CLINICAL PRACTICE GUIDELINE

The Diagnosis of and Treatment Recommendations for Anxiety Disorders

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SUMMARY

Background: Anxiety disorders (panic disorder/agoraphobia, generalized anxiety disorder, social phobia, and specific phobias) are the most common mental illnesses. For example, the 12-month prevalence of panic disorder/agoraphobia is 6%.

Methods: This guideline is based on controlled trials of psychotherapy and pharmacotherapy, retrieved by a systematic search for original articles that were published up to 1 July 2013. Experts from 20 specialty societies and other organizations evaluated the evidence for each treatment option from all available randomized clinical trials and from a synthesis of the recommendations of already existing international and German guidelines.

Results: 403 randomized controlled trials were evaluated. It was concluded that anxiety disorders should be treated with psychotherapy, psychopharmacological drugs, or both. Response rates to initial treatment vary from 45% to 65%. Cognitive behavioral therapy is supported by higher-level evidence than any other psychotherapeutic technique. Psychodynamic therapy is recommended as a second-line treatment. Among anxiolytic drugs, the agents of first choice are selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. The patient's preference should be considered in the choice of treatment. Drug treatment should be continued for 6 to 12 months after remission. If psychotherapy or drug treatment is not adequately effective, then the treatment should be switched to the other form, or to a combination of both.

Conclusion: The large amount of data now available from randomized controlled trials permits the formulation of robust evidence-based recommendations for the treatment of anxiety disorders. Future work should more closely address the necessary duration of psychotherapy and the efficacy of combined psychotherapy and drug treatment.

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Anxiety disorders are the most common mental illnesses (1). Women are much more frequently affected than men. Specific phobias, with a 12-month prevalence of 10.3%, are the most common type of anxiety disorder (2), although persons suffering from them rarely seek treatment. The next most common type is panic disorder/agoraphobia (6.0%), followed by social phobia (2.7%) and generalized anxiety disorder (2.2%). Anxiety disorders have not become more common in recent years and decades (3, 4). They often arise in combination with other anxiety disorders, major depression, somatoform disorders, and addictive disorders (5). They are now thought to originate from an interaction of psychosocial, genetic, and neurobiological factors.

The S3 guideline on anxiety disorders

The S3 guideline on anxiety disorders (6) is available free of charge, in both short and long versions, on the website www.awmf.org/leitlinien (in German). S3 guidelines are required to meet the highest qualitative requirements of the DELBI criteria (7). This guideline was issued by 20 specialty societies and other organizations (*eTable 1*). It was created over the period 2008–2014 by a guideline committee of 36 persons, including specialists, general practitioners, and patient representatives (*eTable 2*). After ten working sessions, the final text of the guideline was created by a steering committee (B. Bandelow, M. Beutel, T. Lichte, S. Rudolf) and put to a vote of the remaining participants in two consensus conferences. Each participating group had one vote; recommendations were accepted if they received at least 75% of all votes cast. The resulting guideline was presented to the boards of the participating societies. Professor Ina Kopp of the Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften*, AWMF) assisted in the creation of the guideline and moderated all working sessions and consensus conferences.

This guideline, like other guidelines, is explicitly not intended to serve a regulatory function; it neither mandates nor forbids anything. Rather, it provides important contextual information for individual treatment decisions, which should also properly depend on the treating person's experience and on the preference of the patient.

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It is planned that this guideline will be disseminated through presentations by members of the guideline committee at scientific conferences and at continuing medical education sessions, and by providing a patient version (www.awmf.org/leitlinien). An update in 5 years is projected.

Because of the large number of clinical trials evaluated for the guideline, references will not be given for every statement in this article; rather, the reader is referred to the long version of the S3 guideline (in German only) for more information.

Methods

Already existing guidelines on the subject were sought by electronic search. Guidelines meeting the specified quality criteria were selected in a peer-review process (*eTable 3*). The guideline committee performed its own literature searches when discrepancies between existing guidelines were found, when subject areas were not adequately covered, or when new trials potentially resulting in different evidence levels were found to have been published since the appearance of the reference guidelines. All available randomized controlled trials (RCTs) on the treatment of anxiety disorders published up to 1 July 2013 were examined. The inclusion criteria were: original publication in a peer-reviewed journal; therapeutic trials of anxiety disorders defined according to ICD or DSM (panic disorder/agoraphobia, generalized anxiety disorder, social phobia, or specific phobia) in adults; not exclusively subgroup analysis; use of a control group (for drug trials, a placebo or reference drug; for psychotherapy trials, a waiting list, an active control [i.e., a supportive conversation with the patient, without applying specific therapeutic techniques], or treatment as usual [TAU]); for drug trials, use of a commercially available and approved drug.

