

Current Pharmacological and Non-Pharmacological Treatments of Panic Disorder/Agoraphobia

Review Article

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Abstract

Anxiety disorders represent the most prevalent psychiatric disorders, however, many patients who might benefit from treatment are not diagnosed or treated. This may partly be due to lack of awareness of the anxiety disorders by primary care practitioners and by the sufferers themselves. In addition, the stigma still associated with psychiatric disorders and lack of confidence in psychiatric treatments are factors leading to no/under recognition and treatment, or the use of unnecessary or inappropriate treatments. This paper aims to provide a comprehensive review of the pharmacological treatment of panic disorders (PD).

The first-line treatments include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Tricyclic antidepressants (TCAs) are similarly effective, but are less well tolerated than the SSRIs/SNRIs. In treatment-resistant cases, benzodiazepines like alprazolam may be used in patients with no history of dependency and tolerance. Other treatment options include irreversible and reversible monoamine-oxidase inhibitors, hydroxyzine, and others. Atypical antipsychotics may also be effective in resistant cases.

Besides pharmacological treatments, some psychological strategies have been shown to be effective, in particular, cognitive behavior therapy (CBT) and other variants of behavior therapy have been sufficiently investigated in controlled studies, and, therefore, will be reviewed herein.

Keywords: Panic Disorder; Tricyclic Antidepressants; Selective Serotonin Re-uptake Inhibitors; Benzodiazepines; Non-Pharmacological Treatment.

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Introduction

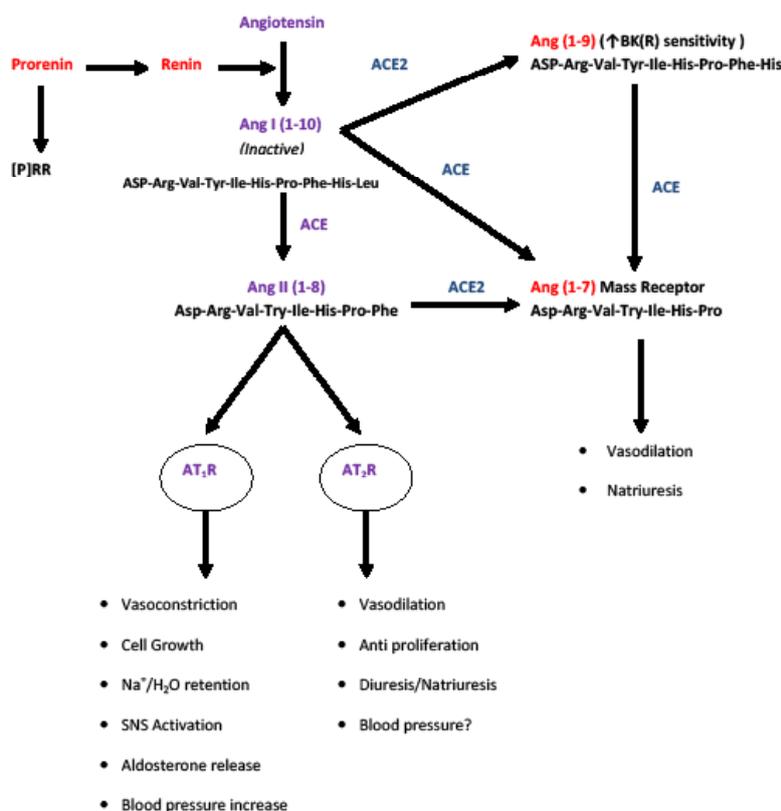
Panic disorder (PD) is one of the most common anxiety disorders, with a lifetime prevalence of about 5% in the general population and up to 8.3% in clinical settings, and is still associated with relevant impairment of the quality of life [1]. Despite this, there have been only few therapeutic advances in the past years and several critical issues remain open. PD is a heterogeneous psychiatric condition characterized by a discrete period of intense fear or discomfort in the absence of real danger that is accompanied by somatic or cognitive symptoms. The attack has

