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REVIEW ARTICLE

Brazilian Medical Association guidelines for the diagnosis and differential diagnosis of panic disorder

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Objective: To present the most relevant findings regarding the Brazilian Medical Association guidelines for the diagnosis and differential diagnosis of panic disorder.
Methods: We used the methodology proposed by the Brazilian Medical Association for the Diretrizes Project. The MEDLINE (PubMed), Scopus, Web of Science, and LILACS online databases were queried for articles published from 1980 to 2012. Searchable questions were structured using the PICO format (acronym for ''patient'' [or population], ''intervention'' [or exposure], ''comparison'' [or control], and ''outcome'').
Results: We present data on clinical manifestations and implications of panic disorder and its association with depression, drug abuse, dependence and anxiety disorders. In addition, discussions were held on the main psychiatric and clinical differential diagnoses.
Conclusions: The guidelines are proposed to serve as a reference for the general practitioner and specialist to assist in and facilitate the diagnosis of panic disorder.

Keywords: Panic disorder; anxiety; guidelines; diagnosis; differential diagnosis

Introduction

Panic disorder (PD) is characterized by the presence of sudden anxiety attacks accompanied by somatic symptoms (panic attacks) and development of a persistent concern about their recurrence and possible implications.[1] PD a disabling condition associated with long-term negative consequences such as decreases in productivity, welfare, social relations and self-realization, and may lead to high utilization of medical resources.[2] The lifetime prevalence of PD is estimated to range from 1.5 to 5%.[3]

Many patients begin to avoid situations or places where they previously experienced a panic attack or believe one may occur, developing an avoidance known as agoraphobia. People with PD are often not recognized as having the disorder. It is common for patients to seek several experts depending on their predominant somatic complaints (e.g., heart, stomach, respiratory symptoms) and undergo a variety of tests before being diagnosed with PD. Without a correct diagnosis, the appropriate treatment cannot be provided and the disorder tends to become chronic.[4] PD often occurs alongside other psychiatric comorbidities. Community surveys have showed a high frequency of substance abuse, depression, and suicide attempts in these patients.[5] The difficulty in establishing the diagnosis of PD or the distinction between PD and other diseases prevents early treatment and a better quality of life for these patients.

Based on this evidence, the Brazilian Medical Association (BMA) and the Brazilian Psychiatric Association (BPA) have developed guidelines to help medical professionals through the general diagnosis and differential diagnosis of PD.

Methods

We reviewed articles written between 1980 and 2012 and indexed in the following databases: MEDLINE (PubMed), Scopus, Web of Science, and LILACS. Relevant publications and diagnostic manuals, such as the DSM-IV and the ICD-10, were also included. The search strategy was based on structured questions formulated according to the PICO format, which stands for ''patient'' (or population''), ''intervention'' (or exposure), ''comparison'' (or control), and ''outcome,'' as recommended by the BMA. The use of objective and structured clinical questions enables the development of strategies for finding the best

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evidence. For example, the search strategy we used for the question: ''Is there current evidence of the role of genetic factors in the etiology of PD?'' was as follows: P – patients with PD (panic disorder OR panic agoraphobia), I – indicators of genetic influence (genetic predisposition to disease genetics OR* models, genetic linkage OR chromosome mapping genetic markers, OR family twin studies OR dizygotic twins, monozygotic twins), C – no control group, O – no outcome. This strategy led to articles that were chosen according to the following steps: selection of evidence, critical evidence, extraction, and translation of the results according to the grade of recommendation and strength of evidence. These criteria were arranged as follows: a) experimental or observational studies with better consistency; b) less consistent experimental and observational studies; c) case reports; and d) opinions devoid of critical evaluation, based on physiological studies or animal models.

For intersections in accordance with the proposed question, we used the following keywords: panic disorder, agoraphobia, diagnosis, questionnaires, sensitivity and specificity, classification, epidemiology, prevalence, prevention and control, life change events, Severity of Illness Index, prognosis, recurrence, age factors, age distribution, risk factors, comorbidity, phobic disorders, generalized anxiety disorder, depression, post-traumatic, sleep, sleep disorders, polysomnography, genetic predisposition to disease, genetics, genetic markers, social environment, phenotype, differential, lactates/diagnostic use, carbon dioxide/diagnostic use, respiration/drug effects, heart/pathophysiology, heart diseases, cardiovascular diseases, arrhythmias, hypertension, blood pressure, heart rate, electrocardiography, thyroiditis, autoimmune, cerebral cortex/abnormalities, image processing, magnetic resonance imaging, antidepressive agents, cognitive therapy, and combined modality therapy.

