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REVIEW/MINI-REVIEW ▸

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Posttraumatic Stress Disorders

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Summary

In this report, recommendations for the pharmacological treatment of anxiety and obsessive-compulsive disorders are presented, based on available randomized, placebo- or comparator-controlled clinical studies.

Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for panic disorder. Tri[2]-cyclic antidepressants (TCAs) are equally effective, but they are less well tolerated than the SSRIs. In treatment-resistant cases, benzodiazepines like alprazolam may be used when the patient does not have a history of dependency and tolerance. Due to possible serious side effects and interactions with other drugs and food components, the irreversible monamine oxidase inhibitor (MAOI) phenelzine should be used only when first-line drugs have failed. In generalised anxiety disorder, venlafaxine and SSRIs can be recommended, while buspirone and imipramine may be alternatives. For social phobia, SSRIs are recommended for the first line, and MAOIs, moclobemide and benzodiazepines as second line. Obsessive-compulsive disorder is best treated with SSRIs or clomipramine.

Key words: *anxiety disorders, drug treatment, guidelines.*

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Abbreviations

5-HT	5-Hydroxytryptophan; serotonin
CBT	Cognitive behaviour therapy
DBPC	Double-blind placebo-controlled study
GAD	Generalised anxiety disorder
SAD	Social anxiety disorder
OCD	Obsessive-compulsive disorder
PTSD	Posttraumatic stress disorder
MAOI	Monoamine oxidase inhibitor
RIMA	Reversible inhibitor of monoamine oxidase A
SSNRI	Selective serotonin noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressants

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1 Introduction

According to the principles of evidence-based medicine, the present guideline is based on evidence from controlled clinical studies. To be recommended, a drug must have shown its efficacy in double-blind placebo-controlled (DBPC) studies. When an established standard treatment exists for a specific disorder, a drug must have been compared with this reference drug (comparator trial). However, a comparator trial alone without a placebo control is not regarded as sufficient, as there is the risk that inferiority of the new drug to the reference drug may not be detected due to the low statistical power of a study, as large sample sizes are needed for the test of equal efficacy. The categories of evidence used in this guideline are described in Table 1. These categories are based on efficacy only, without regard to other advantages or disadvantages of the drugs, such as side effects or interactions.

Table 1

Categories of evidence. In Table 6, the categories of evidence are given for all recommended drugs.

↑	**A. Positive Evidence** is based on: 2 or more randomised double-blind studies showing superiority to placebo And 1 or more positive double-blind study showing superiority to or equal efficacy as established comparator drug In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator drug), these must be outweighed by at least 2 more positive studies. Studies must fulfil established methodological standards (e.g. standard diagnostic criteria, optimal sample sizes, adequate psychometric scales, adequate statistical methods, adequate comparator drug etc.).
(↑)	**B. Preliminary Positive Evidence** is based on: **B1.** 1 or more randomised double-blind study showing superiority to placebo Or **B2.** 1 or more positive naturalistic open studies Or **B3.** 1 or more positive case reports And No negative studies exist
↔	**C. Inconsistent Results** Controlled positive studies are outweighed by an approximately equal number of negative studies
↓	**D. Negative Evidence** The majority of controlled studies shows non-superiority to placebo or inferiority to comparator drug
Ƶ	**E. Lack of Evidence** Adequate studies proving efficacy or non-efficacy are lacking

Only studies that fulfilled certain methodological requirements, including standard diagnostic criteria, adequate sample size, use of a control group, randomisation, double-blind conditions, use of appropriate psychometric rating scales, use of appropriate statistical tests, fulfilment of good clinical practice (GCP) criteria, and approval by an ethics committee were included.

