

CONTINUING MEDICAL EDUCATION

The Diagnosis and Treatment of Generalized Anxiety Disorder

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SUMMARY

Background: Generalized anxiety disorder (GAD) is a common and serious disease with a lifetime prevalence of 4.3% to 5.9%. It is underdiagnosed in primary care.

Methods: Recommendations on the treatment of GAD are given on the basis of all available findings from pertinent randomized trials, retrieved by a selective search of the literature.

Results: Among psychotherapeutic techniques, various kinds of cognitive behavioral therapy (CBT) have been found useful in controlled trials. The drugs of first choice include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and the calcium-channel modulator pregabalin. Tricyclic antidepressants are also effective but have more adverse effects than SSRIs. Although benzodiazepines are effective anxiolytic agents for short-term use, they should not be given over the long term because of the danger of addiction. Buspirone, an azapirone, was found to be effective in a small number of trials, but the findings across trials are inconsistent. The response rate of GAD to CBT in published studies lies between 47% and 75%, while its response rate to drug treatment lies between 44% and 81%.

Conclusion: The treatment of GAD with CBT and drugs is evidence-based and has a good chance of improving the manifestations of the disorder.

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Generalized anxiety disorder (GAD) is a common and disabling disease. The ICD-10 diagnostic criteria for GAD are listed in *Box 1* and *eBox 1*: It is characterized by worries based on extant dangers (e.g., of a spouse having an automobile accident) whose likelihood is overestimated and whose negative consequences are viewed as catastrophic. Worries can rapidly generalize to multiple areas of everyday experience in sufferers from GAD, including health, family relationships, and their occupational or financial situation (or that of persons close to them). These worries typically induce defensive and avoidant behavior; for example, any activities held to be dangerous, such as travel, may be postponed or simply not undertaken. Somatic manifestations of anxiety arise, often leading to extensive medical diagnostic evaluations (1).

The differential diagnosis includes somatic disorders, including neurological ones, but mainly other psychiatric conditions, and, in particular, other anxiety disorders. Among these, panic disorder involves periodic attacks of physical and emotional manifestations of anxiety, such as palpitations, shortness of breath, a sensation of tightness in the chest, diaphoresis, feelings of helplessness, and paresthesias. It is often combined with agoraphobia. Patients with panic disorder worry mainly about the potential consequences of such attacks for their health, or about a supposed somatic illness underlying them; unlike patients with GAD, they do not worry that other persons close to them might become ill. In social anxiety disorder, the sufferer's worries and fears are limited to social situations in which he or she might be observed or criticized. 40% to 67% of patients with GAD also suffer from depression (e1, e2). In such cases, if the patient's worries are

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Generalized anxiety disorder

GAD is characterized by worries based on extant dangers (e.g., of a spouse having an automobile accident) whose likelihood is overestimated and whose negative consequences are viewed as catastrophic.

accompanied by such manifestations as mood fluctuations (regularly worse in the morning), early morning awakening, guilt feelings, or suicidal ideation, it must be determined whether depression is affecting the patient more severely than GAD. It may also be difficult to differentiate GAD from a somatoform disorder with varying bodily symptoms that have no organic correlate, such as palpitations, shortness of breath, dysphagia, or unexplained abdominal discomfort. Such patients repeatedly demand medical evaluation and, unlike GAD patients, often reject a psychosomatic explanation of their problems. Some of the avoidable errors in the diagnosis of GAD are listed in *Box 2*.

Epidemiological surveys of the general population have shown that GAD has a lifetime prevalence of 4.3% to 5.9% and a 12-month prevalence of 0.2% to 4.3% (2, 3). Among patients in general medical practice, the one-month prevalence is 7.9% to 9% (4). GAD is twice as common in women as in men. It is most often seen in persons aged 45 to 59, with a lower peak in persons aged 30 to 44 and a decline after age 60 (5). If untreated, GAD usually takes a chronic course, with most patients still suffering from its symptoms six to twelve years after the diagnosis is made. Only two out of five affected persons find their way to appropriate treatment (7).

Causes

The causes of GAD are not yet well understood. Traumatic life experiences, faulty conditioning, genetic influences, and neurobiological dysfunction are considered to be potential etiological factors for GAD and other anxiety disorders (8). GAD tends to cluster in families (9). Twin studies have shown a moderate hereditary influence (10), which is, however, less intense than in other anxiety disorders, e.g., panic disorder. The neurobiological factors under discussion include disturbances of various neurotransmitter systems (serotonin, epinephrine/norepinephrine, GABA) (11–13). Structural and functional neuroimaging of GAD patients has revealed abnormalities in the amygdala, the dorsomedial prefrontal cortex, and other brain areas (e3–e6).

