DEPRESSION AND ANXIETY 27:113–133 (2010)

Review

AGORAPHOBIA: A REVIEW OF THE DIAGNOSTIC CLASSIFICATORY POSITION AND CRITERIA

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The status of agoraphobia (AG) as an independent diagnostic category is reviewed and preliminary options and recommendations for the fifth edition of The Diagnostic and Statistical Manual (DSM-V) are presented. The review concentrates on epidemiology, psychopathology, neurobiology, vulnerability and risk factors, clinical course and outcome, and correlates and consequences of AG since 1990. Differences and similarities across conventions and criteria of DSM and ICD-10 are considered. Three core questions are addressed. First, what is the evidence for AG as a diagnosis independent of panic disorder? Second, should AG be conceptualized as a subordinate form of panic disorder (PD) as currently stipulated in DSM-IV-TR? Third, is there evidence for modifying or changing the current diagnostic criteria? We come to the conclusion that AG should be conceptualized as an independent disorder with more specific criteria rather than a subordinate, residual form of PD as currently stipulated in DSM-IV-TR. Among other issues, this conclusion was based on psychometric evaluations of the construct, epidemiological investigations which show that AG can exist independently of panic disorder, and the impact of agoraphobic avoidance upon clinical course and outcome. However, evidence from basic and clinic validation studies remains incomplete and partly contradictory. The apparent advantages of a more straightforward, simpler classification without implicit hierarchies and insufficiently supported differential diagnostic considerations, plus the option for improved further research, led to favoring the separate diagnostic criteria for AG as a diagnosis independent of panic disorder. Depression and Anxiety 27:113–133, 2010.

Key words: *agoraphobia; panic disorder; classification; diagnostic criteria; DSM-V*

INTRODUCTION

This review focuses on key critical issues pertaining to the definition of agoraphobia (AG) and its relationship to panic disorder (PD), and its future diagnostic classificatory conceptualization in the fifth edition of *The Diagnostic and Statistical Manual* (DSM-V). Starting with an historical account of various conceptualizations of AG and associated diagnostic criteria, we address several core issues that are and have been controversial since DSM-III-R.[1] It should be noted that this discussion also occurs in the context of several other relevant reviews, such as the reviews on panic attack (PA) and PD[2] as well as Specific Phobia,[3] which also includes a review on the relationship between AG and Specific Phobia. In light of these other reviews, we only peripherally address these disorders and their

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This article is being co-published by *Depression and Anxiety* and the American Psychiatric Association.
The authors report they have no financial relationships within the past 3 years to disclose.

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Received for publication 13 October 2009; Accepted 30 October 2009

DOI 10.1002/da.20646
Published online in Wiley InterScience (www.interscience.wiley.com).

implications for the core issues. This article was commissioned by the DSM-V Anxiety, Obsessive–Compulsive Spectrum, and Posttraumatic and Dissociative Disorders 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. It should also be noted up front that despite consensus in the Task Force there was no unanimous consensus among all advisors to the Task Force with regard to the conclusions summarized in this document.

STATEMENT AND SIGNIFICANCE OF THE ISSUES

Three core issues are addressed, most of which have been discussed controversially in previous revisions of the DSM revision processes.[1] First, what is the evidence that AG exists independently from PD in terms of its epidemiology and the classical validators for diagnoses? Second, should AG be conceptualized as a subordinate form of PD as currently stipulated in DSM-IV-TR or is it better defined as an independent disorder, as in the International Classification of Diseases 10th revision (ICD-10)? Finally, we also comment on how changes in the diagnostic criteria for AG may improve precision, reliability, and ease of administration. These questions are considered to be particularly relevant from the perspective of recognition, treatment, and management, because there have been concerns that the residual status of AG and its definition might be associated with underdiagnosis and undertreatment. There have also been concerns that the description of AG and the relationship of AG to PA and PD are unnecessarily complex, making its use complicated and possibly reducing its clinical utility. Additionally, doubts have been expressed on whether the assumed causal role of PA and panic-like features is a valid assumption in agreement with empirical evidence and whether it is needed at all. Finally, the position and definition of AG is one of the rare examples where DSM-IV-TR and the ICD-10 deviate from each other, leading potentially to continued discrepancy in how these patients are being diagnosed worldwide.

The review consists of three major sections. The first section addresses the question of whether recent studies provide evidence that AG exists independently from PD and PAs. Using available evidence and selected core publications before 1990, core questions focused on: (1) How frequently does PD occur with and without AG? (2) How frequently does AG occur without a history of PA? (3) What are the characteristics of PD with and without AG as well as AG without PA with regard to gender, age of onset, impairment, and associated factors? In the second section, we review available evidence with regard to vulnerability and risk factors for AG to examine evidence for AG being a separate construct using classical validators. In the final section, we use this evidence to address the question of whether AG should be conceptualized as a subordinate form of PD, as currently stipulated in DSM-IV-TR, or whether it should be defined as an independent disorder.

It should be noted upfront that changes in the DSM nomenclature and/or the use of ICD criteria have partially resulted in corresponding changes in diagnostic assessment instruments used for research studies. Such changes and the use of different diagnostic criteria complicate considerably the interpretation of research findings and the conduct of this systematic review of AG. At the very least, results from different studies must be interpreted in light of whether DSM or ICD diagnostic rules were utilized. At worst, results from different studies and across different versions of the manual are rendered incomparable. Given this limitation and considering the length of manuscript, this paper could not fully appreciate in detail several, undoubtedly important, clinical distinctions surrounding the expression of agoraphobia and its measurement.

HISTORICAL PERSPECTIVE OF AGORAPHOBIA IN REVISIONS OF THE ICD AND DSM

The first account of AG is credited[4] to Westphal's classical description (1871) of the syndrome that, during the major part of the last century, served as a model paradigm for anxiety disorders in general.[5] From that time until the introduction of DSM-III-R,[6] AG was frequently described and reported in the literature as a common and distressing phobic disorder, or as phobic neurosis in the older literature.[4,7,8] Internationally, AG was introduced and codified as an independent diagnostic entity and distinctive syndrome of multiple fears in the 1970s (ICD-9),[9] where it retains this status even today (ICD-10).[10] In the United States and the DSM system, AG also appeared as the result of subdividing phobic neurosis and anxiety neurosis (DSM-III).[11] The DSM-III definition "marked fear and avoidance of being alone or in public places from which escape might be difficult or help not available in case of sudden incapacitations" did not differ much from that of other phobic disorders in DSM-III and the ICD definition of AG. The text description in DSM-III, however, already stipulated in 1980 that the diagnosis of AG is more closely linked to PAs than to phobias. "Agoraphobia with Panic Attacks" should be coded if "the initial phase of the disorder consisted of recurrent panic attacks," thus leading the individual to develop anticipatory fear of having such an attack and to avoid situations associated with these attacks. Only when there was no history of PA (or the information was lacking), the diagnosis of "Agoraphobia without Panic Attacks" was made.

Starting with DSM-III-R[6]—and unlike the ICD-9—AG was specifically defined as a classically conditioned response to situations in which PAs had occurred. In response to increasing experimental and clinical evidence,[12–17] AG in DSM-III-R was not only conceptually attached to PA and PD, but was also seen explicitly and exclusively as a temporally secondary complication. In fact, with each consecutive DSM revision, the residual status of AG within the construct of PA and PD has been increasingly more pronounced. DSM-IV-TR[18] acknowledges the relevance of AG as a syndrome by describing criteria that state upfront that AG (in itself) "is not a codable disorder." Instead, allowances are made and codes provided for those disorders in which AG occurs, namely PD with AG or AG without the History of Panic Disorder (AG w/o PD). The latter, however, restricts the diagnosis to those patients where AG is related to fear of developing panic-like symptoms (e.g., dizziness or diarrhea). The DSM-IV-TR formulation results in a fairly complex (12 pages) differential diagnostic scheme with lengthy differential diagnostic considerations. Unlike all other disorders, two core psychological syndromes, namely PAs (that may occur in the context of many mental disorders) and AG (only relevant for PD and AG w/o PD), are described first before the specific diagnoses are described.

