ORIGINAL PAPER

Jules Angst · Robert Sellaro · Kathleen Ries Merikangas Multimorbidity of psychiatric disorders as an indicator of clinical severity

Received: 9 November 2001 / Accepted: 2 January 2002

Abstract The present study examines the clinical and research significance of the high frequency of multiple diagnoses emanating from the non-hierarchical descriptive approach to classification in the current psychiatric diagnostic systems. Data from a 15-year prospective cohort study of young adults from the general community were employed to evaluate the frequency of multiple disorders (i. e., multimorbidity), and the extent to which patterns of multiple disorders are associated with indicators of severity of psychopathology. The average number of lifetime disorders in this community-based sample was 2.1 with a range from 0 to 7. Associations within diagnostic spectra were more common than those between diagnostic spectra. The results confirm the link between comorbidity and severity demonstrated in several previous studies and further show that there is a direct increase in nearly all of the indicators of severity by the number of disorders for which the subjects met criteria across 15 years. Each of the major diagnostic categories, particularly depression, contributed to increased severity rather than representing a non-specific effect of the number of disorders. These findings demonstrate the importance of characterization of multiple syndromes rather than applying arbitrary hierarchical distinctions between diagnostic categories.

Key words comorbidity · multimorbidity · severity

J. Angst (⊠) · R. Sellaro Zurich University Psychiatric Hospital Mail Box 68 Lenggstr. 31 8029 Zurich, Switzerland Tel.: +41-1/3 84-26 29 Fax: +41-1/3 84-24 46

K. Ries Merikangas Genetic Epidemiology Research Unit Department of Epidemiology & Public Health Yale University School of Medicine 40 Temple Street New Haven, CT 06510, USA

Introduction

Evolution of the diagnostic criteria

Advances in the development of operationalized criteria and standardized diagnostic interviews in the 1970s generated major changes in the classification of psychiatric disorders. Both the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (American Psychiatric Association 1994) and the International Classification of Diseases (ICD-10) (World Health Organisation 1992) adopted a basically "atheoretical" empirically-based descriptive approach to diagnosis in order to enhance the reliability, coverage across diverse settings, and clinical and research utility of standardized diagnostic criteria.

The goal of broader coverage of specific subtypes of the major categories has led to a dramatic increase in the number of disorders and subtypes thereof. For example, the number of major categories grew from 30 in the ICD-9 to 100 in ICD-10 (Sartorius 1988). Likewise, the number of psychiatric disorders increased from 106 in DSM-I to 292 in DSM-III-R and about 400 in the DSM-IV. The newer descriptive approach has been criticized because of the large number of categories (for example, termed "nosologo-mania" by Van Praag (1995)), which tend to result in multiple diagnoses (i. e., multimorbidity) per patient. With the exception of some exclusion criteria, the traditional explicit hierarchical distinctions, such as the primary-secondary distinction based on temporal contiguity between most disorders have now been abandoned (First et al. 1990). Although characterization of an individual according to multiple disorders may reduce the clinical utility of the classification in terms of both treatment and prediction of course, it may also facilitate research on the relationship between and within diagnostic classes and subtypes thereof.

Magnitude of comorbidity

Studies of both clinical and community samples have consistently shown that the frequency of subjects with comorbidity is more common than that of single disorders. For example, the matrix of associations in large scale population-based studies of the U.S. demonstrate positive associations between the lifetime occurrences of numerous disorders (Kessler et al. 1995). Similar patterns of comorbidity have also been found in both clinical and community samples of adolescents (e. g., Kovacs 1990, Caron and Rutter 1991, Bird et al. 1993, Lewinsohn et al. 1995a). Most of these studies reveal that the majority of children with a major psychiatric disorder also manifest a second disorder, most commonly anxiety and depression (Kovacs 1990, Caron and Rutter 1991).

The prevalence periods on which associations between disorders are based are another essential aspect of evaluating the significance of comorbidity. Most studies examine retrospectively-reported comorbidity across the lifetime, irrespective of temporal concurrence. However, as noted by Kraemer (1995) it is critical to distinguish between concurrent and lifetime comorbidity. In light of the low reliability of recall of single lifetime diagnoses (Rice et al. 1987), the accuracy of retrospective data in characterizing order of onset as well as temporal associations would be expected to be even lower.

