

Distinguishing generalized anxiety disorder from major depression: prevalence and impairment from current pure and comorbid disorders in the US and Ontario

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ABSTRACT *Estimation of comparative disease burden in epidemiological surveys is complicated by the fact that high comorbidities exist among many chronic conditions. The easiest way to take comorbidity into consideration is to distinguish between pure and comorbid conditions and to evaluate the incremental effects of comorbid conditions in prediction equations. This approach is illustrated here in an analysis of the effects of pure and comorbid major depression (MD) and generalized anxiety disorder (GAD) on a number of different measures of role impairment in the US National Comorbidity Survey (NCS) and the Mental Health Supplement to the Ontario (Canada) Health Survey (the Supplement). Pure MD and pure GAD were found to have roughly equal independent associations with role impairments. The incremental effects of having comorbid MD and GAD were found to vary depending on the outcome under investigation. The paper closes with a discussion of the methodological complexities associated with generalizing to comorbidities that involve rare conditions or more than two disorders.*

Key words: comorbidity, major depression, generalized anxiety disorder

Background

It is widely known that a number of different physical disorders (Verbrugge and Patrick, 1995; Stewart, Greenfield and Hays, 1989) and mental disorders (Ormel, Von Korff, Üstün, Pini, Korten and Oldehinkel, 1994; Ormel, Kempen, Deeg, Brilman, Van Sonderen and Relyveld, 1998) cause role impairments. Some of these impairments have substantial implications for the economy, such as the \$17 billion average salary-equivalent work absenteeism in the US estimated to be caused by major depression (Greenberg, Stiglin, Finkelstein and Berndt, 1993). Results such as these have led to an interest among

health-policy researchers in the possibility that expanded outreach and guideline-concordant treatment of impairing chronic conditions might represent an investment opportunity for employers (Kessler, Greenberg, Mickelson, Meneades and Wang, 2001) as well as for governments (Murray and Lopez, 1996).

The World Health Organization (WHO) Global Burden of Disease (GBD) Study is the most ambitious attempt to estimate the comparative burdens of many different diseases. These estimates were obtained by combining estimated prevalences from community epidemiological surveys with estimated impairments from the ratings made by expert raters. A methodological

problem with this procedure, as well as with much of the related research carried out and the broader literature on illness-related role impairments, is the lack of attention to comorbidity. Many people with chronic conditions suffer from more than one disorder (Dewa and Lin, 2000). Pure disorders are, in general, much less impairing than comorbid disorders in clinical samples (Ormel et al., 1994). Comorbidities of mental disorders with commonly occurring chronic physical disorders are of special importance as a number of such comorbidities have been documented in both general population samples (Neeleman, Ormel and Bijl, 2001) and in primary care samples (Berardi, Berti Ceroni, Leggieri, Rucci, Üstün and Ferrari, 1999). Clinical studies have also found excess impairment associated with mental-physical comorbidities (Sullivan, La Croix, Russo and Walker, 2001).

It is possible to address this problem empirically in epidemiological surveys that collect information on a wide range of disorders and assess impairments independently of the disorders (to obtain information on actual impairments rather than respondent reports of their perceptions regarding the separate impairments associated with each of their illnesses). The impairments associated with pure disorders can be compared empirically in such studies, adjusting for possible confounding variables, to generate a rank ordering of pure effects. Comparisons of the incremental increases in impairments associated with comorbid disorder clusters versus pure disorders can also be compared to determine whether the effects of specific disorders vary depending on the presence or absence of other disorders.

The present report illustrates this approach by examining the separate and joint effects of major depression (MD) and generalized anxiety disorder (GAD) on role impairment. MD-GAD comorbidity is of special interest in this regard both because MD was rated as one of the most burdensome diseases in the world by the GBD investigators (Murray et al., 1996) and because MD is known to be highly comorbid with GAD (Kessler, Andrade, Bijl, Offord, Demler and Stein, in press). Indeed, the comorbidity of GAD with MD is so high in some clinical studies that several commentators have suggested that GAD might be a subtype of MD rather than an independent disorder (Brawman-Mintzer, Lydiard, Emmanuel, Payeur, Johnson, Roberts, Jarrell and Ballenger, 1993; Brown, Barlow and Liebowitz, 1994; Gorman, 1996; Roy-Byrne, 1996).

The controversy about the diagnostic status of GAD illustrates one important advantage of community epidemiological studies over clinical studies of comorbidity: help-seeking bias sometimes associated with comorbidity is removed when analysis is based on community studies. In the case of comorbid MD-GAD, community epidemiological studies that compared respondents who sought treatment with those who did not seek treatment have shown that the estimated comorbidity of GAD with MD is spuriously inflated in treatment samples because comorbid MD is a strong predictor of help seeking among people with GAD (Wittchen, Zhao, Kessler and Eaton, 1994).

