The Clinical Presentation of Generalized Anxiety in Primary-Care Settings: Practical Concepts of Classification and Management

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On the basis of our long-term experience in treating family-practice patients and conducting clinical research with them, we propose a practical clinical nosology that takes into account the subsyndromal spectrum of generalized anxiety, as well as patterns of illness, particularly for the family-practice setting. We present an alternative proposal of how to conceptualize generalized anxiety disorders clinically into *acute anxiety, subacute anxiety, chronic anxiety*, and *double anxiety*. This is followed by a discussion of the implications for choosing from among the various anxiolytic treatment options available to the family physician and of the importance of the therapeutic context in which treatment is provided. Anxiolytics are not a panacea, but only tools to allow the patient to help himself or herself. Irrespective of which anxiolytic is chosen, and irrespective of the chronicity of the anxiety, short-term (2 to 6 weeks) anxiolytic therapy—if necessary provided more than once on an intermittent basis—should be the treatment approach of first choice. Data are presented to suggest that 50% of all chronically ill patients who have generalized anxiety disorder could benefit from such a treatment approach.
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Anxiety disorders are widespread in this world. The lifetime prevalence of generalized anxiety (GAD) based on DSM-III-R and ICD-10 criteria is estimated to range from 6% to 10% in the general population with females having a higher incidence than males.[1,2] The mean age at onset is in adolescence, and the duration is frequently chronic, recurrent, or fluctuating. Generalized anxiety often produces social and functional impairment, and it can be incapacitating.[2,3] Less than half of patients who have GAD seek appropriate treatment.[2] This may be a result of the persistent stigma of talking with a physician about an emotional disorder or the low level of recognition of anxiety disorders in primary care, where these disorders are seen most frequently.[4] In fact, GAD accounts for a disproportionate share of health-care dollar utilization.[5] Generally, treatment is provided in primary-care settings. The benzodiazepines are still, as they were 30 years ago, the treatment of choice for many physicians. However, other drugs such as buspirone, a 5-HT_{1A} partial agonist, and antidepressants such as imipramine are also indicated. The risk of physical dependence and the withdrawal symptoms that occur on discontinuation are the major problems with the benzodiazepines, especially when used chronically. How generalized anxiety presents and how it should be managed clinically are the topics of this brief review.

THE SPECTRUM OF CLINICAL ANXIETY

A certain degree of anxiety is integral to human life. Thus, only abnormal or excessive anxiety, out of proportion to identifiable stressors in terms of severity, persistence, or disability, necessitates treatment. In fact, for most anxious patients, their anxiety produces a degree of suffering that is underestimated by outside observers. It pervades the whole spectrum of their activities; it changes the way they look at the environment, hinders them from performing normal life functions, and causes considerable economic expense.

The anxiety states have been defined in the various DSM classifications, the most recent one being the DSM-IV.[6] For the purposes of research, anxiety states have been ever more rigidly defined, with a resulting decrease in the number of patients identified as having GAD in private psychiatric practice. This, however, is quite different in family practice, where these patients frequently present for the first time with their symptoms.

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Table 1. Anxiety Conceptualization and Its Treatment, Revisited*

Type of Anxiety	DSM-IV Diagnosis	Recommended Treatments
Acute anxiety		
Transient anxiety (acute reaction to situational stress)	Nonpathological reaction to stress Acute stress disorder Anxiety not otherwise specified	Passage of time Support 1–7 days of benzodiazepine treatment
Short-term anxiety (reaction to specific life events)	Nonpathological reaction to stress Acute stress disorder Anxiety not otherwise specified	Passage of time Brief (1–4 weeks) anxiolytic therapy Brief counseling Combination of above
Subacute anxiety		
Minor anxiety Brief, intermittent anxiety	Adjustment disorder Anxiety not otherwise specified	Passage of time Brief (2–4 weeks), possibly intermittent, anxiolytic therapy Counseling, including interpersonal therapy Combination of above
Chronic anxiety Continuous anxiety Intermittent anxiety Double anxiety Mild-to-moderate continuous anxiety with episodic bouts of full-fledged anxiety	Generalized anxiety disorder Anxiety not otherwise specified Comorbid symptoms not fulfilling diagnostic criteria Depressive Social phobic Obsessive Panic	Anxiolytic therapies Benzodiazepine Buspirone (preferred choice) Antidepressants (imipramine) (Intermittent drug therapy) Psychological therapies Counseling Interpersonal Cognitive Change of life situation Combination of drug and psychological therapies