As an example, the literature search on panic disorder/agoraphobia was carried out in the following way, according to the PRISMA Statement (8): PubMed search algorithm: (“panic disorder”{Title}} OR [“agoraphobia”{Title}]) AND [“randomized”{All fields}] AND [“treatment” OR “therapy”{All fields}]; date: 1980/01/01 to present; in ISI Web of Science: Title=[panic disorder OR agoraphobia] AND Topic=[randomized] AND Topic=[therapy]; timespan: >1979; Search language=English, German). 1296 publications were retrieved by this search, and 21 further ones were identified by a manual search. Of the 1317 publications found in total, 1100 were excluded after screening of the titles and abstracts. The full texts of the remaining 217 articles were obtained. 48 were excluded because they met specifically defined exclusion criteria (e.g., double publication, subgroup analysis only, sample size <10 for each arm at study baseline, and lack of an adequate control group, among others); 169 were included in the analysis. A similar procedure was followed for the remaining anxiety disorders (see the long version of the guide-

line). Finally, a total of 403 RCTs were evaluated for the guideline.

The quality of each trial was evaluated according to the criteria enunciated in the SIGN Statement (9). Methodological flaws led to the exclusion of trials or to downgrading of their evidence level. Common reasons for downgrading the evidence level included small sample size (particularly in non-inferiority comparisons), failure to state the primary efficacy measure, or respectively failure to apply a Bonferroni correction for multiple testing, and inappropriate methods of statistical analysis.

Decisions to base guideline recommendations on the results of RCTs alone have often met with criticism in the past, and, indeed, in the case of the present guideline, this decision was controversial within the guideline committee itself. It was pointed out that RCTs generally involve a selected group of patients: patients with comorbidities are often excluded, and suicidal patients are as a rule excluded. Yet an analysis of psychotherapy and drug trials evaluated for the guideline did not indicate that these types of treatment differed systematically with respect to the inclusion of comorbid patients. In uncontrolled studies, it cannot be determined whether an observed improvement was due to the treatment itself or to spontaneous remission, tendency of regression to the mean, or non-specific attention effects; therefore, the guideline committee agreed that the recommendations should, essentially, be based on the results of RCTs. Although, according to the protocol, results from open studies, case series, and single case reports were also admissible, there was no concrete case in which a decision about an evidence level had to be made on the basis of such publications. This was due to the lack of sufficiently informative non-randomized studies, and the sufficient availability of controlled trials.

While the evidence categories were based exclusively on the efficacy of the various treatments studied, the recommendation grades also took risks into account, e.g., drug adverse effects (*eTable 4*).

Diagnosis

In Germany, anxiety disorders are evaluated in the outpatient and inpatient settings according to the 10th edition of the International Classification of Diseases in its German modification (ICD-10 GM) (10; see brief description in *Table 1*). In primary care, the diagnosis “mixed anxiety and depressive disorder” (ICD-10 F41.2) is often made; according to ICD-10, however, this diagnosis is impermissible if either anxiety or depression is severe enough to merit being diagnosed in itself. As no clinical trials have been conducted on the treatment of this entity according to its proper, restricted definition, the present guideline does not contain any recommendations about its treatment.

Anxiety disorders often go unrecognized, partly because patients frequently complain of pain, sleep

TABLE 1

Brief descriptions of the main anxiety disorders according to ICD-10 (29)

