Review

PANIC DISORDER: A REVIEW OF DSM-IV PANIC DISORDER AND PROPOSALS FOR DSM-V

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This review covers the literature since the publication of DSM-IV on the diagnostic criteria for panic attacks (PAs) and panic disorder (PD). Specific recommendations are made based on the evidence available. In particular, slight changes are proposed for the wording of the diagnostic criteria for PAs to ease the differentiation between panic and surrounding anxiety; simplification and clarification of the operationalization of types of PAs (expected vs. unexpected) is proposed; and consideration is given to the value of PAs as a specifier for all DSM diagnoses and to the cultural validity of certain symptom profiles. In addition, slight changes are proposed for the wording of the diagnostic criteria to increase clarity and parsimony of the criteria. Finally, based on the available evidence, no changes are proposed with regard to the developmental expression of PAs or PD. This review presents a number of options and preliminary recommendations to be considered for DSM-V. Depression and Anxiety 0:1–20, 2010. © 2010 Wiley-Liss, Inc.

Key words: *panic attacks; panic disorder; DSM*

INTRODUCTION

The purpose of this review is to evaluate the diagnostic criteria for panic attacks (PAs) and panic disorder (PD) in light of empirical evidence gathered since DSM-IV, and to propose changes for DSM-V where change is clearly and reliably indicated by the evidence. The review was guided by questions posed in the DSM-IV Sourcebook (Vol. 2); chapter titled "Panic Disorder and agoraphobia",[1] a review conducted as part of the DSM-V Stress Induced and Fear Circuitry Disorders Workgroup Conference, titled "Panic Disorder" (Faravelli et al., in press), and questions posed by the DSM-V Work Group. This review does not cover issues pertaining directly to agoraphobia which are covered elsewhere (see Wittchen et al., in this series). The current article was commissioned by the DSM-V Anxiety, Obsessive–Compulsive Spectrum, Post-Traumatic, and Dissociative Disorders Work Group. It represents the work of the authors for consideration by the work group. Recommendations provided in this article should be considered preliminary at this time; they do not necessarily reflect the final recommendations or decisions that will be made for DSM-V, as the DSM-V development process is still ongoing. It is possible that this article's recommendations will be revised as additional data and input from experts and the field are obtained.

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PANIC ATTACKS

STATEMENT OF THE ISSUES

PAs currently are defined as a brief period of intense fear or discomfort in which four or more of a list of 13 symptoms develop abruptly and reach a peak within 10 min (Table 1). The questions being addressed are the degree to which the list of symptoms, the cutoff of four or more symptoms, and the time to peak intensity should be revised based on evidence regarding reliability, validity, or clinical utility.

SIGNIFICANCE OF THE ISSUES

PAs are common to anxiety disorders, and are a significant marker of risk for the development and manifestation of psychopathology more broadly. As such, PAs may be utilized as a specifier or as a dimension across all DSM diagnoses. It therefore behooves DSM to review the current criteria for PAs and recommend changes where appropriate for enhancing the reliability of their detection, validity, and clinical utility.

METHOD OF LITERATURE REVIEW

The literature review focused on data published since 1994, with the publication of DSM-IV, augmented by replicated data published since 1980, with the publication of DSM-III. In addition to reviewing the DSM-IV Source Book and DSM-IV Options Book, A PubMed and PsychINFO search was conducted using the keywords PAs, unexpected PAs, expected PAs, cued PAs, uncued PAs, situational PAs, and situationally predisposed PAs. This produced a list of over 1,599 (PsychINFO) and 1,404 (PubMed) overlapping articles, many of which did not provide relevant information. This review was supplemented by an inspection of bibliographies from key articles. These searches were then refined by restriction to articles written or translated into English.

THIRTEEN PA SYMPTOMS

Only a limited number of studies investigated the symptoms of PAs. However, the results from extant studies are very consistent, in that each of the 13 PA symptoms are endorsed by at least one-quarter of the respective samples. Cox et al.[2] evaluated PA symptoms in a group of 212 patients diagnosed with PD (The term "patient" is used throughout to represent clinical or treatment-seeking samples; nonclinical or nontreatment seeking samples are referred to as community or epidemiological samples.). The most frequently endorsed symptoms were "heart pounding" (97%) and dizziness (96%), and the least frequently endorsed was paresthesias (73%) (endorsement refers to rated as being present to at least some degree). In a DSM-IV field trial, Brown et al.[3] reported symptom endorsement rates for typical PAs in the last month in 122 patients diagnosed with PD, who underwent two independent administrations of a diagnostic interview (Anxiety Disorders Interview Schedule-R).[4] Again, the most frequently reported symptom was tachycardia (86.1%), and the least frequently reported symptom was choking (31.1%). Also, inter-rater agreement for symptom endorsement across the two interview administrations ranged from 68 to 88.5%, indicating good reliability.

Epidemiological data yield similar endorsement rates. Ietsugu et al.[5] evaluated symptom ratings from 1,213 respondents in the NCS study[6] who met diagnostic criteria for a PA. All of the 13 PA symptoms were endorsed relatively frequently, with endorsement rates ranging from 36.4 to 96.6%. The most commonly endorsed symptom was palpitations. Also, their exploratory factor analysis yielded a primary factor that accounted for 42% of the variance, thereby suggesting a relatively unidimensional factor structure to PA symptoms. Finally, in 5,913 participants who endorsed experiencing a PA over their lifetime in the NIAAA NESARC surveys,[7] the percentage symptom endorsement for worst, out-of-the-blue PAs ranged from 24% (feeling of choking) and 29% (paresthesias) to 83% (palpitations, pounding heart, or accelerated heart rate) (Andrews, unpublished data).

Diagnostic interview data (which represents a retrospective estimate) have been corroborated by self-monitored data (i.e., recording PAs as they occur) from 97 patients with PD who monitored PAs for 6 weeks before treatment.[8] From that sample, who monitored 1,805 PAs, palpitations were most frequently endorsed (78%); paresthesias were least frequently endorsed (26%), but nonetheless were endorsed in approximately one-quarter of the monitored PAs. Notably, self-monitored data indicate high levels of variability in symptoms across PAs within the same individual. In their patient sample based on DSM-III PA criteria,[9]

TABLE 1. DSM-IV criteria for panic attack

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 min
1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
10. Fear of losing control or going crazy
11. Fear of dying
12. Paresthesias (numbness or tingling sensations)
13. Chills or hot flushes

found that only 0.9 symptoms out of 14 possible symptoms were consistently recorded in every self-monitored PA (and only 2.8 symptoms in at least 50% of the PAs) during a 2-week interval. De Beurs et al.[8] similarly reported that only 13% of their patient sample had a stable pattern of symptoms across self-monitored PAs over 6 weeks. These findings suggest that data regarding PA symptoms gathered during diagnostic interviews, although relatively reliable from one interview to the next, most likely represent an amalgam of symptoms frequently experienced across PAs rather than symptoms experienced in each and every PA.

Given that even the least frequently endorsed symptom from the PA symptom checklist is endorsed by approximately 25% of persons, in both community and patient samples, and in both interview-based retrospective judgment and self-monitored methodologies, it can be argued that there is no reason to exclude items from the current 13-item symptom list. However, there is a lack of research analyzing the relative importance of each symptom for the detection of PAs (Faravelli et al., 2009). Ietsugu et al.[5] used item response theory analyses to assess each symptom in terms of the degree to which it provides information about different severity levels of the latent construct of panic. The results indicated that palpitations, being the most frequently reported symptom, provided little information about the severity of panic, whereas paresthesias, choking, and fear of dying were good markers of severe PAs. However, for purposes of clinical utility, further analysis is needed of the degree to which the number of PA symptoms can be reduced without detrimentally effecting diagnostic reliability and validity.

From the perspective of cultural validity, there is also a call to expand the list of symptoms because the current list of 13 symptoms does not include symptoms most commonly reported as occurring during PAs in other cultural groups. These include higher rates than in general population samples for paresthesias among African Americans,[10] trembling among Caribbean Latinos,[11] dizziness among several East Asian groups,[12] and fear of dying among Arabs and African Americans.[10,13] Lower rates of depersonalization/derealization and loss of control have been found in some cultural settings, whereas these are very frequent symptoms in Puerto Ricans.[11,14,15] Possible reasons for this variation include differences in the content of catastrophic cognitions leading to differential symptom emphasis, such as fear of diabetes among African Americans leading to higher reports of paresthesias[10] and the influence of local ethno-physiologies and cultural syndromes on symptom expression (Hinton and Lewis-Fernández, in press). For example, symptoms that are understood to "run together" in a particular culture, or are recognized by the group as a coherent syndrome, are more likely to be reported as a cluster than symptoms that are not seen as related.[16]

Khyâl (wind) attacks are a Cambodian cultural syndrome resembling PAs that are attributed to dysregulation of a putative wind-like substance in the body. Consequently, *khyâl* attacks are characterized by a mix of PA symptoms (e.g., dizziness) and culture-specific symptoms attributed to *khyâl* dysregulation, such as tinnitus and neck soreness. Due to the availability of this cultural syndrome, clinical interviews regarding PA symptoms are more likely in Cambodia than elsewhere to evoke other symptoms of *khyâl* attacks, such as tinnitus, due to the cultural association of these symptoms in a known illness cluster.[17] Other examples of cultural syndromes that influence the cross-cultural presentation of PAs include *ataque de nervios* (attack of nerves) among Latin Americans and *trung gio* (wind)-related attacks in Vietnam.[18–20] This topic is reviewed in detail by Hinton and Lewis-Fernández in this issue.

