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Heterogeneity in Comorbidity between Major Depressive Disorder and Generalized Anxiety Disorder and its Clinical Consequences

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Abstract

Major Depressive Disorder (MDD) and Generalized Anxiety disorder (GAD) are highly comorbid and, as diagnoses, problematic because they are heterogeneous, may impair functioning even in sub-clinical manifestations, and may not predict important external criteria as well as an empirically-derived classifications. The present study employed a Latent Class Analysis using data from National Comorbidity Survey (1990–1992) and focused on respondents who endorsed at least one screening question for MDD and one for GAD (N=1009). Results revealed 4 symptom domains (Somatic Anxiety, Somatic Depression, Psychological Anxiety, and Psychological Depression) reflecting the heterogeneity of MDD and GAD, and 7 respondent classes. Analysis revealed that people in classes with a high prevalence of either somatic anxiety or somatic depression symptoms presented with the highest levels of disability, distress and service utilization. Evidence also was found for clinically meaningful sub-threshold co-morbid conditions. Anxiety-related and depression-related symptoms can be meaningfully differentiated, but differentiating between somatic and psychological symptoms has the greatest practical significance.

Keywords

Major Depressive; Disorder Generalized Anxiety Disorder; Psychiatric Comorbidity; Psychiatric Nosology

Introduction

It has been widely recognized for many years that the co-occurrence of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) is common in both clinical and community samples (Barlow et al, 1986; Kessler, 1994; Kessler et al, 2005b). Several hypotheses have been proposed to describe the relationship between these diagnoses. However, most studies have focused on co-morbidity-- co-occurrence of diagnoses --not on patterns of symptom co-occurrence.

There are several advantages of focusing on symptoms rather than diagnoses. First, examining the shared symptoms of MDD and GAD allows for assessment of heterogeneity in the overlap between these conditions—clusters of symptoms and types of people. Second, focusing on symptoms allows for the analysis of co-occurrence between these conditions below their diagnostic cutoff points that is not possible when using diagnosis as the focus of analysis. Thus, detailed analyses at the symptom level can be useful for understanding potential differences

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in comorbidity between MDD and GAD and can be usefully applied to understanding the consequences of their co-occurrence.

This study analyzes the lifetime symptoms included in the DSM criteria for MDD and GAD using a Latent Class Analysis to empirically derive classes of shared symptom patterns. By comparing these empirically derived classes to the diagnostic categories of MDD and GAD using various clinical validators such as service use, disability and distress, heterogeneous presentations of comorbidity above and below the diagnostic thresholds can be assessed in relation to the validity of these diagnostic criteria.

Comorbidity between MDD and GAD

Large community studies such as the National Comorbidity Survey (NCS) and the follow-up NCS-R have demonstrated considerable co-morbidity between Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) (Kessler et al, 2005a; Kessler et al, 1994; Wittchen, 1994). These and other studies have found that over half of individuals diagnosed with depression have a comorbid anxiety disorder and vice versa (Kessler, 1994; Kessler et al, 2005a; Mineka et al, 1998). Various models have been developed to explain this extensive overlap.

One way of specifying the relationship between MDD and GAD is to lump the disorders together. The Liability-Spectrum Model does this by grouping mental disorders and differentiating along internalizing and externalizing dimensions. The internalizing dimension specifies degrees of anxious-misery/fear, with MDD and GAD, along with Dysthymia, forming the core of anxious-misery (Krueger, 1999; Krueger et al, 2006; Vollebergh et al, 2001). A separate but related framework for understanding the relationship between MDD and GAD is the Tripartite Model (Clark et al, 1991; Watson, 2005). Unlike the Liability-Spectrum Model, the Tripartite Model argues that MDD and GAD have similarities and differences. The three components of this model are negative affect, positive affect and physiological hyperarousal (Watson, 2005). MDD and GAD share high levels of negative affect including sadness, worry, and guilt, but are distinguished by differing degrees of positive affect, with MDD characterized by low levels of happiness, interest in activities, and confidence (Kendler et al, 2003; Watson, 2005). Recent studies comparing the Liability-Spectrum Model to the Tripartite Model have tended to support the latter (Olinio et al, 2007). However, all of these studies used diagnoses or scale scores as the unit of analysis.