Anxiety disorder: ICD-10 classification	Description	Diagnostic tips
Panic disorder F41.0	Anxiety attacks of sudden onset, with physical manifestations of anxiety (palpitations, irregular heartbeat, sweating, tremor, trembling, dry mouth, dyspnea; feeling of choking or of tightness in the throat; chest pain, pressure, or tightness; nausea or other abdominal discomfort; dizziness, unsteadiness, lightheadedness, or faint feelings; feeling of unreality, as if in a dream, or as if "not really there"; chills or hot flashes; numbness, paresthesia) and fear of losing control, going mad, losing consciousness, or dying. These panic attacks develop abruptly and reach a peak within 10 minutes.	Panic attacks can arise out of the blue; in the majority of cases, however, panic disorder is associated with agoraphobia.
Agoraphobia F40.0 without panic disorder F40.00 with panic disorder F40.01	In agoraphobia with panic disorder, patients experience not only panic attacks as described above, but also fear of places where it might be difficult or embarrassing to escape if a panic attack should occur. Such patients most commonly have panic attacks in crowds, on public transport, or in confined spaces (e.g., elevators). Fear of being alone is also common. Having an accompanying person on hand lessens anxiety.	When a patient reports agoraphobia, the diagnosis of panic disorder should be considered.
Generalized anxiety disorder F41.1	Patients suffer from somatic anxiety symptoms (tremor, palpitations, dizziness, nausea, muscle tension, etc.) as well as from difficulty concentrating, nervousness, insomnia, and other psychic symptoms. They usually cannot say what, in particular, they are afraid of, yet they are plagued by constant worry, e.g., that they (or a relative) might have an accident or become ill. They also worry about being in a permanently worried state ("meta worries").	In contrast to panic disorder, the physical manifestations of anxiety do not arise together in the form of an attack, but rather in shifting combinations, as a more or less permanent state. Patients with panic disorder fear for their own health; patients with generalized anxiety disorder worry more about the health of close persons or relatives.
Social phobia F40.1	These patients are afraid of situations in which they are the center of attention – e.g., public speaking, visits to authorities, conversations with superiors on the job, or with persons of the opposite sex. They are afraid of appearing clumsy, embarrassing themselves, or being judged negatively.	In many cases, the affected persons are ashamed to discuss their social fears, with the result that the condition remains undiagnosed.
Specific (isolated) phobias F40.2	Such phobias are restricted to individual, circumscribed situations, often related to animals, or other natural phenomena (e.g., cats, blood, heights).	Patients very rarely seek professional help for isolated phobias.
Mixed anxiety and depressive disorder F41.2	The simultaneous presence of anxiety and depression, with neither predominating. However, neither component is sufficiently severe to justify a diagnosis of anxiety or depression in itself.	If the criteria for both an anxiety disorder and major depression are fulfilled, both diagnoses should be made, rather than mixed anxiety and depressive disorder.

disturbances, or other somatic problems as their main symptom, rather than of the underlying anxiety (11). The differential diagnosis of anxiety disorders must include other common mental disorders, such as other anxiety disorders, major depression, and somatoform disorders, as well as somatic diseases such as coronary heart disease, bronchial asthma, and others (Table 2).

Health care provision

The primary care physician is often the first doctor contacted by the patient, and therefore plays a major role in its care. Some 15% of patients remain exclusively under the treatment of their primary care physicians and do not consult a specialist (12). Psychotherapy is provided by psychotherapists, who can be either physicians or certified psychologists in Germany. If the symptoms fail to improve sufficiently, if the patient becomes suicidal, or if other complications arise, the patient should be referred to a psychiatrist. Anxiety disorders can usually be treated on an outpatient basis. Indications for hospitalization include suicidality, lack of further options

for outpatient management, very severe anxiety, and marked comorbidity.

Treatment recommendations

The accepted indications for treatment are: the presence of an anxiety disorder as defined by ICD-10 GM, moderate to severe subjective distress as perceived by the patient, and psychosocial problems and other complications resulting from the anxiety disorder (e.g., substance abuse). The treatment recommendations are summarized in Table 2 (for a more detailed version, cf. Table 1 in the text of the guideline [in German]). Anxiety disorders can be treated with psychotherapy and/or drug treatment and other interventions. In meta-analyses, both psychotherapy and medication have been found to have moderate to high effect sizes in pre-post comparisons and in comparisons with control groups. Response rates for the form of treatment initially chosen are in the range of 45% to 65%.

The treatment plan should be chosen after careful consideration of individual factors (the patient's preference, previous treatment attempts, severity,

TABLE 2

Summary of recommendations on the treatment of anxiety disorders

Treatment	Recommendation	Level of evidence	Recommendation grade				
Psychotherapy and psychotropic drugs	Patients with P/A, GAD, or SPh should be offered: – Psychotherapy – Medication The preference of the well-informed patient should be respected. The patient should be informed, in particular, about the onset and duration of action, side effects, and availability of treatment modality.	Ia	A				
	If psychotherapy or psychotropic drugs are not effective, the other form of treatment or a combination of both should be offered.	Expert consensus	CCP				
Psychotherapy and other measures							
Cognitive behavioral therapy (CBT)	Patients with P/A, GAD, SPh, or specific phobias should be offered CBT.	Ia	A				
Psychodynamic psychotherapy	Patients with P/A, GAD, or SPh should be offered psychodynamic psychotherapy if CBT is unavailable or ineffective, or if they express a preference for psychodynamic psychotherapy after being informed about all available types of treatment.	IIa	B				
Exercise (endurance training, e.g., jogging 5 km three times a week)	Patients with P/A can be given a recommendation for exercise (endurance training) as an adjunctive measure to other standard treatments.	Expert consensus	CCP				
Patient self-help and family support groups	Patients and their families should be informed about self-help and family support groups and encouraged to participate, if appropriate.	Expert consensus	CCP				
Psychotropic drugs							
		Anxiety disorder			Daily dose		
	Drug	P/A	GAD	SPh			
	Citalopram*1	x			20–40 mg	Ia	A
	Escitalopram*2	x	x	x	10–20 mg	Ia	A
	Paroxetine	x	x	x	20–50 mg	Ia	A
	Sertraline	x		x	50–150 mg	Ia	A
	Duloxetine		x		60–120 mg	Ia	A
	Venlafaxine	x	x	x	75–225 mg	Ia	A
	Tricyclic antidepressants	Clomipramine (if drugs with a grade A recommendation are ineffective or poorly tolerated)	x			75–250 mg	Ia
Calcium modulators	Pregabalin		x		150–600 mg	Ia	B
Tricyclic anxiolytics	Opipramol (if drugs with a grade A or B recommendation are ineffective or poorly tolerated)		x		50–300 mg	Ib	0
Azapirones	Buspirone (if drugs with a grade A or B recommendation are ineffective or poorly tolerated)		x		15–60 mg	Ib	0
RIMA	Moclobemide (if drugs with a grade A or B recommendation are ineffective or poorly tolerated)			x	300–600 mg	Expert consensus	CCP