This procedure has deepened discrepancy between DSM and ICD. The ICD-9 and the ICD-10 do not assume that AG necessarily arises from PAs, and thus have retained AG as a separate disorder, independent of PD. Furthermore, in the DSM-IV-TR, the definition of AG is substantially different from the definition used for other phobic disorders in that the diagnostic criteria for AG are tied not only to the concept of PA or PD but also to "panic-like symptoms" (AG w/o PD). This conceptual development in DSM was based mainly on the observation in some studies[15,19,20] that among clinical samples in research settings in the United States, that use DSM-III-R criteria, AG patients without PAs or panic-like features appear to be extremely rare—an observation that continues to date.[20] Fava et al.[21] attributed this largely to the fact that the diagnostic criteria and assessment instruments are by now so "biased" toward the temporally primary causal role of PAs or panic-like features that it is impossible to diagnose AG outside the context of primary PAs or panic-like features. Thus, to date, the implicit hierarchical criteria in DSM-IV have rendered it impossible to collect systematic data to resolve this issue, if one sticks strictly to the current DSM-IV-TR definition. The lack of resolution has led to the unfortunate situation of two discrepant diagnostic criteria sets worldwide, and use of different criteria in different diagnostic interviews. This makes direct comparisons of findings in this domain difficult and in some areas impossible.

It is important to note that in contrast to the definition of AG and the assumed causal role of PA or panic-like features, there is *no to little controversy* regarding the diagnostic criteria of PA or PD or the fact that *both are frequently comorbid with AG*. Further, both positions agree that, by and large consistent with the classical literature, that PA and panic-like features *may* play a core role in the development of some but not all AG patients.[7,22] The *disagreement* mainly surrounds whether (a) AG exists at all independent of initial primary PAs or panic-like features,[23–33] (b) whether PA or panic-like features are invariably causally linked to AG, or (c) whether there is any clinical utility in diagnosing AG as a separate disorder,[34–37] and (d) whether at all and if yes how to define and specify the explicit criteria for AG in a better way.[37–39] Further, some uneasiness has been expressed as to whether the DSM-IV-TR conceptualization of AG as a residual of PD (AG without the history of PD) is in line with the overarching principles of DSM-III and its successors to be atheoretical and descriptive unless persuasive aetiopathogenic mechanisms have been established. Although such persuasive evidence is lacking, DSM-IV-TR's explicit diagnostic hierarchy rules assume such an etiological role of PA and PD for AG, resulting in a near unconditional priority of PD over the diagnosis of AG.

To summarize, since DSM-III-R, AG is diagnosed only within the context of PD (PD with AG) or as the result of PA or panic-like features (AG without a history of PD). This convention is in contrast to the ICD-10, where AG in fact takes precedence over PAs, and prior diagnostic conventions in DSM-III, where AG was defined similar to phobias.

Another unresolved question is how to diagnose patients who fail to report panic-like symptoms as required by DSM-IV-TR. Assuming that such cases might exist, should such cases be diagnosed as anxiety disorder NOS or as a specific phobia in DSM? This issue has been identified as particularly critical by developers of diagnostic interviews and epidemiological research.[26,40] The current DSM-IV-TR provides little guidance in this respect, which constitutes a potential problem. Unlike phobic disorders, where separate criteria are specified, the current "broad" AG definition lacks specification for what constitutes agoraphobic situations and cues beyond the occurrence or fear of panic-like symptoms. Further, unlike phobic disorders, AG criteria do not specify the additional mandatory criteria for phobic disorders, such as the "exposure" criterion (B), the criterion that the person recognizes his fear as excessive or unreasonable (C), or the distress and impairment criterion (E). As stipulated in the ICD-10 criteria for research,[10] AG should be diagnosed when the AG syndrome occurs in at least two out of a total of four prototypical situations to qualify for what is called in both systems as "a characteristic cluster." In response to this, most recent diagnostic interview versions assign the diagnoses whenever two or more situations are endorsed. Because DSM-IV-TR lacks such a precise definition, numerous and mostly older DSM studies assigned the diagnoses

even when only one situation is endorsed and without additional mandatory criteria used for all phobic disorders (Social Phobia or Specific Phobias).

Beyond these core issues, revisions of DSM-III have added some modifications of the diagnostic specification of AG[37] that were critically reexamined. In the DSM-III-R,[6] an AG diagnosis was assigned when the person was anxious about having a PA that s/he restricts travel (avoidance), needs a companion to travel (use of companions), or endures AG situations despite intense anxiety (distress). These criteria have been criticized as lacking proof of incremental validity and being overinclusive[39] because they do not restrict AG to exhibiting avoidance behavior. That is, patients might be able to travel extensively even though they need a companion to do so, or they might even be able to travel alone while experiencing significant distress. Further, DSM-III-R delineated situational avoidance as the central issue to be considered by classifying AG across four different levels (none, mild, moderate, severe). In the DSM-IV,[18,41] this is no longer the case with situational avoidance on equal footing with distress and use of companions in making a dichotomous AG diagnosis (absent, present). This has been criticized by Schmidt and Cromer[37] as potentially decreasing clinical utility as well as predictive value, because situational avoidance has been de-emphasized in making AG diagnosis. Further, the reduction of specification of AG from a dimensional AG 4-point rating to a dichotomous (present/absent) approach suggests that a dichotomous method of organizing agoraphobic behaviors is superior to the more finely graded assessment of phobic avoidance. However, no data have been presented to support this. Schmidt and Cromer[37] assumed that this decision might have reduced the clinical utility of an AG diagnosis.

Given these controversies and unresolved issues, this article was commissioned by the DSM-V Anxiety, Obsessive–Compulsive Spectrum, Posttraumatic, and Dissociative Disorders Work Group to review this critical issue again, to explore whether new data allow a resolution of these issues.

METHODS OF LITERATURE REVIEW

SEARCH STRATEGY AND SELECTION CRITERIA

We searched the "Web of Science," "PubMed," and "PsychINFO" databases in April 2008 for peer-reviewed articles on AG, and updated the review in March 2009. Reference lists of retrieved articles were searched for additional studies. Only articles in English and German were considered, and over 30 search terms were used (full list available on request). Articles on AG printed after 1990 were targeted, but compelling articles published before 1990 were also included. Articles were selected if they were peer-reviewed and addressed issues of epidemiology, therapy, experimental procedures, neurobiology, psychopathology, diagnosis, or assessment. The DSM-IV Source Book[1] and DSM-IV Options Book[42] were also reviewed.

DATA COLLECTION AND ANALYSIS

The method section of each study was examined first with respect to its assessment/diagnosis of AG. Studies that examined AG independent of PA and PD were marked and selected for priority review. Given the paucity of such studies, quantitative analysis of results was rendered impossible. As such, articles that utilized hierarchical DSM-IV rules were also considered. Studies were further grouped according to the following thematic areas: prevalence and incidence, developmental issues and age of onset, natural course and outcome, patterns of co-morbidity and transition between disorders, vulnerability and (causal) risk factors, including genetic and family genetic factors, temperamental antecedents, cognitive and emotional processing abnormalities, neural substrates and shared biomarkers, and treatment/treatment response.

DESCRIPTION OF STUDIES/ METHODOLOGICAL QUALITY OF INCLUDED STUDIES

All search terms and databases revealed a total of 2,112 citations, 469 of which were judged relevant for this review. Of these, less than 5% assessed AG independent from present DSM hierarchical rules. Findings from studies tied to the current DSM cannot inform about the independence of the diagnosis or its relation to specific phobia or PD. The overall frequency of relevant articles per thematic topic was as follows: Conceptualization ($n = 21$), Relationship between AG, PA, PD, and Specific Phobia ($n = 66$), Co-morbidity ($n = 47$), Transition between disorders ($n = 21$), Temperament Antecedents ($n = 19$), Cognitive/Emotional Processing Abnormalities ($n = 35$), Vulnerabilities and Risk Factors (Environmental and Genetic) ($n = 57$), Familiality ($n = 26$), Developmental Patterns ($n = 22$), Assessment Complications ($n = 27$), Neural Substrates ($n = 19$), Shared Biomarkers ($n = 20$), Symptom Similarity ($n = 9$), and Treatment Response ($n = 80$).

