Mixed Anxiety and Depressive Disorder: An Illness that Psychiatrists should not Overlooked

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Abstract

Recognition of anxiety and depressive disorders in primary-care settings is now considered to be extremely important in health-care delivery. It has been suggested that there may be a group of patients who fail to fulfill conventional diagnostic criteria for either an anxiety or depressive disorder but who, when the total constellation of anxiety and depressive symptoms is considered in aggregate, seem to warrant a psychiatric diagnosis. This diagnostic category has now been referred to as mixed anxiety and depressive disorder (MADD).

Although the coexistence of anxiety and depression is a common clinical finding, we have to exclude the comorbid condition of major depression with any anxiety disorders or, vice-versa, the condition of any anxiety disorders (panic disorder, social phobia, obsessive-compulsive disorder, and generalized anxiety disorder) comorbid with depression. Hence, MADD should be diagnosed by ruling out pure anxiety disorders, pure depressive disorders, and comorbidity of depressive disorders with anxiety disorders and vice versa.

From primary care population prevalence studies in Canada and Thailand, it was found that 12.8% of patients in Canada and 10.9% in Thailand had a combination of subsyndromal anxiety and depressive features that fulfilled ICD-10 criteria for MADD. These findings support not only the existence but also the potential importance of MADD among primary-care patients.

However, before MADD will be granted status as a diagnostic entity, many questions must be answered in several areas such as; the temporal stability of MADD, the longitudinal course of MADD, the determination of how (and if) to treat it and examination of whether or not treatment diminishes the disability of patients. J Psychiatr Assoc Thailand 2000; 45(1): 99-109.

Key words: mixed, anxiety disorder, depressive disorder, comorbidity, primary care

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Introduction

Many studies have shown that anxious and depressive symptoms frequently coexist in patients seen in clinical practice. Although early research and psychopharmacologic treatment studies tended to distinguish anxiety disorders from depression, emphasizing one end of the spectrum or the other, recent developments are now reversing this trend. Stahl proposed three predominant points of view on how symptoms of anxiety and depression are related.

The traditional point of view suggests that generalized symptoms of anxiety and depression can be dichotomized into one syndrome known as major depressive disorder (D) and another known as generalized anxiety disorder (A). The comorbid point of view suggests a third category, namely the presence of both anxiety and depression (DA). This has proven to be particularly true in cases of panic disorder, obsessive compulsive disorder, and social phobia, in which a high incidence of current or past major depressive disorder is recognized. Depressive disorder in such cases is not seen as being part of the anxiety disorder, but as a concomitant, comorbid illness. Finally, the subsyndromal point of view considers that depression and anxiety can coexist to a degree that is greater than normal but less than that required for a full diagnostic syndrome of depression or anxiety. Thus, anxiety (a) and depression (d) and mixed anxiety depression (da) can be subsyndromal. Furthermore, full syndromal and subsyndromal mixtures can also occur (e.g. ad and da).

The 10th International Classification of Disease (ICD-10) introduced the concept of mixed anxiety and depressive disorder in order to provide a clinical definition for patients who present with both anxiety and depressive symptoms of only limited number and/or intensity. Details of ICD-10 diagnostic guidelines and DSM-IV research criteria of mixed anxiety and depressive disorder (MADD) have been reviewed elsewhere. Therefore, this article will review the topics of clarification of the terminology, prevalence of MADD in primary care setting, and the process involved in diagnosing MADD.

Clarification of the terminology

Mixed anxiety-depression is a potentially ambiguous term because it is often used to refer to different situations.

First, it refers to symptoms of mixed anxiety-depression found in any patient. In this sense, the abbreviation MADS is used to stand for “mixed anxiety and depressive symptoms”.

Second, it refers to the simultaneous presence or the comorbidity or the concomitant occurrence of threshold levels of two disorders such as major depression and generalized anxiety disorder (DA) or major depression and panic disorder (DA), or major depression and social phobia (DA), etc.

Third, it refers to subsyndromal or subthreshold level of one disorder concomitant with the threshold level of another disorder such as major depression with anxiety symptoms (Da) or generalized anxiety disorder with depressive symptoms (Ad) or panic disorder with depressive symptoms (Ad), etc.

Fourth, it refers to a specific disorder
according to ICD-10\textsuperscript{9} or DSM-IV\textsuperscript{10} or any specific criteria, for which the abbreviation MADD is used to stand for “mixed anxiety and depressive disorder”.

Fifth, it refers to subsyndromal mixed anxiety-depression that does not meet criteria of ICD-10 or DSM-IV.

Finally, it has a general meaning that includes all five groups above, which makes it very difficult to interpret data published in various journals.

