

Dissolving the Burden of Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is a common disorder marked by excessive anxiety, worry, and somatic manifestations lasting over 6 months. GAD occurs relatively early in life in the majority of individuals; it is often chronic and comorbid with other anxiety disorders, affective disorders, and/or medical conditions. GAD is as functionally debilitating as major depression even without comorbidity and, hence, is associated with considerable economic and societal burdens as well as health care utilization. Underrecognition of GAD and undertreatment of this disorder are major factors contributing to the individual and societal burden of GAD. Earlier long-term studies in GAD reported low remission rates despite treatment. More recent data support the potential for achieving remission in GAD with appropriate treatment. There is a critical need to enhance mental health literacy programs and translate the efficacy data into effectiveness schemes in clinical practice by improving disease management strategies. A conceptual basis for achieving these goals is provided by moving from a disorder model to a disease model in psychiatric practice. This move allows for staging of psychiatric illnesses, with GAD as a prototypical example. For the clinician, the critical paradigm shift is in modifying the treatment goal from the attenuation of symptoms, as in a "response," to the achievement of a state of "remission" (i.e., a virtually asymptomatic state). Remission of symptoms allows for improvement of psychosocial functioning and quality of life and potentially wellness. In this review, a synopsis of the epidemiology, natural history, economic and social cost, and clinical management issues is given as a road map to dissolving the burden of GAD.

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The postmodern world stigmatizes fear and anxiety as weaknesses. "No fear" is worn as a badge of valor, and those who fear are considered vulnerable and inferior. Fear focuses primarily on physical threat, while anxiety is driven more by social or abstract threats (i.e., to one's self-esteem). Although fear and anxiety overlap considerably in subjective experience, there are important differences in the triggering mechanisms for their activation. Thus anxiety, if controlled with treatment, does not void the fear response in appropriate situations.

Generalized anxiety disorder (GAD), according to the DSM-IV-TR criteria,¹ is characterized by excessive anxiety and uncontrollable worry that persist for longer than 6 months. Thus, at its core, GAD has emotional and cognitive components. Additional symptoms required for the DSM-IV diagnosis of GAD include at least 3 of the fol-

lowing 6 symptoms, which are present for the majority of days: restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and impaired sleep cycle. However, GAD can also present with prominent somatic symptoms in the absence of end-organ abnormality and without prominent emotional symptoms. Such individuals with prominent somatic concerns quite often argue that their excessive worry is an appropriate response to their perception of a realistic medical danger.

A recent national survey of mental health has shown that of the patients who met the criteria of GAD in the previous year, only about one third achieved remission.² Similar low remission rates have been reported in other long-term studies of GAD.^{3,4} Thus, approximately two thirds of individuals with GAD continue to exhibit symptoms, prolonging the burden of the disease. Following is a synopsis of the epidemiology, natural history, economic and social cost, and clinical management issues pertaining to GAD that will lay the groundwork for an assessment of why the burden of GAD persists.

EPIDEMIOLOGY AND NATURAL HISTORY

The Epidemiologic Catchment Area (ECA) program of the National Institute of Mental Health showed a 1-year prevalence of 3.8% (including comorbid disorders) and a

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Table 1. Comparison of 1-Year and Lifetime Prevalence Rates of Generalized Anxiety Disorder: Data From the Epidemiological Catchment Area (ECA)^a Study and the National Comorbidity Study (NCS)^{b*}

Study	N	1-Year Prevalence, %	Lifetime Prevalence, %
ECA ^a	8329	3.8 ^c (2.7 ^d)	4.2–6.6
NCS ^b	8098	3.1 ^c (1.1 ^d)	5.1

*Adapted, with permission, from Judd et al.⁶

^aBlazer et al.⁵

^bWittchen et al.⁷

^cComorbid mental disorders included.