RESULTS OF REVIEW

EPIDEMIOLOGICAL AND CLINICAL EVIDENCE FOR AG

Prevalence. Since 1980s, a wide range of community studies in the United States,[43–46] Europe,[47] and the rest of world[48–52] have examined the lifetime and 12-month prevalence of PAs, PD, and AG, according to the criteria of DSM-III, III-R, and IV. Despite some variation in lifetime prevalence estimates, they almost all converge on the following: (a) PAs according to

DSM-III-R and IV are very frequent manifestations with estimates of 20% or above for most samples, (b) lifetime rates of PD are in the range of 3–5%; depending on the study, approximately 35–65% of subjects with PD meet criteria for PD with AG, whereas the remaining report PD without AG, and (c) rates for AG without history of PD are typically found to be at least as high or even higher as those for PD. However, they also reveal a large degree of variation of prevalence across studies, ranging from about 1% to a high of 22% (median for older and more recent studies = 7.8%; mediation for studies since 1990 = 3.8%), probably due to methodological factors. AG without PD have been reported to occur in both children[53] and in the elderly.[51]

A recent review by Faravelli et al.[54] summarized five epidemiological studies that convergently found that 46–85% of all individuals with AG do not have PAs. He also showed, however, that in clinical samples (eight studies mostly with a few dozen patients), AG without PA is considerably less frequent (0–31%), with four studies finding not a single case. In studies published since 1990,[45,55,56] which used a stricter definition of AG requiring at least two agoraphobic situations consistent with ICDs and DSMs stipulation of a typical "cluster" of situations, the 12-month rates for PD with and without AG was found to be 1.8% (interquartile range [IR]: 0.7–2.2) and 1.3% (IR: 0.7–2.0) for AG without PAs. The variation between studies has been attributed to design, methodological, and assessment variation rather than reflecting true differences; for example, as a function of cultural or regional effects.[47,55] An important example of such a methodological factor is the different conventions used for the DSM-IV "A" criterion. In contrast to studies in the 1980s with the Diagnostic Interview Schedule (DIS), where even one single AG situation may qualify for a diagnosis, most recent studies using the Composite International Diagnostic Interview (CIDI) required two or more situations to meet criteria for DSM-IV-TR. This change led to decreases in rates of AG by approximately 50%. It also affected the rates for PD with AG, revealing now—in contrast to older studies—more cases of PD without AG than PD with AG.[26,33,56]

To summarize, consistent with a previous review of this issue by Ballenger and Fyer,[1] the prevalence of AG without a history of PD and even the prevalence of AG even without the presence of PA and panic-like symptoms (as is possible in the CIDI/ICD-10) was at least as high as the combined rates of PD with and without AG across all epidemiological studies.[33,45,56–61] Thus, even when conservative definitions are utilized (i.e., strict reliance on DSM-IV-TR criteria), as in the most recent NCS-R findings,[45,62] roughly 25% of all subjects with panic/AG syndromes met AG criteria without qualifying for either PAs or PD. Therefore, persuasive evidence has documented substantial rates of AG without PD and without PA in the community that are approximately as frequent as those that occur concurrently with PD.

According to US studies, the situation in clinical settings appears to differ. As reviewed by Ballenger and Fyer[1] and Barlow,[19,20] at least the diagnosis of "AG without the history of PD" is rarely assigned in clinical practice. Faravelli et al.[54] reviewed eight clinical studies, seven with low sample sizes, citing four studies with not a single case of AG without panic and four studies reporting 2–31% of PA among AG patients.

Temporal relationship of PA, PD, and AG. Some studies used longitudinal data to specifically examine the question of whether AG is always related to primary spontaneous PAs or at least panic-like symptoms.[21,26,28,33,40,63] Consistent with other evidence from similar inquiries in epidemiological[44] and clinical samples,[32,64,65] these explorations found no consistent evidence to support these assumptions. In community samples, the majority of agoraphobics never experienced any PA or panic-like symptoms or psychophysiological symptoms of other type that clearly preceded the onset of agoraphobic avoidance. If they reported such symptoms, they were frequently secondary to AG onset, and longitudinal evidence suggests that AG just as frequently precedes PA as PA precedes AG.

Mostly smaller (less than 70 patients) clinical studies in the United States[17,66,67] find that in the vast majority of patients with AG/PD or AG with PA, agoraphobic avoidance clearly occurs temporally secondary to the PA. Ballenger and Fyer[1] concluded after examination whether primary PAs also affect the natural course of secondary AG that, although agoraphobic avoidance does not seem to be related to variables, such as type of PA frequency or severity of attacks, it does seem to be related to the expectation of panicking in specific AG situations. However, these findings do not imply that "panic expectancy is of causal significance for the development of agoraphobia avoidance" (Ballenger and Fyer,[1] p 455).

Other lines of evidence for inconsistent findings come from clinical retrospective studies that used sensitive methods to detect subclinical symptomatology prior to the onset of PAs. Fava et al.[64] found that the majority of 40 patients with PD with AG experienced prodromal symptoms (AG, hypochondriasis, generalized anxiety) before the first PA. The findings were obtained with considerable methodological precautions: careful dating of symptom onset, rigorous symptom definition by a reliable and validated probe suitable for prodromal and subclinical symptoms, and delay of the interview until the acute disturbance has passed (to minimize distortions of recall). These methodological features may account for the striking differences from studies performed in the mid-eighties, which relied on self-rating instruments, unstructured interviews, and diagnostic instead of symptomatic focus. Not surprisingly, the findings were confirmed by subsequent studies. Garvey et al.[68]

found that 28% of 32 PD patients had prodromal symptoms of anxiety that lasted a median of 5 years before the occurrence of the first PA. Lelliott et al.[32] reported that 70% of 57 patients with PD with AG had prodromal depression, anxiety, or avoidance. Agoraphobic avoidance preceded the first PA in 23% of patients. Argyle and Roth[69]considered the sequence of the events in 56 cases of PD associated with AG. They found that the majority of patients (55.4%) had their onset in the same 6-month period as the onset of PD, with 19.6% of patients for whom an AG clearly preceded panic and 25% of patients with the reverse sequence of events. Other diagnoses, especially social phobia and generalized anxiety disorder, however, frequently predated the onset of panic. In the same vein, long-standing hypochondriasis was found to precede the onset of PAs not associated with AG. Perugi et al.[70] studied 126 consecutive cases of PD by means of semi-structured interviews and substantially replicated the findings of Fava et al.[64] Further, in several studies,[32,70,71] the large majority of patients experienced their first PAs in public places and phobogenic situations.

This considerable degree of discrepancy in findings has not yet been resolved because of methodological problems inherent in studies. But it could be at least summarized; there is fairly consistent evidence that PA precedes AG in up to 50% of all individuals with AG, providing some support for the assumed aetiopathogenic pathway implied in DSM-IV-TR. However, the fact that up to 50% of AG does not reveal indications for this pathway is suggestive of the existence of other pathways. It should also be noted that these data are not fully consistent with the panic–agoraphobia spectrum concept[72,73] that assumes a reciprocal relationship, meaning that either condition raises the probability of the other one. The epidemiological evidence does not support this reciprocal relationship. A major limitation of these studies is that the majority of them rely heavily on retrospective reports about the onset of each condition. Further, subjects were studied sometimes decades after onset, making retrospective appraisals highly problematic. This problem becomes easily apparent when examining age of onset reports for PAs and AG onset, reviewed below in a separate paragraph.

Prospective longitudinal investigations in well-defined age groups might resolve such issues, but are rare. In fact, we found only one recent prospective longitudinal multiwave study that systematically described incidence characteristics of PA, PD, and AG.[33] This prospective study found that 23.5% with an initial PA subsequently developed AG, as did approximately 50% developed PD. This constitutes a 17-fold risk increase for developing AG and a 38-fold risk for PD. It should be noted, though that PAs were highly associated with all types of disorders, including other anxiety, mood, and substance disorders, and thus are not very specific for either AG or PD.[74] It is also noteworthy that cases with temporally primary AG (without PA according to DSM-IV-TR or even panic-like features (as defined by "fearful spells") were not at increased risk for subsequent PA or PD; only 11.6% of all primary AG developed a subsequent PA and only 2.4% developed PD.

