Generalised anxiety disorder

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Generalised anxiety disorder is a persistent and common disorder, in which the patient has unfocused worry and anxiety that is not connected to recent stressful events, although it can be aggravated by certain situations. This disorder is twice as common in women than it is in men. Generalised anxiety disorder is characterised by feelings of threat, restlessness, irritability, sleep disturbance, and tension, and symptoms such as palpitations, dry mouth, and sweating. These symptoms are recognised as part of the anxiety syndrome rather than independent complaints. The symptoms overlap greatly with those of other common mental disorders and we could regard the disorder as part of a spectrum of mood and related disorders rather than an independent disorder. Generalised anxiety disorder has a relapsing course, and intervention rarely results in complete resolution of symptoms, but in the short term and medium term, effective treatments include psychological therapies, such as cognitive behavioural therapy; self-help approaches based on cognitive behavioural therapy principles; and pharmacological treatments, mainly selective serotonin reuptake inhibitors.

History

Generalised anxiety disorder is a relatively recent diagnosis. Before 1980 it was subsumed under the label of anxiety neurosis, a disorder first delineated by Freud in 1894[1] and characterised by persistent feelings of unattached fearfulness described as free-floating anxiety.[1] However, the disorder described by Freud also included the symptom of panic, and when panic disorder was subsequently identified as a separate illness by Klein,[2] the part of anxiety neurosis that did not include panic became known as generalised anxiety disorder. This classification was unsatisfactory because there were no features that defined generalised anxiety disorder; it became a residual diagnosis for anxiety disorders that had no other diagnosis; and it had substantial overlap with other disorders, known contentiously as comorbidity.[3–5] However, the diagnosis of generalised anxiety disorder is now embraced by epidemiologists and clinical psychopharmacologists, although other clinicians, especially those working in primary care, are less enthusiastic. The comorbidity seen in generalised anxiety disorder accounts for a substantial amount of morbidity and disability.[6,7]

Some clinicians argue that generalised anxiety disorder remains an ill-defined diagnosis, which supports the notion that it was constructed to support the validity of other diagnoses in the anxiety group rather than being a useful homogeneous clinical entity.[8] Generalised anxiety disorder was almost excluded from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[9] classification in 1994, on the grounds that its diagnostic status could be faulted on the grounds of poor reliability. Supporters of this diagnosis argue that, despite its overlap with other disorders, a diagnosis of generalised anxiety disorder is an advance on previous categorisations, and that the criterion that it has a 6-month duration has created a more homogenous disorder. Additionally, the associated social, occupational, and economic burden is similar to that of major depression, and the increasing prevalence of generalised anxiety disorder with advanced age distinguishes it from other anxiety disorders, which suggests that this diagnosis will not be abandoned.

Search strategy and selection criteria

The evidence for methods for treatment of generalised anxiety disorder was obtained by searching PubMed using the term "generalized (generalised) anxiety disorder" for each drug class ("antidepressants", "tricyclic", "selective serotonin reuptake inhibitor", "benzodiazepine", "antipsychotic", and "beta-blocker"), and for named drugs ("citalopram", "escitalopram", "fluoxetine" "fluvoxamine", "paroxetine", "sertraline", "amitriptyline", "clomipramine", "imipramine", "alprazolam", "diazepam", and "lorazepam"), "randomized controlled trial", "placebo", and "efficacy". We also reviewed recent national and international guidelines for the treatment of anxiety; published or draft reviews by the UK National Institute of Clinical Excellence, that referred to generalised anxiety disorder; and recent abstracts from relevant international conferences. The reference lists of articles identified by this strategy were also checked and papers were selected if judged relevant.

Clinical features

The requirements for the diagnosis of generalised anxiety disorder have changed with time. The symptoms have always included generalised and persistent excessive anxiety[10,11] and a combination of various psychological and somatic complaints. These psychological and somatic complaints are given prominence in the WHO's International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) criteria, where at least one symptom of autonomic arousal (palpitations, sweating, trembling, or dry mouth) is essential for the diagnosis, together with up to three other symptoms (table 1). Three of the symptoms of restlessness, being easily fatigued, difficulty in concentrating, irritability, sleep disturbance, and muscle tension, are necessary for a DSM-IV diagnosis (table 1). The additional symptom of worry over minor matters is included in the DSM-IV criteria but is not in ICD-10. This new criterion allows the diagnosis to be made irrespective of any overlap in anxious symptoms, and seems to separate generalised anxiety from other disorders that involve anxious symptoms.[12,13] These disorders include hypochondriasis (health anxiety),[14] panic disorder,[15] medically unexplained symptoms (somatisation disorder),[16] obsessive-compulsive disorder,[17] social anxiety disorder,[18] and eating disorders.[19] Anxiety is also a common complication of substance misuse disorders, including