Methods

Study populations

The data come from the US National Comorbidity Survey (NCS) (Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman, Wittchen and Kendler, 1994) and the Mental Health Supplement (the Supplement) to the Ontario Health Survey (OHS) (Offord, Boyle, Campbell, Cochrane, Goering, Lin, Rhodes and Wong, 1994). Both surveys were carried out in 1990 using a psychiatric interview that assessed a core set of disorders using identical questions about symptoms and impairments. The NCS is a nationally representative survey that was administered in face-to-face in-home interviews to a sample of 8,098 persons aged 15 to 54 in Part I. The response rate was 82.4%. Part II of the NCS was a series of questions about risk factors and consequences of mental illness administered to a subsample of 5,877 respondents consisting of all those who screened positive for mental disorder in the Part I interview and a random subsample of others. The data on role impairments reported here are from the Part II subsample and are weighted to adjust for differential probabilities of selection and non-response. The Supplement is a representative survey of residents of Ontario that was administered to a follow-up sample of 9,953 respondents aged 18 and above who were randomly selected from those living in households that participated in one quarterly replicate of the OHS. The OHS response rate in the Supplement replicate was 88.1% and, in these households, 76.5% participated in the Supplement, for an overall response rate of 67.4%. In order to have a comparable age range across the two surveys, the current analysis is limited to the 7,340 Supplement respondents who were age 18–54 at the time of interview.

Diagnostic assessment

Diagnoses are based on a modified version of the Composite International Diagnostic Interview (CIDI) (World Health Organization, 1990), a fully structured interview designed to be administered by interviewers who are not clinicians and to generate diagnoses according to the definitions and criteria of both Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (American Psychiatric Association, 1987) and the International Classification of Diseases (ICD-10) (World Health Organization, 1991). The current report uses DSM-III-R criteria. Although the focus is on the prevalences of GAD and MD within the 30 days prior to interview, we also control for 30-day prevalences of the other disorders assessed in the surveys. These include other anxiety disorders (panic disorder, simple phobia, social phobia, agoraphobia, and post-traumatic stress disorder), mania, substance-use disorders (alcohol and drug abuse and dependence), and, in the NCS, non-affective psychosis (NAP). Diagnoses are made without hierarchy rules. An NCS clinical reappraisal study found good test-retest reliability and procedural validity of all the diagnoses compared to clinical reassessments (Kessler, Wittchen, Abelson, McGonagle, Schwarz, Kendler, Knäuper and Zhao, 1998), with the exceptions of mania and NAP. Cases of mania were limited to those with a euphoric-grandiose symptom profile, based on the finding that the CIDI only validly assesses this subtype (Kessler, Rubinow, Holmes, Ableson and Zhao, 1997). Based on the finding that the CIDI substantially overdiagnoses NAP (Kendler, Gallagher, Abelson and Kessler, 1996), cases of NAP were limited to those identified in clinical reinterviews. These clinical reinterviews were carried out with all NCS respondents who screened positive for NAP with the CIDI.

The DSM diagnostic hierarchy rule for GAD and MD stipulates that an episode of generalized anxiety that occurs exclusively within a major depressive episode is not classified as GAD. This rule was operationalized in the NCS and the Supplement in a series of three questions asked of all respondents who met criteria for both GAD without hierarchy and MD. The first asked whether the GAD never, sometimes, or always occurs during times when the respondent is depressed. If sometimes or always, the respondent is asked which syndrome starts first during these episodes

of overlapping symptoms – the depression, the anxiety, both at the same time, or whether it varies. The third question was similar to the second except that it asked which symptoms end first, when and if either of them ever resolves. Of the 54 respondents in the two surveys combined who met criteria for 30-day comorbid GAD without hierarchy, only three reported that their episodes of GAD occurred exclusively within their episodes of MD and the majority of the others reported both that the GAD usually starts first and that the MD usually resolves first.

Measures of role impairment

Respondents in both surveys were asked how many days in the past 30 they were 'totally unable to work or carry out your normal daily activities' because of problems with their physical or mental health and, if any, how many of these disability days were due to problems with their emotions, nerves, or mental health. Respondents were then asked how many days in the past 30, exclusive of these disability days, they had to 'cut back on the amount of time you worked or not get as much done as usual' because of problems with their physical or mental health and, if any, how many of these cutback days were due to problems with their emotions, nerves, or mental health. This report focuses on the prevalences of disability and cutback days due to emotions, nerves, or mental health, collectively referred to as impairment days or role impairment.