After analyzing this material, we selected articles that had higher recommendation grades and greater strength of evidence to support these guidelines. The following sections list the most important findings of the BMA and BPA guidelines that relate to both the diagnosis and differential diagnosis of PD.

Results and discussion

What is the significance of scales in the identification and evaluation of patients with PD?

Scales for assessment of panic attacks are widely used in clinical trials, ensuring that information collected regarding specific symptoms is standardized and compared with other studies for later application in clinical practice. The goal of initial evaluation is to characterize the clinical picture systematically and quickly and cover a wide range of symptoms. The collected data are transformed into a numerical score that reflects the total frequency and severity of symptoms. Assessment may be repeated throughout treatment to investigate the clinical improvement and therapeutic effects of the administered treatment and to provide objective data on the clinical progress of the patient[6] (D).

Diagnostic identification has been determined through semi-structured clinical interviews, such as the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[7] (D) and the Mini International Neuropsychiatry Interview (MINI) – Brazilian version[8] (B), which are both based on the DSM-IV[1] (D). Administered to a Brazilian population suspected of suffering from PD with agoraphobia, MINI showed a sensitivity of 44% and specificity of 97%, yielding a likelihood of disease (LR+) of 14.67 (95%CI 4.71-45.69), increasing the LR+ from 5 to 44%[8] (B).

Scales that assess symptoms of PD may be divided into global scales of anxiety, scales of the frequency and intensity of panic attacks, scales of phobic avoidance, and scales of distorted cognition regarding physical reactions of anxiety[6] (D). Several scales have been translated into Portuguese, but no specific scale for clinical features or identification of patients with PD has been validated in a Brazilian sample. The scales most commonly used in Brazilian practice are described below.

The Clinical Global Impression (CGI), which provides an overall assessment of the severity of PD on a scale of 1 to 7 according to the frequency and intensity of panic attacks, anticipatory anxiety levels, levels of phobic avoidance, and family/occupational dysfunction, has been used to evaluate the severity of panic after pharmacological treatment[9] (D). The Hamilton Anxiety Scale (HAM-A) measures overall anxiety and consists of 14 items divided into two groups: seven mood symptoms related to anxiety and seven physical symptoms of anxiety. This scale exhibits better diagnostic capacity when studying depression in relation to anxiety[10] (B).

The Panic Disorder Severity Scale (PDSS) measures the severity of core symptoms of PD. The PDSS is a five-point Likert scale that includes the frequency of panic attacks and limited symptom episodes, the anguish caused by these attacks, anticipatory anxiety, fear, agoraphobic avoidance, social impairment, and loss of productivity in work activities caused by panic attacks[11] (A). This scale has better diagnostic capacity for patients with agoraphobia, a sensitivity of 99%, and a specificity of 98%, yielding a LR+ of 49.50 (95%CI 12.55-195.2), increasing the diagnostic certainty from 5% (prevalence/pretest probability) to 72%.[12] For patients without agoraphobia, the PDSS has low diagnostic power, with a sensitivity of 83.3% and a specificity of 64%, yielding a LR+ of 2.31 (95%CI 1.75-3.04) and increasing the diagnostic probability to only 11%[13] (A).

The Panic Associated Symptoms Scale (PASS) measures the severity of the following core symptoms of PD: panic attacks, anticipatory anxiety, and agoraphobia. Using a cutoff point of 7.6, it has a sensitivity of 99% and specificity of 98%, providing a LR+ of 49.50 (95%CI 12.55-195.22), increasing the diagnostic certainty from 5% (prevalence) to 72%[14] (B). The HAM-A shows good correlation with the PASS[14] (B), with $r = 0.78$.

