Insight into the heterogeneity of depressive disorders

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2012

document version
Publisher's PDF, also known as Version of record

Chapter 10

An examination of Generalized Anxiety Disorder and Dysthymic Disorder by Latent Class Analysis

ABSTRACT

Background The nosological status of Generalized Anxiety Disorder (GAD) versus Dysthymic Disorder has been questioned. The aim of this study is to examine qualitative differences within GAD and Dysthymic Disorder symptomatology.

Method Latent Class Analysis was applied to anxious and depressive symptomatology of respondents from three population based studies (National Study of Mental Health and Well-Being-2007, National Comorbidity Study-Replication and NEMESIS-2) (Triple-study) and respondents from a multi-site naturalistic cohort (Netherlands Study of Depression and Anxiety (NESDA)). Socio-demographics and clinical characteristics of each class were examined.

Results A three-class (Triple-study) and two-class (NESDA) model best fitted the data, reflecting mainly different levels of severity of symptoms. In the Triple-study, no division into a predominantly GAD or Dysthymic Disorder comorbidity subtype emerged. Likewise, in spite of the presence of pure GAD and Dysthymic Disorder cases in the NESDA-sample, LCA did not identify specific anxiety or depressive profiles in the NESDA-study. Next, socio-demographics and clinical characteristics of each class were examined. Classes only differed in levels of severity.

Conclusions The absence of qualitative differences in anxious or depressive symptomatology in empirically derived classes questions the differentiation between GAD and Dysthymic Disorder.

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INTRODUCTION

Once subsumed under the general category of neurosis, in 1980 Generalized Anxiety Disorder (GAD) and Dysthymic Disorder were separated into two different disorders in DSM-III. It was decided that GAD belonged to the anxiety disorders, whereas Dysthymic Disorder was part of the depressive disorders. Ever since, the nosological status of both GAD and Dysthymic Disorder has been topic of debate (Andrews at al., 2002; Beesdo et al., 2010; Kendler et al., 1996; Kessler, 2000). Andrews et al. (2002) found that the associations between GAD and Dysthymic Disorder (odds ratio (OR) 12.6) were similar in magnitude to the ORs within diagnostic groupings, such as between panic and social phobia (OR 8.6). In addition, in clinical practice, both disorders can be treated in an effective manner using cognitive behavioural therapy (CBT) and anti-depressant medication. In fact, transdiagnostic therapies have demonstrated recently that both GAD and depressive disorders may be treated with a common CBT protocol (Titov et al., 2011).

Given the strong relationship between the two disorders and the observation that these two disorders co-occur more often than not (Hidalgo and Sheehan, 2012; Judd et al., 1998; Kessler et al., 2005; Lamers et al., 2011; Simon, 2009), and considering that comorbidity is associated with a greater level of distress and impairment in comparison to experiencing one of the disorders alone (Hidalgo and Sheehan, 2012; Simon, 2009; Kessler et al., 2002), it is imperative that researchers and clinicians gain a greater understanding of how these two disorders occur and present in the general population. This could lead to improvements in tailored treatments and prevention, and could provide knowledge on the nosological confusion that surrounds both disorders. Despite this, there is little known about the presence of specific sub-types or sub-groups of people with differing GAD and Dysthymic Disorder symptom profiles. The polythetic nature of the DSM symptom criteria enables people within the population who present with symptoms of both GAD and Dysthymic Disorder to experience a different level and various types of GAD and Dysthymic Disorder comorbidity. For example, it is possible that a group of people experiences predominately GAD symptoms with some Dysthymic Disorder symptoms, another group experiences predominately Dysthymic Disorder symptoms with some GAD symptoms, another group experiences GAD and Dysthymic Disorder symptoms equally, while other groups could experience another combination of the two disorders symptoms.

To examine the presence of various subtypes or subgroups of GAD and Dysthymic Disorder comorbidity, the current study aims to use Latent Class Analysis (LCA) on a group of people at higher risk of experiencing GAD and Dysthymic Disorder symptoms using three general population based surveys from three different countries. We attempt to further support the findings from the general population surveys using a more clinical-based survey, the Netherlands Study of Depression and Anxiety (NESDA). Finally, we examine socio-demographics, comorbidity and clinical characteristics of the identified classes to see

whether the identified classes differ. The main goal of our study is to examine whether there are qualitative differences in GAD and Dysthymic Disorder symptomatology.

METHODS

Study sample

Data were derived from three general population studies, namely i) the National Survey of Mental Health and Wellbeing-2007 (NSMHWB-2007), Australia, ii) the National Comorbidity Survey-Replication study (NCS-R), the United States of America and iii) the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), henceforth called the Triple-study. Analyses were repeated with data from NESDA, a study among the general population, general practices, and mental health organizations.