	ICD-10	DSM-IV
Main symptom	Prominent tension, worry, and feelings of apprehension about everyday events and problems	Excessive anxiety and worry (apprehensive expectation) about a number of events or activities
Additional major feature	..	Difficulty controlling the worry
Duration of symptoms	At least 6 months	At least 6 months
Number of symptoms required for diagnosis	At least four, including one autonomic arousal symptom	At least three
Specific symptoms		
Autonomic arousal	Palpitations, sweating, trembling, dry mouth	..
Chest and abdomen	Difficulty breathing, feeling of choking, chest pain, nausea	..
Mental state	Dizziness, feelings of unreality (depersonalisation or depression), fear of losing control, fear of dying	Difficulty in concentrating or mind going blank
General	Hot flushes or cold chills, numbness or tingling, muscle tension or aches and pains, restlessness and inability to relax, sensation of lump in throat (difficulty swallowing)	Restlessness or feeling keyed up or on edge, being easily fatigued, irritable, muscle tension
Sleep disturbance	..	Difficulty falling or staying asleep, restless unsatisfying sleep
Effects on social functioning	Not included	Clinically significant distress or impairment in social, occupational, or other important functions
Exclusion criteria related to overlapping symptoms	Does not meet the criteria for panic disorder, phobic anxiety disorder, obsessive-compulsive disorder, or hypochondriasis	Focus of worry not confined to features of an associated disorder, such as panic disorder, obsessive-compulsive disorder, separation anxiety disorder, anorexia nervosa, somatisation disorder, or post-traumatic stress disorder
Other exclusion criteria	Symptoms not caused by a physical disorder such as hyperthyroidism, an organic mental disorder, or substance-related disorder (eg, benzodiazepine withdrawal)	Disturbance is not caused by direct physiological effects of a substance or medication, or to a general ailment (eg, hyperthyroidism), and does not exclusively occur during a mood disorder, psychotic, or pervasive developmental disorder

Table 1: **Criteria for the diagnosis of generalised anxiety disorder**

alcohol misuse,[20] and so these too have to be excluded. Because none of the individual symptoms are specific to generalised anxiety disorder, it is therefore necessary to exclude the other anxiety conditions before making the diagnosis. Exclusion of these other disorders is not always easy, especially if the patient has more than one disorder. Two diagnoses can only be made when the specific features of the other disorders can be discriminated reliably.

When the predecessor to DSM-IV, DSM-III, was introduced in 1980 the duration of symptoms necessary for a diagnosis of generalised anxiety disorder was 1 month and there was a diagnostic hierarchy that excluded the diagnosis if a depressive, phobic, or panic disorder was present.[21] This hierarchy was soon recognised to be inappropriate as the concurrent presence of other disorders was the norm rather than the exception[22] so the criteria for diagnosis were changed. However, if the symptoms of generalised anxiety disorder occurred only in the course of a mood disorder, the hierarchy still applied. Subsequent enquiry has suggested that the hierarchical relation is not fully representative for all patients, because patients with anxiety and depressive symptoms have greater morbidity than those with a mood disorder alone.[23] The duration of symptoms necessary for a diagnosis of generalised anxiety disorder was raised from 1 to 6 months in later editions of DSM and ICD,[11] in recognition of its status as a chronic illness, although there is little difference between patients who have a duration of symptoms of 1–6 months and those who qualify for diagnosis when their symptoms cross the 6-month threshold.[24]