P/A = panic disorder/agoraphobia; GAD = generalized anxiety disorder; SPh = social phobia; CCP = clinical consensus point; RIMA = reversible monoamine oxidase A inhibitor.

^{*1} Do not exceed recommended dose (QT_c interval prolongation). Maximal dose with diminished hepatic function 30 mg/day, for older patients 20 mg/day.

^{*2} Do not exceed recommended dose (QT_c interval prolongation). Maximal dose for persons over age 65, 10 mg/day

comorbidity including substance abuse, suicide risk, and others). All interventions should be performed on the basis of a functioning and sustainable therapeutic relationship. Treating physicians and psychologists must inform patients of the diagnosis and the likelihood of improvement with each potential treatment, in the light of the available evidence. They must

also inform them of the alternatives when multiple treatments, any of which may be indicated, are associated with markedly different burden of distress, risks, or chances of improvement.

The patients' relatives should be integrated into the treatment, and the economic aspects of treatment should also be considered. A detailed discussion of

TABLE 3

Stepwise plan for alternative drug treatment if the drug initially used to treat an anxiety disorder is ineffective or poorly tolerated* (modified from [30])

Measure	Procedure
Switch from one standard drug to another	<ul style="list-style-type: none"> – Switch from one SSRI to another – Switch from an SSRI to an SNRI, or vice versa – Switch to a TCA – Switch to pregabalin (only in GAD)
Switch to non-standard drugs	
Switch to a drug that is approved for other anxiety disorders	<ul style="list-style-type: none"> – Switch to pregabalin – Switch to moclobemide, opipramole, or hydroxyzine – Switch to a benzodiazepine (only in rare cases, when clinically justified)
Switch to a drug that is not approved for the anxiety disorder in question but has been found effective in RCTs	<ul style="list-style-type: none"> – Panic disorder: Mirtazapine, quetiapine, phenelzine, valproate, inositol – GAD: Quetiapine; in refractory cases, addition of risperidone or olanzapine to treatment with an antidepressant – Social phobia: Mirtazapine, gabapentin, pregabalin, olanzapine
Switch to a drug (or drug combination) that has been found effective in open studies	<ul style="list-style-type: none"> – Panic disorder: Combined SSRI and TCA, olanzapine monotherapy, combined SSRI and olanzapine or a TCA, addition of pindolol to an SSRI, combined valproate and clonazepam. In refractory cases, open studies have documented the efficacy of olanzapine and of the addition of fluoxetine to a TCA, of a TCA to fluoxetine, and of olanzapine to an SSRI. Ziprasidone – GAD: levetiracetam, topiramate, tranylcypromine; in refractory cases, addition of buspirone to an SSRI – Social phobia:
Switch to a drug (or drug combination) that has been reported to be effective in case reports	<ul style="list-style-type: none"> – Panic disorder: The addition of lithium to clomipramine and the combination of valproate and clonazepam have been reported to be effective in refractory cases

* Not all drugs mentioned in this article are currently approved in all countries for the indications, in the populations, or at the doses being discussed. Refer to your local prescribing information. SSRI, selective serotonin reuptake inhibitor; SNRI, selective serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; GAD, generalized anxiety disorder

the treatment of generalized anxiety disorder can be found in Bandelow et al. (2013) (13).

Psychotherapy

The large number of RCTs of cognitive behavioral therapy (CBT) carried out to date for each of the four types of anxiety disorder have documented the efficacy of CBT in comparison to active controls and to waiting lists. CBT should be based on empirically validated treatment protocols (manuals). Patients with avoidance behavior (e.g., agoraphobic patients) should receive CBT with exposure, i.e., confrontation with anxiety-inducing situations. Exposure therapy was found to be more effective when the patient was accompanied by the therapist (14).