^dPanic disorder and major depressive disorder excluded.

lifetime prevalence of 4.2% to 6.6% for GAD.⁵ The National Comorbidity Survey (NCS) reported similar findings^{6,7} (Table 1). Thus, an estimated 9 million Americans will suffer from GAD during their lives.^{6,8} Several reports, however, have suggested that the prevalence of GAD within special populations, such as psychiatric outpatients and patients with human immunodeficiency virus (HIV) infection, may be much higher than that reported for the general population.^{7,9,10}

Data from the Harvard/Brown Anxiety Research Project (HARP) indicate that the age at onset of GAD varies depending on whether it is a primary or secondary anxiety disorder.¹¹ The age at onset for GAD may be as early as 13 years when it is the primary disorder and as late as 30 years when it is secondary to another anxiety disorder.¹¹ The mean age at onset for GAD is 21 years.³

The mean duration of GAD has been reported to be 20 years, with fluctuations in severity throughout the course of illness.³ Using DSM-III criteria, the ECA study reported that roughly 40% of GAD patients continued to have symptoms for 1 to 5 years, and 10.1% to 16% continued to have symptoms for more than 20 years.⁵ Thus, the symptoms of GAD may be chronic but are not necessarily continuous. This is consistent with a recent study by Wittchen and colleagues¹² indicating that GAD may not be as persistent as the earlier literature indicates because symptoms of anxiety tend to wax and wane.

Distressing life events may trigger the development of anxiety.¹³ The social risk factors associated with GAD are gender (female), age (older than 24 years), marital status (separated, divorced, or widowed), and employment status (being unemployed).⁷ Women are twice as likely as men to suffer from GAD.^{7,14} Because factors such as being a homemaker or being unemployed have been identified as significant correlates for GAD, the ramifications of traditional sex roles may contribute to the gender differences in the prevalence of this disorder.⁷ Moreover, GAD appears to correlate with social risk factors indicative of a generally stressful life.¹⁵ The high prevalence of GAD in the unemployed may reflect social and familial stress experienced by unemployed individuals,⁵ hence, those with clinically significant anxiety may

Table 2. Prevalence Rates of Lifetime Comorbid Mood Disorders Among National Comorbidity Study Respondents With Lifetime Generalized Anxiety Disorder (N = 418, weighted)^a

Disorder	Prevalence, %
No mood disorder	15.9 (± 2.0)
Any unipolar disorder (minor, dysthymic, or major depressive disorders)	67.4 (± 2.9)
Any bipolar disorder (mania or hypomania)	16.7 (± 2.5)
Total	100

^aAdapted, with permission, from Judd et al.⁶

be unable to muster the motivation necessary to enter the work force.⁷

COMORBID MOOD AND ANXIETY DISORDERS

One of the hallmark features of GAD is the prevalence of comorbid mood and anxiety disorders. Using DSM-III-R criteria, the NCS reported that 89.8% to 90.4% of patients with GAD had a comorbid psychiatric disorder during their lifetime and 65% to 66.3% had a current comorbid psychiatric disorder.⁷ Comorbidity is generally associated with greater severity and persistence of anxiety and mood disorders.¹⁶ The most common disorders to co-exist with GAD are major depression, dysthymia, panic disorder, and agoraphobia.^{5,7} Unipolar depression is the most common mood disorder that is comorbid with GAD (~ 67%) (Table 2),⁶ and it is projected to be a leading cause of disability-adjusted life-years in 2020.¹⁷ Preventive and palliative measures to reduce the incidence of unipolar depression should include similar measures for GAD because of its high comorbidity. Data from the HARP study showed that GAD was equally likely to occur as either a primary anxiety disorder or a secondary anxiety disorder (see review by Kessler¹⁸).

THE ECONOMIC AND SOCIETAL COSTS OF GAD

A study by Greenberg and colleagues¹⁹ utilized NCS data in a multivariate regression analysis to calculate the cost associated with anxiety disorders (adjusting for demographic characteristics and comorbid psychiatric conditions). Anxiety disorders cost the health care system approximately \$68.1 billion annually (in 1998 dollars). Nonpsychiatric direct medical costs accounted for 54% of total costs,¹⁹ partly the result of the somatic expressions of the illness. Physicians are prone to order multiple medical tests to document absence of end-organ pathology, often without considering GAD in their differential diagnoses. Appropriate diagnosis and successful treatment of GAD hold the potential for enormous medical cost savings. Direct psychiatric treatment accounted for an additional 31% of total costs. Workers with anxiety disorders are at high risk for cutting back in at-work performance due to

