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ARTICLE

The psychological development of panic disorder: implications for neurobiology and treatment

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Abstract
Objectives: The aim of this study was to survey the available literature on psychological development of panic disorder with or without agoraphobia [PD(A)] and its relationship with the neurobiology and the treatment of panic. *Methods:* Both a computerized (PubMed) and a manual search of the literature were performed. Only English papers published in peer-reviewed journals and referring to PD(A) as defined by the diagnostic classifications of the American Psychiatric Association or of the World Health Organization were included. *Conclusions:* A staging model of panic exists and is applicable in clinical practice. In a substantial proportion of patients with PD(A), a prodromal phase and, despite successful treatment, residual symptoms can be identified. Both prodromes and residual symptoms allow the monitoring of disorder evolution during recovery via the rollback phenomenon. The different stages of the disorder, as well as the steps of the rollback, have a correspondence in the neurobiology and in the treatment of panic. However, the treatment implications of the longitudinal model of PD(A) are not endorsed, and adequate interventions of enduring effects are missing.

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Introduction

The current emphasis of psychiatry is on cross-sectional assessment of symptoms, resulting in diagnostic criteria and comorbidity identification. The latter may be identified by both the co-occurrence of Axis I psychiatric disorders and association of Axis I and II disturbances. The use of diagnostic criteria is derived from the traditional method of clinical medicine, in which they provide operating specifications for making a clinical decision about the existence of a particular disease.[1] However, clinicians usually also evaluate issues in their daily practice that do not pertain only to the severity of the disorder, such as its longitudinal development; social support and adaptation; resilience and reaction to previous conflicts, threats or losses; motivation and treatment compliance; pre-morbid personality and potential abnormal personality traits.

Over the time, a clinical reasoning which goes through a series of "transfer stations,"[2] where potential connections between presenting symptoms and pathophysiological processes are drawn and which are amenable to longitudinal verification and modification as long as therapeutic goals are achieved,[3] has been proposed. Nevertheless, a lack of attention to the longitudinal development of the disorders has been maintained and apparently has deprived the clinical process of a number of important "transfer stations".

The father of this innovative and emerging staging approach for assessment was Feinstein who introduced the term "clinimetrics" in 1987 to indicate a field concerned with indices, rating scales, and other expressions used to describe or measure symptoms, physical signs, and other distinctly clinical phenomena in medicine. Further, the purpose of the science of clinimetrics has been to provide a domain for a number of clinical phenomena which do not find room in customary clinical taxonomy, such as types, severity, and sequence of symptoms; rate of progression in illness (staging); severity of comorbidity; problems of functional capacity; reasons for medical decision; and other aspects of daily life, such as well-being and distress.[1,4,5] In recent years, Fava et al.[6] have shown several examples of this approach in reviews of research on mood disorders and anxiety.

Although current diagnostic entities (i.e., the Diagnostic and Statistical Manual of Mental Disorders - DSM) are based on clinimetric principles, their use is still strongly influenced by psychometric models.[3,7-9] This means that the severity of each disorder is determined by the number of symptoms rather than its intensity or quality, just as scoring on a self-rating scale depends on the number of symptoms scored as positive.[7-10] As a consequence, the preferential target of therapy tends to become the syndromes resulting from a certain number of symptoms (which may be of mild intensity and of doubtful impact on quality of life), instead of individual symptoms that may be incapacitating for the patient.[3] Moreover, clinicians may find some difficulties in formulating a treatment plan for people who, for instance, do not reach the known diagnostic threshold since it might be difficult to answer to questions such as: Should these symptoms the patient is complaining about be addressed for treatment? Should the conditions be addressed in an integrated way and, if so, whose responsibility is it to design and deliver such treatment?

Methods

A computerized search was carried out (PUBMED 1960-2012) using the key words: "staging/subclinical symptoms/prodromes/residual symptoms and panic", "neurobiology and staging/subclinical symptoms/prodromes/residual symptoms and panic", "treatment/subclinical symptoms/prodromes/residual symptoms and staging and panic". In addition, the reference lists from existing reviews and from the articles retrieved were inspected. Only English language papers published in peer-reviewed journals were included.

The following inclusion criterion was applied: the diagnosis of panic disorder (PD) with or without agoraphobia had to be made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Third Edition, Revised, Fourth Edition, or Fourth Edition, Text Revision) or the International Classification of Diseases (ICD) (Ninth or Tenth Edition).

In order to work with an approach as conservative as possible, non-significant results or trends only were reported as "no difference".

Discussion

The staging model of panic disorder

In 1993, Fava et al.[11] proposed to use in psychiatry a staging method that allows to characterize a disorder according to seriousness, extension, features, and longitudinal development following standardized and well defined models. They published a seminal paper suggesting a staging model for schizophrenia, mood, and PD. The core concept was that these psychiatric disorders develop according to main stages. The first stage usually involves the presence of predisposing factors (e.g., genetic vulnerabilities, pre-morbid personality, lack of psychological well-being); the second is characterized by the acute symptoms; the third includes the residual symptoms; the fourth implies sub-chronic symptoms; and the fifth, when present, is characterized by the chronic illness.