Despite the large number of diagnostic categories, systematic evaluation of the criteria for each of these disorders or subtypes is obviously beyond the scope of any diagnostic assessment. In both clinical practice and research in adult psychiatry, there are practically only 5 or 6 major spectra applied (i.e., schizophrenia and related disorders, mood disorders, anxiety disorders, substance disorders, behavior disorders, and somatoform disorders). The major source of disagreement emanates from the criteria for the specific subtypes of the major classes of disorders (bipolar disorder vs. major depression; specific vs. social phobia, etc) and the inter-relations between the major categories (e.g., anxiety and mood disorders). Indeed, the dramatic increase in the focus on "comorbidity" is in part an artifact of the diagnostic system which makes no attempt to infer distinct boundaries or to assume homogeneity within specific diagnostic classes.

In examining the problem of multiple diagnosis resulting from the current diagnostic classification system, it is important to distinguish between "homologous" associations, or those that occur within a major diagnostic spectrum, such as "double depression" (i. e., the combination of both major depression and dysthymia (Keller and Shapiro 1982) from "heterologous" associations, those which occur *between* the major diagnostic spectra, such as anxiety disorders and substance disorders. Whereas the former may truly represent differential manifestations of the same underlying disorder, the latter may be etiologically independent, causally associated or disparate manifestations of the same underlying risk factors. The present study applies the current descriptive diagnostic system to data from a cohort of young adults from the general community which was followed prospectively with five interviews over a total of 15 years. The major goals of this report are:

- to examine the degree to which multiple diagnostic categories and major classes of disorder emerge when applying the descriptive approach of the DSM-III and III-R Axis I criteria;
- to investigate the frequencies of specific and major diagnostic categories among those with multiple diagnoses;
- to examine the extent to which patterns of multimorbidity are associated with indicators of severity of psychopathology; and
- to evaluate the clinical and research significance of multimorbidity.

Methods

Subjects

The Zurich young cohort study is comprised of a adult cohort of 4,547 (m = 2201; f = 2346) representative of the canton of Zurich in Switzerland who were screened in 1978 with the Symptom Checklist 90-R (Derogatis 1977). In order to enrich the probability of psychiatric syndromes, a subsample of 591 subjects was selected, with two thirds consisting of high scorers (defined by the 85th percentile or more of the SCL-90) and a random sample of those with scores below the 85th percentile. The sample was investigated prospectively with five interviews between 1979 and 1993. Further details of the methodology were described in other papers (Angst et al. 1997). Sixty-nine percent of the original sample remained in the cohort across the 15 years of the study. Those who had dropped out did not differ significantly in their baseline measures in terms of demographic characteristics, or risk group at study entry. Data are weighted to yield estimates of the population rates using coefficients which reflect the representation of the subjects with respect to the entire population assessed.

Diagnostic interview

A direct interview, the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology (SPIKE), was administered by psychiatric residents and clinical psychologists with extensive clinical training. This interview schedule assesses a number of somatic syndromes, including headache, gastrointestinal, cardiovascular, and respiratory syndromes, as well as psychological syndromes, including depression, anxiety, phobia, obsessive-compulsive, and substance abuse. Psychiatric diagnoses were made according to both the DSM-III criteria for most disorders with the exception of neurasthenia (ICD-10), hypomania (DSM-IV), and substance disorders, which were derived by the DSM-III-R Criteria (American Psychiatric Association 1987). Screening probes based solely on the major phenomenologic feature of each syndrome (e.g., depressed, irritable, sad mood) were administered for each diagnostic category. Positive endorsement of the entry probe were followed by queries about specific symptoms, duration, frequency, severity, treatment history and impairment. A dimensional measure of subjective distress was included in each diagnostic section of the interview. Personal and family history of the syndromes were also assessed for all subjects, irrespective of endorsement of the diagnostic screening question for each section.

The period of prevalence of disorders in the current analyses was based on the cumulative one-year prevalence rates of all disorders for which the individual met criteria across the 15 years of the study. The major disorders examined in the present analyses were selected on the basis of their frequency and the availability of diagnostic criteria across at least three waves of interviews of the study. Some disorders (e. g., obsessive-compulsive disorder, bipolar I disorder) were too rare in this general community sample to permit meaningful analysis. Other disorders for which operational criteria were only available during the last two waves of the study (e.g., bulimia) were not included in the present analyses. Analyses of comorbid disorders that were strictly concurrent within the one year intervals preceding each of the five diagnostic interviews were also conducted, yielded similar results to those reported in the present paper.

For the longitudinal diagnostic variables, either DSM-III or DSM-III-R were employed depending upon whether the criteria for the evolving classification systems were available. The number of specific disorders was defined as the total number of the 10 specific diagnostic categories for which each subject met criteria across the 5 waves of the study (ranging from 0–10). Likewise, the number of diagnostic categories was defined as the total number of the 4 major diagnostic categories including mood disorders (mania/hypomania; major depression; dysthymia); anxiety disorders (panic disorder; generalized anxiety disorder); phobic states (agoraphobia; social phobia; specific phobia); and substance disorders (alcohol or drug abuse/dependence), for which each subject met criteria across the 5 waves of the study (ranging from 0 – \geq 3).

