Generalized Anxiety Disorder: Nature and Course

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Generalized anxiety disorder (GAD) is a chronic and highly prevalent disorder in the adult population, yet it remains a relatively poorly understood condition. Clinicians may be familiar with the symptoms of enduring excessive worrying, anxiety, and hypervigilance that are characteristic of GAD, but may not necessarily recognize that these are usually symptoms of a distinct psychiatric disorder. Despite changes in diagnostic criteria, estimates of prevalence for GAD are remarkably consistent across epidemiologic studies. Lifetime prevalence in the general population is estimated at 5% (DSM-III and/or DSM-III-R criteria), with rates as high as 10% among women aged 40 years and above, and cross-sectional rates among primary care attenders are about 8%, making GAD the most prevalent anxiety disorder in primary care. The age at onset of GAD differs from that of other anxiety disorders: prevalence rates are low in adolescents and young adults but increase substantially with age. Females are at greater risk than males, and the disorder is correlated with being unemployed or a housewife or having a chronic medical illness. GAD is frequently associated with comorbid depression and other anxiety and somatoform disorders. Significant GAD-specific disability occurs even when comorbidity is not present. *(J Clin Psychiatry 2001;62[suppl 11]:15–19)*

Generalized anxiety disorder (GAD) has, until recently, been a relatively poorly understood disorder. The recent increased interest in the condition has stemmed from the finding that GAD is the second most frequent disorder in primary care after depression,[1–3] the availability of reliable diagnostic criteria and instruments,[4] and the development of new treatments for this condition. However, a number of concerns remain regarding the nosology of GAD as a separate psychiatric condition. Questions have been raised concerning the diagnostic validity of standard criteria, the prevalence in the general population, and in particular, the meaning and implications of comorbid anxiety and depressive disorders frequently seen in clinical settings. Other key concerns are whether the disorder causes GAD-specific disabilities and whether the impairments are due to comorbid conditions. This review explores the nature of GAD by examining current research into its epidemiology (prevalence rates in both the general population and in primary care are considered), onset, course, risk factors, and associated comorbidity and impairment.

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EPIDEMIOLOGY OF GAD

A number of critical clinical and research issues affect the reliability and understanding of GAD studies. Most clinicians and clinical epidemiologists are familiar with the clinical syndrome of generalized anxiety characterized by excessive worrying and marked symptoms of hypervigilance and anxiety as the essential aspects of what was formerly labeled *anxiety neurosis* before the 1980s. However, confusion exists concerning the diagnostic criteria for GAD as a distinct and treatable psychiatric disorder. Indeed, few primary care physicians are aware that specific diagnostic criteria and diagnostic tools exist. Research into GAD in the past has also been complicated by the use of different definitions. The concept and diagnostic criteria of GAD have changed significantly since its formal introduction in DSM-III in 1980, several times in the subsequent revisions, and, to date, there are still differences in the understanding of GAD between Europe and the United States. These differences are predominantly due to the use of differing diagnostic criteria: in Europe the use of the 10th *International Classification of Diseases* (ICD-10) prevails, whereas in the United States and in research the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) is preferred.

Historically, the study of GAD has been further hindered by methodological difficulties occurring during research. For example, few reliable assessment methods have been available until recently. Considerable developmental work during the 1990s resulted in more appropriate diagnostic modules,[5] although the instruments that are in use still differ in their conceptual backgrounds, which can result in variability in their findings. Some measures are polythetic,

Table 1. Prevalence of Generalized Anxiety Disorder in General Population Surveys[a]

