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Biological and Clinical Markers in Panic Disorder

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Objective Classifying mental disorders on the basis of objective makers might clarify their aetiology, help in making the diagnosis, identify "at risk" individuals, determine the severity of mental illness, and predict the course of the disorder. This study aims to review biological and clinical markers of panic disorder (PD).

Methods A computerized search was carried out in PubMed and Science Direct using the key words: "marker/biomarker/clinical marker/neurobiology/staging" combined using Boolean AND operator with "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.

Results Structural changes in the amygdala, hippocampus, cerebral blood level in the left occipital cortex, serotonin 5-TH and noradrenergic systems activation, aberrant respiratory regulation, hearth rate variability, blood cells and peripheral blood stem cells, hypothalamic–pituitary–adrenal axis dysregulation were identified as potential candidate biomarkers of PD. Staging was identified as clinical marker of PD. According to the staging model, PD is described as follows: prodromal phase (stage 1); acute phase (stage 2); panic attacks (stage 3); chronic phase (stage 4).

Conclusion The clinical utility, sensitivity, specificity, and the predictive value of biomarkers for PD is still questionable. The staging model of PD might be a valid susceptibility, diagnostic, prognostic, and predictive marker of PD. A possible longitudinal model of biological and clinical markers of PD is proposed.
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Key Words Biomarker, Clinical marker, Staging, Residual symptoms, Prodromal symptoms.

INTRODUCTION

In the last decade increasing efforts have been made to classify mental disorders on the basis of objective makers[1-4] claiming that markers can clarify the aetiology of psychiatric diseases, confirm a diagnosis, identify "at risk" individuals, determine the severity of mental illness, predict the course of the disorder.[1,2,5] Some authors also suggested that the use of markers might lead to personalized psychiatric treatments approach and inform about the type, timing, and course of interventions to be used as well as monitoring the clinical response to them.[1,2,5] Of course, markers must have at least a moderate level of sensitivity, specificity, and predictive value[2] to be useful. In this vein, markers were classified as: 1) susceptibility/risk marker, i.e., the marker indicates the potential for developing a disease in an individual who, from a clinical standpoint, does not have that disease or medical condition clinically relevant, yet; 2) diagnostic marker, i.e. a marker used to identify individuals with the disease or to define a subset of the disease; 3) prognostic markers, i.e., markers used to identify the likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest; 4) predictive markers, i.e., markers used to identify individuals who are more likely than those without the marker to experience a favourable or unfavourable effect from specific intervention or exposure; it provides a forecast of the potential for a patient to respond to one or more specific treatments.[6-8]

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METHODS

A computerized search was carried out in PubMed and Science Direct. Search terms were: "marker/biomarker/clinical marker/neurobiology/staging" combined using Boolean AND operator with "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.

RESULTS

Biological markers in panic disorder

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic interventions.[3,4] We will here illustrate the biological markers proposed for panic disorder (PD) on the basis of the literature.

Structural or activity changes in brain regions

According to Bandelow et al.,[9,10] structural changes in the volume of amygdala, hippocampus, parahippocampal gyri, and brainstem nuclei are candidate biomarkers of panic disorder. Volume reduction or increase in these areas as well as increased activation of amygdala and hippocampus in response to fearful stimuli have been reported in PD patients but not in controls (p value ranging from 0.002−0.005).[9,10] Some evidences suggested a greater activation in PD patients than in controls at the level of the insular cortices, of the left inferior frontal gyrus, of the dorsomedial prefrontal cortex, and of the left caudatum.[9,10] A negative correlation between left amygdala volume and anxiety was found in PD patients (r=-0.54; p=0.02).[11]