The indicators of severity in the present analyses were derived from the diagnostic interview. The indicators of severity employed in the present analyses included: age at onset, age at first treatment, subjective distress, occupational impairment (analog scales ranging from 1–100), quality of life, history of treatment, history of psychotropic medications, family history, social impairment, and suicide attempts. The maximum of the indicators across disorders and interviews was used in these analyses; however, similar findings were obtained when the average of the indicators was employed. Two factor analytically derived (Scheidegger 1992) scales of the SCL–90-R (Derogatis 1977), which was administered seven times from the ages 19 to 35, were used to assess the global severity of psychiatric symptoms. Quality of life was measured via a self-reported rating scale (Bech and Angst 1996) at the age of 35.

Results

Table 1 presents the distribution of 10 specific disorders and 4 major diagnostic categories by the total number of disorders across 15 years. Mood disorders, particularly dysthymia, were the most common disorder involved in comorbidity, followed by panic disorder, agoraphobia, and drug abuse. The average number of diagnoses across the entire period of observation was 2.1, with a range from 0–7. Inspection of frequencies of specific disorders reveals that comorbidity is far more common for major depression than for any of the other mood, anxiety or substance disorders. In contrast, the frequency of multiple concomitant disorders is far lower for alcohol abuse and social phobia, which more often occur as the sole disorder than any of the other disorders examined herein.

Table 2 presents the distributions of the 4 major diagnostic categories according to the number of diagnoses across 15 years ranging from 0 to 3. These results reveal that anxiety states and substance disorders were more frequently associated with other disorders than

 Table 1
 Proportion of subjects (total N = 343) with each specific disorder* by the number of DSM-III axis I disorder (0–10) across 15 years

		Numb	Number of diagnoses							
		1	2	3	4	5*				
Spec	cific disorders	142	101	56	23	21				
		%	%	%	%	%				
1	Major depressive episodes	33.1	49.5	71.4	78.3	85.7				
2	Dysthymia	0.8	8.4	14.8	30.4	60.0				
3	Hypomania	8.9	14.0	10.7	26.1	19.1				
4	Panic disorder	3.5	8.9	14.3	39.1	57.1				
5	Generalized anx. disorder	9.9	23.8	25.0	34.8	57.1				
6	Agoraphobia	5.6	10.9	33.9	43.5	61.9				
7	Social phobia	12.0	30.7	53.6	47.8	76.2				
8	Simple phobia	13.4	19.0	42.6	39.1	40.0				
9	Alcohol abuse	9.9	23.8	21.4	56.5	52.4				
10	Drug abuse	4.9	15.8	14.3	8.7	42.9				

* Not mutually exclusive

 Table 2
 Proportion of subjects (n = 343) with each major diagnostic category* by the number of DSM-III major diagnostic categories (0-4) across 15 years

	1 172		2 123	-		3 37		4 11	
Major diagnostic categories	N	%	N	%	N	%	N	%	
Mood Anxiety Phobias Substance disorders	68 20 57 27	39.5 11.6 33.1 15.7	92 43 71 40	74.8 35.0 57.7 32.5	36 25 29 21	97.3 67.6 78.4 56.8	11 11 11 11	100.0 100.0 100.0 100.0	

* Not mutually exclusive

were the mood disorders or phobic states. That is, mood disorders and phobias were more often the sole diagnosis than anxiety states and substance abuse, whereas the latter tended to co-occur with other disorders than to occur alone.

Tables 3 and 4 show the longitudinal associations between the 10 subtypes of the major diagnostic categories, and the 4 major diagnostic categories, respectively. As expected, the subtypes within major categories (e.g., odds ratio for social phobia and agoraphobia = 7.1; odds ratio for alcohol and drug abuse/dependence and alcohol abuse/dependence = 4.4) were more strongly associated than subtypes between the major categories (e.g., odds ratio for agoraphobia and mania = 0.5; odds ratio for abuse/dependence and simple phobia = 1.4). Whereas 88% of the homologous categories were significantly associated, only 38% of the heterologous categories had generally quite high and significant co-occurrence. There were also strong associations between the major diagnostic categories (Table 4), with odds ratios ranging from 1.9 for phobias with anxiety disorders and for anxiety disorders and substance abuse/dependence to 3.7 for mood disorders and substance abuse/ dependence.