The NSMHWB-2007 is a nationwide household survey of adults (aged 16 to 85 years). The survey was conducted in 2007 by the Australian Bureau of Statistics (ABS), under the Census and Statistics Act, 1905. Respondents were selected at random from a stratified, multistage area probability sample of private dwellings. The total sample consisted of 8841 respondents (response rate: 60%). Written informed consent was obtained. The method of recruitment and data collection was extensively described elsewhere (Slade et al., 2009). The NCS-R is a nationally representative household survey of adults (aged 18 years and older) in the United States. The respondents were selected from a multistage clustered area probability sample of households. The total sample consisted of 9282 persons for diagnostics assessment (response rate: 71%). Verbal informed consent was obtained. Procedures were approved by the Human Subjects Committees of both Harvard Medical School (Boston, MA) and the University of Michigan. The method of recruitment and data collection was extensively described elsewhere (Kessler et al., 2004). With the courtesy of the NCS-R, we downloaded the public use version of NCS-R data-part 1 (http://www.icpsr.umich.edu/CPES). NEMESIS-2 is a naturalistic, prospective, epidemiological cohort survey among the general adult population (aged 18 to 64 years). The sampling procedure consisted of a multistage, stratified, random sample. Procedures were approved by an ethics committee and written informed consent was obtained. The total sample consisted of 6646 persons (response rate: 65%). The method of recruitment and data collection was extensively described elsewhere (De Graaf et al., 2010). Finally, NESDA is a multi-site naturalistic cohort study of adults (aged 18-65 years) recruited from the general population, general practices, and mental health organizations. The total sample consisted of 2981 persons. The study protocol was approved by the Ethical Review Board of the VU University Medical Center and written informed consent was obtained. The method of recruitment was extensively described elsewhere (Penninx et al., 2008).

The surveys of the Triple-study employed the Composite International Diagnostic Interview (CIDI), version 3.0, which was developed by the World Health Organization (WHO)-World

Mental Health (WMH) Survey Initiative (Kessler and Ustün, 2004), generating diagnoses according to DSM-IV (APA, 2001) criteria. NESDA employed CIDI version 2.1, also generating DSM-IV diagnoses. Clinical calibration studies conducted in various countries have found that CIDI 3.0 (Haro et al., 2006) and earlier versions (Andrews and Peters, 1998; Wittchen, 1994) assess anxiety and mood disorders with generally good validity compared to blinded clinical reappraisal interviews (Haro et al., 2006; Andrews and Peters, 1998; Wittchen, 1994).

CIDI 3.0 starts with a screening section with key questions for most disorders. Participants responding affirmatively to a key question were administered the CIDI section of the disorder involved. For the Triple-study, we selected and combined adults (aged 18 years and older) from the three surveys who answered positively on the CIDI 3.0 screening questions for both GAD and Dysthymic Disorder (NSMHWB-2007: n=207, NCS-R: n=264, NEMESIS-2: n=125), irrespective of whether they fulfilled the criteria for CIDI diagnoses of GAD and/or Dysthymic Disorder or not. In NESDA, measures of anxiety, worry and depression, other than CIDI-derived items, were available for all respondents. Hence, analyses did not necessarily rely on CIDI-derived items, thus enabling inclusion of pure GAD and Dysthymic Disorder. For the NESDA-study, we selected adults (aged 18 years and older) with a CIDI 6-month GAD (n=464) and/or a 6-month Dysthymic Disorder (n=305) (Total n=630) from the baseline measurement. Six-month prevalence rates were chosen to select persons with current pathology, because 1-month prevalence rates did not yield a sufficient numbers of persons. Organic exclusion rules were used in making diagnoses, but hierarchical exclusion criteria, as applied by the CIDI were ignored, thus allowing for the examination of comorbidity.

Symptoms of depression and anxiety

For the Triple-study, a total of 12 CIDI lifetime symptoms were used in the LCA, consisting of six symptoms of GAD and six symptoms of Dysthymic Disorder. The screening items for GAD and Dysthymic Disorder were not included in the LCA because, due to our selection strategy, all respondents endorsed the lifetime screening questions of GAD and Dysthymic Disorder. The final items consisted of the depressive symptoms of changes in weight or appetite, sleep disturbance, low energy, low self-esteem, poor concentration, hopelessness, and anxiety symptoms of feeling restless/keyed up, fatigue, irritable, poor concentration, feeling tense, and sleep disturbance.

For the NESDA-study, we used symptoms of anxiety and/or worry and/or depression as indicator variables in LCA, assessed by the 21-item Beck Anxiety Inventory (BAI)(Beck et al., 1988), the 11-item Penn State Worry Index (PSWQ) (Meyer et al., 1990) and the 16-item Quick-Inventory of Depressive Symptomatology – Self report version (QIDS-Depressive Symptomatology – Self report version (QIDS-SR, www.ids-qids-org) (Rush et al., 1986, 1996), respectively. The BAI was designed to measure general anxiety during the last week prior to assessment. Its reliability and validity have previously been demonstrated (Beck et al., 1988).

The 11-item Penn–State Worry Index was designed to measure the extent to which persons worry frequently and extensively (Meyer et al., 1990). No particular time frame was applied. It was found not to correlate with other measures of anxiety or depression, indicating that it is tapping an independent construct (Meyer et al., 1990; Chelminski and Zimmerman, 2003). Its reliability and validity have previously been demonstrated (Meyer et al., 1990). The QIDS-SR was designed to assess the severity of depressive symptoms during the last week prior to assessment and proved to be a valid and reliable instrument for the self-report of depressive symptoms (Rush et al., 1986). In order to reduce the total number of items involved as well as to avoid interdependence of items, we reduced the 21-item BAI to four previously identified factors (Beck and Steer, 1990; Osman et al., 1997), namely neurophysiological symptoms, panic symptoms, subjective anxiety symptoms and autonomous symptoms. Likewise, we reduced the 16-item QIDS to 9 items, according to the scoring-guidelines (www.ids-qids-org) by combining several items. The final (aggregated) items of the QIDS consisted of sleep, depressed mood, weight, concentration, negative self-view, suicidal ideation, anhedonia, fatigue, and psychomotor changes. All items, derived from BAI, PSWQ and QIDS were dichotomized into 0= absence of symptoms, versus 1= presence of a symptom. Eleven persons had missing values on all three parameters used for the LCA and were excluded from the LCA.