*Abbreviation: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

An example of the clinical effect of the increasingly restrictive conceptualization of GAD in the DSM-IV diagnosis is the shift in the duration criteria from a 1-month to a 6-month minimum. This eliminates a large proportion of the spectrum of anxiety disorders observed in clinical settings in the interest of establishing a clean and well-documented core diagnosis. As a result, GAD with a 6-month duration criterion has become the only valid target of clinical research today. This precludes the testing of anxiolytics for clinical forms of generalized anxiety that are commonly observed in most medical settings.

Not only have the diagnostic boundaries of GAD shifted in terms of course of illness, but the defining symptoms of the illness itself have shifted. The present diagnostic criteria favor worries and psychic symptoms of anxiety over somatic ones. This shift has major implications for treatment since somatic symptoms are targeted most effectively by the benzodiazepines. In contrast, buspirone[7] and imipramine[8] appear to be somewhat more effective than the benzodiazepines, at least initially, in the treatment of psychic symptoms.

Thus, shifts in how GAD is defined may alter which medications are most effective and how these medications are used—whether intermittently or chronically. In practice, despite the chronicity of GAD, a significant indication for the benzodiazepine anxiolytics is not the chronic, continuous prescription of medication, but the treatment of the many transient and short-term anxiety conditions that all individuals at times experience. These bouts of generalized anxiety clearly benefit from short-term targeted pharmacotherapy lasting a few days to a few weeks at the most.

CLINICAL CATEGORIES OF ANXIETY

On the basis of our long-term experience in treating family-practice patients and conducting clinical research with them, we propose that additional anxiety-disorder presentations and patterns of illness should be taken into account, particularly for the family-practice setting. As a starting point, we have borrowed from an NIMH-sponsored Insomnia Consensus Conference,[9] as well as from parallel research in affective illness.[10,11]

An alternative proposal of how to conceptualize anxiety disorders (excluding obsessive-compulsive, phobic, and panic disorders) clinically into *acute anxiety*, *subacute anxiety*, *chronic anxiety*, and *double anxiety* is given in Table 1. *Acute anxiety* may be further divided into *transient anxiety*, caused by an acute reaction to situational stress, and *short-term anxiety*, defined as a reaction to specific life events. *Subacute anxiety* (here we borrow from the depression literature) might be divided usefully into *minor anxiety* and *brief intermittent anxiety* lasting, at the most, a few weeks at a time.

Chronic anxiety may be subdivided into either continuously or intermittently present anxiety, and *double anxiety*

Figure 1. Schematic Representation of Transient and Short-Term Anxiety in a Patient Without Chronic Anxiety

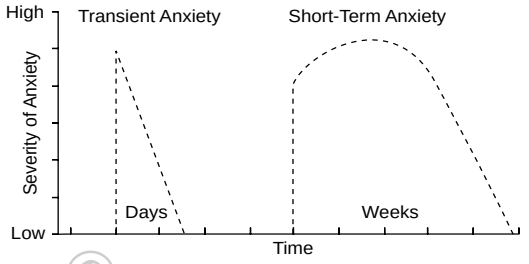
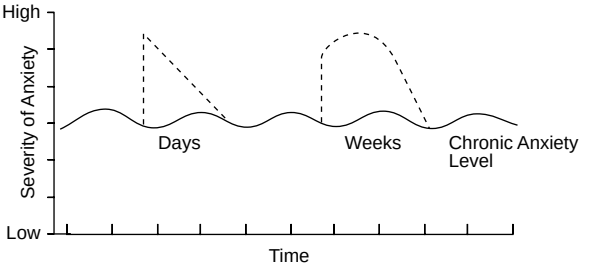


