codeine-based analgesics, and some antiarrhythmics (e.g., flecainide and encainide), are metabolized by IID6. Fluvoxamine and, to a lesser extent, fluoxetine inhibit the P450 3A3/4 isoenzyme that metabolizes a number of classes of medications including macrolide antibiotics, nonsedating antihistamines, and calcium channel blockers. There has been one case report of EKG changes in a patient receiving both terfenadine and fluoxetine. Thus, careful clinical monitoring of patients receiving an SSRI together with any of these medications is warranted. Citalopram and sertraline appear to cause lesser degrees of P450 enzyme inhibition, and thus may be useful in the management of the panic patient on multiple medications for other psychiatric or medical reasons. Another relative contraindication would be

administration of an SSRI or indeed any antidepressant-like agent to patients with additional diagnoses of bipolar disorder or a psychotic illness. This caution is of some relevance, clinically, since PD appears to be over represented in bipolar populations (Rotondo et al. 2002). Whether SSRIs are less likely to induce hypomania than tricyclics bears further study (Howland 1996). In the bipolar/panic disordered patient, it may be preferable to avoid SSRI use and attempt stabilization of both syndromes with anticonvulsants (e.g., valproate, gabapentin, and lamotrigine), which are now being increasingly used for both syndromes. Another area of concern is the potential for serotonin syndrome (confusion, diaphoresis, agitation, fever, and tachycardia) and movement disorder to occur in SSRI/SNRI treated patients, who are subsequently given the common anti-emetic agent, metoclopramide (Fisher and Davis 2002). This observation, based on a recent report of two cases, may be the result of a pharmacodynamic interaction between SSRIs and metoclopramide. Within the SSRI class there is no available comparative efficacy data that would lead one to select one agent over another. Pharmacokinetic factors are of some importance in selecting an appropriate SSRI in PD. For example, an agent with a long $t_{1/2}$ such as fluoxetine should be considered in patients in whom the tapering phase of treatment may be complicated. Also, there may be subtle differences in side-effect profile that guide treatment selection. For example, paroxetine tends to be more sedating than other SSRIs and may be preferable in patients in whom sleep disturbance is a significant symptom. The SSRIs are generally safe agents for use in special populations such as the elderly, pregnant or lactating women, and children and adolescents (Murphy et al. 2000). There is some concern about growth-delaying effects of SSRIs exposure during the prepubertal and pubertal period (Weintrob et al. 2002). PD disproportionately affects women, and not infrequently declares itself during pregnancy or the post-partum period. Thus, it is clinically useful to know that SSRIs have a low teratogenic potential and, although excreted in breast milk, appear, thus far, to have limited effects on the newborn (Misri et al. 2000). One caveat to SSRI therapy in elderly patients is the slight risk of a syndrome of inappropriate ADH secretion, suggesting the need for electrolyte monitoring in this group.

3.1 Treatment Implementation

Many people with PD do not respond fully to a first-line treatment due to a various factors including an inability to tolerate treatment (American Psychiatric 2009). In general, panic patients are extremely side-effect sensitive, especially to the stimulant properties of agents that modify 5-HT and NE function, and therefore should be commenced on half the usual starting dose used for major depression (Louie et al. 1993). Not uncommonly, co-treatment with a benzodiazepine is necessary to minimize the impact of this side-effect. Recent work endorses the benefit of early regular co-administration of the benzodiazepine, clonazepam, with SSRIs for the rapid stabilization of moderate–severe PD (Goddard et al. 2001; Pollack et al.