Patients seen in primary care and at risk of psychiatric disorders may be evaluated using the Patient Health Questionnaire (PHQ-PD)[15] (B). The PHQ-PD found that 4.8% of patients suffer from PD, with a higher rate of

7.6% in patients who already had psychiatric comorbidities and 9.8% of patients before they presented inexplicable physical complaints. This questionnaire has a sensitivity of 71% and a specificity of 83%, providing a LR+ of 4.18 (95%CI 2.66-6.56), which increases the pretest probability (prevalence of disease) from 5 to 18% for the general population and 10 to 32% for patients with inexplicable somatic complaints[15] (B).

For screening, the Panic Disorder Self-Report (PSR) is a self-enforcement questionnaire, based on the DSM-IV[1] (D), which showed 100% specificity and 89% sensitivity as compared with a structured diagnostic interview. This instrument also features test-retest reliability, discriminant validity, and clinical validity, but has not yet been validated in Portuguese[16] (B). The PSR provides a LR+ of 89 (95%CI 12.64-626.42), which increases the pretest probability of disease from 5 to 82%.

What are the clinical manifestations of PD in adults?

Individuals with PD have recurrent, unexpected anxiety attacks. A panic attack is defined as a brief period of intense fear or discomfort, during which somatic symptoms develop abruptly[1] (D). For the diagnosis of PD, the patient must present spontaneous panic attacks which occur ''out of the blue.'' Often, the attacks become situational, associated to previous places or situations where the patient had a spontaneous panic attack, such as crowds or traffic[1] (D).

The other feature of PD is anticipatory anxiety. The patient develops a concern about the recurrence of panic attacks, maintaining heightened awareness of bodily sensations. Once the anxiogenic situations associated with panic attacks are avoided, agoraphobia soon develops[17] (D). In this phase, there is avoidance of places or situations in which it is difficult or embarrassing to obtain help in the case of a panic attack. In general, the agoraphobic patient tends to avoid being alone and in crowded places. Thus, safety behaviors are developed, such as the use of anxiolytic drugs and ensuring that one is in the company of others, which greatly restrict functionality[17] (D).

According to the DSM-IV[1] (D), panic disorder is a period of intense fear and discomfort in which four or more of the following symptoms are present: 1) shortness of breath (dyspnea) or choking sensation; 2) dizziness, unsteadiness, lightheadedness, or feeling faint; 3) palpitations or accelerated heart rate (tachycardia); 4) trembling or shaking; 5) sweating; 6) smothering; 7) nausea or abdominal distress; 8) depersonalization or derealization; 9) paresthesias (numbness or tingling); 10) chills or hot flushes; 11) chest pain; 12) fear of dying; and 13) fear of going crazy or losing control. Furthermore, there must be at least 1 month of persistent concern about having another panic attack, worry about possible implications or consequences of panic attacks, or a significant behavioral change related to the attacks.

The ICD-10 criteria for the diagnosis of PD[18] (D) include: 1) recurrent attacks of severe anxiety (panic attacks) that are not consistently associated with a certain situation or circumstance, i.e., are unpredictable; 2) symptoms include sudden onset of palpitations, chest pain, choking sensations, dizziness, and feelings of unreality (depersonalization or derealization). Moreover, there is often a secondary fear of dying, losing control, or going mad.

What are the clinical manifestations of PD in children and adolescents?

Symptoms of PD in children and adolescents are similar to those experienced by adults, such as palpitations, tremors, restlessness, dizziness, shortness of breath, weakness, sweating, chest pain, abdominal discomfort, nausea, numbness, and fear of losing control[19-21] (B). Although PD is considered rare in young individuals, the frequency of the disorder may range from 0.5[22] (B) to 2%[21] (B); rates as high as 6% have been reported. No epidemiological data are available for agoraphobia, except from patients referred to pediatric clinical services, with rates between 15[23] (B) and 18%[22] (B).

As has been reported in several studies and is often noted in clinical practice, many adults with PD report that their symptoms began in childhood or adolescence. When comparing demographic and clinical characteristics of children and adolescents with and without PD, there were no gender differences in expressing symptoms of the disorder; however, there was a higher occurrence of PD in girls.

Regarding differences in the manifestations of PD in each age group, several authors argue that cognitive symptoms (e.g., fear of losing control) would be more present during adolescence and adulthood than in childhood[23] (B). Contrary to this finding, other studies argue that there are no differences in the symptoms presented by children and adults or children and adolescents[19,21] (B).