a sudden onset and builds to a peak rapidly, generally in 10 minutes or less, and is accompanied by a sense of imminent danger or impending doom and an urge to escape. The anxiety of PD is different from generalized anxiety, in fact the first is discrete, paroxysmal and severe [2]. The disorder is characterized by repeated unexpected panic attacks, persistent anticipatory anxiety and behavioral modification as a direct result of the attacks. A lot of patients show also agoraphobia, often associated with situational panic attacks. PD pathophysiology is still unclear and several potential mechanisms may be involved. Instability of respiratory regulation and/or an abnormally sensitive central neural network of CO₂/H⁺ chemoreception has been implicated both in experimentally induced panic attacks by CO₂ inhalation and lactate infusions and in spontaneous panic [3,4]. Crucial advances might be made if panic attacks could be evoked in the laboratory so that the underlying mechanisms might be deconstructed. PD is relatively unique among psychiatric illnesses, in that symptoms resembling the illness can be provoked by a number of chemicals called panicogens. Moreover, the biological mechanisms of the panicogens themselves might tell us a lot about the neurobiology of the illness. Examples of agents with the potential ability to evoke panic attacks include carbon dioxide (CO₂), sodium lactate, doxapram, cholecystokinin (CCK-4) and related agonists, flumazenil, caffeine, adrenergic agonists (isoproterenol, yohimbine, epinephrine), serotonin receptor activators (d-fenfluramine, metachlorophenylpiperazine (m-CPP), and perhaps opioid receptor antagonists. The symptoms provoked by these agents can closely resemble naturally occurring attacks [5]. Other mechanisms have been implicating in PD pathophysiology: the inappropriate activation of a central fear network, including the amygdala and its connections with hippocampus, thalamus, hypothalamus as well

as the periaqueductal gray region, locus coeruleus and prefrontal cortex; this could result in misinterpretation of sensory harmless information and conditioning processes, leading to panic attacks, anticipatory anxiety and phobic avoidance [6]. Several neurotransmitters play a crucial role in modulating these processes, acting in different CNS areas and influencing each other, and till now the mechanisms of action of the existing anti-panic drugs are not completely understood [7]. In addition, studies have consistently shown that genetic factors explain about half of the variance. The most cases of PD have a complex genetic basis. Several data suggest, however, that the genetic architecture underlying PD is heterogeneous and differs between cases. For example, the degree of genetic complexity, and the pattern of genes involved might differ in familial versus non-familial cases, in early- versus late-onset cases, or when different comorbid conditions, gender and potential intermediate or sub-phenotypes are considered. At the molecular genetic level, linkage and association studies-the latter including traditional candidate gene and recent genome-wide studies-have been used to study PD. Although no molecular genetic findings have emerged so far, it is conceivable that the first PD susceptibility genes will be identified in the future. Such findings could have a major impact on our understanding of the pathophysiology of this disorder, and would provide important opportunities to investigate genotype-phenotype correlations, as well as the interaction between genetic and environmental factors involved in the pathogenesis of PD [8]. PD is a condition characterized by recurring severe panic attacks. These attacks typically last about 10-15 minutes, but can be as short-lived as 1-5 minutes and last as long as 30 minutes or until medical intervention. However, attacks can wax and wane for a period of hours (panic attacks rolling into one another), and the intensity and specific symptoms of panic may vary over the duration. Common symptoms of an attack include rapid heartbeat, perspiration, dizziness, dyspnea, trembling, uncontrollable fear and hyperventilation. Other symptoms are sweating, shortness of breath, sensation of choking, chest pain, nausea, numbness or tingling, chills or hot