2003). Gradual clonazepam tapering after several weeks of co-administration appears to be well-tolerated and limits the development of physiological dependence associated with long-term benzodiazepine use. Guidelines for the duration of SSRI therapy generally depend on the time at which a full response has been obtained. This is usually defined as a remission of both full and limited symptom panic attacks. At this time, a further 6 months of maintenance therapy is considered sufficient (Rosenbaum et al. 1996) before a trial of SSRI taper is indicated. 5-HT/NE anxiolytics have the advantage of being relatively easy to taper with this population in contrast to benzodiazepine agents. However, abrupt discontinuation should be avoided because of the flu-like syndrome that has been observed to occur in this context (Coupland et al. 1996). Additional controlled clinical research data are still needed to guide the long-term management of PD. Recent work with PD patients on imipramine suggests that they may benefit from an extended maintenance period (up to 2 years; Mavissakalian and Perel 2001). Similarly, continued SSRI therapy (18 months) appeared to prevent clinical relapse. Thus, maintenance pharmacotherapy may be necessary for some patients to protect against relapse. Large, controlled maintenance studies are underway to determine important questions concerning the ideal length of and combination of treatments, and the clinical indications for extended maintenance treatment in a subgroup of patients who might be sensitive to relapse (e.g., patients with multiple previous episodes of panic). Treatment is generally monitored by frequent assessment of clinical status and treatment compliance. Drug plasma levels are generally not needed as a guide to dosing. With respect to imipramine treatment, there appears to be a linear relationship between antipanic effects and total imipramine plasma levels (Mavissakalian and Perel 1994). Treatment resistance is a relatively uncommon problem and can usually be addressed by careful diagnostic reassessment and then moving through the top four classes of agents in a step-wise manner (Rosenbaum et al. 1996). However, partial responses are fairly common and can usually be managed by optimization of the existing regimen or co-administration of another therapeutic agent, for example, a benzodiazepine, or another 5-HT/NE anxiolytic (e.g., low-dose desipramine). If response to treatment remains unsatisfactory following an adequate trial; it is appropriate to consider a change (American Psychiatric 2009) either through augmentation with another agent or the addition of another modality (e.g., cognitive behavioral therapy). An individual approach to augmentation is required as there is little work on the benefit of other augmentation strategies in panic (e.g., lithium augmentation) that have been routinely applied in depression, where treatment-resistance is a more prevalent clinical issue.

4 Pharmacologic Treatments

Selection of a specific medication for the treatment of PD will require the consideration of the specifics of a patient's presentation and which medicine best fits in terms of properties of the medication itself (e.g., half-life) and its associated features (e.g., side effects, cost). This is because the classes of medications used

[SSRIs, serotonin/norepinephrine reuptake inhibitors (SNRIs), TCAs and benzodiazepines] are comparable in terms of efficacy (Kessler et al. 1994). As such, SSRIs and SNRIs are likely the best choice of initial pharmacotherapy for many patients with PD as they do not carry the significant side effects associated with TCAs and have no liability for abuse as is found with benzodiazepines. SSRIs, SNRIs, and TCAs all provide antidepressant effects, but all have delayed primary antipanic effects. Benzodiazepines, despite their greater propensity for side effects, are still used very frequently because of their rapid onset of action. Studies (Pollack et al. 2003) have suggested benzodiazepines in combination with antidepressants to control symptoms until the antidepressant takes effect followed by tapering of the benzodiazepine. PD patients frequently are hypersensitive to medication side effects, and it is recommended to educate patients about the likely course of both primary and side effects of the medications. It is also recommended that starting doses of SSRIs, SNRIs, and TCAs be approximately half of those given to depressed patients (Louie et al. 1993). This initial dose should be maintained for several days and then gradually increased as tolerated by the patient.

5 Mechanisms of Action

The fear circuit is highly complex, and unsurprisingly, involves several neurochemical systems that modulate and mediate responses. However, from this complexity we can draw out the key role played by the amygdala in the coordination of the components (e.g., cognitive, affective, neuroendocrine, cardiovascular, respiratory, musculoskeletal) of this circuit. Within the context of the cognitive component, it is important as a modulator of fear and anxiety responses and also as a component in the conditioning and extinction of fears. Perhaps this serves as a partial explanation for the status of PD as the most treatment sensitive of the anxiety disorders with 70–80% of patients having satisfactory responses (Rosenbaum et al. 1996). The medications used to treat PD are thought to modify components in this circuit through modification of the neurochemical systems associated with the stress response including serotonin (5-hydroxytrptamine; 5-HT), norepinephrine (NE), γ-aminobutyricacid (GABA), glutamate, and peptides.