As psychodynamic methods have rarely been considered in previous guidelines due to a lack of studies, the guideline group carried out an independent literature search in order to integrate recently published studies of manualized short-term psychodynamic therapy. The RCTs on psychodynamic therapy were markedly fewer in number, and lower in quality, than those on CBT, and some comparison studies have shown CBT to be superior. It is thus recommended that patients with panic disorder/agoraphobia, generalized anxiety disorder, or social phobia should be offered psychodynamic psychotherapy if CBT is

ineffective or unavailable, or if the (adequately informed) patient expresses a preference for psychodynamic treatment. For specific phobias, the available studies are exclusively of behavioral therapy, which should be performed as exposure treatment.

The current state of the data does not permit any valid generalization about the necessary duration of psychotherapy, as most trials were conducted for periods of 10 to 24 weeks, and only a few of them involved a comparison of the efficacy of treatment when carried out for a shorter or longer time. The duration of treatment should be planned individually depending on the severity of illness, comorbidities, and the overall psychosocial situation. For specific phobias, the available studies show that exposure treatment can be performed successfully in a few sessions.

The guideline committee also investigated nontherapist-supported techniques that are performed via computer or over the Internet. Many studies of such treatments have been published in the last few years, but there is, as yet, insufficient evidence to conclude that they are as effective as individual CBT. Moreover, treatments without personal contact are not reimbursable by the statutory health insurance carriers in Germany. Medicolegal

problems can also arise (e.g., in case of suicidality), and the matter of data privacy has not yet been adequately addressed. Patients with panic disorder/agoraphobia can be offered therapist-unsupported interventions based on CBT and involving books, audio material, computers, or the Internet as a form of self-help, to bridge the time interval before therapy is scheduled to begin or as adjunctive treatment to face-to-face therapy.

Group CBT has also been studied in randomized controlled trials, but there is still too little evidence to conclude that group CBT is as effective as individual treatment. It seems reasonable, however, to conduct self-assurance training in groups, e.g., for patients with social phobia; in such cases, the treatment should involve both individual and group therapy. Offering group therapy is also justified if individual therapy is unavailable.

The guideline committee found too little evidence to support any recommendation about other forms of psychotherapy (applied relaxation, interpersonal therapy, client-centered therapy, others).

Pharmacotherapy

Grade A recommendations were issued for drugs from two categories: the selective serotonin reuptake inhibitors (SSRI) and the serotonin-norepinephrine reuptake inhibitors (SNRI). Grade B recommendations were issued for the tricyclic antidepressant clomipramine (for panic disorder) and for pregabalin (for generalized anxiety disorder). Benzodiazepines, though effective, should not be prescribed, as they have major side effects (including the development of dependence). Only in exceptional cases—e.g., in the setting of severe heart disease, contraindications for the standard drugs, suicidality, and other situations—benzodiazepines can be given for short-term use after their risks and benefits have been carefully weighed.

Drug treatment should be conducted according to generally accepted medical standards. The patient must be informed about adverse effects, possible interactions, contraindications, and warnings; the prescriber should obtain this information from the current summary of product characteristics for the drug in question. Patients starting treatment with antidepressants should be told that they generally take effect after a latency period of about two weeks (range, 1 to 6 weeks).

SSRI and SNRI have a relatively flat dose-response curve, i.e., about 75% of patients respond to the initial (low) dose. For some patients, it is reasonable to begin treatment at half of the usually recommended dose. Dose adjustment may be necessary in patients with impaired hepatic function. To prevent agitation and insomnia at the start of treatment, the drug should be given in the morning or at midday. Some patients will need doses at the upper end of the indicated range and should be given them if necessary. Treatment with an SSRI or an SNRI should be continued as maintenance therapy at the

same dose that was successful in acute treatment. Once remission has been achieved, pharmacotherapy should be continued for 6 to 12 months, or even longer if drug discontinuation leads to recurrent anxiety, if the anxiety disorder is especially severe, or if the patient's history indicates that prolonged treatment may be needed. The dose should be slowly tapered at the end of treatment to avoid discontinuation syndromes.

There is too little evidence to support any recommendation for drug treatment for specific phobias.

Combined psychotherapy and drug treatment, and the management of refractory anxiety

There have been a number of comparative studies of psychotherapy, drug treatment, and a combination of both in the treatment of panic disorder; most have indicated that a combination is superior to monotherapy of either type. For generalized anxiety disorder, studies of this type are lacking; for social phobia, the evidence is inconsistent. No study indicated that combination therapy was worse. If either psychotherapy or drug treatment is ineffective in an individual case, there should be a switch to the other type of treatment, or to a combination of the two. If there is no response to the first drug after 4 to 6 weeks of treatment, a second standard drug should be given instead. In case of a partial response, raising the dose can be considered first. *Table 3* contains a stepwise plan for drug treatment options in case of drug inefficacy or intolerance. If a switch to a different standard drug is unsuccessful, there can be another switch to drugs recommended as a second-line treatment, e.g., tricyclic antidepressants or pregabalin. Medicolegal issues should be considered whenever drugs that have not been approved for the treatment of anxiety (e.g. quetiapine [in Europe]) are given off label.