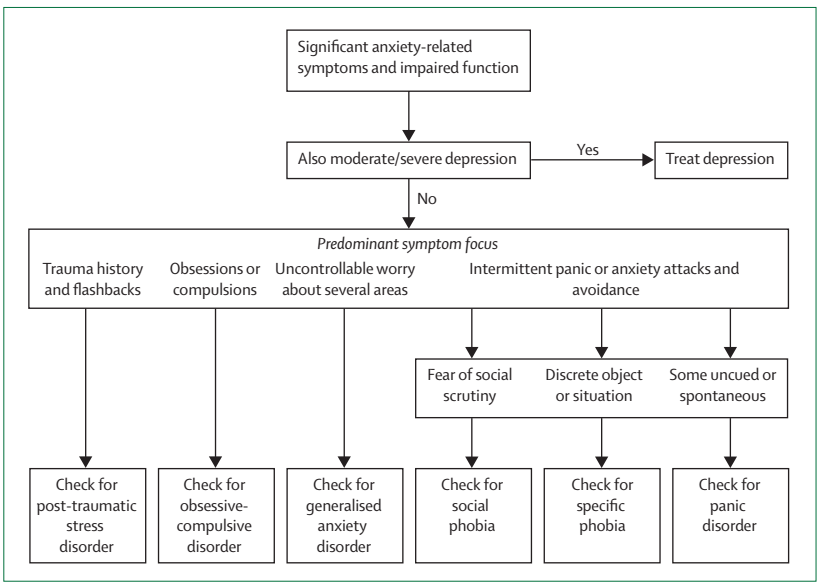

Figure: **Suggested scheme for exploration of a suspected anxiety disorder**
Taken from British Association for Psychopharmacology evidence-based guidelines for treating anxiety disorders.[25]

Assessment

Anxiety is a relatively easy symptom to detect in both primary and secondary care settings; the diagnostic difficulty lies in its interpretation. The scope for the use of screening or other instruments to aid the diagnosis or to assess the severity of generalised anxiety disorder is therefore restricted. A simple symptom-based algorithm to aid diagnosis of anxiety disorders has been proposed

(figure 1).[25] One of the most widely used scales is the Hospital Anxiety and Depression Scale, which includes anxiety and depression subscales, is both sensitive and specific in identifying pathological anxiety,[26,27] and asks questions about symptoms that can distinguish people who have anxiety symptoms associated with other medical conditions. The best-known instrument used in research is the Hamilton Rating Scale for Anxiety[28] but this instrument might include too many physical symptoms, is not simple to use, and alternatives are becoming widely employed; some of these are more specific to generalised anxiety disorder than the Hamilton scale.[29,30] All these instruments are useful in recording the severity of anxiety quantitatively but are not diagnostic assessments. The formal diagnosis has to be made by clinical or structured interview.[30,31]

Origin and neurobiology

Anxiety is a normal human emotion that has analogues throughout the animal kingdom; to some degree, anxiety is probably of biological value. The higher prevalence of generalised anxiety disorder in women (almost double that of men) suggests an advantage of greater anxiety in the protection of offspring. However, patients with generalised anxiety disorder could have a specific cognitive bias that leads to increased attention to threat-related information and to misinterpretation of ambiguous stimuli as threatening: this bias has been shown to diminish with both cognitive behavioural therapy[31] and after selective serotonin reuptake inhibitor (SSRI) treatment.[32]

In 1977 it was discovered that the benzodiazepines interacted with a specific binding site in the CNS, which suggested that a natural substance (endogenous ligand) associated with benzodiazepines must be present in the brain. This binding site was found to be an integral part of the γ-aminobutyric acid A ($GABA_A$) receptor complex, which was isolated and sequenced in 1987.[33] $GABA_A$ is known to have 19 subunit variants, each encoded by a different gene; $GABA_A$ receptors are divided into eight different classes by sequence differences of the subunits.

The α1 subunit seems to be responsible for the sedative, amnestic, and anticonvulsant properties of benzodiazepines, whereas the α2 subunit appears to be involved in anxiolytic effects. The role of the α3 subunit is unknown. The α5 subunit has high density in the hippocampus and is involved in memory. $GABA_A$ receptor subtype agonists could therefore exert anxiolytic effects with a reduced risk of unwanted side-effects such as sedation.[34] Tiihonen and colleagues[35] showed decreased binding of a radiotracer ligand for $GABA_A$ receptors in the left temporal pole—an area involved in experiencing and controlling fear and anxiety. The $GABA_A$ receptor complex is affected by a cluster of genes on chromosome 5,[36] but there is no evidence of any chromosomal abnormality specifically associated with generalised anxiety disorder.

There could be abnormalities of serotonergic and noradrenergic neurotransmission in patients with generalised anxiety disorder:[36,37] for example, giving meta-chlorophenylpiperazine (a non-specific $5HT_1$ and $5HT_2$ agonist) to patients with this illness has been found to increase anxiety.[38] Additionally, the reduced growth hormone response to clonidine (an α2 adrenoceptor agonist) seen in patients with generalised anxiety disorder suggests decreased α2 adrenergic receptor sensitivity, although this response was also seen in patients with major depression.[39]

Genetic studies suggest that generalised anxiety disorder and major depression could have a common genetic basis and that the environment affects their manifestation.[40] Advanced genetic studies suggest that heterozygous $GABA_A$ γ2 subunit knockout mice are less sensitive to benzodiazepines, and display anxiety and hypervigilance, and show decreases in $GABA_A$ ligand binding throughout the brain, compared with normal mice.[41]