The cerebral blood flow in the left occipital cortex and the serotonin (5-TH) and noradrenaline (NE) system activation were also proposed as putative biomarkers.[9,10] Compared to controls, patients with PD showed a higher cerebral blood flow (mean±SD 1.35±0.01 vs. 1.24±0.02, p<0.05)[12] and lower 5-TH plasma levels[9,10] in addition a significant association between a hyperactivation of the NE system, anxiety, and somatic symptoms was found in PD patients but not in patients with other psychiatric disorders (e.g., generalized anxiety disorder, obsessive compulsive disorder, depression and schizophrenia).[9,10,13] These findings were consistent with Gorman's neuroanatomical hypothesis of PD.[14]

Respiratory patterns

Several theories sharing the hypothesis of a causal relationship between aberrant respiratory regulation and panic have been developed.[15-19] Both respiratory symptoms during panic attacks and behavioral and respiratory hypersensitivity to hypercapnic gas mixture inhalation have been found in PD patients.[15-19] In these subjects, hyperventilation may be chronic.[16] In addition, hyperventilation (e.g., higher baseline mean minute ventilation, lower end-tidal partial pressure of CO_2, and lower venous pCO_2), higher variability of mean minute ventilation, higher respiration rate, higher tidal volume, higher rate of sighs and apnoea in respiratory patterns were found in PD patients but not in healthy controls (effect size Hedges' g ranging from -0.73 to 0.39, p<0.01). Grassi et al.[17] verified whether these respiratory abnormalities are specific to PD or are also present in anxiety disorders other than PD. Lower baseline mean et-pCO_2, indicating a condition of hyperventilation (effect size Hedges' g ranging from -0.28 to -0.56, p<0.01) and higher respiration rate (effect size Hedges' g ranging from 0.25 to 0.47, p<0.01) were found in PD patients but not in those with social phobia or generalized anxiety disorder.[17] Thus, the aberrant respiratory pattern (i.e., hyperventilation and higher respiration rate) seems to be a biomarker specific for PD.

Hearth rate variability, blood cells, peripheral blood stem cells

The hearth rate variability (HRV) (i.e., the extent to which the interval between beats varies with time) was also assumed as a candidate biomarker for PD.[9,20] HRV is a core feature of cardiovascular diseases[21] which was found to be positively correlated with panic attacks across clinical and non-clinical samples.[9,22,23] The HRV was considered a possible core feature of PD[9,10,22,23] on the basis of studies reporting an increased risk of cardiovascular diseases in PD patients than in subjects without psychiatric disorders[24] and a prevalence of panic disorder ranging from 4% to 12.5% in cardiac outpatients. HRV is measured using the time domain (i.e., differences between adjacent beat intervals) and frequency domain (i.e., measures based on power spectral analysis, which allows detection of lower and high frequency oscillation).[9,10,20] A meta-analysis[20] reported that time and frequency domains were significantly lower in patients with PD than in healthy controls, beyond potential confounding effects of medication use and medical and psychiatric co-morbidity (effect size Hedges' g ranging from -0.69 to -0.29, p<0.05). Chalmers et al.[20] reported similar findings comparing patients with anxiety disorders other than PD (i.e., post traumatic stress disorder, generalized anxiety disorder, social anxiety) with healthy controls; they showed that HRV is an aspecific marker across anxiety disorders.[9,10,20]

Recent findings[25] observed increased platelet distribution width (PDW), red cell distribution width (RDW), and mean platelet volume (MPV) in PD patients if compared to healthy controls. These results emphasized the role of blood cells and peripheral blood stem cells as possible biomarkers of PD[25-27] in accordance with the theory of the inflammatory origin of PD.[26]

Hypothalamic–pituitary–adrenal axis dysregulation

It has been assumed that panic attacks might be a result of

a disturbance in stress response regulation by the strong activation of the hypothalamic–pituitary–adrenal (HPA) axis.[28] The HPA axis is the major endocrine system which regulates the physiological response to stress and as a result drive how an organism might adapt its own behavior or environment in order to copy with that stress.[29-31] When the stress is persistent, the negative feedback system, which dampens the HPA axis activation, is impaired inducing chronic cortisol release[29,32] which may provoke flatter circadian variation and heightened daily cortisol secretion.[29-32]

