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The spectrum of generalised anxiety in clinical practice: the role of short-term, intermittent treatment*

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Background DSM–IV generalised anxiety disorder (GAD) has a high lifetime prevalence, but subthreshold anxiety states are even more common, particularly in family practice.

Method Generalised anxiety is conceptualised as a spectrum of disorders, with transient anxiety at one end and GAD at the other.

Results Based on long-term experience with family practice patients, the authors suggest that most anxious patients, wherever on this continuum they are placed, could be treated with short-term, possibly intermittent, rather than chronic anxiolytic therapy. Data are presented which show that 50% of chronic GAD patients are only in need of such short-term intermittent therapy.

Conclusions Further clinical research is needed to refine short-term, intermittent treatments for anxiety spectrum disorders, to make effective treatments available to those suffering from anxiety but falling short of diagnostic criteria for GAD, and to target more effectively the different treatment strategies.

Generalised anxiety has a high lifetime prevalence. Even if one applies the restrictive six-month duration criterion to generalised anxiety disorder (GAD), lifetime prevalence ranges from 6 to 10%, depending whether one uses DSM–III–R or ICD–10 criteria (Blazer *et al*, 1991; Wittchen *et al*, 1994). In fact, in family practice settings, the *current* GAD prevalence is estimated to be approximately 10% (Fifer *et al*, 1994). This percentage does not include the many short-term anxiety conditions that are frequently treated in family practice, but which never come to the attention of the psychiatrist.

Anxiety states not limited by duration and intensity have significantly higher prevalence rates than DSM–IV diagnosable anxiety states. Olfson *et al* (1996) recently reported that subthreshold psychiatric symptoms are more common in family practice than their respective Axis I DSM–III–R disorders (GAD: 6.6 *v.* 3.7%, panic disorder: 10.5 *v.* 4.8%). Yet most patients with subthreshold disorders still are significantly impaired.

Pre-DSM–III surveys of the prevalence of anxiety disorders, which were not limited by a duration criterion, found higher rates of psychiatric morbidity in family practice. For example, Shepherd *et al* (1966) reported psychiatric consultant rates of 30% for a psychiatric diagnosis and an additional 10% for 'psychiatric associated conditions' in general practice settings. Hesbacher *et al* (1976) reported that 30% of 1192 family practice patients surveyed were being diagnosed with either an anxiety condition or a mixed anxious–depressive disorder according to DSM–II. Over half of these patients never had been treated for their anxiety. It appears likely, then, that our present DSM–IV diagnostic system may, in the interests of achieving strict diagnostic homogeneity, exclude a large portion of the spectrum of anxiety disorders – at least among patients treated in primary care settings. Studies utilising DSM–III–R criteria suggest that the undiagnosed, subthreshold portion of the anxiety spectrum is well over 50% of all cases (Olfson *et al*, 1996). In addition to the high prevalence of all anxiety disorders as a principal diagnosis, comorbid anxiety disorders significantly affect the quality of life of patients with such chronic medical illnesses as hypertension and diabetes (Sherbourne *et al*, 1996). There is a growing recognition that untreated anxiety, whether occurring as a primary diagnosis or as a comorbid condition, may have a significant debilitating effect on psychosocial functioning.

Although minor, transient levels of anxiety are an integral part of the human condition. If they become excessive and out of proportion to identifiable stressors in terms of severity, persistence and disability, then they probably deserve to be treated. Such forms of anxiety are very common, but tend to fall outside the compass of current nosology and current treatment research. If GAD and panic disorder may be likened to chronic obstructive pulmonary disease and asthma, then these short-term anxiety states are the equivalent of viral upper respiratory infections: not severe but probably the cause, in the aggregate, of almost as much distress and disability.

The anxiety states with which we are concerned here, appear to have grown in numbers in recent years, largely as an artefact of the more restricted definition of GAD. Two major shifts in the DSM diagnostic criteria for GAD have served to markedly redefine the disorder. The first is the shift in the duration criterion from one to six months. This eliminates a large proportion of the spectrum of anxiety disorders observed in clinical settings in the interest of establishing a clean and homogeneous diagnosis. The second shift, also in the interest of defining a more homogeneous diagnosis, has been the increased emphasis on worry and secondary psychic symptoms, and the elimination of most of the somatic symptoms of anxiety. This decision has had the consequence of orphaning an enormous population of patients suffering from generalised anxiety that is more transient and somatic in its focus, and that typically presents, not to psychiatrists, but in primary care settings.