**How common is mixed anxiety-depression**

Epidemiologic studies carried out in the community have shown that subsyndromal mixed anxiety-depression occurs in 0.8% to 2.5% in the general population.\textsuperscript{6} In a U.S. study using the DSM-III-R criteria, the 1-year prevalence of mixed subsyndromal anxiety and depressive symptoms was found to be 2.5%\textsuperscript{19} while other studies have demonstrated higher rates of 5-15\%.\textsuperscript{14,17,18}

The DSM-IV field trial indicated that the prevalence of subsyndromal symptomatology was even higher in psychiatric outpatient clinics (12\%) than in primary care (6.5\%)\textsuperscript{19} which is close to the 10\% to 15\% of patients presented at an anxiety clinic in Quebec, Canada.\textsuperscript{1}

Estimates of the prevalence of mixed anxiety-depression in primary care clinical settings may be more instructive. Roy-Byrne et al. found 5.1\% of patients with subsyndromal mixed anxiety-depressive symptoms compared with 6.4\% with generalized anxiety symptoms.\textsuperscript{14} In another study of a much larger sample in a health maintenance organization (HMO) setting, 5.5\% of patients had subsyndromal mixed anxiety-depressive symptoms.\textsuperscript{20}

Some studies in primary care offer data on mixed anxiety-depression and ability to function. In the study of Ormel and his co-workers,\textsuperscript{21} 40\% of patients with subsyndromal anxiety and 43\% with subsyndromal mixed anxiety and depression had at least mild impairment in social role, while 30\% of patients with subsyndromal anxiety and 57\% with subsyndromal mixed anxiety and depression had at least mild impairment in occupational role.

Rates of impairment are significantly higher than in normals. At 1-and 3 1/2-year follow-up, patients with anxiety showed improvement in occupational but not social disability while the mixed group showed improvement in both but continued residual social disability.\textsuperscript{21}

However, those reports mentioned earlier mainly focussed on mixed anxiety-depressive symptoms (MADS). Very few studies have been reported on a distinct mixed anxiety and depressive disorder (MADD).

To the best of the author, there is no epidemiologic data using the proposed criteria for MADD in the DSM-IV appendix. However, there are at least two papers which studied MADD in primary care setting using ICD-10 criteria or their own operational criteria and found that 10.9\% and 12.8\% of psychiatric patients studied in Thailand\textsuperscript{22} and Canada\textsuperscript{23} respectively had MADD.

The first diagram compares these two studies. The left side is the study in a primary care clinic in Manitoba, Canada.\textsuperscript{23} Seven hundred eighty eight clinic attendees gave informed written consent to complete the Beck depression and anxiety
Diagram 1  Comparing MADD studies in Canada and Thailand

<table>
<thead>
<tr>
<th>Country</th>
<th>Canada</th>
<th>Thailand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study site</td>
<td>1 site multiphysician primary-care clinic in Manitoba</td>
<td>4 site of primary care setting in central Thailand</td>
</tr>
<tr>
<td>Age</td>
<td>18-70</td>
<td>18-60</td>
</tr>
<tr>
<td>Number of clinic attenders</td>
<td>796</td>
<td>843</td>
</tr>
<tr>
<td>gave informed written consent to complete BDI, BAI</td>
<td>-</td>
<td>GHQ-12</td>
</tr>
<tr>
<td>agreed to participate in diagnostic interview</td>
<td>788</td>
<td>GHQ ≤ 1</td>
</tr>
<tr>
<td>selected for interview BDI &gt; 14 or BAI &gt; 14 or BDI + BAI &gt; 17</td>
<td>-</td>
<td>GHQ ≥ 2</td>
</tr>
<tr>
<td>diagnostic interview by SCID - FM</td>
<td>501 (64%)</td>
<td>402</td>
</tr>
<tr>
<td></td>
<td>88 (18%)</td>
<td>randomization</td>
</tr>
<tr>
<td></td>
<td>78</td>
<td>Experiment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>137</td>
</tr>
<tr>
<td></td>
<td></td>
<td>265</td>
</tr>
<tr>
<td>CIS - R assessment via PROQSY</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>68 (49.6%)</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>met ICD-10</td>
<td>did not meet ICD-10</td>
<td></td>
</tr>
<tr>
<td>MADD = 10 (12.8%)</td>
<td>MADD = 33 (10.9%)</td>
<td></td>
</tr>
</tbody>
</table>
inventories (BDI and BAI), and 501 of these subjects agreed to participate in a diagnostic interview. Only 88 patients were selected for interview on the basis of their questionnaire scores BDI or BAI more than 14, or BDI plus BAI more than 17. Ten subjects could not be interviewed for various reasons leaving 78 subjects who received in-person diagnostic interviews. The diagnostic interview was conducted using a version of the structured clinical interview for DSM-III-R modified by their research group to facilitate the efficient diagnosis of anxiety or depressive disorders as well as MADD. They called this instrument the SCID-FM, which stands for structured clinical interview for DSM-III-R, Family Medicine version.