Critical methodological aspects. The failure of epidemiological studies to support the assumption that PAs and panic-like symptoms almost always play a core pathogenic role for the onset of AG has been repeatedly challenged on methodological grounds. Against the background of observations that AG without PA/PD is rarely seen in clinical samples,[15,19,20] methodological concerns were raised that current diagnostic instruments might not be able to assess panic features with sufficient accuracy and validity, or more generally, that the diagnostic interviews were not diagnostically valid. Horwath et al.[25] and Goisman et al.[15] conducted careful clinical reappraisals that, however, were based only on a few dozen patients. In response, Wittchen et al.[26] conducted a careful clinical reappraisal of all AG cases in the Early Developmental Stages of Psychopathology (EDSP) data set. The clinical appraisal of each case was conducted by independent clinicians who were blind toward the interview diagnosis. The outcome of this appraisal (based on clinical questions like "What are you afraid of?") failed to raise *any* doubts that these cases were AG cases, without indications of prior PAs or panic-like symptoms whenever the diagnosis was based on at least two out of a total of five (plus "other") agoraphobic situations were met. The reappraisal also indicated that cases meeting all criteria, but only reporting one of the prototypical situations, were often better reclassified as specific phobia, mostly of situational type. Similar evidence was also provided by Faravelli et al.[75] and Fava et al.[76] The publication of the studies in the 1990s led the CIDI criteria to be changed. They now require at least two situations to be reported before assigning a diagnosis of AG; cases below this threshold are classified as phobia NOS. It should be noted that this change in the diagnostic interview reduced substantially the rates of AG in general, as well as the rates of PD with AG. This algorithmic change is also responsible for the decline in rates of AG in more recent studies since the 1990s. It should be noted though that despite the considerable sophistication in such methodological appraisals, some task force advisors still believe that methodologically sound, and full appreciation of all critical concerns is still lacking.

How frequent is AG without panic attacks or PD? Based on these revised, more stringent AG criteria and a careful prospective longitudinal investigation about the relationship of PAs and PD with AG, Wittchen et al.[33] conducted a comprehensive analysis of the incidence patterns and temporal relationship of mutually exclusive classes of various liberal definitions of panic-like features (labeled fearful spells) in a sample of 3,021 subjects.

This longitudinal characterization (see Fig. 1) revealed that the cumulative lifetime prevalence of AG without any indications of even the most liberally defined fearful spells is 1.5%. This rate is approximately

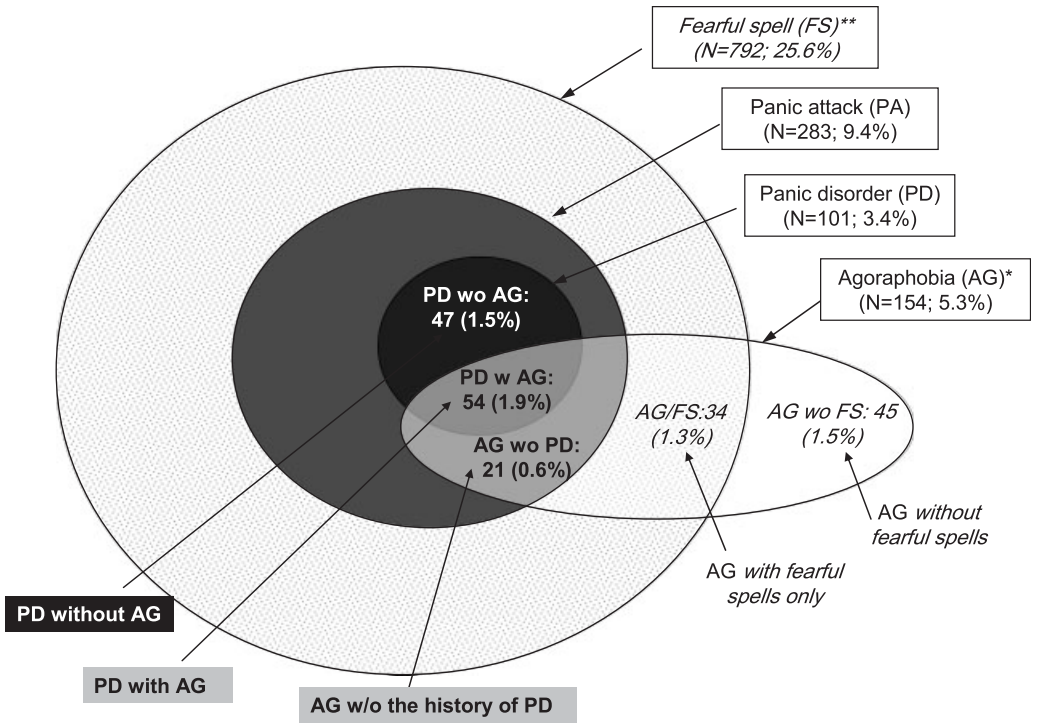

Figure 1. Modified from Wittchen et al., 2008.[33] The prevalence and mutually exclusive combinations of fearful spells (FS), DSM-IV-TR panic attacks (PA), DSM-IV-TR panic disorder (PD), and Agoraphobia (AG) as assessed with the M-CIDI in the community. Numbers indicate the number of cases and the weighted prevalence estimate. *The definition of agoraphobia is only partially (namely for subsets of those with PD with AG, as well as AG w/o PD (but with PA)) consistent with the DSM-IV-TR criteria of either PD with AG or "Agoraphobia without history of PD." AG/FS cases meet all AG criteria, but despite fearful spells no "panic-like symptoms." AG w/o FS report not even fearful spells. The latter two groups would not be diagnosed as AG according to DSM-IV-TR. **Subjects with fearful spells (FS) have acknowledged the CIDI question: "Have you ever had an attack of fear or panic, when all of a sudden you felt frightened, anxious or uneasy? Some people call this a panic attack." They failed, however, meeting the criteria of PA, for example by not reporting any or only an insufficient number of symptoms or by denying that the attack occurred out of the blue.

the same rate with which PD without AG occurs. In addition to AG without fearful spells (1.5%), 1.3% of cases report fearful spells after the onset of AG. The strict DSM-IV-TR definition of AG without a history of PD is only met by 0.6%, whereas the rate of PD with AG is 1.9%. Along with other information and transitional analyses, this study concluded that AG is a clinically significant disorder that may exist independently from PA and PD in a substantial proportion of subjects. This exploration also shed light on a second problem inherent in DSM-IV criteria and diagnosis of PD and AG, namely that the subjects in the population without PA and PD remain undiagnosed because of the DSM stipulation that AG syndromes occur in response to panic-like symptoms. As documented in this study, a substantial number of subjects fail to report or experience any such symptoms.

Gender and age of onset of PA, PD, and AG. A stronger female preponderance was found for AG without panic than for PD.[47,77] To our knowledge, there are no studies that have reported significant age × gender interaction differences between PD and AG. Age of onset characteristics of PAs as well as PD with and without AG are well studied and suggests little differences. According to retrospective cross-sectional community studies covering ages 18+, all three groups reveal a mean age of onset of 21–23 years with overall strikingly similar age of onset curves.[56] As a function of different sample composition, some studies reported slightly higher ages (23–36).[48,78,79] The studies consistently show that two thirds of all PD cases develop before age 35, with a substantial incidence risk in late adolescence and rarely in childhood.[80] There are some indications for a bimodal high risk distribution for PAs, with one peak around ages 15–19 and another one at higher ages (35–50).[59,81–83] Some studies suggest that the presence of AG seems to affect the age of onset of PD with some inconsistent indications for a later age of onset.[35,84] Overall, age of onset characteristics of AG without PA are less well established. Among those specifically addressing AG without PAs, a slightly later mean onset of AG was shown, ranging from 25–29 years of age,[59,78,83,85] with some indications for a bimodal distribution (second high incidence period after age 40) regarding onset risk. This is only partially consistent with other findings that indicate that AG may occur as early as childhood in greater frequency than PD.[26,53]

To summarize, despite some differences between AG without PAs and PD with AG, the size of the differences and the extent of evidence is not sufficient to conclude that age of onset characteristics of AG differ substantially from those observed for PD.

Impairment. The few available studies,[33,62,86] which have directly compared differences in impairment and disability between PD with and without AG and AG (without PAs or panic-like features), consistently find greatest impairment for those with PD/AG and lowest impairment for those with PAs without meeting criteria for either disorder, with PD (without AG) and AG (without PAs or panic-like features) in between. It is noteworthy that PD without AG has significantly fewer impairments than PD/AG in all available indices (i.e., role functioning, work productivity, disability days, Panic Disorder Severity Scale, Sheehan Disability Scale) and does not differ from the impairment observed for AG without panic.[33] It should also be highlighted that these findings are consistent with findings suggesting that the degree of AG seems to be a more potent determinant of disability than number and severity of PAs.[87] This seems to suggest that (a) with the exception of PA, all three conditions are quite impairing disorders, with PD/AG cases revealing the most severe expressions, (b) AG without PAs is as impairing as PD without AG, and (b) that AG in PD patients considerably worsens functioning and degree of disability.