Subtypes of Depression and Anxiety

Diagnosis focused studies of comorbidity do not address the potential for heterogeneous clinical subtypes among comorbid people, especially when considering sub-threshold comorbidity. Evidence of heterogeneous presentations of MDD and GAD along with evidence of the clinically significant impact of sub-threshold conditions suggests that these considerations are worthy of further study (Krueger et al, 2006). It is well documented that depression is heterogeneous. Depression has been differentiated based on levels of severity, sub-types of depression and proposed etiology (Rush, 2007). One prominent depression sub-typing involves distinguishing “typical” from “atypical” depression (Matza et al, 2003; Sullivan et al, 1998; Thase, 2007). Atypical depression is distinguished from typical depression by the presence of hypersomnia, excessive eating or weight gain and interpersonal sensitivity. Endogenous depression is another sub-type, distinguishing between persons with somatic symptoms such as lack of energy and psychomotor retardation from exogenous depression characterized by psychological symptoms such as feelings of worthlessness and hopelessness (Haslam et al, 1994; Joiner, 2001; O’Leary, 1996). Likewise anxiety in general has been sub-typed into various categories such as anxious-worry, anxious-phobic and anxious-interpersonal sensitivity (Hantouche et al, 2005). Additionally, more psychological anxiety symptoms, such

as worry, have been separated from the more somatic anxiety symptoms, such as increased heart rate or excessive sweating, illustrated by the removal of most of the somatic anxiety symptoms from the GAD criteria between DSM III-R and DSM-IV (Watson, 2005).

Given the extensive overlap between MDD and GAD, and the well documented heterogeneity within these disorders, there is reason to believe that there will be a heterogeneous collection of subtypes of comorbid MDD and GAD (Barbee et al, 2003). However, only a few studies have investigated patterns of joint MDD and GAD symptom occurrence. Using clinical convenience samples of adolescents, three studies have found that anxiety symptoms tended to be more prevalent than depression symptoms (Ferdinand et al, 2005; van Lang et al, 2005; Wadsworth et al, 2001).

The only adult study published to date examined MDD/GAD symptoms along with somatization disorder symptoms. Using symptom patterns, patients were empirically categorized into 6 distinct patient types: a somatization type, a sporadic symptom type, a mixed anxiety depression type, a GAD type, a sleep problem type and an anxious panic type (Piccinelli et al, 1999). Only somatization was recognizable as a distinct category. Other classes found in the study all exhibited qualities reminiscent of those found among patients with co-occurring MDD-GAD and provide preliminary evidence for heterogeneity in the comorbid presentation of these disorders.

Unlike previous studies of the joint symptoms of MDD and GAD, the present study examines symptoms common to MDD and GAD in a population-based sample of adults. MDD and GAD symptoms were combined in a common item pool and, in accordance with best psychometric practice, used to identify an underlying data structure with respect both to the symptoms themselves and the people endorsing the symptoms. The intention was to shed light on heterogeneity present in comorbid MDD and GAD, considering both clinical and sub-threshold levels of distress. We also compare these empirically derived classes to original MDD and GAD diagnoses in terms of their association with a set of clinical indicators that include demographics, service utilization, other comorbid diagnoses, disability and personality characteristics.

Specifically two hypotheses are examined: 1) That empirically derived subtypes of comorbid MDD/GAD symptoms will produce distinct classes that are clinically meaningful and 2) that these empirically derived classes will better account for a variety of clinical indicators compared with the DSM diagnoses MDD and GAD.

Methods

Data source

The data for this study was taken from the NCS, which was conducted between 1990 and 1992 and employed a nationally representative, cross-sectional probability sample of individuals ranging in age from 18 to 54. The total sample size of the NCS was 8098. The NCS used a stratified, multistage area probability sample with sampling weights to account for the probability of being included in the sample (Kessler, 1994). The Latent Class Modeling and the bivariate and multivariate models all accounted for the differing population-based probability of being sampled by incorporating weights into the analysis. (Muthén et al, 1998–2007; StataCorp., 2007).

All NCS participants were asked a series of screening questions for various diagnoses as part of the University of Michigan Composite International Diagnostic Interview (UM-CIDI) (Kessler, 1994). The UM-CIDI is stem-and-probe format questionnaire designed to be administered by non-clinical interviewers and to assess the presence of multiple DSM III-R

diagnoses, including MDD and GAD. The stem and probe format means that when individuals endorsed one of the screening questions, they were asked a more complete diagnostic battery of questions. In this study, only respondents who endorsed at one of two Major Depressive Disorder screening questions (depressed mood for 2 weeks or loss of interest in things) and the Generalized Anxiety Disorder screening question (worry about multiple areas for 6 months) were included in the sample (n = 1009). This selection criterion means that all individuals in this sample have endorsed at least one symptom for both MDD and GAD at some point in their lifetimes. One important caveat is that because the UM-CIDI only assessed for lifetime presence or absence of symptoms it is not possible to distinguish between MDD and GAD symptoms occurring simultaneously and symptoms separated in time.