Their operational criteria for MADD are as the following.

1. Failure to meet any DSM-III-R diagnosis for a depressive or anxiety disorder
2. At least 10 days of either
   a) Feeling depressed or down most days, or
   b) Noticeable loss of interest in activities nearly every day
3. Consistent presence of at least two of the remaining DSM-III-R criteria for major depression
4. Consistent presence of at least 3 out of 18 DSM-III-R symptoms of generalized anxiety disorder.

Both depressive and anxiety symptoms in criteria 2, 3 and 4 must have at least 6 symptoms and must be nonoverlapping to meet a diagnosis of MADD. These operational criteria for MADD correspond approximately to the ICD-10 definition of MADD but are somewhat different from the proposed criteria for MADD in the DSM-IV appendix which will be pointed out later.

By using these criteria, it was found that MADD was the most common psychiatric disorder (12.8%) of patients interviewed together with pure anxiety disorders (12.8%) followed by pure depressive disorders (10.7%).

Limitations of this study are the use of 1-month duration criteria for GAD as opposed to the standard 6-month definition. As a result some cases diagnosed as GAD may not have lasted for 6 months and some of these patients may have fallen into the MADD category. The second limitation related to MADD is that their own operational definition of MADD is different from proposed criteria in DSM-IV, as they did not exclude persons with a prior history of mood disorders or generalized anxiety disorder.

The study also found that patients with MADD were more impaired than controls on measurement of the social and family/home life subscale of the Sheehan disability scale. However, MADD patients did not differ significantly from depressive or anxiety disorders and impairment of MADD was higher than in a pure anxiety group but less than in a pure depression group.

The right side of the diagram is the study in 4 sites of primary care setting in the central part of Thailand. The sites were representative of rural, semi-rural, urban, and suburban areas.

Eight hundred and forty three consecutive patients visiting 4 health centres were screened for psychiatric morbidity by the GHQ-12. Their functional disability was simultaneously assessed by the Brief Disability Questionnaire (BDQ). Patients with a GHQ score of 2 or more were classified
as probable psychiatric cases and those with a score of 0 or 1 as non-cases. Four hundred and two cases were GHQ positive and these were allocated into two groups, control and experiment with the ratio of 2:1. There were 137 patients in the experimental group who performed the computerised self-assessment version of the clinical interview schedule revised (CIS-R) called the PROgrammable Questionnaire System (PROQSY) to diagnose non-psychotic disorder in the primary care setting. Sixty eight out of 137 subjects (49.6%) met ICD-10 criteria for non-psychotic mental disorders. Of these patients, MADD was still found to be the most common diagnosis (10.9%) in primary care, followed by neurasthenia (6.0%) phobic disorders (3.4%), depression (1.6%), panic disorder (0.3%) and generalized anxiety disorder (0.3%). It was found that the mean BDQ score of patients with MADD (5.7) fell between depressive patients (7.4) and patients with anxiety disorders (5.4), and all of them were higher than the mean BDQ score of subjects with psychiatric diagnosis (4.5, SD=3.0).

Limitations of this study are the use of self-administered computerised assessment to diagnose cases instead of interview by clinician and the method of interpreting MADD which comes from exclusion of all possible major non-psychotic disorders according to ICD-10 criteria.

However, both studies support not only the existence but also the potential importance of MADD among primary-care patients.

How to diagnose MADD

The first step in the diagnostic evaluation of mixed depressive and anxiety symptoms is to consider potential underlying medical causes. There is, of course, no recipe that can be followed for a routine workup for every patient. The extent of the diagnostic workup must be guided by the patient's medical history and review of systems. For example, in a patient with lung cancer who had mixed anxiety-depressive symptoms (MADS), there must be a high index of suspicion for central nervous system tumor involvement and a diagnostic workup might well include neuroimaging and metabolic studies such as calcium and blood counts. In a physically healthy patient with a negative medical review of systems, there is little cost effectiveness in any routine laboratory screening. Medical risk factors should guide the extent of the workup. A thorough medication history, including drug and substance use, is critical.

The second step involves looking for MADS caused by the direct physiological effects of a drug of abuse (e.g. alcohol or cocaine) or the side effects of a medication (e.g. steroid).

After ruling out medical causes and drug or substance use, the third step is to differentiate patients with MADS into four groups of mental disorders according to diagnostic guidelines in ICD-10 or diagnostic criteria in DSM-IV.

1. Patients with a primary Anxiety disorders with depressive symptoms (Ad) such as panic disorder or generalized anxiety disorder or obsessive compulsive disorder or social phobia with mild depressive symptoms or subthreshold level of depressive disorder.

2. Patients with a primary Depressive disorders with anxiety symptoms (aD) such as major depression, dysthymic disorder with mild
anxiety symptoms or subthreshold level of anxiety disorder.