For example, in a survey of 1000 family practice patients, Spitzer *et al* (1994) reported that 16% of their patients received a DSM–III–R GAD or anxiety not otherwise specified (NOS) diagnosis and that a

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further 13% had a subthreshold anxiety diagnosis. In addition, 14% of patients received a somatoform diagnosis, a diagnosis frequently overlapping with somatic anxiety.

The understandable result of this diagnostic revisionism is that GAD, with a six-month duration criterion and a psychic focus, has become the only valid target of clinical research today. This precludes the testing of anxiolytics for clinical forms of generalised anxiety that are of less than six months' duration but are commonly observed in most medical settings. If GAD has been neglected in terms of treatment research relative to its prevalence, then short-term anxiety states are not even on the map.

It is perhaps unfortunate that such a large proportion of generalised anxiety states have been relegated to a research limbo. This is illustrated by several studies suggesting a differentiated treatment response for somatic *v.* psychic symptoms of GAD. Evidence from controlled studies suggests that somatic symptoms are targeted most effectively by the benzodiazepines (Rickels *et al*, 1993). In contrast, buspirone (Rickels *et al*, 1982) and imipramine (Rickels *et al*, 1993) 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 found to be most effective, and how these medications are used – whether intermittently or chronically. In practice, and despite the chronicity of GAD, a significant indication for treatment with 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, even patients who are not chronically anxious. These bouts of generalised anxiety clearly benefit from short-term targeted pharmacotherapy lasting a few days to a few weeks at the most.

CLINICAL CATEGORIES OF ANXIETY

Based on long-term experience in treating family practice patients and conducting clinical research with them, the authors propose that generalised anxiety disorder be conceptualised as a spectrum of disorders with GAD at one end, defined by its high chronicity. As a starting point for this reconceptualisation, we have borrowed from a National Institute of Mental Health (NIMH)-sponsored Insomnia Consensus Conference (NIMH Consensus Conference, 1984), as well as from parallel research in affective illness (Keller *et al*, 1983; Angst & Hochstrasser, 1994).

We propose clinically to conceptualise the spectrum of generalised anxiety into *acute anxiety*, *subacute anxiety*, *chronic anxiety* and *double anxiety* (Table 1). This reconceptualisation is intended solely as a pragmatic guide for treatment decision-making in primary care settings. *Acute anxiety* may be further divided, based on whether its duration is limited to days or weeks, 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* (and here we borrow from the depression literature) might usefully be divided into *minor anxiety*, if its course pattern is continuous and low grade, and *brief anxiety*, if it has an intermittent course pattern. *Chronic anxiety* may also have either a continuous or recurrent course pattern. Finally, *double anxiety* has a course pattern analogous to double depression, which consists of those patients who experience episodic bouts of fully-fledged GAD superimposed on mild to moderate levels of chronic trait anxiety (Rickels & Schweizer, 1995).

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 either a non-pathological reaction to stress, an acute stress disorder, an adjustment disorder, or anxiety 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 DSM–IV, be best diagnosed as GAD or anxiety NOS. In addition, in the chronic anxiety diagnostic groups, many patients also suffer from comorbid symptoms, which do not completely fulfil DSM–IV diagnostic criteria, such as depressive, social phobic, obsessive, and panic symptoms. More questionable is the diagnostic identification of GAD patients with a fully fledged additional DSM–IV diagnosis such as major depressive disorder or panic disorder. Such cases should not be diagnosed as GAD but as major depressive disorder or panic disorder unless the GAD is clearly the principal diagnosis by virtue of its severity, temporal precedence and associated disability (Downing & Rickels, 1974).

Table 1 Anxiety conceptualisation

Type of anxiety	DSM–IV diagnosis
Acute anxiety	• Non-pathological reaction to stress
• Transient anxiety (acute reaction to situational stress)	• Acute stress disorder • Adjustment disorder
• Short-term anxiety (reaction to specific life events)	• Anxiety NOS
Subacute anxiety	• Adjustment disorder
• Minor anxiety	• Anxiety NOS
• Brief anxiety	
• Brief, intermittent anxiety	
Chronic anxiety	• GAD
• Continuous anxiety	• Anxiety NOS
• Intermittent anxiety	
Double anxiety	• GAD
• Mild to moderate continuous anxiety with episodic bouts of fully-fledged anxiety	• Anxiety NOS

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It should be noted that most of our proposed clinical categories of anxiety could acceptably be forced into the residual DSM–IV diagnostic category of anxiety NOS. Yet anxiety NOS is a 'wastebasket' diagnosis that provides the non-psychiatric physician – and for that matter, also the psychiatrist – no guidance in the choice of therapy for his or her anxious patients.