Table 3. Service Utilization Over a 3-Month Period^a

Resource	GAD With	GAD Without	p Value
	Comorbidity (N = 604) %	Comorbidity (N = 395) %	
Hospitalization	11.8	5.1	< .001
Emergency room + surgery	4.0	1.8	< .05
Psychiatry	3.6	1.8	NS
Internal medicine	4.5	1.8	< .05
Diagnostic and laboratory tests	39.7	25.8	< .001
Biochemistry, hematology tests	32.8	22.8	< .001
X-rays, computed tomography	5.8	2.5	< .05
Electrocardiograms, cardiovascular tests	15.7	7.6	< .001
Others	11.8	5.3	< .01
Consultations with general practitioners	59.9	60.6	NS
Consultations with psychiatrists	61.8	57.2	NS
Consultations with other specialists	29.0	14.7	< .001
Use of medication			
Anxiolytics	82.8	74.2	< .001
Psychotropics	28.2	14.7	< .001
Cardiovascular drugs	8.4	2.8	< .001
Others	11.4	2.8	< .001

^aAdapted, with permission, from Sou tre et al.²⁰

emotional problems, i.e., the extent of absenteeism tends to be greater among anxious employees.¹⁹ Hence, with reference to total costs, workplace-related costs account for 10%; pharmaceutical costs and mortality costs account for 2% and 3% of the total economic burden, respectively. In comparison to “pure” GAD, GAD with comorbid psychiatric illnesses is associated with higher total costs^{19,20} arising from higher rates of emergency room use, general medicine-related hospitalization, laboratory testing, consultation with specialists, and use of pharmaceutical treatments (Table 3),²⁰ as well as indirect costs.

The social costs of anxiety disorders are multifactorial. A relatively high percentage of patients with GAD are likely to be unemployed or dependent on public assistance.^{21,22} Social impairment substantially contributes to the indirect costs. A study using the Social Disability Schedule (which measures adjustment to daily routine, energy, and performance; contact with coworkers; and other daily activities) showed that patients with GAD are significantly impaired—39%, to a marked degree.²³ In addition, in a comparison of patients with GAD and patients with chronic somatic diseases, the presence of GAD for at least a month was associated with social disability that was either comparable to or higher than that seen in patients with chronic somatic diseases. This finding is corroborated by data showing self-reported impairments in work and social roles in patients with anxiety disorders.¹³ Predictably, the rate of psychosocial dysfunction is even higher in cases of psychiatric comorbidity involving GAD and/or other anxiety disorders.^{6,13,23,24} It is noteworthy that the social impairment observed in pure GAD is similar to that in noncomorbid major depressive disorder.²⁴

More than 28% of individuals with GAD report that the disorder interferes in their lives, and many individuals with GAD have reported interference with daily activities, professional help-seeking, and use of medication.⁷ GAD patients have self-reported poorer mental health than the general population and those with panic disorder.^{22,24} Concurring data were obtained from a quality of life survey by Wittchen et al.²⁵ of patients with pure and comorbid GAD (according to DSM-IV diagnostic criteria) and major depression, respondents with pure GAD had significantly poorer scores on several Short-Form Health Survey scales than respondents with pure major depression. Essentially, with or without comorbid depression, GAD leads to considerable impairment in aspects of work productivity, functionality, and overall quality of life.

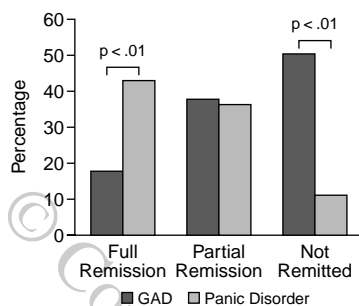
TREATING TOWARD REMISSION

As described in the previous section, GAD is associated with high nonpsychiatric direct medical costs, a finding that is consistent with the reported association between anxiety disorders and medical morbidity.^{26,27} Health care initiatives geared toward improving the recognition and treatment of GAD can lead to a reduction in health care utilization and improvement in quality of life.