Figure 2. Double Anxiety: Schematic Representation of Two Patterns of Acute, Time-Limited Exacerbation in Chronic Anxiety



consists of episodic bouts of full-fledged GAD anxiety that are superimposed on mild-to-moderate levels of chronic trait anxiety.[12]

The equivalent DSM-IV diagnoses that these proposed clinical categories map onto are also given in Table 1. *Acute anxiety* could well be diagnosed within the framework of DSM-IV as a nonpathologic reaction to stress, an acute stress disorder, or anxiety not otherwise specified (NOS). *Subacute anxiety* would probably fit best into the DSM-IV diagnostic categories of adjustment disorder or anxiety NOS, and *chronic* and *double anxiety* could, according to the DSM-IV, be best diagnosed as GAD or anxiety NOS. In addition, in the chronic-anxiety diagnostic groups, many patients have comorbid symptoms that do not completely fulfill DSM-IV diagnostic criteria, such as depressive, social phobic, obsessive, and panic symptoms. More questionable is the diagnostic identification of GAD patients who have a full-fledged additional DSM-IV diagnosis such as major depressive disorder (MDD) or panic disorder. Such cases should not be diagnosed as GAD but as MDD or panic disorder unless the GAD is clearly the principal diagnosis by virtue of its severity, temporal precedence, and associated disability.

Figure 1 provides a schematic presentation of transient and short-term anxiety occurring in patients free from neurotic or chronic trait anxiety, and Figure 2 illustrates the course-of-illness pattern in patients suffering from double anxiety, i.e., those patients suffering from chronic mild-to-moderate trait levels of anxiety interrupted by short-term exacerbations of their anxiety.

CLINICAL MANAGEMENT OF GENERALIZED ANXIETY

One observation stands out: Most of our proposed clinical categories of anxiety could be acceptably forced into the DSM-IV diagnosis of anxiety NOS. Yet anxiety NOS is a "wastebasket" diagnostic category that provides the nonpsychiatric physician no guidance in the choice of therapy for his or her anxious patients.

Acute and short-term anxiety includes many of thosepatients who at times respond to various stressors with short-term, time-limited anxiety. For these patients, treatment may not be crucial but still may be beneficial in speeding up relief of symptoms. For such acute, short-term anxiety, the benzodiazepines currently are the treatment of choice, since, as mentioned earlier, buspironeand the antidepressants work more slowly than the benzodiazepines. Thus, *acute anxiety* is probably treated best with the passage of time, simple support, or, at most, afew days of targeted treatment with a fast-acting anxiolytic or hypnotic benzodiazepine. *Short-term* anxiety, not lasting more than several weeks, may also be treated with the passage of time—particularly for those patients who are able to cope with their excessive but brief episode of anxiety—or with 1 to 4 weeks of therapy with a benzodiazepine anxiolytic and possibly also buspirone (provided, we hope, within the context of psychological support given by the physician). Similarly, *subacute anxiety* could be managed pharmacologically with 2 to 6 weeks of anxiolytic therapy (benzodiazepine or buspirone), which, in brief intermittent anxiety, may have to be given in multiple brief courses. In subacute anxiety, one should, at least for some patients, also consider psychological counseling or psychotherapy of an interpersonal or cognitive nature.

Finally, for *chronic* and *double anxiety*, the available treatments that have demonstrated efficacy in controlled trials are the benzodiazepines, the 5-HT_{1A} partial agonist buspirone, and possibly the antidepressant imipramine. When these drugs are used for chronic anxiety, many clinicians prefer intermittent to continuous drug therapy. In light of estimates suggesting that more than 3% of the adult population at some time will suffer from chronic (> 1 year) generalized anxiety,[1] it is surprising that research studies designed to address this treatment of chronic anxiety are almost nonexistent. Frequently crucial to the success of such lengthy drug therapy is concomitant psychological support, including counseling, interpersonal or cognitive therapy, a combination of the above, or simply a change in life situation.