Major Depressive Disorder and Generalized Anxiety Disorder Models

Answers to complete UM-CIDI diagnostic interviews were compiled into a 23-item dichotomous scale (Table 1). This 23-item scale is based on the DSM-III-R criteria A for Major Depressive Disorder (9 symptoms) and a modified version of the DSM-III-R Criteria C for Generalized Anxiety Disorder (11 symptoms). The UM-CIDI asks about symptoms related to the specific diagnostic condition, so for symptoms occurring in both diagnostic categories, such as decreased sleep or decreased concentration, there are two versions, one set asked in the context of depression and one set asked in the context of anxiety. Both sets of questions were included in this analysis.

The NCS used the DSM III-R as the template for its questions. The DSM III-R and IV symptoms for MDD are very similar, but the symptoms for GAD are different (Wittchen et al, 1995). The DSM III-R Criteria C has 18 symptoms, even though only six symptoms appear in the DSM IV criteria. The rationale for this change was to separate the more psychologically-based worry symptoms from the more somatically-based anxiety symptoms, retaining only the worry symptoms in the GAD criteria (Kubarych et al, 2005). For this study, the 18 GAD symptoms appearing in DSM III-R were recoded to match the 6 symptoms of the DSM IV. The remaining 12 symptoms of the DSM III-R criteria were collapsed into 5 somatic anxiety symptoms. For example, separate questions about the presence of nausea and pain in the stomach were highly correlated and were collapsed into a single item called stomach problems. These somatic anxiety symptoms are included in this analysis both to understand their association with the clinical validators, and to provide greater comparability with DSM III-R GAD diagnoses used in the NCS and this study.

Clinical Validators: Disability, Diagnostic and Demographic Data

Demographic data including education, gender, marital status, ethnicity and income were taken from the NCS dataset. Additional variables from the NCS dataset were used as indicators of clinical validity. We used the NCS diagnostic categories of lifetime MDD, GAD, Dysthymia, Bipolar Disorder, Social Phobia, Simple Phobia, Panic Disorder, Non-affective Psychotic Disorder, PTSD, Alcohol Disorder and Drug Use Disorder³. A count of these 9 non-MDD/GAD diagnoses was calculated and used as an indicator of overall level of psychiatric comorbidity. Dichotomous indicators of mental health service utilization were constructed from a series of questions that asked, "Did you ever in your lifetime go to see ... (psychiatrist, social worker, psychologist, counselor) ... for problems with your emotions or nerves or your use of alcohol or drugs?" Similar variables were used to reflect whether individuals went to an outpatient psychiatric clinic, saw other providers for their mental health or substance use, took medications, were hospitalized for emotional problems, were hospitalized for drug or alcohol problems, or reported a suicide attempt.

³Alcohol and Drug Disorder combined the Dependence and Abuse Disorder categories.

Dichotomous indicators were coded out of questions asking respondents if they had days of being unable to work or do daily activities because of emotional problems or drug and alcohol use. A similar indicator was created if individuals reported that it was an effort to perform work or daily activities. A polytomous indicator was coded from the question “How would you rate your overall mental health? Is it excellent, very good, good, fair, or poor?”. Measures of two personality attributes, extroversion and neuroticism, were included in the NCS. The extroversion scale was made unidirectional by reverse coding items that indicated increasing introversion. Both scales had value ranges of 10 to 40 after summing up the polytomous items. Higher values on the neuroticism and extroversion scales indicate more neuroticism or extroversion.

Analysis Plan

A Latent Class Analysis (LCA) was performed on the 23 symptoms of MDD and GAD using Mplus 4.21 (Muthén et al, 1998–2007). Latent Class Models generate latent homogeneous subgroups or latent classes that differ from one another in their response patterns. LCA assumes that within classes, responses are conditionally independent after accounting for class membership (McCutcheon, 2002). Thus, LCA allows for the modeling of heterogeneity of people based on symptom patterns.

Models ranging from 2 to 10 classes were evaluated. Individuals were assigned to the latent class most likely to account for their response patterns. Because Latent Class Models with different numbers of classes are not nested, model fit statistics such as Bayesian Information Criterion (BIC) were used to compare models (Table 2). BIC statistics are modified log likelihood values that adjust for differences in the number of parameters between models. Lower BIC statistics are considered to indicate better statistical fit of the model to the data (Nylund et al, 2007). BIC statistics along with qualitative assessments of the interpretability of classes guided the model selection process.

Bivariate tests, including chi-squares for dichotomous or ordinal variables or F tests with continuous variables, were used to determine whether classes differ on the clinical validators including demographics, diagnoses, service use, distress, and personality variables.