Treatment

The following recommendations are based on an evaluation of all randomized controlled trials of treatment for GAD that we were able to retrieve by a literature

BOX 1

The diagnosis of generalized anxiety disorder according to ICD-10

- Tension, worries, and fears about everyday events and problems for at least six months, with the following symptoms and signs:
 - vegetative manifestations such as increased heart rate, diaphoresis, tremor, or dry mouth
 - symptoms in the chest or abdomen (respiratory symptoms, feeling of tightness, chest pain, abdominal discomfort)
 - mental symptoms (dizziness, derealization, fear of losing control, fear of dying)
 - general symptoms (hot or cold flashes, paresthesiae)
 - symptoms of tension (muscle tension, agitation, foreign-body sensation in throat)
 - other, nonspecific symptoms (exaggerated startle response, lack of concentration, irritability, difficulty falling asleep)

Patients are tormented by constant worries, e.g., that they (or their loved ones) might have an accident or become ill. Activities that are perceived as dangerous are avoided or postponed. Patients also worry about the fact that they are always worrying (“meta-worries,” e.g., “All this worrying is sure to give me an ulcer”).

BOX 2

Avoidable errors in the diagnosis of anxiety disorders

- In primary care, 45% of anxiety disorders are not recognized as such (23).
- Anxiety disorders are often misdiagnosed because the patients present with somatic complaints: for 87% of patients with generalized anxiety disorder, the primary symptom is not anxiety, but rather pain or sleep disturbance (24, e110).
- Patients with GAD are often considered to have some type of mental disturbance, but two-thirds are not diagnosed as having either any anxiety disorder or GAD, and thus do not receive appropriate treatment (1).
- In patients with depression, a coexisting anxiety disorder is often missed and therefore not treated (24).

Lifetime prevalence

Generalized anxiety disorder (GAD) is a common and serious disease with a lifetime prevalence of 4.3% to 5.9%. It is underdiagnosed in primary care.

The causes of GAD

Traumatic life experiences, faulty conditioning, genetic influences, and neurobiological dysfunction are considered to be potential etiological factors for GAD and other anxiety disorders.

BOX 3

The components of cognitive behavioral therapy (CBT) for generalized anxiety disorder*

● **Nonspecific effects**

- Establishment of a robust therapeutic relationship
- Discussion of all of the patient's problems and his or her life story, rather than focusing exclusively on symptoms

● **Psychoeducation**

- Information about the disorder
- Explanation of the somatic manifestations of anxiety as a natural fight-or-flight response
- Explanation of the rationale for treatment
- Recommendation of suitable information brochures and self-help materials

● **Cognitive strategies**

- Reevaluation of unrealistic assumptions about the utility and disadvantages of worries
- Development of a realistic assessment of the probability that various types of problems will have negative consequences, and of the amount of suffering this will cause
- Putting the type and frequency of the patient's worries in perspective ("What do other people do in this situation?")
- Examining catastrophic expectations with homework exercises involving prediction of what will come next (identification of "worry chains")
- Recognition of negative fluency (What opportunities do I have for positive or negative thinking?)

- Distancing oneself from worries and controlling them (practicing the ability to anticipate positively; inner self-distancing dialogues)
- Dealing with problems caused by perfectionism and the inability to tolerate uncertainty
- Working on meta-worries ("I am worried that my constant worrying will give me an ulcer")
- Building up resources ("Are there any areas of life in which I have no worries?")

● **Exposure**

- Patients are instructed to try not to engage in safety behavior (e.g., telephoning their children to make sure they are healthy). The tendency to put off activities perceived to be dangerous, such as travel, is also therapeutically addressed.
- *In sensu* exposure to particular things about which the patient is worried

● **Emotional regulation**

- Muscle relaxation techniques

● **Problem-solving techniques**

- Practicing problem-solving strategies to lessen inappropriate approaches to problems (worrying)
- Establishment of goals and life plans, participation in enjoyable activities, increased perception of emotional well-being

*modified from (26, 27)

search; the latter involved both automated searching in databases (Medline and the Web of Science database of ISI Web of Knowledge) and a manual search. A structured evaluation of each trial for correctness of method (size of study population, blinding, randomization, statistics, instruments, etc.) was performed according to the recommendations of the Scottish Intercollegiate Guidelines Network (SIGN, www.sign.ac.uk). The trials evaluated here include all of those that were

analyzed for the guidelines of the World Federation of Societies for Biological Psychiatry (2008) (14) along with 21 further randomized controlled trials that have appeared since these guidelines were published. As will become clear below, some of the trials of drug treatment or of psychotherapy had negative or inconclusive results. Only treatments that were found to be effective in a majority of trials in which they were tested are recommended here.