Studies addressing the role of HPA axis activation in panic disorder used cortisol secretion as index of the HPA functioning during panic attacks or compared PD patients with controls. These studies provided inconsistent results. Some reported a higher cortisol secretion during panic attacks compared to the values obtained in the same individuals at comparable times on panic-free days.[28,33] Other studies reported unchanged or only marginal HPA axis activation during spontaneous attacks.[28] In addition, while some evidences reported higher cortisol secretion in PD patients when compared to controls, other studies showed comparable levels of cortisol between PD patients and healthy controls.[9,10,28,32,34] As pointed out by Bandelow et al.,[35] it is not clear whether the dysfunctions of the HPA axis are a potential cause of PD or a consequence of permanent stress induced by recurrent panic attacks.

These heterogeneous findings might be explained by several elements; first, at the beginning of the panic attack the HPA axis activation might be due to an arousal in reaction to novelty cues and/or to anxiety anticipatory about further attack and/or the avoidance of places where having an attack is embarrassing develop;[32,34,36,37] second, after the acute phase of a panic attack, the HPA axis might normalize due to a successful habituation to the repeated experiences of panic.[32,34,38] However, the role of cortisol secretion as biomarker of PD is not fully confirmed.

Classification of putative biomarkers of PD

As previously reported, markers might be categorized as susceptibility/risk markers; diagnostic, prognostic, and predictive markers.[6-8] Given that the biomarkers illustrated were found in PD patients and not in controls,[9,10,16,17,20,25] they might be considered susceptibility and/or diagnostic biomarkers, however longitudinal studies are warranted to confirm this. Also the HPA axis dysregulation and the heart rate variability might be considered prognostic biomarkers given that higher cortisol secretion was found to predict poorer long-term outcome in PD patients at 2−4 year follow-up ($p<0.003$)[39,40] and lower HRV in PD patients might increase vulnerability to cardiovascular diseases.[41] Predictive biomarkers of PD are still unclear due to the inconsistency of results. Grambal et al.[42] suggested that increased pre-treatment activation of the dorsolateral prefrontal cortex, right parietal cortex, left frontal eye field, orbito-frontal cortex, and left amygdala predict poor outcome in cognitive behaviour therapy; Bandelow et al.[9] and Fisher et al.[43] reported that neither brain regions structural changes nor basal cortisol concentrations predict responses to psychological treatments. In Table 1 we reported a proposal for classifying PD biomarkers.

The biomarker crisis

A body of research on biomarkers considered single brain region/circuit or a specific neurotransmitter without ravelling one-to-one relationships with a specific disease.[4] Given that mental disorders are multidimensional in their description, multifactorial in their origins, and involve non-linear interactions in their development,[44] it is unlikely that a single biomarker might explain the multifaceted nature of a specific psychiatry disease.[2,45] Multimodal approach where the diagnosis and/or the course of diseases are explained by a com-

Table 1. Putative makers of panic disorder classified as: susceptibility/risk marker; diagnostic marker, prognostic marker, predictive marker[6-8]

	Susceptibility/ risk marker	Diagnostic marker	Prognostic marker	Predictive marker
Biomarkers				
Structural changes in the amygdala, hippocampus		•		
Cerebral blood level in the left occipital cortex		•		
Serotonin 5-TH and noradrenergic systems activation		•		
Aberrant respiratory regulation		•	•	
Hearth rate variability		•		
Blood cells and peripheral blood stem cells		•		
Dysregulation hypothalamic–pituitary–adrenal axis/Cortisol secretion		•	•	
Clinical marker				
Staging	•	•	•	•