The number of disorders by several indicators of clinical severity and social impairment are presented in Table 5. There is a direct association between the num-

	Major depression	Dysthymia	Panic	Generalized anxiety	Agoraphobia	Social phobia	Specific phobia	Alcohol abuse/dep	Drug abuse/dep
Mania Major depression Dysthymia Panic Generalized anxiety Agoraphobia Social phobia Specific phobia Alc/drug	1.9 (1–3.8)	0.6 (0.1–2.6) 3.2 (1.6.6.6)	1.5 (0.5–4.1) 2.1 (1–4) 7.5 (3.4–16.9)	1.3 (0.5–3.2) 3.1 (1.8–5.3) 3.5 (1.6–7.4) 3.5 (1.7–7.2)	0.5 (0.1–1.7) 1.9 (1–3.3) 3.1 (1.4–7.1) 2.7 (1.3–5.8) 2.6 (1.4.5.1)	$\begin{array}{c} 0.4 \\ (0.1-1.1) \\ 1.6 \\ (1-2.6) \\ 4.7 \\ (2.3-9.6) \\ 3.9 \\ (2-7.6) \\ 1.3 \\ (0.7-2.5) \\ 7.1 \\ (4-12.6) \end{array}$	$\begin{array}{c} 0.5\\ (0.1-1.6)\\ 1.5\\ (0.9-2.6)\\ 1.6\\ (0.6-3.7)\\ 0.9\\ (0.3-2.2)\\ 0.9\\ (0.4-1.8)\\ 2.9\\ (1.5-5.5)\\ 3.2\\ (1.8-5.4) \end{array}$	$\begin{array}{c} 3.1 \\ (1.4-6.8) \\ 4.2 \\ (2.4-7.3) \\ 4.2 \\ (1.9-9.3) \\ 3.2 \\ (1.5-7.2) \\ 1.5 \\ (0.7-3.2) \\ 2.2 \\ (1-4.6) \\ 1.9 \\ (1-3.5) \\ 1.4 \\ (0.6-2.9) \end{array}$	$\begin{array}{c} 1.5\\ (0.5-4.5)\\ 2.6\\ (1.3-5.2)\\ 1.0\\ (0.3-3.5)\\ 1.4\\ (0.5-4.2)\\ 1.4\\ (0.5-3.4)\\ 3.2\\ (1.4-7.6)\\ 1.7\\ (0.8-3.6)\\ 1.4\\ (0.6-3.5)\\ 4.4\\ (2.2-8.8) \end{array}$

* Ajusted for sex, sampling

150

Table 4 Adjusted odds ratios* (\pm 95% confidence intervals) of associations among DSM-III major diagnostic categories across 15 years

Major diagnostic categories	Anxiety	Phobias	Substance abuse/ dependence
Mood	3.3 (2.1–5.3)	2.0 (1.4–2.9)	3.7 (2.3–6.1)
Anxiety	_	1.9 (1.2–3)	1.9 (1.1–3.2)
Phobias	-	_	2.0 (1.2–3.3)

* Adjusted for sex, sampling

ber of disorders and each of the severity indicators as well as social indicators of impairment investigated herein. The results of Table 5 show significantly earlier age at onset, greater subjective distress, greater work impairment, poorer quality of life, and greater current symptom scores on the SCL-90-R by the number of disorders for which the subject met criteria during the 15 years of the study. Particularly noteworthy was the extent to which the number of disorders was associated with increasingly earlier onset in childhood. The only clinical factor that was not associated with an increasing number of disorders was the age of first treatment for which the average age was 21 across groups. Not shown here, inspection of the association between the number of major diagnostic categories and the indicators of severity shown in Table 5 revealed a similar relation between the number of categories and clinical severity.

Table 6 presents the effects of the specific major diagnostic categories on the two key indicators of severity including the analogue ratings of subjective distress and work impairment. All of the diagnostic categories contributed significantly to both the stepwise and full models with mood disorders accounting for the largest proportion of the variance. The total model including all of the major diagnostic categories as well as sex and sampling explained approximately 25% of the variance in subjective distress.

Discussion

Significance of associations between disorders

There have now been numerous epidemiologic studies that have demonstrated strong associations between and within diagnostic spectra. Aggregation of these data across studies reveals consistent patterns of comorbidity, despite large variation in base rates and disparate methodologic approaches (Merikangas et al. 1996, Kessler et al. 1996b, Kessler et al. 1996a, Merikangas et al. 1998b, Merikangas et al. 1998a). The stability of these findings suggest the validity of some common underlying patterns of symptom expression between disorders, particularly since the differential magnitude of comorbidity tends to be quite consistent across studies.