Thus, it appears to us that our proposed pragmatic classification of the various anxiety disorders provides improved guidance to the family physician in how to treat his or her anxious patients.

It is important to note that many patients suffering from chronic levels of trait anxiety are not always continuously highly anxious. In fact, they may suffer from a more chronic low level of anxiety, indicated by a Hamilton Rating Scale for Anxiety (HAM-A) score of 12 to 16, for example, but at times experience additional bouts of short-term anxiety occurring with or without obvious external stresses. This exacerbation is frequently the reason that brings a patient to his or her physician for treatment or makes a person respond to an advertisement for a research trial. In our clinical and research experience, many chronically anxious patients, if suffering from these exacerbations, could well be treated for only several weeks, not months, with anxiolytics. One might hypothesize that if one treats patients intermittently for short periods of time with effective anxiolytics, with repeated courses of treatment, even their chronic trait anxiety level will gradually decrease without the need of year-long, continuous administration of medication. This speculation lends itself to study in well-controlled clinical research; any findings produced would have great clinical and economic relevance.

Where do the currently available anxiolytics fit into this practical clinical categorization of anxiety? The advantage the benzodiazepines have over other anxiolytics, besides their rapid effect, is their unparalleled, consistent efficacy, great ease of use, and wide margin of safety when prescribed for only a few weeks. The main risk of short-term benzodiazepine therapy is sedation, to which tolerance frequently develops. However, even acute therapy of 3 to 4 weeks carries the risk of the occurrence of rebound anxiety on benzodiazepine discontinuation.[13,14] This rebound phenomenon frequently cannot be differentiated by the patient and physician from the original anxiety and thus may lead to unnecessary long-term drug therapy. Finally, after long-term (4 to 6 months or more) chronic therapy, withdrawal symptoms clearly occur in many patients after treatment discontinuation.[15–17] Other than dependence and withdrawal, the main risk of long-term benzodiazepine treatment appears to be anterograde amnesia. Anterograde amnesia occurs in both patients treated for the first time with a benzodiazepine and patients treated with benzodiazepines for many years.[18] Thus, though tolerance appears to develop to most other psychomotor effects, it does not develop for the amnestic effect, the clinical significance of which, however, has not yet been established.

When treating patients who are classified by DSM-IV criteria as having GAD, long-term management is often the rule and not the exception. In this case, drugs such as buspirone, which do not cause discontinuation symptoms, may be considered treatments of first choice. Also, emergent comorbidity, at least in less than diagnosis-specific intensity, is the rule rather than the exception in many clinically anxious GAD patients, and such comorbidity may determine the selection of an appropriate anxiolytic or antidepressant.

Table 2. Percentage of GAD Patients Maintaining Clinical Improvement for at Least 2 Weeks When Switched to Placebo After 4- or 6-Week Anxiolytic Therapy

Treatment	N	≥ 2-Wk Improvement
Study I[13]		
Lorazepam	16	75%
Clorazepate	19	75%
Study II[19]		
Alprazolam	34	50%
Clorazepate	42	57%
Study III[20]		
Diazepam	61	50%

MANAGEMENT OF CHRONIC AND DOUBLE ANXIETY: INTERMITTENT VS. CONTINUOUS ANXIOLYTIC THERAPY

GAD is a chronic disorder. Yet, in contrast with MDD, no good clinical or research evidence from well-conducted clinical research exists that demonstrates that all or most chronically anxious patients are in need of long-term continuous drug therapy for management of their symptoms. In fact, results of several studies conducted by our research group may illustrate this point. Table 2 describes three studies in which patients were treated for 4 to 6 weeks with benzodiazepines.[13,19,20] In two studies, patients were examined 2 weeks after 4 weeks of acute treatment. In the third study, patients were kept under double-blind conditions for 3 additional months on placebo. We observed that in these chronically anxious GAD patients treated for 4 to 6 weeks, 50% to 70% of patients still were asymptomatic 2 weeks after discontinuation of therapy, and 50% were still asymptomatic 3 months after discontinuation in the third study. These data provide strong support for the decision made by many physicians not to treat all chronically anxious patients continuously with medication.