Regarding panic disorder, they described a staging model suggesting that, in a substantial proportion of patients, agoraphobia, hypochondriacal fears and beliefs, and generalized anxiety precede the first panic attack. This 4-stage model is consistent with symptomatic patterns of improvement upon behavioral PD treatment as well as with the rollback phenomenon upon drug treatment. However, since, at least in some patients, the first panic attack can apparently occur without conspicuous prodromal symptoms, while anticipatory anxiety, phobic avoidance, and hypochondriasis may develop subsequently, Sheehan and Sheehan outlined a different staging process: stage 1 (subpanic) characterized by panic attacks with limited symptoms; stage 2 (panic); stage 3 (hypochondriasis); stage 4 (single phobia, that is the setting in which panic occurs); stage 5 (social phobia); stage 6 (agoraphobia); stage 7 (depression).[12]

Over the time, the staging models of bipolar disorder, unipolar depression, and schizophrenia have been largely discussed and refined. An updated staging model of panic has also been described (for details see Table 1).[13] In this 4-stage model, the first stage is represented by the presence of predisposing factors, such as genetic vulnerability, premorbid personality, anxiety sensitivity, hypochondriacal fears and beliefs, impaired psychological well-being. The

Table 1 Stages of agoraphobia according to Fava et al.[13]

	Stages
1	Pre-agoraphobia. Presence of anxiety (including health anxiety and anxiety sensitivity) and/or isolated fears and/or personality factors such as dependence and harm avoidance and/or impaired psychological well-being.
2	Agoraphobia. Fear of being in places or situations from which escape might be difficult, of mild (some avoidance or endurance with distress but relatively normal lifestyle) or moderate (constricted lifestyle) severity according to DSM-IV criteria.
3	Panic disorder (acute phase). Appearance of panic attacks and development of panic disorder (DSM-IV). Worsening of agoraphobia and anxiety. Health anxiety may turn into hypochondriasis and/or disease phobia and/or thanatophobia. Demoralization and/or major depression may occur.
4	Panic disorder (chronic phase). Agoraphobia may become severe (avoidance results in being nearly or completely housebound) according to DSM-IV, and hypochondriacal fears and beliefs may become accentuated, when panic disorder exceeds 6 months. Increased liability to major depression.

relative weight of these factors may vary from patient to patient and lead to subtle avoidance patterns and ultimately to agoraphobia (stage 2). Thus, panic attacks start and are likely to induce a considerable worsening of prodromal symptomatology (stage 3). The duration of Panic Disorder with Agoraphobia (PDA) can predispose to the development of other psychiatric complications, notably depression (stage 4). Stressful life event can play a role in the development of panic or secondary depression.

This staging method may be applied also to generalized anxiety disorder and social phobia, thus Fava et al.[13] suggested to consider the onset of panic disorder as a stage of development of anxiety disorders and hypochondriasis, instead of a specific disease. This may increase the clinicians' diagnostic sharpness and substitute undifferentiated treatments with stage-guided therapeutic tools. A confirmation of such view comes from Kessler et al.[14] who found that isolated panic attacks are quite common and significantly comorbid with other DSM-IV disorders but the vast majority of people with isolated panic attacks fail to meet PD criteria.

A growing literature has supported the existence of the above mentioned clinical stages in the longitudinal development of panic.

Roy-Byrne et al.[15] reviewed 16 studies, each including at least 25 patients observed over a minimum follow-up period of one year, and found that, despite the availability of effective anti-panic treatments, panic disorder remains a chronic illness – although most patients improved, only few were "cured." The presence of agoraphobia, major depression, and personality disorder seemed to predict a poor outcome.

In the general population of the Epidemiologic Catchment Area study, the prodromal period was shown to be about 10-15 years long. Panic attacks occurring in the year before the first interview as well as the perception that one is a "nervous person" were strong predictors of the onset of PD.[16]

In 126 patients with a diagnosis of PD or PDA, Perugi et al.[17] found that characterological and prodromal antecedents represent a putative phobic-anxious temperamental substrate occurring in at least 30% of the sample. These temperament antecedents consisted of increased sympathetic activity with repeated sporadic and isolated autonomic manifestations; marked fear of illness; hypersensitivity to separation; difficulty to leave familiar surroundings; marked need for reassurance; oversensitivity to drugs and substances.

In a study of 71 PD and 323 PDA patients, subjects with PD at 1-year after study inclusion had a 0.68 probability of reaching a condition of "panic-free interval" for 8 consecutive weeks compared with a 0.36 probability of having had "full remission". In addition, the probability of having a panic-free interval by 12 months was 0.68 for subjects with PD and 0.55 for those with PDA. The odds for a panic-free interval were found to be 1.4 times greater for the PD subjects than for the PDA ones.[18]

Faravelli et al.[19] evaluated 84 PD cases for more than 12 months, 81 for 24 months, 78 for 36 months, and 76 for more than 60 months and observed a probability of achieving recovery only in 25.6% of the subjects at the end of the first year and 31.3%, 33.8%, 36.3%, and 37.5% by the end of years 2, 3, 4, and 5, respectively. Among the 99 patients followed for more than 12 months, 12 showed complete and long-lasting remission of any symptoms and 47 satisfied the criteria for improvement. Of these, 9 cases had a positive outcome followed by a single recurrence considered mild; 15 showed persistence of one single mild symptom; 23 had more than one recurrence but maintained well-being for more than 80% of the time; 11 had a recurrent pattern with well-being lasting for between 40% and 80% of the time; 29 patients had a poor outcome; 22 never met the criteria for amelioration or good response; whereas 7 had recurrences that lasted for more than 60% of the time. The only independent predictor of poor outcome was a greater duration of illness. In particular, patients having a shorter duration of illness most frequently experienced recovery or improvement.