Thus, clinical utility of the list of PA symptoms may be improved by reducing the number of symptoms, whereas cultural validity may be improved by increasing the number of symptoms. In the absence of data pertaining to either perspective, no recommendation is made to significantly change the list of PA symptoms. However, two minor changes are recommended. First is to replace the term "hot flushes" with "heat sensations." Feelings of heat in specific parts of the body (head, chest, neck) may be divergent across cultural groups during PA.[21–24] For example, sensations of "heat in the head" have been reported among Nigerian groups,[23,24] and sensations of heat in the chest appear in *ataque de nervios*.[21] These variations are not well captured by the phrase "hot flushes," which suggest full-body heat sensations, whereas "heat sensations" may better encapsulate both localized and general feelings of heat. The second recommendation is to add a note to the list of PA symptoms to indicate the types of cultural variations that may occur; "NOTE: Culture-based symptoms (e.g., tinnitus, neck soreness, headache, and uncontrollable screaming or crying) may be seen. However, four or more symptoms are required from the 13 listed symptoms for a full blown PA."

Furthermore, for purposes of increased clarity, it is recommended that the two fear symptoms (fear of losing control or going crazy, and fear of dying) be moved to the last two items of the list, thereby reorganizing the symptom list to 11 physical symptoms (with the last physical symptom being derealization/depersonalization) and 2 fear symptoms. In addition, it is recommended that the accompanying text description clarify that "fear of going crazy" is a colloquialism, often used by patients, that is not intended as a pejorative or diagnostic term.

FOUR OR MORE SYMPTOM CUT-OFF

Currently, PAs are defined as involving four or more of the list of 13 symptoms; PAs involving fewer than

four symptoms are designated as limited symptom PAs. Without ongoing self-monitoring data, ascertaining the presence of a full blown PA depends on retrospective recall of symptoms experienced during PAs. Such recall is likely to be biased, especially for PAs that occurred a long time ago, which is the case for certain individuals with PD whose avoidance strategies effectively minimize PAs.[25] Several studies have shown that patients with PD endorse fewer symptoms during ongoing self-monitoring of PAs in comparison to retrospective estimates obtained during diagnostic interviewing.[9,26] In addition to factors such as shifts in the nature of PAs over time, and reactivity to self-monitoring, biases are likely to distort retrospective judgments of symptoms. For example, a bias to catastrophize[27] may result in recalling more symptoms than actually occurred, just as chronic pain clients tend to recall significantly more pain than they had actually experienced 3–4 weeks earlier.[28,29]

Although these biases likely represent processes that are inherent to the anxiety and distress associated with PAs and PD, they may limit the veracity of the "four or more symptoms" cutoff. That is, it is unclear whether a retrospective judgment of experiencing four or more PA symptoms, for example, represents actual number of symptoms experienced vs. overall levels of distress and anxiety. Nonetheless, such biases caution against "reducing" existing cut-off points, as inflationary biases may be even more problematic at low cut-off levels.

With that caveat in mind, very few studies have addressed the cutoffs for number of symptoms, although several have reported upon the typical number of PA symptoms. For example, in a DSM-IV field trial reanalysis of the epidemiological ECA data,[30] 64% of those who reported lifetime PAs ($n = 1,593$) endorsed four or more symptoms in one or more of their *worst* PAs. In the Developmental Stages of Psychopathology epidemiological study (EDSP) of 3,021 adolescents and young adults aged 14–24 years, 58% of all reporting lifetime PAs endorsed four or more symptoms.[31] Of those who reported at least one lifetime PA in the NCS epidemiological data, 47.8% endorsed four or more PA symptoms, not specific to their worst PA.[5] In a PD patient sample, approximately 60% of *all* PAs self-monitored over a 6-week interval involved four or more symptoms,[8] although the number of patients who endorsed at least one PA with four or more symptoms was not indicated.

In terms of the significance of symptom number,[30] ECA analysis found that risk for suicide attempts and emergency room use was elevated by 20% for each additional PA symptom (treated as a continuous variable), controlling for the presence and absence of impairment associated with the PAs and the presence of uncued [spontaneous] PAs. Also, the symptom threshold of four or more symptoms predicted a two-fold increase in risk for psychiatric hospitalization. Further, receiver operator characteristic curves, designed to maximize the true-positive and minimize the false-positive rates associated with alternative thresholds for the number of PA symptoms, were tested with respect to emergency room use, suicide, and hospitalization. Optimal sensitivity and specificity were achieved with three or more symptoms, but the criterion of four or more symptoms was nearly as effective. Other data indicate that although limited symptom attacks are associated with greater comorbidity than no PAs, they are associated with less comorbidity, overall symptom severity, and health-care utilization than full PAs in patient samples.[32] However, these data are limited to retrospective judgment of symptom number (vs. self-monitoring) and as indicated such retrospection may be heavily influenced by overall anxiety and distress.

In conclusion, extant data indicate that approximately 50–60% of community and patient samples recall experiencing four or more symptoms during PAs. Also, extant findings indicate increased severity (i.e., emergency room use and suicidality) as a function of increased PA symptom count, and provide support for the current cutoff of four or more symptoms (with one study suggesting 3 or more may be slightly more effective). However, the studies are limited in number and rely on retrospective judgments of symptom number, which may be inflated as a function of anxiety or distress.[9,26] Thus, further research is needed of the dimensional quality of PA symptoms (both frequency and intensity) in relation to indices such as comorbidity, health-care utilization, and course, in both community and clinical samples. Such analyses may lead to reconsideration of this criterion and/or may give impetus to shifting from a categorical cutoff to a dimensional approach to PA symptoms.

SYMPTOMS REACH PEAK WITHIN 10 MIN

To capture the essence of PA as an abrupt surge of fear arousal, DSM-IV criteria require that the symptoms of a PA reach their peak within 10 min of the first symptom. The abrupt surge quality of PAs is evident in physiological recordings (usually of heart rate), where naturally occurring PAs present as discrete periods of arousal that peak within a few minutes and subside within minutes. For example, in a patient PD sample undergoing relaxation, spontaneous PAs were observed to peak within 3 min and subside shortly thereafter.[33] In an ambulatory monitoring study of PD patients, naturally occurring PA-related heart rate elevations usually subsided within 5 min.[34] Another ambulatory study of PD patients reported that time to peak heart rate was 4 min ($SD = 2.7$) and duration of elevated heart rate was 20 min ($SD = 1.3$).[31]

In contrast to physiological recordings, however, a number of individuals report PAs that do not peak within 10 min, at least from epidemiological survey data. In the ECA data,[35] one-third of individuals who otherwise would have met criteria for PD did not satisfy the 10 min requirement, although[31] reported

that only 8.4% failed to do so in their epidemiological study. From the Bremer Adolescent Study[36] of 1,035 adolescents, only 35% reported that their PA symptoms worsened in the first 10 min.

Cross-cultural research on this issue is limited.[12] Episodes of *ataque de nervios* with clear PA phenomenology may be subjectively experienced as peaking over a longer period. Among Dominican and Puerto Rican anxiety clinic outpatients with *ataque* ($N = 66$), 36% met full PA criteria including the requirement of peaking within 10 min; an additional 23% would have met criteria for PA if this crescendo criterion had been relaxed.[19]

Also, comparisons between those who do vs. do not report PAs that peak within 10 min show little differences. One study[37] evaluated 864 individuals who contacted NIMH for information about PAs and who met criteria for PD based on responses to a questionnaire. Those whose PAs usually achieved peak intensity within 10 min ($n = 707$, 81.8%) were compared to those whose peak intensity was usually arrived at after 10 min ($n = 157$, $n = 18.2\%$). The two groups did not differ on any variable, including PA symptom number and severity (with one exception, the symptom of nausea being more common in the prolonged onset group), comorbid symptoms of agoraphobia, social anxiety, generalized anxiety, fear of panic leading to avoidance, depressed mood, suicidality, and obsessive compulsive symptoms. Similar findings were established from a sample of 489 college students;[38] 22.1% reported a PA in the past year, but only 4.3% reported both an onset within 10 min and at least four symptoms. The remaining 18%, termed Limited Panickers, were so classified mostly because they did not report a peak within 10 min; only 39.3% of them reported peak intensity within 10 min for their *typical* PAs. There were few differences between Full Panickers and Limited Panickers on measures of anxiety, depression, and family history of PAs. Moreover, the two groups did not differ in terms of ratings of anticipatory anxiety about future attacks, or average symptom severity of typical, most recent or worst PAs. Also notable is that within the Full Panickers group, descriptions of *worst* PAs yielded mostly longer durations to reach peak intensity, with only 43% reaching peak within 10 min. These data suggest that the subjective report of time to peak for PA symptoms is of little relevance, although the studies have been limited to community and college samples.