Analysis procedures

Cross-tabulations were used to estimate the overlap between 30-day GAD and MD. Cross-tabulations and calculations of subsample means were then used to study the associations of pure and comorbid GAD and MD with role impairments. Multiple linear regression analysis was then used to estimate the associations of GAD and MD with role impairments. All regression equations were controlled for sociodemographic variables (age, gender, education, race-ethnicity, employment status, marital status, urbanicity and, in the US, region of the country) as well as for the other DSM-III-R mental and substance use disorders assessed in the surveys. Equations were estimated for the separate and joint effects of MD and GAD on the outcomes.

Both surveys were based on multistage area probability samples that featured geographic clustering and

weighting to correct for differential probabilities of selection. Design-based methods were consequently required to estimate significance tests. The method used in all tests reported in this paper is the method of jackknife repeated replication (Kish and Frankel, 1974). This method uses repeated subsampling to generate empirical distributions of coefficients of interest. All evaluations of statistical significance were made at the 0.05 level using two-sided tests.

Results

The prevalences and comorbidity of 30-day GAD and MD

As shown in Table 1, the 30-day prevalences (with standard errors in parentheses) of GAD are 1.5% (0.2) in the US and 0.6% (0.0) in Ontario, and the 30-day prevalences of MD are 4.6% (0.4) in the US and 1.9% (0.1) in Ontario. A substantial proportion of respondents with 30-day GAD in both the US (40.2%) and Ontario (36.8%) also have 30-day MD, whereas 12.9% of the respondents with MD also have GAD in the US and 11.4% in Ontario.

The impairments associated with independent and comorbid GAD and MD

Scores on the measures of impairment are presented in Table 2. Four results are noteworthy. First, the role impairments associated with comorbid GAD and MD, GAD only, and MD only are all substantially higher than those found among respondents who have neither

GAD nor MD (statistically significant at the 0.05 level in 31 of 36 comparisons). The prevalences for any disability, any cutback, or any disability or cutback range between 1.0% and 5.9% among respondents with neither MD nor GAD compared to a range between 4.3% and 63.1% among respondents with one or both of these disorders.

Second, comparing those with GAD only to those with MD only shows no consistently higher impairment for one disorder than the other. Five of the 12 comparisons are statistically significant at the 0.05 level, with two showing more impairment for GAD than MD, and the other three showing higher impairment for MD than GAD.

Third, a comparison of results in the first column of the table with later columns shows that 30-day prevalences of any disability days (full days of role impairment), any cutback days (days of partial role impairment), and any days of either disability or cutback are more prevalent among respondents with 30-day comorbid GAD and MD (12.6% to 63.1%) than among those with either GAD only (4.3% to 34.5% – statistically significant difference in five of six comparisons) or MD only (14.2% to 36.3% – statistically significant difference in three of six comparisons) in both surveys. The only exception is that the prevalence of any disability days in Ontario is significantly lower among respondents with comorbid GAD and MD (12.6%) than those with either GAD only (20.2%) or MD only (18.6%). The same general pattern holds for the ‘number/any’ columns in Table 2,

Table 1. Thirty-day prevalences and comorbidity of DSM-III-R generalized anxiety disorder (GAD) and major depression in the two surveys¹

	United States		Ontario	
	%	(se)	%	(se)
Generalized anxiety disorder (GAD)	1.5%	(0.2)	0.6%	(0.0)
Major depression (MD)	4.6%	(0.4)	1.9%	(0.1)
MD among those with GAD	40.2%	(5.4)	36.8%	(2.4)
GAD among those with MD	12.9%	(2.3)	11.4%	(1.4)
(n)	(5877)		(7340)	

¹ GAD requires a minimum duration of six months. Thirty-day prevalence consequently means that respondents have been in an episode during the past 30 days and that the hierarchy rules, with the stipulation that the classification of MD but not GAD (MD Only) was given to the small number of respondents who reported that all their episodes of GAD occurred exclusively within episodes of MD (the MD started prior to the GAD and remitted after GAD).

Table 2. The 30-day role impairments associated with DSM-III-R generalized anxiety disorder (GAD) and major depression (MD) in the two surveys