Prevalence and comorbidity

The high prevalence of concurrent psychiatric disorders is the most damaging criticism of the diagnosis of generalised anxiety disorder (and many other anxiety disorders). Epidemiological studies in Europe suggest that the illness has a lifetime prevalence of 4·3–5·9% and a probable 12-month prevalence of 1·2–1·9%. Comorbidity with major depression is present in three out of five cases and a similar proportion have other anxiety disorders.[42] Only two out of five patients seek treatment for their disorders[43] and for these patients the rates of full or partial remission in the long term (5 years or more) are fairly disappointing at 38–41%. Comorbidity with personality disorder is a major handicap to recovery.[44,45] Comorbid diagnosis is associated with greater social and occupational impairment than generalised anxiety disorder alone and also confers a worse prognosis.[45,46] Attempts have been made to regard primary generalised anxiety disorder (ie, when generalised anxiety disorder is the initial illness that the patient has diagnosed)[47,48] as fundamentally different from the secondary equivalent; comorbidity during follow-up is increased for secondary generalised anxiety disorder.[49] The association of anxiety with depressive symptoms is the most difficult aspect for the clinician in forming a diagnosis. This combined disorder, which has been called "cothymia",[50] is given separate status in ICD-10 as "mixed anxiety and depressive disorder", but only when "neither type of symptom is present to the extent that justifies a diagnosis if considered separately".[11] However, even using this restricted definition, mixed anxiety and depressive disorder is by far the most common mental disorder in epidemiological surveys and raises the 1-week prevalence of neurotic disorder to one in eight in men and one in five in women.[51]

The personality trait neuroticism, or negative affectivity, characterises the link between anxiety and depression.[52] Neuroticism seems to develop early in life and has led to the suggestion that the highly comorbid anxiety and

depressive disorders, together with a dependent, avoidant, or obsessional personality, are part of a general neurotic syndrome[8,53,54] and should be separated from single disorders that are often self-limiting and have a reasonable outcome. However, even after comorbidity is taken into account, a core generalised anxiety disorder associated with substantial social dysfunction still exists.[42,55,56] Generalised anxiety disorder is now accepted as an illness that results in substantial morbidity and leads to poor quality of life.[57,58]

Outcome

Generalised anxiety disorder is typically regarded as a chronic illness. Most patients are still highly affected 6–12 years after diagnosis,[44–45] and in one study, personality disorders showed less stability and greater improvement over 2 years than all anxiety disorders.[59] Most of these studies were done in affluent countries with wide access to treatment and even here, long-term morbidity remains high. One of the problems in assessment of outcome is determination of the role of concurrent disorders such as hypochondriasis,[60] social anxiety disorder,[61] or avoidant personality disorder.[62] Avoidant personality disorder itself is very difficult to distinguish from generalised social phobia,[63] and so the negative outcome could be as much a consequence of generalised anxiety disorder acting as a precursor of these other disorders as from the original anxiety disorder.

There are no specific associations between anxiety and other physical disorders–the association with thyrotoxicosis is often cited but the anxiety in this disorder is often recognised as qualitatively different from other spontaneous anxieties. Mortality is raised in patients with generalised anxiety disorder,[64] but not specifically from suicide.[65] The cost of care for generalised anxiety disorder is high because of its chronic nature, although the cost (mainly of consultations with non-psychiatric clinicians) is less than that of panic disorder or post-traumatic stress disorder.[66] The cost of treatment for anxiety with comorbid depression or general neurotic syndrome is nearly twice that of a single diagnosis of generalised anxiety disorder.[67]

General principles of treatment

That generalised anxiety disorder, together with other anxiety disorders, is best treated in primary care wherever possible, is now generally agreed. Most patients are seen and are almost entirely managed in this setting. However, that the necessary time and services, especially psychological therapies, are not readily available in such settings is a concern,[68] and so treatment could be chosen according to what is available rather than what is best. Psychological therapies are widely thought to be preferable to drug treatments, but frequently cannot be given because of limited resources. However, there is not much evidence to support increased efficacy or acceptability of psychological therapies. For the immediate future, doctors in most western countries will probably prescribe drug treatment most commonly, irrespective of patient choice.