Figure 1 provides a schematic representation of the course of illness pattern for transient and short-term anxiety occurring in patients free from neurotic or chronic trait anxiety. Also shown are patterns for chronically anxious patients whose time-limited bouts of acute anxiety are superimposed on a baseline of waxing and waning chronic trait anxiety. This latter condition, the authors propose, could best be diagnosed as 'double anxiety'.

CLINICAL MANAGEMENT OF GENERALISED ANXIETY: SHORT-TERM INTERMITTENT TREATMENT

The authors propose that many patients suffering from these anxiety spectrum disorders would probably benefit from short-term treatment, as long as the severity of their anxiety is such as to impair the patient's functioning. Certainly, the anxious patients whom we have proposed to classify as suffering from acute and subacute anxiety will most likely only be in need of a very brief course of therapy. The transiently anxious patients may need an anxiolytic for only three to seven days or only on an as-needed basis, whereas patients with short-term or subacute anxiety may be in need of such treatment for anywhere from two to four weeks. Such a course may need to be repeated for some patients diagnosed as subacutely anxious after an extended anxiety-free period, yet for most other patients an additional course of anxiolytic therapy is probably not necessary. In addition, the authors propose that while for GAD patients long-term management is the rule rather than the exception, many chronically anxious GAD patients could also be effectively managed with intermittent, four- to six-week courses of anxiolytic therapy.

It is a long-established clinical observation (one that antedates DSM–III) that symptoms of chronically anxious patients frequently wax and wane, with some patients at times reaching normative anxiety levels while others maintain a low level of anxiety which is usually not disabling (for example a Hamilton Anxiety Scale (HAM-A) score of less than 15) (Hamilton, 1959). Onto these low-grade levels of chronic anxiety, however, intermittent exacerbations of anxiety may be superimposed. These intermittent episodes are more severe and incapacitating, occurring both with and without obvious external stressors. These episodes are frequently the reason that brings a patient to his or her physician for treatment.

In the authors' clinical and research experience, many chronically anxious patients, if suffering from these exacerbations, could well be treated briefly, for several weeks, with anxiolytics. One might hypothesise that if one treats chronically anxious patients (with and without double anxiety) with targeted, intermittent, fast-acting anxiolytic therapy, that potential benefit might accrue also to their underlying chronic trait anxiety but without the need of year-long, continuous medication. This speculation lends itself to be studied by well-controlled clinical research; any findings produced would have great clinical and economic relevance. Yet, research studies designed to address the pharmacological treatment of chronic anxiety are almost non-existent. In contrast to major depressive disorder, there exists no good clinical or research evidence based on well-conducted clinical research that demonstrates that all or most chronically anxious patients are in need of long-term continuous drug therapy for their symptom management. For how long should we treat such patients? Is it enough to reduce the short-term anxiety increase in patients with double anxiety? At the other extreme, is it necessary to treat all chronically anxious GAD patients with medications for the rest of their lives, similar to the person with diabetes, for example?

There is some research evidence in the literature that such proposed intermittent pharmacotherapy might be sufficient for at least half of all GAD patients. This research group has shown in two studies (Rickels, 1985; Rickels *et al*, 1988) that GAD patients treated for four weeks with benzodiazepines, followed by two weeks on placebo, maintained a remission rate of 50–70% during these two weeks. In a third study, in which GAD patients were treated for six weeks with diazepam and then switched double-blind to placebo for several months, 50% of patients remained asymptomatic for at least three months (Rickels *et al*, 1983). These data thus provide some support for the use of short-term, intermittent drug therapy for chronically anxious patients, even if one-year follow-up data indicate that about 65% of all GAD patients who improved with acute therapy experience a relapse (Rickels *et al*, 1986). In fact, in a 40-month follow-up of GAD patients treated for six months with either clorazepate or buspirone (Rickels *et al*, 1988), Rickels & Schweizer (1990) reported that 41% of all former study patients suffered at that follow-up period from moderate to severe anxiety; clearly an indication that GAD is frequently a chronic condition, but not necessarily an indication that all GAD patients are in need of