The treatment of anxiety disorders in older patients

The treatment of older patients has been studied only in generalized anxiety disorder, probably because the other anxiety disorders are less commonly seen in older patients. The few available studies on CBT in persons over age 65 have shown a lower degree of efficacy than in adults aged 18 to 65. As for drug treatment in older patients, a few studies have shown efficacy for duloxetine, venlafaxine, pregabalin, and quetiapine. In older patients, possible drug interactions and contraindications must be considered carefully, along with the following additional factors: increased sensitivity to anticholinergic effects, the increased risk of orthostatic hypotension and ECG changes, the increased risk of falling, and possible paradoxical reactions to benzodiazepines.

Pregnancy and breastfeeding

For pregnant women, the risk of an untreated anxiety disorder must be weighed against the risk of damage

to the unborn child as a result of treatment. The physician should consider whether psychotherapy may be preferable to drug treatment for this reason. Some authors report increased risks with antidepressant drugs (15–17), which should, therefore, be given with caution. Likewise, a risk assessment has to be done when the patient is breast feeding.

Exercise

Exercise is recommended as a treatment for panic disorder (aerobic training, e.g., jogging 5 km three times a week). There is, however, too little evidence to support a recommendation for exercise as monotherapy. In the studies performed to date, exercise was less effective than a drug (18) and no more effective than relaxation as a control treatment (19).

Self-help groups

Patients should be informed about self-help and family support groups and encouraged to participate if appropriate.

KEY MESSAGES

- Anxiety disorders should be treated with psychotherapy, medication, or both.
- Of all psychotherapeutic techniques, cognitive behavioral therapy is supported by the highest-level evidence.
- Psychodynamic therapy is recommended as second-line treatment.
- The anxiolytic drugs of first choice are the selective serotonin reuptake inhibitors (SSRI) and the serotonin-norepinephrine reuptake inhibitors (SNRI).
- If either psychotherapy or psychotropic drugs are inadequately effective, the treatment should be switched to the other form, or to a combination of both.

Conflict of interest statement

All participants in the creation of this guideline have declared their conflicts of interest (e.g., having received lecture honoraria from drug companies or having been an advocate for a particular form of treatment). The guideline committee tried to base its recommendations exclusively on objective evaluation of the scientific evidence despite these potentially distorting influences. Participants with a relevant conflict of interest abstained when recommendations were put to a vote.

Prof. Bandelow has served as a paid consultant to Lilly, Lundbeck, Otsuka, and Pfizer and has received reimbursement of meeting participation fees and of travel and accommodation expenses from Pfizer and Servier. He has received honoraria for lectures at scientific meetings and continuing medical education events from AstraZeneca, Glaxo, Janssen, Lilly, Lundbeck, Meiji-Seika, Otsuka, Pfizer, and Servier.

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Dr. Rudolf, Prof. Lichte, and PD Wiltink declare that no conflict of interest exists.

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CLINICAL PRACTICE GUIDELINE

The Diagnosis of and Treatment Recommendations for Anxiety Disorders

Borwin Bandelow, Thomas Lichte, Sebastian Rudolf, Jörg Wiltink, Manfred E. Beutel

eTABLE 1

Participating medical societies, professional associations, and other organizations

No.	Abbrev.	Organization
1	APK	Aktion psychisch Kranke Support for the Mentally Ill
2	BPTK	Bundespsychotherapeutenkammer Federal Chamber of Psychotherapists in Germany
3	BVVP	Bundesverband der Vertragspsychotherapeuten Federal Association of Contract Psychotherapists
4	DAG SHG	Deutsche Arbeitsgemeinschaft Selbsthilfegruppen German Working Group Self-help Groups
5	DASH	Deutsche Angst-Selbsthilfe German Self-Help Association for Anxiety Sufferers
6	DÄVT	Deutsche Ärztliche Gesellschaft für Verhaltenstherapie German Medical Society of Behavioral Therapy
7	DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin German College of General Practitioners and Family Physicians
8	DGPM	Deutsche Gesellschaft für Psychosomatische Medizin und Ärztliche Psychotherapie German Society for Psychosomatic Medicine and Medical Psychotherapy
9	DGPPN	Deutsche Gesellschaft für Psychiatrie, Psychotherapie, Psychosomatik und Nervenheilkunde German Association for Psychiatry, Psychotherapy and Psychosomatics