Drug treatment

Acute treatment

Many systematic reviews of randomised placebo-controlled trials in generalised anxiety disorder have been done since 1980, and in general these suggest that many drugs are effective in the short term and sometimes the medium term (table 2). Despite initial claims that panic disorder was a specific indication for antidepressant therapy but that generalised anxiety disorder was not responsive,[69] evidence that antidepressants are effective treatments in both generalised anxiety and in the closely related panic disorder has now been shown. This dual

	SSRIs	TCAs	Benzodiazepines	Others
Acute treatment				
Reduction of anxiety symptoms in short-term studies	Escitalopram, paroxetine, sertraline	Imipramine	Alprazolam, diazepam	Venlafaxine, duloxetine, cognitive behavioural therapy, buspirone, hydroxyzine, pregabalin, trifluoperazine, opipramol, tiagabine
Long-term efficacy				
Reduction in anxiety symptoms in long-term (typically 6–12 months)	Escitalopram, paroxetine			Cognitive behavioural therapy, venlafaxine
Relapse prevention				
Prevention of return of anxiety symptoms after successful acute treatment	Paroxetine, escitalopram			Cognitive behavioural therapy, pregabalin
Enhances the efficacy of psychological treatment				
Reduction in symptoms either in combination with psychotherapy or after non-response to psychotherapy			Diazepam	
After non-response				
				Olanzapine, risperidone

SSRIs=selective serotonin reuptake inhibitors. TCAs=tricyclic antidepressants. Empty cell indicates absence of published placebo-controlled data.

Table 2: **Generalised anxiety disorder: pharmacological and psychological treatment approaches supported by findings of placebo-controlled studies**

efficacy was first shown by Kahn and colleagues[70] with imipramine, and similar benefit has been shown with other tricyclic antidepressants.[71,72] Most of these antidepressants were available before generalised anxiety disorder was a recognised diagnosis so few randomised controlled trials have been done for these treatments.

Table 2 shows many drugs of different classes that are similarly efficacious treatments for generalised anxiety disorder.[25,72–76] Differences in efficacy have been shown in a few trials, but often the differences can be explained in terms of dosage, and these differences diminish after comparison of many meta-analyses.[74]

The choice of drug depends on the perceived nature of adverse effects and risks, the presence of co-existent depressive symptoms, and the need for an early onset-of-action. Benzodiazepines can be effective within 15–60 min, whereas buspirone takes up to 72 h to act and its action is often preceded by mild dysphoria.[77] Antidepressants take up to 4 weeks to show effectiveness but clinically significant improvement can be noted after as little as 2 weeks.[71,78] Benzodiazepines are associated with risk of dependence after long-term use[77,79] and are more likely to lead to requests for long-term prescription than antidepressants (although there can sometimes be withdrawal effects with antidepressants[80]). The size of effect of treatment in generalised anxiety is greater for benzodiazepines than for antidepressants in the first 2 weeks of treatment, but at varying times from 3–8 weeks onwards the antidepressants show better effectiveness.[71] Initial treatment should probably be with combined benzodiazepines and an antidepressant and the benzodiazepine dose should be tapered off after 2–3 weeks when the antidepressant becomes effective. This method of treatment is now common in clinical practice[81] and is recommended frequently,[82] although it has not been tested in controlled trials.

Small differences between antidepressants have been seen in some studies,[83,84] but are probably not enough to lead to firm conclusions regarding the superiority of any one class or individual drug over another. Most consensus guidelines and reviews suggest that tricyclic, SSRI, and serotonin and noradrenaline reuptake inhibitor (SNRI) classes have similar overall efficacy.[25,74,85] The choice of treatment is determined by the range of adverse effects rather than by anxiolytic supremacy. Thus, if insomnia and restlessness are major symptoms it might sometimes be more appropriate to choose a tricyclic drug with sedative activity, such as amitriptyline or trimipramine rather than an SSRI or SNRI because these drugs can cause an increase in anxiety and restlessness in the early stages of treatment. The range of adverse effects with SSRIs (nausea, dizziness, anorexia) is generally considered to be less serious than that of tricyclic antidepressants (dry mouth, sedation, postural hypotension, difficulty in micturition), so an SSRI (eg, escitalopram or paroxetine) is usually recommended as first-line treatment.[25,72,85] Escitalopram 10 mg per day seemed superior to paroxetine 20mg per day in a 12-week randomised placebo-controlled trial[86] and was better tolerated in a comparative 6-month study.[87] The SNRI venlafaxine is effective[25] but because of tolerability concerns is often only recommended for use as a second line treatment.[85]