Characteristics

We examined the distribution of various characteristics across the identified classes. Due to differences in methodology and design in the three national surveys, only a limited number of characteristics could be examined in the Triple-study, consisting of gender, age and variables derived from the CIDI diagnostic interview (12-month diagnosis of GAD +/ Dysthymic Disorder +/ Major Depressive Disorder (MDD), comorbid 12-month anxiety disorders, number of depressive, dysthymic and GAD symptoms and age at onset of depression or anxiety). Age was included as a continuous variable. Comorbid anxiety disorders included a 12-month diagnosis of Panic Disorder (with or without Agoraphobia); Agoraphobia without history of Panic Disorder; and Social Phobia. For age at onset, earliest age was used for those with comorbid disorders.

In NESDA, we were able to examine the distribution of some additional characteristics across the identified classes. Characteristics included gender, age, level of education, 12-month diagnosis of GAD +/Dysthymic Disorder +/MDD, comorbid anxiety disorders, severity of anxiety, worry and depression, age at onset, presence of a family member with depression, number of somatic illnesses, level of functioning and level of neuroticism and extraversion. Age was included as a continuous variable. Level of education was measured by years of education. In accordance with the Triple-study, 12-month diagnoses of GAD +/Dysthymic Disorder +/ MDD, comorbid 12-month anxiety disorder, number of depressive, dysthymic and GAD symptoms and age at onset were assessed by the CIDI. As a measure of

severity of anxiety, worry and depression, we computed the total scores of the 21-item BAI (Beck et al., 1988), the 11-item PSWQ (Meyer et al., 1990) and the 9-item QIDS (http://www.ids.qids.org) (Rush et al., 1986, 1996), respectively. The presence of a depressive disorder in first degree family members was assessed using the family tree method (Fyer and Weissman, 1999). The presence of somatic conditions was examined by counting the number of somatic diseases (including cardiovascular disease, diabetes, lung disease, osteoarthritis, cancer, gastrointestinal disease, liver disease, epilepsy, thyroid disease) for which one receives medical treatment, at the moment of the interview. The level of functioning was measured by total scores on the 36-item WHO Disability Assessment Schedule II (WHO-DAS II) (Chwastiak and Von Korff, 2003). The WHO-DAS II queries difficulties in various domains of life during the last 30 days. We computed total scores based on five domains of the WHO-DAS II (cognition, mobility, self-care, interpersonal interactions, and participation in society). Neuroticism and extraversion were assessed by means of the neuroticism and extraversion dimensions of the NEO personality questionnaire, a 60-item questionnaire measuring five personality domains (Costa and McCrae, 1995).

Statistical analyses

To investigate the presence or absence of distinct classes among persons with anxious and depressive symptomatology, we performed Latent Class Analysis (LCA). Free from any a priori assumptions, data-driven techniques such as LCA that cluster persons based on a given outcome, may result in an empirically based classification, which can then be compared with the DSM-IV-TR classification. LCA, often described as a 'categorical equivalent' of factor analysis, assumes that an unobserved, latent categorical variable explains the association among a set of observed symptoms. It starts with one class, suggesting one classification fitting for all persons. Then successively more classes are added to determine the best-fitting model. Since LCAs and other mixture models are susceptible to converging on local, rather than global solutions (Nylund et al., 2007), we increased the number of random starting values when necessary to avoid local solutions. The LCAs were conducted using M-plus version 5 (Muthén and Muthén, 2007).

To determine which model best fitted the data, we examined the Bayesian Information Criterion (BIC), sample size adjusted BIC (ssaBIC), entropy, the Lo-Mendell-Rubin likelihood ratio test (LMR), the proportion of respondents in each class, and the interpretability and clinical relevance of the latent classes. Of the traditionally used Information Criterions, such as Akaike's Information Criterion (AIC) and BIC, the BIC performs best (Nylund et al., 2007). The accuracy of the AIC decreases as the sample size increases, since there is no adjustment for sample size (Nylund et al., 2007). Lower BIC and ssaBIC values indicate better model fit. The Lo-Mendell-Rubin test (LMR) provides a p-value, which indicates whether the *k*-1 class model is rejected in favor of the *k* class model. Entropy, as a measure of the quality of classification, is presented for models with more than one class. Values for entropy can

range between 0 and 1 with values closer to 1 indicating greater classification accuracy. Finally, the proportions of individuals in each class are presented. In order to identify clinically relevant classes, we aim to identify classes greater than five percent of the sample. Currently there is no consensus on which criterion best identifies the best fitting number of classes.

After the identification of the classes, persons were assigned to their most likely class based on model probabilities. Then, we examined the identified classes by testing the distribution of putative validators across the identified classes using two-tailed chi-square statistics for categorical variables and one-way-analysis of variance statistics (ANOVA) for continuous variables. Additional pairwise comparisons were performed to test for differences between pairs of classes. All comparisons were conducted using SPSS (version 15) (SPSS, 2006).