Furthermore, data regarding self-reported duration of PAs tend to indicate lengthier intervals than would be expected based on physiological monitoring. For example, self-monitoring of PAs by a PD patient sample[9] indicated a mean duration of 23.6 min; although, the median of 12.6 min was similar to the physiological recordings by Taylor et al.[39] Other self-monitoring studies in PD patients indicate mean durations of 31 min[26] and 45 min,[8] and fail to report median values. We were unable to locate diagnostic interview data regarding the duration of PAs with the exception of a survey study of college students, in which the majority of Full Panickers indicated that their PAs typically lasted less than 10 min (71.4%).[38] Albeit limited to one study, these data suggest that nonclinical samples may report shorter PAs than patient samples.

Cross-cultural research on this issue is limited.[12] Episodes of *ataque de nervios* with clear PA phenomenology may be subjectively experienced as peaking over a longer period. Among Dominican and Puerto Rican anxiety clinic outpatients with *ataque* ($N = 66$), 36% met full PA criteria including the requirement of peaking within 10 min; an additional 23% would have met criteria for PA if this crescendo criterion had been relaxed.[19] However, no physiological studies have been conducted with culturally defined syndromes that may inform the distinction between physiological arousal and subjective reporting of the crescendo criterion.

The self-report of PAs taking longer than 10 min to reach peak intensity, and the self-report of them lasting considerably longer than would be expected, may represent discordance between the physiological response and the subjective response.[40] Additionally, it may represent lack of precision in self reporting, as clinical expertise suggests that individuals frequently include anticipatory anxiety in the build up to a PA and/or residual anxiety following a PA when describing their PAs. The current wording of the PA criteria does not clearly specify that time to peak intensity should be assessed independently of ongoing anxiety. By making explicit that PAs can occur from an anxious state as well as from a calm state, respondents and clinicians may be prompted to separate the onset of PA from existing anxiety. Also, the current criteria do not specify the duration of PA following the peak; clinical expertise suggests that duration following the peak is less significant to the identification of PAs than is the time to peak intensity. However, explicit reference to the PA peak lasting "only a few minutes" in the text that accompanies the diagnostic criteria may further facilitate the separation of PA from surrounding anxiety. These changes to the wording of the diagnostic criteria and text can be accompanied by a graphical depiction of PAs peaking from either a calm state or an anxious state, followed by return to either an anxious state or a calm state. However, further research is needed to identify specific differences along temporal and intensity dimensions for self-report vs. physiology during PAs.

Finally, the use of the term "discomfort" may contribute to the merging of surrounding anxiety with the surge of panic, as well as contribute to mistakenly diagnosing paroxysmal episodes other than PAs (e.g., anger attacks) as PAs. On the other hand, certain subsets of the population (e.g., elderly) may be less inclined to use the word "fear" and more inclined to use the word "discomfort" to describe PAs

(see Castriotta et al., this issue), and some individuals report nonfearful PAs (see Kircanski et al., 2009). Thus, there is reason to retain the term "discomfort," although inclusion of the descriptor "intense discomfort" may enhance the boundaries with surrounding anxiety.

Thus, a wording change is recommended. Specifically, "*An abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four or more of the following symptoms occur. The abrupt surge can occur from a calm state or an anxious state*" (The text description will include a graphical depiction of PA peaking from a calm and an anxious state, as depicted in Fig. 1.).

Further, it is recommended that the text include more discussion about PAs lasting only a few minutes, before returning to either an anxious state or a calm state, and possibly peaking again (again as depicted in the figure), ways of differentially diagnosing PAs from other paroxysmal states, and age-related or other-related differences in terminology. These textual changes will also clarify the evaluation of PAs across cultural settings, as certain cultures (e.g., Caribbean Latinos) tend to group panic-like and anger-like paroxysms under a single cultural syndrome (i.e., *ataque de nervios*).[11]

SUMMARY AND PRELIMINARY RECOMMENDATIONS FOR DSM-V

Available data support the inclusion of all 13 PA symptoms, as endorsement rates for each symptom are at least 25% across community and patient samples, even though endorsement rates may represent symptoms experienced during some and not necessarily all PAs for each respondent. Specific recommendations are to replace the term "hot flushes" with "heat sensations" to increase cultural validity, and to reorder the list by grouping physical symptoms first followed by "fear" symptoms to increase clinical utility. Existing data, limited in nature, do not justify changes to the four-or-more-symptom cutoff for defining full blown vs. limited symptom PAs, although further research is needed on the dimensional quality of PA symptoms. Finally, changes are recommended to the wording of the criteria and accompanying text to improve the distinction between PAs and surrounding anxiety and the evaluation of PAs across cultural groups.

SHOULD PAS BE A SPECIFIER ACROSS ALL DISORDERS?

STATEMENT OF THE ISSUES

The question addressed herein is whether the presence of PAs in the context of any anxiety or nonanxiety disorder provides clinically relevant information such as predicting treatment response, comorbidity, or course.

SIGNIFICANCE OF THE ISSUES

The DSM IV describes PAs as being relevant to all anxiety disorders, and ways in which the nature of PAs
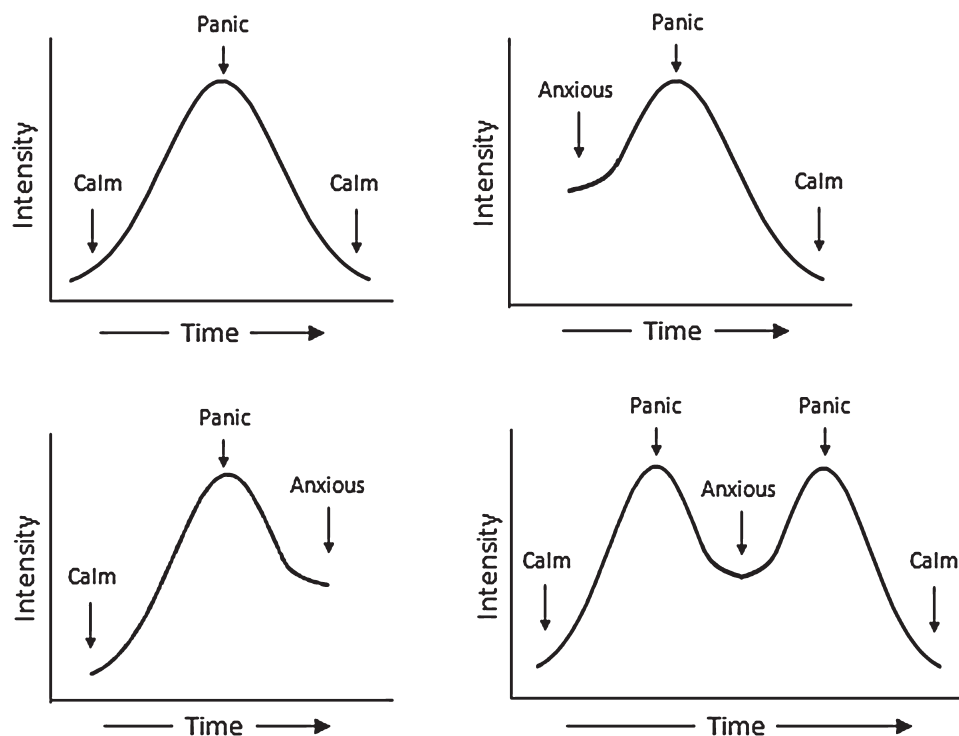

Figure 1. Depiction of panic attacks occurring from a calm state or an anxious state and returning to a calm state or an anxious state.

(uncued vs. situationally predisposed vs. situationally bound) helps to differentiate among them. However, questions remain with regard to whether PAs are a clinically significant indicator in the context of any disorder. The goal of this section is to evaluate the degree to which PAs predict comorbidity, course, and treatment response in the context of any DSM disorder. Evidence for PAs as a significant marker of psychopathology in general would support their designation as a specifier or a dimension to be used across DSM. However, it should be noted at the outset that few available studies have distinguished between the effects of PAs per se, different types of PAs (e.g., expected, unexpected), and PD, and only some of the studies controlled for possible correlates of PAs and comorbid disorders (e.g., neuroticism, depression) that may have influenced the findings.

METHOD OF LITERATURE REVIEW

The current literature review focused on data published on or after 1994, with the publication of DSM-IV. A PubMed and PsychInfo search was conducted using a combination of the following keywords: PAs, comorbidity, course, and treatment. This yielded a list of 694 articles, not all of which provided relevant information. This review was supplemented by a PubMed and PsychINFO search using disorder-specific keywords (e.g., bipolar disorder, depression, posttraumatic stress disorder) and an inspection of bibliographies from key articles. The main focus of the review considered the degree to which these published articles provided information relevant to the impact of PAs on co-occurring psychiatric disorders.