Long-term treatment

Generalised anxiety disorder is a chronic condition, so long-term treatment should be anticipated and planned accordingly. Most evidence of efficacy is from acute treatment studies and recommendations for treatment beyond 12 weeks are on the basis of few data. The SSRIs escitalopram and paroxetine have both shown efficacy in placebo-controlled relapse-prevention studies.[88,89] Continued treatment with venlafaxine is better than continued treatment with placebo, in the proportion of patients that achieve symptomatic remission, but venlafaxine was not efficacious at relapse prevention.[90] Relapse is frequent after drugs are withdrawn, even after the period of withdrawal symptoms has passed. Randomised trials including both treatment and withdrawal components have shown that the effectiveness of placebo increases strikingly.[91] The concern about benzodiazepines causing dependence has led to recommendations that these drugs should be avoided in the long-term,[25,72,73,85] but the alternative of continuous antidepressant therapy is supported by little evidence. Buspirone is an anxiolytic drug that has been suggested to be of value in the long-term treatment of generalised anxiety disorder because it does not result in addiction. Buspirone is thought to be especially useful in patients with alcohol dependence, but again this use has little supporting evidence.[92]

Second-line drug treatments

Other drugs might also be of use in the treatment of generalised anxiety disorder. β blockers such as propranolol, although widely used for anxiety in primary care,[93] have unproven efficacy[94] in generalised anxiety disorder, although studies done before the disorder was delineated suggested some value in patients who had marked somatic manifestations of anxiety that seemed to be mediated through β-adrenergic receptors.[95] Some evidence suggests that propranolol combined with a benzodiazepine could be more effective than a benzodiazepine alone in generalised anxiety disorder[96] and this combination could help with the subsequent withdrawal of the benzodiazepine.[97]

Monoamine oxidase inhibitors such as phenelzine might also be effective in the treatment of intractable generalised anxiety disorder. This class of drugs is highly effective in severe anxiety but their potential for adverse reactions with tyramine-containing foods (mainly cheese) and sympathomimetic drugs has restricted their use and they have not been formally tested in generalised anxiety disorder. However, their effectiveness in so-called endogenous anxiety[98] suggests a role for these drugs in

secondary care settings when other treatments have failed. The safer reversible monoamine oxidase inhibitor, moclobemide, is not as effective as the irreversible monoamine oxidase inhibitors[99] but has shown efficacy in social phobia.

The psychological symptoms of anxiety might respond better to antidepressant drugs than to benzodiazepines, but few comparator-controlled studies have been done, and most showed no significant differences in efficacy between active compounds.[74,75] Antidepressant treatment is preferable to benzodiazepine anxiolytics in cothymia and other mixed conditions, because benzodiazepines have restricted efficacy against depressive symptoms.[25,73,74] Advice that benzodiazepines should only be prescribed for up to 4 weeks in regular doses and then tapered off has provoked some reaction since this method can be less efficacious than placebo.[91] Some clinicians argue that patients who respond well to benzodiazepines have chronic disorders for whom continued treatment is desirable and justifiable,[100] but this remains a controversial view.

Although low doses of antipsychotic drugs have been used in primary care settings to treat anxiety symptoms, formal evidence of efficacy of antipsychotic treatment as monotherapy seems limited to a single placebo-controlled study of the conventional antipsychotic, trifluoperazine: although it was superior to placebo from the first week, it was poorly tolerated.[101] The sedative effects of antihistamines have sometimes been used to dampen troublesome anxiety symptoms, and this strategy is supported by the proven efficacy of hydroxyzine as a short-term treatment.[102,103]

Despite the abundance of guidelines, there is confusion over the best method of treating generalised anxiety disorder with drugs. In practice, patients who were formerly treated with benzodiazepines alone are now being treated with benzodiazepines and antidepressants (usually SSRIs)[104] with the intention of stopping the benzodiazepine treatment. However, removal of the benzodiazepine is not always possible.

Little is known about the management of patients who have not responded to first-line treatment. An increase in overall response with dose-escalation in patients after an initial non-response to a lower dose has not been proven, but switching between treatments with proven efficacy could be helpful.[25] Small placebo-controlled studies with the antipsychotic drugs olanzapine and risperidone suggested they can enhance the response to the SSRI fluoxetine[105] or to anxiolytics.[106]

Psychological treatment

Acute treatment

Some psychological therapies have proven efficacy in the treatment of generalised anxiety disorder. Traditional treatments, such as hypnosis, have rarely been tested in formal trials but have some evidence of effectiveness,[107] which deserves further exploration. The most common psychological treatments used for generalised anxiety disorder are cognitive behavioural therapy, dynamic psychotherapy, and behaviour-based treatments such as anxiety-management training. A review of 14 studies of psychological treatment in generalised anxiety disorder revealed modest improvements in symptoms, with 50% of patients achieving relief of somatic symptoms and a similar proportion attaining normal function after treatment.[108] However, this compares favourably with drug treatment and in a review of 35 studies the most effective psychological treatment, cognitive behavioural therapy, was shown to have a similar effect size (0·7) to that of drug treatment (0·6).[109] Comparison of cognitive behavioural therapy, analytical psychotherapy, and anxiety-management training showed cognitive behavioural therapy to be best both at the end of treatment and at 6 month follow-up[110] and could be delivered effectively in 8–10 sessions.