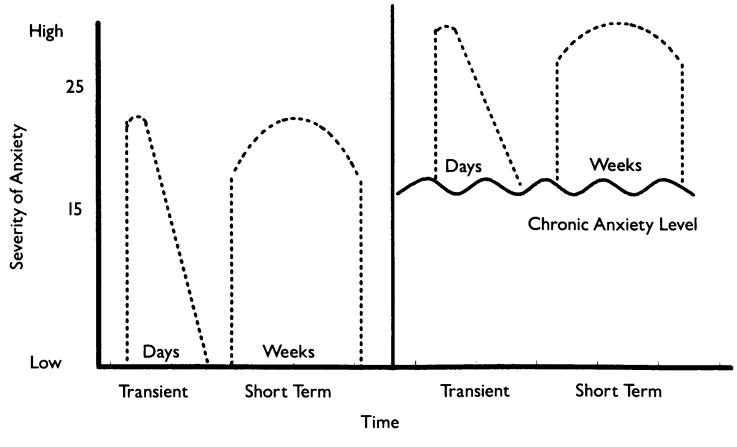

Fig. 1 Schematic representation of transient and short-term anxiety in patients without and with chronic anxiety.

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continuous, uninterrupted pharmacotherapy. Note that the research reported here was conducted on patients meeting full syndromic GAD criteria. The benefits of targeted intermittent therapy are likely to be even greater in patients who fall into the rest of the anxiety spectrum.

Further support for the appropriate use of short-term, intermittent anxiolytic treatment is provided by the many studies conducted with experimental anxiolytics, in which frequently a two-week placebo period has been added to the four- to eight-week double-blind treatment period to assess possible discontinuation symptoms. Studies with ipsapirone (Cutler *et al*, 1993; Mandos *et al*, 1995) and with gepirone (Rickels *et al*, 1997) may serve as examples. In both studies patients were shifted for two weeks to placebo after eight weeks of double-blind treatment. The HAM-A improvement change scores were 14.1 for ipsapirone and 13.7 for gepirone. During the two weeks of placebo substitution no worsening in HAM-A eight-week scores was observed for either drug (HAM-A change −0.4 and −0.6, respectively).

Having thus presented some preliminary data to support our contention that at least 50% of chronic GAD patients could possibly be managed with short-term therapy, even if it may have to be provided intermittently, there remains the other 50% of chronically anxious GAD patients who experienced in our research a recurrence of symptoms within one to two weeks after four to six weeks of acute therapy. These are the patients who cannot benefit, at least initially, from short-term intermittent therapy and probably must be offered a longer course of anxiolytic treatment.

PSYCHOPHARMACOLOGICAL AGENTS

The pharmacological agents available for the family physician to treat his or her anxious patients are the benzodiazepines, the non-benzodiazepine anxiolytic buspirone, and antidepressants such as imipramine. Of the drugs presently available for the use of intermittent therapy, the benzodiazepines have the advantage of rapidity of onset, consistent efficacy, great ease of use, and wide margin of safety when prescribed for only a few weeks (Hollister *et al*, 1993). The main risk of short-term benzodiazepine therapy is sedation, to which tolerance frequently develops. However, even acute treatment of four weeks' duration presents the risk of rebound anxiety occurring upon benzodiazepine discontinuation (Fontaine *et al*, 1984; Rickels *et al*, 1988). Rebound phenomena frequently cannot be differentiated by patient and physician from the original anxiety and thus may lead to unnecessary long-term drug therapy. Finally, after long-term (four to six months or more) chronic therapy, withdrawal discontinuation symptoms clearly occur in many patients after treatment discontinuation (Winokur *et al*, 1980; Rickels *et al*, 1990; Schweizer *et al*, 1990). Other than dependence and withdrawal, the main risk of long-term benzodiazepine treatment appears to be anterograde amnesia. Anterograde amnesia occurs both in patients treated for the first time with a benzodiazepine and in patients having been on benzodiazepines for many years (Lucki *et al*, 1986). Thus, although tolerance appears to develop to most other psychomotor effects, it does not develop for the amnestic effect, whose clinical significance, however, has not yet been established.

The other class of anxiolytics presently available to the physician are the 5-HT_{1A} partial agonists, of which only buspirone is presently on the market (Rickels *et al*, 1982; Murphy *et al*, 1989; Pecknold *et al*, 1989, Enkelmann, 1991). Since buspirone, similar to the antidepressants, has a relatively slow onset of anxiolytic action, it is probably not the drug of choice for short-term one- to two-week intermittent anxiolytic treatment. However, buspirone is probably the drug of choice for those GAD patients in need of more prolonged and continuous, rather than intermittent, therapy. Buspirone has relatively few side-effects, and even with long-term therapy, does not cause discontinuation symptoms (Rickels *et al*, 1988). Buspirone's advantage over the benzodiazepines is in terms of its efficacy on symptoms of depression, so often comorbidly present with GAD (Robinson *et al*, 1990). And presently, since the benzodiazepines already cause problems after only four weeks of therapy in terms of rebound anxiety, even for such short-term intermittent therapy, buspirone might be considered an alternative to the benzodiazepines. The same might also be true for the antidepressant imipramine (Kahn *et al*, 1986; Hoehn-Saric *et al*, 1988; Rickels *et al*, 1993). However, tricyclic antidepressants such as imipramine have a number of disturbing side-effects, mainly anticholinergic ones, which probably would not make them the drugs of first choice for the treatment of anxiety.