bination of different biomarkers could be more reliable.[2,4,45] Moreover, it is likely that different biomarkers are associated with a cluster of symptoms rather than to a specific diagnosis.[2,4,45] A further hurdle is that some biomarkers, as for example structural changes in the amygdala and/or hippocampus, although they showed acceptable reliability,[9,10] can be used in clinical practice rarely for practical and economic reasons.[45] To facilitate the use of biomarkers on a broad-based scale, we would need simple and cost-effective biomarkers[2,45] such as for instance urine or saliva cortisol, heart rate variability, blood cells, peripheral blood stem cells, or respiratory pattern.[9,10,16,17,20,25] However, although the biomarkers mentioned for PD showed high sensibility in distinguishing PD from the healthy condition, they did not show enough specificity in distinguishing PD from other psychiatric disorders.[9,10] Basically, the identification of biomarkers is based on observations that the specific biomarker is detected in PD patients and not in healthy controls or in patients with other psychiatric disorders.[9,10,45] This might lead to interpretative bias given that, due to an overlap in pathophysiological findings among psychiatric disorders, biomarkers might be shared by different psychiatry disorders. Most of the candidate biomarkers described above (e.g., structural brain morphology, lower 5-HT plasma, norepinephrine, hypo/hyper secretion of cortisol, instability of the cortical arousal system, HRV, PWD and RDW) differentiate PD patients form healthy controls but not PD patients from patients having other psychiatric disorders, such as anxiety disorders, schizophrenia, mood disorders.[9,10,46-58]

The lack of availability of biomarkers with high specificity has been widely discussed.[45,59,60] As reported by Kapur et al.,[60] psychiatry seems to be in a Catch-22 given that the contemporary diagnostic system was not designed to facilitate biological differentiation. In addition, current diagnostic definitions of psychiatric disorders based on symptoms encompass very heterogeneous populations and are thus likely to yield spurious results when exploring biological correlates of mental disturbances.[59]

To be also noted that biomarkers are influenced by environmental and lifestyle factors such as stress, physical activity, comorbidity, psychotropic medications.[45] Psychotropic drug treatments, particularly after long-term use, might cause or precipitate adverse effects on the course, characteristics, and responsiveness of an illness that do not necessarily subside with discontinuation of the drug or of modifying responsiveness to subsequent treatments.[61,62] Such vulnerabilities are subsumed under the rubric of iatrogenic comorbidity.[61,62]

Psychometric and clinimetric approach

The psychometric approach aims to develop instruments that measure a single construct using multi-items,[63] given that, its customary goal is to achieve a unidimensional construct in which the relatively homogeneous components all measure essentially the same phenomenon.[63,64] Methodological difficulties in applying psychometric principles to diagnostic testing and to detect changes related to the course of illness and/or to difference between pre- and post-treatment have been outlined.[64] Wright and Feinstein[65] provide an explanation for the disappointing performance that multi-item scales may present. In psychometrics, the homogeneity of components is considered as the most important requirement for a rating scale; however, the same properties that give a scale a high score for homogeneity, as the redundant nature of the items of a scale, may obscure its ability to detect change decreasing its sensitivity.[65] A high correlation between scales is also regarded as evidence that the two scales measure the same factor, but a high correlation does not indicate similar sensitivity: a common content of two scales may ensure a high positive correlation between them, but the items they do not share may be important in determining their sensitivity.[64,66] On the basis of the psychometric approach all items of a scale have same weight.[66] Although multi-item scales might be valid and reliable, it might show lack sensitivity.[66,67]

Fava et al.[66] suggested that psychometrics has now become an obstacle to the progress of clinical research in psychiatry and clinical psychology and that the more clinically oriented clinimetrics could offer a valid alternative. Clinimetrics' is the term introduced by Feinstein in the early 1980s[68] to indicate a domain concerned with the measurement of clinical issues that do not find room in customary clinical taxonomy. Such issues include types, severity and sequence of symptoms; rate of progression in illness (staging); severity of comorbidity; problems of functional capacity; reasons for medical decisions (e.g. treatment choices), and many other aspects of daily life, such as well-being and distress.[68] Differently from the psychometric approach, in clinimetrics homogeneity of components is not needed and single items may be weighed in different ways: what matters is the capacity of an index to discriminate between different groups of subjects and to reflect changes in experimental settings.[64,66] In addition, the clinimetric approach is directed at the development of instruments to measure multiple constructs with a single index that might be divided into ailment-oriented indexes (refer to specific diseases, states and clinical manifestations) and general indexes (refer to general health and functional states that are not distinctive for a particular disease or condition).[64,66] The clinimetric analysis proposed convergent, discriminant, and incremental validity as important features that determine the sensibility of a clinical measurement.[69-71]