There has been substantial research regarding the sources of comorbidity or links between diagnostic spectra (i. e., heterologous associations). Numerous study paradigms and sampling strategies have been employed to investigate specific mechanisms for comorbidity. Most informative are family studies and twin studies, which investigate the specificity of expression of different disorders or subtypes thereof within families (e.g., Merikangas 1990) or twins (e.g., Kendler et al. 1993) and prospective longitudinal studies, which examine the stability vs. switching of diagnostic categories within spectra over time (e.g., Angst et al. 1990, Angst et al. 2000). For example, several studies have shown that despite the high magnitude of co-occurrence between alcoholism and major depression, they do not appear to Table 5 Clinical and social indicators of severity by the number of DSM-III axis I disorders (0–10) across 15 years

	Number of diagnostic classes (0–10)						
	no Dx 248	1 Dx 142	2 Dx 101	3 Dx 56	4 Dx 23	5+ Dx 21	р
Demographic and family history Females (%) Divorced (%) Positive family history (%) Family history for treatment (%)	48.0 4.8 55.0 14.7	48.6 9.2 77.4 17.3	47.5 4.0 79.0 23.0	60.1 16.0 87.5 16.7	34.8 21.7 82.6 26.1	85.7 19.1 85.7 33.3	0.002 0.001 0.001 n. s.
Clinical factors Age of onset (means) (s. d.) History of suicide attempts (%)	_ 2.0	10.3 (5.5) 7.8	9.9 (5.1) 17.8	8.8 (5.8) 23.2	8.3 (84.9) 21.7	6.8 (4.4) 57.1	0.02 0.001
Treatment Treated (5 intv) (%) Prescribed medication (%) Age of first TX (means) (s. d.)	8.9 5.7 22.2 (4.6)	32.4 13.4 22.4 (4.8)	43.6 17.8 21.8 (4.7)	44.6 23.2 20.4 (3.8)	69.6 34.8 22.0 (6.8)	85.7 71.4 18.0 (5.4)	0.001 0.001 0.0001
Impairment Work impairment (0–100) (means) (s. d.) Social impairment (%)	-	27.5 (28.4) 79.6	37.3 (29.8) 95.1	45.1 (31.1) 94.6	56.5 (35.5) 100.0	58.0 (31.9) 100.0	0.0001 0.001
Subjective distress Analog rating (0–100) (means) (s. d.)	_	78.5 (21.4)	86.4 (15.2)	88.3 (12.3)	94.6 (5.9)	93.4 (7.2)	0.0001
Quality of life Physical well-being Psychological well-being	3.6 (0.86) 3.6 (0.86)	3.4 (0.71) 3.5 (0.86)	3.3 (0.89) 3.3 (0.90)	3.0 (0.96) 3.1 (0.75)	2.8 (1.03) 2.9 (1.03)	2.7 (0.92) 2.9 (1.11)	
Global everity SCL 90-R (5 intv) (means) (s. d.)	-	65.1 (10.2)	67.7 (8.9)	68.1 (8.6)	74.6 (10.7)	75.5 (9.5)	0.0001

Table 6 Effects of specific disorders and number of disorders on indicators of severity

	Subjectiv	ve distress		Work im	Work impairment			
Disorder/covariate	Order	Partial r ²	Model <i>r</i> ²	Order	Partial r ²	Model r ²		
Mood	1	0.10	0.10	1	0.09	0.09		
Anxiety	4	0.02	0.22	2	0.03	0.11		
Phobia	3	0.05	0.20	4	0.02	0.15		
Substance	6	0.01	0.25	3	0.02	0.13		
Sex	5	0.01	0.23	6	0.005	0.16		
Risk	2	0.06	0.16	5	0.007	0.16		

have common underlying risk factors. In contrast, at least some subtypes of anxiety states and depression appear to result from common underlying risk factors. Prospective observations of children suggest that there is age-dependent expression of anxiety and depression, with anxiety appearing earlier in the developmental course (Kovacs 1990). Heterologous associations may also emerge because perturbation of one system could lead to a cascade of expression in other systems.