Cognitive behavioral therapy

The goal of treatment is for the patient to develop the ability to recognize, eliminate, and correct his or her dysfunctional (faulty, one-sided) assumptions and thoughts in order to behave more appropriately in various situations.

Demonstration of efficacy

The efficacy of CBT has been demonstrated in many randomized clinical trials. A number of trials showed CBT to be superior to being placed on a waiting list or to treatment with psychological placebo conditions.

BOX 4

Treatment recommendations for generalized anxiety disorder (GAD); accompanying psychotherapy is recommended in all cases

● **Drugs of first choice**

- SSRIs, e.g. escitalopram^{*1} 10–20 mg or paroxetine^{*1} 20–60 mg
- SNRIs, e.g. duloxetine^{*1} 60–120 mg or venlafaxine^{*1,2} 75–225 mg
- pregabalin^{*1} 150–600 mg

● **Drugs of second choice**

- buspirone^{*1} 15–60 mg, usually 30 mg
- imipramine 75–200 mg, usually 100–150 mg
- opipramol^{*1} 100–300 mg, usually 200 mg
- hydroxyzine^{*1} 37.5–75 mg

For concomitant treatment with an antidepressant until the onset of the antidepressant effect, alprazolam^{*1} 1.5–6 mg, usually 3 mg

● **Procedure for patients who do not respond to standard pharmacotherapy**

No more than a partial response in 4–6 weeks

- raise dose and treat for a further 4–6 weeks

No response at all in 4–6 weeks

- Change of drug (although an analysis of multiple studies of patients with GAD who did not respond to 2 weeks of SSRI treatment showed that only 38% went on to have a response by 8 weeks [28])
- Possible strategies for drug-switching (in the absence of relevant clinical studies):
 - switch to another drug of first choice (SSRI, SNRI, pregabalin)
 - switch to a drug of second choice (tricyclic antidepressant, buspirone, opipramol)
 - switch to a drug known from clinical trials to be effective against other anxiety disorders, but not yet adequately tested against GAD (e.g., moclobemide, mirtazapine)
 - switch to quetiapine (off-label)
- Possible add-on strategies:
 - administration of pregabalin or olanzapine in addition to an SSRI or SNRI (e111; e112)

^{*1}approved in Germany for the treatment of anxiety states/disorders

^{*2}Most of the available evidence is for the extended-release formulation of venlafaxine.

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

Psychotherapy

Cognitive behavioral therapy (CBT)—Cognitive behavioral theories start from the presumption that anxiety disorders, like other mental disorders, are caused in part by distorted, illogical, or unrealistic cognitions (e7). The goal of treatment is for the patient to develop the ability to recognize, eliminate, and correct his or her dysfunctional (faulty, one-sided) assumptions and thoughts in order to cope more appropriately

with various situations (e8–e10). Psychoeducation, confrontational techniques (e.g., *in sensu* exposure to the things the patient fears, e.g., anticipated catastrophic events) (e11, e12), and problem-solving techniques are further components of CBT. The creation of a robust therapeutic relationship is, of course, another important element of behavioral therapy. The therapeutic components of CBT for GAD are summarized in *Box 3* (e10, e11).

Internet-based cognitive behavioral therapy

Internet-based CBT involves either pure self-therapy with the aid of various materials or else self-therapy enhanced by brief contacts with therapists by e-mail or telephone.

Internet-based therapy: current evidence

Internet-based therapy cannot now be recommended, as there have not been any trials comparing it to traditional CBT, in which the patient and therapist are in personal contact.

The efficacy of CBT has been demonstrated in many randomized clinical trials. A number of trials showed CBT to be superior to being placed on a waiting list (e13–e19), and several studies comparing CBT to a “psychological placebo” showed that CBT has not only nonspecific psychotherapeutic effects, but also specific ingredients (e20–e23). The rate of response to behavioral therapy in therapeutic trials ranges from 47% to 75%, with varying definitions of a “response.”

