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Diagnostic Overlap of Generalized Anxiety Disorder and Major Depressive Disorder in a Primary Care Sample

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Abstract

Background—Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are highly comorbid. A possible explanation is that they share four symptoms according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text Revision (DSM-IV-TR). The present study addressed the symptom overlap of people meeting DSM-IV-TR diagnostic criteria for GAD, MDD, or both to investigate whether comorbidity might be explained by overlapping diagnostic criteria.

Methods—Participants (N = 1,218) were enrolled in the Coordinated Anxiety Learning and Management (CALM) study (a randomized effectiveness clinical trial in primary care). Hypotheses were: 1) the comorbid GAD/MDD group would endorse the overlapping symptoms more than the non-overlapping symptoms, and 2) the comorbid GAD/MDD group would endorse the overlapping symptoms more than GAD only or MDD only groups, whereas differences would not occur for non-overlapping symptoms.

Results—The overlapping GAD/MDD symptoms were endorsed more by the comorbid group than the MDD group but not the GAD group when covarying for total symptom endorsement. Similarly, the comorbid group endorsed the overlapping symptoms more than the non-overlapping symptoms and did not endorse the non-overlapping symptoms more than the GAD or MDD groups when covarying for total symptom endorsement.

Conclusions—The results suggest that comorbidity of GAD and MDD is strongly influenced by diagnostic overlap. Results are discussed in terms of errors of diagnostic criteria, as well as models of shared psychopathology that account for diagnostic criteria overlap.

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Keywords

generalized anxiety disorder; major depressive disorder; comorbidity; primary care; diagnostic criteria

Of all the mood and anxiety disorders, generalized anxiety disorder (GAD) and major depressive disorder (MDD) have the highest rate of comorbidity,^[1,2] ranging from 40% to 98% in treatment studies.^[3–6] In epidemiological studies (National Comorbidity Survey; NCS), 67% of people with lifetime GAD retrospectively report MDD, and 20% of people with MDD retrospectively report GAD.^[7] Data from the NCS also showed MDD and GAD were highly comorbid with an odds ratio (*OR*) of 7.5 (95% *CI*: 5.5–10.3).^[8] Additionally, in a nationally representative epidemiological sample in Germany (*N* = 4181), 40% of all GAD cases had current (past 30 days) MDD, and 59% had MDD within the last year (more than any other disorder).^[9, 10] Even with relaxed criteria, as is done in some epidemiological studies, GAD has been shown to have similar comorbidity with other disorders (86.3%) with one month of worry, non-excessive worry, and two or more “C” criteria versus the full requirements of the DSM-IV-TR (92.1%; see Table 1).^[11, 12]

Several models have been put forth to explain this high rate of comorbidity. In the hierarchical model of mood and anxiety disorders, each disorder has a common component and a unique component.^[2,13–14] The common component (i.e., general distress) is a higher order factor common to anxiety and mood disorders. However, each disorder has a unique aspect, as well. For example, excessive worry in several domains is unique to GAD, whereas anhedonia is unique to MDD. The model posits that high levels of comorbidity are due to the influence of the higher order factor on each anxiety and mood disorder.^[13] In light of this, it has been recommended that the current classification system be replaced with a hierarchical model of the mood and anxiety disorders in the upcoming Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5).^[2]

Various risk factors may also contribute to high comorbidity between GAD and MDD.^[8, 15] The genetic correlation between GAD and MDD is high.^[8, 14, 16, 17] Roy, et al.^[18] found a genetic correlation of 1.00 between GAD and MDD, a 0.28 correlation with unique environments (i.e., environments not shared with family members), and no correlation of environments shared with family members. Similarly, Kendler, et al.^[19] found that, when analyzed with panic disorder and the phobias, the genetic factors of GAD and MDD group together with loadings of .64 and .47, respectively. Gorwood^[20] sums this argument in a review stating that the same gene may be responsible for both GAD and MDD. Furthermore, neuroticism, or a trait disposition to experience negative affect, is a general risk factor for anxiety and unipolar depression.^[21] Neuroticism has been shown to be a higher-order risk factor for GAD, mediated by more specific vulnerabilities (e.g., intolerance of uncertainty and negative metacognitions)^[22], as well as for MDD, being associated with self-esteem,^[23] adversity,^[24] and cognitive reactivity (i.e., how easily negative thinking is reactivated due to mild low mood).^[25] Genetic risk factors also link neuroticism to anxiety and depression,^[26] indicating the interconnectedness of the risk factors. However, research has also shown that GAD may have a stronger association with other anxiety disorders than with MDD^[27] and that GAD may itself be a precursor to MDD.^[28]

Other studies suggest that the high comorbidity rates may be largely due to an artifact of the current diagnostic system.^[1,3, 29–35] That is, there is a strong overlap in diagnostic criteria of GAD and MDD. Table 1 provides the list of GAD and MDD symptoms according to the DSM-IV-TR.^[12] As can be seen, GAD and MDD’s diagnostic criteria share four symptoms:

difficulty sleeping, difficulty concentrating, being easily fatigued, and psychomotor agitation.