	GAD and MD			GAD only ¹			MD only ¹			Neither						
	Any ² %	(se)	\bar{x}	Number/any ² (se)	Any ² %	\bar{x}	Number/any ² (se)	Any ² %	\bar{x}	Number/any ² (se)	Any ² %	\bar{x}				
I. United States																
Disability ³ days	40.7	(8.4)	12.0	(2.3)	6.0*†	(2.5)	10.7	(4.4)	14.2*†	(2.8)	4.7*	(0.5)	2.2*	(0.2)	5.5*	(1.2)
Cutback ³ days	44.6	(6.0)	11.7	(1.6)	31.1	(1.6)	5.8*†	(1.7)	28.2*	(3.2)	10.1†	(1.3)	5.2*	(0.3)	5.2*	(0.5)
Disability or cutback days (n)	63.1	(7.5)	16.1	(2.2)	34.5	(2.2)	7.2*	(1.7)	34.7	(3.6)	10.1*	(1.3)	5.9*	(0.3)	6.7*	(0.8)
			(35)				(52)				(236)				(5,554)	
II. Ontario																
Disability ³ days	12.6	(1.4)	20.5	(1.1)	20.2*	(0.5)	30.0†	(0.0)	18.6*	(2.4)	12.8*†	(1.2)	1.0*	(0.0)	4.1*	(0.5)
Cutback ³ days	32.0	(3.2)	21.7	(0.5)	4.3*	(0.7)	6.2	(5.2)	26.7	(4.9)	7.3*	(0.3)	2.8*	(0.1)	4.8*	(0.1)
Disability or cutback days (n)	39.5	(3.9)	24.1	(0.3)	24.5*†	(1.1)	25.8†	(0.2)	36.3†	(4.5)	11.9*†	(0.7)	3.2*	(0.1)	5.4*	(0.2)
			(16)				(28)				(125)				(7,171)	

* Significantly different from the prevalence or mean level of impairment in the comorbid 'GAD and MD' subsample at the 0.05 level, two-sided test.

† Significant differences in the prevalences or mean levels of impairment in the 'GAD only' versus the 'MD only' subsamples at the 0.05 level, two-sided test.

1 'GAD only' and 'MD only' are defined as 30-day prevalences of one and only one of these disorders. Respondents in these subsamples may or may not have other comorbid DSM-III-R disorders.
 2 The entries in the 'Any' columns are the prevalence of any 30-day impairment. For example, the 40.7% entry in the upper left column of the table means that 40.7 of respondents with 30-a day comorbid 'GAD and MD' reported at least one disability day. The entries in the 'Number/any' columns show the average (mean) number of 30-day role impairment days among respondents who reported any impairment. For example, the 12.0 entry in the first row and third column of the table means that respondents with 30-day 'GAD and MD' who reported any disability had an average of 12 disability days during the past 30 days.

3 Disability days are defined as days on which respondents were 'totally unable' to work or carry out their normal daily activities because of problems with their emotions, nerves, or mental health. Cutback day are defined as days, exclusive of these disability days, on which respondents had either to reduce the amount of time they worked or to accomplish less than usual because of these same problems.

which show the average (mean) number of 30-day role-impairment days among respondents who reported any impairment. A comparison across subsamples shows that these average frequencies are consistently higher for respondents with comorbid GAD and MD (11.7 to 24.1 days) than for respondents with MD only (4.7 to 12.8 days – statistically significant difference in five of six comparisons) in both surveys and for respondents with GAD-Only in the U.S. (7.2 to 10.7 – statistically significant difference in two of three comparisons) but not Ontario (6.2 to 30.0 – no statistically significant differences).

Fourth, a rough evaluation of the incremental effects of MD over GAD and of GAD over MD can be made by comparing

- the sum of the increases in the outcomes associated with pure disorders (MD only or GAD only versus neither) with
- the increase associated with comorbidity (GAD and MD versus neither).

For example, in the first row of Table 2, we see that GAD only and MD only are associated with 3.8% and 12% increases respectively, in proportion with any disability compared to neither MD nor GAD. Generalized anxiety disorder and MD, in comparison, is associated with a 38.5% increase compared to neither MD nor GAD. As 38.5% is greater than the sum of 3.8% and 12.0%, this suggests that the effect of comorbid MD and GAD is ‘greater than the sum of its parts’ with regard to this outcome.

A formal significance test of whether the effect of comorbid MD and GAD is greater than the sum of its parts can be made using regression analysis with interaction terms. It is important to note, however, that the existence of a statistically significant interaction is dependent on the model used to describe the data (Kraemer, Stice, Kazdin, Offord and Kupfer, 2001). For example, an interaction in a model that assumes linear associations (such as an ordinary least-squares linear regression equation) evaluates the difference between the observed value of the outcome among people with comorbidity compared to the sum of the linear effects of the pure disorders, whereas an interaction in a model that assumes multiplicative associations (such as a logistic regression equation) evaluates the effect of comorbidity in relation to the product of the linear effects of the pure disorders (Rothman, Greenland and Walker, 1980).