The current diagnostic systems, the Diagnostic and Statistical Manual of Mental Disorders (DSM)[72-76] and the Interna-

tional Classification of Diseases (ICD),[77-80] are mostly influenced by psychometric models according to which the severity of the disorder is determined by the number of symptoms rather than to their intensity or quality.[66,81,82] Thus, all symptoms have an equivalent value and load in determining the severity of a psychiatric disorder, unlike in clinical medicine where major and minor symptoms are often differentiated (e.g., the Jones criteria for rheumatic fever).[68] This might bias the diagnostic process given that psychological symptoms that do not reach the diagnostic threshold might be not considered[83] although they might affect the quality of life of the patient and lead to pathophysiological and therapeutic implications.[67] In addition, different patients could meet the diagnostic criteria for the same disorder but presenting different scores on a rating scale which reflect different symptom severities, perceptions, and illness attitudes, that in turn might affect the clinical course of the disorder.[67] Differently form the psychometric models, clinimetrics assumed that different symptoms have different weigh.[67] Moreover, clinimetrics approach focuses on symptoms sequence, rate of progression of illness, and comorbidity, and on problems of functional life, such as well-being.[64,66,67]

Clinical markers in panic disorder

From cross-sectional diagnostic systems to the staging model

Even thought the current diagnostic systems[72-80] showed acceptable reliability, their clinical utility remains elusive.[84-86] In a large epidemiological survey run on a sample of 1,764 users of ICD or DSM, it was evident that 1,123 subjects (64%) rated those diagnostic systems as with low utility in selecting a treatment and assessing probable prognosis.[84] This might be partially explained by the several reasons. First, the taxonomy in psychiatry derived from the traditional method of clinical medicine which provides operating specifications for making a clinical decision about the existence of a specific disease.[87] As a consequence, the diagnostic reasoning process ends with the identification of a disorder[88] while, in reality, the clinical judgment should go through a series of 'transfer stations' where potential connections between presenting symptoms and pathophysiological processes are drawn and are amenable to longitudinal verification and modification as long as therapeutic goals are achieved.[81,89-91] Second, the diagnostic systems are mostly influenced by psychometric models;[81-83] as a result: 1) patterns of symptoms, severity of illness, effects of comorbid conditions, timing of phenomena, rate of progression of illness (staging), responses to previous treatments, and other clinical distinctions that might demarcate major prognostic and therapeutic differences among patients who otherwise might be deceptively similar since they share the same psychiatric diagnosis are poorly taken into account; 2) the target of therapy tends to become syndromes resulting from a certain number of symptoms, that could be of mild intensity and of doubtful impact on quality of life, instead of symptoms that might be incapacitating for the patient.[81] Within a sample of patients with major depressive episode, the number of symptoms (either including all depressive symptoms or selecting only those relevant to a DSM diagnosis) does not correlate with the illness severity which was instead strongly correlated with certain symptoms than other ones.[92] Exclusive reliance on diagnostic criteria impoverishes the clinical process and does not reflect the complex thinking that underlies decisions in psychiatric practice.[89] The mental disorders are not static, sharply defined illnesses with separate aetiologies and courses, but rather syndromes that overlap and develop in stages.[86,93]

Moving from a cross-sectional nosography to the longitudinal view of the development of psychiatric disorders, staging was proposed as a strategy to improve the diagnostic and treatment process in psychiatry and clinical psychology.[67,68,86]