Source	Diagnostic Criteria[b]	Lifetime Prevalence, %	12-Month Prevalence, %	Current Prevalence, %
Weissman et al,[10] United States	RDC	…	…	2.5
Angst et al,[11] Zurich, Switzerland	DSM-III	…	3.8	…
Blazer et al,[12]				
ECA study, Durham, NC	DSM-III	6.6	3.6	1.2
ECA study, St Louis, Mo	DSM-III	6.6	2.9	1.3
ECA study, Los Angeles, Calif	DSM-III	4.1	2.0	1.4
Stefansson et al,[13] Iceland	DSM-III	21.7	…	…
Chen et al,[14] Shatin, Hong Kong	DSM-III	7.8 males 11.1 females	…	…
Faravelli et al,[15] Florence, Italy	DSM-III-R	5.4	…	2.8
Wittchen et al,[16] NCS, United States	DSM-III-R	5.1	3.1	1.6
Offord et al,[17] Ontario, Canada	DSM-III-R	…	1.1	…
Feehan et al,[18] Dunedin, New Zealand	DSM-III-R	…	[1.8]	…
Canals et al,[19] Spain	DSM-III-R	…	…	[0]
Wittchen et al,[20] Munich, Germany	DSM-IV	[0.8]	[0.5]	…
Jenkins et al,[21] Great Britain	ICD-10	…	…	6.4
Bhagwanjee et al,[22] South Africa	DSM-IV	…	…	3.7
Carter et al,[23] GHS, Germany	DSM-IV	…	1.5	…

[a]Adapted, with permission, from Carter et al.[23] Abbreviations: DSM = *Diagnostic and Statistical Manual of Mental Disorders*, ECA = Epidemiologic Catchment Area, GHS = German National Health Interview and Examination Survey, ICD = International Classification of Diseases, NCS = National Comorbidity Survey, RDC = Research Diagnostic Criteria. Prevalence rates in brackets indicate that the sample comprised only adolescents.
[b]All studies using DSM-III used 1-month instead of 6-month criteria (as used in DSM-III-R and DSM-IV).

for example, the Structured Clinical Interview for DSM (SCID)[6] and the World Health Organization's Composite International Diagnostic Interview (CIDI),[7] both designed specifically for administration of the apportionalized DSM criteria. On the other hand, others are of a syndromal nature, for example, the Clinical Interview Schedule (CIS)[8] and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN),[9] resulting in differing rates.

As a consequence of these issues, direct cross-study comparisons are difficult, especially when interpreting findings not based on the same diagnostic system or instrument (DSM-III-R, DSM-IV, or ICD-10 criteria). Therefore, clear epidemiologic evidence for prevalence and risk factors for GAD has, until recently, been poor.

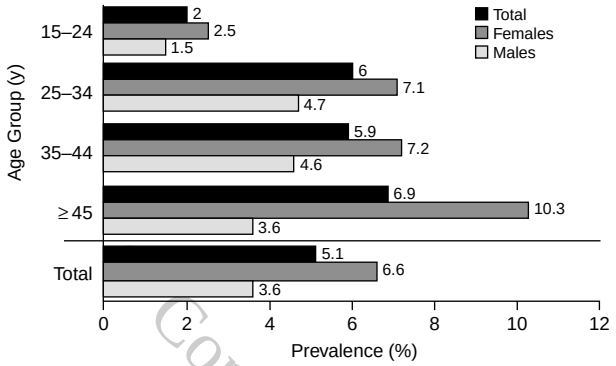
Prevalence of GAD

Despite the fact that there have been many changes in the diagnostic criteria for GAD during recent years, reported lifetime prevalence estimates in the general population (Table 1) are remarkably stable, compared with the considerable variance observed with other psychiatric disorders, such as depression and panic disorder, over a similar age span. Based on more recent studies, the most likely lifetime prevalence rates for GAD in the general population are 5% using DSM criteria and may be slightly higher when using the wider ICD-10 criteria (6.5%). Current and 12-month prevalence rates for GAD are also reported in Table 1; these estimates depend largely on the rigidity of the definition of point prevalence and are subject to more variation than lifetime prevalence estimates. The most likely current prevalence rate in the general population seems to be in the range of 2% to 3% (DSM criteria).