In a sample of 45 patients with current panic disorder with or without agoraphobia [PD(A)], 20 remitted patients with a lifetime diagnosis of PD who had been panic-free for at least 6 months, 50 individuals with infrequent panic attacks, 27 with simple phobias, and 46 normal controls, Ehlers found that a significant proportion of patients who had initially been in remission (41%) reported panic attacks during follow-up. Treated patients who continued to suffer from PD had initially shown more depression, avoidance, and greater cardiac awareness than patients who had fewer attacks and did not worry about them for at least one month. Similarly, initially remitted patients who re-experienced panic attacks had better heartbeat perception and more avoidance than those who stayed in remission. For untreated PD patients, trait anxiety and anxiety sensitivity distinguished those with and without panic disorder at follow-up.[20]

O'Rourke et al.[21] almost confirmed the above results observing that during a six month period of follow up, 70.6% of the PD patients evaluated sustained their initial recoveries or continued to improve and 20% had persistent panic disorder symptoms. At 12 month follow-up, 23 (33.8%) had recovered and remained well, 12 reported relapses and remissions, 19 had improved, but short of full recovery, and 14 had persistent panic disorder, of whom half remained severely impaired. The strongest predictor of sustained recovery was

good clinical status between 6 and 12 months from baseline, while personality dysfunction was the most important characteristic of patients with persistent PD.

Over a 15-60 month period of follow up, Cowley et al.[22] found that only 10% of the PD patients were asymptomatic. Thirty percent were panic-free at 12 months and 28% at the time of follow-up, with 43% experiencing at least three panic-free months during the follow-up period. The strongest predictors of overall improvement were avoidance coping for outcome at 12 months and Axis I comorbidity for outcome at the time of the follow-up evaluation.

One hundred thirty two PDA patients were treated in an out-patient clinic with behavioral methods based on exposure homework and followed for a median period of 8 years (minimum 2, maximum 14 years). Twenty-three per cent of them had a relapse, and the estimated cumulative percentage of patients remaining in remission was 93.1 for at least 2 years, 82.4 after 5 years, 78.8 after 7 years, and 62.1 after 10 years. The presence of a personality disorder was associated with a worse prognosis, as well as the pretreatment level of depressed mood. Another risk factor for outcome was concerned with the level of residual agoraphobia: patients who completely overcame agoraphobic avoidance had a better outcome. Two additional risk factors involved the use of psychotropic drugs. Patients who were still taking benzodiazepines at the end of exposure therapy had a less favorable outcome than those who were drug free. Similarly, patients who used antidepressant drugs before starting behavioral therapy had a worse outcome than those who did not take them.[23]

Subclinical symptomatology

The staging model also allows the identification of symptoms that, in clinical medicine, are defined as subclinical. They consist of prodromes; residual symptomatology; and subclinical fluctuations in chronic disorders. Prodromes can be identified with the early symptoms and signs of a disease. The prodromal phase connotes a time interval between the onset of prodromal symptoms and the onset of the characteristic manifestations of the fully developed illness. Residual symptoms have been identified with the persistent symptoms and signs despite apparent remission or recovery. Finally, in any chronic and recurring medical illness, subclinical fluctuations, both in terms of symptomatology and laboratory markers, may occur.[24]

Detre et al.[25] provided a model for relating prodromal and residual symptomatology in psychiatric illness, defined as the "rollback phenomenon": as the illness remits, it progressively recapitulates, even though in a reverse order to the many stages and symptoms that were seen during the time it developed.[24,25] According to the rollback model, there is also a temporal relationship between the time of development of a disorder and the duration of the phase of recovery. Moreover, there appears to be a relationship between residual and prodromal symptomatology, as certain prodromal symptoms may persist and progress to become prodromes of relapse.

Fava et al.[24,26,27] reviewed the literature on the prodromal and residual symptoms of unipolar major depression, bipolar disorder, and panic disorder paving the way for the characterization of the phenomenological development of these illnesses[28] and the application of sequential treatment.[3]

Regarding PDA, Fava et al.[27] reported prodromes from the Klein's model[29] who observed that when patients are suddenly struck by the first panic attack, they develop persistent anticipatory anxiety and hypochondriacal fears, leading to avoidant behaviour and agoraphobia. This view has been supported over time.[17,30-32] However, different sequences of events have also been observed. For instance, Wittchen et al.,[32] although stating that the occurrence of PD significantly increases the odds of developing agoraphobia, also pointed out that 45.1% of individuals at risk with PD and 76.5% of those at risk for panic attacks did not develop agoraphobia (AG). In 2010, Wittchen and colleagues further strengthen these results observing that there is no empirical evidence which unequivocally demonstrates that agoraphobia is temporally primarily and exclusively a function of panic attack (PA) or has panic-like features. However, the fact that up to 50% of all agoraphobic fail to report or remember such primary PA or panic-like experiences, together with the finding that a substantial number of cases with PA or PD fail to develop agoraphobia, lends considerable support to the notion that agoraphobia emerges for reasons other than or in addition to panic. Thus, agoraphobia is a clinically significant disorder that also exists independently from PD, and even PA and panic-like features, in a substantial number of cases.[33] Moreover, Faravelli et al.[34] re-interviewed 41 subjects with a lifetime history of agoraphobia 4 years after the first evaluation and found that 12 cases had the original diagnosis of agoraphobia without a history of panic attacks and the remaining 29 cases had PDA. Interestingly, at reassessment, 2 patients no longer met the criterion for agoraphobia: one turned into social phobia and the other into specific phobia.