The use of staging in psychiatry

Staging[86,94] allows to define the extent of progression of a disorder at a particular point in time and where a person is currently located along the continuum of the course of the illness; define prodromes (e.g. early symptoms and signs that differ from the acute clinical phase) and residual symptoms (e.g. persistent symptoms and signs despite apparent remission or recovery); characterize a psychiatric disorder development according to different stages.[94] In 2013, Cosci and Fava[86] systematically reviewed the literature to synthesize the different models of staging available in psychiatry and clinical psychology across different diagnostic categories such as schizophrenia, unipolar depression, bipolar disorder, panic disorder, substance use disorders, anorexia and bulimia nervosa.

As stage 1 they found the prodromal phase, defined as the time interval between the onset of prodromal symptoms and the onset of the characteristic manifestations of the fully developed illness.[86] After the acute phase (stage 2), it might be difficult to assess whether partial or full remission has occurred; attenuated symptoms, the so called residual symptoms, might be observed at stage 3; they are due to partial persistence of the disorder or an aggravation of a pre-existing abnormal personality trait.[86] Stage 4 represents chronicity of the psychiatric disorder.[86]

Staging as clinical marker of panic disorder

In 1993, Fava and Kellner[94] described a staging model for PD with agoraphobia based on the fact that, in a substantial

proportion of patients, agoraphobia, hypochondriacal fears and beliefs, and generalized anxiety precede the first panic attack. However, given that for some patients, the first panic attack can occur without conspicuous prodromal symptoms, while anticipatory anxiety, phobic avoidance, and hypochondriasis may develop subsequently,[95] Sheehan and Sheehan[96] proposed different staging process: stage 1 characterized by panic attacks with limited symptoms (subpanic); stage 2 is panic; stage 3 is hypochondriasis; stage 4 is single phobia; stage 5 is social phobia; stage 6 is agoraphobia, and stage 7 is depression.

In 2008, Fava et al.[97] proposed an updated version of the staging model of PD[94] which was described as follows: stage 1 defined by pre-agoraphobia with predisposing factors, such as health anxiety and anxiety sensitivity, genetic vulnerability, premorbid personality, hypochondriacal fears and beliefs and impaired psychological well-being; the relative weight of these factors may vary from patient to patient and lead to subtle avoidance patterns and to the stage 2, which is agoraphobia; stage 3 is characterized by the occurrence of panic attack; health anxiety may turn into hypochondriasis and/or disease phobia and/or thanatophobia; demoralization and/or major depression may occur; stage 4 in which the duration of PD with agoraphobia might predispose to the development of other psychiatric complications, as depression; agoraphobia may become more severe and hypochondriacal fears and beliefs may be accentuated.

As regard to the sub-clinical symptoms, the most common prodromal symptoms in PD were depressed mood, illness phobia, distress and avoidance of closed spaces, excessive worries, negative affectivity, anxiety sensitivity and health anxiety or fear of disease; whereas the more prevalent residual symptoms were generalized anxiety, somatic anxiety, health anxiety, low self-esteem, agoraphobia, hypochondriasis, reduced psychological and physical well-being, limited symptoms of panic attacks, anticipatory anxiety and depression.[86,95,98,99] Within the framework of the Diagnostic Criteria for Psychosomatic Research,[100] the following subclinical symptoms were proposed given that all of them were found to be associated with PD and agoraphobia:[99] disease phobia, somatization, irritable mood. Disease phobia might be part of the hypochondriacal syndrome, yet they may also occur independently; disease phobia differs from hypochondriasis for three characteristics: fears concern a specific disease and are unlikely to be shifted to another disease or organ system; fears tend to manifest themselves in attacks rather than in constant worries as in hypochondriasis; it often results in the avoidance of internal and external illness-related stimuli, while hypochondriasis involves reassurance-seeking or checking behaviors.[100] Somatization is conceptualized as a clustering of somatic symptoms involving different organ systems probably due to an enhanced general sensitivity to pain and discomfort.[100] Irritable mood refers to the concept of irritability that might be part of psychiatric syndromes; it is always unpleasant for the individual and its overt manifestation lacks a cathartic effect.[100]