Interpretation of the meaning of multiple diagnoses depends upon the extent to which there is empirical evidence regarding the sources of associations between and within diagnostic spectra. Our data confirm that the homologous associations were much greater than heterologous associations, as would be expected by the common symptoms and related features within the spectra of depression, phobias, anxiety states and substance abuse. Increasing evidence suggests that the subtypes within homologous categories may represent differential patterns of expression of the same underlying

condition. For example, the results of prospective studies of clinical (Corvell et al. 1991, Sherbourne et al. 1994, Maier et al. 1997) and community samples (Angst and Dobler-Mikola 1985, Blazer et al. 1988, Judd et al. 1994, Skodol et al. 1994, Angst and Merikangas 1997, Angst et al. 1997, Kessler et al. 1997, Angst et al. 2000) reveal that depression exists on a spectrum with considerable overlap between subtypes of depression at both the diagnostic level as well as those at the subthreshold level. Based on this evidence, the ICD-10 has now added categories for numerous subtypes of depression not previously included in the diagnostic system (e.g., minor depression, recurrent brief depression). In fact, recent epidemiologic (Kessler et al. 1996c, Angst and Merikangas 2001) and twin study data (Kendler and Gardner 1998) have shown that depression is far better characterized dimensionally with independent evaluation of each of the major components of depression including symptoms, duration, and recurrence. In contrast, the distinction between alcohol abuse and dependence introduced in the DSM-III and ICD-9 has been validated in several subsequent studies (Merikangas et al. 1998b).

Although more attention has been devoted to comorbidity between psychiatric and non-psychiatric disorders, there are few community studies that systematically evaluate the association between medical and psychiatric disorders. For example, Keitner (1991) showed that the course of depression was worse among those with either psychiatric or medical comorbidity. This was the true intent of the term comorbidity as coined by Kaplan (1974), who warned of the importance of characterizing comorbid disorders in evaluating course and the outcome of clinical trials.

Multimorbidity as an indicator of severity

The results of the present study confirm the link between multimorbidity and severity demonstrated in several previous studies of both adults and children (Coryell et al. 1988, Wittchen and Essau 1989, Angst et al. 1990, Lewinsohn et al. 1995b, Merikangas et al. 1996). However, our data further show that there is a direct increase in nearly all of the indicators of severity by the number of disorders for which the subjects met criteria across 15 years. In fact, Kovacs (1990) postulated that depression may be a marker of severity rather than a distinct disorder in youth. Our findings illustrating a direct association between the number of disorders, and nearly all of the indicators of severity and course would tend to confirm this observation.

Study limitations

The findings of this study should be interpreted in terms of heir limitations including: the sampling of a single age cohort, the availability of increasing amounts of information over time with evolution of more extensive diagnostic systems, the attrition rate of 30% over time, and the possible role of a response set that is biased towards positive responses on both the diagnostic questions as well as the validity indicators. However, the strengths of this study render these data ideal to address the key study questions of this paper: the community-based sample; the non-hierarchical approach to diagnosis; collection of data on all of the major features of disorders in the diagnostic interview without including skip-outs if one or two key phenomenologic symptoms were not endorsed; administration of the interview by experienced clinical interviewers; and the prospective longitudinal design which is based on multiple interviews over time rather than retrospective recall of lifetime disorders.

Implications for classification system

The debate over the hierarchical versus descriptive approach to the classification of psychiatric disorders de-

pends upon the purpose of the classification. Converging evidence suggests that a hierarchical system without evidence of validity has neither research nor clinical utility. However, there are numerous examples in which the DSM-III hierarchical system was grossly misleading since several subgroups with distinct etiology were found to be subsumed within single categories. Thus, the development of the current approach of multiple diagnosis is the first step in providing descriptive data with which to investigate the etiologic links between disorders, significance of diagnostic categories for treatment and course, and the value of retaining a categorical system.

The evolution of diagnostic classification to provide greater coverage and empirical description in order to eliminate unsubstantiated hierarchical distinctions between disorders has necessarily yielded far more diagnostic categories. This has naturally artificially induced more comorbidity than that derived from previous diagnostic systems (Frances et al. 1990). However, despite the fact that the introduction to the DSM-IV clearly states that the increase in the number of categories does not imply that each category is either independent or homogeneous, critics of this approach bemoan the decrease in clinical utility in terms of both treatment planning and paper work induced by the greater number of categories necessary for health insurance reimbursement! One possible solution would be to rank each syndrome according to the extent to which it induces impairment, subjective distress, or major life interference with others. The validity of such distinctions could be enhanced through ratings of severity of each syndrome and its chief components rather than through global ratings of severity of the individual, as applied by Axis V. Similar to the differential diagnostic approach of general medicine, the significance of each syndrome could be rank ordered by severity rather than probability.

The retention of multiple diagnoses in the current system may also have clinical utility in terms of their relevance to treatment. Since comorbidity is far more common than single disorders both in clinical and community settings, clinical trials would be far more generalizable if comorbidity were to be incorporated into the design rather than comprising an exclusion criterion.