It is important to note that these investigations primarily based their inclusion criteria on a history of PAs, and the majority did not stratify their analyses to compare persons who met the DSM-IV criteria for PD vs. PAs only. Consequently, the results cannot be always attributed specifically to PAs outside of the context of PD, although studies that included only participants meeting DSM-IV criteria for PD were excluded. Furthermore, studies reviewed herein infrequently separated expected (cued) from unexpected (uncued) PAs.

COMORBIDITY

Although PAs themselves are not considered a disorder or a condition that necessarily requires treatment, they often present in the context of various anxiety and nonanxiety disorders. Several studies, albeit mostly epidemiological or community samples, have shown that PAs may serve as a risk marker for a wide range of psychiatric disorders,[41–43] multimorbidity, and more severe disease status.[44] Moreover, individuals with PAs (prevalence of uncued PAs unknown) report higher levels of trait anxiety, state anxiety, and depression compared to individuals who have never experienced PAs.[45]

Anxiety disorders. PAs have been associated with an increased likelihood of having other anxiety disorders, aside from PD and agoraphobia.[46] In particular, in their 5-year prospective longitudinal examination within a community sample, Goodwin and Gotlib[46] showed that PAs at baseline were associated with significantly greater odds of developing social phobia (OR = 4.4), specific phobia (OR = 3.4), obsessive–compulsive disorder (OR = 9.5), generalized anxiety disorder (OR = 16.4), and posttraumatic stress disorder (OR = 3.9). From the NCS-R data, Kessler et al.[47] reported 45.0% comorbidity with other anxiety disorders in their PA-only group (i.e., PAs without a history of PD or agoraphobia), with highest comorbidity rates for specific phobia (21.0%) and social phobia (18.8%). Other studies have suggested that the presence of panic symptoms at the time of a traumatic event (i.e., a "cued" PA in response to trauma) may be associated with higher rates of an ensuing acute stress disorder[48,49] or posttraumatic stress disorder[50–52] compared to individuals who do not show panic symptomatology at trauma. As discussed by,[48] the association of PAs and acute stress disorder may be explained by an overlap in their symptomatology (e.g., derealization, fear of dying), a common predisposition to develop both conditions, and PAs intensifying the level of stress during the traumatic event.

Mood disorders. Cross-sectional[46] and longitudinal[53] studies, again in community samples, have documented an association between PAs and the risk of developing mood disorders. In the NCS-R data, Kessler et al.[47] reported a 36% comorbidity rate of mood disorders with their PA-only subgroup. Goodwin et al.'s[53] 21-year birth cohort study found that PAs in the preceding 3 years increased the risk for developing a current (past month) major depressive episode among young adults, after controlling for early behavioral risk factors for psychopathology such as past history of depression, childhood abuse, and personality characteristics. In the prospective EDSP study, covering age up to 30, Goodwin et al.[54] found that primary PAs were associated with increased risk for incident major depression (9 vs. 22%, OR = 2.8), controlling for age, gender, and other comorbid conditions. Finally, in a 10-year prospective longitudinal examination of the same data set by Beesdo et al.[55] the occurrence of PAs in individuals with social anxiety disorder (i.e., cued panic in social situations) increased the risk for subsequent depression.

There are several possible explanations. For example, Goodwin et al.[53] speculated that the onset of PAs may lead to demoralization or distress, which in turn increases the risk for subsequent depression. Alternately, comorbid panic-depression may represent a more severe subtype of depression.[56] Additionally, there may be third variables that account for this link

such as environmental adversities,[57] common trait vulnerabilities such as neuroticism,[58] or shared neurobiological mechanisms, as both conditions respond to the same pharmacological treatments (SSRIs).

Psychotic disorders and severe psychopathology. Recent prospective data suggest that PAs are associated with more severe and persistent psychiatric comorbidities. In the 5-year longitudinal examination of the EDPS,[44] PAs at baseline were associated with high levels of comorbidity and multimorbidity (i.e., meeting criteria for several simultaneous psychiatric disorders) across alcohol dependence, psychotic disorders, somatoform, and eating disorders. Additionally, longitudinal data indicated that PAs in adolescence were associated with significantly increased levels of psychoticism among young adults, after controlling for neuroticism, socioeconomic status, family conflict, and other psychiatric comorbidities,[54] although "psychoticism" is not synonymous with psychosis. These authors discussed the common symptomatology among panic and psychotic disorders, such as reality distortion and fear of going crazy, and suggested that PAs may therefore reflect a prodromal phase of psychotic disorders. Finally, in a 10-year longitudinal study,[59] having two or more unexpected PAs during adolescence was associated with an increased risk of developing personality disorders (all clusters) during young adulthood. It remains unclear whether PAs directly influence the development of personality disorders (e.g., PAs compromise coping behaviors and impact longstanding relational patterns) or whether the comorbidity is due primarily to shared vulnerabilities (e.g., overlapping heritability).

Substance use. In a state-wide cross-sectional sample of adults in Colorado, a lifetime history of PAs was associated with an increased rate of lifetime alcohol dependence (but not alcohol abuse or use,[60] and with psychedelic abuse and dependence (but not psychedelic use)[61] Goodwin et al.[44] found significant cross-sectional associations with alcohol dependence and nicotine dependence. Another cross-sectional study looking at a wider range of substances (opioids, sedatives, cocaine, and amphetamines) found that lifetime and past year PAs were associated with past year substance use disorders (as well as anxiety and depressive disorders), after controlling for neuroticism, gender, and co-existing anxiety disorders.[41] Kessler et al.[47] reported a comorbidity rate of 21.4% with substance use disorders in their PA-only subgroup (i.e., individuals without a history of PD or agoraphobia). The negative findings reported in younger samples (aged 9–17)[46] may be explained by less frequent use of substances in that age range. All of these studies have used cross-sectional designs, thereby limiting assessments to retrospective reports and potential reporting biases. However, positive findings have been corroborated in a longitudinal investigation, where PAs at baseline (ages 14–24) were associated with the development of substance use disorders (especially alcohol) by 5-year follow-up.[44]

There are several possible explanations such as some individuals with PAs using substances to reduce their anxiety.[62] Alternatively, Bonn-Miller et al.[61] proposed that use of substances, especially psychedelic drugs, may increase the risk for future PAs due to repetitive exposure to interoceptive processes associated with the substance. Finally, there may be a third variable such as a common genetic link or personality[63] between PAs and substance use disorders. Whatever the source of the linkage, it appears that PAs are diagnostically unspecific, yet potential markers for neuropsychiatric dysfunctions.[43]

CLINICAL PRESENTATION

PAs may increase symptom severity as well as rates of comorbidity and suicide. For example, in a patient sample, cued PAs in the context of social phobia were associated with elevations in distress and impairment.[64] Also, epidemiological/community samples studies reliably show increased severity. For example, individuals with co-occurring bipolar disorder and PAs have elevated rates of comorbid psychopathology and earlier onset of illness compared to those with bipolar disorder without PA.[65] The co-occurrence of PA and psychosis[66] or schizophrenia[67] also appears associated with increased likelihood of psychiatric comorbidity and suicidality compared to individuals with psychotic disorders without PA. Finally, Roy-Byrne et al.[68] found that individuals with comorbid PA-depression showed greater depressive symptoms and an increased number of suicide attempts compared to individuals with depression without PA, after controlling for additional comorbid diagnoses. Moreover, they found only a slightly higher odds ratio for comorbid depression and PD compared to comorbid depression and PAs. In contrast, other findings suggest that whereas individuals with PAs only (without PD) and individuals with PD both have higher rates of suicidal ideation than controls, only individuals with PD have higher rates of suicide attempts after adjusting for comorbid psychiatric disorders and early trauma.[69]

TREATMENT

The presence or increased severity of PAs appears to negatively impact treatment response in a number of disorders, including unipolar depression,[70] bipolar disorder,[71,72] PTSD,[73] and psychotic disorders.[74]

PRESENTATION OF PAS ACROSS DISORDERS

If PAs are to become a specifier or dimensional rating across disorders, then ideally, the operationalization of PA would be independent of surrounding diagnostic status. However, there are very little data on the symptom profiles in the context of other disorders. Many studies evaluate the presence or absence of PAs in PD relative to other disorders in response to

laboratory challenges such as carbon dioxide inhalations and hyperventilation,[75] but do not report the symptoms of panic.

Two earlier studies compared PA symptoms across different anxiety disorders. Rapee et al.[76] found that respondents with PD reported more paresthesias, dizziness, faintness, unreality, dyspnea, fear of dying and fear of going crazy/losing control in comparison to respondents with specific phobia, social phobia, and obsessive–compulsive disorder. Rachman et al.[77] compared PA symptoms reported to occur during PAs by patients with claustrophobia or PD. Although there were few differences overall, claustrophobic subjects reported dyspnea, choking, dizziness, and fears of dying and going crazy more frequently than did PD patients, who in turn reported more palpitations, hot flashes and trembling than claustrophobic participants.

We were unable to locate any comparisons of PA symptoms across nonanxiety disorders (e.g., mood disorders). The only relevant study evaluated 19 patients with schizophrenia who reported a history of PAs;[78] seven reported uncued PAs, whereas the remaining patients tied their PAs to delusional fears or paranoid ideas. They averaged 7.9 ($SD = 3.2$) PA symptoms, with all endorsing dyspnea, and none reporting fears of dying or going crazy. However, no comparisons were made with any other group.