In the last few years, a number of trials of Internet-based CBT have been carried out, involving either pure self-therapy with the aid of various materials or else self-therapy enhanced by brief contacts with therapists by e-mail or telephone (e24–e26). All but one of these trials revealed significant differences between CBT and being placed on a waiting list; in a single trial, neither Internet-based CBT nor Internet-based psychodynamic therapy was any more effective than being placed on a waiting list (e27). Internet-based therapy cannot now be recommended, as there have not been any trials comparing it to traditional CBT, in which the patient and therapist are in personal contact. Moreover, Internet-based therapy is difficult to reimburse and is fraught with other medicolegal and ethical difficulties (for example, if the patient is suicidal).

Psychodynamic (depth-psychological/psychoanalytical) therapy—There are a number of approaches to the psychodynamic treatment of GAD. A special type of psychoanalytic focal therapy for GAD (e29, e30) has been developed on the basis of supportive-expressive psychotherapy (e28). This type of treatment proceeds from the hypothesis that patients with GAD have insecure relationships and that their mental symptoms are caused by a central relational conflict. As in other types of psychodynamic conflict, the transference relationship is exploited for therapeutic purposes. Current psychodynamic treatment for GAD often consists of short-term therapy in which an active therapeutic attitude is preferred.

Our extensive literature search yielded only two evaluable randomized controlled trials of the effect of psychodynamic therapy for GAD. In one trial, behavioral therapy was found to be more effective than psychodynamic therapy, both acutely and in later follow-up (e31, e32). In the other trial, the authors concluded that psychodynamic therapy was about as effective as CBT; in fact, however, the numerical results they reported were markedly better for CBT, but the differ-

ences were not significant. Thus, in our view, this study was underpowered to demonstrate either therapeutic equivalence or a therapeutic difference (e33, e34). The overall state of the evidence does not yet permit any concrete recommendation. Comparisons with waiting lists and active controls (psychological placebos) are also lacking.

Because of the lack of published data, nothing can yet be said about the possible efficacy of other types of psychodynamic therapy (psychotherapy based on depth psychology, long-term psychoanalysis, or others).

Drugs

There have been many controlled trials of pharmacotherapy for generalized anxiety disorder, with response rates ranging from 44% to 81% (e35, e36). The dosages used are given in *Box 4*. The advantages and disadvantages of various classes of drugs and their adverse effects are listed in *Table 1*.

Whenever GAD is treated with drugs, the treating physician must continue to maintain an empathic and attentive psychotherapeutic relationship with the patient. Antidepressants often have adverse effects in the first few days of treatment before their therapeutic effect sets in; compliance with treatment can be increased by a preventive preliminary discussion of the types of adverse effects that might arise, e.g., agitation at the beginning of treatment with selective serotonin reuptake inhibitors (SSRIs). Telling the patient in advance that antidepressants generally take time to work often obviates the need for benzodiazepines at the beginning for treatment. A proactive discussion of possible sexual dysfunction (e37) or weight gain (e38) has also proved useful in practice.

Selective serotonin reuptake inhibitors (SSRIs)—A number of controlled trials have demonstrated the efficacy of the SSRIs escitalopram (e39–e45), paroxetine (e46–e49), and sertraline (e50–e52).

SSRIs are generally well tolerated. Adverse effects such as agitation, nervousness, and worsened anxiety may arise in the first few days or weeks of treatment and may impair compliance. After longer periods, sexual dysfunction may arise, or there may be withdrawal phenomena differing from those seen in benzodiazepine withdrawal (15). SSRIs should be taken in the morning to avoid nocturnal restlessness and insomnia at the start of treatment. The anxiolytic effect usually sets in with a latency of two to four weeks.

Empathic patient care

Whenever GAD is treated with drugs, the treating physician must continue to maintain an empathic and attentive psychotherapeutic relationship with the patient. Antidepressants often have adverse effects in the first few days of treatment.

SSRIs and SNRIs

Adverse effects such as agitation, nervousness, and worsened anxiety may arise in the first few days or weeks of treatment with these drugs and may impair compliance. Their anxiolytic effect usually sets in with a latency of two to four weeks.

TABLE

The advantages and disadvantages of drugs used to treat generalized anxiety disorder^{*1}