Is there evidence of the role of genetic factors in the etiology of PD?

Among biological factors, the role of genetics in the onset and maintenance of PD has been investigated[24] (D). Family studies show a higher incidence of PD among first-degree relatives of patients[25] (D), with heritability being estimated at 43-48% for PD and 61% for agoraphobia[26] (B).

A number of chromosomal regions have been associated with susceptibility to PD, specifically 2q[27] and 15q[27] (B), chromosome 7[28] (B), chromosome 1q[29] (B), chromosome 9q[30] (B), 12q[31] (D), 22q,[32] and 13q[32] (B). Several studies also suggest that anxiety disorders, including phobias and PD, are complex traits that share at least one susceptibility locus in relation to chromosome 4q[33] (B).

It is important to note that, despite genetic factors, phenotypic expression is established through the interaction between genes and the environment[34] (D). Twin studies have indicated moderate heritability in PD and

suggest that environmental and genetic contributions are equally important[24,35] (B).

Is there evidence of the role of environmental stressors in the etiology of PD?

A number of studies note the high prevalence of stressful life events, such as serious illness or an accident involving a family member or close friend, personal physical illness, worsening relations with one's spouse, trouble with one's boss, and worsening conditions in the workplace, prior to development of PD[36,37] (B).

In a study of 187 patients with PD, the average number of significant life events was 7.8, with a mean value of 3.6 for positive events and 5.3 for negative events. Twenty-five percent of events were considered highly undesirable, while 22% were considered very desirable. In addition, adverse life events were associated with worse psychopathology[38] (B).

A 5-year longitudinal study assessed the factors involved in the onset of panic attacks in 2,000 office workers in a factory. Recent stressful events had a direct effect on the first episode of panic (standardized path coefficient of 0.06), with the strongest predictive value among other variables that were evaluated[39] (A).

What is the importance of agoraphobia in the diagnosis of PD?

In recent years, agoraphobia has been viewed as directly related to recurrent panic attacks, and in most cases, it appears as a consequence or complication of PD[40] (D). Other authors believe agoraphobia may be conceptualized as an independent disorder, with more specific criteria that are residual and subordinate to PD[41] (D).

In patients with different subtypes of PD, it was observed that situational panic attacks were more related to the presence of agoraphobia and anticipatory anxiety was higher when agoraphobia was accompanied by PD[42] (B). Results from the National Comorbidity Survey Replication found that lifetime prevalences of 22.7% for panic attack as an isolated event, 3.7% for PD without agoraphobia, and 1.1% for PD with agoraphobia, the latter being associated with a greater number of panic attacks and a greater persistence of the disorder. The presence of agoraphobia was associated with increased severity and a greater number of comorbidities[3] (A). Despite the high prevalence of agoraphobia in PD, this condition is often underdiagnosed and undertreated[40] (D).

PD patients with agoraphobia tend to have a more chronic disorder than do those without agoraphobia. In a 3-year cohort study of PD patients with and without agoraphobia, those who had only PD recovered more often than did patients with PD with agoraphobia. Nevertheless, there were no between-group differences in disease recurrence rates at the end of the follow-up period[43] (A). Recovery rates tended to be lower, estimated at 18-64%, in individuals diagnosed with PD and agoraphobia[44] (D).

Likewise, a longitudinal study and a naturalistic observation, the Harvard/Brown Anxiety Research Project, found that the probability of remission for patients with PD at 1-year follow-up was 39%. When agoraphobia was present, this rate fell to 17%[45] (A). In patients who were studied for 8 years, the percentage of remission was higher (38%) among those initially diagnosed as having PD without agoraphobia than for those diagnosed with agoraphobia (20.6%)[46] (B).

Are there differences between PD patients with or without agoraphobia?

PD may exist either with or without agoraphobia, but cases of agoraphobia without a history of PD are more uncommon[47] (B) and this diagnostic categorization is still controversial.

Comparisons between outcomes in PD with agoraphobia and in PD without agoraphobia are inconclusive. People with PD and agoraphobia interpret stimuli with a catastrophic way of thinking; yet, research has suggested that the consequences of catastrophizing events were not sufficient to differentiate between the two groups[48] (B). Moreover, it has been observed that, in patients with PD and agoraphobia who were treated with exposure to panicogenic situations, the presence of residual agoraphobia was a strong predictor of relapse[49] (B).