As many as 50% of individuals with GAD do not seek treatment for this mental health problem, a factor contributing to the underrecognition of this disorder.² Some of those who do seek psychiatric assistance are inadequately treated. These findings strongly suggest that there is a need to raise the level of effectiveness of current practice by implementing clinical practice guidelines, enhancing mental health literacy programs, and improving disease management strategies.² An important clinical management strategy is to modify the treatment goal toward the attainment of remission.

The current criteria for assessing treatment efficacy are based on scales that largely measure symptom severity, such as the Hamilton Rating Scale for Anxiety (HAM-A), or global measures of illness severity and improvement, such as the Clinical Global Impressions scale (CGI). Scales that measure signs and symptoms can have appropriate psychometric properties such as reliability but may not validly capture the full range of the impairment resulting from the underlying pathophysiology. For example, the correlation between symptom and functional measures in GAD is only modest. It is quite possible that the fundamental pathology in GAD is neuropsychological deficits that mediate functional impairment but are not necessarily reflected as subjective symptoms or objective clinical signs. Global measures such as the CGI address symptom manifestations and functioning and are structured in a manner that is dependent on the judgment of the rater. Thus, the behavioral manifestations of signs and symptoms should be considered surrogate markers for the

Figure 1. Rates of Remission of Generalized Anxiety Disorder (GAD) and Panic Disorder at 5-Year Follow-Up Period Using the Psychiatric Rating Scale Score From the Longitudinal Interval Follow-Up Evaluation^a



^aAdapted, with permission, from Woodman et al.⁴

illness of GAD. The truer measure of illness severity may be functional status. With advances in the neurosciences, a day will dawn when the true pathophysiology of GAD can be assessed and the relationships between symptoms, neuropsychological deficits, and functioning can be examined. For now, a comprehensive profile of the disease of GAD requires measuring symptoms and functioning independently.

The duality of symptoms and functioning is also reflected in the conceptual distinction between response and remission. Patients who exhibit a 50% symptomatic improvement from baseline HAM-A or Hamilton Rating Scale for Depression (HAM-D) scores can still have subsyndromal symptoms that can be manifested as suboptimal functioning and social impairment. As in depression, the presence of these residual symptoms may contribute to higher relapse rates.^{28,29} On the other hand, remission is the resolution of illness on both symptomatic as well as functional measures. The patient's presentation is within the normative range of the unaffected population, possessing close to full if not full functionality.³⁰ Some studies have shown that only about one third of individuals who met the criteria for GAD in previous years achieved remission within 5 years²⁻⁴—significantly fewer patients with GAD achieved remission at follow-up (Figure 1).⁴ Data on the response and remission rates with medications like venlafaxine extended release (XR) in the treatment of GAD (see Sheehan³¹ article in this supplement) suggest the potential to enhance the remission rates in the community with appropriate treatment. By setting remission as the goal of treatment, attention is also focused on the quality of life and social functionality of the individual.

Recently, Ballenger³⁰ recommended clinical guidelines for treating GAD to remission. According to these guidelines, the first step is to minimize anxiety, as indicated by the attainment of either a HAM-A score $\leq 7-10$ or a 70% improvement on the HAM-A. The next goal is to eliminate depression, by attaining a HAM-D score ≤ 7 or a 70% im-

provement on the HAM-D. This is followed by the prevention of recurrence of anxiety and depression. The final goal is a resolution of functional impairments. This may be measured by the achievement of a score ≤ 1 on the Sheehan Disability Scale.³⁰ These guidelines suggest that the time course for the resolution of functional impairments may be as long as 3 to 12 months, whereas the initial step of minimizing anxiety may be accomplished within 8 to 12 weeks of the start of treatment.³⁰ This distinction may be particularly important in pharmacotherapy. The immediate alteration in neurochemistry by an antidepressant or anxiolytic agent may be useful in resolving symptoms. However, it is possible that the underlying neural structures that subservise functionality that may have degenerated as a result of illness may take longer to structurally recover and regenerate in response to pharmacotherapy. Therefore, psychosocial functionality may take longer to achieve. Data indicate, however, that even for symptom reduction necessary to achieve remission and a HAM-A score ≤ 10 , treatment for longer than 12 weeks may be required.³⁰

Comorbidity may have implications for the outcome and course of GAD.³ Therefore, depression is considered in the remission guidelines for GAD. Choices of therapeutic intervention and duration of treatment should strongly consider current or probable comorbidity of GAD with depression or other disorders.³⁰ At least 12 months of treatment is recommended to achieve remission of both anxiety and depression.³⁰ It should be noted, however, that guidelines for the treatment of GAD do not specify when it is safe to terminate treatment without the risk of relapse.