10	DGPPR	Deutsche Gesellschaft für Klinische Psychologie und Psychosomatische Rehabilitation German Society for Clinical Psychology and Psychosomatic Rehabilitation
11	DGPs	Deutsche Gesellschaft für Psychologie German Psychological Society
12	DGPT	Deutsche Gesellschaft für Psychoanalyse, Psychotherapie, Psychosomatik und Tiefenpsychologie German Society for Psychoanalysis, Psychotherapy, Psychosomatic Medicine, and Depth Psychology
13	DGRW	Deutsche Gesellschaft für Rehabilitationswissenschaften German Society for Rehabilitation Sciences
14	DGVM	Deutsche Gesellschaft für Verhaltensmedizin und Verhaltensmodifikation German Society for Behavioral Medicine and Behavior Modification
15	DGVT	Deutsche Gesellschaft für Verhaltenstherapie German Society for Behavioral Therapy
16	DKPM	Deutsches Kollegium für Psychosomatische Medizin German College for Psychosomatic Medicine
17	DPG	Deutsche Psychoanalytische Gesellschaft German Psychoanalytic Society
18	DPV	Deutsche Psychoanalytische Vereinigung German Psychoanalytic Association
19	DVT	Deutscher Fachverband für Verhaltenstherapie German Professional Association for Behavior Therapy
20	GAF	Gesellschaft für Angstforschung Society for Anxiety Research

eTABLE 2

Members of the consensus group and of the steering committee (designated with an asterisk); abbreviations as in eTable 1

Name	Specialty society / organization	Abbreviation
Prof. Dr. rer. nat. Georg W. Alpers	German Psychological Society	DGPs
Prof. Dr. med. Borwin Bandelow, Dipl.-Psych.*	German Association for Psychiatry, Psychotherapy and Psychosomatics; Society for Anxiety Research	DGPPN; GAF
Prof. Dr. phil. Cord Benecke	German Psychoanalytic Society	DPG
Prof. Dr. med. Manfred E. Beutel, Dipl.-Psych.*	German College for Psychosomatic Medicine	DKPM, coordination
Prof. Dr. med. Jürgen Deckert	German Association for Psychiatry, Psychotherapy and Psychosomatics	DGPPN
Prof. Dr. med. Annegret Eckhardt-Henn	German Psychoanalytic Association	DPV
Dr. med. Christian Ehrig	German Medical Society of Behavioral Therapy	DÄVT
Dr. med. Kerstin Engel	German Association for Psychiatry, Psychotherapy and Psychosomatics; Society for Anxiety Research	DGPPN; GAF
Prof. Dr. med. Peter Falkai	German Association for Psychiatry, Psychotherapy and Psychosomatics	DGPPN
Prof. Dr. med. Franziska Geiser, Dipl.-Psych.	German Society for Psychosomatic Medicine and Medical Psychotherapy	DGPM
Prof. Dr. Alexander L. Gerlach	German Society for Behavioral Medicine and Behavior Modification	DGVM
Prof. Dr. phil. Stephan Hau, Dipl.-Psych.	German Psychoanalytic Association; German Society for Psychoanalysis, Psychotherapy, Psychosomatic Medicine, and Depth Psychology	DPV; DGPT
Dipl.-Psych. Timo Harfst	Federal Chamber of Psychotherapists in Germany	BPTK
Prof. Dr. med. Peter Joraschky	German College for Psychosomatic Medicine	DKPM
Prof. Dr. med. Michael Kellner	German Association for Psychiatry, Psychotherapy and Psychosomatics; Society for Anxiety Research	DGPPN; GAF
Prof. Dr. med. Volker Köllner	German Society for Psychosomatic Medicine and Medical Psychotherapy	DGPM
Univ.-Doz. Dr. med. Gernot Langs	German Society for Behavioral Therapy in Medicine	DÄVT
Prof. Dr. med. Thomas Lichte*	German College of General Practitioners and Family Physicians	DEGAM
Dr. rer. nat. Heinz Liebeck	German Society for Behavioral Therapy	DGVT
Dipl.-Psych. Jürgen Matzat	German Working Group Self-help Groups	DAG SHG
Dipl.-Psych. Markus Reitt	Research	
Dr. med. Sebastian Rudolf*	German Professional Association for Behavior Therapy	DVT
Prof. Dr. med. Heinrich Peter Rüddel	German Society for Clinical Psychology and Psychosomatic Rehabilitation	DGPPR
Hr. Gerhard Schick	German Self-Help Association for Anxiety Sufferers	DASH
Prof. Dr. med. Ulrich Schweiger	German Professional Association for Behavior Therapy	DVT
Dr. Regine Simon	Federal Association of Contract Psychotherapists	BVVP
Prof. Dr. med. Andreas Ströhle	German Association for Psychiatry, Psychotherapy and Psychosomatics; Society for Anxiety Research; Support for the Mentally Ill	DGPPN; GAF; APK
Dipl.-Psych. Anne Springer	German Society for Psychoanalysis, Psychotherapy, Psychosomatic Medicine, and Depth Psychology	DGPT
Prof. Dr. med. Hermann Staats	German Psychoanalytic Society	DPG
Dr. Walter Ströhm	German Professional Association for Behavior Therapy	DVT
Dipl.-Psych. Benedikt Waldherr	Federal Association of Psychotherapists	BVVP
Prof. Dr. phil. Birgit Watzke	German Society for Rehabilitation Sciences	DGRW
Dr. med. Dirk Wedekind	German Association for Psychiatry, Psychotherapy and Psychosomatics; Society for Anxiety Research	DGPPN; GAF
PD Dr. med. Jörg Wiltink, Dipl.-Psych.	Coordination	
Dipl.-Soz.-Päd. Christian Zottl	German Self-Help Association for Anxiety Sufferers	DASH
Prof. Dr. med. Peter Michael Zwanzger	German Association for Psychiatry, Psychotherapy and Psychosomatics; Society for Anxiety Research	DGPPN; GAF