SUMMARY AND PRELIMINARY RECOMMENDATIONS FOR DSM-V

PAs appear to predict the onset of various forms of psychopathology and, in the context of co-occurring psychiatric disorders, have been associated with increased symptom severity, higher rates of comorbidity and suicidality, and poorer treatment response. Most studies fail to separate PAs from PD, and some studies do not control for third variables influencing both PAs and comorbid conditions, but those that did so found moderate evidence that PAs alone increase comorbidity and negatively impact course of disorder. Thus, the available evidence raises the possibility that PAs may be a valuable specifier or dimensional rating for anxiety, mood, eating, personality, psychotic, and substance use disorders, and possibly for other disorders as well, although further research is needed to address gaps in the literature to date.

PANIC DISORDER

STATEMENT OF THE ISSUES

The question addressed in this section is whether the evidence supports a revision to the criteria of A (1) (recurrent unexpected PAs) and A (2) (followed by at least one month of one or more of the following: persistent concern about having additional attacks, worry about the implications of the attack or its consequences, or a significant change in behavior related to the attacks) (see Table 2).

SIGNIFICANCE OF THE ISSUES

With DSM-IV, the focus shifted from a minimum number of PAs (i.e., four) in a designated interval or time (i.e., 4 weeks) to "recurrent" PAs, or two or more PAs, in a lifetime. Also, the term "unexpected" (uncued) PA was defined as an attack for which the individual does not associate onset with an internal or external situational trigger, such that it is perceived as occurring "out of the blue." The requirement of 1 month or more of concern, worry or behavioral change was included to represent anxiety about having PAs and the resultant impairment they produce. The issues being addressed in this section are the degree to which these criteria A (1) and A (2) should be revised based on evidence regarding their reliability, validity, or clinical utility.

METHOD OF LITERATURE REVIEW

The literature review focused on data published since 1994, with the publication of DSM-IV. These data were augmented by data published since 1980, with the publication of DSM-III and subsequently DSM-IV, which provided initial evidence that was similar to or replicated by later findings. A PubMed and PsychIN-FO search was conducted using the keywords recurrent unexpected PAs, recurrent PAs, anxiety about panic, worry about the next attack, worry about the implications of panic, significant behavioral change as a function of PAs, PD diagnosis, DSM-IV PD, diagnostic criteria for PD, PD impairment, epidemiology of PD, and prevalence of PD, which produced a list of 51 articles. The keyword PD yielded 2,456 articles, not all of which were relevant. These searches were then

TABLE 2. DSM-IV criteria for panic disorder with (and without) agoraphobia

A. Both (1) and (2)
  1. Recurrent unexpected Panic Attacks
  2. At least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
    a. Persistent concern about having additional attacks
    b. Worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
    c. A significant change in behavior related to the attacks
B. The presence (or absence) of Agoraphobia
C. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism)
D. The panic attacks are not better accounted for by another mental disorder, such as social phobia (e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to a specific phobic situation), obsessive–compulsive disorder (e.g., on exposure to dirt in someone with an obsession about contamination), Posttraumatic stress disorder (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives)

refined by restriction to articles written or translated into English.

RECURRENT PAS

Very few studies have evaluated the issue of number of PAs, and none since 1994. As concluded by the DSM-IV workgroup literature review,[1] a substantial number of persons experience infrequent PAs, and they closely resemble persons with more frequent PAs in terms of clinical phenomenology, family history, and biological challenge data. In their DSM-IV field trial in outpatient clinics, Fyer et al.[79] compared DSM-III-R criteria, which included the criterion of four PAs in 4 weeks, with DSM-IV criteria of at least one attack followed by worry about the next attack or the implications of an attack or its consequences. Using panic-related impairment as the case criterion, they found that the two sets of criteria had equal sensitivity and specificity. Also, they resulted in similar rates of prevalence, demographic characteristics, and comorbidity. Another DSM-IV field trial by Horwath et al.[30] involving reanalysis of the ECA data, found that three or more PAs in 3 weeks predicted psychiatric hospitalization, but not suicide attempts or emergency room use. However, significant impairment (emergency room use, medical care, psychiatric care, use of medications, hospitalization, and financial dependency) was also observed with infrequent PAs (both cued and uncued). Thus, they concluded that the requirement of four or more PAs in 4 weeks underestimates the significance of infrequent PAs. They recommended the term "recurrent" PAs instead. We were unable to locate additional studies addressing the frequency criterion since that time. Thus, there is no evidence to justify a revision to the A (1) diagnostic terminology for frequency of PAs in PD.

UNEXPECTED (UNCUED) PAS

The term "unexpected PA" in Criterion A (1) is described as spontaneous or uncued, in that the individual (i.e., not the clinician) does not immediately associate the PA with a situational (external or internal) trigger. In the literature review for DSM-IV, Ballenger and Fyer[1] emphasized the degree to which unexpected PAs enhanced the boundaries between PD and other anxiety disorders, and particularly when combined with the term "recurrent." That is, whereas other anxiety disorders frequently involve expected PAs, and sometimes involve a single, unexpected PA in the onset of the disorder (e.g., social phobia that emerges following an unexpected PA in a performance situation), only PD is characterized by *recurrent unexpected PAs*.

However, this is not to say that PD is devoid of expected or cued PAs. In their analysis of the NCS-R study ($n = 9,282$), Kessler et al.[47] compared four groups; PAs only (PA); PAs and agoraphobia (PAA); PD (defined by four or more uncued PAs and 1 month or more of concern, worry or behavioral change) only

(PD); and PD and agoraphobia (PDA). About half of individuals in the PD group reported cued PA, although they were less likely to endorse cued PAs than individuals in the PAA, PDA, or PA groups (47% vs. 68 to 88%). On the basis of comorbidity, impairment, and treatment seeking, Kessler et al.[47] concluded that the distinction between cued and uncued PAs may not be as great as initially thought.

Somewhat consistent with that point of view, others have argued that all PAs are cued;[80,81] that uncued PAs are actually cued by subtle changes in physiological state that are not consciously perceived by the individual. For example, uncued PAs have been conceptualized as conditional reactions to subtle physiological changes of which the person is not aware but which have become conditional stimuli through their pairing with prior PAs.[81] The overlap between uncued and cued PAs is supported by the lack of a reliable difference in symptom profile between them. That is, whereas several studies report that cued PAs are self-monitored as more severe in terms of intensity and number of symptoms than uncued PAs,[26,39,82] others report no differences in self-monitored symptoms,[83] and others still, using retrospective estimation, report more severe symptoms during unexpected/uncued PAs than cued PAs.[76,84]

On the other hand, uncued (or unpredicted) PAs have been associated with greater subsequent anxiety than cued (or predicted) PAs, when both types of attacks occurred within a PD patient sample.[83] These findings are consistent with much experimental evidence for the negative impact of unpredictability of aversive events,[85] and suggest that the perception of PAs being uncued, whether a cue actually exists or not, is important. Also, in the DSM-IV field trial, Horwath et al.[30] demonstrated that *unexpected* PAs were associated with a significant increased risk for psychiatric hospitalization relative to other PD diagnostic criteria. Further support for the significance of uncued PAs is longitudinal evidence that uncued PAs increase the risk for the development of PD,[25,86] although their predictive value has not been compared to cued PAs. Finally, as mentioned, recurrent uncued PAs are a distinguishing feature of PD relative to other anxiety disorders, and therefore serve an important role in differential diagnosis among the anxiety disorders.

In sum, there is no compelling evidence to justify a revision to the concept of "unexpected PAs" as a defining feature of PD. However, changes are recommended to the text accompanying the criteria. The DSM-IV Criterion A (1) (i.e., recurrent unexpected PAs) may lead some clinicians to believe that the presence of cued PAs along with uncued or expected PAs is a contraindication to the diagnosis of PD. As already noted, it is estimated that 47% of individuals with PD experience cued PAs along with their uncued PAs[47] (although the degree to which classification as "cued" included situationally bound as well as situationally predisposed is not fully clear). Thus, the

accompanying text should clarify that the presence of cued/expected PAs does not rule out the diagnosis of PD. A separate but related issue is that the criteria do not specify a time frame, meaning that the PAs could have occurred at any time over the lifespan. Clinical expertise would indicate that the length of time since the last PA is of limited significance in the presence of criterion A (2); for example, it is not uncommon for patients to indicate years since their last PA and yet to remain highly anxious about and avoidant of future PAs. However, further analysis of the effects of "time since the last PA" upon other features of clinical expression of PD is warranted.