Unfortunately, many psychological treatment studies have design deficiencies that reduce the confidence that clinicians have in the results. The use of a "waiting list" group for comparison with an active treatment group, is not an adequate psychological placebo treatment, which is a flaw that undermines the results of some studies.[111] There have been few comparative studies of pharmacological and psychological treatment approaches, and the studies that have attempted such a comparison have used benzodiazepines for short periods only rather than antidepressants that have proven efficacy in generalised anxiety disorder. The sequential treatment of drugs and psychotherapy, is of some value in related disorders, but has not been shown to be useful in generalised anxiety disorder.[112]

Long-term treatment

Psychological treatments could maintain their effectiveness better than drug treatments, but there have been few long-term comparisons. Relapse might be less frequent after stopping cognitive behavioural therapy (although booster treatment sessions can be necessary) than with drug treatments, and initial improvement can be maintained for up to 2 years, especially if the original treatment is done by an experienced therapist.[113] However, in the long term (8–14 years) only around a third of patients make a good recovery and a similar proportion, especially those with the most severe symptoms, do not show any substantial improvement.[114] The patients who have the best initial improvement have the best long-term outcome[115,116] and intensive psychological treatment does not confer greater benefits over time than short-term treatments.[116]

Combined drug and psychological treatments

Although a combination of psychological and drug treatments in generalised anxiety disorder seems

appropriate, evidence for added benefit with combination treatment does exist, but is rare. This could be because of patient choice; those who ask for one type of treatment are often averse to the other and avoid it if possible. In one study, buspirone improved the symptoms of both generalised anxiety disorder and panic disorder when combined with cognitive behavioural therapy,[117] but this was not shown in another study with buspirone in patients with generalised anxiety disorder alone.[118] A primary care study noted that diazepam with cognitive behavioural therapy was more efficacious than either treatment given alone. However, there was no significant difference between diazepam and placebo.[119] Another study suggested that combination treatment was less effective than psychological treatment alone.[120] Combined therapy might be effective in patients who also have a concurrent personality disorder[121] but this has not been replicated in specific anxiety disorders.

Guidelines based on full literature reviews all suggest that there is insufficient evidence to recommend combined psychological and pharmacological treatment initially, although this can be considered if initial treatment fails.[25,74,85]

Self-help

The effects of pharmacological and psychological treatments are sometimes disappointing and patients seem to prefer convenient or natural remedies, which has encouraged the development of many self-help therapies across the range of anxiety disorders. However, there have been few randomised controlled trials of the efficacy and acceptability of these self-help approaches in patients with homogeneous diagnoses that have used reliable outcome measures and robust statistical analysis.

A systematic review of six randomised controlled trials suggests that self-help is effective in primary care patients with mixed anxiety disorders, and greatest usefulness was seen if patients were given detailed instruction for use of self-help manuals (bibliotherapy).[122] A systematic review of complementary therapies showed some evidence for use of relaxation training, exercise, and kava in generalised anxiety disorder.[123] Kava is now not available in many countries because of concerns about hepatotoxicity. In primary care, patients with a range of emotional problems that included anxiety, depression, and "stress", counselling seemed more effective in the short term than standard general practitioner care, with or without antidepressant treatment, but long-term effectiveness was not seen.[124]

Cognitive behavioural therapy has been adapted to be used as computer software, which constitutes a self-help approach. Early results with this treatment have been encouraging and show that the treatment could be especially suited to primary care.[125] In 2002, the UK National Institute for Clinical Excellence announced that there was insufficient evidence to recommend the general introduction of computerised cognitive behavioural therapy for anxiety symptoms or disorders.[126] However, a large controlled trial in both anxious and depressed patients showed that computer-aided therapy was more effective than usual treatment,[127] and perhaps of greatest importance, that it was substantially more cost effective. The mean cost of providing the treatment was UK£40 but the saving in terms of lost employment regained (patients returning to work sooner) was £407.[128] As use of computers and the internet continues to grow it is probable that these technologies will lead to a widespread and useful application of an effective treatment that is useful in primary care. The demand for psychological treatments will probably never be met from live therapists, so computerised therapists could be a valuable alternative.