The clinical literature concentrating on this area has been mainly derived from the studies of panic patients, and whether these data have more general implications for anxiety disorders remains to be seen. There is evidence that 5-HT mechanisms may have an important role in mediating the antipanic effects of several classes of anxiolytic agents. For example, successful SSRI treatment of PD seems related to the net enhancement of 5-HT function that occurs with the administration of these agents (Blier and Abbott 2001). This outcome appears to be due to the desensitization of somato-dendritic 5-HT_{1A} autoreceptors and possibly 5-HT_{1B} terminal autoreceptors that occurs following chronic SSRI administration (Blier 2001). In conclusion, enhancement of 5-HT neurotransmission is a common mechanism of several major classes of anxiolytic and may be a key factor in controlling pathological anxiety.

NE mechanisms may be also responsible for the therapeutic effects of some of the medications reviewed. In animal studies chronic application of both tricyclics and MAOIs has a variety of inhibitory effects on NE function, including reduction in LC firing rates, NE turnover, tyrosine hydroxylase activity, and postsynaptic β receptor number and functioning. These pre- and postsynaptic events are likely to contribute to stabilization of NE system function in syndromes associated with NE dysregulation such as PTSD and PD. In addition, 5-HT/NE interactions have been implicated in the successful treatment of panic symptoms. For example, preclinical work indicates that long-term but not short-term paroxetine administration is associated with decreased LC/NE cell firing (Szabo et al. 2000). Consistent with this finding of reduced NE activity following SSRI administration in the lab is the clinical observation that chronic SSRI treatment of panic results in the attenuation of anxiogenesis from NE system stimulation with the α-2 adrenergic antagonist, yohimbine. Newer therapeutic agents that are likely to have broad anxiolytic effects such as the 5-HT/NE reuptake blocker, venlafaxine, and the NE reuptake inhibitor, reboxetine, similarly modify LC/NE activity with chronic administration (Szabo and Blier 2001).

GABA neuronal mechanisms have been implicated in the anxiolytic effects of several classes of medications. There is evidence that $GABA_A$/NE interactions may be an important therapeutic mechanism in PD as benzodiazepine treatment blocks panicogenesis induced by yohimbine. It is conceivable, then, that enhancement of GABA function is a common therapeutic pathway for effective antipanic treatments (Jefferson 2001).

There is some evidence that antipanic treatment effects could be related to effects on heart rate variability in PD. Successful treatment (with either cognitive–behavior therapy or imipramine) is associated with normalization of heart rate variability patterns, and recent preliminary data suggest that SSRI treatment with paroxetine has a similar effect (Tucker et al. 1997). Patients with PD may have decreases in vagal tone, permitting a predominance of sympathetic activation of cardiac function. Reversal of these effects by effective treatment may decrease the tendency towards spontaneous panic.

Finally, antipanic agents may modify the functioning of the CRF/HPA axis to bring about therapeutic effects. Preclinical studies have observed decreased HPA axis function on a number of measures following chronic administration of moclobemide and the tricyclic nortryptiline (Reul et al. 1994), while benzodiazepines also appear to decrease CRF function by directly inhibiting CRF release (Plotsky et al. 1995). However, one clinical study of panic patients did not support the notion that HPA axis down modulation (and by implication reduction in central CRF function) was necessary for the occurrence of long-term clinical improvement (Abelson and Curtis 1996).