In addition, the accompanying text description for describing different types of PAs uses a variety of terms inconsistently (unexpected–expected, uncued–cued, situationally bound, situationally predisposed, spontaneous) (see Table 3). [Note, this includes text that accompanies the diagnostic criteria for both PAs as well as PD.] The text implies that unexpected/uncued PAs are attacks that (1) occur without any obvious trigger or cue, or (2) occur unexpectedly upon exposure to a cue that sometimes triggers panic (also referred to as situationally predisposed, and "cued but unexpected"). For purposes of clinical utility, simplification of the terminology is recommended, limiting the terminology to expected–unexpected, and cued–uncued, and excluding reference to situationally bound, situationally predisposed or spontaneous. Also, clinical expertise suggests that the identification of cued (vs. uncued) PAs may be aided by explicit recognition that the cue was apparent at the time of the PA, as opposed to a post-PA attribution, or recognition some time later that a particular event may have triggered the PA of which the respondent was not aware at the time of the PA. In addition, the inclusion of internal as well as external cues in the text description requires further clarification. For example, as currently written, clinicians may construe symptoms of PAs (e.g., fear of dying, elevated heart rate) as an internal cue when such symptoms may be either a cue (e.g, a specific appraisal of dying produces a PA, or an elevated heart rate from exercising induces a PA) or a symptom (e.g., a PA leads to a specific appraisal of dying, or an elevated heart rate). Although there is no empirical evidence pertaining to clinician errors of this kind, explicit reference to the concept that cues *precede* PAs may be helpful in this regard. It is also conceivable that when patients gains insight regarding internal cues that precede their PAs, such as over the course of PD or as a result of psychological treatment, PAs may no longer meet the "unexpected" criterion even though other aspects of the disorder remain the same. This issue warrants further discussion.

Although still under consideration, possible revisions to the wording of the text accompanying PAs and PD are as follows:

Expected/Cued: A PA is expected when, from the person's perspective, there is an obvious cue or trigger to his/her PA at

TABLE 3. DSM-IV-TR text description of types of panic attacks

There are three characteristic types of panic attacks: unexpected (uncued), situationally bound (cued), and situationally predisposed. Each type of panic attack is defined by a different set of relationships between the onset of the attack and presence or absence of situational cues that can include cues that are either external (e.g., an individual with claustrophobia has an attack while in an elevator stuck between floors) or internal (e.g., catastrophic cognitions about the ramifications of heart palpitations). Unexpected (uncued) panic attacks are defined as those for which the individual does not associate onset with an internal or external situational trigger (i.e., the attack is perceived as occurring spontaneously "out of the blue"). Situationally bound (cued) panic attacks are defined as those that almost invariably occur immediately on exposure to, or in anticipation of, the situational cue or trigger (e.g., a person with social phobia having a panic attack upon entering into or thinking about a public speaking engagement). Situationally predisposed attacks are similar to situationally bound panic attacks but are not invariably associated with the cue and do not necessarily occur immediately after the exposure (e.g., attacks are more likely to occur while driving but there are times when the individual drives and does not have a panic attack or times when the panic attack occurs after driving for half hour).

An unexpected (spontaneous, uncued) panic attack is defined as one that an individual does not immediately associate with a situational trigger (i.e., it is perceived as occurring out of the blue). Situational triggers can include stimuli that are either external (e.g., a phobic object or situation) or internal (e.g., physiological arousal) to the individual. In some instances, although a situational trigger may be apparent to the clinicians, it may be not readily identifiable to the individual experiencing the panic attack. For example, an individual may not immediately identify increased autonomic arousal induced by a hot, stuffy room, or feelings of faintness produced by quickly sitting up as triggers for a panic attack, and as such, these attacks are considered at the time to be unexpected. … Individuals with panic disorder frequently also have situationally predisposed panic attacks (i.e., those more likely to occur on, but not invariably associated with, exposure to situational trigger). Situationally bound attacks (i.e., those that occur almost invariably and immediately on exposure to a situational trigger) can occur but are less common.

the time of its occurrence. The PA may occur in anticipation of or in the presence of the cue or trigger.*

Unexpected/Uncued: A PA is unexpected when, from the person's perspective, there is no cue or trigger to his/her PA at the time of its occurrence. In other words, it appears to the person to occur from out of the blue.

Over time, a subtype of unexpected PA may develop in which a PA sometimes but not invariably occurs in response to a cue.

Cues or triggers can be external situations, events, or objects (e.g., driving on a freeway, performing in front of an audience) or internal sensations (e.g., racing heart) or thoughts (e.g., thoughts of dying). Cues or triggers precede the PA.

In addition, the text should discuss the role that culture plays in linking particular cues to the onset of PAs, as this may affect the likelihood that PAs are

considered cued. As noted, in certain cultures, the triggers to PAs may be specified by cultural syndromes; these syndromes create fear of certain "situations." These "situations" vary cross-culturally, and can range from interpersonal arguments (e.g., associated with *ataque de nervios* in Latin America), to types of exertion (e.g., standing up and *khyâl* attacks in Cambodia), to other exposures (e.g., atmospheric wind and *trung gio* attacks in Vietnam) (Hinton and Lewis-Fernández, in press). For example, if a Vietnamese individual has a PA after walking out into a wind storm, he/she is more likely than a non-Vietnamese individual to attribute the PA to the exposure to wind, as a result of the cultural syndrome linking these two experiences.[20] As a result, individuals' assessment of whether their PAs are expected/cued depends in part on their cultural background. Taking this into account may facilitate questioning regarding the cuedness of PAs (i.e., individuals may be able to better distinguish between cued or uncued PAs once the details of the cultural attributions are clarified).

AT LEAST ONE MONTH OF APPREHENSION

Several issues pertain to Criterion A (2) (i.e., followed by at least 1 month or more of one or more of the following: persistent concern about having additional attacks, worry about the implications of the attack or its consequences, or a significant change in behavior related to the attacks). First, based on questions raised by the DSM-IV review process,[1] we re-considered whether DSM-IV Criterion A (2) is redundant with Criterion A (1), meaning that they are so highly correlated that only one would be needed for the diagnosis of PD. In the analysis of the epidemiology of PAs, PD, and agoraphobia from the NCS-R study ($N = 9,282$),[47] 12% of individuals with PAs alone and 10.7% of individuals with PAs and agoraphobia reported a sufficient number of lifetime uncued PAs for a diagnosis of PD (i.e., four or more uncued PAs) but failed to meet other PD criteria. This implies that there are some individuals who meet criterion A (1) by having recurrent unexpected PAs, but who do not meet criterion A (2), suggesting that the two criteria are not fully redundant. Also, smaller scale studies of college students indicate considerably higher rates of occasional unexpected PAs (e.g., 12%) than PD (e.g., 2.4%).[86,87] Thus, the existing evidence, albeit limited to nonclinical samples, suggests that Criterion A (1) and (2) are not fully overlapping, and should be retained as separate features (as Criterion B (1) and (2)).

A related question is the degree to which the three options within DSM-IV Criterion A (2) ([a] persistent concern about having additional attacks; [b] worry about the implications of the attack or its consequences, such as losing control, having a heart attack, or "going crazy"; and [c] a significant change in behavior related to the attacks) are overlapping or distinct options. We were unable to locate any

published studies addressing this issue, although unpublished data were available. Of approximately 4,300 participants who endorsed experiencing a PA over their lifetime in the NIAAA NESARC surveys,[7] 46.6% reported concerns about having additional attacks, 40.1% reported worry about the implications of the attack or its consequences, and 40.7% reported a significant change in behavior (Andrews, unpublished data). The rates of joint endorsement were 57.2% (concern and behavioral change), 61.3% (worry and behavioral change), and 77% (concern and worry). These data suggest that persistent concern and worry about the implications of PAs overlap to a greater degree with each other than with behavioral change, which is not surprising given the conceptual overlap between "persistent concern" and "worry about." For purposes of clarity and simplification, options [a] and [b] could be collapsed into one option.

Options [a] and [b] within Criterion A (2) provide an ideational content to PD, consistent with cognitive models.[88] It is important to consider whether such ideational content should be made a *necessary* (vs. optional) feature, in the same way that ideational content is necessary for the diagnosis of social phobia. One study compared concern about panic symptoms and worry about the implications of panic symptoms across different anxiety disorders. Using scores on the Body Sensations Interpretation Questionnaire across PD and generalized anxiety disorder, social phobia, and nonpatient control groups,[89] PD patients were more likely to believe interpretations of ambiguous autonomic sensations as signals of impending physical or mental catastrophe, building on the results of earlier studies.[90] However, concern about individual panic symptoms is not synonymous with concerns about having a PA. Other evidence indicates that scores on the Anxiety Sensitivity Index, a measure of the tendency to believe that physical symptoms of anxiety are harmful, are particularly elevated in PD.[91–93] However, Anxiety Sensitivity is also elevated across most anxiety disorders relative to healthy controls.[92] Moreover, as a trait vulnerability factor, anxiety sensitivity predicts the development of not only PD but any anxiety disorder.[94,95] These data suggest that anxiety sensitivity is a particularly strong feature of PD, but is not exclusive to PD. Furthermore, as with the Body Sensations Interpretation Questionnaire, scores on the Anxiety Sensitivity Index measure beliefs about individual symptoms of panic and anxiety, and as such, they may not directly index concern or worry about the implications of PAs per se. Overall, findings suggest that the ideational content should remain an optional component of the diagnosis of PD, but further direct evidence is needed to establish whether it should be changed to a necessary component.