Some authors also found generalized anxiety to be a prodromal of panic;[35] others observed that agoraphobic avoidance, generalized anxiety, hypochondriacal fears and beliefs occur before the first panic attack;[36,37] further works showed that some patients have prodromal depression, anxiety or avoidance.[38]

More recent studies substantially confirmed such observations. In a research on adolescents, Hayward et al.[39] found that major depression, negative affectivity, and anxiety sensitivity predicted the onset of panic attacks. The findings on depression, however, were not confirmed by Karsten et al.[40] who, in the frame of a prospective cohort study with 1,167 participants, found that depression predicted generalized anxiety disorder and social phobia but not panic disorder or agoraphobia. However, the analysis of trajectories for the development of PD in children of PD parents revealed that separation anxiety disorder significantly increased the risk to develop panic.[41] And, in a follow-up study of young women aged between 18 and 24 years for 17 months, Rudaz et al.[42] found that those with a current PDA reported more fear of disease and bodily sensations associated with anxiety than controls. The fear of bodily sensations also differentiated women with current PDA from those with current social phobia, suggesting that, whereas fear of disease is a more general marker of present anxiety disorders, fear of bodily sensations is a more sensitive marker of PDA in particular.

Thus, the most common prodromal symptoms seem to be depressed mood, illness phobia, distress and avoidance of closed spaces, excessive worries, negative affectivity, anxiety sensitivity, health anxiety or fear of disease, separation anxiety.

Since the 90s, panic disorder has been recognized as a chronic illness with little spontaneous improvement, high rates of relapse after remission, and longer episodes when agoraphobia is a part of the constellation of symptoms.[18] Thus, residual symptoms were found to be extremely common and encompassing phobic and anxiety disturbances, social impairment, and dependence.

In interesting brief reports Fava et al.[43,44] assessed psychological well-being and residual symptoms in a sample of 30 patients who had recovered from PDA and 30 control subjects. Remitted patients displayed significantly more psychological distress (anxiety, depression, somatic symptoms) than controls. The most common residual symptoms were generalized anxiety, somatic anxiety, low self-esteem, agoraphobia, and hypochondriasis. Patients with panic disorder also showed less psychological and physical well-being than controls. In particular, regarding psychological well-being, they had difficulty managing everyday affairs, a sense of personal stagnation, a sense of lack of direction, and felt dissatisfied with themselves. Moreover, in the group of patients, residual symptoms were strongly and negatively correlated with psychological well-being.[43] This study shows the evidence of persistence of substantial residual symptomatology in panic disorder, despite successful treatment. It also suggests the need of a multidimensional assessment (including psychological well-being) in determining recovery and paves the way for sequential treatment strategies that may lead to therapeutic efforts of more enduring quality.[44]

On the contrary, Corominas et al.[45] evaluated a clinical sample of 64 PD(A) outpatients comparing those who developed residual symptoms at 1-year of follow-up with those who did not. Surprisingly, the two groups did not differ in terms of achieved improvement measured by the frequency of panic attacks, the degree of avoidant behavior, the depressive symptoms, or the anxious symptoms. Moreover, those who developed residual symptoms differed from those who did not develop residual symptoms in terms of history of anxious disorders in childhood, number of pretreatment panic attacks, presence of depersonalization and derealization symptoms during the panic attacks, global rates of comorbidity, and comorbidity with simple phobia. However, in all these measures, the patients without residual symptoms showed higher rates. In addition, the assessment of personality traits showed that those patients with residual symptoms at 1-year had lower scores on the extraversion-introversion dimension at baseline. Finally, the likelihood of developing residual symptoms was higher in patients who were more introverted at the time of initial assessment and in patients who reported dyspnea as the main symptom during panic attacks.

Finally, in a study conducted by Marchesi et al.,[46] 65 PD patients were followed over 12 months and randomly treated with paroxetine or citalopram. Temperament and character were evaluated, according to Cloninger's model,[47] before and after 1-year of pharmacological treatment. Complete remission was achieved only by 47.6% of the sample; whereas in the remaining patients, limited symptom of panic attacks, anticipatory anxiety, phobic avoidance, and depression were still present at the end of the study. Before treatment, non-remitted and remitted patients showed different patterns of temperament and character (i.e., the first group was characterized by an alteration of both temperament and character, whereas in the second only an alteration of temperament emerged). After treatment, temperament changed in both groups, while character changed only in non-remitted patients. The likelihood of achieving complete remission was positively related to the score on the pre-treatment levels of self-directedness. Interestingly, the persistence of anxious symptoms after treatment was associated with a worsening of personality features (self-directedness and cooperativeness). Therefore, personality disorders reduce the effectiveness of pharmacological treatment in PD patients and, in turn, the persistence of anxious symptoms after treatment worsens the personality disorder.