Helpseeking and treatment. Few studies have examined help-seeking rates for all three conditions considered. Wang et al.[88] reported for the United States that PD (41.2%) and AG without PD (42.1%) rank among the mental disorders having most frequently received "at least minimally adequate treatment." However, AG without PD differs substantially from PD patients in that they received less treatment by psychiatrists and the general health care sector. Similar results were reported from a comprehensive analysis of 14 European Union studies.[47] The lower rates for AG cases in psychiatric and general health care are consistent with clinical observations that such patients are rarely seen in specialized care.[15] More detailed analyses by Nocon[89] in Germany further reveals that professional help-seeking among those with PD/AG and those with AG with PA occurred significantly more often because of panic problems than AG problems. It should be noted, however, that such patterns depend heavily on characteristics of the health care system. For example, AG without PA in Germany is predominantly seen by psychotherapists, whereas PD is more frequently seen by psychiatrists. Kessler et al.[45] reported similar indications for the United States, although they were not statistically significant.

Socio-demographic correlates. There is no consistent evidence that salient correlates differ across the diagnostic groups, with one noteworthy exception. Namely, individuals who have AG without PA and PD/AG are noticeably more frequently unemployed and disabled than individuals without AG.[26,45]

Co-morbidity patterns. Few studies exist that allow for direct comparisons of co-morbidity patterns in community samples. There is agreement, however, that PD and AG both are rarely seen in pure forms and both are significantly associated with many other diagnoses, including other anxiety, mood, substance, and somatoform disorders.[54,56,62,90–92] Direct comparisons reveal higher co-morbidity rates with depressive disorders for PD/AG (52%) and AG with PA (52.3%) than those who have AG without PA (33.1%). Thus, PD/AG and AG with PA are similarly strong predictors for increased depression risk. Co-morbidity with other anxiety disorders was found to be in the same range for all groups (49–64%), with no significant differences, though AG without PA appeared to be more comorbid with other phobic disorders. In terms of transitions from one syndrome to another, a number of authors[26,74,93] have highlighted that temporally primary PAs are a sensitive marker of subsequent psychopathology (over 90% developed at least one mental disorder), but not necessarily specific for PD, AG, or other anxiety disorders.[1] Similarly, high associations were found for mood disorders, psychotic disorders, and substance use disorders. In contrast, AG is more closely and specifically linked to anxiety disorders (highest probability) and secondary depression.[89,91,94]

Summarizing the available evidence from epidemiological studies in the community with regard to associated factors in PD, PD/AG, and AG, there seems to be considerable evidence that AG without PAs and even panic-like features exists and reveals similar impairment and disability findings as PD without AG. Overall PD/AG seems to be the most impairing conditions. Beyond some indications for minor differences in the other factors considered, there is little persuasive evidence for the existence of major differences between AG without PAs and PD. Co-morbidity analyses, however, reveal that AG appears to be more specifically linked to other anxiety disorders and phobias in particular, whereas PA and PD are associated with a broader spectrum of comorbid disorders.

VULNERABILITY AND RISK FACTORS

In the next section, we will consider evidence for differences between PD and AG without PA in vulnerability and risk factors as well as selected clinical aspects.

Genetic and familial factors. There is considerable evidence for the *familial aggregation* of PD from various types of clinical and family studies. Studies fairly consistently show higher rates of PD in all first-degree relatives[95–97] of PD patients as compared to controls. Hayward et al.[98] suggest that parental

history of PD/AG may have a core role in the development of PAs in offsprings. However, one should caution this conclusion because PA and PD also increase the morbidity risk of offsprings for a whole broad range of other disorders.[99,100] Nevertheless, the handful of studies that accounted for other disorders[95,101–104] suggest that there is at least some specificity for PD/AG. Only a few studies examined whether there is a differential familial aggregation of PA/PD and AG. Harris et al.[105] found that the increased risk of relatives of agoraphobic patients is not confined to AG (33% vs. 15% in controls), but also for PD (32%) and other phobias. In contrast, Smeraldi et al.[106] reported an increased risk only for AG and not for PD. Further, Tsuang et al.[107] reported that AG among those with PA is familial, yet AG in twins is not associated with increased PD aggregation, suggesting that AG and panic liability are not positioned on an agoraphobia-panic continuum. Nocon et al.[108] found that PD and AG aggregate in families; AG without PD is not familial but it might enhance the familial transmission of PD. Both parental AG and PD similarly increase the risk in offspring to develop any anxiety disorder.[109]

Heritability has been estimated to be 43–48% for PD[110–112] and 61% for AG.[112,113] Kendler et al.[113] estimated for phobias among females a high heritability (40–60%), suggesting a "phobia proneness" with AG revealing the strongest and most specific associations.[114,115]

Molecular genetic strategies have been used extensively in PD (reviewed in[89]) and have identified a wide range of candidate genes and suggested mechanisms related to neurobiological and pharmacologic targets, most of which remain controversial: Locus coeruleus (NTRK3), dopamine (D4DR, DAT), Serotonin (5HT-1A, 5HT-2C, 5HTTLPR), Katechoalminsystem (MAO-A, COMT), Neuropeptide (NPY Y1, Y2, Y5), Adenosinreceptors (ADORA1, ADORA2a), and CCK (e.g., CCKAR).[116,117] In addition, there is a wide range of studies that conducted genomewise scans without any clear replicated candidates. More importantly, there are only very few studies that specifically separate PD and AG. Politi et al.[118] reported no association between Glyoxalas-1-Polymorphisms and PD/AG, unless they exclude AG cases. Rothe et al.[116] reported differential findings with regard to the 5HT Transporter polymorphism for PD with and PD without AG. Hettema et al.[119] reported association with the COMT-gene for females in PD and AG.

To summarize, there is little evidence for diagnostically specific genetic mechanisms in either PD or AG; nor is there sufficient evidence for different mechanism between them.

Other neurobiological factors. Although the psychophysiology and neuroendocronological mechanism of panic-agoraphobia are well studied (see reviews:[120–122]), including studies in the context of panic provocation tests (see reviews by[123–128]), to our knowledge there have been surprisingly few studies that examined differences between PD, PD/AG, and AG without panic. A notable exception is a study by Garvey and Noyes[129] that directly and specifically examined whether PD and AG are variants of the same disorder or distinct diseases by laboratory measures. They examined 91 AG patients, without specifying though the existence of PA and 24 PD patients in terms of levels of the urinary lysomal enzyme NAG that has been discussed to be a marker of serotonin binding and metabolism. This study revealed that NAG levels were significantly lower in patients with PD as compared to AG, providing limited support that PD and AG may be distinct illnesses.

Family climate. Most studies in patients with PD and AG describe the family climate or child rearing behavior as being characterized by reduced warmth and increased overprotection.[89,130–133] This relationship is best established for PD,[132,134,135] but this factor has been rarely considered specifically in studies with AG without PAs. Some indication for specificity has been reported by Kendler et al.[136] who showed that AG, but not PD, in females was significantly associated with parental lack of warmth, overprotection, and autoritarism.

Critical life events. There is evidence that negative events in childhood (e.g., separation, death of parent, etc.) are associated with both AG and PD.[114,137–141] Increased rates of critical life events have been associated with the onset of various disorders, with little evidence for diagnostic specificity.[141,142] However, few studies suggest that early death and separation was associated with PD, while only death (not separation) was associated with AG.[114,143] Similarly, there is no evidence that AG and PD nor any other anxiety disorder reveal differences in the structure and frequency of life events over the life span; all conditions were increased when significant life events were (retrospectively) reported.[144]

Temperamental antecedents and personality. Similar to all anxiety disorders, behavioral inhibition and neurotic disposition (i.e., neuroticism, negative affect, anxiety sensitivity) are associated with AG, phobic disorders, PD, and a range of other conditions. Overall, there is little convergent evidence that these dispositional measures are diagnostically specific. Behavioral inhibition has been shown cross-sectionally and prospectively to be associated with many anxiety disorders,[140,145–149] including PD and AG.[140,142,150,151] Similarly, neuroticism[79,152] and negative affect[153–155] confirmed this association with little to no evidence for differences. It should be noted, however, that specific tests between PD, PD/AG, and AG without PAs were not conducted.