RESULTS

Table 1 displays the characteristics of the four surveys that contributed to the current study. The surveys that contributed to the Triple-study were similar in age and gender distribution, while persons in the NESDA study were slightly older. Diagnostic differences between the Triple-study and NESDA reflect differences in selection strategies. Whereas in the Triple-study a small number of persons did not have a lifetime diagnosis of GAD, Dysthymic Disorder or MDD, in the NESDA study all persons had at least one lifetime diagnosis, reflecting the inclusion criteria of a 6-month diagnosis of GAD and/or Dysthymic Disorder. Likewise, persons with MDD only were absent in NESDA. Furthermore, it is noteworthy, that in all surveys around 85% of the persons had a (comorbid) MDD, illustrating the high comorbidity rates between GAD and/or Dysthymic Disorder and MDD.

Table 1. Characteristics of the study population of Triple-study (n=596) and NESDA-study (n=630).

	NSMHWB	NCS-R	NEMESIS-2	Overall statistics (Triple-study)	NESDA
	n=207 (34.7%)	n=264 (44.3%)	n=125 (21.0%)	X^2 /F (df) p-value	n=630 (100%)
Socio-demographics					
Female (n, %)	130 (62.8)	183 (69.3)	87 (69.6)	2.7 (2) 0.3	407 (64.6)
Age, mean (±SD)	46.8 (14.6)	44.4 1(3.3)	45.8 (11.8)	1.8 (2) 0.2	41.9 (12.0)
Lifetime DSM-IV diagnosis (mutually exclusive)					
No diagnosis of GAD/Dysthmia/MDD (n, %)	2 (1.0)	11 (4.2)	1 (0.8)		0
Dysthymia only (n, %)	6 (2.9)	8 (3.0)	4 (3.2)		21 (3.3)
GAD only (n, %)	0	0	9 (7.2)	75.2 (14)	57 (9.0)
MDD only (n, %)	4 (1.9)	5 (1.9)	0	<.001	0
Dysthymia and GAD (n, %)	10 (4.8)	9 (3.4)	2 (1.6)		11 (1.7)
GAD and MDD (n, %)	0	0	5 (4.0)		208 (33.0)
Dysthymia and MDD (n, %)	37 (17.9)	78 (29.5)	34 (27.2)		121 (19.2)
Dysthymia, GAD and MDD (n, %)	148 (71.5)	153 (58.0)	70 (56.0)		212 (33.7)

Table 2. Parameters of fit of Latent Class Analysis

Class	Maximum Likelihood	BIC *	ssaBIC *	Entropy	Lo-Mendell-Rubin		Proportion of individuals in class			
					2LL*	P	1	2	3	4
Triple-study										
2	-3019.0	6197.8	6118.4	0.69	312.1	0.003	0.77	0.23		
3	**-2973.7**	**6190.3**	**6069.6**	**0.69**	**90.6**	**0.03**	**0.62**	**0.33**	**0.04**	
4	-2952.3	6230.5	6068.6	0.70	42.9	0.70	0.54	0.34	0.08	0.05
NESDA-study										
2	**-3475.1**	**7267.2**	**7111.7**	**0.86**	**691.6**	**<.001**	**0.81**	**0.19**		
3	-3405.4	7286.5	7051.5	0.87	141.5	0.14	0.16	0.78	0.06	
4	-3358.5	7353.5	7039.2	0.76	93.7	0.005	0.33	0.06	0.10	0.51

* Abbreviations: BIC= Bayesian Information Criterion; ssaBIC= sample size adjusted Bayesian Information Criterion; 2LL= 2 log likelihood; p=p-value

In Table 2 the maximum likelihood values, BIC, ssaBIC, entropy, LMR-likelihood ratio tests and the proportion of individuals in each class of each LCA model for both the Triple-study and the NESDA-study are presented. In the Triple-study, the 3-class model provided the best fit for the observed data. However, class 3 consisted of only 4.4% of the respondents. Previously, it was noted that small classes (prevalence less than 5% of the sample) are considered spurious classes, a condition often associated with extracting too many classes (Hipp and Bauer, 2006). However, since all parameters for fit consistently pointed at the 3-class model, we decided that this model best fitted the data. Figure 1 shows the probability of endorsement per item of the three identified latent classes in the Triple-study. The first

class was labeled 'severe' (prevalence 62.2%) and was characterized by high endorsement of both depressive and anxiety items. The second class was labeled 'moderate' (prevalence 33.4%) and showed a high endorsement of both depressive and anxiety items, albeit of lesser magnitude than class 1. The third class was labeled 'pure dysthymic' (prevalence 4.4%) and showed a low endorsement of GAD symptoms with moderate endorsement of depressive symptoms, indicating a "pure" dysthymic profile. In the NESDA-study, the parameters were best for the 2-class model (BIC, LMR-test), although ssaBIC continued to decrease across higher class models. The probabilities of endorsement per item are displayed in Figure 2. The first class was labeled 'severe' (prevalence 80.6%) and was characterized by high endorsement of both depressive and anxiety items. The second class was labeled 'moderate' (prevalence 19.4%) and also showed a high endorsement of anxiety and worry items, albeit of a slightly lower magnitude, and a lower endorsement of depressive symptoms than class 1.