Sunderland, et al.^[1] used the 2001–2002 National Epidemiological Survey on Alcohol and Related Conditions to investigate whether the high rate of comorbidity of GAD and MDD was due to similarity in diagnostic criteria. If comorbidity was due to criteria overlap, the authors hypothesized that individuals with comorbid GAD and MDD would have a different symptom profile comprised more of the overlapping symptoms than individuals with MDD alone. Participants (N = 43,093) were assessed using the Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS), a fully structured diagnostic interview for DSM-IV Axis I disorders. They found no evidence to suggest that people with MDD had a different symptom profile whether or not they had comorbid GAD. However, there were some limitations to their research. The data retrieved using the AUDADIS did not allow evaluation of the two cardinal MDD symptoms: depressed mood and anhedonia. Also, they used retrospective lifetime reports of disorder symptoms, which have been shown to be highly unreliable,^[36] so much so that even people diagnosed with MDD may not meet lifetime diagnosis in a follow-up assessment 25 years later.^[37]

The present study used baseline data from the Coordinated Anxiety Learning and Management (CALM) study to investigate whether comorbidity between GAD and MDD may be due to diagnostic overlap based on complete evaluation of GAD and MDD symptoms. Data included symptom profiles of participants with GAD, MDD, and comorbid GAD/MDD. If the comorbidity of GAD and MDD in the CALM study was driven in part by the four symptoms that overlap between GAD and MDD (i.e., double-counting these symptom endorsements in both MDD and GAD), one would expect a specific, different symptom profile for participants with comorbid GAD/MDD versus GAD and MDD. Two hypotheses were developed to test this. First, it was hypothesized that participants with comorbid GAD/MDD would endorse the four overlapping symptoms more than the non-overlapping symptoms. Second, participants with comorbid GAD/MDD were hypothesized to endorse the four overlapping symptoms more than participants with GAD or MDD, whereas such differences would not be found for the non-overlapping symptoms.

METHODS

Participants

Participants were taken from a sample of individuals who participated in the CALM study and who attended a primary care facility at one of four CALM study sites (Los Angeles, San Diego, Seattle, Little Rock). From that sample (N = 1,620), we included all participants who met criteria for GAD, MDD, or both (N = 1,298). Twenty participants with GAD, 20 with MDD, and 40 with GAD/MDD were excluded because of missing symptom data. The final participant numbers were 298 with GAD, 249 with MDD, and 671 with GAD/MDD (N = 1,218 total). All sites' Institutional Review Boards approved study protocols, and all participants gave informed consent after the nature of the study was explained.

Measures

Mini International Neuropsychiatric Interview (MINI)—An electronic version of the MINI was used. The MINI is a fully structured diagnostic interview that assesses for (in chronological order) major depressive episode, major depressive disorder with melancholic features, dysthymia, suicidality, manic episode, hypomanic episode, panic disorder, agoraphobia, social phobia (social anxiety disorder), obsessive-compulsive disorder, posttraumatic stress disorder, alcohol dependence, alcohol abuse, substance dependence, substance abuse, psychotic disorders, mood disorder with psychotic features, anorexia

nervosa, bulimia nervosa, anorexia nervosa binge eating/purging type, generalized anxiety disorder, and antisocial personality disorder.^[38] The time frame covered for all MDD questions is the past two weeks, and, if the participant answered “Yes” to either 1) “Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks” or 2) “In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?,” the questions regarding the remaining seven MDD symptoms were asked and a diagnosis was reached. Similarly, the time frame covered for all GAD questions is the past six months, and, if the participant answered “Yes” to both “Have you worried excessively or been anxious about several things over the past 6 months?” and “Are these worries present most days?,” the hierarchical relationship between GAD and other disorders (including MDD) was addressed (see DSM-IV-TR, GAD, Criterion F.: “The disturbance... does not occur exclusively during a Mood Disorder”).^[12] The MINI question reads: “Is the patient’s anxiety restricted exclusively to, or better explained by, any disorder prior to this point?”^[38] “Prior to this point” refers to all of the diagnostic questions from the start of the MINI to the GAD questions of the MINI. Because GAD is assessed after MDD in the MINI (and after all disorders except antisocial personality disorder), in order to receive a diagnosis of GAD, the answer to this question had to be “No.” Furthermore, the test-retest reliability of the MINI is high (with kappas of .78 and .87 for GAD and MDD, respectively), as is the reliability with diagnoses ascertained using the Structured Clinical Interview for the DSM-III-R (with kappas of .70 and .84 for GAD and MDD, respectively).^[38]