Multivariate models were also used to test for associations between class membership, MDD/GAD diagnosis and the clinical validators including service use, distress, and personality variables. Three different sets of multivariate models were used. The first set of multivariate models used traditional, logistic or ordinal logistic regressions to examine the association between class membership and the clinical validators, while controlling for other diagnoses and demographic characteristics. The second set of models parallels the first, with the class membership variables replaced by the diagnostic categories MDD and GAD. The third set of models includes both class membership and diagnostic categories, providing a multivariate comparison of the two classification systems while controlling for demographic characteristics. Wald Tests were used to determine whether removing either class membership or diagnostic categories had a statistically significant effect on the model.

Results

Latent Class Model

The Bayesian Information Criterion (BIC) was used to identify the best fitting model from among the two to 10 class models examined (Muthén, 1998–2004; Muthén et al, 2000). The seven-class solution had the lowest BIC values (Table 2) indicating that it was the best fitting model. This fit criteria, along with interpretable classes, led to the selection of the 7 class model. The probabilities of endorsing the MDD and GAD symptoms given class membership in this

seven-class model are displayed in Table 3. We used probabilities of endorsing the 23 symptoms, frequency of being diagnosed (Table 5), and the clinical validators (Table 6) to name the classes.

The classes are ordered from least severe to most severe. For most symptoms Classes 1, 2 and 3 have rates of endorsement below the mean for study respondents. Class 1 (N= 108) members have the lowest rates of symptom endorsement (Table 3) compared to all the other classes. We refer to this class as low distress. Class 2 (N=113), referred to as mild psychological depression, is characterized by high rates of endorsement for depressed mood and feelings of worthlessness, but lower rates of endorsement for all the other symptoms when compared to the whole study sample. Class 3 (N=191), referred to as mild somatic anxiety, is characterized by mildly higher rate of endorsement for somatic anxiety symptoms, such as excessive sweating, dry mouth and racing heart due to anxiety, compared with the whole study sample.

Classes 4 and 5 represent moderately severe levels of a mixed anxious-depression. Class 4 (N=222), the largest class, has moderate rates of endorsement for the depression symptoms and the anxiety symptoms decreased concentration and decreased sleep, both of which are shared with depression. We refer to Class 4 as psychological anxious-depression. Class 5 (N=60) is the smallest class. Called anxious-misery, Class 5 is characterized by increased sleep, weight and appetite along with feelings of worthlessness, thoughts of death and high rates of fatigue. These symptoms are consistent with the atypical depression subtype. Class 5 also has moderately high rates of somatic anxiety symptoms compared to the whole study population.

Classes 6 and 7 represent the most severely distressed classes, with higher rates of symptoms endorsement for almost all symptoms compared with the whole study population. Class 6 (N=152), called somatic depressed – anxiety, is characterized by the highest rates of the somatic anxiety symptoms and the depression symptom decreased appetite/weight as well as high rates of decreased sleep and lack of interest. Class 7, which we refer to as restless somatic – depression is characterized by high rates of somatic depression symptoms, such as psychomotor retardation and psychomotor agitation, as well as the highest rates of psychological anxiety symptoms, such as feeling fatigued. Members of Class 7 also have relatively high rates of endorsing the somatic anxiety symptoms compared with the whole study sample.

Analysis of Latent Classes

To determine whether latent classes are associated with clinically relevant heterogeneity, we examined the association between class membership and diagnoses, demographics and the clinical validators. The demographic composition of the study sample and all 7 classes is presented in Table 4. Statistically significant differences at the $p < 0.05$ level were found between the 7 classes and each of the demographic variables income, gender and marital status. The gender difference is particularly notable; while men were underrepresented overall in the sample, they were over represented in Classes 1 and 2, the least symptomatic.

Table 5 displays the relationship between the 7 empirically derived classes and various DSM III-R diagnoses. There were statistically significant differences in rates of diagnoses across the classes for all diagnoses except for alcohol disorder, drug disorder and psychotic disorder. As expected, Classes 1, 2 and 3 had the lowest rates of comorbid MDD/GAD. Class 3, the mild somatic anxiety class had the highest rates of GAD only. Classes 4 and 5 had the highest rates of MDD only. Class 5, the anxious-misery class, had high rates of comorbid MDD/GAD and the highest rates of dysthymia. Classes 6 (somatic depressed-anxiety) and 7 (restless somatic depression) had the highest rates of comorbid MDD/GAD along with other anxiety diagnoses including phobias and panic disorder.