eTABLE 3

Existing guidelines on the treatment of anxiety disorders that were used in the creation of the present guideline, in order of publication date. The four columns at right indicate which of the four disorders discussed in the present guideline (panic disorder, generalized anxiety disorder, social phobia, specific phobia) were covered by the guideline in question.

Guideline	Society	Authors	PD	GAD	Social phobia	Specific phobia
Recommendations on the treatment of anxiety and obsessive-compulsive disorders	Medicines Committee of the German Medical Association (<i>Arzneimittelkommission der deutschen Ärzteschaft, AkdÄ</i>)	(20)	x	x	x	x
Evidence-based guidelines for the pharmacological treatment of anxiety disorders	British Association for Psychopharmacology (BAP)	(21)	x	x	x	x
Clinical Practice Guidelines, Management of Anxiety Disorders	Canadian Psychiatric Association	(22)	x	x	x	x
Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders – First Revision	World Federation of Societies of Biological Psychiatry (WFSBP)	(23)	x	x	x	x
Practice guideline for the treatment of patients with panic disorder	American Psychiatric Association	(24)	x			
Evidence-based guidelines on psychotherapy for panic disorder with or without agoraphobia and for agoraphobia without panic disorder	German Psychological Society (<i>Deutsche Gesellschaft für Psychologie, DGPs</i>)	(25)	x			
Evidence-based guidelines on psychotherapy for social anxiety disorder	German Psychological Society (<i>Deutsche Gesellschaft für Psychologie, DGPs</i>)	(26)			x	
Management of Anxiety (Panic Disorder, with or without Agoraphobia, and Generalised Anxiety Disorder) in Adults in Primary, Secondary and Community Care	National Institute for Health and Clinical Excellence (NICE)	(27)	x	x		

eTABLE 4

Evidence levels (from Eccels and Mason, 2001 [28]) and recommendation grades

Level of evidence	Definition	
Ia	Evidence from a meta-analysis of at least three randomized controlled trials (RCTs)	
Ib	Evidence from at least one RCT or a meta-analysis of fewer than three RCTs	
IIa	Evidence from at least one methodologically sound, non-randomized controlled trial	
IIb	Evidence from at least one methodologically sound, quasi-experimental descriptive study	
III	Evidence from methodologically sound, non-experimental observational studies, e.g., comparative studies, correlation studies, and case studies	
IV	Expert committee reports or expert opinion and/or clinical experience of recognized authorities	
Recommendation grade	Positive recommendation	Negative recommendation
A	“Must” recommendation: at least one RCT of good overall quality and consistency supports the recommendation directly, without extrapolation (evidence levels Ia and Ib)	“Must not”: recommendation against the measure in question based on level Ia and Ib evidence.
B	“Should” recommendation: well-conducted clinical trials, other than RCTs, support the recommendation either directly (evidence levels II or III) or by extrapolation (evidence level I) if the studies do not directly address the subject in question.	“Should not”: recommendation against the measure in question based on level II and III evidence.
0	“May” recommendation: expert committee reports or expert opinion and/or clinical experience of recognized authorities (evidence level IV) or extrapolation from evidence of levels IIa, IIb, or III. This recommendation grade indicates that no directly applicable clinical studies of sufficiently high quality are available for consideration.	Recommendation against the measure in question based on level IV evidence or extrapolation from evidence of levels IIa, IIb, or III.