6 Serotonergic Agents

Currently, six SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram) are available in the United States (American Psychiatric 2009). Although there is no evidence for differential efficacy between them, differences in

side-effect profile, drug half-life, propensity for interactions with other medications, and the availability of generic formulations may influence choice of initial medication (Fava 2006). These drugs, because of their broad therapeutic spectrum (Haas et al. 2009; Gorman and Kent 1999), have the advantage of affording treatment for other common, co-morbid conditions (usually other anxiety disorders or mood disorders), a significant clinical problem in this population. Within this category of agents, the SSRIs are now preferred because of their favorable side-effect profile, ease of administration, and safety. Many of these agents acutely inhibit reuptake of brain 5-HT and/or NE. This is especially true of tricyclic agents, the SSRIs, and the SNRI, venlafaxine. The MAOIs and RIMAs (reversible inhibitors of MAO-A) are quite effective for PD.

Some patients with PD experience increased side effects when beginning treatment with an SSRI. Because of this, starting doses are lower than that for other indications. According to the most recent APA treatment guidelines, the recommended daily starting dose for each is as follows: fluoxetine is 10 mg or less, sertraline 25 mg, paroxetine 10 mg (IR) or 12.5 mg (CR) depending on the formulation used, 10 mg of citalopram, and escitalopram at 5–10 mg (American Psychiatric 2009). It is further recommended that this lowered starting dose be maintained for approximately 3–7 days and then gradually increased based on tolerability (Stein 2005) to standard doses as presented in Table 1. Abruptly stopping SSRIs can lead to discontinuation syndrome (Shelton 2006). Tapering treatment over a week or longer can minimize this risk.

SSRIs have few serious side effects, are rarely lethal in overdose, and have few serious effects on cardiovascular function (American Psychiatric 2009). The most common side effects of this class of medications are headaches, irritability, nausea, insomnia, sexual dysfunction, weight gain, increased anxiety, drowsiness, and tremor.

Table 1 Evidence for efficacy of serotonergic agents

Agent	Normal dosage range (mg/day)	$T_{1/2}$ (h)	FDA anxiety indications	PD[a]
SSRIs				
Fluoxetine	20–80	24–72	OCD, PD	A
Paroxetine	20–60	21	OCD, PD, GAD, SAD, PTSD	A
Sertraline	50–200	24	OCD, PD, SAD, PTSD	A
Fluvoxamine	50–300	15	OCD	A
Citalopram	20–60	35		A
Escitalopram	10–20	27–32	OCD, PD, GAD, SAD, PTSD	A
SNRI				
Venlafaxine	75–225	5–11	Extended release – PD, GAD, SAD	A
Duloxetine	40–60	12	GAD	C

SSRI Selective serotonin reuptake inhibitor; *SNRI* Serotonin norepinephrine reuptake inhibitor; *GAD* Generalized anxiety disorder; *PD* Panic disorder; *SAD* Social anxiety disorder; *OCD* Obsessive compulsive disorder; *PTST* Post traumatic stress disorder; *A* Established treatment (replicated, large scale RCTs); *B* Promising treatment approach (e.g., one or more RCTs of moderate size); *C* Limited evidence (open trials; case series literature); *D* Very limited evidence (only preclinical evidence, theoretical prediction, or anecdotal reports)

[a]Level of evidence supporting use in anxiety disorders

How these side effects are experienced is highly individual, with some being transient and some lasting the duration of treatment.

6.1 Efficacy of 5-HT and NE Reuptake Blockers

Paroxetine was the first SSRI to receive a US FDA indication specifically for PD. Both short-term and long-term (up to 12 months) efficacies have been demonstrated with paroxetine (McHugh et al. 2009). Sertraline has also exhibited both short- (Londborg et al. 1998; Pohl et al. 1998; Pollack et al. 1998) and long-term efficacies for panic, was effective in preventing relapse with chronic administration (Rapaport et al. 2001), and, over a 6-month period, was associated with reduction in the medical services utilization often seen in unstable panic patients (Roy-Byrne et al. 2001). Positive multicenter trial data have also been obtained with fluvoxamine (Asnis et al. 2001), citalopram (Leinonen et al. 2000a), and fluoxetine (Michelson et al. 2001a). Thus far, within the SSRIs class, agents appear to exhibit antipanic effects of similar magnitude (Perna et al. 2001). On the issue of between-class efficacy comparisons, findings from a recent meta-analytic study of clinical trials conducted in over 2,300 panic patients suggested that SSRIs treatment effects could even be more robust than those observed with imipramine or the benzodiazepine and alprazolam (Boyer 1995), although a more recent effect size analysis failed to find significant differences in efficacy between SSRIs and older-generation 5-HT/NE agents (Otto et al. 2001). The antipanic benefit of the serotonin/norepinephrine reuptake inhibitor (SNRI), venlafaxine, has been established (Leinonen et al. 2000b; Sheikh et al. 2000; Michelson et al. 2001b). Pharmacologic data indicate that venlafaxine may exhibit dose-dependent reuptake effects, with SRI effects occurring in lower doses and additional NRI effects becoming more apparent at higher dose levels (Asnis et al. 2001).