Several studies have addressed the issue of sequential improvement of symptoms in patients with PD undergoing behavioral[48-51] or pharmacological[52-55] treatment. A seminal paper was proposed by Fava et al.[48] in 1991, in which they specifically investigated the rollback phenomenon in 25 PD(A) patients who received 12 sessions of exposure. After the first 6 sessions, agoraphobia was significantly improved, while 12 sessions of treatment yielded the disappearance of panic attacks and a further reduction of agoraphobic avoidance. The phenomenological sequence observed retrospectively for the prodromal symptoms of PD(A) was: phobic avoidance and hypochondriasis leading to panic, which led to more phobic avoidance and hypochondriasis. On the other hand, the rollback phenomenon observed was: a decrease in avoidance by exposure, which seemed to improve agoraphobia and panic, with eventual disappearance of panic in patients, whereas agoraphobia persisted although to a less degree. Prodromal symptoms of PDA thus tend to become residual symptoms which, in turn, may progress to prodromal symptoms of relapse.

Other authors also found interesting results. For instance, Bouchard et al.[56] observed that cognitive changes precede changes in the level of panic apprehension both when treated with cognitive restructuring or exposure. Changes in apprehension were preceded by changes in belief in three cases, by changes in self-efficacy in six cases, and by changes in both belief and self-efficacy in the remaining three cases. Hoffart et al.[51] administered an integrated cognitive and behavioral model of agoraphobic avoidance to patients with PDA and found a feedback loop of effects during treatment: the anxiety elicited by bodily sensations influenced catastrophic beliefs, and such beliefs influenced avoidant behavior. A reduction of avoidance, in turn, decreased the fear of bodily sensations. Thus, it appears that avoidant behavior is maintained by cognitive appraisal, while avoidance itself maintains anxiety conditioned to bodily sensations.

The role of subclinical symptoms has been further increased by the development of the Diagnostic Criteria for Psychosomatic Research (DCPR).[57,58] Fava et al.[59] suggested to modify the DSM IV category concerned with psychological factors affecting medical conditions into an expanded category of psychological factors affecting either identified or feared medical conditions. They proposed a new section with 6 most frequent DCPR syndromes. Among them, the

DCPR health anxiety, disease phobia, persistent somatization, demoralization, and irritable mood offer interesting specifiers for subclinical symptoms. For instance, health anxiety, that encompasses nonspecific dimensions of abnormal illness and somatic amplification that readily respond to appropriate reassurance, may be the prodromal or residual symptom of panic disorder. Indeed, Fava et al.[60] found a significant association between PD(A) and DCPR syndromes of health anxiety, disease phobia, patterns of somatization (i.e., functional somatic symptoms secondary to a psychiatric disorder), and irritable mood.

The importance of DCPR should not be underestimated, as they are good predictors of impaired psychosocial functioning in medically ill persons[61] and high sensitive instruments for detecting sub-threshold psychological distress as well as sub-threshold psychiatric comorbidity.[62]

Psychological development of panic and neurobiology

A longitudinal view of PD, encompassing prodromal and residual symptoms, can find interesting links to the neurobiology of panic.

In 1989, Gorman et al.[63] proposed a neuroanatomical hypothesis of PD positing that a panic attack stems from loci in the brainstem that involve serotonergic and noradrenergic transmission and respiratory control, that anticipatory anxiety arises after the kindling of limbic area structures, and that phobic avoidance is a function of pre-cortical activation. The hypothesis then asserted that medication exerts its therapeutic effect by normalizing brainstem activity in patients with PD, whereas cognitive behavioural therapy works at the cortical level.[63] However, this original idea has been surpassed because it was almost completely divorced from research that has mapped out the neuroanatomical basis for fear. For this reason, Gorman et al.[64] proposed in 2000 a revised neuroanatomical hypothesis of PD.[64] According to this model, the sensory input for the conditioned stimulus runs through the anterior thalamus to the lateral nucleus of the amygdala and is then transferred to the central nucleus of the amygdala which stands as the central point for dissemination of information that coordinates autonomic and behavioural responses. Efferents of the central nucleus of the amygdala have many targets: the parabrachial nucleus, producing an increase in respiratory rate; the lateral nucleus of the hypothalamus, activating the sympathetic nervous system and causing autonomic arousal and sympathetic discharge; the locus coeruleus, resulting in an increase in norepinephrine release and contributing to increases in blood pressure, heart rate, and the behavioral fear response; and the paraventricular nucleus of the hypothalamus, causing an increase in the release of adrenocorticoids. A projection from the central nucleus of the amygdala to the periaqueductal gray region is responsible for additional behavioral responses, including phobic avoidance. There are also important reciprocal connections between the amygdala and the sensory thalamus, prefrontal cortex, insula, and primary somatosensory cortex. So, although the amygdala receives direct sensory input from brainstem structures and the sensory thalamus enabling a rapid response to potentially threatening stimuli, it also receives afferents from cortical regions involved in the processing and evaluation of sensory information. Potentially, a neurocognitive deficit in these cortical processing pathways could result in the misinterpretation of sensory information known to be a hallmark of panic disorder, leading to an inappropriate activation of the "fear network" via misguided excitatory input to the amygdala. It is thus conceivable that the misinterpretation of sensory information, which in clinical practice can be represented by prodromal health anxiety/hypochondriacal beliefs and fear, can kindle the fear network inducing a panic attack.