A notable exception is anxiety sensitivity, or the trait to disposition to believe that symptoms of anxiety are harmful, as measured by the Anxiety Sensitivity Index (ASI). A review by Hirshfeld-Becker et al.[156] suggests that the ASI is a specific predictor for PD but not for other anxiety disorders. However, Hayward and

Wilson[157] find that the ASI also predicts AG without the presence of PA.

To summarize, the distinction between PD, PD/AG, and AG without PA has been rarely specifically addressed in studies on vulnerability and risk factors. Due to design and assessment problems, there is no conclusive evidence that reliably informs us about differences among these conditions. The same, however, also applies to the direct examination of differences between other anxiety and mood conditions. Increased research on diagnosis-specific vulnerability, risk factors and possible interactions may reveal specific risks.

Clinical-phenomenological aspects. There is convergent evidence from studies that AG—measured with various instruments—is a reliable construct that appears in virtually all taxometric investigations as one of the major classes.[38,87,158–162] It has been repeatedly associated with social role impairments and clinical and cognitive correlates.[163–166] The consistency with which this has been found in the context of PD led some to suggest that AG is an indicator of severity for PD.[56,167] Using AG indicators from various sources, Slade et al.[87] examined the latent structure of AG in patients with PD and PD/AG and a community sample, and identified an underlying dimensional structure that suggests AG should be best conceptualized as a continuum of avoidance. Although this study did not include a group of AG without PA, it adds to our knowledge of AG as an important construct. Another interesting exploration by Schmidt and Cromer[37] has suggested that an AG specifier provides meaningful information regarding the expression of PD, specifically with regard to social functioning impairment and total distress experienced.

An important finding from this report[37] is the clear suggestion that the highest level of clinical utility might be achieved by reverting to a dimensional measure that is specific to situational avoidance (vs. distress or use of companions). Among the different outcomes that were assessed, avoidance, and in particular the dimensional measure of avoidance, consistently explained the most variance beyond that accounted for by overall severity, the three core panic variables (frequency, intensity, and worry) and DSM-IV AG diagnosis. These data provide some further indirect support for the importance of AG, particularly in terms of greater clinical utility. Although this exploration does not address the independent diagnostic status of AG, it suggests that evaluating the level of situational avoidance would also avoid some of the criticism of the expanded criteria AG,[39] and might also improve diagnostic reliability[168] toward the use of avoidance (vs. distress and use of companions). Although situational avoidance appears to have important clinical utility in the context of a PD diagnosis, it is not clear why this is the case. Feldner et al.[169] found that patients with PD utilize more avoidance-based coping strategies and ultimately view these strategies as more effective, when compared to controls. Moreover, avoidant-based coping strategies are associated with higher levels of anxious responding and increased distress in response to bodily sensations.[168,170] Thus, it may be that underlying cognitive or psychological factors (e.g., coping style) dispose certain PD patients to develop AG. If this is the case, these underlying factors may help account for the clinical utility associated with situational avoidance.

Clinical course and outcome. The clinical course of PD and AG in clinical and epidemiological samples have been reported as being chronically persistent (AG) and chronically recurrent (PD).[171] Emmelkamp and Wittchen[94] found that AG without panic ranks among the most persistent disorders over a period of 10 years follow-up, with a homotypic continuity greater than the one found for PD. They also reported that in comparison to all other phobias, complete remissions are rare;[77] none of the initial AG cases assessed in that study achieved complete remission.[94] This is true, despite considerable variations in severity and various degrees of syndromal shifts that might occur as with regard to comorbid disorders, in particular the occurrence of depression. Regarding predictors of long-term outcome of PD, the presence of severe AG has been the most consistent finding.[32,66,81,172,173] AG severity was shown to reduce the chance of full remission, to increase risk of relapse, and to enhance chronicity. In the longest follow-up study of PD with AG treated by exposure (2–14 years), the presence of residual AG was a strong predictor of relapse into panic.[174] Additional factors that significantly contribute to chronicity and relapse are comorbid depression, personality disorders, and high scores on dispositional measures. It is noteworthy though that there are no studies that specifically compared PD, PD/AG, and AG patients in this respect.

Treatment. A large body of research suggests that various forms of CBT and antidepressives are highly effective in treating PD/AG, including long-term efficacy.[175] There is some controversy whether all these treatments are equally effective and whether combined treatments provide additional benefits.[175,176] Some meta-analyses suggest that PD/AG improvements are greater with CBT alone than with pharamacotherapy alone or combined with psychological treatment, yet this conclusion has been criticized as being flawed.[177] There is an impressive body of evidence (reviewed by[4]) on the efficacy of exposure in treating AG. It is difficult, however, to extrapolate from pre-DSM-III literature whether samples were predominantly associated with panic or not. Similar considerations apply to the efficacy of pharmacological treatment (particularly, imipramine).[4] Homework exposure treatment directed to agoraphobic avoidance has been used to treat PD with AG. In the London–Toronto study,[178] homework exposure targeted agoraphobic avoidance, and pharmacological placebo was found to be significantly more effective than alprazolam and a psychological placebo (relaxation)

directed to panic. In one study,[179] the mechanisms of change of PAs during exposure treatment of AG were specifically investigated. Improvement in AG preceded amelioration and subsequent disappearance of panic. Similarly, in the year before relapse of panic, an increase in agoraphobic avoidance was observed.[180]

In terms of differential treatment effects with regard to PD, PD/AG, and AG without PA, the results were inconclusive due to the fact that pharmacological trials in AG are, to our knowledge, lacking. Within psychotherapeutic approaches, exposure treatment appears to be favored in AG over cognitive approaches, providing some limited evidence for a separation of AG.

DISCUSSION/PRELIMINARY RECOMMENDATIONS FOR DSM-V

The purpose of this review was to examine whether recent studies provide evidence that AG exists independently from PD and history of PAs and, using classical validators, to review available evidence regarding whether AG is a separate construct. Overall, we come to the conclusion that AG is a clinically significant disorder that also exists independently from PD, and even PA and panic-like features in a substantial number of cases. We conclude this based on seven main points. First, considerable epidemiological evidence from community studies documents consistent and sizeable rates (of about 50%) of AG without any signs of PA. These cases do not meet current DSM-IV-TR criteria of AG without the history of PD. This finding is incongruent with most, but not all, clinical studies in the United States that have failed to identify such patients in significant numbers. Second, consistent epidemiological, but inconsistent clinical results, fail to find that AG *always* occurs secondary to PA or panic-like symptoms. Third, consistent results document that AG without panic symptoms is associated with significant impairment/disability and a persistent course with low rates of spontaneous remissions. Fourth, evidence also suggests differences in patterns of incidence and gender differentiation between PA, PD, and AG, as well as differences in response to treatment. Fifth, additional indirect evidence comes from the consistent replication of AG as one of the major dimensions in psychometric and taxometric investigations of clinical and epidemiological data, as well as the finding that AG avoidance is an independent contributor to severity, course, and outcome in PD. Sixth, some, but not all, evidence suggests differences in the temporal progression and syndrome stability between PD, PD/AG, and AG. Finally, it is noteworthy that those studies that have used specific and explicit criteria for Agoraphobia—similar or identical to those used in other phobias, have high interrater and test-retest reliability.

Taken together, these facts and conclusions are similar to those reached in the DSM-IV Source Book (Ballenger and Fyer,[1] p 457), namely that in the majority of cases, AG seems to be associated with preceding PA or panic-like symptoms and/or are subsequently mediated by the expectation of panicking in particular situations. But there is still no empirical evidence as yet, which unequivocally demonstrates that AG is temporally primarily and exclusively a function of PA or panic-like features. However, the fact that those up to 50% of all agoraphobics fail to report or remember such primary PA or panic-like experiences together with the finding that a substantial number of cases with PA or PD fail to develop AG, lends considerable support to the notion that AG emerges for reasons other than or in addition to panic. Thus, the most plausible interpretation is the existence of multiple pathogenic pathways involved in AG. The diagnostic implication is that AG should be defined as a category in its own right and not merely as a residual to PD or PAs.