Table 6 presents the rates of the clinical validators across the 7 classes and MDD/GAD diagnoses. There were statistically significant differences between classes for each of the clinical validators with the exception of the extroversion measure. Consistent with the previous findings, Class 1, the low distress class, had the lowest rates of service utilization and the best perceived mental health. Class 2 had the highest rates of drug or alcohol treatment but otherwise also had relatively low service utilization compared with this sample as a whole. Class 5, the anxious-misery class, had the highest rates of visiting a mental health provider and suicide attempts and high rates of visiting an outpatient psychiatric clinic. Class 6, the somatic depressed-anxiety class was the most likely to receive any service and also had relatively high rates of psychiatric hospitalization. Class 7, the restless somatic-depression class, had the highest rates for psychiatric hospitalization, seeing a non-mental health provider for mental health treatment, and high rates of suicide attempts. Members of Class 7 also reported the most disability with daily activities and the worst perceived mental health. Classes 5, 6 and 7 had scores indicating high levels of neuroticism. Not surprisingly, the comorbid MDD/GAD diagnostic category had the most clinical consequences including the highest rates of suicide attempts of any group reported here.

Table 7 shows the results of multivariate models comparing latent class membership to the diagnoses MDD and GAD, controlling for demographic variables and other co-morbid diagnoses. These models allow for the comparison of the symptoms based classes and MDD/GAD diagnoses with respect to the clinical validators. The first set of models tested the association between the 7 classes and the clinical validators. Class 4 (psychological anxious-depression) was used as the reference category for the classes because it was the closest class to pure depression and because it represents the middle level of severity. Compared to Class 4 members of Class 5 (anxious-misery) had higher odds of seeing a mental health provider (2.83), while Class 7 (restless somatic depression) had higher odds of seeing a non-mental health provider (2.15) and higher odds of psychiatric hospitalization (2.46). Members of Class 6 (somatic depressed-anxiety) had half the odds for seeing no service provider compared with those in Class 4. Classes 6 and 7 had over 2 times the odds for reporting difficulty accomplishing daily tasks compared with Class 4. Members of Class 5 (anxious-misery) scored an average of 2.2 points higher on the Neuroticism scale, a modest but statistically significant increase compared to Class 4. Class 2 (Mild Psychological Depression) had 9.4 times the odds of visiting a drug or alcohol clinic compared with Class 4.

The second set of models displayed in Table 7 tests the association between the clinical validators and the diagnostic variables MDD, GAD, comorbid MDD/GAD or neither disorder. MDD only was used as the reference category. Appropriately, individuals with no diagnoses were the least likely to see any provider for mental health concerns. Individuals with a GAD only diagnosis had almost 0 odds of visiting a Drug or Alcohol clinic. Individuals with comorbid MDD/GAD had more than 2 times the odds of reporting a psychiatric hospitalization compared to the MDD only group.

The third set of models displayed in Table 7 used both the 7 classes and the MDD/GAD diagnostic categories along with the control variables to compare the association between these two representations and the clinical validators. Following the estimation of the model, Wald Tests were used to assess whether removing the classes or diagnoses had a statistically significant independent effect on the different models while controlling for the other representation. Because of the multicollinearity between these two representations of depression and generalized anxiety, these results should be considered conservative. Most of the Wald Tests were not significant, indicating that the classes and diagnoses performed similar functions in modeling the clinical validators. However, the diagnoses statistically had independent effects on psychiatric hospitalization and suicide attempts. The class variables had statistically independent effects on perceived mental health.

Discussion

This study sought to answer two questions. First, are there meaningful subtypes, represented in this paper by latent classes, of comorbid MDD and GAD that have clinically meaningful implications? Second, are these classes better able to account for indicators of clinical significance than the DSM diagnostic categories MDD and GAD? The findings presented above support the argument that there is meaningful heterogeneity in the presentation of comorbid MDD – GAD. However, the current diagnostic categories compare favorably with the symptom-based, empirically derived classes, especially when considering serious clinical outcomes such as suicide attempts and psychiatric hospitalization.

Sample selection criteria required that respondents endorsed at least one of 2 depression screening questions and the generalized anxiety disorder screening question. Not surprisingly, as displayed in Table 3, this study sample had high lifetime prevalence for most of the 23 joint MDD and GAD symptoms. Consistent with previous research on these joint symptoms and theories of comorbidity between MDD and GAD, the anxiety symptoms restlessness (91%), poor concentration from anxiety (88%) and depression (63%), irritability (71%), lack of energy (78%), fatigue (66%) and decreased sleep from anxiety (76%) and depression (68%) formed a common set of symptoms across this sample. This seems to suggest that there is a depressed-anxiety condition common to the vast majority of these individuals. Despite the relatively high prevalence these symptoms, this Latent Class Analysis was able to detect clinically relevant differences between individuals pointing to the presence of meaningful subtypes within this general depressed-anxiety condition.

