Mixed Anxiety Depression Should Not Be Included in *DSM-5*

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Abstract: Subthreshold anxiety and subthreshold depressive symptoms often co-occur in the general population and in primary care. Based on their associated significant distress and impairment, a psychiatric classification seems justified. To enable classification, mixed anxiety depression (MAD) has been proposed as a new diagnostic category in *DSM-5*. In this report, we discuss arguments against the classification of MAD. More research is needed before reifying a new category we know so little about. Moreover, we argue that in patients with MAD symptoms and a history of an anxiety or depressive disorder, symptoms should be labeled as part of the course trajectories of these disorders, rather than calling it a different diagnostic entity. In patients with incident co-occurring subthreshold anxiety and subthreshold depression, subthreshold categories of both anxiety and depression could be classified to maintain a consistent classification system at both threshold and subthreshold levels.

Key Words: Anxiety, classification, depression, diagnosis, mixed anxiety depression.

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Depressive and anxiety symptoms are extremely common in the general population and in primary care (Batelaan et al., 2007; Cuijpers et al., 2004; Katon and Roy-Byrne, 1991; Olfson et al., 1996; Ormel et al., 1993; Rucci et al., 2003; Zinbarg et al., 1994), and they frequently co-occur (Das-Munshi et al., 2008; Piccinelli et al., 1999; Preisig et al., 2001; Spijker et al., 2010). Co-occurring subthreshold depression and subthreshold anxiety are associated with impaired functioning (Das-Munshi et al., 2008; Preisig et al., 2001; Roy-Byrne et al., 1994). For example, one fifth of work loss days occurred in those with co-occurring subthreshold depression and subthreshold anxiety (Das-Munshi et al., 2008). Moreover, seeking treatment is common in this group, suggesting significant levels of distress (Preisig et al., 2001; Roy-Byrne et al., 1994). For example, of those with comorbid subthreshold anxiety and subthreshold depression, as diagnosed on a lifetime basis, 63% had ever sought treatment for their complaints (Preisig et al., 2001). Individuals with co-occurring subthreshold anxiety and subthreshold depression lack a specific psychiatric diagnosis in the *DSM* classification system, whereas a psychiatric classification may be justified based on the associated significant distress or associated impairment.

To enable classification of those with co-occurring subthreshold anxiety and subthreshold depression, a distinct diagnosis has been proposed. Since 1992, classifying mixed anxiety and depressive disorder is possible using the ICD-10 classification system (World Health Organization, 1992). However, in ICD-10, the criteria have not been defined very precisely. According to the ICD-10, the category of Mixed Anxiety and Depressive Disorder should be used "when symptoms of anxiety and depression are both present, but neither is clearly predominant, and neither type of symptom is present to the extent that justifies a diagnosis if considered separately. When both anxiety and depressive symptoms are present and severe enough to justify individual diagnoses, both diagnoses should be recorded and this category should not be used" (World Health Organization, 1992). The appendix of the *DSM-IV* included research criteria for mixed anxiety–depressive disorder that are more specific (Table 1) (American Psychiatric Association, 1994). Recently, criteria have been proposed to be included in *DSM-5* using the term *mixed anxiety depression* (MAD) (American Psychiatric Association, 2012a). For *DSM-5*, the draft diagnostic criteria of MAD read as follows. Three or four of the symptoms of major depression must be present, which must include depressed mood and/or anhedonia. These symptoms should be accompanied by anxious distress, defined as having two or more of the following: irrational worry, preoccupation with unpleasant worries, having trouble relaxing, motor tension, and fear that something awful may happen. Symptoms must have lasted at least 2 weeks, are occurring at the same time, and no other *DSM* diagnosis of anxiety or depression must be present (American Psychiatric Association, 2012a) (Table 2). These criteria are still tentative. For example, it has not been decided whether the minimum number of required depressive symptoms should be three or four. Field trials investigating the feasibility, clinical utility, and reliability of the draft criteria of MAD have been conducted. The proposed criteria may be revised after the field trials (American Psychiatric Association, 2012b).

Slightly different names have been used for this disease concept. For reasons of clarity, the term *mixed anxiety depression* (MAD) will be used throughout this article.