In this framework, Gorman et al.[64] also hypothesised the possible neurobiological mechanisms of Selective Serotonin Reuptake Inhibitors (SSRIs) as leading pharmacological treatment of PD. They observed that serotonergic neurons originate in the brainstem raphe region and project widely throughout the entire central nervous system. Three of these projections are of particular relevance to an understanding of the SSRI antipanic effect. First, the projection of serotonin (5-HT) neurons to the locus coeruleus is generally inhibitory, such that the greater the activity of the serotonergic neurons in the raphe, the smaller the activity of the noradrenergic neurons in the locus coeruleus. This suggests that SSRIs, by increasing serotonergic activity in the brain, have a secondary effect of decreasing noradrenergic activity leading to a decrease in many of the cardiovascular symptoms associated with panic attacks, including tachycardia and increased diastolic blood pressure. Second, the projection of the raphe neurons to the periaqueductal gray region appears to modify defense/escape behaviors. Thus, the serotonergic projections from the dorsal raphe nuclei play a role in modifying defense/escape responses by means of their inhibitory influence on the periaqueductal gray region. Third, long-term treatment with a SSRI may reduce hypothalamic release of corticotropin-releasing factor (CRF). CRF, which initiates the cascade of events that leads to adrenal cortical production of cortisol, is also a neurotransmitter in the central nervous system and has been shown to increase fear. According to Gorman et al.[64] equally intriguing was the possibility that SSRIs, by increasing serotonergic activity, have an effect on the central nucleus of the amygdala itself, this may be a prime site for the anxiolytic action of the SSRIs, whereby an increase in 5-HT inhibits excitatory cortical and thalamic inputs from activating the amygdala. In addition to their psychic effects, drugs such as SSRIs may eliminate most of the troubling physical effects that occur during panic by affecting heart rate, blood pressure, breathing rate, and glucocorticoid release. This would then lead to a secondary decrease in anticipatory anxiety as a patient recognizes that the seemingly life-threatening physical manifestations of panic have been blocked. It is not uncommon, particularly in the early stages of medication treatment of a patient with PD, to hear: "I sometimes feel as if the attack is coming on but then nothing happens. My thoughts don't seem to be able to cause a panic attack anymore". It is thus conceivable that SSRIs induce a rollback phenomenon in which pharmacological treatments first reduce the severity and frequency of panic attacks and then, indirectly, ameliorate anticipatory anxiety and avoidance.

In 2005, Ninan et al.[65] intriguingly matched the sequence of events in a prototypical panic attack and what follows with potential neurobiological alterations. They gave the example

of a young lady experiencing an unexpected panic attack while driving on the highway. Some confluence of events triggers the amygdala, the central command switch and activates a fixed action pattern of responses in her brain and body. Thus, she pulls over the side of the road paralyzed with fear and, after a few minutes when the worst is over, she gathers up her courage and slowly drives to the safety of her home. The terrifying experience leaves her an emotion memory (i.e., a strengthening of synapses in the lateral nucleus of amygdala that represents the experience). Subsequent experiences, either anticipated or actual, that match components of that emotional memory, now trigger the anxiety response. The conventional memory system also remembers the panic attack. Explicit memory involves the hippocampus which is crucial for the autobiographical memory of the attack. Moreover, the involvement of hippocampus has also a role in recording the context in which the attack occurred. Thus, for instance, the highway is now associated with panic attack, and driving may elevate the risk of a further panic attack. Although not previously connected with fear, driving is now associated with vigilance, anxiety, arousal. The anticipation of driving on a highway may become dysphoric, and the situation may be therefore avoided. The functional anatomy of such avoidance is the medial/orbital prefrontal cortex and its reciprocal connections with the amygdala. Excessive activation of the amygdala decreases prefrontal activity, which, in turn, reduces the inhibitory control of amygdala. Thus, the learning of new information that may counter the initial association is impaired and avoidance becomes lasting. Once again, this matched sequence of events of a panic attack and the corresponding neurobiological alterations might identify different stages of the development of PD, which are the mirror of what happens during the rollback.

Finally, in 2008 Graeff and Del-Ben further clarified the neuroanatomical model of panic focusing on the role of 5-HT as enhancer of inhibitory avoidance in the forebrain and inhibitor of the one-way escape in the midbrain periaqueductal gray (PAG).[66] Indeed, experimental studies led to the association of escape with PD; functional neuroimaging show activation of the insula and upper brain stem (including the PAG), as well as deactivation of the Anterior Cingulated Cortex (ACC) during experimental panic attacks; and voxel-based morphometric analyses of brain magnetic resonance images suggest an increase of grey matter volume in the insula and upper brain stem, and a decrease in the ACC of panic patients as compared to healthy controls. Since the insula and the ACC are thought to translate interoceptive stimulation into feeling, and panic patients overestimate bodily signals, they are a likely neural substrate of interoceptive supersensitivity, and a possible site of action of both drug and cognitive behavior therapy. As a complement, antidepressants seem also to prevent panic attacks by enhancing 5-HT inhibition in the PAG.