3. Patients with both primary diagnoses of Anxiety disorders and Depressive disorders (AD) such as major depression comorbid with panic disorder.

4. Patients with subsyndromal manifestation of both anxiety and depression (ad) and having symptoms fulfilling the criteria of MADD according to ICD-10 or DSM-IV.

Some clinicians suggest to differentiating other mental disorders such as somatoform disorders and personality disorders. Among the latter, avoidant, dependent and obsessive-compulsive personality disorders may have symptoms that resemble those of mixed anxiety-depressive disorder.25

Therefore the algorithm in diagram 2 is suggested by the author as a decision tree for differential diagnosis of patients with MADS.

**Conclusion**

At this time MADD is only included as a provisional category in the DSM-IV; it is designated as a separate diagnostic category in ICD-10. Epidemiologic studies support the existence and also the potential importance of MADD among primary care patients. Patients with MADD rated their disability as being comparable to that of patients with anxiety or depressive disorders. Although some studies support the high prevalence rate of MADD among primary-care settings, making it eligible to be a distinct disease entity, further longitudinal studies are needed to map the temporal stability of MADD, i.e., that is whether or not MADD evolves into “full-blown” anxiety or depressive disorders within a specific time frame. If such were the case, then MADD would be best conceptualized as a transitional state rather than a disorder in need of a new diagnostic rubric. Other issues that need to be addressed include: the determination of how (and if) to treat, and whether or not treatment diminishes the disability of patients.
Diagram 2  Differential Diagnosis of Mixed Anxiety and Depressive Symptoms

MADS
(Mixed anxiety and depressive symptoms)

↓
Due to the direct physiological effects of a general medical condition

↓ No
Due to the direct physiological effects of a substance (e.g. a drug of abuse or a medication)

↓ No
Has any other current Mood Disorders or Anxiety Disorders (including those in partial remission)

↓ No
Has any other current Somatoform Disorders or any Personality Disorders

↓ No
Cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

↓ No
No Mental Disorder

↓ Yes
Anxiety disorder due to a General Medical Condition

↓ Yes
Substance-Induced Anxiety Disorder

↓ Yes
Major depression Dysthymic Disorder Panic Disorder GAD

↓ Yes
Somatoform Disorders Personality Disorders - Avoidant - Dependent - OCPD

↓ Yes
MADD
References


ปกครองบวกสู่กลุ่มโรคภูมิคุ้มกันและโรคติดเชื้อในประชาบัณฑิตภูมิมีความสำคัญมากขึ้น อย่างไรก็ตาม ซึ่งมีผู้ป่วยอีกกลุ่มหนึ่งที่มีอาการโรคภูมิคุ้มกันและเชื้อสำรา แต่ไม่สามารถจัดจับกับโรคภูมิคุ้มกันได้ โดยเฉพาะในกลุ่มของโรคภูมิคุ้มกันหรือโรคติดเชื้อสำราได้ ผู้ป่วยกลุ่มนี้จึงถูกจัดเป็น "โรคภูมิคุ้มกันและเชื้อสำราผสมกัน" โดยทั่วไปแล้วอาการโรคภูมิคุ้มกันอาหารเชื้อสำราเน้นจะพบมากกันได้ยนต์มากในทางคลินิก แต่ทางปฏิบัติแล้วขึ้นต่อเนื่องกันได้จะต่างจากโรคภูมิคุ้มกัน ผู้ป่วยรายนี้มีอาการโดยเป็นอาการหลักหรืออาการนำมาก่อน แล้วมีอาการอื่นเกิดขึ้นตามมาภายหลัง หรือผู้ป่วยเป็นทั้งสองโรค คือ เป็นทั้งโรคภูมิคุ้มกันและลำปางกับเป็นโรคภูมิคุ้มกันชนิดใดชนิดหนึ่ง จึงมีวินิจฉัยแยกภาวะดังกล่าวที่จะชัดเจนไปได้แม้ว่าจะค่อนข้าง "โรคภูมิคุ้มกันและเชื้อสำราผสมกัน" จากการศึกษาผู้ป่วยที่ไปตรวจตามสถานบัณฑิตภูมิงานทางการแพทย์ระดับสูง ภูมิมีร้อยละ 12.8 ของผู้ป่วยที่มีค่าตามเกณฑ์การวินิจฉัย "โรคภูมิคุ้มกันและเชื้อสำราผสมกัน" ของ ICD-10 รายงานไม่เพียงแต่ยืนยันถึงการต่างอยู่ของโรคเท่านั้น แต่ยังพบกลุ่มอาการสำคัญของโรคระดับภูมิงานทางการแพทย์ระดับสูง

คำสำคัญ โรคภูมิคุ้มกัน โรคติดเชื้อ ผสม ร่วมกัน เซลปิบิบิบุญภูมิภูมิ

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