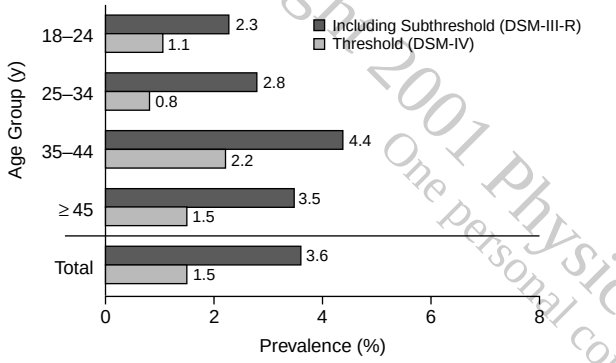
The National Comorbidity Survey (NCS),[24] performed in a representative sample of the U.S. general population (aged 15–54 years), is the largest study to report epidemiologic findings for GAD to date.[16] Using CIDI/DSM-III-R criteria in more than 8000 respondents, a lifetime prevalence estimate of 5.1% (3.6% in males and 6.6% in females) and a 12-month prevalence rate of 3.1% (2.0% in males and 4.3% in females) were reported. The lifetime prevalence estimate is in relatively good agreement with the findings of several other large epidemiologic studies that have been conducted throughout the world in recent years (see Table 1). The 12-month prevalence rate found by the NCS should be regarded with caution, however, since the CIDI is designed to gather lifetime prevalence rates and did not assess the presence of all of the disorder's criteria in the preceding 12 months and thus might include a high proportion of people with lifetime GAD who have only had some significant signs of the disorder during the previous month. The 12-month prevalence estimates of threshold GAD were recently found to be lower in the German National Health Interview and Examination Survey, Mental Health Supplement (GHS).[23] This study used the slightly stricter DSM-IV criteria (which use the additional criteria of difficulty controlling the worrying and a restricted range of associated symptoms), which increase the duration criterion from 1 month to 6 months compared with DSM-III-R, to examine GAD and other disorders in a representative sample of the German population (over 7200 adults). Using a 12-month version of the Munich-CIDI,[25] the 12-month prevalence rate for GAD (meeting all DSM-IV criteria) was found to be 1.5% (1.0% in men and 2.1% in women). If, however, lifetime GAD cases with still

Figure 1. Prevalence of Generalized Anxiety Disorder[a]

A. Lifetime Prevalence (CIDI and DSM-III-R criteria)[b]



B. Twelve-Month Prevalence (Munich-CIDI and DSM-IV criteria)[c]



[a]Abbreviations: CIDI = Composite International Diagnostic Interview, DSM = *Diagnostic and Statistical Manual of Mental Disorders*.
[b]Data from the National Comorbidity Survey.[16]
[c]Data from the German National Health Interview and Examination Survey, Mental Health Supplement.[23]

existing 12-month subthreshold GAD syndromes are counted as well—as was the case in the NCS study—an almost identical 12-month rate of 3.6% (2.4% in men and 4.9% in women) was confirmed. In addition, the disorder was found significantly more frequently in women than in men (odds ratio [OR] = 2.1, $p < .05$). The investigators also determined prevalence rates for subthreshold expressions of GAD by using different time criteria for duration, such as worrying for at least 1 month (7.8%) or worrying for at least 3 months (4.1%), and concluded that long periods of anxious worrying associated with subthreshold GAD symptoms are much more widespread in the community than threshold GAD.

When prevalence data from the NCS and GHS are examined by age, it is clear that for both lifetime and 12-month prevalence rates, the lowest rates for GAD occur in the younger age groups and the highest rates are found in the older study participants (Figure 1).[16,23] In the GHS, the likelihood of receiving a diagnosis of GAD increased significantly with age (18–34 vs. 35–65 years: OR = 1.0, $p < .05$) when controlling for differences in gender, with point prevalence rates up to 4.4% in women aged 45 or older. These findings are consistent with the lower prevalence rates for GAD recorded in studies of adolescents and young adults (see Table 1).

GAD, in common with panic disorder, is unique among anxiety disorders in that patients commonly present to primary care physicians for treatment.[2] An international World Health Organization study used ICD-10 criteria with the CIDI to assess GAD and estimated the current prevalence of GAD to be approximately 8% of all primary care attendees.[1] A more recent reanalysis confirmed these results by using more sophisticated analyses, finding a mean current prevalence rate of 7.9%.[2] This study also found a wide range of prevalence rates across the participating countries, for example, 3.8% in Italy and 14.8% in Greece, possibly owing to differences in the way that countries and regions organize the provision of primary care services. It is noteworthy that this study suggests that the point prevalence rate of GAD is considerably higher in primary care than that reported in the general population (see Table 1), suggesting that GAD patients are high utilizers of primary care resources. This is in contrast to social anxiety disorder and most other anxiety disorders, for which the point prevalence in the general population is much higher than in primary care and subjects are unlikely to present to their family doctor owing to the nature of the condition.[26]

COURSE OF GAD

The presentation of GAD in primary care is similar to that of other anxiety disorders in that patients are unlikely to present directly and openly with complaints of anxiety symptoms.[1] In fact, it is most likely that patients with GAD will present with somatic and sleeping problems.

