Generalized Anxiety Disorder: Nature and Course

Hans-Ulrich Wittchen, Ph.D., and Jürgen Hoyer, Ph.D.

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.

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eralized 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, the availability of reliable diagnostic criteria and instruments, 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.

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, 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,
for example, the Structured Clinical Interview for DSM (SCID)\(^8\) and the World Health Organization’s Composite International Diagnostic Interview (CIDI),\(^2\) 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.\(^6\) 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,\(^23\) 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

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<th>Source</th>
<th>Diagnostic Criteria</th>
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\(^a\)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).
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).\(^1^6,2^3\) 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.\(^2^6\)

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,\(^2^7\) prevalence rates for GAD in adolescents and young adults are usually low and then increase substantially with age.\(^2^3\) Notably in the GHS,\(^2^3\) 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 patients.
older adults (aged 55–85 years), which found that GAD was the most frequent anxiety disorder in this elderly population (7.3%).

Results from the GHS 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.

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. GAD is frequently associated with depression or other anxiety disorders but it is only infrequently associated with substance abuse disorders. 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. 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. (For further discussion of comorbidity with GAD, see the article by Stein in this supplement.)

CORRELATES AND RISK FACTORS FOR GAD

The NCS and GHS 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. The NCS was also able to conclude that urbanicity, income, education, and religion lack significant association with GAD.

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%. 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. 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 conducted a combined analysis of 2 U.S. general population studies (NCS and Midlife Development in the United States Survey) 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. The analysis used data from the GHS obtained from the Work Productivity and Activity Impairment questionnaire (WPAI) and the 36-item short-form (SF-36). 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, and the associated social disability is as severe as that seen with chronic somatic diseases.

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.

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Dr. Nutt: Is there any work on life events in generalized anxiety disorder (GAD)? In a situation where there is a threat of redundancy, for example, you could imagine that GAD would increase and eventually evolve into depression.

Dr. Wittchen: George Brown has done work on that in the past [Finlay-Jones R, et al. Psychol Med 1981;11:581–599], although possibly using different concepts of GAD, and found that danger events as opposed to threat events play a role in depression. The problem in GAD, however, as a chronic long-term disorder, is that it is extremely rare to have life events that are not confounded with the disorder. As part of a longitudinal data set, we have looked into the question of when GAD starts and what precedes it [Wittchen H. In: Angermeyer MC, ed. From Social Class to Social Stress. Berlin, Heidelberg, Germany: Springer-Verlag: 1987]. For adults, you almost never get nonconfounded life events or conditions, except for the finding that GAD is associated with an increased number of events relating to chronic physical diseases as well as other negative stressful conditions rather than events. Beyond this, it is hard to decide whether the event or chronic condition has been caused by GAD or vice versa. Even in young people, our more recent prospective data [Krause P, et al. Fortschritte der Medizin. In press] have rarely revealed specific life events as significant predictors for GAD. There are, however, some indications that chronic difficulties (as opposed to events) regarding the patient’s family health and work or school domains seem to be related to the subsequent onset of GAD. So, maybe there are daily hassles making life extremely difficult for individuals with GAD rather than significant life events, as typically seen in depressive disorders.

Dr. Ballenger: Is there a history of trauma in individuals with GAD? You could certainly ask about that.

Dr. Wittchen: In the young cohorts (14- to 24-year-olds), we have seen that the onset of GAD is preceded in 57.1% of the sample by traumatic events. Perkonigg et al. [Acta Psychiatr Scand 2000;101:46–59] also confirmed a significantly adjusted hazard ratio of posttraumatic stress disorder (PTSD) as a significant predictor for the onset of GAD.

Dr. Davidson: I wonder if GAD could be a nonphobic form of PTSD, without the recurrent intrusions.

Dr. Wittchen: That is an interesting thought that to my point of view had not been examined so far. The work of Perkonigg et al. suggests in 14- to 24-year-olds simply that GAD and PTSD are highly comorbid and that among these people the majority of GAD cases have a preceding PTSD as well as predominantly preceding traumatic events. However, I want to add caution to this finding because we do not know whether this relationship is also present in older adults, and that probably needs further investigation.

Dr. Borkovec: Yes, it is a confusing picture. Around 50% of the adults with GAD we see report a PTSD criterion A traumatic event at some time in their past, but so will 25% of our healthy control group. Yet, when we ask them about the origin of GAD, they are rarely able to specify a particular event.

Dr. Lecrubier: Your comments about the likelihood of developing GAD are extremely interesting. You remarked that among younger people with a short-term anxiety condition, 20% will develop GAD and 80% will not [Lieb R, et al. Acta Psychiatr Scand 2000;101:194–208]. Do we have any criteria to define these 2 groups?

Dr. Wittchen: No, we have not examined this so far. These people were observed over 5 years with intervals of about 1 to 2 years between assessments. Symptomatology was assessed at all timepoints, but a full description of GAD symptoms was made only if the duration was more than 1 month. Thus there was some imprecision. Interpretation of data, such as stating that “22% are fully remitted,” means that people with full GAD in previous waves said “no” to the stem question at follow-up. This means that they had not even 1 month during the past year in which they were worrying almost every day. They might have had 3 weeks and then during the next week they had 2 bad days and 3 good days, but then they would not answer questions from that section of the assessment instrument at all. So, we are unable to describe adequately the situation in people who are simply symptomatic over short periods of time.

Dr. Lecrubier: Since remission rates are low, even with some intervention, there is a justification for long-term treatment. The fact that individuals with GAD are seeking help in primary care, and consulting frequently, shows that the current system is not handling them properly.