Drug	Advantages	Disadvantages	Adverse effects
Drugs of first choice			
Selective serotonin reuptake inhibitors (SSRIs)	<ul style="list-style-type: none"> – No dependence – Safe in case of overdose 	<ul style="list-style-type: none"> – Latency of action 2–6 weeks – At the start of treatment: agitation, nervousness, increased symptoms of anxiety – Possible cytochrome P-450 interactions 	Agitation, nausea, diarrhea, constipation, gastrointestinal symptoms, headache, decreased or increased appetite, weight loss, weight gain, diaphoresis, hot flashes, dry mouth, fatigue, tremulousness, sexual disturbances, nightmares, mania, withdrawal phenomena, and other adverse effects
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	<ul style="list-style-type: none"> – No dependence – Safe in case of overdose 	<ul style="list-style-type: none"> – Latency of action 2–6 weeks – At the start of treatment: agitation, nervousness, increased symptoms of anxiety – Possible cytochrome P-450 interactions 	Agitation, sleep disturbances, nausea, loss of appetite, gastrointestinal symptoms, dry mouth, constipation, diaphoresis, headache, dizziness, palpitations, rise in blood pressure, drop in blood pressure, tremulousness, shaking chills, sexual disturbances, mania, disturbances of micturition, sensory disturbances, visual disturbances, confusion, and other adverse effects
Pregabalin	<ul style="list-style-type: none"> – Rapid onset of action – No cytochrome P-450 interactions – Positive effect on sleep 	<ul style="list-style-type: none"> – Lack of concentration and drowsiness are common, particularly at the start of treatment 	Somnolence, drowsiness, insomnia, euphoria, lethargy, confusion, memory disturbances, irritability, sexual disturbances, increased appetite, weight gain, dizziness, motor disturbances, tremulousness, sensory disturbances, dysequilibrium, visual disturbances, vomiting, dry mouth, constipation, edema, and other adverse effects
Drugs of second choice			
Tricyclic ^{***} antidepressants (TCA)	<ul style="list-style-type: none"> – No dependence 	<ul style="list-style-type: none"> – No data available from long-term trials – latency of action 2–6 weeks – dangerous in case of overdose 	Fatigue, dry mouth, hypotension, dizziness, tremulousness, diaphoresis, increased appetite, weight gain, disturbances of micturition, palpitations, visual disturbances, confusion, constipation, mania, withdrawal phenomena, and other adverse effects
Buspirone	<ul style="list-style-type: none"> – No dependence – Relatively safe in case of overdose 	<ul style="list-style-type: none"> – Less effective than other drugs in several clinical trials – Latency of action 2–6 weeks 	Somnolence, nausea, headache, nervousness, dizziness, overexcitement, diaphoresis, sweaty palms, and other adverse effects
Benzodiazepines	<ul style="list-style-type: none"> – Rapid onset of action – Relatively safe in case of overdose 	<ul style="list-style-type: none"> – Dependence possible 	Fatigue, "hangover" on the following day, dizziness, prolonged reaction times, visual disturbances, unsteady gait, dysarthria, memory disturbances, forgetfulness, confusion, respiratory depression, paradoxical agitation, muscle weakness, weight change, danger of falling in elderly patients, and other adverse effects. <i>In prolonged use:</i> dependence <i>After abrupt withdrawal:</i> withdrawal phenomena (agitation, insomnia, feeling sick, nausea, vomiting, palpitations, drop in blood pressure, diaphoresis, tremulousness, muscle tension, and other symptoms)
Hydroxyzine	<ul style="list-style-type: none"> – No dependence – Rapid onset of action 	<ul style="list-style-type: none"> – Few trials documenting efficacy – No long-term trials 	Somnolence, fatigue, insomnia, dry mouth, gastrointestinal symptoms, weight gain, concentration difficulties, tachycardia, arrhythmia, headache, abnormal liver function, and other adverse effects
Opipramol	<ul style="list-style-type: none"> – No dependence 	<ul style="list-style-type: none"> – Very few trials documenting efficacy – No long-term trials – Latency of action 2–6 weeks 	Fatigue, sedation, shortened reaction times, dry mouth, nasal congestion, hypotension, and other adverse effects

^{*1}modified from (13)

Drugs of first choice

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin-norepinephrine reuptake inhibitors (SNRIs)
- pregabalin

Drugs of second choice

- tricyclic antidepressants (TCA)
- buspirone
- benzodiazepines
- hydroxyzine
- opipramol

Serotonin-norepinephrine reuptake inhibitors (SNRIs)—A number of trials have demonstrated the efficacy of the SNRI venlafaxine (e35, e44, e53–e60); only one found it to be no better than placebo (e61). It is generally given in an extended release formulation. Duloxetine was effective against GAD in controlled trials (e56, e57, e62–e65). At the start of treatment with an SNRI, adverse effects such as nausea, agitation, or sleep disturbances may impair compliance. The anxiolytic effect sets in with a latency of two to six weeks, or sometimes even later.

Pregabalin—Multiple controlled trials have shown that pregabalin is effective against GAD (e36, e58, e66–e70). The anxiolytic effect arises rapidly: Significant efficacy is demonstrable from the fourth day of treatment onward (e67), with respect to both the mental and the physical symptoms of GAD (e54). Sleep disturbances improve (e67). Impaired concentration and drowsiness are the most common adverse effects.