The independent and joint effects of GAD and MD in predicting role impairments

Results of linear regression analyses for the effects of independent and comorbid GAD and MD in predicting 30-day role impairments are reported in Table 3. The equations controlled for a variety of socio-demographic variables (age, gender, employment status, marital status, urbanicity and, in the US, region of the country and race-ethnicity) and for the other DSM-III-R disorders assessed in the surveys. To the extent that these control variables mediate the effects of MD and GAD on the outcomes, they might represent over-controls. However, we felt that it was important to err on the side of presenting lower bound estimates rather than risk the possibility of incorrectly interpreting effects actually due to these controls as being due to MD or GAD.

The results in the first column show that, in the subsample of respondents without 30-day MD, 30-day GAD is consistently associated with elevated role impairments in both the US and Ontario (four of six coefficients statistically significant) compared to respondents without GAD. These effects are in the range of 1.5 to 5.6 excess disability and/or impairment days. Importantly, these effects hold after controlling for sociodemographic variables and for the other DSM-III-R disorders assessed in the surveys. Results in the next column show parallel effects for MD in the subsample of respondents without GAD. There is a consistent elevation of role impairments in both the US and Ontario (six of six coefficients statistically significant) compared to respondents without MD, with excess impairment days in the range 0.4 to 3.7.

The results in the next column compare the impairments associated with GAD without MD versus those associated with MD without GAD. There is no consistent pattern to these results, which means that the impairments associated with these two disorders are comparable in magnitude. None of the six coefficients is statistically significant at the .05 level.

The last columns of the table show that the effects of GAD and MD are cumulative. Focusing first on GAD, the results show fairly consistent evidence that GAD is associated with an incremental increase in role impairment among respondents with MD. Five of the six coefficients in this column are greater than zero (indicating an increase in impairment associated with GAD) and four are statistically significant at the 0.05 level, with coefficients in the range 2.2–4.7 days. All

six coefficients are also positive (four of six statistically significant) in evaluating the incremental effect of MD on impairment among respondents with GAD, with coefficients in the range 3.6–10.2 days.

We can also evaluate, finally, whether comorbidity has effects that are equal to the sum of its parts, greater than the sum of its parts, or less than the sum of its parts. As noted above, this can be done for a linear specification by estimating a linear regression equation that includes both main effects of MD and GAD and an interaction between the two in predicting the outcome. It is also possible to evaluate linear effects on dichotomous outcomes (Rothman et al., 1980). When the interaction is significant, it means that either

- the effect of GAD varies depending on the presence or absence of MD – a difference that can be evaluated by comparing the coefficients in the first column of the table (GAD without MD) with those in the fourth column (GAD over and above MD), and/or
- the effect of MD varies depending on the presence or absence of GAD – a difference that can be evaluated by comparing the coefficients in the second column (MD without GAD) with those in the fifth column (MD over and above GAD).

Three of the six comparisons of the first type are statistically significant in Table 3. Two of these three show that the effect of GAD is less in the presence than the absence of MD (disability days in Ontario and the sum of disability and cutback days in Ontario), whereas the third shows that the effect of GAD is greater in the presence of MD than in its absence (disability days in the US). Two of the six comparisons of the second type are statistically significant, both of them showing that the effect of MD is greater in the presence than the absence of GAD (cutback days in Ontario and disability and cutback days in Ontario).

Discussion

Consistency with previous research

The results reported here are similar to those of previous studies in general population (Robins, Locke and Regier, 1991; Kendler, Walters, Neale, Kessler, Heath and Eaves, 1995), primary care (Sherbourne, Jackson, Meredith, Camp and Wells, 1996; Olfson, Fireman, Weissman, Leon, Sheehan, Kathol, Hoven and Farber,

1997), and mental health specialty samples (Shores, Glubin, Cowley, Dager, Roy-Byrne and Dunner, 1992; Pini, Cassano, Simonini, Savino, Russo and Montgomery, 1997) in showing that MD is more prevalent than GAD and that there is strong comorbidity between GAD and MD. However, the comorbidity between GAD with MD found here is a good deal lower than in treatment studies due to the help-seeking bias noted in the introduction.

The observation that the majority of people with current GAD do not have current MD, when combined with three additional findings by other investigators, has implications for the controversy mentioned in the introduction regarding whether GAD is an independent disorder or only a subtype of MD. The first of these three findings is that symptom profiles of GAD and MD can be distinguished in patient samples by the relative importance of positive affectivity (higher in GAD), negative affectivity (higher in MD), and autonomic suppression (higher in GAD) (Clark, Beck and Beck, 1994; Brown, Chorpita and Barlow, 1998). The second finding is that the sociodemographic predictors of MD and GAD are significantly different in community epidemiological surveys (Skodal, Schwartz, Dohrenwend, Levav and Shrout, 1994). The third finding comes from twin studies, which show that the environmental determinants of GAD and MD are distinct (Kendler, Neale, Kessler, Heath and Eaves, 1992).