In 2013, the staging model was updated[86] as follows (Table 2): the prodromal phase (stage 1) was defined by the presence of subclinical symptoms of agoraphobia, social phobia, generalized anxiety disorder, hypochondriasis; these symptom being stable during the acute phase (stage 2); panic attack start with subsequent worsening of anxiety and hypochondriacal symptoms and possible co-occurrence of demoralization and major depression (stage 3); PD might endure, in persistent or attenuated form, with agoraphobia and/or social phobia and/or generalized anxiety disorder and/or hypochondriasis, which in turn might predispose to the development of other psychiatric complications as depression (chronic phase, stage 4).

The phenomenological clinical sequence of PD might be defined as follow: phobic avoidance and hypochondriasis leading to panic, which, in turn, leads to more phobic avoidance and hypochondriasis. The rollback phenomenon might thus favour a decrease in avoidance by exposure, which improves agoraphobia and panic, with eventual disappearance of panic, whereas agoraphobia persists although to a less degree.[95] Prodromal symptoms of PD might tend to become residual symptoms, which, in turn, may progress to prodromal symptoms of relapse.[95] Alternatively, the rollback phenomenon might be characterized by anxiety elicited by bodily sensations, which influences catastrophic beliefs and such beliefs influence avoidant behaviour.[95]

According to the staging model, the acute phase of PD represents a "transfer station" from prodromal to residual symptoms.[86] Within the staging framework seems unlikely that

Table 2. Staging of panic disorder[86]

Stage 1	Prodromes: agoraphobia and/or social phobia and/or; generalized anxiety disorder and/or hypochondriasis
Stage 2	Acute manifestations of agoraphobia and/or social phobia and/or generalized anxiety disorder and/or hypochondriasis
Stage 3	Panic attacks occur, panic disorder with aggravation of anxiety and/or hypochondriacal symptoms; demoralization and/or major depression
Stage 4	Chronic (attenuated or persistent form): panic disorder and/or agoraphobia and/or social phobia and/or generalized anxiety disorder and/or hypochondriasis. Increased vulnerability to major depression