Tricyclic antidepressants (TCA)—The findings of controlled trials support the use of imipramine to treat GAD (e71, e72). Especially at the beginning of treatment, TCAs can cause adverse effects such as intensified anxiety, anticholinergic effects, sedation, or weight gain. Adverse effects are more common with TCAs than with the more recently introduced antidepressants (SSRIs and SNRIs), and the latter should therefore be preferred. If these standard medications turn out to be ineffective or are poorly tolerated, TCAs may be a good treatment option. Their latency of effect is two to six weeks, or longer.

Benzodiazepines—A number of benzodiazepines have been investigated for efficacy against GAD: alprazolam (e71, e73–e76), diazepam (e69, e72, e73, e77–e84), lorazepam (e67, e68), and bromazepam (e85).

The anxiolytic effect appears as soon as treatment is begun. Benzodiazepines are considered safe, but they have a tranquilizing effect on the central nervous system, potentially causing sedation, dizziness, prolonged reaction times, and other problems. After prolonged treatment (i.e., four to eight months), as many as 40% of patients become dependent on the drug, especially if they are predisposed to dependency (16, 17); low-dose dependency is the usual type.

Tolerance, expressing itself in the need for a steadily increasing dose, is rare (18). Generally speaking, benzodiazepines should only be used in the acute phase of treatment (i.e., for four to eight weeks). They are usually given at the start of antidepressant treatment to tide the patient over until the antidepressant effect sets in. Their long-term use may be indicated in rare individual cases if other drugs are ineffective or poorly tolerated. Patients with a history of substance abuse should be excluded. It should also be borne in mind that benzodiazepines have little or no effect on the depressive symptoms that often accompany GAD.

Other drugs

The 5-HT_{1A} agonist buspirone has been found to be effective in a number of trials (e59, 74, e82–e84, e86–e88), but it was less effective than venlafaxine in one study (e59). In one trial, it was no better than placebo (e89).

A few controlled trials have demonstrated the efficacy of hydroxyzine, an antihistamine drug (e85, e89–e91), but no recurrence-prevention trials have been conducted over a time span of six to twelve months. Hydroxyzine has not become established in the routine treatment of generalized anxiety disorder.

Opipramol, an anxiolytic drug chemically resembling the tricyclic antidepressants, was found to be more effective than placebo and just as effective as alprazolam in a three-armed trial (e76). No long-term trials have been reported.

Quetiapine, an atypical antipsychotic drug originally developed for the treatment of schizophrenia, is also effective against GAD at a dose much lower than the usual anti-schizophrenic dose (e43, e92–e96). This drug, however, has not been approved for the treatment of GAD and can only be considered for use in patients for whom standard treatments have been ineffective or poorly tolerated. When giving this drug, physicians should be aware of its potential adverse effects, including the metabolic syndrome.

Agomelatin, a new antidepressant, is a melatonin agonist and 5-HT_{2C} antagonist. It was more effective than placebo against GAD in one trial (e97), and a recurrence-prevention trial likewise showed its superiority to placebo (e98). This drug has not yet been approved for the treatment of GAD. It can elevate the values of liver function tests; such tests are recommended before and during treatment with agomelatin.

Benzodiazepines

Benzodiazepines are usually given at the start of antidepressant treatment to tide the patient over until the antidepressant effect sets in.

Homeopathic preparations

Only one controlled trial of a homeopathic preparation has been carried out to date. The preparation was no more effective than placebo.

Herbal and homeopathic preparations

In a single trial without placebo control, a standardized lavender-oil extract was found to be as effective as lorazepam (e99); this trial, however, had only 77 subjects and was inadequately powered for non-inferiority testing. Moreover, lorazepam was only given once daily (instead of three times), even though its half-life is relatively short; this may well have lessened the benefit of treatment in the lorazepam arm of the trial. The placebo-controlled trials performed to date in persons with “sub-syndromic” anxiety disorders do, however, indicate a possible effect of lavender-oil extract (e100, e101) that would merit further study in trials comparing it to standard medications.

Only one controlled trial of a homeopathic preparation has been carried out to date. The preparation was no more effective than placebo (e102).

Long-term and recurrence-prevention trials

Generalized anxiety disorder often persists, needing long-term treatment. Recurrence-prevention trials over time spans of six to twelve months have shown SSRIs (escitalopram, paroxetine), SNRIs (venlafaxine, duloxetine), and pregabalin to be more effective than placebo for long-term recurrence prevention. A meta-analysis on the treatment of GAD with antidepressants showed robust treatment effects. These findings imply that the treatment should be continued for six to twelve months after the onset of improvement.