Data were extracted from the MEDLINE Database and the Science Citation Index at Web of Science (ISI) (until April 2002). Recommendations from consensus conferences (e.g. APA 1998; Ballenger et al 1998a, b; Ballenger 1999; NIH 1992) and from expert polls were taken into account (e.g. Uhlenhuth et al 1999).
Some of the drugs recommended in this guideline may not (or not yet) have received approval for the treatment of anxiety disorders in every country. As the approval by national regulatory authorities is dependent on many factors, this guideline is exclusively based on the available evidence.
These principles of practice are considered guidelines only. Adherence to them will not ensure a successful outcome in every case. The individual treatment of a patient should be planned by the psychiatrist in the light of clinical data presented by the patient and the diagnostic and treatment options available.

1.1 Overview of available treatment guidelines for anxiety disorders

In Table 2, the published results of recent expert consensus conferences are summarised briefly.

1.2 Epidemiology

Anxiety disorders are the most frequent psychiatric disorders. According to representative population surveys, one-year-prevalence rates of 12.6-17.2% were found for anxiety disorders (Kessler et al 1994; Regier et al 1993). As the clinical significance of community-based rates has been questioned, these estimates have been adjusted by including only clinically significant cases (Narrow et al 2002), still revealing high prevalence rates (Table 3).
For obsessive-compulsive disorders, a one-year prevalence rate of 2.1% was found (Regier et al 1993).
Epidemiological data collected from a variety of countries have documented differences in prevalence rates for the anxiety disorders (Bandelow, 2002).

Patients with anxiety disorders are frequent users of emergency medical services (Klerman et al 1991), are at a high risk for suicide attempts (Weissman et al 1989) and substance abuse (Brady and Lydiard 1993). Costs associated with the anxiety disorders represent approximately one third of the total expenditures for mental illness (DuPont et al 1996).
In primary care, anxiety disorders are usually underdiagnosed (Sartorius et al 1996) or

Table 2
Recent guidelines for anxiety disorders and OCD. Abbreviations: CBT = cognitive behaviour therapy, SSRI selective serotonin reuptake inhibitors, SSNRI = serotonin-norepinephrine reuptake inhibitors, TCA = tricyclic antidepressants

Disorder	Expert Panel	Summary of recommendations	Recommended minimum duration of pharmacotherapy
Panic Disorder	American Psychiatric Association (APA 1998)	CBT or pharmacotherapy	12-18 months
	International Consensus Group on Depression and Anxiety (Ballenger et al 1998a)	SSRIs	12-24 months
Generalised Anxiety Disorder	International Consensus Group on Depression and Anxiety (Ballenger et al 2001)	SSRIs, SSNRI, TCA and CBT	No recommendation (lack of data)
Social Anxiety Disorder	International Consensus Group on Depression and Anxiety (Ballenger et al 1998b)	SSRIs	12 months
Specific Phobia	No consensus guidelines available		No reliable data available
Obsessive-Compulsive Disorder	Expert Consensus Panel for Obsessive-Compulsive Disorder (1997)	CBT or SSRIs/clomipramine alone or in combination	12-24 months
	American Academy of Child and Adolescent Psychiatry (AACAP 1998)	CBT or CBT combined with SSRIs or clomipramine	12-18 months
Posttraumatic Stress Disorder	International Consensus Group on Depression and Anxiety (Ballenger et al 2000)	SSRIs, CBT	12-24 months

Table 3
Anxiety disorders, one-year prevalence rates from the National Co-morbidity Survey, clinically significant cases (Narrow et al 2002)

Anxiety Disorder	One-Year Prevalence Rate
Any Anxiety Disorder	12.1%
Panic Disorder with or without Agoraphobia	3.9%
Generalised Anxiety Disorder	2.8%
Social Phobia	3.7%
Specific Phobia	4.4%
Posttraumatic Stress Disorder	3.6%

recognized only years after onset. Frequently, clinicians fail to take advantage of available effective treatment strategies (Bandelow et al 1995; Cowley et al 1997).