Comparison of the treatments administered to patients with PD with or without agoraphobia showed that, in both groups, a combination of psychotherapy and drug therapy was more effective than monotherapy during the acute phase (first 8-12 weeks of treatment), while patients in the chronic phase (after 12 weeks) should be treated with combined therapy or psychotherapy alone[50] (A). In the acute phase, there is a relative risk reduction associated with combination therapy vs. pharmacotherapy alone, with RR = 1.24 (95%CI 1.02-1.52), and combination therapy vs. psychotherapy alone, with RR = 1.16 (95%CI 1.03-1.30). For treatment during the chronic phase, combination therapy is more effective than pharmacotherapy alone, which reduces the relative risk to RR = 1.61 (95%CI 1.23-2.11), whereas no significant differences between combination therapy and psychotherapy were found (RR = 0.96, 95%CI 0.79-1.16)[50] (A). Additionally, there were no significant differences between the types of pharmacological treatment for PD with and without agoraphobia[51] (B).

What is the impact of depression on the diagnosis and prognosis of patients with PD?

Anxiety disorders and depression co-occur with great frequency, and most cases of depression are secondary to an anxiety disorder (67.9%)[52] (A). Studies show that, because depression is the most common mood found in PD, it must be addressed during PD treatment, especially due to its association with worse severity of PD[53] (A). In a WHO study involving 25,916 patients who were treated in the primary health care setting, the likelihood of

depressed patients presenting comorbid PD were 12 times greater than expected[54] (A).

In a population survey, the lifelong prevalence of depression in patients with PD was significantly higher (55.6%, OR = 6.8) than that of PD in people with depression (11.2%, OR = 6.2). In addition, people with PD and depression reported significant more physiological symptoms during attacks (9.1%) than those without depression ($p \leqslant 0.001$). Patients were also more likely to use psychiatric services when suffering comorbid conditions as opposed to one condition[53] (A).

In general, studies have shown that depression in PD is associated with a more severe psychopathology[54] (A), worse prognosis[55] (B), poor response to treatment[56] (B), an increased number of suicide attempts[57] (B), and limited functioning[58] (B) than PD or depression alone. Patients should also be evaluated for presence of the demoralization syndrome, which is characterized by low self-esteem and feelings of inadequacy and guilt arising from the limitations of PD[59] (D) and is sometimes confused with depression. In this syndrome, symptoms improve after successful treatment of PD, often with no need for specific mood-directed treatments. Early diagnosis of PD can reduce the risk of developing depression[52] (A).

What is the impact of alcohol and illicit drug abuse and dependence on the diagnosis and prognosis of patients with PD?

Patients with PD may engage in alcohol abuse. There are several explanations for this co-occurrence: a) PD leads to alcohol abuse, which is often used as self- medication for the improvement of anxiety symptoms; b) chronic alcohol use and withdrawal induce neurochemical changes that lead to panic attacks; and c) a third factor, such as familial transmission, leads to the development of the two conditions[60] (D). In a 3-year prospective epidemiological study of women, occasional intake of large amounts of alcohol (binge drinking) was associated with an increased risk of PD, with OR = 2.23 (95%CI 1.01-4.91)[61] (A).

In 73.1% of PD patients, the onset of alcohol use preceded the onset of PD. It has been observed that patients with PD and alcoholism may experience a more severe disorder, with an increased number of panic attacks and increased anticipatory anxiety[62] (B). Other psychoactive substances, such as cocaine, cannabis, and nicotine, also appear to be able to trigger panic attacks or increase the frequency and intensity of these attacks[63] (D).

Moreover, patients with both PD and alcohol abuse or dependence tend to frequently report a history of depression and use of other psychoactive substances. Alcoholic patients with comorbid PD often have other comorbidities as well, such as depression, dysthymia, and a history of more suicide attempts[64] (B). Individuals who experience panic attacks attempt suicide more often, especially if they abuse alcohol[57] (B).

What are nocturnal panic attacks? What is the significance of nocturnal panic attacks in the diagnosis of PD?