Before the treatment is entirely discontinued, the dose of the drug should be lowered slowly, in steps. Benzodiazepines are not recommended for long-term treatment except when other drugs or CBT have been ineffective.

In the trials of behavioral therapy, treatment was provided for a total of 8 to 28 hours; no trials have addressed the question whether longer treatment works any better than, or more durably than, shorter treatment. Experience suggests that severely affected patients may need to be treated for longer times.

Intractability

For patients who do not respond to standard drug treatment, further treatment is recommended as summarized in *Box 4*.

The treatment of elderly patients

Only a few trials have specifically dealt with patients over age 65. The efficacy of pregabalin and queti-

pine in elderly patients with GAD was demonstrated in placebo-controlled trials (e103). In one trial, escitalopram had a higher response rate than placebo (e41). An analysis of the elderly patients in four GAD trials led to the conclusion that duloxetine is effective (e104); an analysis of the elderly patients in five trials revealed that venlafaxine was more effective than placebo with respect to CGI (Clinical Global Impression) score, but not in all primary measures of effectiveness (e105). In summary, pregabalin or duloxetine can be recommended for the treatment of elderly patients. In intractable cases, quetiapine can be given off-label.

CBT has also been shown to be effective in elderly patients, albeit with a lesser treatment effect than in patients under age 65 (e18, e106–e109).

Comparison of psychotherapy with drug treatment

Hardly any comparative data are available regarding psychotherapy versus pharmacotherapy for GAD. Two small trials (both of which had methodological problems) revealed no difference between the two, although the combination of CBT and diazepam was found to be more effective than diazepam alone (e13, e23). This finding cannot be applied to combinations of psychotherapy with the currently recommended drugs. As both forms of treatment are known to be effective and have comparable effect strengths, it seems that combining them is recommendable. The decision whether to treat a particular patient with psychotherapy, drugs, or both should be based both on considerations of efficacy and on the following important factors: the patient's preference, the adverse effects of medication, the latency of effect, the severity of the patient's condition, comorbidities, if any, cost, time, the availability of psychotherapy, and the qualifications of the therapist. In practice, drug treatment is often begun at once, while patients may have to wait several months to begin psychotherapy even in places with relatively high availability (20). If the patient is suffering from GAD in combination with comorbid depression, antidepressant medication should not be omitted (21).

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Treating elderly patients with GAD

Elderly patients with GAD can be treated with pregabalin or duloxetine.

Combination therapy

As psychotherapy and drug treatment are both effective, a combination of the two can be recommended.

Conflict of interest statement

Prof. Dr. Bandelow has received consultant's fees from Lilly, Lundbeck, Ono, Otsuka, and Pfizer. He has received reimbursement of conference participation fees from Servier and Pfizer. He has received honoraria for lecturing at continuing medical education events from AstraZeneca, Boehringer-Ingelheim, Glaxo, Janssen, Lilly, Lundbeck, Pfizer, Servier, and Wyeth.

Dr. Boerner has received reimbursement of travel and accommodation costs and payment for preparing continuing medical education events from Pfizer. He has received consultant's fees from Pfizer.

Prof. Kasper has received research support and lecture honoraria from, and has served on advisory boards or as a consultant for, AstraZeneca, CSC, Eli Lilly, Alkermes, Lilly, Lundbeck, Merck Sharp & Dohme (MSD), Neuraxpharm, Bristol Myers Squibb, GlaxoSmithKline, Pfizer, Organon, Janssen, Novartis, Pierre Fabre, Schwabe, Sepracor, Servier, and Wyeth.

Prof. Linden has received consultant's fees and lecture honoraria from Pfizer, Lilly, Servier, and Janssen-Cilag. He has received payment from Servier for preparing scientific articles.

Prof. Wittchen has received reimbursement of conference participation fees and travel and accommodation costs from Pfizer. He has received payment for preparing continuing medical education events from Pfizer.

Prof. Möller has received consultant's fees and payment for preparing continuing medical education events from Pfizer.

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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Which of the following manifestations are included in the definition of generalized anxiety disorder?

- a) Episodes of intense fear without any evident reason
- b) Fear of crowds
- c) Vegetative symptoms such as palpitations, diaphoresis, or tremor
- d) Muscle tension
- e) Restless legs syndrome

Question 2

What are “meta-worries”?