1.3 Aetiology

Hypotheses on the aetiology of anxiety disorders and obsessive compulsive disorder (OCD) are the subject of controversial discussion. Most probably, anxiety disorders are caused by an interaction of a specific vulnerability and environmental and psychosocial factors. These psychosocial influences include traumatic childhood experiences, child-rearing styles, recent life events, model learning, faulty conditioning and other factors. The vulnerability may be based on genetic factors associated with neurobiological changes of the central nervous system. Neurobiological dysfunctions that have been found in anxiety and OCD patients include dysfunctions of serotonin, norepinephrine, dopamine, gamma-aminobutyric acid, cholecystokinin and other receptor systems or the hypothalamic-pituitary-adrenal (HPA) axis. The reader is referred to comprehensive reviews of the field (Charney and Bremner 1999; Connor and Davidson 1998; Gorman et al 2000; Jetty et al 2001; Li et al 2001; Nutt et al 1998; Schneier et al 2000; Stein 2000; van Ameringen et al 2000).

1.4 Diagnosis

In Table 4, a short overview over the various anxiety disorders is given. There is a high overlap among the anxiety disorders and co-morbidity with other psychiatric disorders such as depression (Bandelow, 2002).

2 Treatment

2.1 Indication for treatment

Treatment is indicated in most patients who fulfil the ICD-10 or DSM-IV criteria for an anxiety disorder or OCD. The treatment plan is based on the patient's preference, severity of illness, co-morbidity, concomitant medical illnesses, complications like substance abuse or suicide risk and the history of previous treatments. In some health systems, costs may be a factor. Treatment options include drug treatment and psychological therapy.

2.2 Drug treatment

Before drug treatment is initiated, the mechanisms underlying psychic and somatic anxiety should be explained to the patient.

Cooperation with drug treatment can be improved when the advantages and disadvantages of the drug such as the delayed onset of effect or side effects like initial jitteriness, are explained carefully to the patient. Patients with anxiety disorders sometimes express groundless or exaggerated fear of side effects of psychopharmacological drugs, e.g. addiction (even with drugs without known addiction potential).

Table 4
Short description of anxiety disorders as defined by ICD-10 (WHO 1991) and DSM-IV (APA 1994)

Panic Disorder
Panic disorder is characterised by recurrent panic attacks. Panic attacks are discrete periods of intense fear or discomfort, accompanied by at least four of fourteen somatic and psychic symptoms (13 in DSM-IV). A panic attack reaches a peak within 10 minutes and lasts 30-45 minutes on average. Usually the patient is afraid that he has a serious medical condition such as myocardial infarction.
Agoraphobia
About two thirds of all patients with panic disorder suffer from agoraphobia, which is defined as fear in places or situations from which escape might be difficult or in which help may not be available in the event of having an unexpected panic attack. These situations include being in a crowd or standing in a line, being outside the home alone, or travelling in a bus, train or automobile. These situations are avoided or endured with marked distress.
Generalised Anxiety Disorder
The main features of generalised anxiety disorder are excessive anxiety and worry. The patients suffer from somatic anxiety symptoms as well as from restlessness, irritability, difficulty concentrating, muscle tension, sleep disturbances and being easily fatigued. Patient may express constant worry that the patient or a relative will shortly become ill or have an accident.
Specific Phobia
Specific phobia is characterised by excessive or unreasonable fear of single objects or situations (e.g. flying, heights, animals, seeing blood, etc.).
Social Phobia (Social Anxiety Disorder)
This disorder is characterised by marked, persistent, and unreasonable fear of being observed or evaluated negatively by others in social performance or interaction situations and is associated with somatic and cognitive symptoms. The feared situations are avoided or else are endured with intense anxiety or distress. These situations include fear of speaking in public, speaking to unfamiliar people or being exposed to possible scrutiny by others.
Obsessive-Compulsive Disorder (OCD)
OCD is characterised by recurrent obsessions or compulsions, or both, that cause impairment in terms of distress, time, or interference with functioning. Concerns involving contamination, hoarding, and sexual, somatic and religious preoccupations are the most common obsessions. Compulsions include washing, checking, repeating, ordering, counting, hoarding and touching.