Prevention

Evidence for the effective prevention of generalised anxiety disorder is scarce, other than from studies of tertiary prevention in patients with an established disorder. The link between personality traits and generalised anxiety disorder is formed early in life and Akiskal and colleagues[129,130] have suggested that the disorder is best regarded as an anxious temperament. The links between generalised anxiety disorder and the personality trait neuroticism are very strong and are heavily affected by genetic factors. Hettema and colleagues[131] found an 0·80 correlation of between neuroticism and generalised anxiety, and concluded that "the genetic factors underlying neuroticism are nearly indistinguishable from those that influence liability to generalized anxiety disorder".[131]

Anxiety is a fundamental drive that has evolutionary value. Removal of anxiety should not only be regarded as relief of a symptom. Many patients with generalised anxiety disorder are able to function well, often better than those with other mood and related disorders,[132] and intervention is appropriate only when symptoms interfere with normal social function. With the growth of self-help through the internet and group psycho-educational community interventions for anxiety and depression,[133] people will probably be able to receive earlier help at a time when it could be more valuable. Data suggest that anxiety as both a personality and clinical problem becomes more prominent with increasing age[134–136] so any intervention with preventive value would be highly prized.

Treatment decisions

Generalised anxiety disorder is a broad diagnosis and to respond to its detection with an automatic treatment intervention would be unwise. Many patients who fulfil diagnostic criteria for generalised anxiety disorder are likely to respond to the minimum intervention (eg, assessment and recognition of the problem); in others, symptoms will resolve spontaneously, especially in primary care.[42,137] Clinicians should not rush into treatment approaches that carry some risk, such as the

use of SSRIs in the treatment of depression in children and adolescents, where the evidence of efficacy is unproven[138] (although the claims that these drugs can provoke suicidal behaviour were not supported[139]). The decisions of when and how to treat should be discussed between therapist and patient, to review the varying treatment options and to share decision-making, as recommended in recent guidelines.[25,85] These reviews should also include a frank discussion of the placebo effect, since this effect is generally more marked than in other disorders.[140]

Conclusions

Generalised anxiety disorder is common, it has many manifestations, and it overlaps with other personality disorders. The disorder has strong genetic and environmental precursors and often becomes noticeable in early adult life. Generalised anxiety is relatively easy to detect and most management should be done in primary care. Generalised anxiety has no predictable outcome and the time to symptom resolution can vary from a period of a few days to not at all, with complete persistence of symptoms and handicaps, magnified by comorbid psychiatric and physical diagnoses. Most treatments have similar efficacy and much of the evidence for their value comes from studies of single treatments rather than combinations. The choice of intervention should be determined by the clinical features of the patient (for example, the presence of concurrent disorders and history of response to previous treatments), patients' preferences, and the local availability of individual services. With both drug and psychological treatments, patients should be told that they will not respond immediately, that symptoms can sometimes briefly worsen during treatment, and that long-term treatment might be needed to maintain an initial response. For psychological treatment, resources are in short supply, but cognitive behavioural therapy, the most effective form of psychological treatment, is being adapted for computerised use, which will reduce demands on therapists' time.

Generalised anxiety disorder can be thought of as a risk factor for the development of many other disorders, either linked disorders such as depression, or secondary disorders such as alcohol or benzodiazepine dependence. Because generalised anxiety disorder as a single condition is relatively rare and tends to persist over time, clinicians should choose treatments with potential to be given long-term, with a wide range of activity that might also be effective in treating depression, other anxiety disorders, and somatoform disorders. For these reasons, current guidelines[73,74,85] that recommend use of either cognitive behavioural therapy or an SSRI as first choice treatments, with a preference for cognitive behavioural therapy, if readily available, should be followed. The importance of regular monitoring when treatment is first started is of the highest importance.

Conflict of interest statement

Peter Tyrer is a member of the Board of the Global Initiative on Psychiatry, and is also Editor of the *British Journal of Psychiatry*. He has received grants from the Mental Health Foundation, Wellcome Trust, Sir Jules Thorn Charitable Trust, and Medical Research Council to assess the benefits of cognitive behavioural therapy in psychiatric disorders. David Baldwin has acted as a consultant to several companies with an interest in anxiety and depressive disorders (Asahi, Cephalon, Eli Lilly, GlaxoSmithKline, Lundbeck, Pfizer, Organon, Pharmacia, Pierre Fabre, Roche, Servier, Sumitomo, Wyeth). He holds or has held research grants on behalf of his employer from a number of companies with an interest in anxiety and depressive disorders (Cephalon, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Pfizer, Pharmacia, Roche, Wyeth). He has accepted paid speaking engagements in industry-supported satellite symposia at international and national meetings, but does not accept hospitality or travel not related to a speaking engagement. He was co-chair of the BAP consensus group on treatment of anxiety disorders and is a medical patron of the National Phobics Society.

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