Table 3 gives data from a 6-month trial comparing clorazepate with buspirone in GAD patients.[21] The data indicate that after 6 months of treatment, followed by a 4-week placebo period, only 24% of both buspirone- and clorazepate-treated patients experienced a relapse, while 76% did not. These relapse rates are similar to those observed in an 8-month study of panic disorder we conducted with alprazolam and imipramine.[22] Thus, good evidence exists, obtained from controlled clinical research, that at least 50% of patients who have chronic GAD can be treated successfully for only a 4- to 6-week period and remain symptom free for weeks or months afterward.

Table 3. Percentages of Patients Who Experienced Relapses After Treatment Discontinuation: Comparison of Two Studies

Treatment	N	Number of Weeks After Discontinuation	Percentage Who Experienced Relapse After Discontinuation
Study I[a]			
Clorazepate	21	3	24
Buspirone	17	3	24
Study II[b]			
Alprazolam or imiprimine	38	3–5	29

[a]Patients who had generalized anxiety disorder, treated with anxiolytic therapy for 6 months.[21]
[b]Patients who had panic disorder, treated with alprazolam or imiprimine for 8 months.[22]

However, 1-year follow-up data on short-term treatment of GAD also demonstrate that about two thirds of all GAD patients treated for 6 weeks again experience anxiety symptoms, with half of these patients requiring additional anxiolytic therapy.[23] Regrettably, we still cannot predict which patients will need prolonged anxiolytic therapy. In a 40-month follow-up of patients treated for 6 months with either clorazepate or buspirone,[21] we[24] found that 50% of patients previously treated with clorazepate but only 25% of patients treated with buspirone still suffered from moderate-to-severe anxiety; in addition, 60% of patients previously treated with clorazepate were again taking anxiolytic medication, even if only p.r.n., and none of the patients previously treated with buspirone were taking medication. We speculated at that time, admittedly post hoc, that patients treated with buspirone—a slightly less potent, less sedating, less euphoriant anxiolytic—continued to improve their coping skills, whereas patients treated with the more potent sedative benzodiazepine did not. Only further research can support or refute this speculation.

Recently, Scheibe[25] reported a similar finding. At a 4-year follow-up of anxious patients treated originally for 3 weeks with either lorazepam or buspirone, 64% of lorazepam-treated but only 38% of buspirone-treated patients took a benzodiazepine during the follow-up period.

Thus, slow-acting anxiolytics such as buspirone,[21] and possibly also antidepressants such as imipramine,[8] are the treatments of first choice for those 50% of chronically ill GAD patients who need prolonged medication therapy. However, the other 50% may well benefit from short-term, possibly intermittent drug therapy with benzodiazepines probably representing the first choice and buspirone the second choice of compounds. The benzodiazepine anxiolytics would allow short-term and p.r.n. anxiety management but would engender, even after only 3 to 4 weeks of therapy, the risk of rebound or withdrawal symptoms. Therefore, newer agents such as the beta carboline abecarnil, the partial gamma-aminobutyric acid agonist discussed in this symposium, may well find a role in anxiety management if it turns out that abecarnil will be as effective as the benzodiazepines but with fewer discontinuation symptoms.

When prescribing any type of medication for the treatment of anxiety, one should prescribe the medication not as a panacea to solve all of the patient's problems, which in fact drugs do not do, but as a tool for the patient to become less anxious and to be able to help himself or herself. In other words, we should create realistic rather than unrealistic goals for therapy. Frequently drug therapy of chronically anxious patients is combined with at least a minimal amount of counseling, and the family physician should refer more treatment-resistant patients to a mental health professional for further therapy. Such a treatment approach will, we hope, not only lead to symptom reduction but also contribute to better adaptation and coping skills and to an improved quality of life.