Of clinical importance are studies that have investigated the role of genetics in the efficacy (or lack thereof) of drug treatments. A large portion of SSRI-treated PD patients do not respond sufficiently. Recent research has shown that the presence of the long allele of the serotonin transporter (5-HTT) gene is associated with favorable response (Tiwari et al. 2009). To date, the most promising strategy in clinical practice appears to include testing of the functional CYP450 gene variants to avoid over or under dosing poor or rapid metabolizers. Pharmacogenetic studies are beginning to refine and individualize drug therapy for PD (Mancama and Kerwin 2003).

6.1.1 Tricyclic Antidepressants

There are multiple controlled clinical trials documenting the short-term efficacy of these agents in panic. The most tested agent in this regard is the tricyclic, imipramine (Jefferson 1997). Imipramine's therapeutic benefit appears to be maintained over the intermediate and longer-term, as evidenced by data from a study of over

1,000 panic patients (Cross-National and Group 1992) and a multi-site US trial (Barlow et al. 2000) in which, for panic patients with mild or no agoraphobia, CBT was at least as effective as imipramine, and both were superior to placebo, over a 9-month treatment interval. Imipramine has distinct advantages in the management of panic symptoms. It has been thoroughly scrutinized by clinical trial methodologies, has predictable clinical effects, and is inexpensive. Its main disadvantages are an appreciable side-effect burden and the potential for lethality when ingested in overdose. The degree of efficacy of imipramine in panic (approximately 60%–70% of patients are responders) has not been clearly exceeded by newer agents. Other tricyclic agents, most notably clomipramine and desipramine, appear to be similarly beneficial for PD (McHugh et al. 2009).

In conclusion, there is a wealth of clinical data documenting reliable treatment effects of both tricyclics and SSRIs for PD. These treatment effects appear to be maintained over the short- and longer-term.

6.2 Other Agents with 5-HT and NE Mechanisms

Older, but no less efficacious for PD, are the nonselective, irreversible MAOIs such as phenelzine. A number of clinical trials have confirmed their efficacy, and some studies have suggested that MAOIs may even have antiphobic properties in addition to their ability to suppress panic attacks (Liebowitz et al. 1990). The newer generation RIMAs, such as moclobemide and brofaromine, are also another viable treatment option for panic patients with several large-scale trials in the world literature, indicating their panicolytic effects (van Vliet et al. 1993; Tiller et al. 1999). The newer selective NE reuptake blocker, reboxetine, in one controlled study was efficacious and well-tolerated by PD patients (Versiani et al. 2002) and may be especially useful for those with resistant symptoms (Dannon et al. 2002). The antipanic benefit of the 5-HT_2 antagonist, nefazodone, and the selective α-2 and 5-$HT_{2/3}$ antagonist, mirtazapine, has not yet been established. However, there are now several positive open-label trials with these agents, suggesting that follow-up controlled trials could be worthwhile (Berigan et al. 1998; Bystritsky et al. 1999; Carpenter et al. 1999). These agents could be of particular benefit for the panic patient with multiple co-morbidities or those with appreciable sleep disturbance as a part of their clinical presentation.