Dr. Wittchen: Yes, maybe, but you have to take into account that in terms of treatment our past analyses have asked only about generalized anxiety “problems” and whether sufferers had contacted any primary care physician or mental health specialist about these problems at any time. Around 80% tell us that they had talked with their doctor several times, but we have not seen in our data that they had received any specific type of intervention for these problems. So taking these crude indications for treatment, you might be right.

Dr. Ballenger: So, one issue is that these individuals have chronic illness but are getting no treatment for GAD
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and depression. You stopped short of your integrated hypothesis. Can you say something about that?

**Dr. Wittchen:** Certainly, one way of analyzing and handling our data, beyond merely the diagnostic findings and comorbidity, is to examine generalized anxiety as a syndrome with a certain duration, similar to the way we deal with major depressive syndromes. Our epidemiologic database allows such examination from cross-sectional as well as longitudinal perspectives. This type of syndromal analysis reveals, consistent with the comorbidity findings, some people with both cross-sectional and pure generalized anxiety syndromes, as well as considerable overlap between syndromes. With a 1-month duration for generalized anxiety syndromes, the overlap with depression is large (52%), but with a 6-month duration, the overlap is small [Wittchen H-U, et al., unpublished data]. Taking into account risk factors and vulnerabilities, our preliminary analyses seem to suggest that generalized anxiety and depressive syndromes are 2 different key manifestations of most “internalizing” mental disorders, separated by partly different yet partly overlapping risk factors and vulnerabilities. This type of preliminary modeling exercise will hopefully tell us whether GAD and depression are part of a same syndrome spectrum of problems or whether there are sufficiently unique types of associations justifying the separation of generalized anxiety and major depression.

**Dr. Ballenger:** Is this neuroticism reborn?

**Dr. Wittchen:** I consistently avoid the word neurotic; it takes us back to the past of poorly defined conditions. The construct is in this context unspecific and potentially misleading. I think it is of high priority and would be a more promising approach for the future to determine which specific cognitive, affective, and behavioral aspects of neuroticism are clinically useful and correspond behaviorally to specific phenomena of the disorder. In general, our research does not favor the neurotic spectrum hypothesis at this point.

**Dr. Ballenger:** What do you think about the data suggesting that GAD precedes depressive disorders?

**Dr. Wittchen:** In about one third of cases, GAD is clearly followed by depression, but it is also noteworthy that there are a considerable number of other disorders that may precede GAD as well, such as anxiety disorder and somatoform conditions. This has been a neglected area of research so far, and we are currently analyzing our prospective data in that respect. We need to clarify this issue further in the near future.

**Dr. Stein:** Can you specify time lines?

**Dr. Wittchen:** Retrospectively, in our unpublished EDSP study, the occurrence of secondary depression was reported in the majority of the subjects several years after first onset of GAD. However, in the prospective longitudinal data of our EDSP study, a slightly different and diffuse picture emerges. Some GAD subjects with an early onset, for example, do report increased behavioral inhibition in kindergarten. Later on, there are signs of phobic disorders or other anxiety features such as panic attacks. Then later still a waxing and waning course of GAD symptoms is observed, before full GAD develops in later adolescence. Taking these longitudinal data with subthreshold expression of GAD, we see a much shorter time interval, of only several months to 1 to 2 years, between the onset of full GAD and onset of secondary depression. Thus the question is what is the onset of GAD—the occurrence of significant GAD symptoms, or the time you meet all criteria for a period of 6 months?

**Dr. Stein:** What is the time line for depression? You say one third start off with GAD, but how long does it take before depression develops?

**Dr. Wittchen:** The time frame differs by the type of anxiety disorder. I have not yet analyzed these data in detail in this respect. In social phobia, the highest risk for developing depression is, on average, after 6 to 7 years.

**Dr. Ballenger:** So you do not think there is anything specific about the way GAD moves on to depression?

**Dr. Wittchen:** I am not aware of any study that has looked into this issue. It is an interesting idea to examine vulnerabilities and risk factors directly for various anxiety disorders and compare the similarities and differences with regard to other anxiety disorders and GAD in predicting secondary onset of depression.

**Dr. Nutt:** Do you have personality measures in any of these studies?

**Dr. Wittchen:** Yes, but we have been discouraged so far because high scores on these measures are confounded by the presence of mental disorders. A person with an anxiety disorder for 6 years is almost certain to have a high somatic symptom score on measures for neuroticism, simply because both measures cover similar domains. Also in our unpublished EDSP study, the number of people scoring high on any of the personality measures but having no mental disorder is quite low. So it is a challenge to establish causality. What is interesting with regard to the association of GAD and personality is that GAD in the majority of cases has a pattern of late onset in the early 20s. This finding speaks against the hypothesis that GAD is simply a variant of a personality disorder or a dysfunctional trait of a person.

**Dr. Nutt:** There is a clinical issue of diagnosing GAD in primary care. As in social phobia, in which people say it is “just shyness,” with GAD they say it is “just worrying.”

**Dr. Wittchen:** First let me note that our data have not shown that shyness and social phobia are so closely related. In fact, for women, shyness in childhood might even be a protective factor in some respects. However, there is a significant difference between GAD and “worrying” whenever you use the 6-month duration criterion for GAD. A condition of this duration will almost always cause impairments and disabilities similar in magnitude to those associated with major depression. This clearly speaks against the notion that GAD is “just worrying.”