Procedures

After being referred to the CALM study by their primary care physician for an anxiety disorder, participants were diagnosed using the MINI^[38] by anxiety clinical specialists (ACSs), who were primary care staff.^[39] ACSs were trained on MINI administration via didactic presentation, and, though diagnostic reliability was not formally assessed using conventional means, the ACSs had a 94% match on diagnoses of five mock MINI assessments.^[40] While the MINI is a fully structured interview, ACSs in CALM were trained to administer it as a semi-structured instrument by asking follow-up questions to clarify diagnostic questions/issues. ACSs reviewed each MINI with study psychologists and psychiatrists for diagnostic accuracy.

Data Analysis

Hypothesis 1 was analyzed with a two-tailed paired samples t-test comparing the number of *overlapping* symptoms versus the number of *non-overlapping* symptoms endorsed by each comorbid GAD/MDD participant. Scores for symptom endorsement ranged from 0–100% (e.g., endorsing 6 out of 8 overlapping symptoms would yield a score of 75%). Hypothesis 2 was analyzed using two-tailed univariate ANOVAs measuring the number of overlapping and non-overlapping symptoms endorsed by comorbid GAD/MDD, GAD, and MDD participants, covarying for total GAD and total MDD symptom endorsement. Hypothesis 2 used a 0–4 scale for the number of overlapping symptoms endorsed for GAD and MDD, a 0–5 scale for the number of non-overlapping MDD symptoms endorsed, and a 0–4 scale for the number of non-overlapping GAD symptoms endorsed.

RESULTS

Tables 2 and 3 show the percentage of participants in each diagnostic group who endorsed each of the GAD and MDD symptoms, and Table 4 shows the mean number of overlapping symptoms endorsed by each diagnostic group.

Hypothesis 1 – Overlapping vs. non-overlapping symptoms within the comorbid group

The results support Hypothesis 1; participants with comorbid GAD/MDD endorsed significantly more of the four overlapping symptoms ($M = 90.57\%$, $SD = 12.93\%$) than the non-overlapping symptoms ($M = 81.47\%$, $SD = 11.76\%$) ($t = 14.53$, $p < .001$).

Hypothesis 2 - Overlapping and non-overlapping symptoms between comorbid GAD/MDD, GAD, and MDD groups

See Table 5 for the mean number of overlapping GAD and MDD symptoms, non-overlapping GAD symptoms, and non-overlapping MDD symptoms endorsed by each diagnostic group. Comorbid GAD/MDD participants endorsed more of the nine total MDD symptoms than MDD participants ($F(1, 918) = 6.17$, $p = .013$): GAD/MDD ($M = 7.10$, $SD = 1.12$) vs. MDD ($M = 6.88$, $SD = 1.28$) and more of the eight total GAD symptoms than GAD participants ($F(1, 967) = 45.29$, $p < .001$): GAD/MDD ($M = 7.48$, $SD = .78$) vs. GAD ($M = 7.09$, $SD = .96$). Thus, the total number of symptoms endorsed for each disorder was included as a covariate in subsequent analyses to provide a more conservative estimate. Results comparing the GAD/MDD and MDD groups support Hypothesis 2: there was a group difference ($F(1, 918) = 6.863$, $p = .009$) where the GAD/MDD group endorsed more overlapping symptoms than the MDD group. However, the results for Hypothesis 2 were not significant for the GAD/MDD and GAD groups ($F(1, 967) = .242$, $p = .623$). Finally, as hypothesized, no group differences were found for non-overlapping symptom endorsement between the GAD/MDD and the MDD group ($F(1, 918) = .654$, $p = .419$) nor between the GAD/MDD and the GAD group ($F(1, 967) = .918$, $p = .338$).

DISCUSSION

Comorbidity rates for anxiety and mood disorders are high, with GAD and MDD being the most frequent mood-anxiety pair.^[2,6] The overlapping DSM-IV-TR diagnostic symptoms for GAD and MDD^[1] may be responsible for artifactually increasing comorbidity rates.^[29] We investigated the symptom profiles of a sample of primary care patients with GAD, MDD, or comorbid GAD/MDD.