This conclusion is limited by the fact that some segments of the validation process, namely biologically based data such as neurobiologic and genetic data, are not yet available. Further, despite calls for careful examination of critical issues for a decade (i.e., How does AG without panic differ from AG with PA or PD? What are agoraphobics without panic afraid of? What are panic-like features and are full PA functionally different from subthreshold or limited attacks?),[1] such studies have not been conducted in a way that provide definite answers. This might be due to the fact that past DSM versions no longer provided the possibility to systematically examine differences between PD, PD/AG, and AG without PA or panic-like features. This is because AG in DSM III-R to DSM-IV-TR was defined as a residual diagnosis and most established diagnostic instruments reflected this fact, thereby precluding the examination of such distinctions.

THE OPTIONS FOR DSM-V

Before outlining a proposal on how to ultimately define AG in DSM-V, it might be helpful to review available options: (1) The first option would be to delete AG as a diagnosis entirely from the classification, but to emphasize AG avoidance as a dimensional construct by either using a specifier or a separate criterion with PD. (2) A second option would be to move AG to Specific Phobia, as a situational subtype. (3) A third option would be to leave the diagnostic categories as they are, namely to retain PD without AG, PD with AG, and AG without the history of PD as a residual, including the retainment of PA and AG as syndromes. (4) The fourth option would be the segregation of PD and AG by specifying more explicit diagnostic criteria for AG as an independent diagnostic category in its own right. This would also imply that

DSM-IVs description chapter and the criteria of AG as a syndrome could be dropped entirely.

According to this review, as well as the review by LeBeau et al.[3] there is clearly no empirical evidence that option 1 (AG specifier) nor option 2 (specific phobia subtype) are reasonable improvements or remedies to solve the existent problems (Table 1). There are no data to support these changes. Further, they seem to be associated with a range of additional and far-reaching problems and complications previously discussed.[3]

It is more difficult to decide which of the remaining options are preferable because some clinical experts and advisors to the Task Force find the evidence for AG as an independent diagnosis inconclusive (and thus favor option 3), while the Task Force members and others see substantial evidence of the need for making AG an independent diagnosis. The strongest arguments in favor of retainment of the current conventions are: (a) The current conventions work well, (b) AG patients without PAs and panic-like features are practically not existent in treatment settings, and (c) concerns about alternative definitions of AG. The position statements of those favoring an independent status of AG are: (a) The residual status of AG as assigned by DSM-IV-TR, inappropriately and unconditionally implies that one etiological pathway is emphasized to the exclusion of others, and this is inconsistent with available data. (b) The DSM perspective links AG directly to the primary mechanism of spontaneous PA and their assumed neurobiological and neuropsychological role in subsequent AG. Despite unequivocal agreement that this pathway has been established as one frequent pathway to AG, substantial evidence points to the existence of other pathways in a substantial proportion of cases. (c) The current DSM-IV-TR criteria—unlike the ICD-10 criteria[21] for research that are consistent with an independent conceptualization of AG—have and will prohibit the collection of data that help to clarify these alternative pathways and offer empirical guidance for its resolution. (d) With respect to concerns about the treatment implications of changing the diagnosis, two positive consequences are likely. First, the non-assignment of an AG diagnosis, a disorder for which behavioral treatments have been established for decades[181–183] might result in underrecognition and undertreatment as suggested by extant epidemiological data reviewed above. Further, the DSM perspective may suggest targeting primarily panic-related symptoms and associated catastrophic cognitions. In contrast, individuals with AG who have never had a panic-like symptom may differ considerably and therapy may require predominantly targeting agoraphobic avoidance by situational exposure.[181,184–186]

THE PROPOSAL FOR DSM-V

Given that this review and the Work Group discussions have not led to an unanimous consensus decisions, we propose with the Work Group consensus a core proposal, supplemented by an alternative suggestion put forward recently by some of our advisors and experts. We are further considering reanalyses of existing clinical data sets and suggest further exploration and feedback from the field as part of the DSM-V field trials with regard to our proposal. We acknowledge at this juncture, however, that the imperfect nature of current diagnostic assessment instruments with regard to the core critical issues might render parts of this exercise difficult and ultimately unable to provide definite answers. Another possible strategy might be to take other accounts into consideration. One would be the consideration that a revision should not endorse an etiopathogenic pathway that remains at least partially controversial. Given that there is substantial disagreement, this would favor a segregation of PD and AG and the deletion of the implied hierarchy. Another consideration in favor of AG as an independent diagnosis might be the considerable simplification of the DSM structure and text resulting from our proposal.

DSM-IV-TR	DSM-V Proposal
Panic attack (*not a codable disorder*)	*Panic attack* (*not a codable disorder*)
Agoraphobia (*not a codable disorder*)	–
Panic Disorder w.o. Agoraphobia	Panic Disorder
Panic Disorder w. Agoraphobia	–
Agoraphobia w.o. History of Panic Disorder	Agoraphobia

A segregation of the two conditions would allow the lengthy differential diagnostic consideration as well as the chapter of AG as a syndrome to be dropped entirely; the two diagnostic variants PD with and without AG would simply be coded as comorbid diagnoses. This would further increase clinical utility by using a dimensional AG specifier on the one hand and the established PA specifier on the other, and could be used for those cases where the full diagnostic criteria were not met. A third consideration would be that the proposed changes have the advantage that they have been comprehensively tested in epidemiological research in the past, which revealed high reliability and validity, and would bring the ICD and DSM systems closer together.

In consideration of these issues and because we cannot foresee any negative effects or clinical implications, we propose in the following the Task Force's core criteria proposal for AG (Table 2). Additionally, we present in Table 3 the alternative suggested by some

TABLE 1. Comparison of Core Agoraphobic Criteria in DSM-III, DSM-III-R, DSM-IV (TR), ICD-9[a], and ICD-10

DSM-III	DSM-III-R	DSM-IV (TR)	ICD-10 DCR
Anxiety disorders	Anxiety disorders (or anxiety and phobic neurosis)	Anxiety disorders	F40–F48 neurotic, stress-related and somatoform disorders
Phobic disorders (or phobic neurosis)			F40 phobic anxiety disorders
Criteria for Agoraphobia: A. The individual has a marked fear of and thus avoids being alone or in public places from which escape might be difficult or help not available in case of sudden incapacitations B. There is increasing constriction of normal activities until the fears or avoidance behavior dominate the individual's life		Criteria for Agoraphobia (Note: not a codable disorder): A. Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed Panic Attack or panic-like symptoms. Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home alone; being in a crowd, or standing in a line; being on a bridge; and traveling in a bus, train, or automobile Note: Consider the diagnosis of Specific Phobia if the avoidance is limited to one or only a few specific situations, or Social Phobia if the avoidance is limited to social situations B. The situations are avoided (e.g., travel is restricted) or else are endured with marked distress or with anxiety about having a Panic Attack or panic-like symptoms, or require the presence of a companion C. The anxiety or phobic avoidance is not better accounted for by another mental disorder, such as Social Phobia (e.g., avoidance limited to social situations because of fear of embarrassment), Specific Phobia (e.g., avoidance limited to a single situation like elevators), Obsessive–Compulsive Disorder (e.g., avoidance of dirt in someone with an obsession about contamination), Posttraumatic Stress Disorder (e.g., avoidance of stimuli associated with a severe stressor), or Separation Anxiety	F40.0 Agoraphobia: A. Marked and consistently manifest fear in or avoidance of at least two of the following situations: (1) crowds; (2) public places; (3) traveling alone; (4) traveling away from home B. Symptoms of anxiety in the feared situation at some time since the onset of the disorder, with at least two symptoms present together, on at least one occasion, from the list below, one of which must have been from items (1) to (4): Autonomic arousal symptoms (1–4), Symptoms concerning chest and abdomen (5–8), Symptoms concerning brain and mind (9–12), General symptoms (13–14) The presence or absence of panic disorder (F41.0) on a majority of occasions when in the agoraphobic situation may be specified by using a fifth character:

TABLE 1. Continued

DSM-III	DSM-III-R	DSM-IV (TR)	ICD-10 DCR
		Disorder (e.g., avoidance of leaving home or relatives)	
300.22 Agoraphobia without panic attacks [DSM text portion: Where there is no history of Panic Attacks (or this information is lacking), the diagnosis of Agoraphobia without Panic Attacks should be made]	300.22 Agoraphobia without history of Panic Disorder A. Agoraphobia: Fear of being in places or situations from which escape might be difficult (or embarrassing) or in which help might not be available in the event of suddenly developing a symptom(s) that could be incapacitating or extremely embarrassing. Examples include: dizziness or falling, depersonalizaton or derealization, loss of bladder or bowel control, vomiting, or cardiac distress. As a result of this fear, the person either restricts travel or needs a companion when away from home, or else endures agoraphobic situations despite intense anxiety B. Has never met the criteria for Panic Disorder. *Note: Includes specifier for limited symptom attacks (with or without)*	300.22 Agoraphobia without history of Panic Disorder A. The presence of Agoraphobia related to fear of developing panic-like symptoms (e.g., dizziness or diarrhea) B. Criteria have never been met for Panic Disorder	F40.00 Agoraphobia without Panic Disorder *Note: Severity in F40.00 may be rated by indicating the degree of avoidance, taking into account the specific cultural setting. Severity in F40.01 may be rated by counting the number of panic attacks*
300.21 Agoraphobia with Panic Attacks [DSM text portion: Often the initial phase of the disorder consists of recurrent panic attacks. The individual develops anticipatory fear of having such an attack and becomes reluctant or refuses to enter a variety of situations that are associated with these attacks. When there is a history of panic attacks associated with avoidance behavior, the diagnosis of Agoraphobia with Panic Attacks should be made.]	300.21 Panic Disorder with Agoraphobia A. Meets the criteria for Panic Disorder B. Agoraphobia: Fear of being in places or situations from which escape might be difficult (or embarrassing) or in which help might not be available in the event of a panic attack. (Include cases in which persistent avoidance behavior originated during and active phase of panic disorder, even if the person does not attribute the avoidance behavior to fear of having a panic attack) As a result of this fear, the person	300.21 Panic Disorder with Agoraphobia A. Both criteria for Panic Disorder met (not listed here) B. The presence of Agoraphobia	F40.01 Agoraphobia with Panic Disorder *Note: Severity in F40.01 may be rated by counting the number of panic attacks*

	either restricts travel or needs a companion when away from home, or else endures agoraphobic situations despite intense anxiety. Commonagoraphobic situations include being outside the home alone, being in a crowd or standing in a line, being on a bridge, and traveling in a bus, train, or car *Note: Includes* *severity specifiers for agoraphobic avoidance (mild, moderate, severe)* *course specifier for agoraphobic avoidance (in partial remission, in full remission)* *severity specifier for panic attacks (mild, moderate, severe)* *course specifier for panic attacks (in partial remission, in full remission)*		
Anxiety states (or anxiety neurosis)			F41 other anxiety disorders
300.01 Panic disorder D. The disorder is not associated with Agoraphobia	300.01 Panic disorder without agoraphobia A. Meets the criteria for Panic Disorder B. Absence of Agoraphobia, as defined above *Note: Includes* *severity specifier for panic attacks (mild, moderate, severe)* *course specifier for panic attacks (in partial remission, in full remission)*	300.01 Panic disorder without agoraphobia A. Both criteria for Panic Disorder met (not listed here) B. Absence of Agoraphobia *Note: Does not include any specifiers anymore*	F41.0 Panic disorder [episodic paroxysmal anxiety] *Note: The range of individual variation of both content and severity is so great that two grades, moderate and severe, may be specified, if desired, with a fifth character:* *F41.00 Panic disorder—moderate: at least four panic attacks in a four-week period.* *F41.01 Panic disorder—severe: at least four panic attacks per week over a four-week period*
Agoraphobia has primary consideration over Panic Disorder	*Agoraphobia is considered secondary to Panic Attacks* *Agoraphobia—unlike social or simple phobia—has no specific diagnostic criteria anymore (exposure provoked anxiety reaction, avoidance, recognition, distress, and impairment has been merged into one big criterion)*	*Agoraphobia is considered secondary to Panic Attacks; Panic Disorder has primary consideration over Agoraphobia* *Agoraphobia—unlike social or simple phobia—has no specific diagnostic criteria anymore (exposure provoked anxiety reaction, avoidance, recognition, distress, and impairment has been merged into one big criterion)*	*Agoraphobia has primary consideration over Panic Disorder*

[a]ICD-9: 300.2 Phobic disorders: 300.22 Agoraphobia without Panic Attacks, 300.21 Agoraphobia with Panic Disorder; 300.0 Anxiety States: 300.01 Panic Disorder without Agoraphobia (*Note: Agoraphobia has primary consideration over Panic Disorder*).

TABLE 2. DSM-V Task Force Core Proposal for Agoraphobia

A. Marked fear or anxiety about more than one situation from a characteristic cluster of agoraphobic situations. Agoraphobic situations typically include: being outside the home alone; public transportation (e.g., traveling in a bus, train, ship, plane); open spaces (e.g., parking lots and market place); being in shops, the theater, or cinemas; standing in line or being in a crowd
B. The individual fears and/or avoids these situations because escape might be difficult or help might not be available in the event of incapacitation or panic-like symptoms
C. The agoraphobic situations almost invariably provoke immediate fear or anxiety
D. The agoraphobic situations are avoided, require the presence of a companion, or are endured with intense fear or anxiety
E. The fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations
F. The duration is at least 6 months[a]
G. The fear, anxiety, and avoidance cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
H. The fear, anxiety, and avoidance are not restricted to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., cardiopulmonary disorders)[b]
I. The fear, anxiety, and avoidance are not restricted to the symptoms of another mental disorder, such as Specific Phobia (e.g., if limited to one or a few circumscribed phobic objects or situations), Social Phobia (e.g., in response to feared social situations), Obsessive–Compulsive Disorder (e.g., in response to dirt in someone with an obsession about contamination), Posttraumatic Stress Disorder (e.g., in response to stimuli associated with a traumatic event), or Separation Anxiety Disorder (e.g., in response to being away from home or close relatives)[c]

Note: Agoraphobia *is a codable disorder*.
[a]The construct duration was added to reduce reliane on impairment and distress. A 6-month duration is considered for all phobias, awaiting secondary data analyses and field testing.
[b]The criterion is retained provisionally, although no empirical evidence for physiologic mechanism relating to agoraphobia is available.
[c]The differential diagnostic considerations proposition suggest provisionally the word "not restricted to" instead of "not better accounted for" awaiting more general decisions of the DSM-V committee.

TABLE 3. Alternative Option Proposed (without accompanying Literature Review)

A. Anxiety about being, or anticipating being, in places or situations from which escape might be difficult or embarrassing, or in which help may not be available, in the event of having a panic attack, being suddenly incapacitated, or having sudden physical symptoms (including panic-like symptoms or other somatic events such as dizziness, vomiting, or diarrhea)
Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home alone; being in a crowd or standing in a line; being in the center of a theater row or on a bridge; traveling in a bus, train, automobile, or plane; or being in open spaces (e.g., parking lots and market place)
B. Situations from which escape might be difficult are avoided (e.g., travel is restricted); endured with marked distress or with anxiety about having a Panic Attack, panic-like, or other symptoms; or require the presence of a companion
C. The fear, anxiety, or avoidance cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
D. The anxiety or phobic avoidance is not restricted to the symptoms of another mental disorder, such as Social Phobia (e.g., avoidance limited to social situations because of fear of embarrassment), Specific Phobia (e.g., avoidance limited to one or only a few specific situations like dogs or elevators), Social Phobia (e.g., avoidance limited to social situations), Obsessive–Compulsive Disorder (e.g., avoidance of dirt in someone with an obsession about contamination), Posttraumatic Stress Disorder (e.g., avoidance in response to stimuli associated with a traumatic event), or Separation Anxiety Disorder (e.g., avoidance of leaving home or relatives)

Note: Agoraphobia *is a codable disorder*.

advisors that agree on making agoraphobia a separate codable disorder, but suggest slightly different criteria to stimulate discussion. The Task Forces core proposal would considerably simplify the current DSM classification by allowing the clinician to diagnose only AG (in the absence of PD criteria or if PD criteria are only partially met), PD and AG (if criteria are fully met for both), or only PD. Because degree of agoraphobic avoidance in PD is an important marker in PD (severity, prognosis, treatment) and the fact that the proposed AG criteria have a high threshold, one should further consider a dimensional specifier for PD whenever full AG criteria are not met. This would be similar to the specifier for presence of PA in AG as well as in other disorders, as currently recommended for consideration for DSM-V.[1] The proposal further uses the same criteria as for other phobic disorders—thus increasing consistency—and specifies the syndrome by multiple criteria that are, by and large, identical to those used for specific and social phobia.

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