Nocturnal panic attacks are characterized by a sudden awakening from sleep in a state of panic, which is defined as an abrupt and rapid period of intense fear or discomfort, accompanied by physical or cognitive symptoms. These panic attacks occur without an obvious trigger[65] (B). They are distinguished from night terrors, sleep apnea, and nightmares[66] (D), and their prevalence ranges from 44 to 71% of patients with PD[66] (D). On the other hand, diurnal panic attacks occur when the subject is awake and can be spontaneous or situational.

A polysomnographic study of PD patients showed respiratory irregularities in the subgroup of patients with panic attacks, which suggests that nocturnal panic attacks could be a variant of PD[67] (C). Similarly, another study indicated that patients with prominent respiratory symptoms are more sensitive to CO_2 inhalation and have higher rates of nocturnal panic attacks, which is related to a more severe subtype of panic, a longer duration of the disease, and more intense phobic symptoms[68] (B). Patients with nocturnal panic attacks are more often depressed or have other psychiatric symptoms[69] (B) and tend to be more prone to developing anorexia nervosa and somatization disorder[70] (B).

Thus, diurnal and nocturnal panic attacks seem to develop in different ways. In nocturnal panic attacks, biological factors such as dysfunction of the autonomic nervous system can be a crucial aspect, whereas cognitive and psychological factors may act as an initial stimulus for diurnal panic attacks[71] (D).

Several pharmacological agents are more effective in patients with nocturnal panic attacks, while cognitive and behavioral strategies may be more suitable for daytime panic attacks[72] (D). It is also possible that patients with diurnal and nocturnal panic attacks are similar with respect to comorbidities, symptoms of negative affect, and impact in interpersonal functioning. Patients with nocturnal attacks tend to have more sleep disturbances and less agoraphobic avoidance, because the association between panic situational factors is less frequent,[73] (B) but do not differ from patients with diurnal panic attacks in sleep architecture, sleep physiology, sleep quality, or self-reported severity of PD[66] (D). Likewise, in a short-term prospective study of 57 patients taking nortriptyline, both groups showed similar features in terms of phenomenological results[65] (B).

Should psychiatrists screen PD patients for sleep disorders?

Subjective reports have shown high rates of sleep complaints in PD patients as compared with control groups[74] (A). Although the findings of polysomnographic studies of PD patients are still inconsistent[75] (B), decreases in the efficiency and duration of sleep have been reported[76,77] (B). In general, lack of sleep has been

strongly associated with comorbid depression, with a prevalence rate of 30-40%[78] (A).

Chronic complaints about sleep occur in up to 53% of PD patients without comorbidities. When there is a comorbid mood disorder, this rate reaches 86%[79] (B). The most common complaints are often confused with depression and are related to initiating and maintaining sleep, early awakening, difficulty awaking, oversleeping, lethargy, and daytime sleepiness[79] (B).

In general, a high percentage of patients (77%) with nocturnal panic attacks reported sleeping problems[79] (B). Nocturnal panic attacks may disturb sleep, buth by interrupting it and because of subsequent anticipatory anxiety, which is characterized by fear of sleeping and having a panic attack. This fear leads to the avoidance of sleep and then to sleep deprivation, which further aggravates anxiety. Polysomnography is of particular importance in the clinical diagnosis because it allows for the differential diagnosis of panic attack, night terrors, nightmares, and sleep apnea[66] (D).

In the case of panic attacks in a social situation, how does one make the differential diagnosis between social anxiety disorder (SAD) and PD?

Symptoms related to social anxiety and PD may be confused, especially when the patient's only avoidance is social situations[80] (A). Identifying the focus of fear is essential to establishing a diagnosis. In cases of social anxiety, fear and somatic symptoms are triggered by situational activators, such as exposure and social performance. In PD, these symptoms are sudden and often do not result from a trigger.

Beliefs related to fear are also different. In the context of SAD, fears are related to the fear of being humiliated in a social situation or displaying excessive anxiety. In PD, beliefs are associated with fear of having a panic attack in public and the inability to receive help in a social environment.

What are the differences between the most common concerns of patients with generalized anxiety disorder (GAD) and patients with PD?