It is important to note, in mentioning the results of twin studies, that these studies also suggest that GAD and MD share similar genetic determinants (Kendler et al., 1992). This could be construed to mean that the two syndromes are different manifestations of the same underlying disorder, but differ in their presentation because of environmental factors. However, this interpretation can be challenged because the genetic model on which this conclusion is based assumes implausibly that the joint effects of genes and environment are additive. Such a model presupposes that the effects of environmental determinants of GAD and MD are not influenced by the presence or absence of genetic predispositions to the two disorders. A more realistic interactive model might well show differentiation of genetic effects. Unfortunately, this latter possibility cannot be tested with conventional twin data. However, data from family studies have shown differential aggregation of mental disorders in the families of patients with GAD and MD (Merikangas, Risch and

Table 3. The independent and joint effects of comorbid DSM-III-R generalized anxiety disorder (GAD) and major depression (MD) in predicting 30-day role impairments, while controlling for sociodemographics and other DSM-III-R disorders in the two surveys¹

	GAD without MD ²		MD without GAD ²		GAD without MD versus MD without GAD ³		GAD over and above MD ⁴		MD over and above GAD ⁴	
	b	(se)	b	(se)	b	(se)	b	(se)	b	(se)
Disability days ⁵										
United States	0.31	(0.30)	0.38*	(0.13)	0.13	(0.47)	3.43*	(1.10)	2.06	(1.27)
Ontario	5.61*	(0.15)	2.24*	(0.43)	1.03	(1.20)	-1.09	(0.78)	1.57	(1.13)
Cutback days ⁵										
United States	0.31	(0.70)	2.02*	(0.41)	-0.78	(0.89)	1.30	(1.13)	3.56*	(1.39)
Ontario	5.65*	(0.33)	2.84*	(0.58)	0.69	(1.28)	4.14*	(0.66)	9.35*	(1.51)
Disability and cutback days ⁵										
United States	1.51	(0.74)	2.41*	(0.45)	-0.65	(1.09)	4.73*	(1.49)	5.63*	(1.83)
Ontario	5.43*	(0.34)	3.71*	(0.72)	-0.07	(1.38)	2.65*	(0.65)	10.16*	(1.52)

* Significant at the 0.05 level, two-sided test.

¹ Results were obtained from linear regression equations with controls for region, age, gender, education, race/ethnicity, employment status, marital status, urbanicity, and, in the US, region of the country, and the other DSM-III-R mental and substance use disorders assessed in the surveys.

² The 'GAD only' coefficients were obtained from a series of linear regression equations estimated in the subsample of respondents without 30-day MD that evaluated the effect of GAD in predicting impairment with controls for the other predictors listed in footnote 1. The 'MD only' coefficients were obtained from a parallel series of equations estimated in the subsample of respondents without 30-day GAD that evaluated the effect of MD.

³ The 'GAD without MD versus MD without GAD' coefficients were obtained from a series of equations estimated in the subsample of respondents with one and only one of the two 30-day disorders that evaluated the relative effects of 'GAD only' (coded 1) versus 'MD only' (coded 0) with controls for the other predictors listed in footnote 1. Regression coefficients greater than zero mean that 'GAD only' is associated with more impairment than 'MD only', whereas coefficients with less than zero mean the reverse. The coefficients in this column do not equal the difference between the coefficients in earlier columns because the slopes of the control variables were not constrained to be equal in the different samples.

⁴ The 'GAD over and above MD' coefficients were obtained from a series of equations estimated in the subsample of respondents with 30-day MD that evaluated the incremental effect of also having GAD with controls for the other predictors listed in footnote 1. The 'MD over and above GAD' coefficients were obtained from a parallel series of equations estimated in the subsample of respondents with 30-day GAD that evaluated the incremental effects of also having MD.

⁵ The outcome variables are coded as continuous variables with a range between 0 and 30. 'Disability days' counts only days when respondents were totally unable to carry out their usual activities for an entire day. 'Cutback days' counts only days when respondents had to reduce their daily activities (they did not function, but accomplished less than on a usual day). 'Disability and cutback days' counts both.

Weissman, 1992; Reich, 1993), raising the intriguing possibility that comorbid GAD and MD might be a distinct disorder from either pure GAD or pure MD (Reich, 1995).

Our finding that impairments associated with GAD only are equivalent to those associated with MD only differs from two recent studies of primary care samples, which found that pure GAD is not associated with significant impairment (Olfson et al., 1997; Schonfeld, Verboncoeur, Fifer, Lipshutz, Lubeck and Buesching, 1997). However, these primary care studies included very few respondents with pure GAD, introducing substantial instability into the findings. The fact that there is inconsistency of results across studies suggests that this issue should be re-examined in other available datasets.