DSM-IV Criterion A 2 [c] refers to "a significant change in behavior related to the attacks" and Criterion B refers to "absence of agoraphobia." The distinction between "change in behavior related to the attacks" vs.

agoraphobia is not clear from the criteria and thus further specification of "behavioral change" is warranted. Clinical expertise would suggest that the behavioral change that is central to PD is behavior designed to minimize or avoid PAs or their consequences, and specifically maladaptive behavior (such as avoidance behavior, reliance on illicit drugs) as compared to adaptive behavior (such as treatment seeking). Furthermore, one option being considered for DSM-V is to separate agoraphobia from the diagnosis of PD (this issue is reviewed in detail by Wittchen et al., in this issue), such that agoraphobia would become a codable diagnosis independent of PD. Nonetheless, agoraphobic avoidance is a common maladaptive behavior designed to avoid PAs within the context of PD. Based on these considerations, it is recommended that Criterion A (2) [c] is *reworded as "significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having the PAs), which may include agoraphobia avoidance,"* and that Criterion B (i.e., the presence or absence of agoraphobia) is deleted. Furthermore, for purposes of simplification and clarity, it is recommended that DSM-IV Criterion A (2) [a], [b], [c] become a new Criterion B (1) and (2).

Another issue pertains to the cutoff of "1 month." We were unable to locate any studies investigating the clinical relevance (e.g., relationship to indices of impairment or comorbidity) of differing intervals of time in which concern about having additional attacks, worry about the implications of attacks or their consequences, and/or behavioral change as a result of PAs, are exhibited. Clearly, further research on the duration criterion would be valuable.

In sum, for the sake of simplification and clarity in criteria, changes are recommended for Criterion A 2 [a], [b], [c], although what follows is preliminary and remains under consideration.

Criterion B. At least one of the attacks has been followed by 1 month (or more) of one or both of the following:

1. *Persistent concern or worry about additional PAs or their consequences* (*e.g., losing control, having a heart attack, going crazy*).
2. *Significant maladaptive change in behavior because of the attacks* (*e.g., behaviors designed to avoid having PAs*), *which may include agoraphobia avoidance*.

EXCLUSIONARY CRITERIA

The only change recommended to Criterion C, which states that the PAs are not due to the effects of a substance or a medical condition, is to add another example to the medical conditions, which is very relevant to issues of differential diagnosis that being cardiopulmonary disorders. For Criterion D, which is intended primarily to facilitate differential diagnosis from other anxiety disorders, it is recommended that

the term "not better accounted for" be replaced by "not restricted to" for purposes of clarification. However, the exact phrasing for exclusionary criteria and the general strategy for exclusionary criteria warrant further testing in field trials.

REMISSION

According to DSM-IV, remission is defined generically as showing only some signs or symptoms of the disorder (partial remission) or no longer showing any signs or symptoms of the disorder (full remission). However, this does not address the time interval over which the symptoms and signs must be absent before remission is declared. Shear et al.[96] proposed that 6 months is an appropriate duration over which to judge remission for PD, although this was based on clinical expertise without the support of empirical data. Thus, further analysis is recommended for establishing the duration over which symptoms of PD have abated in order to establish remission status.

SUMMARY AND PRELIMINARY RECOMMENDATIONS FOR DSM-V

In general, empirical investigation of the reliability, validity, and clinical utility of the diagnostic criteria for PD is sparse, especially since the early 1990's. In terms of criterion A (1), there have been no studies as those involved in the DSM-IV field trials that have directly evaluated the frequency of PAs, and thus there is no justification at this time to revise the term "recurrent." Unexpected (uncued) PAs, as perceived by the individual who panics, that occur recurrently, continue to be viewed as a distinguishing feature of PD. However, the text accompanying the criteria may warrant revision to explicitly recognize that many individuals with PD experience expected/cued PAs along with their unexpected/uncued PAs. Furthermore, a revision to the accompanying text is recommended to simplify the operationalization of "unexpected/uncued" vs. "expected/cued" and the contribution of cultural attributions.

Available evidence suggests that Criterion A (2) is not redundant with criterion A (1) and that both features should be retained. Within DSM-IV Criterion A (2), options [a] (persistent concern about additional attacks) and [b] (worry about the implications of the attack or its consequences) are commonly and more frequently jointly endorsed relative to options [a] and [c] (significant change in behavior related to the attacks) or [b] and [c]. For purposes of simplification and clarity, a reorganization is under consideration that combines [a] and [b] into one option. Furthermore, greater specification of what is meant by "significant behavioral change" is recommended, with inclusion of agoraphobia avoidance as a possibility (to be complemented by deletion of the DSM-IV Criterion B). Also for purposes of simplification, it is recommended that DSM-IV Criterion A (2) [a], [b], [c] become a new

Criterion B (1) and (2). There is no evidence to change the requirement of 1 month or more for DSM-IV Criterion A (2), although further research could provide more guidance on that cutoff. Very minor changes are recommended to the exclusionary Criteria C and D. Finally, the addition of guidelines for remission is recommended.

DEVELOPMENTAL ISSUES

SIGNIFICANCE OF THE ISSUES

In children and adolescents, much like in adults, PAs occur as part of various other anxiety disorders besides PD. Thus, for example, children with specific or social phobia can exhibit PA-symptoms when confronted with a specific feared objects or situation; and children with separation anxiety disorder can exhibit PA symptoms when separated from a parent. The current section does not focus on these instances but rather only specifically on the occurrence of uncued PAs. Also, given some research linking PD in adulthood to separation anxiety disorder in childhood, this section also reviews whether the presence of separation anxiety disorder, during childhood or adolescence, relates to risk for, or expression of, PD at later stages of life. This section also briefly considers the degree to which any other childhood presentation might represent a developmental expression of a diathesis to experience uncued PAs (or PD) at later stages in development.

METHOD OF LITERATURE REVIEW

The current literature review began with an initial PubMed search, using the key words "panic" and "PA" and restricting the search to English language articles in peer-reviewed journals, published since 1980 and focusing specifically on children and adolescents. This search generated a total of 262 articles focused on the presence of PAs or disorder occurring in individuals between the ages of 6 and 19. This initial pool was further refined by reviewing the bibliographies from relevant chapters and review papers. Review of data contained in these articles was used to support the current document, focused specifically on diagnostic criteria, developmental considerations, and clinical expression of PAs and PD in children and adolescents.

DIAGNOSTIC CRITERIA

This first part of this section considers data emerging from studies attempting to apply DSM criteria for uncued PAs to children and adolescents. More than 10 studies have used structured psychiatric interviews to apply DSM-III, DSM-III-R, or DSM-IV criteria for the diagnosis of uncued PAs or PD in samples of children and adolescents.[97–108] As results from these studies have been reviewed in detail elsewhere,[109–110] the current summary only focuses on the main, general conclusions that arise from these earlier reviews. First,

the overall prevalence of PD is quite low in children and adolescents, and is considerably lower than virtually all other anxiety disorders that manifest during childhood and adolescence. Second, the rate of PD shows a gradual increase during adolescence, particularly in girls, and possibly following the onset of puberty.[102] Although the main gender differentiation occurs in adolescence, the gender difference is already observable before the age of 14.[25]

The low rate of uncued PA in children places limits on attempts to examine potential developmental differences in the presentation of PD and the application of diagnostic criteria across age groups. Given this low prevalence, relatively few studies are able to assemble large samples of PD cases; this in turn limits statistical power to definitively establish differences between symptomatic presentations at one age relative to another. Although the low rate could relate to difficulties in symptom reporting among children, this seems unlikely for a few reasons. For example, the fact that readily noticeable PAs occur in situations where they are cued, such as when children with phobias are exposed to feared objects, suggests that children are fully capable of exhibiting and expressing features of prototypical PAs. Moreover, the increase in the prevalence of PAs occurs relatively abruptly in some studies, around the age of puberty.[25,43,102,111] This increase occurs during a time when few similarly marked or abrupt developmental changes occur that would affect markedly adolescents' ability to report on their symptoms. Thus, these data most clearly support the view that uncued PAs are rare in children, relative to other forms of anxiety such as fears of specific objects or situations.

Nevertheless, despite the low rate of PAs in childhood, the available epidemiologic data clearly establish that DSM-III, DSM-III-R, or DSM-IV criteria can be successfully and reliably applied to samples of children and adolescents. This includes application of both uncued PA and PD criteria. To the extent that the issue has been examined, no data demonstrate sufficient difference in the clinical presentation among adolescents and adults to justify the use of alternative criteria or definitions across age groups either for PAs or for PD. One relevant study found that 14 to 17-year olds as compared to 18 to 24-year olds worried less about additional attacks and about their implications, and less frequently changed their behavior in response to attacks, although the age groups appeared to show similar rates of avoidance.[31]

As with other types of anxiety, children and adolescents can express symptoms of PA differently from adults.[110,112] For example, adolescents might be less willing than adults to openly discuss such feelings or to become concerned that such symptoms might represent manifestations of occult medical problems. Therefore, clinicians should be aware that uncued PAs do occur in adolescents, much as they do in adults, and be attuned to this possibility when encountering

adolescents presenting with unexplained paroxysmal conditions involving crescendo anxiety. Finally, the low prevalence before puberty is important to note. Although PD and PAs are very rare in childhood, first occurrence of fearful spells is frequently dated back to childhood (4–5% up to age 12).[25,31] Uncued PAs can present with various medical conditions, as reviewed elsewhere. Therefore, it is important to recognize this possibility in situations where presentation of uncued PAs would be unusual, such as in pre-pubertal children.