Psychological development of panic and treatment

A longitudinal view of PD as well as its staging model has been strongly related to treatment in many fields of psychiatry, and particularly in unipolar depression, bipolar disorder, and schizophrenia. On one hand, it has been observed that it allows to recognize a disorder early enough to treat it precociously;[67,68] that is, making early intervention and prevention. On the other hand, it has been observed that it may help in identifying possible therapeutic strategies for treatment resistant cases.

Unfortunately, current therapeutic models for panic disorder, as exemplified by the Practice Guideline for the treatment of patients with panic disorder by the American Psychiatric Association[69] and the Australian and New Zealand Clinical Practice Guidelines for the treatment of panic disorder and agoraphobia by the Royal Australian and New Zealand College of Psychiatrists,[70] disregard staging as well as subclinical symptomatology. Yet, emphasis of treatment should be more and more shifted to long-term outcome due to the chronic nature of PD; disappearance of residual symptoms, upon abatement of panic attacks, should be the final target of therapy since they constitute a substantial risk of relapse; and adequate treatments of enduring effects should become of paramount importance including, at least in some patients, long-lasting treatment, and sequential or stage-oriented combination of different therapeutic modalities.

In this framework, Shear et al.[71] proposed to use a better system to monitor the patient's progress because, if residual symptoms are identified clearly and the progress of treatment can be mapped, clinicians may be induced to appropriately increase or possibly decrease medication dosage.

For a long time, the literature has also suggested to increase the rates of remission combining pharmacological and psychological treatments. However, more recent evidence seems not to strongly agree with it. Indeed, while, for instance, in 1997 van Balkom et al.[72] suggested to combine antidepressants and exposure in vivo in the treatment of PD(A) on the basis of a meta-analysis of 106 studies; more recently, Furukawa et al.,[73] in their Cochrane review, demonstrated the sustained advantage of the combination of psychotherapy and antidepressant over antidepressant alone for 6 to 24 months but no differential effectiveness over psychotherapy alone at 6 to 24 months. In terms of differential effectiveness of various forms of psychotherapy, only behavior therapy and cognitive-behavior therapy were homogeneously effective, while brief psychodynamic and cognitive-interpersonal therapy produced mixed results which lead to increased heterogeneity. In conclusion, Furukawa et al.[73] suggested that either combined therapy or psychotherapy alone may be chosen as first line treatment for PD(A) and that antidepressants alone are not recommended as first line treatment.

Similar results were also found by Watanabe et al.[74] when they evaluated the effects of combined psychotherapy plus benzodiazepines in the treatment of PD. The combined therapy did not provide a significant advantage over psychotherapy alone either during or at the end of treatment. Thus, for those who have access to appropriate behavior therapy services, treatment with a benzodiazepine alone might not be warranted. Furthermore, psychotherapy alone might be more favorable than the combination of psychotherapy and benzodiazepine, considering the long-term adverse outcomes, such as cognitive impairments and development of dependence with benzodiazepine use.

Preliminary evidence also suggests a relative effectiveness with the addition of cognitive behavioral therapy (CBT) compared to any medication optimization for patients with

panic disorder who do not remit with SSRIs. Comparable benefit was found for the addition of CBT or clonazepam and optimization of the antidepressant dose.[75]

Over the time, different treatment approaches have been proposed. Some authors evaluated the effects of a sequential treatment; that is, a planned sequential administration of different therapies based on specific effects induced by each therapy that provide additional benefits in the course of time.

Goldstein administered a 8-week treatment program, starting with alprazolam and switching gradually to imipramine, to 6 PD(A) patients. Five completed the treatment program and, among them, 4 had no panic attacks by the end of the first week of treatment and maintained the improvement throughout the shift to imipramine. Goldstein explained the effectiveness of the sequential treatment by the early symptom relief provided by alprazolam.[76]

Thereafter, Mavissakalian proposed a sequential treatment involving both pharmacological and psychological interventions. Thirty-eight PDA patients received 8 weeks of treatment with imipramine followed by 8 weeks of treatment with imipramine combined with behavior therapy. Sixty-three percent of the patients responded markedly to the sequential treatment and most of the improvement in panic occurred during the first 8 weeks when imipramine alone was used, whereas improvement in severity, anxiety, depression, and phobias, in particular, continued to be significant between mid-treatment and end of study. Further analyses revealed that improvement in phobic anxiety and avoidance in the first 8 weeks of treatment, rather than improvement in panic, predicted final outcome.[77]

De Beurs et al.[78] investigated whether the effects of exposure for PD(A) could be enhanced by adding specific interventions before the start of exposure treatment. Thus, they compared fluvoxamine plus exposure, psychological panic management plus exposure, and exposure alone and found that the combination of fluvoxamine and exposure demonstrated efficacy superior to that of other treatments at the end of the trial.[78] However, these advantages faded at a 2-year naturalistic follow-up (de Beurs et al.[79]).