6.2.1 Benzodiazepines

Benzodiazepeines are generally well-tolerated and highly effective medications for PD. Alprazolam has the largest number of studies supporting its efficacy (Curtis et al. 1993; Tesar et al. 1991; Dager et al. 1992; Schweizer et al. 1993), but the efficacy of clonezapam (Tesar et al. 1991; Moroz and Rosenbaum 1999; Valenca et al. 2003) and other benzodiazepines (e.g., diazepam, lorazepam) (Savoldi et al. 1990; Schweizer et al. 1992; Noyes et al. 1996) is also well-supported. Alprazolam

is efficacious, but because of its short half-life, multiple daily doses are required, which creates both clinical and practical difficulties. Clonezapam has a longer half-life, which requires fewer doses and results in less severe withdrawal symptoms and better compliance (Moroz and Rosenbaum 1999). Because of the reduced complexity of clonezapam, it is frequently the preferred medicine. The risks associated with benzodiazepines include sedation, fatigue, ataxia, slurred speech, memory impairment, and weakness (Schweizer et al. 1992). These side effects should be discussed with patients prior to treatment initiation.

6.3 Other Agents

The use of anticonvulsants in the treatment of PD has limited support. Only one randomized controlled trial of gabepentin (Pande et al. 2000) has provided support for the safety and efficacy of its use in PD. Other open-label trials have suggested utility for valproic acid in PD (Woodman and Noyes 1994) and only case-report level information is available for levetiracetam, tiagabine, and vigabatrin. Further research is needed before any of these treatments can be recommended. The use of first-generation antipsychotics in PD is not recommended. There is no evidence that they are effective and potential side effects outweigh any potential benefit (Canadian Psychiatric Association 2006). There is limited support for the use of olanzapine (Hollifield et al. 2005) and risperidone (Simon et al. 2006) with severe, treatment-resistant PD, but this must be balanced with growing concern about potential side effects (e.g., metabolic syndrome) with these agents. The use of beta-andrenergic blocking agents such as propanolol and atenolol in PD is not supported by the literature (Munjack et al. 1989; Ravaris et al. 1991), but they are occasionally used to help reduce somatic sensations by some clinicians. There is limited evidence for the potential efficacy of pindolol when used as an augmentation for patients with SSRI-resistant PD (Hirschmann et al. 2000), but given the side effect profile of these agents, they are not generally recommended. Buspirone has been investigated and found ineffective as monotherapy for PD (Sheehan et al. 1993) or as an augmentation to enhance the efficacy of CBT (Cottraux et al. 1995).

7 Novel Treatment Approaches

7.1 Anxiolytic Drug Development

Research in this area, while continuing to explore the role of 5-HT receptor subtypes (e.g., 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3) in anxiolysis, has targeted neurotransmitters and modulators beyond the monoamine systems. Neuropeptides implicated in stress and anxiety, such as CCK and CRF, have been the focus of some of these efforts. However, selective CCK_B receptor antagonists, while

initially promising in preclinical models of anxiety, have been disappointing clinical anxiolytics, partly due to their poor bioavailability (Goddard et al. 1998). A recently discovered class of hypothalamic peptide hormones, the orexins (ORX), has been implicated in anxiogenesis in some animal fear models. Preclinical studies (Johnson et al. in press) suggest that ORX neurons are more active during lactate-induced panic in panic-prone rats (with GABA deficits in the dorsomedial hypothalamus), and that ORX 1 antagonists can block lactate panic in these animals. Thus, orexin antagonists appear to be a promising class of anxiolytics, with particular relevance for the treatment of PD. In addition, Neuropeptide S plays an important role in sleep–wake cycles and also seems to have anxiolytic effects as well (Reinscheid 2008), but the mechanism is not known and much more work is needed to elucidate the details of this curious neurotransmitter.