flashes, and some sense of altered reality. In addition, the patients usually have some thoughts of impending doom. Panic attack can be unexpected (spontaneous) or associated with a situational triggers that can include internal (e.g., physiological arousal) or external (e.g., a phobic object or situation) stimuli to the subject. The patients fear the implication or consequences of the panic attacks, the presence of an undiagnosed or severe illness, to become crazy, to lose the control. Individuals suffering from an episode have often a strong wish of escaping from the situation that provoked the attack. It may also include significant behavioral change lasting at least a month and of ongoing worries about the implications or concerns about developing other attacks. The frequency and the severity of the panic attacks is variable. Some patients show a course characterized by attacks that occur regularly once a week, others more frequent attacks (daily) separate by weeks or months without any episode or with less frequent attacks over many years. PD is a chronic and debilitating condition associated with a high rate of relapse and co-morbidity, including other anxiety and affective disorders, suicide attempts, abuse of psychoactive substances and cardiovascular diseases [9]. Between 20 and 40% of patients with PD do not fully respond to pharmacotherapy, although when recommended medications are used and the doses and the length of treatment are adequate. Similarly, 30-40% of patients with PD and agoraphobia do not achieve significant improvement with cognitive behavioral therapy (CBT) and so far the combination of CBT and pharmacotherapy does not appear to fill this gap [10]. In addition, 25-50%, of patients relapse within 6 months after drug discontinuation and up to 40-50% of subjects still have residual panic-phobic symptoms and up to 20-30% still have full-blown disorder after 3-6 years; finally, the maintenance of benefit following therapy discontinuation appears to be more influenced by the attainment of a complete remission before interruption than the duration of treatment, underscoring the relevance of maximizing improvement obtained from initial pharmacotherapy [11]. When severe, these symptoms can be debilitating, par-

Figure 1: Schematic presentation of renin angiotensin system



ticularly for the large number of patients who are refractory to current therapies. Identifying new therapies may require understanding of why panic attacks occur and what triggers them, knowledge that is currently lacking. The present paper aims to present a comprehensive review of those pharmacological and non-pharmacological strategies most often adopted in PD, focusing especially on those pharmacological treatments which appear most promising.

Pharmacological treatments

Tricyclic Antidepressants (TCAs)

It has been widely demonstrated that PD may symptoms may improve with TCAs, in particular with imipramine and clomipramine. In any case, adverse events are reported more frequently than with the SSRIs, so that these latter are now the first-line drugs for the treatment of PD [12-18].

Imipramine

Imipramine resulted effective in PD since some decades ago [19-21] in double-blind, placebo controlled and in comparator-controlled studies [22-25]. It was more effective than placebo and equally effective as alprazolam in one relapse-prevention study (acute study over 8 weeks, followed by up to 35 weeks relapse-prevention) [26]. In another trial, it was as effective as alprazolam for 8 weeks, but less effective than alprazolam in a 26-week double-blind, placebo controlled extension [27]. In a 26-week long-term study, it was seen to be as effective as fluoxetine [12].

Clomipramine

Clomipramine demonstrated a similar efficacy of imipramine in double-blind, placebo controlled [28,29] and in comparator-controlled studies [18,30-33]. It was as effective as the SSRI paroxetine in a relapse-prevention trial performed over 36 weeks [16].

Selective Serotonin Reuptake Inhibitors (SSRIs)

In several controlled studies, SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram) have been shown to be significantly effective in PD, and are currently considered as the first-line drugs for the treatment of this disorder. Single compounds will be reviewed separately, as follows.

Fluoxetine

Fluoxetine showed efficacy in The Fluoxetine Panic Disorder Study Group [34,35], as well as in comparator-controlled trials [15,36]. It proved as effective as imipramine in one 26-week long-term study [12]. It was also seen to be as effective as the RIMA moclobemide in a 52-week long-term study [37].

Fluvoxamine

Fluvoxamine was shown to be effective in a number of The Fluvoxamine Panic Disorder Study Group [38-43]. In one study, fluvoxamine and the comparator imipramine proved equally effective, and both were seen to be more effective than placebo [13]. No superiority over placebo was demonstrated on the main efficacy measure in one small study, although it was seen on some other instruments [44]. In another study, fluvoxamine showed no efficacy, at variance with imipramine [23].