- a) The coexistence of multiple anxiety disorders
- b) Long-term fears of losing one’s economic footing
- c) Worries about one’s own health, rather than that of loved ones
- d) Fears that one may become ill from constant worrying
- e) The comorbidity of anxiety disorder and depression

Question 3

A 36-year-old dental hygienist is seen in a hospital emergency room. She has the following symptoms and signs: palpitations, shortness of breath, a feeling of tightness in the chest and neck, abdominal discomfort, trembling, diaphoresis, dizziness, feeling faint, tingling paresthesias, and fear of dying. The general medical and neurological examination is normal, as are all relevant laboratory findings.

What is the most likely diagnosis?

- a) Angina pectoris
- b) Pheochromocytoma
- c) Somatization disorder
- d) Generalized anxiety disorder
- e) Panic disorder

Question 4

Which of the following is a drug of first choice for the treatment of generalized anxiety disorder?

- a) Hydroxyzine
- b) Pregabalin
- c) Imipramine
- d) Opipramol
- e) Buspirone

Question 5

What is the typical latency of the anxiolytic effect of SNRIs?

- a) 1–2 weeks
- b) 2–4 weeks
- c) 2–6 weeks
- d) 6–8 weeks
- e) 8–10 weeks

Question 6

What is the most common adverse effect of pregabalin?

- a) Nausea
- b) Agitation
- c) Sexual dysfunction
- d) Somnolence
- e) Insomnia

Question 7

Which of the following types of psychotherapy has been best documented as an effective treatment for generalized anxiety disorder?

- a) Long-term psychoanalysis
- b) Interpersonal therapy
- c) Cathartic imagery experience
- d) Client-centered talk therapy
- e) Cognitive behavioral therapy

Question 8

What is the response rate of generalized anxiety disorder to drug treatment in published trials?

- a) 11%–19%
- b) 22%–33%
- c) 44%–81%
- d) 85%–95%
- e) 100%

Question 9

A 42-year-old woman working as a caregiver for elderly patients complains of the following symptoms: racing heartbeat, irregular pulse, shortness of breath, headache, arthralgia, abdominal pain, diarrhea alternating with constipation, esophageal reflux, nausea, bloating, itching, burning, urinary frequency, muscle weakness, dysphagia, and sensory disturbances. Her symptoms frequently vary. Organic causes have been excluded. The patient cannot accept the judgment of numerous physicians that her symptoms have no bodily cause. She demands further medical evaluation and treatment.

What is the most likely diagnosis?

- a) Anxiety combined with depression
- b) Hyperthyroidism
- c) Panic disorder
- d) Generalized anxiety disorder
- e) Somatoform disorder

Question 10

Which of the following is a typical technique in the treatment of generalized anxiety disorder with cognitive behavioral therapy?

- a) Practicing safety behavior
- b) Family constellation
- c) *In sensu* exposure to feared catastrophes
- d) Ignoring the bodily expressions of fear (natural fight-or-flight response)
- e) Resource deconstruction (“Is there anything I ought to worry more about?”)

CONTINUING MEDICAL EDUCATION

The Diagnosis and Treatment of Generalized Anxiety Disorder

Borwin Bandelow, Reinhard J. Boerner, Siegfried Kasper, Michael Linden, Hans-Ulrich Wittchen, Hans-Jürgen Möller

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eBOX

Generalized anxiety disorder—definition according to the ICD-10 research criteria (abbreviated version)*

Tension, worries, and fears about everyday experiences and problems lasting for at least six months, accompanied by at least four of the following types of symptoms (including at least one of symptoms 1–4):

● Vegetative symptoms

1. Palpitations, sensation of heartbeat, rapid heart rate
2. Diaphoresis
3. Fine or coarse tremor
4. Dry mouth

● Thoracic and abdominal symptoms

5. Respiratory symptoms
6. Feeling of tightness in the chest
7. Chest pain or discomfort
8. Nausea or abdominal discomfort

● Mental symptoms

9. Feeling dizzy, unsteady, faint or light-headed
10. Derealization or depersonalization
11. Fear of loss of control, going insane, or “cracking up”
12. Fear of dying

● General symptoms

13. Hot or cold flashes
14. Numbness or tingling

● Symptoms of tension

15. Muscle tension
16. Agitation and inability to relax
17. Feeling of being wound up, nervousness, emotional tension
18. Feeling of something sticking in the throat, dysphagia

● Other, nonspecific symptoms

19. Exaggerated startle response
20. Concentration difficulties, feeling of emptiness
21. Persistent irritability
22. Difficulty falling asleep because of worries

*modified from (22)

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