However, the use of lifetime symptoms in this study has several implications that affect the interpretation of these findings. The key problem is that we are unable to separate out shared symptoms patterns that are due to a longitudinal relationship between these disorders from those that are due to a simultaneous, co-occurring relationship. This is a particularly important problem when examining anxiety and depression because there is evidence that anxiety symptoms precede and are a causal factor in the development of depression (Merikangas et al, 2003). The inability to separate sequential depression and anxiety symptom patterns from simultaneous patterns means that longitudinal relationships and simultaneous co-occurring relationships between MDD and GAD are confounded in this analysis. Furthermore, the use of lifetime symptoms compounds well known problems with the recall of symptoms and may over represent the level of co-occurrence of symptoms (Kraemer et al, 2006). Additional limitations include the confounding of mental health and substance abuse service utilization on several service use variables, such as seeing providers, and the change in the diagnostic criteria between the DSM III-R and DSM IV.

While the use of lifetime symptoms has some potential to obscure the interpretation of these findings, there are several interesting results to consider, particularly in regard to the types of heterogeneity identified by the latent class analysis. The kind of heterogeneity most useful in differentiating between classes was the distinction between psychological and somatic symptoms of both depression and generalized anxiety. For example Class 6 (Somatic Depressed-Anxiety) and Class 7 (Restless Somatic Depression) had high rates of endorsement for all studied symptoms. However, Class 6 members had more prominent somatic anxiety symptoms, such as dry mouth and stomach problems, while Class 7 members had more prominent psychological depression symptoms, such as psychomotor retardation and lack of energy. The same distinction appears at the lower level of severity with Class 2 (Mild Psychological Depression) having low levels of somatic depression and anxiety symptoms such as psychomotor retardation and dry mouth, while having higher rates of psychological depression symptoms, such as feelings of worthlessness. This distinction is consistent with both the Liability-Spectrum Model and the Tripartite Model that separate psychologically

oriented depression and generalized anxiety from the more somatically based phobias and panic disorder. However, the evidence here suggests that there is considerable overlap across these dimensions within comorbid MDD and GAD.

There are several other meaningful kinds of heterogeneity between the classes. The most obvious is severity. Class 1 (Low Distress) has very little indication of clinical stress while Class 7 has rather severe clinical distress. The inclusion of individuals with no diagnoses allowed for the assessment of severity below the diagnostic cut-offs for MDD and GAD. For example Class 4 (Psychological Anxious-Depression) displayed moderate levels of clinical severity with 13% of individuals in this class reporting a suicide attempt; however 20% of these individuals did not receive a diagnosis of either MDD or GAD. Likewise, while Classes 5, 6, and 7 displayed high levels of comorbid MDD and GAD, approximately half of the respondents in these classes were diagnosed with only one of these disorders but had disability and distress levels similar to those with comorbid diagnoses. While not conclusive, this evidence does suggest that some individuals who do not meet the diagnostic criteria for either MDD or GAD still do have clinically meaningful conditions when the symptoms of the disorders are combined. Other important distinctions are consistent with the previous literature on subtypes of depression and anxiety. For example Class 5 (Anxious-Misery) had prominent features of atypical depression. Class 2 (Mild Psychological Depression) displayed low levels of MDD and even lower levels of GAD but did have the highest rates of substance abuse. These heterogeneities provide interesting avenues for future research, replicating them and determining consequences.

The Relevance of Symptom-Based Analysis

For purposes of analysis, starting from symptoms rather than diagnostic categories allows for assessment of sub-threshold conditions and assessment of heterogeneity within diagnostic categories. The evidence presented here provides support for the idea that using symptom based empirically derived classes as a unit of analysis can produce a more nuanced accounting of comorbidity between depression and generalized anxiety. Comparing classes derived from present data with DSM-based MDD and GAD categories, and other DSM categories, allows for assessment of whether employing empirically-derived classes enjoys any substantive advantage over employing DSM categories. This framework is generalizable to many other questions in psychiatric nosology where the validity of diagnostic categories or algorithms is in question. In particular symptom-based analysis allows for the assessment of strengths and weaknesses of the current diagnostic structure (Pickles et al, 2003).

While symptoms-based analysis is important, these results suggest that symptoms alone do not exhaust useful information contained in diagnostic categories. Diagnostic categorization relies on information not used in latent class analysis such as symptom count cutoffs and duration of symptoms. Thus, data analytic results indicated that for key clinical indicators, such as psychiatric hospitalization and suicide attempts, the latent class categorization did not capture all the predictive power of the diagnostic categories. These are clinically and socially serious events, and these results suggest that the current diagnostic categories provide valuable information beyond that contained in symptoms alone. However, diagnostic categorization provides no additional information for prediction of other outcomes, such as perceived mental health, after accounting for latent class membership, suggesting that symptoms play a strong role in individuals' understanding of their own mental health.