In GAD, patient concerns are focused on situations of everyday life, and are accompanied by stress, worry, and fear of the worst, e.g., family violence or health problems. There is no focus on bodily sensations or fear of having a panic attack, but rather an excess of continued anxiety symptoms[1] (D).

In the event of an extremely anxiogenic situation, how does one differentiate between PD and post-traumatic stress disorder (PTSD)?

In PTSD, the patient must have experienced or witnessed a situation posing real danger to their life or to others. After the traumatic experience, a person with PTSD usually has distressing memories of the event and intrusive dreams. Because the memories are painful, the person tends to avoid thoughts, activities, and places related to the trauma. Other symptoms such as insomnia, irritability, and difficulty concentrating tend to occur[1] (D).

Conversely, in PD, there is no history of direct or indirect exposure to the types of situations that typically cause PTSD. Instead, the panic attack is spontaneous, sudden, with no apparent cause, and may even occur during sleep.

Which clinical diseases should be considered in the differential diagnosis of PD?

The set of symptoms that characterize panic attacks or PD may be confused with a series of clinical medical conditions[81] (D). In the differential diagnosis of PD and clinical entities of an organic nature, late onset (after the age of 45 years) and the presence of atypical symptoms, such as dizziness, unconsciousness, and loss of sphincter control, suggest that an organic cause may be associated with the attacks[82] (D). It is also important to note that clinical diseases may co-occur with PD, in which case both conditions must be treated.

The differential diagnosis should include the following clinical diseases, stratified by organ system involved: 1) cardiovascular system – acute myocardial infarction may be the clinical situation that most often resembles PD, because its symptoms – such as chest tightness, shortness of breath, palpitations, sweating, and feeling of impending death – may also occur in anxiety attacks and coexist in both situations (thus, the patient should undergo tests such as ECG and serum cardiac markers to rule out an organic etiology; normal ECG and cardiac markers confirm the diagnosis of PD[82] [D]); other cardiovascular diseases from which PD must be differentiated include congestive heart failure, hypertension, mitral valve prolapse, angina pectoris, and atrial tachycardia[83] (B); 2) neurological system – neurological conditions such as temporal lobe epilepsy, space-occupying lesions, multiple sclerosis[82] (D), and Parkinson disease[84] (C) can mimic a panic attack; 3) endocrine system – Addison's disease, Cushing's syndrome, diabetes, hypoglycemia, hyperthyroidism, hypoparathyroidism, self-immune thyroiditis[85] (C), and pheochromocytoma can mimic a panic attack[82] (D); in addition to these conditions, premenstrual syndrome and menopausal disorders can also exhibit characteristics that may warrant inclusion into the differential diagnosis of PD[82] (D); 4) acute lung diseases – asthma, pulmonary embolism, and chronic obstructive pulmonary disease or acute anxiety can trigger situations with clinical manifestations similar to those found in PD[87] (D); 5) other medical conditions – drug use (hallucinogens, marijuana, cocaine, amphetamines, and nicotine) and withdrawal syndromes (alcohol, benzodiazepines, opiates, and cocaine) can also mimic the symptomatology of PD[82] (D).

What are the results of laboratory studies of PD?

Pharmacological induction of panic attacks in the laboratory has been one of the strategies used in PD

research. This technique enables study of panic attacks under controlled conditions and evaluation of the efficacy of pharmacotherapy for PD.

In one study, unmedicated patients with PD (n=31) were subjected to inhalation of 35% CO_2 and compressed atmospheric air. Overall, 71% of the patients (n=22) had panic attacks with CO_2, whereas none of the subjects reacted to the compressed air[86] (B). In another study by the same group, panic attacks were blocked by clonazepam (2 mg/day) but not by placebo, and patients who took clonazepam did not present any panic attacks at the end of the study ($p \leqslant 0.001$)[87] (B).

In a trial of antidepressant treatment of PD, after the 7th day, responses to CO_2 diminished significantly in groups receiving imipramine (20 mg/day, $p = 0.004$), paroxetine (10 mg/day, $p = 0.001$), and sertraline (25 mg/day, $p = 0.004$)[88] (A).

In general, hyperventilation or breath-holding maneuvers, despite inducing respiratory alkalosis with transient breathlessness, dizziness, and anxiety, have not been proven to cause panic attacks in most patients who undergo this experiment, except in patients who are more susceptible[89] (D).