DEVELOPMENTAL EXPRESSIONS OF PD DIATHESIS

Beyond the diagnosis of PD, per se, some authors suggest that the underlying processes that give rise to uncued PA in adolescents or adults might be expressed in alternative clinical forms in young children. This suggestion emerges based on the fact that rates of PD, per se, are low during childhood, despite the fact that young children born to parents with PD can be differentiated on various indices from young children born to healthy parents.[110,113–116] The alternative clinical forms include night terrors, behavioral inhibition, high levels of anxiety sensitivity, or various other childhood anxiety-disorder states[114,117] and separation anxiety disorder. As the most extensive data pertain to separation anxiety disorder as an early-life manifestation of PD, it is the focus of the current review.

Beyond observations on associations with high retrospectively recalled rates of separation anxiety disorder in adult patients with PD,[118,119] three main sets of data support the presence of some relationship between PD and separation anxiety disorder. First, family studies clearly link a history of PD in parents to a history of separation anxiety disorder in offspring, as has been found in at least four studies.[110] Moreover, some work in adults suggests that a history of separation anxiety disorder in parents identifies particularly familial forms of PD. Nevertheless, Although an association with separation anxiety disorder represents perhaps the strongest and most consistent finding in family studies conducted among anxious parents, offspring of parents with PD also exhibit high rates of various other anxiety disorders besides separation anxiety disorder.[120–122] Moreover, major depression in parents, even in the absence of co-occurring PD, has been linked to separation anxiety disorder in offspring.[120,121] Therefore, while consistent observations of family-based associations do emerge, these associations are not sufficiently specific to justify a view of separation anxiety disorder and PD as alternative manifestations of the same process.

Second, longitudinal studies examine the associations between the diagnosis of separation anxiety disorder during childhood and the diagnosis of PAs or PD during adulthood. Data in this area provide a particularly strong test of the hypothesis that these two entities represent alternative manifestations of the same underlying process. Much like the data from family studies, the data in this area are mixed. Seven studies were identified that relied on structured psychiatric interviews to diagnose separation anxiety disorder in children or adolescents and PAs or PD at a later point in development, at least 3 years after the initial diagnosis of separation anxiety disorder. None of the seven provides strong support for a view of the two conditions as alternative expressions of the same entity, though, as with family-based data, suggestive data emerge supporting the presence of some association. In two studies,[105,123] both based in community cohorts, no support for the association between the two conditions emerged. Specifically, the association between an initial childhood separation anxiety disorder diagnosis and a later PD or PA diagnosis did not emerge, despite the fact that other childhood anxiety disorder diagnoses did predict the occurrence of PAs or PD in adults. In three studies, support was reasonably strong[119,124,125]: the diagnosis of separation anxiety disorder did consistently predict across a few analytic approaches the occurrence of PAs or PD in adults. Nevertheless, even in these studies providing the strongest support, other childhood diagnoses in two of the studies also predicted the occurrence of adult PAs. Moreover, the association between childhood separation anxiety disorder and adult PD was clinically meaningful but only moderately large, exhibiting odds ratios in the 2.0–4.0 range. Relatively strong associations were found in Bruckl et al.[124] but childhood separation anxiety also predicted a wide range of other disorders, and thus was not a specific predictor for PD. This is lower than the magnitude for other conditions, such as oppositional defiant disorder and conduct disorder, which have been considered alternative manifestations of the same underlying syndrome. In the final two studies,[99,126] somewhat weaker support for the association emerged.

Third, biological studies provide some support to link the pathophysiologic processes associated with PD to those associated with separation anxiety disorder. The strongest support in this area derives from work on respiration, extending observations from Klein.[118] Adult patients with either PAs or PD consistently have been shown to exhibit perturbations in respiration. These perturbations manifest in various measures, albeit mostly subjective, including clinical reports of respiratory complaints, such as dyspnea during PAs, a low threshold for experiencing various anxiety symptoms when exposed to respiratory stimulants, and various perturbations in respiratory physiology, although the latter are not consistent. Studies in children and adolescents clearly demonstrate a strong and specific association between the diagnosis of separation anxiety disorder and the same set of respiratory perturbations that occur in PD. Two studies in more than 100 children and adolescents demonstrated such perturbations in separation anxiety disorder but not social anxiety disorder.[127–130] Moreover,

a series of epidemiological studies also link the diagnosis of separation anxiety disorder to various conditions, such as asthma, that produce respiratory perturbations.[131–134] Although findings in this area probably appear stronger than for either family-based or longitudinal studies, even here, support for grouping the two entities is only moderate. In addition, only a subset of patients with PD or PAs exhibit such respiratory perturbations (see Kircanski et al., 2009). Overall, data provide equivocal support for considering any condition to be an alternative, developmental expression of the diathesis for PAs or PD, as typically manifests in adolescence or adulthood.

CLINICAL EXPRESSION

Most research on developmental expressions of uncued PAs, PD, or early childhood precursors either focuses on epidemiological investigations or associations on pediatric anxiety states such as behavioral inhibition or separation anxiety disorder. This work is reviewed above. Very little data examine issues pertinent to the clinical expression of the PD diagnosis in children or adolescents. Thus, in terms of research on therapeutics, virtually no research considers the diagnosis of PD in children or adolescents. Specifically, no published randomized control trial in children or adolescents was identified that used either psychotherapy or medication to randomize as many as 30 PD patients to one or another treatment. As a result, no comparisons can be made concerning age-related aspects of treatment response. Similarly, very few studies examine stability of the PD, although the most consistent observation emerges from work on uncued PAs.[99,135] As in research among adults, the full-blown diagnosis of PD frequently arises following earlier, isolated episodes of uncued panic.[25] Finally, relatively few studies examine genetic contributions to PAs or PD in children and adolescents. The few available studies in this area generally document associations in juveniles that are comparable to those found in adults.[136–139] Thus, research on the clinical expression of PAs or PD in children and adolescents does not support the inclusion of any age-specific criteria when considering the diagnosis.

SUMMARY AND PRELIMINARY RECOMMENDATIONS FOR DSM-V

The available evidence indicates that differences in clinical presentation of PAs or PD are not sufficient to justify alternative criteria or definitions across age groups. Also, extant data are insufficiently reliable and robust to warrant consideration of other conditions, such as separation anxiety disorder, to be an alternative developmental expression of the diathesis for PAs or PD. Finally, there is no evidence to support the inclusion of age-specific criteria for the diagnosis of PD.

CONCLUSION

A review of the literature since the publication of DSM-IV on the topics of PAs and PD has led to the following recommendations for DSM-V. With respect to the criteria for PAs, the available data support the retention of all 13 PA symptoms, although further research is needed on the clinical utility of reducing the list without sacrificing diagnostic validity or reliability, and conversely, on the cultural validity of adding cultural prototype symptoms. Specific recommendations are made to the rephrasing of "hot flushes" to "heat sensations" and to reordering the list of symptoms. Also, there is insufficient evidence to change the four or more symptom cutoff for full-blown vs. limited symptom PAs, although further research on the dimensional quality of PAs is needed. The extant literature indicates that the physiological panic response is an abrupt response that peaks and subsides within minutes. To facilitate the distinction of this abrupt response from surrounding anxiety, revisions to the wording of the definition of PAs are suggested, which would be further enhanced by the inclusion of graphical depictions in the accompanying text.

With respect to PAs as a diagnostic specifier, the available evidence raises the possibility that PAs may be a valuable specifier or dimensional rating for anxiety, mood, eating, psychotic, and substance use disorders. However, evidence regarding the relevance of PAs to other disorders is lacking as is the degree to which expected (cued) vs. unexpected (uncued) PAs play differential roles in this regard.

With respect to the diagnostic criteria for PD, there have been no studies as those involved in the DSM-IV field trials that have directly evaluated the frequency of PAs, and thus there is no justification at this time to revise the term "recurrent." The perception of PAs that occur without an obvious trigger (i.e., uncued) continues to be judged to be a defining feature of PD. However, the text accompanying the criteria warrant revision in order to explicitly recognize that many individuals with PD experience cued PAs along with their uncued PAs, and to clarify the operationalization of "expected/cued" vs. "unexpected/uncued" PAs, including regarding the role of cultural factors in the attribution of cuedness. Also, for the sake of parsimony and clarity, changes are recommended to the wording and organization of three options currently within DSM-IV Criterion A (2), which would become Criterion B. Minor changes are recommended to the exclusionary criteria C and D.

With respect to developmental issues, the available evidence does not warrant alternative criteria or definitions across age groups, nor age-specific criteria for the diagnosis of PD.

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