Substantive implications

Based on the results reported here, it appears that a substantial proportion of GAD cases in the general population occur independently of MD and that the role impairment due to GAD is comparable to that due to MD even after adjusting for a wide range of other comorbid disorders. It is important to point out that this result holds up when we control for the presence of other DSM-III-R disorders. This implies that GAD is consequential in and of itself and that the impairment associated with GAD is not due to MD. It is also important to note that the magnitude of impairment is substantial. In the absence of MD, GAD is associated with an average of between 1.5 and 5.4 days of role impairment per month after taking into consideration any impairments that might be due to other comorbid DSM disorders.

The incremental effects of GAD among people who also have MD are similar in magnitude (2.6 to 4.7 days) to the incremental effects of MD over GAD. Effects as large as these are in the range that has been found in other studies for such chronic conditions as ulcers, arthritis, and autoimmune disease (Kessler, Greenberg, et al., 2001). The results of this study suggest that GAD should be recognized as an important, seriously impairing disorder that is equivalent in impact to some of the most burdensome diseases in the world today.

Methodological implications

The substantive conclusion at the end of the last paragraph assumes, perhaps incorrectly, that the effects

of GAD only in these two surveys are, in fact, due to GAD rather than to some other comorbid disorder that we failed to measure. It is not possible to evaluate this assumption in the two surveys considered here because they did not include comprehensive assessments of the many chronic physical diseases that have been shown to be significantly comorbid with either MD or GAD (Berardi et al., 1999; Hansen, Fink, Frydenberg, Oxhøj, Sondergaard and Eriksen, 2001). It would not be difficult, in principle, to focus on respondents with pure MD and pure GAD, defined as these disorders in absence of a great many other mental and physical conditions, in a survey that included a comprehensive assessment of all such conditions. As a practical matter, though, such a survey would have to be extremely large in order to yield stable estimates of the impairments associated with truly pure conditions because both MD and GAD are likely to have extremely high rates of comorbidity with at least one other physical or mental disorder. Even in the NCS, which contained only a superficial checklist of commonly occurring chronic physical conditions, more than 90% of the respondents with MD and more than 95% of those with GAD met criteria for at least one other lifetime physical or mental disorder.

Three strategies are available to deal with this type of high comorbidity. One, as noted in the last paragraph, is to work with a very large sample in an effort to have enough cases of pure disorders for stable estimation of effects on impairment. Although this is the ideal strategy, it is important to recognize that the proportion of respondents who continue to be classified as pure will decrease as the number of disorders under consideration increases. The number of pure cases of some highly comorbid disorders will consequently be very small, even in large samples. In the NCS, for example, not a single respondent with bipolar disorder was found not to meet criteria for at least one of the other mental (excluding MD) or physical disorders assessed in the survey.

A second strategy that can be used in such cases is to abandon the goal of working with pure disorders and to focus instead on commonly occurring comorbid disorder profiles. Such profiles can be discovered either by simple enumeration and inspection or by using any number of dimensional reduction strategies. In some cases it might be possible to use a profiling approach to isolate comorbid disorders that are not impairing in themselves and to conceptualize respondents whose

comorbidities consist entirely of these non-impairing disorders as being ‘essentially pure’ with regard to the effects of other disorders. In the NCS, for example, there are a great many respondents with comorbid profiles that consist entirely of a specific phobia and one other disorder. As most specific phobias are associated with little, if any, serious role impairment, these respondents might be considered to have essentially pure disorders of other types.

A third strategy is to use multivariate analysis to develop approximate estimates of pure disorder effect sizes by statistically controlling for the effects of other disorders. This is the approach used in the current report. It is the least desirable of the three approaches because it usually requires the researcher to assume that the joint effects of comorbid conditions are additive. This is the key assumption that we seek to evaluate, rather than to assume, in empirical studies of the effects of comorbid disorders on impairment. When sample sizes are small, it is not possible to evaluate this assumption at all. When sample sizes are somewhat larger, as in the surveys considered here, a mixed strategy might be used in which a small subset of disorders is taken as the focus of attention (for example, MD and GAD) and the pure effects on impairment of the individual disorders in this set that occur in the absence of the others in the set can be approximated by introducing additive controls for the other disorders in multivariate prediction equations.

There is also a question of how to evaluate the effects on role impairment of commonly occurring comorbidity profiles. The MD-GAD example was so simple, involving as it did only two disorders, that the considerations involved in evaluating more complex multivariate comorbidities were not illustrated. Latent class analysis, grade of membership analysis, and other methods of detecting multivariate disorder profiles show that a number of disorder profiles exist that include three, four, five, or even more mental disorders (Kessler, 1997), physical disorders (Dewa et al., 2000), or combinations of mental and physical disorders (Neeleman et al., 2001).