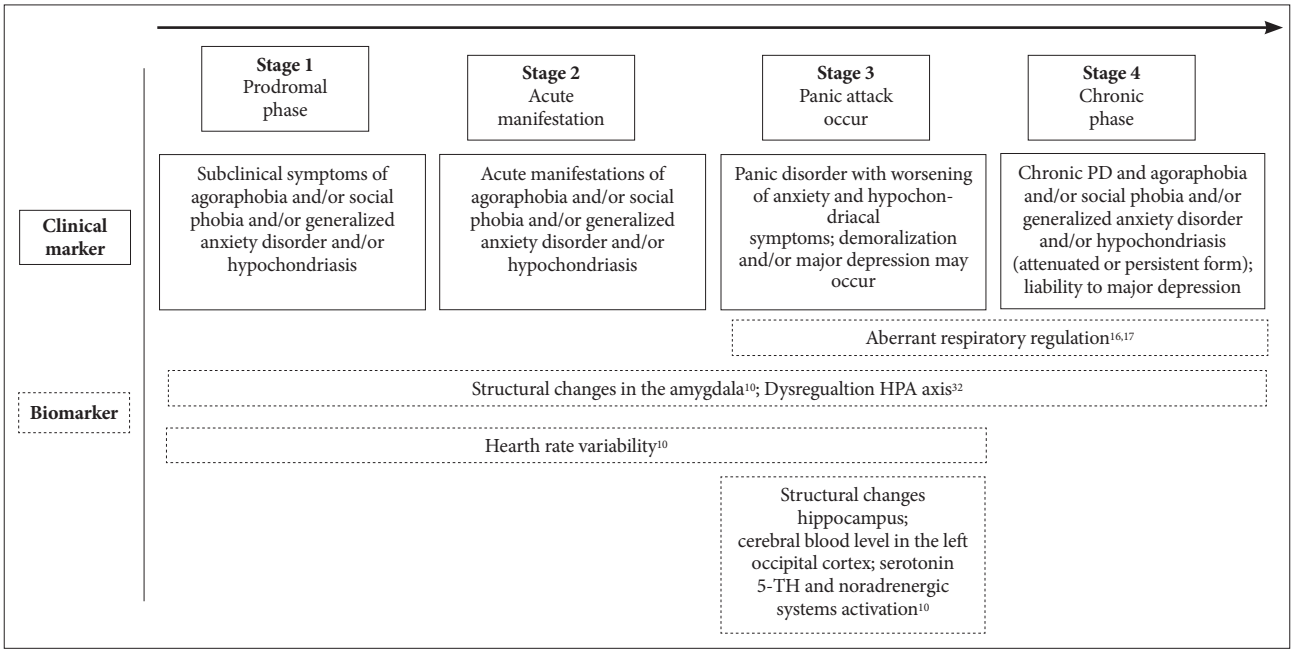

Figure 1. Putative biomarker stage-specific for panic disorder.

panic attack is a pathognomonic features of panic disorder, while it is plausible that it might be a trans-diagnostic risk factor for the development of agoraphobia and/or social phobia and/or generalized anxiety disorder, and/or hypochondriasis.[86] The staging model of PD has been supported by a vast bulk of literature[86] and can be a good clinical marker (Table 2) for PD:

1) It is a "susceptibility/risk marker," allowing to detect the presence of prodromal symptoms of PD (e.g., stage 1);

2) It is a "diagnostic marker," allowing to identify individuals at each single stage of the disorder and the longitudinal evolution of PD across different stages;

3) It is a "prognostic marker," Fava et al.[101] underline the prognostic value of residual symptoms given that they are negatively correlated with psychological well-being[101] and that may represent the onset of prodromes of relapse. Thus, residual symptoms should be a target of therapy;[95]

4) It is a "predictive marker," staging might improve the clinician's ability to select a proper treatment to prevent the progression to further stages or promote regression to an earlier stage.[86] Stage-specific therapies have been shown to be effective for depression.[102] Furthermore, agoraphobic avoidance was found to be a strong predictor of non-response to pharmacotherapy and poor response to CBT.[103,104]

Given that the staging model of PD is specific for panic disorder,[86] it is also a specific marker for PD and its use is easily practically and economically viable in clinics.

DISCUSSION

According to the clinimetric principles,[68,87,88] a valid marker must be sensitive, specific, and predictive.[2] Staging[86] has such properties while biomarkers for PD present low specificity and low predictive value.[9,10,45,49] Biomarkers would be more specific if related to specific stages of panic disorder. We here present an attempt to enrich the staging model of panic disorder with stage-specific biological markers (Figure 1). Changes in amygdala volume, lower HRV, HPA-axis dysregulation were observed in generalized anxiety, social anxiety, and agoraphobia,[9-11,20,28,32] thus they may be specific for stage 1 and 2. All biomarkers here described were studied in samples of patients satisfying the DSM diagnosis of PD, thus having panic attacks. This suggests that these biomarkers can be specific for stage 3 or 4. HPA-axis dysregulation, aberrant respiratory pattern, and changes in amygdala volume might be involved in stage 4 given that: 1) hyperventilation might be chronic;[16,17] 2) higher cortisol levels predict higher symptoms severity at 2−4 year follow-up; 3) lower amygdala volumes were found in patients with mean (±SD) duration of illness of 5.4 (±6.4) years.[11] However, this proposal has the limitation that each biomarker is apparently specific for more than one stage. This underlines the limitations already illustrated for biomarkers which, taken without a clinical marker, are still aspecific and, as a consequence, with limited clinical utility.

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