Figure 1. Probability of symptom endorsement per class- Triple study.

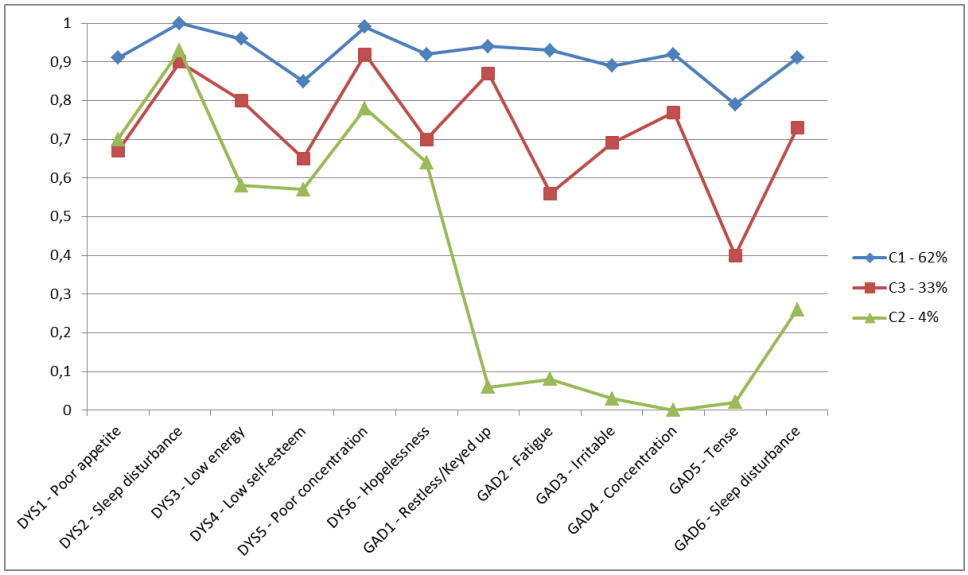
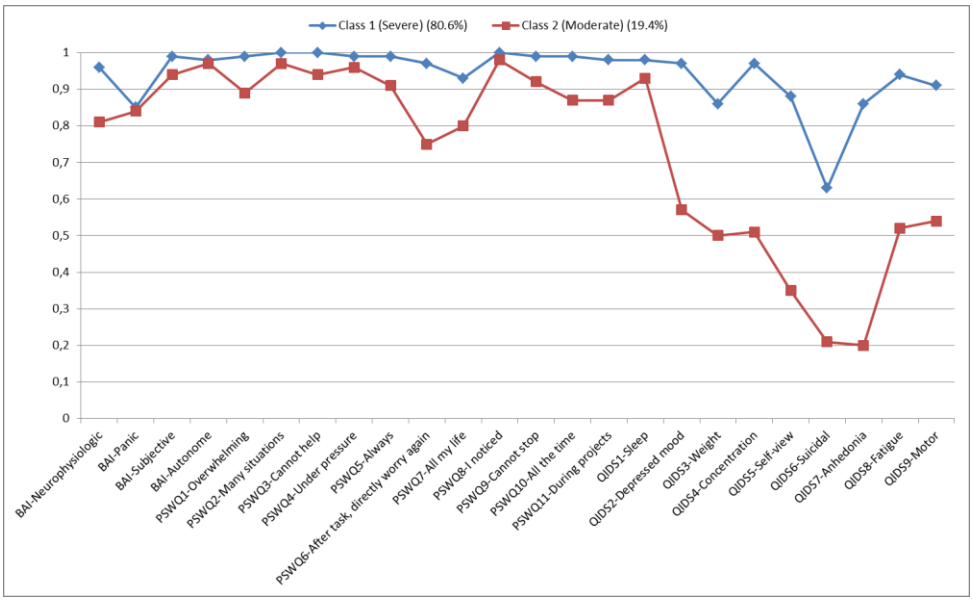


Figure 2. Probability of symptom endorsement per class- NESDA-study.



Next, we examined the distribution of socio-demographics, DSM-IV diagnoses, and clinical characteristics across the three identified latent classes (n=596) in the Triple-study (Table 3). The severe class was characterized by a younger age and a preponderance of females. Considering DSM-IV diagnoses, the classes were not characterized by a clear GAD nor dysthymic profile, rather classes were characterized by level of comorbidity rates. There was a preponderance of pure disorders in the moderate and 'pure dysthymic' class, whereas the prevalence of comorbid disorders was highest in the severe class. Triple comorbidity (GAD, Dysthymic Disorder and MDD) was highest in the severe class, as compared to the other classes. The 'pure dysthymic' class showed lowest comorbidity rates, with absence of comorbidity of 'GAD with any mood disorder'. Next, there was a gradual decrease of comorbid anxiety disorders and number of depressive, dysthymic and GAD symptoms across the classes, with highest prevalence rates and highest symptom endorsement in the severe class (class 1) and lowest in the 'pure dysthymic' class (class 3). In particular, the 'pure dysthymic' class distinguished itself by the low endorsement of GAD-symptoms (mean 0.4 ±0.5), as compared to the two other classes.

Table 3. Distribution of characteristics across the identified latent classes in the Triple-study (n=596).

