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Trying to describe mixed anxiety and depression: Have we lost our way?

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The formal recognition that depression and anxiety symptoms often co-occur dates back to the beginning of psychiatric nosology in the late 19th century. The separation of these symptoms began in the 1960's and 1970's. The rise of psychopharmacology led to drugs being marketed as 'specific' antidepressants (e.g. tricyclics) or anxiolytics (e.g. benzodiazepines), so encouraging the therapeutic separation of depression and anxiety (Moller *et al.* 2016). This spurious dichotomy was compounded during the drafting of DSM-III when different advisory committees for anxiety disorders and mood disorders were established. In effect, DSM-III erected an artificial and arbitrary 'fire wall' between depression and anxiety, and in 1990, ICD-10, largely followed suit and similarly separated anxiety and depression. However, ICD-10 included a Mixed Anxiety and Depressive Disorder (MADD) diagnosis in the Anxiety Disorders section. The rationale behind this decision is not clear but its major use was in general practice and a modified set of guidelines were developed specifically for this patient population (see Table 1).

The DSM-IV Anxiety Disorders Work Group revived the concept of Mixed Anxiety and Depression Disorder (MADD) as a separate entity but, after field trials, decided to relegate the diagnosis to the research appendix due to its poor inter-rater reliability and concerns about validity. However no data using the research MADD criteria were published and therefore available to inform the subsequent DSM-5 Working Group. Interestingly, the responsibility for investigating the utility of MADD was switched from the DSM-5 Anxiety Disorders Work Group to the Mood Disorders Work Group, where it was evaluated in field trials and was deemed to be so unreliable that it was not included in DSM-5.

ICD-11 proposes to continue with MADD as a sub-syndromal comorbid anxiety and depressive disorder (Table 2). The criteria are more elaborate than in ICD-10 which was criticised for being too vague. MADD was also moved from the Anxiety Disorders to the Mood Disorders section, and its name was changed from Mixed Anxiety and Depressive Disorder to Mixed Depressive and Anxiety Disorder (or MDAD presumably).

Somewhat unexpectedly DSM-5 included a new "with anxious distress" specifier in the mood disorders section. Its derivation is also obscure, and it serves only to further confuse matters diagnostically. As Moller et al. (2016) point out, the criteria are closely related to the anxious symptom scale proposed by Goldberg et al (2012) for the primary health care version of ICD-11. For comparison, the DSM-5 criteria are shown alongside the ICD-11 proposal in Table 3.

Prevalence of mixed anxiety and depression

There is little dispute that a substantial number of individuals in the community suffer from comorbid symptoms of depression and anxiety. These symptoms are both sub-syndromal as the diagnosis of MADD requires, and comorbid where both disorders are syndromal. Results of studies regarding the prevalence of MADD are inconsistent. This is not surprising since the ICD-10 and DSM-IV research criteria are discordant. In addition, some prevalence studies exclude individuals with a lifetime history of a diagnosis of depression or anxiety while others do not. For example, one study reported a prevalence of MADD using the DSM-IV research criteria of 0.2% while another study in adolescents found a prevalence approximating 13% (85-fold higher!). Das-Munshi et al. (2008), using ICD-10 MADD criteria, reported a one-month prevalence of 8.8% in a representative survey population. Thus far, the prevalence of the DSM-5 anxious depressive specifier in patients with major depression has only

been reported in one study which found that 54% of outpatients with major depression fulfilled criteria (Gaspersz et al (2017).

Clinical Utility

Are there clinical advantages in using the MADD diagnosis or the DSM-5 anxious depression specifier? For example does it predict the course of the illness or response to one treatment compared with another? Opinions on the MADD diagnosis differ. Some argue that patients suffering from MADD are either transiently affected, or are in a prodromal, or residual, state of a syndromal mood or anxiety disorder (Barkow *et al.* 2004). The MADD diagnosis is therefore useful in identifying vulnerable patients. Others contend that MADD is stable and has an impact on health-related quality of life that is on par with that of syndromal anxiety or depression (Moller *et al.* 2016) and should be treated in its own right.

The evidence of clinical utility for the DSM-5 anxious distress specifier is minimal. One study has developed a self-report measure which reported high reliability and correlations with clinician ratings of anxiety and rates of comorbid anxiety disorder (Zimmerman *et al.* 2014) suggesting clinicians can at least identify it. Another study, which constructed the anxious distress specifier retrospectively, reported its presence significantly outperformed comorbid anxiety disorders in predicting chronicity, time to remission of major depression and functional disability (Gaspersz *et al.* 2017).