Paroxetine

Paroxetine demonstrated efficacy both in double-blind, placebo controlled trials [45-48] and in comparator-controlled studies [14,32,46,49-51]. It also proved as effective as clomipramine in a 36-week relapse-prevention trial [16].

Sertraline

Sertraline was shown to be effective in double-blind, placebo controlled studies [52-54], as well as in one comparator trial [49]. Sertraline was superior than placebo in a relapse-prevention study carried out over 26 weeks and followed by an open fashion over 1 year [55]. In another relapse-prevention study responders after 8-weeks of controlled study were randomized to sertraline or placebo. Except for the relapse rate, sertraline was better than placebo on most measures [56]. Sertraline was superior to placebo and as effective as imipramine in patients with panic disorder and comorbid depression in a 26-week long-term study [57].

Citalopram

Citalopram was effective in a placebo- and comparator-controlled trial [18], and in one comparison with fluoxetine [36]. It was shown to be superior to placebo and as effective as the clomipramine in a relapse-prevention study carried out over 52 weeks [17]. It was also shown to be as effective as fluoxetine in a long-term study in which a double-blind treatment was performed for 24 weeks followed by an open extension of another 26 weeks [36].

Escitalopram

Escitalopram resulted to be effective in a citalopram- and placebo-controlled trial [58,59]. Because escitalopram is the S-enantiomer of the racemate citalopram, it may be that the clinical studies with citalopram are also relevant for escitalopram.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Venlafaxine

The SNRI venlafaxine was shown to be effective in double-blind, placebo controlled studies [60,61]. In several trials, an association was detected with a lower frequency of mean panic attack, with a higher proportion of subjects free of symptoms, with higher response and remission rates. Venlafaxine was also shown to be more effective than placebo and equally effective as the comparator drug paroxetine in two studies [50,62]. In one relapse-prevention study, 12 weeks of open treatment with venlafaxine were followed by 26 weeks of double-blind, placebo controlled treatment [63], and the drug proved more effective than placebo in preventing relapses. The new formulation slow-release venlafaxine is potentially promising, but no

Benzodiazepines (BDZs)

In a number of controlled clinical studies, BDZs have demonstrated effectiveness in PD

Alprazolam

Alprazolam was equal in effect to comparator drugs and superior to

placebo in several studies [22,25,64-67]. In one relapse-prevention study featuring 8 weeks acute study followed by relapse-prevention of up to 35 weeks, it resulted to be more effective than placebo and just as effective as imipramine [26]. Another relapse-prevention study saw it equally as effective as imipramine in an 8-week acute DBPC study, and superior in effect to imipramine in a 26-week The Fluoxetine Panic Disorder Study Group extension [27].

Clonazepam

Clonazepam demonstrated effectiveness in the Clonazepam Panic Disorder Dose-Response Study Group [68-71] as well as in one placebo- and comparator-controlled trial [72].

Lorazepam

Lorazepam resulted as effective as equally effective as alprazolam in a few studies [73,74].

Diazepam

Diazepam was more effective than placebo and similar to alprazolam in two studies [67,75].

Generally BDZs are commonly combined with SSRIs, SNRIs or TCAs in the clinical practice mainly in the initial phases. In one study aimed at examining this combination, patients were treated with either paroxetine and clonazepam or with paroxetine and placebo. Paroxetine and clonazepam in combination resulted in a more rapid response with the SSRI alone, although no differential benefit was demonstrated in the next weeks [76]. The combination, of imipramine and alprazolam [77], or of sertraline and clonazepam [78] led to similar findings. However, the use of BDZs, should be limited at the acute phases of PD for the risk of abuse, development of tolerance and onset of severe side effects, as well as withdrawal symptoms.

Monoamine Oxidase Inhibitors (MAOI)

Although phenelzine is widely used in PD, the evidence is only based on a single study [79] showing that it was more effective than placebo and equal to, or even superior to (according to some measures), imipramine.