Including such a diagnosis in *DSM-5* may have several advantages. A diagnosis of MAD may raise awareness about the frequent co-occurrence of subthreshold anxiety and depression and its clinical and public health significance. Moreover, it would provide the opportunity to investigate the prevalence, consequences, and course while using standardized criteria. By facilitating research, the development of (cost-) effective treatment strategies may be accelerated, as a result of which the burden of disease generated by MAD could be reduced. Finally, the *DSM* classification system would be more compatible with the ICD classification system, although the definitions of these two entities remain divergent. Although acknowledging that co-occurring subthreshold anxiety and depression warrant clinical attention, we seriously question whether including MAD in the classification system of the *DSM-5* is the most rational and valid option available. On the basis of previous research, we discuss several concerns regarding the concept of MAD: a) divergent results of previous research, b) inconsistency in nomenclature between subthreshold and threshold level, and c) limited diagnostic stability over time.

DIVERGENT RESULTS OF PREVIOUS RESEARCH

MAD has been investigated using different sets of criteria, and as a result, previous results on prevalence and course have been

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Editor's note: Proposed *DSM-5* criteria sets do not represent the final *DSM-5* criteria for the disorders.

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TABLE 1. Research Criteria for Mixed Anxiety Depressive Disorder in the Appendix of *DSM-IV* (American Psychiatric Association, 1994)

A. Persistent or recurrent dysphoric mood lasting at least 1 month.
B. The dysphoric mood is accompanied by at least 1 month of four (or more) of the following symptoms:
   1. difficulty concentrating or mind going blank
   2. sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
   3. fatigue or low energy
   4. irritability
   5. worry
   6. being easily moved to tears
   7. hypervigilance
   8. anticipating the worst
   9. hopelessness (pervasive pessimism about the future)
   10. low self-esteem or feelings of worthlessness
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms 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. All of the following:
   1. criteria have never been met for major depressive disorder, dysthymic disorder, panic disorder, or generalized anxiety disorder
   2. criteria are not currently met for any other anxiety or mood disorder (including an Anxiety or Mood Disorder, In Partial Remission)
   3. the symptoms are not better accounted for by any other mental disorder

inconsistent. This hinders a proper assessment of the disease concept. Divergent findings regarding the course are described under the subheading "Diagnostic instability over time." Here, we will elaborate on the prevalence of MAD. Some researchers found MAD to be a highly prevalent condition (Das-Munshi et al., 2008; Schmidt et al., 2007; Zinbarg et al., 1994), whereas others reported marginal prevalence rates (Means-Christensen et al., 2006; Spijker et al., 2010; Weisberg et al., 2005). For example, we found an annual prevalence rate of .6% in the general population by administering the Composite International Diagnostic Interview and by applying criteria almost similar to the research criteria of *DSM-IV*, thus excluding those with a current anxiety disorder or depressive disorder as well as excluding those with a history of a major depressive disorder, dysthymic disorder, panic disorder, or generalized anxiety disorder (Spijker et al., 2010). By contrast, Das-Munshi et al. (2008) reported a 1-month prevalence rate of 8.8% in the general population when classifying MAD in those who scored above the predefined threshold on the Clinical Interview Schedule–Revised and who did not meet ICD criteria of a current anxiety or depressive disorder (Das-Munshi et al., 2008). These examples show the huge impact of diagnostic criteria on prevalence rates. When criteria are too strict, the prevalence will be marginal. This will limit the clinical utility of the diagnosis. When criteria are too loose, there is a risk of false-positives, that is, of making a diagnosis when this is not indicated. This may result in an exponential increase in the target population for mental health care, in unnecessary drug prescriptions or health care visits, and in a substantial economic burden posed on the health care system. In the *DSM-IV* field trials, already high prevalence rates were reported in primary care when symptoms lasting for at least a month were required (Zinbarg et al., 1994). In the proposed criteria for *DSM-5*, the required duration of symptoms has been lowered to only 2 weeks, which will inflate prevalence rates. In addition, there is no requirement in the *DSM-5* criteria to consider the context in which the depressive and anxiety symptoms arose. Many stressful life events may trigger anxiety and depressive symptoms that meet the 2-week duration criterion for MAD, many of which are likely to be a transient and normal response to these stressful life events and thus constitute false-positives if the diagnosis of MAD were applied.

At the time of including MAD in the Appendix of *DSM-IV* in 1994 (American Psychiatric Association, 1994), Zinbarg et al. (1994) stated that the sensitivities and specificities associated with different symptom thresholds should be investigated, as well as the prevalence in the general population. We think that this statement still holds true: given the substantial impact of criteria on prevalence, the limited clinical utility in case of low prevalence rates, and the potentially adverse consequences in case of many false-positives, these issues should be addressed before including MAD in *DSM-5*. Although MAD is on the list of proposed disorders to be investigated in field trials in large academic clinic settings (American Psychiatric Association, 2012b), answering the questions above require investigating MAD in both primary care settings or the general population, neither of which are included in the *DSM-5* Field Trial samples.