In summary, both DSM-5 and ICD-11 allow clinicians to diagnose depression and anxiety as comorbid disorders but each classification has additional ways of coding their overlap that differ significantly. ICD-11 proposes such a diagnosis for mixed symptoms of depression and anxiety which do not reach threshold for a diagnosis of depressive disorder, dysthymia or an anxiety or fear- related disorder and calls this

Mixed Depression and Anxiety Disorder. In contrast, DSM-5 has a specifier "with anxious distress" which may be used in individuals who already satisfy the threshold for major depression. As noted above both these diagnoses appear to be common and this is not surprising given that, clinically, depression often emerges from within an anxious milieu (Malhi et al., 2002). ICD-10 MADD is reported to be the most common psychological problem in general practice setting (Goldberg *et al.* 2012) and the limited evidence available suggests that the majority of patients fulfill criteria for the anxious distress specifier (Gaspersz *et al.* 2017). Yet there is currently no evidence that either diagnosis helps in planning treatment. Having the DSM-5 anxious distress specifier may lead to a worse outcome (Gaspersz *et al.* 2017) but there is no evidence that specific treatments will modify this. Patients diagnosed with Mixed Depression and Anxiety Disorder have symptoms that overlap with depression and anxiety and may develop these disorders or alternatively spontaneously remit. This variability does not inform management.

In addition, "with anxious distress" is difficult to distinguish in clinical practice from "clinically significant distress", which is a mandatory criterion for major depression in DSM-5. The specifier therefore risks becoming tautological. Furthermore, anxiety is also common in many other psychiatric disorders. For example high prevalence rates of anxiety disorders have been reported in schizophrenia (Hall 2017). Should schizophrenia have an anxious distress specifier and would this be of any help to clinicians? Finally, is it conceivable that an individual with depression would not have some degree of 'anxious distress'? If the last point is valid and accepted empirically, then it alone argues against the specifier having any distinct utility.

Conclusion

Thus, we appear to have reached an unsatisfactory compromise. The fabricated distinction between anxiety and depression ignores the fact that the commonest form of mood disorder is mixed anxiety and depression (what used to be labelled as 'neurosis'). The current diagnostic systems allow comorbid diagnoses in both, the subsyndromal Mixed Depression and Anxiety Disorder in ICD-11 and the anxious distress specifier in DSM-5. Neither of the latter two have a consistent evidence base for their reliability or clinical utility. If Mixed Depression and Anxiety Disorder is the commonest mental disorder in the community we urgently need research on its reliability, validity and the optimal evidence-based treatments. Factors allowing the clinician to differentiate between patients who are likely to remit spontaneously and those who are at risk of progression to a syndromal depressive or anxiety disorder would also be useful.

If the majority of patients with DSM-5 Major Depression also have the anxious specifier as the limited evidence suggests then we need to know whether the specifier gives any useful information on treatment or prognosis. While such patient outcomes may be worse, there is no evidence that modifying standard treatments for depression may lead to improvement. The DSM-5 Mood Disorders Workgroup did not indicate why an anxious distress specifier was needed and is of unknown incremental validity beyond the identification of a comorbid anxiety disorder (Zimmerman *et al.* 2014). Thus, it is not surprising that most psychiatrists do not appear to use the construct and we need more research into the implications of the comorbidity of anxiety with depressive disorders.

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Table 1: Mixed anxiety and depressive disorder-diagnostic guidelines for ICD-10 in primary care (World Health Organisation 1996)

Presenting complaints
The patient presents with variety of symptoms of anxiety and depression There may initially be one or more physical symptoms (e.g., fatigue, pain). Further enquiry will release depressed mood and/or anxiety
Diagnostic features
Low or sad mood Loss of interest of pleasure Prominent anxiety or worry The following associated symptoms are frequently present: disturbed sleep, tremor, fatigue or loss of energy, palpitations, poor concentration, dizziness, disturbed appetite, suicidal thoughts or acts, dry mouth, loss of libido, tension, and restlessness

Table 2: Proposed criteria for ICD-11 mixed depressive and anxiety disorder as of August 6, 2016 [26, foundation ID : hhtp//id.who.int/icd/entity/314468192] (World Health Organisation 1996)

7A73 Mixed depressive and anxiety disorder
Definition Mixed depressive and anxiety disorder is characterized by symptoms of both anxiety

and depression more days than not for a period of 2 weeks or more. Neither set of symptoms, considered separately, is sufficiently severe, numerous, or persistent to justify a diagnosis of a depressive episode, dysthymia, or an anxiety and fear-related disorder. Depressed mood or diminished interest in activities must be present accompanied by additional depressive symptoms as well as multiple symptoms of anxiety. The symptoms result in significant distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. There have never been any prior manic hypomanic, or mixed episodes, which would indicate the present of a bipolar disorder.

Inclusion

Anxiety depression (mild or not persistent)

Table 3 : **ICD-11 Anxious Symptoms (Goldberg et al. 2012)**	**DSM-5 Anxious Distress Specifier**
Been feeling nervous, anxious or on edge.	Feeling keyed up or tense.
Not been able to control worrying.	Difficulty concentrating because of worry.
Having difficulty relaxing.	Feeling unusually restless.
Been afraid that something terrible might happened.	Fear that something awful may happen.
Been afraid you might lose control of yourself.	Feeling that the individual might lose control of himself or herself.