Other medications

Some available drugs have shown some preliminary evidence of effectiveness or have given mixed results. These drugs are used "off-label" by some practitioners in patients who did not respond to standard treatments. The reversible inhibitor of monoamine oxidase (RIMA), moclobemide, yielded inconsistent results, as it appeared to be effective or not in different trials [37,80-82]. It is available in Canada, but not in US and in other countries. Among its side effects are restlessness, insomnia, dry mouth, and headache. Reboxetine, a norepinephrine reuptake inhibitor (NARI) was shown to be effective in a controlled study [83]. It was as effective as fluvoxamine in single-blind studies [84], but was not effective as paroxetine [85]. Inconsistent data are available for mirtazapine [86], and two anticonvulsants, valproate [87], and gabapentin [88], and bupropion, a norepinephrine-dopamine reuptake inhibitor [89]. The intracellular second-messenger precursor inositol demonstrated superiority compared to placebo in a small DBPC

study [90], and was as effective as the SSRI fluvoxamine [91]. Buspirone demonstrated no superiority to placebo in panic disorder [92,93], and was found less effective than imipramine [92], clorazepate [94], and alprazolam [93]. Beta blockers, such as propranolol, have been employed in the treatment of PD, because they may influence autonomic anxiety symptoms, such as palpitations, tremor, etc, however, their real effectiveness remains to be demonstrated [95,96].

Comparisons of Drugs

No differences could be found between TCAs and SSRIs in studies comparing their efficacy [12-14,18], except for maprotiline, which demonstrated no effect when compared to fluvoxamine [97]. The SSRIs were seen to be better tolerated than the TCAs in most of these studies, although one analysis found no difference regarding tolerability between SSRIs and imipramine [98]. Further, sertraline and imipramine were equally effective in patients with comorbid PD and major depressive disorder, although sertraline demonstrated a significantly greater degree of tolerability and compliance than did imipramine [57]. Some studies which compared SSRIs revealed no differences regarding their efficacy [46,99], while on some outcome measures escitalopram showed evidence of superiority over citalopram [58]. In the treatment of PD there are no direct comparisons between SSRIs and BDZs. A meta-analysis showed that the amplitude of the effect was greater for SSRIs than for alprazolam [100]. Several studies compared alprazolam with imipramine but no differences were found between the two drugs [22,25,64,101-104].

Refractory PD

Only a few studies have been performed with treatment-resistant PD patients. The only existing preliminary controlled study demonstrated an augmenting effect of pindolol on fluoxetine in patients with treatment-resistant panic disorder [105]. When an initial treatment fails, patients should first be switched to other first-line standard treatments, e.g. from an SSRI to an SNRI or viceversa. Because the SSRIs are chemically different compounds, a switch from one SSRI to another can be justified [106]. The next step should be the use of second-line drugs, such as TCAs. Finally, drugs or drug combinations which showed efficacy in open studies and case reports may be an option. In one study in which there was no control condition, patients presenting residual symptoms despite treatment with a sufficient dose of medication showed improvement following the introduction of CBT [107,108]. Conversely, patients in whom an insufficient response to CBT was seen can show improvement with SSRIs or clomipramine [109,110].

Non-Pharmacological Treatment

Amongst non-pharmacological treatments, cognitive behavioral therapy (CBT) has been investigated thoroughly in PD. Agoraphobia is generally treated with exposure therapy and cognitive therapy, including interoceptive exposure was developed for the treatment of spontaneous panic attacks [111,112]. In the majority of the studies on PD and/or agoraphobia, CBT resulted superior to waiting-list control condition [113-121]. Several trials reported the superiority of CBT to a pill placebo or a psychological- placebo [112,115,122-127], while others detected no difference to the control condition [14,39,128-130]. Three studies comparing CBT or exposure therapy with psychopharmacological treatment, reported drugs to be superior than

other strategies [14,39,128]. However, controversial data are also available [112,114,125,131-134]. In any case, the combination of CBT+drug has proven to be more effective than psychological therapy alone in most studies [20,21,40,46,112,122,128,133,135,136], except that in two [125,132]. The combination of CBT or psychodynamic treatment with a drug was seen to be superior to drug alone in two studies [137,138], while in three studies no difference was found between the combination and CBT alone [122,125,132]. Several meta-analyses regarding the efficacy of the psychological and pharmacological treatment of anxiety disorders have yielded contradictory results [139-149]. Such inconsistent results seem, for the most part, to stem from the inclusion of heterogeneous studies and the influence of selection biases. A recent and accurate meta-analysis highlighted the efficacy of the combination [150].