INCONSISTENCY IN NOMENCLATURE BETWEEN SUBTHRESHOLD AND THRESHOLD LEVELS

Anxiety and depression are highly comorbid at both subthreshold and threshold levels (Das-Munshi et al., 2008; De Graaf et al., 2002; Kessler et al., 2005, 1994; Piccinelli et al., 1999; Preisig et al., 2001; Spijker et al., 2010), anxiety disorders and depressive disorders share a genetic vulnerability (Hettema et al., 2006), and diagnostic conversions occur over time from anxiety disorders to depressive disorders and vice versa (Hagnell and Grasbeck, 1990; Merikangas et al., 2003; Rhebergen et al., 2011). These findings have raised the fundamental question of whether it is justified to regard anxiety and depressive disorders as different disease concepts. Previously, a tripartite model of anxiety and depressive disorders has been postulated (Clark and Watson, 1991), consisting of anxiety, depression, and MAD. According to this model, anxiety and depression share the presence of nonspecific general distress or negative affect. In addition, the lack of positive affect is specific to depression and the presence of hyperarousal to anxiety. According to this model, MAD is predominantly characterized by the presence of nonspecific general distress. In line with this, a profile analysis has shown that subclinical patients most often had a nonspecific symptom profile (Barlow and Campbell, 2000). However, previously, we have found little differences between MAD, pure subthreshold anxiety, and pure subthreshold depression in terms of sociodemographics, care utilization, functioning, and 2-year course (Spijker et al., 2010). Thereby, the benefits of classifying MAD over classifying both subthreshold anxiety and subthreshold depression can be questioned. It will be possible to classify subthreshold depression in *DSM-5* using the term *Subsyndromal Depressive CNEC*, a subcategory of "Depressive Conditions Not

TABLE 2. Proposed Criteria for Mixed Anxiety Depressive Disorder in *DSM-5* (American Psychiatric Association, 2012a)

The patient has three or four of the symptoms of major depression (which must include depressed mood and/or anhedonia), and they are accompanied by anxious distress. The symptoms must have lasted at least 2 weeks, and no other *DSM* diagnosis of anxiety or depression must be present, and they are both occurring at the same time.

Anxious distress is defined as having two or more of the following symptoms: irrational worry, preoccupation with unpleasant worries, having trouble relaxing, motor tension, fear that something awful may happen.

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Elsewhere Classified (CNEC)" (American Psychiatric Association, 2011), presuming that this diagnosis will be approved as an established diagnosis in *DSM-5*. Although proposed revisions for Unspecified Anxiety Disorder are not available yet (American Psychiatric Association, 2012c), a similar option for subthreshold anxiety is to be expected, given that in *DSM-IV*, subthreshold anxiety can be classified as Anxiety Disorder Not Otherwise Specified (American Psychiatric Association, 2012c). If indeed these subthreshold categories will be approved as established diagnoses in *DSM-5*, the category of MAD might be redundant. Probably even more important, adding a MAD category would be inconsistent with current nomenclature in which anxiety and depression are classified separately. It would be irrational to add a new diagnosis of co-occurring anxiety and depression at the subthreshold level while refraining from such a "comorbid diagnosis" at the threshold level. Rather, maintaining a consistent classification system at both threshold and subthreshold levels would be more rational.

LIMITED DIAGNOSTIC STABILITY OVER TIME

At the time of conducting the *DSM-IV* field trials for MAD, it was acknowledged that the validity of MAD needed further study (Zinbarg et al., 1994). To validate a disease concept, diagnostic stability over time is regarded as important: "a rose is a rose because it remains a rose" (Goodwin and Guze, 1996). This implies that prodromal symptoms, symptoms in the context of a disorder, and residual symptoms after remission of the disorder should all be captured within the same disease concept. However, the disease concept of MAD appears to include a rather heterogeneous group of patients.