Aside from the above-cited disadvantages of the empirical descriptive approach of the current nomenclature, the newer systems facilitate empirical research by enhancing diagnostic reliability, increasing international consensus at the descriptive level, and eliminating arbitrary conventions regarding hierarchies within and between diagnostic categories. The significance of multimorbidity within and across the lifetime as well as within and between categories raises a number of questions regarding their inter-relations examined globally rather than taken two at a time. Prospective longitudinal data of the stability of these categories will ultimately lead to a reduction in the number of categories and hopefully lead to the identification of more homogeneous groups of disorders. This approach is the next step in examining the meaning of multimorbidity and should facilitate empirical research on diagnostic validity, which is still the major impediment to progress in psychiatry (Kendell 1989).

Acknowledgment This work was supported by Grant 32–33980.92 of the Swiss National Science Foundation to Professor Angst and a Research Scientist Award from the U. S. National Institute of Drug Abuse (1 R01 DA 00293) to Dr. Merikangas.

References

- 1. American Psychiatric Association (1987) Diagnostic and Statistical Manual for Mental Disorders (DSM-III-R). American Psychiatric Association, Washington DC
- 2. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders (DSM-IV). American Psychiatric Association, Washington DC
- Angst J, Dobler-Mikola A (1985) The Zurich Study a prospective epidemiological study of depressive, neurotic, and psychosomatic syndromes. IV Recurrent and nonrecurrent brief depression. Eur Arch Psychiatry Neurol Sci 234: 408–416
- Angst J, Merikangas KR (1997) The depressive spectrum: diagnostic classification and course. J Affect Disord 45: 31–40
- 5. Angst J, Merikangas KR (2001) Multi-dimensional criteria for the diagnosis of depression. J Affect Disord 62: 7–15
- Angst J, Merikangas KR, Preisig M (1997) Subthreshold syndromes of depression and anxiety in the community. J Clin Psychiatry 58: 6–10
- 7. Angst J, Sellaro R, Merikangas KR (2000) Depressive spectrum diagnoses. Compr Psychiatry 41: 39–47
- Angst J, Vollrath M, Merikangas KR, Ernst C (1990) Comorbidity of anxiety and depression in the Zurich cohort study of young adults. In: Maser JD, Cloninger CR (eds) Comorbidity of Mood and Anxiety Disorders. American Psychiatric Press, Washington DC, pp 123–137
- 9. Bech P, Angst J (1996) Quality of life in anxiety and social phobia. Int Clin Psychopharmacol 11: 97–100
- Bird HR, Gould MS, Staghezza BM (1993) Patterns of diagnostic comorbidity in a community sample of children aged 9 through 16 years. J Am Acad Child Adolesc Psychiatry 32: 361–368
- Blazer D, Swartz M, Woodbury M, Manton KG, Hughes D, George L (1988) Depressive symptoms and depressive diagnoses in a community population. Use of a new procedure for analysis of psychiatric classification. Arch Gen Psychiatry 45: 1078–1084
- Caron C, Rutter M (1991) Comorbidity in child psychopathology: concepts, issues and research strategies. J Child Psychol Psychiatry 32: 1063–1089
- Coryell W, Endicott J, Andreasen NC, Keller MB, Clayton PJ, Hirschfeld RMA, Winokur G (1988) Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. Am J Psychiatry 145: 293–300
- Coryell W, Endicott J, Keller MB (1991) Predictors of relapse into major depressive disorder in a nonclinical population. Am J Psychiatry 148: 1253–1258
- 15. Derogatis LR (1977) SCL-90. Administration, Scoring and Procedures Manual-I for the R (revised) Version and Other Instruments of the Psychopathology Rating Scales Series. Johns Hopkins University School of Medicine, Chicago
- 16. First MB, Spitzer RL, Williams JBW (1990) Exclusionary principles and the comorbidity of psychiatric diagnoses: a historical review and implications for the future. In: Maser JD, Cloninger CR (eds) Comorbidity of Mood and Anxiety Disorders. American Psychiatric Press, Washington DC, pp 83–109
- Frances A, Widiger T, Fyer MR (1990) The influence of classification methods on comorbidity. In: Maser JD, Cloninger CR (eds) Comorbidity of Mood and Anxiety Disorders. American Psychiatric Press, Washington DC, pp 41–59