Guidelines for remission in anxiety outlined by Ballenger³⁰ delineate the standard that remission should include recovery of function. Treatment to complete remission may entail long-term treatment. The goals for treating GAD should parallel our understanding of its natural history and be consistent with current diagnostic criteria. This involves a paradigm shift in psychiatry, a transition from making patients better (response) to making patients well (remission).

STAGING ILLNESSES LIKE GAD

With the explosion of information in the neurosciences, the field of psychiatry is moving from a *disorder* model to a *disease* model. A disorder model is based on signs and symptoms that are clinically present and can be measured reliably. The disorder model does not explore etiology or pathophysiology, since these can overlap in clinical presentations. Reliability of diagnostic criteria is the driving force behind concepts of disorder, and the diagnostic categories are based on clinical distinctions drawn by expert consensus, theoretical formulations, and treatment response. However, each of these sources is fallible and based on limited knowledge. A disorder model focuses

primarily on symptoms and less on dysfunction, because a symptom that cannot be reliably measured is not included in the diagnostic criteria or assessed in treatment response. However, such symptoms may be the basis of functional impairment. For example, in schizophrenia, the neuropsychological deficits mediate negative symptom (the absence of functions normally present) dysfunction, but the reliably measurable symptoms are positive symptoms such as delusions and hallucinations.

A disease model uses the information derived from the disorder model and explores external validators. It assumes a unique pathophysiology and allows for the exploration of etiology of the illness. It also allows for the finer dissection of signs and symptoms based on potentially different neural pathways to behavioral expression. This permits the attribution of symptoms based on brain functions. A disease model includes functional impairment as it can be mediated by neuropsychological/anatomical/physiologic deficits. A disease model also allows for staging of illness from frank illness to wellness.

- Stage 4. Frank illness with symptoms and dysfunction.
- Stage 3. Response—a significant reduction in symptoms. Response equates with crossing of the diagnostic threshold, i.e., subthreshold symptoms. Residual symptoms are present.
- Stage 2. Remission—symptoms are now largely controlled, such that the symptomatic manifestations are within the range of the unaffected population. Additionally, there is functional improvement such that there is minimal to no psychosocial or work impairment.
- Stage 1. Recovery, but with disease vulnerability—sustained, durable remission over time. However, even in the absence of symptoms and dysfunction, individuals who have had an episode of illness carry a vulnerability for subsequent episodes of illness, or may have some vulnerability even before the first episode of illness. This may be an exaggerated sensitivity to psychological or physiologic challenges. This is analogous to an abnormal glucose tolerance test with a normal fasting blood sugar level, indicating a risk for diabetes mellitus. Another example would be the presence of thyroid autoantibodies while baseline thyroid functions are normal. Such vulnerabilities in psychopathology might be expressed as a behavioral sensitivity to particular stressors like separation or temperamental difficulties in interpersonal interactions.

- Stage 0. Wellness. There are no limitations to fulfillment of the individual's potential or the pursuit of happiness. Personal choice is not limited except by external issues. This is the absence of disease.

CONCLUSIONS

The social risk factors associated with GAD indicate, from a public health perspective, that modifications in an individual's environment would be a prudent primary preventive approach. However, the economic and societal burden of GAD is also attributable to the underrecognition and undertreatment of this disorder. This suboptimal health care emphasizes the need to raise the level of effectiveness of current practice by implementing clinical practice guidelines, enhancing mental health literacy programs, and improving disease management strategies. As research and clinical observations have advanced our understanding of GAD, it is clear that clinicians must undergo a fundamental shift in their approach to the treatment of this anxiety disorder. Although a treatment response from a patient is always encouraging, therapeutic expectations must be raised toward the goal of enhanced social functioning and quality of life, i.e., treating toward remission.

Drug name: venlafaxine (Effexor).

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