The pattern of onset with GAD is different from that seen with other anxiety disorders; whereas most anxiety disorders clearly develop before the age of 20 years,[27] prevalence rates for GAD in adolescents and young adults are usually low and then increase substantially with age.[23] Notably in the GHS,[23] few cases of full-blown DSM-IV GAD occurred before the age of 25 years. This was particularly true among men. There was also a strong increase in the incidence of GAD later in life: for women, this occurred after the age of 35 years, whereas in men, the increase occurred after the age of 45 years. Furthermore, among respondents with at least 3 months of worrying, older subjects (aged 35–65 years) were more likely than younger subjects (aged 18–34 years) to have reported that their worrying had lasted for at least 6 months (OR = 3.94, $p < .05$). Thus, older people worry more and for longer periods of time than their younger counterparts. These findings are supported by a community study in over 3100

older adults (aged 55–85 years), which found that GAD was the most frequent anxiety disorder in this elderly population (7.3%).[28]

Results from the GHS[23] also show that the 12-month prevalence of extended worrying (worrying for at least 1 month) is lower in younger than in older participants. However, worrying for long periods of time carries the same risk of developing full syndromal DSM-IV GAD irrespective of the age group.

GAD is a chronic condition in adults with a waxing and waning course. In younger patients, the course is more variable. Full and partial 6-month remission rates among lifetime cases have shown that only one third of all patients with GAD have spontaneous remission.[16]

GAD is frequently associated with other psychiatric disorders. In the NCS, approximately two thirds of current (1-month) DSM-III-R GAD cases fulfilled criteria for at least one other disorder.[16] GAD is frequently associated with depression or other anxiety disorders but it is only infrequently associated with substance abuse disorders.[16,23] At the same time, however, it is noteworthy that these seemingly extremely high rates of comorbidity were shown to be not remarkably different from those of other disorders, such as panic disorder and bipolar disorder.[23,29] Comorbidity especially with major depressive disorder has been shown to significantly lower the probability of diagnosis and treatment of GAD and to increase disability and impairment.[30] (For further discussion of comorbidity in GAD, see the article by Stein in this supplement.[31])

CORRELATES AND RISK FACTORS FOR GAD

The NCS[16] and GHS[23] have both shown that the prevalence of GAD increases with age and that the disorder is more common in females than in males. In addition, a number of significant correlates for GAD have been identified. These include being previously married (separated, widowed, or divorced), not working, or being a housewife.[16] The NCS was also able to conclude that urbanicity, income, education, and religion lack significant association with GAD.[16]

Although GAD is more prevalent in women than in men and occurs more frequently in the unemployed or those that work at home than in employed people, only 16.9% of cases of GAD are found in nonworking homemakers. Even among females with GAD, the proportion of housewives does not exceed 25%.[23] Therefore, GAD is not a disorder that is solely found in housewives.

BURDEN OF GAD

The NCS found that there is a considerable degree of impairment, professional help-seeking, and medication usage to relieve symptoms in people with GAD, whether or not they had a comorbid mental disorder.[16] To assess the disability and impairment caused by pure GAD, analyses of data from studies that control for comorbid disorders, which may affect quality of life, have been implemented. Kessler and coworkers[32] conducted a combined analysis of 2 U.S. general population studies (NCS[16] and Midlife Development in the United States Survey[32]) to assess whether DSM-III-R–defined GAD is itself associated with impairment or whether the impairment is due to comorbid depression or other comorbid disorders. Assessing the proportion of patients with at least 1 day of disability/impairment in the past month, the authors showed that the impairment associated with GAD alone is not only marked, but is equivalent in magnitude to the impairment caused by major depression. The highest levels of impairment were seen when GAD co-occurred with major depression.