- Judd LL, Rapaport MH, Paulus MP, Brown JL (1994) Subsyndromal symptomatic depression: a new mood disorder? J Clin Psychiatry 55: 18–28
- Kaplan MH, Feinstein AR (1974) The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chron Dis 27: 387–404
- Keitner GI, Ryan CE, Miller JW, Kohn R, Epstein NB (1991) 12month outcome of patients with major depression and comorbid psychiatric or medical illness (compound depression). Am J Psychiatry 148: 345–350
- Keller MB, Shapiro RW (1982) "Double depression": superimposition of acute depressive episodes on chronic depressive disorders. Am J Psychiatry 139: 438–442
- 22. Kendell RE (1989) Clinical validity. Psychol Med 19: 45-55
- Kendler KS, Gardner CO Jr (1998) Boundaries of major depression: an evaluation of DSM-IV criteria. Am J Psychiatry 155: 172–177
- Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ (1993) Major depression and phobias: the genetic and environmental sources of comorbidity. Psychol Med 23: 361–371
- 25. Kessler RC, Nelson CB, Mcgonagle KA, Edlund MJ, Frank RG, Leaf PJ (1995)
- Kessler RC, Nelson CB, Mcgonagle KA, Edlund MJ, Frank RG, Leaf PJ (1996a) The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. Am J Orthopsychiatry 66: 17–31
- Kessler RC, Nelson CB, Mcgonagle KA, Liu J, Swartz M, Blazer DG (1996b) Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry 168: 17–30
- Kessler RC, Zhao S, Blazer DG, Swartz M (1997) Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. J Affect Disord 45: 19–30
- Kessler RC, Walters EE (1998) Epidemiology of DSM-III-R Major Depression and Minor Depression Among Adolescents and Young Adults in the National Comorbidity Survey. Depression and Anxiety 7: 3–14
- Kovacs M (1990) Comorbid anxiety disorders in childhood-onset depression. In: Maser JD, Cloninger RC (eds) Comorbidity of Mood and Anxiety Disorders. American Psychiatric Press, Washington DC, pp 271–282
- Kraemer HC (1995) Statistical issues in assessing comorbidity. Statistics Med 14: 721–733
- 32. Lewinsohn PM, Klein DN, Seeley JR (1995a) Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry 34: 454–463
- Lewinsohn PM, Rohde P, Seeley JR (1995b) Adolescent psychopathology: III The clinical consequences of comorbidity. J Am Acad Child Adolesc Psychiatry 34: 510–519
- Maier W, Gänsicke M, Weiffenbach O (1997) The relationship between major and subthreshold variants of unipolar depression. J Affect Disord 45: 41–51
- 35. Merikangas KR (1990) Comorbidity for anxiety and depression: review of family and genetic studies. In: Maser JD, Cloninger RC (eds) Comorbidity of Mood and Anxiety Disorders. American Psychiatric Press, Washington DC, pp 331–348
- 36. Merikangas KR, Angst J, Eaton W, Canino G, Rubio-Stipec M, Wacker H, Wittchen HU, Andrade L, Essau C, Whitaker A, Kraemer H, Robins LN, Kupfer DJ (1996) Comorbidity and boundaries of affective disorders with anxiety disorders and substance misuse: results of an international task force. Br J Psychiatry 168: 58–67
- 37. Merikangas KR, Mehta R, Molnar BE (1998a) Co-morbidity of substance use disorders with mood and anxiety disorders: results of the international consortium in psychiatric epidemiology. Addict Behav 23: 893–907
- Merikangas KR, Stevens DE, Fenton B, Stolar M, O'Malley S, Woods SW, Risch N (1998b) Co-morbidity and familial aggregation of alcoholism and anxiety disorders. Psychol Med 28: 773–788

- 154
- 39. Rice J, Reich T, Andreasen NC, Endicott J, Van Eerdewegh M, Fishman R, Hirschfeld RMA, Klerman GL (1987) The familial transmission of bipolar illness. Arch Gen Psychiatry 44: 441–447
- 40. Sartorius N (1988) International perspectives of psychiatric classification. Br J Psychiatry 9–14
- 41. Scheidegger P (1992) Reproduzierbarkeit von Strukturen in empirischen Daten. Diss. Phil. I University of Zurich, Zurich
- 42. Sherbourne CD, Wells KB, Hays RD, Rogers W, Burnam A, Judd LL (1994) Subthreshold depression and depressive disorder: clinical characteristics of general medical and mental health specialty outpatients. Am J Psychiatry 151: 1777–1784
- 43. Skodol AE, Schwarz S, Dohrenwend BP, Levav I, Shrout PE (1994) Minor depression in a cohort of young adults in Israel. Arch Gen Psychiatry 51: 542–551
- Van Praag HM (1995) Concerns about depression. Eur Psychiatry 10: 269–275
- 45. Wittchen HU, Essau CA (1989) Comorbidity of anxiety disorders and depression: does it affect course and outcome? Psychiatry Psychobiol 4: 315–323
- 46. World Health Organisation (1992) The ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines. World Health Organization, Geneva