What are the results of neuroimaging studies in PD?

With the advent of functional imaging studies, cerebral regions are being mapped and correlated with behavioral disorders, including anxiety disorders[90] (B).

In a study with 12 PD patients and 12 controls, the volume of the right and left amygdala was decreased in PD patients, while controls showed no change in their sizes[91] (B). Following this line of research, other authors found that the left temporal lobe of 11 PD patients exhibited a reduction in volume compared to 11 healthy controls[92] (B).

The hippocampal region of the septum seems to play an important role in controlling anxiety[93] (D). Thus, there is suspicion that the septo-hippocampal system plays a role in the occurrence of PD. In one study, researchers detected a high frequency of cavum septi pellucidi with electroencephalographic abnormalities in patients with PD[94] (B). Another study, however, did not confirm the previous observations in 21 patients with PD compared with 21 controls[95] (B).

When comparing the gray matter of 19 PD patients to 20 healthy volunteers, researchers found an increase in the left insula of this area in PD patients compared to healthy controls and an increase in the superior temporal gyrus, midbrain and bridge. Relative gray matter deficits were observed in the right anterior cingulate cortex. The authors concluded that abnormalities in the brain stem are involved in the generation of panic attacks[96] (B).

Is there any benefit to performing heart tests after a diagnosis of PD has been established?

A study of 5,187 patients showed that the presence of any anxiety disorder diagnosis was significantly associated with the presence of various diseases. PD was associated with vascular conditions (OR = 2.28), bone or joint diseases (OR = 2), and neurological conditions (OR = 1.75). Other anxiety disorders such as GAD, SAD, and simple phobias had less of an association with physical illness than did PD[97] (A). A population-based study in Norway evaluated 64,871 patients to explore the correlation between PD and systolic blood pressure. GAD was associated with the presence of low systolic blood pressure, while patients with PD had a mean systolic blood pressure of 140 mmHg[98] (A).

Decreased heart rate variability was identified as a potential risk factor for sudden death in patients recovering from myocardial infarction[99,100] (B). Evidence suggests that patients diagnosed with PD exhibit reduced heart rate variability compared with controls. These findings suggest that individuals with PD show changes in cardiac autonomic control, and these changes could place them at an increased risk of ventricular arrhythmia[101] (B) and sudden cardiac death[102] (C).

A study of 3,369 postmenopausal women showed that those who experienced at least one full-blown panic attack in the preceding 6-month period were more likely to have the cardiovascular risk factors smoking, hypertension, and diabetes mellitus, as well as a history of cardiovascular morbidity (A).[103]

A 32-year study of 402 cases of coronary heart disease (137 cases of nonfatal myocardial infarction, 134 cases of angina, 131 cases of fatal coronary heart disease, 26 cases of sudden cardiac death, and 105 cases of non-sudden death) and 1,869 individuals without coronary artery disease showed that subjects with coronary disease who reported symptoms of anxiety had a higher risk of fatal outcome, with an OR of 3.20 (95%CI 1.27-8.09) for fatal coronary disease and an OR of 5.73 for sudden death (95%CI 1.26-26.1). An increased risk of myocardial infarction or nonfatal angina was not found[104] (A) These data suggest an association between anxiety and fatal coronary heart disease, particularly sudden cardiac death, in patients with coronary heart disease and symptoms of anxiety, which indicates the need for careful study of this population.

Conclusions

These guidelines, which were designed by the BMA in partnership with the BPA, serve to facilitate and assist in the decisions of physicians and to provide clarity, clinical applicability, and practical relevance for the diagnosis and differential diagnosis of PD.

Due to the close association between PD and autonomic activation, PD is often mistaken for clinical conditions such as stroke and high blood pressure, which can delay treatment. This confusion can also occur with other psychiatric disorders that have symptoms similar to those of PD. In addition to prolonging patient suffering, unsuitable treatment of the patients leads to unnecessary financial costs.

Research on PD has intensified during the last decade, particularly regarding neuroimaging, which reflects the interest of the scientific community in gaining a better

understanding of this disorder. Laboratory studies using panicogenic agents are also important for exploring the mechanisms underlying the development of PD.

Disclosure

The authors report no conflicts of interest.

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