A similar, more elaborate, recently published analysis, which included a wider range of impairment and disability measures, assessed disability in individuals with pure DSM-IV–defined GAD and GAD comorbid with major depression.[30] The analysis used data from the GHS obtained from the Work Productivity and Activity Impairment questionnaire (WPAI)[33] and the 36-item short-form (SF-36).[34] Impairment was defined as number of days completely lost plus number of days limited in the past month. Approximately 48% of patients with comorbid GAD and major depression, 34% of those with pure GAD, and 21% of those with pure major depression had at least 6 days impaired over the past month. This study also considered disability in terms of reduction in work productivity. Approximately 11% of the respondents with GAD and no major depression and 8% of those with major depression and no GAD reported a reduction of at least 50% in activity during the past month; more than 50% and 30% of those respective patients reported some reduction in activity. Thus, GAD is associated with considerable impairment even when no comorbid depression is present.

Since GAD is highly prevalent in the primary care setting, patients with the disorder are likely to be high users of primary care health services, both in terms of the number of visits and the proportion contacting primary care providers because of problems associated with the disorder. GAD is a disabling condition in primary care,[35,36] and the associated social disability is as severe as that seen with chronic somatic diseases.[2]

CONCLUSION

GAD is a highly prevalent psychiatric disorder. The lifetime prevalence rate for GAD in the general population is approximately 5% using DSM-III and/or DSM-III-R criteria and possibly slightly higher (approximately 6.5%) using ICD-10 criteria. In primary care, the point prevalence rate is approximately 8%, making GAD the most frequent anxiety disorder in primary care and the second most frequent psychiatric disorder after depression. In

common with most other anxiety disorders, GAD more often affects women than men, particularly in higher age groups. Unlike other anxiety disorders, GAD rarely occurs in childhood, making it unlikely that GAD is merely a temperament variant, personality trait, or disorder.

GAD is a persistent disorder with a waxing and waning course; only one third of lifetime GAD sufferers in the community experience spontaneous full remission. In the community, GAD also has high, although not necessarily higher, rates of comorbidity with depression and other anxiety disorders compared with the rates of comorbidity found with panic disorder or bipolar disorders. Even in the absence of comorbid disorders, GAD is as disabling as depressive disorders in terms of reduced work productivity and social impairment and is associated with increased use of health care services. GAD is a chronic, prevalent, and impairing psychiatric disorder that requires prompt recognition and effective treatment.