Is there something synergistic about these disorder profiles so that amounts of impairment than are significantly different from what one would expect based on the summation of the linear effects of the component disorders? This question can be answered by analysing data from the sub-sample of respondents consisting of those who either have

- no disorder;
- one and only one of the pure (or ‘essentially pure’) disorders that define the comorbid profile; or
- the full set of disorders that define this profile.

The analysis should include a separate dummy predictor variable for each of the component disorders (coded 1 both for respondents with the pure disorder and for respondents with the comorbid profile), an additional dummy variable for respondents with the comorbid disorder profile, and appropriate controls for potential confounding variables. Synergy is established (assuming that the linearity assumption of the model holds) if the regression coefficient associated with the dummy variable for the profile is statistically significant.

Two observations about this approach warrant comment. These observations are based on our explorations of data from the NCS and other large-scale population surveys using this approach (Kessler, Greenberg et al., 2001; Kessler, Mickelson, Barber and Wang, 2001). First, we find that what might be called ‘negative synergy’ is a dominant tendency in such data. For example, the impairment associated with a profile made up of five individually impairing conditions is usually less than five times as great as the impairment associated with any one of the pure conditions. This tendency is most clearly seen in a multivariate regression equation that includes a separate dummy variable for each of a large number of individual disorders plus a series of summary dummy variables for respondents with exactly two of these disorders, exactly three, exactly four, and so forth. The summary dummy variables almost always have negative coefficients that increase in magnitude as the number of disorders increases, indicating that people with multivariate disorder clusters generally have less impairment than expected on the basis of an additive model.

Second, it is important not to confuse the significance of associations among chronic conditions with the significance of interactions involving these conditions in predicting impairment. The fact that two conditions are highly related to each other, as MD and GAD are, tells us nothing about whether the joint effects of these conditions on role impairment will be additive versus synergistic. As we saw in the analyses reported in this paper, there is no evidence of positive synergy between MD and GAD in predicting role impairment despite a strong relationship of the two

disorders with each other. There is an extremely strong synergy, in comparison, between blindness and deafness in predicting impairment even though these two conditions are not strongly related to each other. The search for synergy of effects, then, should not rely on evidence regarding empirical associations among conditions but should, instead, rely on conceptual reasoning about the sorts of functions that are limited by different conditions and the extent to which the joint occurrence of impairments across these functional domains might combine to create synergistic influences.

Future directions

The World Health Organization's World Mental Health (WMH) surveys are currently being carried out in over 30 countries around the world (Kessler and Üstün, 2000). The total expected sample size of WMH across all these countries is in excess of 250,000 cases. One of the main goals of WMH is to estimate the effects of individual physical and mental disorders on current role functioning. To this end, the WMH interview schedule includes a detailed chronic physical conditions checklist in addition to an in-depth assessment of a wide range of mental disorders and substance disorders. The WHO Disability Assessment Schedule (WHO-DAS; Rehm, Üstün, Saxena, Nelson, Chatterji, Ivis and Adlaf, 1999) is being used to measure role impairment.

Our hope is that the extremely large sample size of the combined WMH surveys will yield a large enough number of respondents with pure disorders to allow direct estimates to be made of the impairments associated with the vast majority of the disorders assessed in the surveys. Sensitivity analyses of these estimates will be carried out to evaluate the consistency of aggregate estimates for individual disorders across countries and the consistency of relative estimates among sociodemographic subsamples pooled across countries. In cases where too few pure cases exist to allow direct estimates to be made, careful analyses of commonly occurring comorbid profiles will be carried out to see if we can develop 'essentially pure' subsamples. If so, these subsamples will be used in the same way as we would use genuinely pure cases to generate proxy estimates of pure disorder effects. In cases where 'essentially pure' subsamples of highly comorbid disorder cannot be found, we will work with comparisons of commonly occurring comorbid profiles in the ways described above.

Our analyses of synergy in the WMH surveys will focus initially on commonly occurring comorbidities, with a special emphasis on mental-physical comorbidities. The goal here will be to make preliminary evaluations of the likely effects on role functioning of interventions aimed at detecting and successfully treating comorbid mental disorders among patients in treatment for seriously impairing chronic physical disorders. Subsequent analyses will turn to a more comprehensive search for positively synergistic comorbidities and an investigation of whether there are any key conditions that account for a number of these effects. Such conditions, if they could be found, would have great public health importance even if they were associated with low impairment as pure disorders. Given that the analyses needed to search for such synergies will necessarily be exploratory, it will be important to take great care to cross-validate results both across different geographic regions of the world and, within regions, across important sociodemographic sectors of the population.

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