	Class 1	Class 2	Class 3	
Class description	Severe	Moderate	Pure dysthymic	Overall statistics X^2/ F (df) p-value
	n=371 (62.2%)	n=199 (33.4%)	n=26 (4.4%)	
Socio-demographics				
Female (%)	72.2 [a]	58.3 [a]	61.5	11.8 (2) .003
Age, mean (±SD)	44.2 (12.4) [a]	48.0 (14.6) [a]	46.7 (16.9)	5.3 (2) .005
12-month DSM-IV diagnosis (mutually exclusive)				
No 12-month diagnosis of GAD/MDD/Dysthymia (%)	28.6	34.2	53.8	
Dysthymic disorder only (%)	0.5	2.5	11.5	
Generalized Anxiety Disorder only (%)	0.8	2.0	3.8	52.6 (14) <.001
MDD only (%)	5.9	6.5	0	
Comorbid Dysthymia and GAD (%)	0	1.5	0	
Comorbid GAD and MDD (%)	0	0.5	0	
Comorbid Dysthymia and MDD (%)	22.6	23.6	30.8	
Comorbid Dysthymia, GAD and MDD (%)	41.5	29.1	0	
Comorbid 12-month anxiety diagnoses				
Panic Disorder +/- agoraphobia (%)	26.4 [a, b]	12.1 [a]	7.7 [b]	23.4 (2) <.001
Agoraphobia (%)	21.6 [a, b]	12.1 [a]	3.8 [b]	11.6 (2) .003
Social Phobia (%)	40.2 [a]	28.1 [a]	23.1	9.9 (2) .007
Clinical characteristics				
No. depressive symptoms (n=596), mean (±SD)	7.6 (1.3) [a, b]	6.4 (1.7) [a]	6.1 (1.7) [b]	52.3 (2) <.001
No. dysthymic symptoms (n=596), mean (±SD)	5.6 (0.6) [a, b]	4.5 (1.1) [a]	4.2 (1.3) [b]	140.7 (2) <.001
No. GAD symptoms (n=596), mean (±SD)	5.4 (0.7) [a, b]	3.7 (1.0) [a, c]	0.4 (0.5) [b, c]	715.7 (2) <.001
Age of onset of depression (n=534), mean (±SD)	21.9 (12.4)	22.1 (13.8)	16.6 (9.3)	ns
Age of onset dysthymia (n=555), mean (±SD)	25.0 (13.2)	26.5 (14.6)	25.2 (14.5)	ns
Age of onset of GAD (n=404), mean (±SD)	24.6 913.7)	24.4 (14.1)	na	ns

Significant differences per class (p<.05): a= class 1 versus class 2, b= class 1 versus class 3, c= class 2 versus class 3

Table 4. Distribution of characteristics across the identified latent classes in NESDA (n=619).

	Class 1	Class 2	
Class description	Severe	Moderate	Overall statistics X^2/ F (df) p-value
	n=499 (80.6%)	n=120 (19.4%)	
Socio-demographics			
Gender (%)	63.5	68.3	0.98 (1) 0.3
Age, mean (±SD)	42.0	41.9	0.01 (1) 0.9
Years of education, mean (±SD)	11.5	12.5	16.3 (1) <.001
12-month DSM-IV diagnosis (mutually exclusive)			
Dysthymic disorder only (%)	4.0	11.7	59.1 (5) <.001
Generalized Anxiety Disorder only (%)	13.8	38.3	
Comorbid Dysthymia and GAD (%)	1.8	0	
Comorbid GAD and MDD (%)	33.9	28.3	
Comorbid Dysthymia and MDD (%)	23.2	11.7	
Comorbid Dysthymia, GAD and MDD (%)	23.2	10.0	
Comorbid 12-month anxiety diagnoses			
Panic Disorder +/- agoraphobia (%)	43.9	35.0	3.1 (1) 0.08
Agoraphobia (%)	11.2	6.7	2.2 (1) 0.1
Social Phobia (%)	47.9	27.5	16.3 (1) <.001
Clinical characteristics			
Total BAI-score, mean (±SD), n=587	43.1	34.3	65.3 (1) <.001
Total PSWQ-score, mean (±SD), n=511	42.3	35.6	53.3 (1) <.001
Total QIDS-score, mean (±SD), n= 616	14.8	6.8	445.6 (1) <.001
Age of onset of MDD, mean (±SD), n=532	26.7	25.2	1.18 (1) 0.3
Age of onset dysthymia, mean (±SD), n=355	28.9	30.7	0.94 (1) 0.3
Age of onset of GAD, mean (±SD), n=474	29.3	27.8	1.18 (1) 0.3
Positive family history of depression (%)	84.0	79.2	1.6 (1) 0.2
Number of somatic illnesses, mean (±SD)	0.8	0.5	4.86 (1) 0.03
WHO-DAS total score, mean (±SD)	77.7	53.8	148.6 (1) <.001
Neuroticism, mean (±SD)	32.9	27.0	95.2 (1) <.001
Extraversion, mean (±SD)	19.5	23.6	41.4 (1) <.001

Table 4 shows the distribution of characteristics across the two identified latent classes (n=619) in the NESDA study. The classes did not differ on gender and age. Level of education was slightly lower in the severe class as compared to the moderate class. Again, we did not find classes with either greater endorsement of anxiety or depressive symptoms. An equal percentage of persons with pure GAD and persons with pure Dysthymic Disorder were allocated to the severe class (respectively 60.0% and 58.8%) (data not shown). As in the Triple-study, the prevalence of pure disorders was highest in the moderate class, whereas comorbidity rates were highest in the severe class. The severe class was further characterized by higher number of comorbid anxiety disorders, a higher number of anxiety, worry and depressive symptoms, a higher number of somatic illnesses, more functional impairment and a higher level of neuroticism and lower levels of extraversion. Comparisons of age at onset did not yield significantly different results.