Previously, it was mentioned that the possibility that MAD is a prodromal stage of MDD or generalized anxiety disorder needed to be ruled out (Zinbarg et al., 1994); that is, if MAD appears to be a prodromal stage of another psychiatric disorder, MAD should be better regarded a prodromal stage of this disorder rather than calling it a different diagnostic concept. Previous research has shown that in primary care, almost half of those with MAD at baseline had developed a threshold psychiatric disorder after a 1-year follow-up (Barkow et al., 2004). Thus, MAD was a prodromal stage in about half the cases. Of note, 27% had developed a depressive disorder, dysthymia, agoraphobia, panic disorder, or comorbid anxiety and depressive disorder, whereas another 22% fulfilled criteria of another ICD-10 disorder such as pain disorder, somatization disorder, hypochondriasis, neurasthenia, or alcohol disorders (Barkow et al., 2004). In addition, the results of a taxometric analysis reported the development of anxiety and depressive disorders over time (Schmidt et al., 2007). In the rationale accompanying the proposed revisions on the *DSM-5* Web site, the progression to full-blown psychiatric disorders is used as an argument to establish MAD as a diagnostic category in *DSM-5* (American Psychiatric Association, 2012a). In our opinion, the progression of MAD to full-blown disorders suggests that its course may be unfavorable and that the condition may therefore warrant attention, but it does not mean that establishing MAD as a separate diagnostic category is the best way to call attention to the condition. Given that at the time of presenting with MAD symptoms, the specific future disorder is not known, subthreshold anxiety and subthreshold depression could be classified instead. Second, limited diagnostic stability has been reported when reassessing those with MAD over time. Several studies reported almost no cases with MAD at baseline that still fulfilled criteria of MAD at follow-up (Barkow et al., 2004; Spijker et al., 2010). Third, some previous findings suggest that a substantial proportion of those with "MAD" experience MAD symptoms in the waxing and waning course of a threshold depressive disorder or threshold anxiety disorder. Roy-Byrne et al. (1994) reported that 95% of the individuals with subthreshold symptoms in primary care have a lifetime psychiatric diagnosis. Moreover, Piccinelli et al. (1999) reported high odds ratios (OR) for having a lifetime history of depression (OR, 4.0), a recent history of depression (OR, 4.8), a lifetime history of panic disorder (OR, 4.6), or a recent history of panic disorder (OR, 3.7) in primary care patients with mixed subthreshold anxiety and subthreshold depression. To ensure that MAD as a diagnostic category would not contain residual symptoms of threshold anxiety and depressive disorders, those with a current anxiety or depressive disorder and those with a history of an anxiety disorder (*i.e.*, panic disorder or generalized anxiety disorder) or depressive disorder (*i.e.*, major depressive disorder or dysthymic disorder) were excluded according to the research criteria of the *DSM-IV* (American Psychiatric Association, 1994) (Table 1). Whereas Zinbarg et al. (1994) reported little impact of these exclusion criteria, we found that applying these exclusion rules resulted in very low annual prevalence rates of 0.6% for MAD. Moreover, applying these exclusion criteria may select a less severe group that may not fulfill criteria of clinical relevance, as suggested by the limited consequences in terms of functioning, care utilization, and course when applying these exclusion rules (Spijker et al., 2010). Those with a history of an anxiety or a depressive disorder are no longer excluded according to the proposed criteria of *DSM-5*, suggesting that those with MAD according to the proposed criteria of *DSM-5* consist of a heterogeneous group of patients including many with either prodromal symptoms or residual symptoms occurring in the long-term course of threshold disorders.

CONCLUSION

A distinct diagnosis of MAD has been proposed to enable classification of patients with co-occurring depressive and anxiety symptoms. Although acknowledging several advantages of a distinct classification, we argue against the proposed category of MAD for several reasons. We pointed out that diagnostic criteria applied have a substantial impact on the prevalence rate. We also argued that creating such a diagnosis is inconsistent with current nomenclature in which such a comorbid diagnosis is absent at threshold level and that evident advantages of classifying MAD over classifying subthreshold categories are unclear. Finally, we questioned the validity of the proposed category based on low diagnostic stability over time.

MAD is on the list of disorders to be investigated in field trials in large academic clinic settings (American Psychiatric Association, 2012b). Although this provides the opportunity to increase knowledge on several important issues, assessing the prevalence requires studies in primary care or the general population too. Moreover, the field trials include only one follow-up evaluation after 4 to12 weeks. Assessing diagnostic changes over time to gain insight into the validity of the MAD concept requires longer follow-up studies.

In conclusion, thorough research is needed before considering to adopt the diagnosis MAD in *DSM-5*. Moreover, in patients with a history of an anxiety disorder or depressive disorder, adopting a longitudinal perspective is more rational. Thus, rather than calling it a different diagnostic entity, attention should be paid to the early signs of recurrences and to long-term fluctuations in symptom level of anxiety and depressive disorders, thus labeling these symptoms as part of the course trajectories of the anxiety or depressive disorder. In patients without previous anxiety disorder and depressive disorder who present with co-occurring anxiety and depressive symptoms of clinical relevance, these symptoms could be classified as (both) subthreshold depression and subthreshold anxiety (*i.e.*, Subsyndromal Depressive Condition Not Elsewhere Classified and Unspecified Anxiety Disorder). In doing so, a consistent classification system at both threshold and subthreshold levels will be maintained.

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