Psychodynamic therapies

Only a limited number of studies have evaluated psychodynamic psychotherapy or other forms of psychotherapies in PD, so that no conclusion can be drawn on the effectiveness of these strategies [151-153].

Conclusions

Drugs used in PD include TCAs SSRIs, SNRIs, BDZs, and MAOI [154,155]. SSRIs affect mainly the serotonergic system, while SNRIs and some TCAs modulate both serotonergic and noradrenergic activities, BDZs affect the GABA system, and some of these drugs may have secondary effects also on other neurotransmitters. The effectiveness of these drugs is due to their effects on several brain pathways potentially involved in pathophysiology of PD including areas of the brain involved in control of ventilation and acid–base balance and in emotional responses, arousal and defensive behaviors, including brainstem respiratory network, the nucleus tractus solitarius, the medullary and midbrain raphe neurons, the amygdala and the hypothalamus, both having CO₂/H⁺ sensitive neurons, and the periaqueductal gray [156]. Despite the wide variety of drugs available, some patients show a partial response, or frequent relapses or even they are refractory. The drugs for PD do not obtain full clinical responses in all of the treated patients and it is still unclear if the more recent compounds with dual mechanisms of action on serotonergic and noradrenergic systems will be able to increase significantly the clinical response. Because serotonin, noradrenaline and GABA act as parts of a complex network including other neurotransmitters and multiple levels of modulation, it has been hypothesized that compounds having new mechanisms of action and/or acting simultaneously on a broader group of neurotransmitters may better respond to the medical needs of patients with PD. Future research for the treatment of PD are focusing on the development of new compounds with novel mechanisms of action and, the potential efficacy of existing drugs, already used for treatment of other psychiatric disorders, with different pharmacodynamic profiles compared to standard drugs for PD. For example glutamate is the excitatory neurotransmitter in the mammalian brain and the modulation of glutamatergic excitatory amino-acid transmission potentially represents a new approach to treat a number of neurological and psychiatric conditions, including PD [157]. The metabotropic glutamate receptors (mGlu) are a novel class of receptors under investigation that modulate glutamatergic neurotransmission by regulating the glutamate release at presynaptic sites or neuronal excitability at postsynaptic sites, and they are localized in the cortex, hippocampus, limbic areas, brainstem and cerebellar regions, suggesting their implication in anxiety respons-

es, emotions and cognition in animal and humans [158]. Preclinical studies showed mGlu receptor agonists may have potential clinical utility in modulating different phenomena in PD, including panic attacks and phobic conditions, with a favorable side effect profile. Recent and scattered data suggest that other intervention possibilities may be associated with modulation of second messengers and opioids. This has led to the proposal of new compounds, in particular inositol, D-cycloserine, riluzole, memantine and morphine, with these demonstrating a certain degree of effectiveness. The pharmacological research on PD appears to be relatively limited, in fact clinical pictures of PD is heterogeneous, but, in clinical trials patients with PD are classified only according to current descriptive nosographical criteria and are considered as a homogeneous group. Moreover trials were performed involving only small patient populations, and have mostly been open-label, so that the ensuing findings should be viewed as preliminary. Similarly, the effectiveness of non-pharmacological strategies remains to be demonstrated, except that for CBT that it is now recognized as a first-line treatment in OCD by several guidelines. However, only a deeper understanding of the biological mechanisms underlying anxiety might permit the development of more targeted and effective compounds beyond the 5-HT system.

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