DISCUSSION

The aim of this study was to empirically investigate qualitative differences within GAD and Dysthymic Disorder symptomatology. We examined whether LCA would identify subtypes that correspond to different GAD/ Dysthymic Disorder-comorbidity types within three large population-based studies and second, whether LCA would identify profiles with varying levels of anxiety versus depressive symptomatology in persons with pure GAD, pure Dysthymic Disorder and their composite state, participating in NESDA. LCAs were conducted, based on i) CIDI-symptomatology among a large cohort of the general population from three countries (Triple-study) and ii) based on depressive and anxiety symptomatology assessed by the QIDS, PSWQ and BAI in a combined cohort, recruited from the general population, general practices, and mental health organizations in the Netherlands (NESDA-study). We hypothesized that different GAD/Dysthymic Disorder-comorbidity types could be identified, including a group of people experiencing predominately GAD symptoms with some Dysthymic Disorder symptoms, another group experiencing predominately Dysthymic Disorder symptoms with some GAD symptoms, another group experiencing GAD and Dysthymic Disorder symptoms equally, while other groups could experience another combination of the two disorders symptoms. On the other hand, if GAD and Dysthymic Disorder reflect a rather homogeneous group of mildly depressed worriers, no distinct profiles should emerge from LCA. Our findings support the latter. In the Triple-study three classes were identified, a severe (62.2%), moderate (33.4%) and a small class, representing 'pure dysthymic' cases (4.4%) with low endorsement of GAD-symptoms. The clinical relevance of the latter class may be questioned due to the small percentage of the population included within this class in comparison to the remaining classes. The other two classes merely differed in levels of severity, with equal endorsement of GAD and Dysthymic Disorder symptoms, albeit of a different magnitude. In particular, no tendency towards endorsing an anxiety or depressive symptom profile was noted. Next, NESDA involved measurements of anxiety, worry and depression with instruments other than the CIDI, hence, allowing for the inclusion of pure GAD and pure Dysthymic Disorder cases. However, even in this sample with pure diagnoses, no predominantly anxiety versus depression profile could be found. A 2-class model best fitted the data, reflecting similar endorsement of anxiety and worry, but different levels of severity of depressive symptoms. Besides differences in presence of a comorbid MDD and other severity related indicators, such as number of symptoms and comorbid anxiety disorders, no profound differences could be found between the identified classes, except for higher levels of neuroticism and lower levels of extraversion.

Absence of a more anxiety-oriented GAD/Dysthymic Disorder-comorbidity type versus a more depression-oriented GAD/Dysthymic Disorder-comorbidity type in the Triple-study and absence of a clear demarcation of an anxiety versus depressive symptom profiles in empirically derived classes in NESDA fuel the debate on the nosology of DSM-IV categories

of GAD and Dysthymic Disorder. Instead of distinct clinical entities, they seem to represent a group of depressed worriers. However, as Wittchen et al. (1999) noted, at a subthreshold level symptoms are shared to a substantial degree by anxiety and depressive disorders. Hence, the lack of distinct classes in the Triple-study might be an artifact of assessment, i.e. that persons were derived from population based studies with inclusion of subthreshold cases and, hence, milder, and probably more overlapping, symptomatology. However, the results of the multi-site NESDA-study, in which persons fulfilled the criteria of a DSM-diagnosis of GAD and/or Dysthymic Disorder, supported results from the Triple-study.

Previously, the discriminant validity of GAD versus depression was already questioned. It has been recognized that GAD and Dysthymic Disorder are highly prevalent disorders that frequently co-occur, both in clinical and general population samples (Tyrer et al., 2003). In the 1997-NSMHWB 17.7% of persons with 1-month diagnosis of GAD also had a 1-month diagnosis of Dysthymic Disorder (OR 6.8 [95% CI 2.0-23.4]) (Hunt et al., 2002). In NCS-data almost 40% of persons with lifetime GAD had also a Dysthymic Disorder (Wittchen et al., 1994). In an Australian adult twin sample 58% of persons with lifetime GAD had a co-occurring Dysthymic Disorder (Andrews, 1996). In addition, it was argued that GAD has a greater affinity for Dysthymic Disorder, than for anxiety disorders (Krueger, 1999; Vollebergh et al., 2001). Others (Clark et al., 1994) had difficulties differentiating between GAD and Dysthymic Disorder by symptomatology. These findings question the nosological status of GAD versus Dysthymic Disorder.

However, results are inconsistent. Kessler (2000) noted that family studies show distinct aggregation of GAD and depression and environmental determinants of GAD and MDD differ, all supporting the view that GAD and depression are distinct diagnostic entities. To what extent this accounts for GAD and Dysthymic Disorder remains to be settled. Likewise, Beesdo et al. (2010) demonstrated that temporal longitudinal patterns of GAD are more closely related to anxiety disorders than to depressive disorders, suggesting the grouping of GAD with anxiety disorders.