The evidence presented here suggests that comorbid MDD and GAD do not spring from separate, unitary phenomenon but rather constitute a heterogeneous collection of clinically meaningful classes including somatic and psychological depression and somatic and psychological anxiety. Future research should examine these subtypes in more detail and separate out the longitudinal associations between these disorders from their simultaneous

presentation. From a clinical perspective, this evidence suggests that comorbidity should not be viewed as a unitary phenomenon but rather that individuals with similar diagnoses may have significant differences in clinical severity based on the particulars of their presentation.

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Table 1

MDD and GAD Diagnostic Symptoms

<u>DSM IV Depression Symptoms</u>	
1	Depressed Mood
2	Lack of Interest in things
3	Decreased appetite and weight
4	Decreased sleep
5	Increased appetite and weight
6	Increased sleep
7	Psychomotor Retardation
8	Psychomotor Agitation
9	Lack of Energy
10	Feelings of Worthlessness
11	Lack of Concentration
12	Thoughts of Death
<u>DSM IV Anxiety Symptoms</u>	
13.	Feeling Restless
14.	Feeling Fatigued
15.	Feeling Irritable
16.	Decreased Concentration
17.	Muscle Tension
18.	Problems Sleeping
<u>Somatic Anxiety Symptoms</u>	
19.	Feeling Dizzy or Faint
20.	Excessive Sweating
21.	Stomach or Digestive Problems
22.	Dry Mouth or Difficulty Swallowing
23.	Racing Heart

Table 2

Bayesian Information Criterion Fit Statistics

Number of Class	BIC Statistic
2	24248.22
3	23935.06
4	23693.15
5	23667.03
6	23653.37
7	23648.82
8	23694.85
9	23723.81
10	23787.13

Table 3

Classes and Rates of Symptom Endorsement

Study Sample	Class 1		Class 2		Class 3		Class 4		Class 5		Class 6		Class 7	
	Low Distress	Mild Psychological Depression	Mild Somatic Anxiety	Psychological Anxious-Depression	Anxious - Misery	Somatic Depressed-Anxiety	Restless Somatic Depression							
Percent of Sample	11%	11%	19%	22%	6%	15%	16%							
N	108	113	191	222	60	152	162							
Depressed mood	86.90%	99.70%	92.70%	98.10%	88.30%	98.90%	99.50%							
Lack of Interest	0.00%	35.20%	9.00%	50.30%	97.10%	68.80%	88.20%							
Decreased Appetite/Weight	0.00%	32.10%	13.60%	54.20%	20.10%	86.80%	63.20%							
Increased Appetite/Weight	0.00%	9.00%	9.30%	18.10%	43.80%	4.50%	56.60%							
Decreased Sleep (D)	6.20%	45.20%	54.70%	89.10%	31.50%	97.20%	98.40%							
Increased Sleep	1.70%	17.50%	0.80%	18.20%	51.60%	14.90%	33.90%							
Psychomotor Retardation	0.00%	0.30%	4.10%	21.60%	11.90%	23.80%	80.40%							
Psychomotor Agitation	0.00%	3.10%	3.90%	27.70%	7.80%	32.40%	48.20%							
Lack of Energy	22.80%	71.40%	67.40%	88.80%	93.10%	92.30%	100.00%							
Feelings of Worthlessness	11.70%	85.80%	62.30%	68.70%	93.80%	81.90%	91.60%							
Decreased Concentration (D)	3.70%	50.00%	32.60%	76.70%	79.00%	91.50%	98.10%							
Thoughts of Death	6.50%	39.00%	24.80%	55.00%	85.10%	75.30%	74.60%							
Feeling Restless	55.10%	62.40%	98.20%	98.70%	100.00%	99.80%	100.00%							
Feeling Fatigued (A)	24.60%	25.80%	65.20%	67.70%	96.40%	78.20%	96.90%							
Decreased Concentration (A)	72.80%	59.10%	85.90%	91.50%	96.40%	99.60%	100.00%							
Feeling Irritable	35.60%	57.90%	71.30%	70.50%	89.80%	82.30%	88.20%							
Muscle Tension	18.50%	3.60%	52.80%	39.20%	43.30%	72.20%	72.90%							
Decreased Sleep (A)	38.40%	40.40%	76.00%	92.40%	42.70%	94.80%	97.20%							
Feeling Dizzy	6.60%	3.00%	50.30%	17.00%	51.40%	82.60%	62.80%							
Excessive Sweating	6.00%	3.40%	59.80%	12.50%	59.40%	88.70%	65.70%							
Stomach Problems	55.11%	19.90%	60.50%	41.70%	69.20%	95.90%	79.50%							
Dry Mouth	40.41%	11.90%	58.50%	10.70%	68.50%	98.80%	43.50%							
Racing Heart	69.23%	32.70%	85.80%	62.90%	75.10%	95.90%	89.90%							