INTEGRATING PSYCHOPHARMACOLOGY AND PSYCHOTHERAPY

Today, in the age of biological psychiatry and the era of the neurotransmitters, anxious patients still should not be treated by simply dispensing a pill as if the physician were an automated vending machine. The best results with anxiolytic therapy are obtained under the supportive umbrella provided by the family physician or psychiatrist. We hope that biological psychiatrists do not make the same mistakes that psychoanalysts did in the 1950s and 1960s, when analysts let ideology run ahead of empiric evidence. The high placebo-response rate observed in the GAD-treatment studies is the most eloquent evidence that powerful nonpharmacologic forces are at work in the treatment of anxiety.

Thirty years ago, one of us (K.R.) chaired the first international symposium on "Nonspecific Factors" held at the 1966 World Congress in Madrid. That symposium discussed the importance of doctor-patient interactions, psychological support, and other factors for the outcome of anxiolytic drug treatment.[26] Anxiolytic therapy, though an important tool for the treatment of anxious patients, certainly is not provided in a vacuum; other factors such as treatment milieu, non-treatment milieu, and patient and physician characteristics all contribute to the patient's response in the pharmacologic management of anxiety (Figure 3).

In the 1960s, in a collaborative effort between the NIMH, Johns Hopkins University, and the University of Pennsylvania,[27–29] extensive research was carried out in the United States to study the effect of various nonspecific factors on drug treatment outcome in anxious outpatients. Significant predictors of treatment outcome identified in these as well as other studies conducted at that time are summarized in Table 4.[30]

More recently, Stuart and Lieberman[31] proposed a short interview, lasting less than 5 minutes, for the assessment

Figure 3. Nonspecific Variables in Anxiolytic Therapy

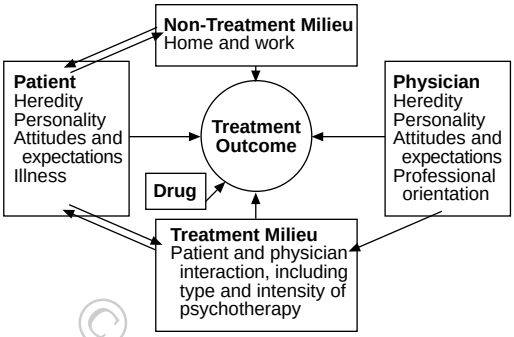


Table 4. Predictors of Good Response to Anxiolytics

Patient
Good ego strength
No Axis II diagnosis
Acute illness
Good response to prior drug therapy
Realistic treatment expectations and goals
Compliant with treatment
Marital stability
Physician
Warmth, empathy
Comfortable with patient
Comfortable prescribing drug for realistic goals (drugs no panacea)

of emotional factors of patients in family practice. The five interview areas, identified with the acronym BATHE, are given in Table 5. To these five areas of inquiry, we would like to add one additional area, namely, a discussion of treatment options.

CONCLUSION

We suggest a pragmatic revision of the diagnostic schema for the anxiety disorders, most frequently diagnosed as GAD, anxiety NOS, and adjustment disorder, which should allow for better diagnostic assessment and management of anxious symptoms by the family physician.

We propose that many chronically anxious GAD patients, not only acutely anxious ones, may need only short-term, not long-term pharmacotherapy. We suggest that intermittent short-term therapy may well lead not only to a decrease of state anxiety but also to a decrease of underlying trait anxiety in patients who have double anxiety. However, this suggestion needs to be subjected to well-controlled clinical research. Nevertheless, existing data indicate that about 50% of all chronically ill GAD patients are not in need of continuous pharmacotherapy but could be managed with intermittent courses of time-limited pharmacotherapy. Finally, the many anxious patients whose diagnoses do not fall into the GAD category are clearly not in need of extended long-term anxiolytic therapy and should be treated with short-term anxiolytic therapy provided within the context of a good doctor-patient relationship.

Table 5. Emotional Assessment and Support in Family Practice[31]

Background	What is going on in your life?
Affect	How are you feeling about that?
Trouble	What troubles you the most?
Handling	How do you handle that?
Empathy	That must be very difficult.

Drug names: alprazolam (Xanax), buspirone (BuSpar), clorazepate (Tranxene), imipramine (Tofranil and others), lorazepam (Ativan and others).

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