Results showed that the comorbid GAD/MDD participants endorsed the four overlapping symptoms shared between GAD and MDD significantly more than the non-overlapping symptoms. Also, after covarying total number of symptoms endorsed, comorbid GAD/MDD participants endorsed the overlapping symptoms significantly more than participants diagnosed with MDD. Though these results are significant, the mean differences are small, which questions the clinical significance of these findings. Finally, the GAD/MDD group did not differ from the GAD group in overlapping symptom endorsement nor the GAD and MDD groups in non-overlapping symptom endorsement.

If comorbid GAD/MDD truly represents an accumulation of depressive and anxious symptoms, the comorbid participants would be expected to equally endorse the overlapping and non-overlapping symptoms, and the comorbid group would also be expected to endorse both the non-overlapping and the overlapping symptoms more than the GAD or MDD groups. However, the data does not reflect these notions; the findings instead suggest that diagnostic overlap was at least partly responsible for the high comorbidity between GAD and MDD.

This questions whether the criteria of the two disorders are too similar and whether this is a cause of the high rate of comorbidity. The diagnostic overlap may represent poorly constructed diagnostic criteria with insufficient boundaries between categories. Of course, this assumes that the underlying pathologies of GAD and MDD are indeed distinct and that the error lies in the nosological specification (GAD in particular has undergone many

revisions since its inclusion in DSM-III^[41]). The present study provides information regarding this topic, though it is beyond the scope of the paper to suggest what, if any, changes should be made in diagnostic criteria. Before any such changes are considered, future research needs to replicate the findings of the present study, as well as determine whether there is a group difference between the comorbid and GAD groups in overlapping symptom endorsement, which the present study did not show.

In addition to diagnostic overlap, another factor that may explain comorbidity is the hierarchical model of anxiety and mood disorders, where GAD and MDD load on the higher order factor of general distress,^[13] perhaps more so than other mood and anxiety disorders. The overlapping symptoms may closely represent the higher order factor. However, each disorder also requires symptoms that represent the lower order factors, which presumably are unique to each disorder (i.e., “anhedonia” for MDD and “worry” for GAD). Thus, comorbidity represents a natural linkage beyond the overlapping symptoms and may be a result of both the hierarchical model and diagnostic overlap.

There are several limitations to this study. First, when comparing the criteria of GAD and MDD, two of the overlapping symptoms fully overlap with one another (i.e., sleep disturbance and fatigue), whereas the other two are compound symptoms that only overlap in part (i.e., GAD: psychomotor agitation and difficulty concentrating/mind going blank; MDD: psychomotor agitation/retardation and difficulty concentrating/making decisions). The dataset used in the present study used a binary 1/0 coding system (i.e., symptom is either present or not present) that did not distinguish whether a person endorsed one part of a symptom, the other, or both parts. For example, if a participant endorsed Criterion A(5) from MDD (i.e., psychomotor agitation/retardation), we cannot be sure whether they endorsed psychomotor agitation, psychomotor retardation, or both. This creates heterogeneity and prevents us from knowing with certainty whether the participant endorsed the sub-symptom that overlaps with GAD (i.e., psychomotor agitation). Though it would have been preferable to record this level of specificity, CALM was an effectiveness study conducted in primary care with time and cost constraints whose main aim was to evaluate the effectiveness of the novel intervention. Future research could benefit from recording sub-symptom diagnostic profiles to further examine the relationships described in this study. Furthermore, we do not have data regarding the onset and severity of the symptoms, so we could not determine whether an overlapping symptom originated during GAD or MDD. We also could not determine whether a comorbid participant developed GAD or MDD first. Despite these limitations, the present study is relevant to investigating how much the comorbidity reported in epidemiological and clinical samples (where diagnoses are conducted in a similar fashion and reach a similar level of symptom specificity) is an artifact of symptom overlap.

Second, the MINI may not be sensitive enough to detect differences between GAD and MDD for the overlapping symptoms since GAD criteria refer to the past six months, whereas MDD criteria refer to the past two weeks. While the MINI is a structured assessment tool with high reliability (kappas of .78 and .87) and validity (kappas of .70 and .84) for GAD and MDD, respectively,^[38] a strength of this study is that the clinicians in CALM were trained to conduct the MINI interviews in a semi-structured fashion, which would likely increase reliability and validity. The interviewers were trained to reliability, and MINIs were regularly reviewed by study psychologists or psychiatrists, which helped clarify differential diagnostic questions.^[40] On the other hand, the DSM-IV-TR criteria may be responsible for inconsistent responses from participants (e.g., endorsing “difficulty sleeping” for GAD but not for MDD). Individuals tend to have difficulty accurately recalling symptoms retrospectively,^[36,37] so asking participants to recall these symptoms over the past six months for GAD may differ from their response for MDD over the past two