Table 4

Demographics Differences Across Classes

	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7	
Education +	Study Sample	Low Distress	Mild Psychological Depression	Mild Somatic Anxiety	Psychological Anxious-Depression	Anxious - Misery	Somatic Depressed-Anxiety	Restless Somatic Depression
Less than HS	15.96	7.81%	8.89%	21.92%	13.79%	16.99%	14.78%	22.54%
High School	37.79	48.41%	35.28%	36.88%	32.60%	44.25%	38.67%	37.73%
Some College	24.24	16.98%	23.09%	16.99%	28.83%	16.45%	31.92%	27.42%
College Grad	22.01	26.80%	32.74%	24.21%	24.78%	22.31%	14.63%	12.31%
Income*								
0-20000	29.53	23.48%	36.56%	30.56%	22.94%	27.00%	41.75%	26.62%
21000-34000	23.76	15.31%	23.31%	23.65%	20.95%	34.45%	20.16%	33.00%
35000-69000	34.98	43.88%	26.13%	33.13%	47.83%	27.54%	25.27%	30.68%
70000+	11.73	17.34%	14.00%	12.66%	8.27%	11.01%	12.82%	9.70%
Ethnicity (ns)								
White	83.48	82.32%	89.02%	85.79%	79.44%	85.76%	82.39%	83.83%
Black	6.28	5.35%	2.90%	9.49%	8.07%	0.00%	6.72%	4.65%
Hispanic	6.78	5.48%	6.98%	2.34%	6.74%	12.47%	9.47%	8.16%
Other	3.46	6.86%	1.09%	2.38%	5.74%	1.77%	1.41%	3.35%
Gender****								
Male	38.88	56.43%	64.86%	37.52%	40.41%	20.49%	29.43%	25.89%
Female	61.12	43.57%	35.14%	62.48%	59.59%	79.51%	70.57%	74.11%
Marital Status**								
Married	64.95	67.79%	52.84%	75.81%	65.27%	72.62%	63.22%	56.48%
Sep. Widow, Div	21.12	15.17%	19.71%	16.56%	21.59%	11.15%	29.56%	26.39%
Never Married	13.92	17.03%	27.45%	7.63%	13.14%	16.23%	7.22%	17.13%
Mean Age +	37.7	37.50	36.47	39.28	37.36	37.05	38.67	35.70
	(10.95)	7.93	10.32	8.47	8.82	9.62	9.30	9.52

**** p< 0.0001

** p< 0.01

* $p < 0.05$

+ $p < 0.10$ (ns) not significant

Table 5

Diagnoses and Classes

	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7
	Study Sample	Mild Psychological Depression	Mild Somatic Anxiety	Psychological Anxious-Depression	Anxious - Misery	Somatic Depressed-Anxiety	Restless Somatic Depression
	Low Distress						
MDD Only	28.15% ^{***}	29.45%	4.89%	46.91%	40.71%	33.61%	36.60%
GAD Only	14.19% ^{***}	3.93%	38.68%	8.09%	7.21%	14.99%	0.00%
Co-morbid MDD/GAD	26.49% ^{***}	0.00%	4.04%	25.20%	45.82%	46.09%	63.40%
Neither	31.17% ^{***}	66.63%	52.39%	19.80%	6.26%	5.32%	0.00%
Alcohol Disorder (ns)	33.64%	45.34%	28.06%	31.43%	24.19%	41.09%	33.16%
Drug Disorder(ns)r	20.41%	25.78%	15.44%	18.52%	17.02%	30.25%	22.17%
Dysthymia	31.55% ^{***}	28.80%	22.95%	30.13%	59.10%	36.87%	50.75%
Bipolar	6.51% ^{***}	1.32%	1.67%	7.37%	5.25%	10.97%	14.80%
Social Phobia	23.64% ^{***}	12.89%	25.75%	11.04%	26.98%	40.23%	37.53%
Simple Phobia	23.38% ^{***}	12.93%	19.51%	19.85%	22.33%	38.47%	40.03%
Panic Disorder	13.37% ^{***}	4.42%	14.14%	3.96%	13.99%	28.56%	23.95%
Psychotic Disorder(ns)	2.41%	1.44%	0.00%	3.25%	0.00%	3.85%	5.78%
PTSD	17.1% ^{**}	5.29%	10.39%	15.09%	8.30%	28.40%	30.49%
Mean (SD) # of Diagnoses other than MDD GAD	1.68 (1.93)	1.38 (1.20)	1.43 (1.29)	1.29 (1.37)	1.87 (1.34)	2.58 (2.00)	2.50 (1.86)

*** p< 0.001

** p< 0.01

* p< 0.05 (ns) not significant

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⁺ p<0.10 (ns) not significant