With respect to the GABA system, there has been an extensive drug development effort focusing on benzodiazepine receptor partial agonists such as bretazenil and abecarnil (Pollack et al. 1997). The development of compounds that act similarly to endogenous anxiolytic neurosteroids (e.g., allopregnenolone) is another approach to GABA neuronal modulation that could provide future clinical benefits. Outcomes of clinical trials using GABAergic agents have been equivocal. Recent research has turned to better understanding the role of GABA and found effects on neuroactive steroid concentrations possibly related to changes in corticosterone concentrations (Zwanzger et al. 2009). GABA enhancement with the gabapentin-like agent, pregabalin, which appears to be more bioavailable than its predecessor, may prove useful across anxiety disorders (Rupprecht et al. 2009). More recently, there have been exciting drug development initiatives underway with compounds that downmodulate glutamatergic function. One group of such compounds, the metabotropic glutamate receptor agonists, seems particularly promising as anxiolytic. An example of this class is the selective mGlu2/3 receptor agonist (LY345740), which suppresses fear-potentiated startle and lactate-induced panic (Selak 2001) in animals. Recent testing in clinical populations (panic patients) has revealed that it has the capacity to attenuate CO_2-induced panic symptoms with chronic administration and thus could have clinical utility (Shekhar and Keim 2000). This drug inhibits release of endogenous glutamate via a presynaptic mechanism only when excessive glutamate release occurs, and thus has little impact on basal glutamatergic function. Newer generation compounds based on this prototype, with improved bioavailability and CNS penetration, are ready for clinical testing.

7.2 New Treatment Strategies

Augmentation strategies could be useful in terms of hastening clinical response to standard medications such as the SSRIs. For example, early co-administration of the benzodiazepine clonazepam with SSRIs (Goddard et al. 2001) can facilitate rapid stabilization of acute PD and may be a useful approach for other anxiety disorders. Coadministration of the 5-HT_{1A} antagonist, pindolol, has hastened the

onset of antidepressant effects of the SSRIs in some studies of depressed patients. This strategy, although not successful in one study of social anxiety (Schmitt and Hiemke 1999), bears exploration in other anxiety disorders. There is now preliminary evidence that the β-blocker propranolol could be a useful secondary preventive strategy for civilian trauma (Stein et al. 2001). Atypical neuroleptic agents may be useful adjunctive agents for the more severe anxiety disorders, such as chronic PTSD (Pitman et al. 2002; Stein et al. 2002). Alternatively, other treatment approaches are focusing on the neural mechanisms that may switch off or extinguish fear responses. For instance, in a recent animal study, acute administration of the anti-TB agent D-cycloserine, a partial NMDA/glycine site agonist, facilitated extinction of conditioned fear (Walker et al. 2002). It is conceivable that targeted use of this agent in combination with cognitive–behavior therapy will improve extinction of a variety of phobic disorders (Otto et al. in press).

8 Conclusions

The last three decades have seen substantial progress in the diagnosis and treatment of anxiety disorders. However, the production of an ideal anxiolytic with a rapid onset of therapeutic action minus problems of physiological dependence has remained a somewhat elusive goal. While benzodiazepines and tricyclics remain useful therapeutic agents for a number of anxiety disorders, they have been supplanted as first-line treatments by the newer 5-HT/NE anxiolytics such as the SSRIs, and the SNRI venlafaxine, which offer improved safety, a more favorable side-effect profile, and a broader spectrum of therapeutic action. PD is very responsive to a range of anxiolytic agents, including SSRIs, tricyclics, benzodiazepines, and MAOIs, and some GABAergic anticonvulsants. To date, much has been learned about short-term efficacy of the anxiolytics mentioned earlier. However, given the chronic course of many anxiety disorders, future research needs to answer many questions concerning longer-term aspects of treatment. Knowledge concerning the pathophysiology of PD and treatment mechanisms has developed considerably over the last two decades. There is renewed interest in the neural circuitry that subserves adaptive fear responses and the ways in which disturbances in this circuitry could contribute to the pathophysiology of PD (Krystal et al. 2001). Not surprisingly, drug development research is focusing on novel anxiolytics that target dysfunction at different levels of the fear circuit.

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