Intermittent anxiolytic therapy which would involve courses of not more than two weeks' duration can, however, safely be conducted with benzodiazepines. As Freeman *et al* (1995) has demonstrated in a study of premenstrual syndrome, alprazolam prescribed for the last two weeks of the menstrual cycle and then discontinued over a one- to two-day taper period, showed no evidence of discontinuation symptomatology development, even when given for five consecutive menstrual cycles. However, as mentioned earlier, once patients are treated for four or more weeks with benzodiazepines, the potential risk of at least some rebound anxiety does exist and may eventually lead to unnecessary long-term treatment and physical dependence.

It is hoped that drugs will be developed which could be used with impunity for three- to six-week periods of treatment, which would have the same fast onset of

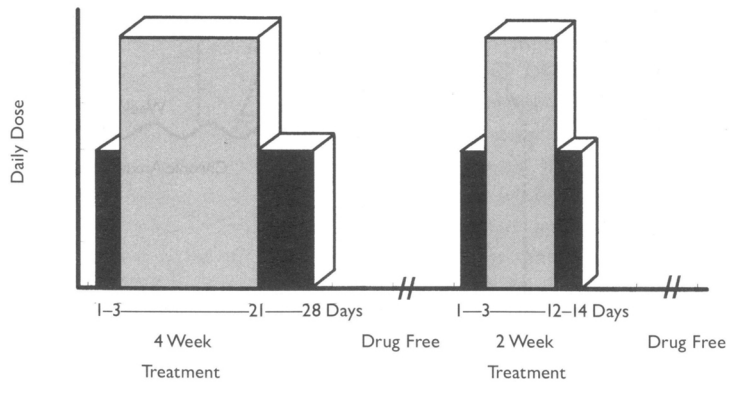

Fig. 2 Schematic representation of intermittent management of GAD and anxiety NOS with anxiolytics.

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action and the same efficacy as the benzodiazepines, and which would have significantly fewer or no discontinuation symptoms on either abrupt or accelerated taper. Here, it is quite possible that compounds such as the beta-carboline abecarnil, a GABA-ergic compound (Lydiard *et al*, 1997; Small & Bystritsky, 1997) might have a useful role in short-term, intermittent treatment strategies. Partial benzodiazepine agonists might be hypothesised to have less severe *acute* sedative and psychomotor impairment, and less likelihood of rebound when discontinued after acute therapy. This emerging pharmacodynamic profile suggests that partial agonists such as abecarnil might be optimally suited for patients who require intermittent treatment of four to six weeks' duration, while patients requiring only one to two weeks of anxiolytic therapy might best be treated with benzodiazepines. For patients who are in need of prolonged and continuous (>1 month) treatment with anxiolytics, buspirone or possibly some antidepressants may represent alternatives to the benzodiazepines.

Figure 2 provides a schematic model for our proposed intermittent two-week and four-week anxiolytic therapy. This treatment approach holds true for both the acutely and subacutely anxious patients, as well as for the chronic GAD and double anxiety patients. Medication could be strip-packaged with a lead-in period of two to three days, a treatment period of several weeks, followed by a taper period of several days by 50% medication reduction or another fast taper schedule. Such a treatment approach is based on the premise that anxiety rebound and discontinuation symptoms can be eliminated, or at least significantly reduced, so that they are not mistaken by patient and physician for a return of original anxiety and do not significantly complicate the management of the anxious patient with intermittent pharmacotherapy.

One final comment: 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. Instead, medications should be introduced as one of several available tools that the patient may use in order to become less anxious, and to empower them to help himself or herself. In other words, the physician should create realistic, not unrealistic treatment goals. Frequently, drug therapy of chronically anxious patients should be combined with at least a minimal amount of counselling, and the family physician should refer more treatment-resistant patients to a mental health professional for further therapy. Such a treatment approach will, it is hoped, not only lead to symptom reduction, but contribute to the acquisition of better adaptation and coping skills, ultimately leading to an improvement in quality of life.

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