To date, several studies on the structure of psychopathology have been conducted. Two main models elaborate on the position of both GAD and Dysthymic Disorder. First, in the Nottingham Study of Neurotic Disorder, Tyrer et al. (2004) demonstrated the poor temporal stability of GAD, Panic Disorder, MDD and Dysthymic Disorder, conditions, once collectively described as neurotic disorders. They concluded that the outcomes give some support to the notion of the general neurotic syndrome- a coaxial diagnosis of mixed anxiety and depression and personality pathology (Tyrer et al., 2003; 2004). Second, a 2-dimensional structure of internalizing and externalizing disorders was demonstrated (Krueger, 1999; Vollebergh et al., 2001; Olino et al., 2012). In addition, some argued, that internalizing spectrum disorders can be further divided into the subdimensions of *anxious-misery*, consisting of Major Depressive Disorder, Dysthymic Disorder and GAD, and *fear* dimension,

consisting of more specific anxiety disorders (phobic disorders, agoraphobia and panic disorder) (Krueger, 1999; Vollebergh et al., 2001; Olino et al., 2012), although the distinction between the anxious-misery and fear dimensions could not be fully replicated by others (Vaidyanathan et al., 2011). A striking feature of all these data-driven models is the suggestion to aggregate GAD and Dysthymic Disorder.

Considering the putative validators of the identified classes, classes differed on measures of severity, like level of comorbidity, and number of symptoms. Noteworthy are the high levels of neuroticism in the NESDA-study. Previously strong links between neuroticism and both GAD and Dysthymic Disorder have been demonstrated (Kotov et al., 2010; Rosellini and Brown, 2011). Extraversion was inversely related to Dysthymic Disorder (Kotov et al., 2010), but links to GAD were less profound (Rosellini and Brown, 2011). Andrews (1996) previously suggested that a personality vulnerability, being under substantial genetic control, may account for the tendency to experience both disorders. Hettema et al. (2006) also showed the substantial overlap between the genetic factors in neuroticism and those that increase liability across the internalizing disorders.

Strengths and limitations

To our knowledge, this is the first study to empirically examine the nosological status of GAD versus Dysthymic Disorder. Despite the high co-occurrence of GAD and Dysthymic Disorder, and irrespective of their shared historical roots in the concept of neurosis, the majority of studies have focused on the nosological status of GAD versus MDD. The aggregation of three major, general population samples from three different continents enabled us to perform LCA on a sufficient number of participants. Furthermore, NESDA, a multisite cohort, in which a different population- including more severe cases and a higher number of pure diagnoses- was examined and an extensive assessment battery was used, enabled us to perform analyses on a wide range of putative validators. The combination of both the Triple-study and NESDA enabled us to examine the full range of subthreshold to severe cases.

Despite these main advantages, the results of our study should be interpreted in the context of the following limitations. First, in the Triple-study we were not able to include pure cases of GAD and Dysthymic Disorder, since the pure GAD or pure Dysthymic Disorder cases did not endorse both CIDI-entry-questions, resulting in automatically partition of the respondents into either the GAD or Dysthymic Disorder section and, consequently, missing values for LCA. This selection bias may have prevented detection of predominantly anxiety or depressive GAD/Dysthymic Disorder-comorbidity subtypes. Next, LCA assumes the independence of items. Considering the CIDI-items of GAD and Dysthymic Disorder, the high degree of similarity in diagnostic criteria might result in interdependence of items. However, previously, it was demonstrated that the endorsement of CIDI symptoms of MDD were not significantly influenced by the presence of comorbid GAD (Sunderland et al., 2010). Hence,

we assumed sufficient discriminative power to detect possible class differences between GAD and Dysthymic Disorder. Next, the aggregation of data from three different national cohorts contains the risk of introducing bias due to differences in design and methods per survey. This resulted in the availability of only a limited number of putative validators of the identified classes, mainly derived from the CIDI-interview. We cannot exclude the possibility that qualitative differences between the identified classes would emerge under consideration of more or other factors. However, the benefit of aggregation of three community based samples, resulting in sufficient numbers for LCA, outweighs the negatives. Finally, previously the BAI has been disputed for its bias towards measurement of symptoms linked to panic (Cox et al., 1996) and lack of power to discriminate between anxiety and depression (Muntingh et al., 2011), although inconsistent results exist (Beck et al., 1988). To what extent this might have obscured differences between GAD and Dysthymic Disorder remains unclear. However, the ability of the PSWQ to discriminate between GAD and depression has previously been demonstrated (Meyer et al., 1990; Chelminsiki and Zimmerman, 2003), suggesting that the absence of distinct profiles in LCA is not due to insufficient discriminative power of the instruments used.

To conclude, utilizing data from three general populations and an independent cohort study, LCA was able to determine that the majority of persons within the population can be classified as cases that experience prolonged feelings of mildly depressed worry. This finding is of great clinical significance. Prevention and intervention programs should be targeting both depressive and worry symptoms to optimize treatment for persons currently categorized as GAD or Dysthymic Disorder. To this end, the DSM-IV classification system could be revised to better reflect the occurrence of GAD and Dysthymic symptom profiles.

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