Finally, 63 patients with a primary diagnosis of PD who had residual symptoms, such as panic attacks, anticipatory anxiety, and phobic avoidance despite being on a stable dose of medications for at least 4 months, were treated with CBT using a group format of 12 sessions over 4 months. Significant reductions in symptoms were evident for all outcome measures (frequency of panic attacks, agoraphobia, and anticipatory anxiety) across treatment, with maintenance of these gains at one-year follow-up. At least a 50% reduction in symptoms was achieved by 78% of the sample for ratings of agoraphobia, 62% for anticipatory anxiety, and 49% for the Hamilton Anxiety Scale score. Overall, 81% of the sample achieved a panic-free status, and 64% met criteria for remission. The presence of dysthymia, generalized anxiety disorder, or social phobia at pre-treatment was associated with a lower likelihood of remission.[80] This study provides further evidence for the efficacy of CBT as a next-step strategy for patients who fail to respond adequately to pharmacotherapy for PD. The improvement was also maintained despite overall reductions in medication use, indicating that CBT can be used as a strategy for medication discontinuation, with longer-term maintenance of treatment gains. However, the high levels of comorbidity of the sample and the open clinical follow-up design can limit the strength and generalizability of such results.

An interesting proposal of stage-oriented therapy comes from Fava et al. They administered well-being therapy or CBT of residual symptoms to 10 patients with a diagnosis of mood or anxiety disorders. A significant advantage of well-being therapy over cognitive behavioral strategies was observed.[81] This study, although preliminary, suggests that a specific psychotherapeutic technique addressed to increasing well-being might decrease residual symptoms in patients with mood or anxiety disorders. The technique is based on Ryff's conceptual model of well-being which results from self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life, and personal growth, and suggests that the absence of well-being creates conditions of vulnerability to possible future adversities (Ryff,[82] Ryff et al.[83]).

Conclusions

Despite the relative paucity of research on psychological development of panic, the reports summarized in this review address important clinical issues that deserve further study.

The prodromal period seems to be about 10-15 years long, the perception that one is a "nervous person"[16] or has a phobic-anxious temperament is a strong predictor of the onset of panic disorder.[17] The most common prodromal symptoms are depressed mood, illness phobia, distress and avoidance of closed spaces, excessive worries, negative affectivity, anxiety sensitivity, health anxiety or fear of disease, separation anxiety. The phenomenological clinical sequence of PDA is: phobic avoidance and hypochondriasis leading to panic, which, in turn, leads to more phobic avoidance and hypochondriasis. On the other hand, the rollback phenomenon is: a decrease in avoidance by exposure, which improves agoraphobia and panic, with eventual disappearance of panic, whereas agoraphobia persists although to a less degree. Prodromal symptoms of PDA thus tend to become residual symptoms which, in turn, may progress to prodromal symptoms of relapse.[48] Alternatively, the rollback might be characterized by anxiety elicited by bodily sensations which influences catastrophic beliefs, and such beliefs influence avoidant behavior.[51]

The translation of staging in the neurobiology of panic identifies different phases in the development of PD. These phases are, indeed, the mirror of those observed during the rollback. Thus, the experience of a panic attack triggers the amygdala which activates patterns of responses in the brain and body. The terrifying experience leaves an emotion memory, which will trigger the anxiety response when there is a subsequent experience (real or anticipated) that matches the components of that emotional memory. Moreover, the hippocampus is involved and records the context in which the attack occurred, so that some details of the threatening experience are now associated with panic attack. The anticipation of such details may become dysphoric, and the situation may be therefore avoided. The functional anatomy of such avoidance is the medial/orbital prefrontal cortex and its reciprocal connections with the amygdala.[65]

The treatment implications of the longitudinal model of PD, although still too disregarded, emphasize the importance to consider residual symptoms as the final target of the

therapy and offer adequate treatments of enduring effects. In this regard, sequential or stage-oriented treatments have shown promising results.

Additional research is encouraged to sharply define the stages of PD or further confirm those already known; increase the knowledge of subclinical symptoms since they are the key clinical features to make an early diagnosis and treatment; describe in details the rollback in order to give to clinicians anchor points to understand at which stage of recovery their patients are; clarify the relationship between staging/subclinical symptomatology/rollback, neuro-anatomy, and brain functions; strengthen the knowledge on possible long-lasting, sequential, or stage-oriented treatments in order to achieve higher remission rates. In particular, study of sequential treatment, whether drug combination therapy, medication and psychotherapy, or combination therapies, and studies of well-being therapy are strongly encouraged; especially if they use small trials of nowhere patients with very well defined treatment history and a sequential parallel comparison design. This might allow maximizing the likelihood of detecting significant differences between active treatments and placebo and, above all, have true progress in treatment research since homogeneous features of nowhere patients do not affect the outcome of the trials.[84]

Further studies on the longitudinal development of panic might also pave the way to its subtyping. A growing literature on major depression is showing that complexes clinical phenomena may need to be split in subtypes in order to be operationalized and promote the development of specific treatments.[85,86] This could lead to the identification of subtypes that are more responsive to certain therapies and select the right treatment for each individual patient. Still in the view of defining the complex clinical phenomenon of panic, researchers on the life-setting factors, exemplified by the term allostatic load, should be encouraged in order to know the role of stress in the disease onset, thus preventing or decreasing its eventual negative impact on health. In this framework, the criteria for allostatic overload suggested by Fava et al.[60] may provide clinical specification of panic disorder.[87]

Such a body of research will entail considerable clinical implications for daily practice and patients' perspectives of remission.

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