REFERENCES

1. Üstün TB, Sartorius N, eds. Mental Illness in General Health Care: An International Study. Chichester, UK: John Wiley & Sons Ltd; 1995
2. Maier W, Gaensicke M, Freyberger HJ, et al. Generalized anxiety disorder (ICD-10) in primary care from a cross-cultural perspective: a valid diagnostic entity? Acta Psychiatr Scand 2000;101:29–36
3. Roy-Byrne P, Katon W, Broadhead WE, et al. Subsyndromal "mixed" anxiety-depression in primary care. J Gen Intern Med 1994;9:507–512
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington DC: American Psychiatric Association; 1994
5. Wittchen H-U, Kessler R, Zhao S, et al. Reliability and clinical validity of University of Michigan-CIDI DSM-III-R generalized anxiety disorder. J Psychiatr Res 1995;29:95–110
6. Spitzer RL, Williams JBW, Gibbon M, et al. The Structured Clinical Interview for DSM-III-R (SCID), 1: history, rationale, and description. Arch Gen Psychiatry 1992;49:624–629
7. World Health Organization. Composite International Diagnostic Interview (CIDI) Version 1.0. Geneva, Switzerland: World Health Organization, Division of Mental Health; 1990
8. Brugha TS, Bebbington PE, Jenkins R, et al. Cross validation of a general population survey diagnostic interview: a comparison of CIS-R with SCAN ICD-10 diagnostic categories. Psychol Med 1999;29:1029–1042
9. Wing JK, Babor T, Brugha T, et al. SCAN: Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry 1990;47:589–593
10. Weissman MM, Myers JK, Harding PS. Psychiatric disorders in a US urban community: 1975–1976. Am J Psychiatry 1978;135:459–462
11. Angst J, Dobler-Mikola A, Scheidegger P. A panel study of anxiety states, panic attacks, and phobia among young adults. Presented at the Research Conference on Anxiety Disorders, Panic Attacks and Phobia; December 9, 1982; Key Biscayne, Fla
12. Blazer DG, Hughes D, George LK, et al. Generalized anxiety disorder. In: Robins LN, Regier DA, eds. Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. New York, NY: The Free Press; 1991: 180–203
13. Stefansson JG, Lindal E, Bjornsson JK, et al. Lifetime prevalence of specific mental disorders among people born in Iceland in 1931. Acta Psychiatr Scand 1991;84:142–149
14. Chen C, Wong J, Lee N, et al. The Shatin Community Mental Health Survey in Hong Kong: major findings. Arch Gen Psychiatry 1993;50:125–133
15. Faravelli C, Guerinni Degl'Innocenti BG, Giardinelli L. Epidemiology of anxiety disorders in Florence. Acta Psychiatr Scand 1989;79:308–312
16. Wittchen H-U, Zhao S, Kessler R, et al. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:355–364
17. Offord DR, Boyle MH, Campbell D, et al. One-year prevalence of psychiatric disorder in Ontarians 15–64 years of age. Can J Psychiatr 1996;41: 559–563
18. Feehan M, McGee R, Raja SN, et al. DSM-III-R disorders in New Zealand 18-year-olds. Aust N Z J Psychiatry 1994;28:87–99
19. Canals J, Domenech E, Carbajo G, et al. Prevalence of DSM-III-R and ICD-10 psychiatric disorders in a Spanish population of 18-year-olds. Acta Psychiatr Scand 1997;96:287–294
20. Wittchen H-U, Nelson CB, Lachner G. Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. Psychol Med 1998;28:109–126
21. Jenkins R, Lewis G, Bebbington P, et al. The National Psychiatric Morbidity surveys of Great Britain: initial findings from the household survey. Psychol Med 1997;27:775–789
22. Bhagwanjee A, Parekh A, Paruk Z, et al. Prevalence of minor psychiatric disorders in an adult African rural community in South Africa. Psychol Med 1998;28:1137–1147
23. Carter RM, Wittchen H-U, Pfister H, et al. One-year prevalence of subthreshold and threshold DSM-IV generalized anxiety disorder in a nationally representative sample. Depress Anxiety 2001;3:78–88
24. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
25. Wittchen H-U, Pfister H, eds. Manual und Durchfuehrungsbeschreibung des DIA-X-M-CIDI. Frankfurt, Germany: Swets & Zeitlinger; 1997
26. Lecrubier Y, Wittchen H-U, Faravelli C, et al. A European perspective on social anxiety disorder. Eur Psychiatry 2000;15:5–16
27. Wittchen H-U, Lieb R, Schuster P, et al. When is onset? investigations into early developmental stages of anxiety and depressive disorders. In: Rapoport JL, ed. Childhood Onset of "Adult" Psychopathology: Clinical and Research Advances. Washington, DC: American Psychiatric Press; 1999:259–302
28. Beekman AT, Bremmer MA, Deeg DJ, et al. Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam. Int J Geriatr Psychiatry 1998;13:717–726
29. Kessler RC. The epidemiology of pure and comorbid generalized anxiety disorder: a review and evaluation of recent research. Acta Psychiatr Scand Suppl 2000;406:7–13
30. Wittchen H-U, Carter RM, Pfister H, et al. Disabilities and quality of life in pure and comorbid generalized anxiety disorder and major depression in a national survey. Int Clin Psychopharmacol 2000;15:319–328
31. Stein DJ. Comorbidity in generalized anxiety disorder: impact and implications. J Clin Psychiatry 2001;62(suppl 11):29–34
32. Kessler RC, DuPont RL, Berglund P, et al. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. Am J Psychiatry 1999;156:1915–1923
33. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353–365
34. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36), 1: conceptual framework and item selection. Med Care 1992;30: 473–483
35. Ormel J, Von Korff M, Üstün B, et al. Common mental disorders and disability across cultures: results from the WHO collaborative study on psychological problems in general health care. JAMA 1994;272:1741–1748
36. Schonfeld WH, Verboncoeur CJ, Fifer SK, et al. The functioning and well-being of patients with unrecognized anxiety disorders and major depressive disorder. J Affect Disord 1997;43:105–119