weeks. Even more difficulty lies in participants recalling whether they endorsed the symptoms more often than not *while anxious* (for GAD) and *while depressed or uninterested* (for MDD). This may have led some participants to report their symptoms inconsistently (e.g., endorsing “difficulty sleeping” for GAD but not MDD). Another limitation of the study is that the CALM study used a treatment-seeking sample, as opposed to a randomized sample, and the results may only reflect the characteristics of treatment-seeking individuals. Related is that the high medical comorbidity in this sample^[39] may limit generalizability to population samples. Lastly, future research could investigate other disorders to examine how much of their comorbidity is due to overlapping criteria.

CONCLUSIONS

In sum, the results indicate that symptom overlap may inflate rates of comorbidity between GAD and MDD. On the one hand, the symptom overlap may represent poorly constructed diagnostic criteria; on the other hand, the symptom overlap may represent the shared psychopathology underlying these conditions, which results in high rates of joint endorsement of not just the overlapping physical symptoms but also the disorder-unique features of anhedonia and excessive worry. It is likely that both diagnostic overlap and the hierarchical model are responsible for high comorbidity.

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Table 1

DSM IV-TR Criteria for Adult MDD and GAD

MDD Criteria	GAD Criteria
A(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)	A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)
A(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)	B. The person finds it difficult to control the worry
A(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day	<i>C(1) Restlessness or feeling keyed up or on edge *</i>
<i>A(4) Insomnia or hypersomnia nearly every day</i>	<i>C(2) Being easily fatigued</i>
<i>A(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)</i>	<i>C(3) Difficulty concentrating or mind going blank</i>
<i>A(6) Fatigue or loss of energy nearly every day</i>	C(4) Irritability
A(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)	C(5) Muscle tension
<i>A(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)</i>	<i>C(6) Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)</i>
A(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	

*
Bold and italicized symptoms are shared between GAD and MDD

Table 2

Percentage of GAD Symptoms Endorsed Across Diagnoses

	Anxiety and worry	Difficult to control worry	Difficulty sleeping	Psychomotor agitation	Fatigue	Difficulty concentrating/indiscreteness	Muscle tension	Irritability
GAD/MDD (N = 671)	100	100	91.1	93.7	92.4	90.2	96.6	84.5
GAD (N = 298)	100	100	81.5	91.6	81.2	85.2	95	74.2

* Bold and italicized symptoms are shared between GAD and MDD

Table 3

Percentage of MDD Symptoms Endorsed Across Diagnoses

	<i>Difficulty sleeping</i>	<i>Psychomotor agitation/retardation</i>	<i>Fatigue</i>	<i>Difficulty concentrating/indiscreteness</i>	<i>Depressed mood</i>	<i>Anhedonia</i>	<i>Appetite/weight</i>	<i>Worthlessness/guilt</i>	<i>Suicidality</i>
GAD/ MDD (N = 671)	87.8	85.4	94.2	90.3	79.3	93.4	79.3	77.8	22.4
MDD (N = 240)	86.3	84.3	92.8	83.5	75.9	95.6	78.3	71.9	18.9

* Bold and italicized symptoms are shared between GAD and MDD

Table 4
Percentage of Participants in Each Diagnostic Group Endorsing 0–8 of the Overlapping Symptoms

# of Overlapping Symptoms	0	1	2	3	4	5	6	7	8
GAD/MDD (N = 671)	Not Possible	0 *	0	0.6	1.8	4.3	14.5	23.4	55.4
GAD (N = 298) **	Not Possible	0.3	14.1	31.2	54.4	---	---	---	---
MDD (N = 249) **	0	0.8	10.5	29.7	59	---	---	---	---

* All number values are given as percentages of the specific diagnostic group
 ** GAD (N = 298) and MDD (N = 249) groups can only endorse a maximum of four overlapping symptoms

Table 5

Mean Number of Symptoms Endorsed by Each Diagnostic Group

	Overlapping GAD/MDD Symptoms (0–4 scale)		Non-Overlapping GAD Symptoms (0–4 scale)		Non-Overlapping MDD Symptoms (0–5 scale)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
GAD/MDD (N = 671)	3.62	.52	3.81	.44	3.52	.95
GAD (N = 298)	3.40	.74	3.69	.55	N/A	N/A
MDD (N = 249)	3.47	.71	N/A	N/A	3.41	.97