A marked placebo effect is a well-known phenomenon in the treatment of anxiety disorders. It is not recommended to use treatments that do not have effects superior to placebo effects, spontaneous remission or tendency of regression to the mean. Placebo effects may fade out with time. Moreover, by using invalidated treatments, patients may be denied available effective alternative treatments. Considerable costs may arise for the general health system and for the society by prescription of treatments without controlled proof of efficacy.

2.3 Duration of drug treatment

Mostly, anxiety disorders have a waxing and waning course. After remission, which may occur later in OCD and PTSD than in the other anxiety disorders, treatment should continue for at least several months in order to prevent relapses. In general, few studies examine relapse prevention after a period of more than one year. Expert consensus conferences generally recommend a duration of pharmacotherapy of at least 12-24 months (Table 2).

2.4 Dosing

Recommended dosages are given in Table 6. SSRIs have a flat response curve, i.e., approximately 75% of patients respond to the initial (low) dose. In some patients, treatment may be started with half the recommended dose. In particular, patients with panic disorder are sensitive to antidepressants and may easily discontinue treatment because of initial jitteriness and nervousness. For tricyclic antidepressants, it is recommended that the drug at a low dose and the initiated dose increased every 3-5 days.

The antidepressant dose should be increased to the highest recommended level when initial treatment with a low or medium dosage fails. For obsessive-compulsive and posttraumatic stress disorder, dosages in the upper range may be adequate in the majority of cases. Although controlled data on maintenance treatment are lacking, it is recommended that the same dose as in the acute phase be used.

In order to increase compliance, it may be feasible to give all the antidepressant medication in a single dose, depending upon the patient's tolerance.

In elderly patients, lower doses are used, especially when using tricyclic antidepressants.

Benzodiazepine doses should be as low as possible but as high as necessary to achieve a complete treatment result.

In patients with hepatic impairment, a dosage adjustment may be required.

2.5 Treatment resistance

Past treatment history of the patient should be used as a guide to practice. Before considering a patient to be treatment-resistant, it should be ascertained that the diagnosis is correct, the patient is compliant with therapy, the dosage prescribed is therapeutic and there has been an adequate trial period. Concurrent prescription drugs, e.g. metabolic enhancers or inhibitors, may interfere with efficacy. Psychosocial factors may affect response, and concomitant personality disorders may lead to poor outcome. Depression and substance abuse are especially likely to complicate anxiety disorders. Psychological

treatments such as cognitive behaviour therapy have to be considered.
When initial treatment fails, the physician has to decide when to change medication. Controlled data are lacking for the anxiety disorders. If the patient shows non-response to treatment in adequate dose after 4-6 weeks (8-12 weeks in obsessive-compulsive or posttraumatic stress disorder), medication should be changed. If partial response is seen after this period, there is still a chance that the patient will respond after another 4-6 weeks of therapy. Elderly patients may take longer to show a response.
Although 'switching studies' are lacking, many treatment-resistant patients are reported to respond when a different class of antidepressants is tried (e.g. switching from SSRI to TCAs or *vice versa*). Special recommendations for the different anxiety disorders are given below.
In order to monitor treatment efficacy, it may be useful to apply rating scales such as the Panic and Agoraphobia Scale (PAS; Bandelow 1999) for panic disorder, the Hamilton Anxiety Scale (HAM-A; Hamilton 1959) for generalised anxiety disorder, the Liebowitz Social Phobia Scale (LSAS; Liebowitz 1987) for social anxiety disorder, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al 1989a) for obsessive compulsive disorder, and the Clinician-Administered PTSD Scale (CAPS; Blake et al 1995) for posttraumatic stress disorder. However, as these assessments are time-consuming, global improvement ratings such as the Clinical Global Impression (NIMH 1976) may suffice in practice settings.

2.6 Non-pharmacological treatment

All patients with anxiety disorders require supportive interviews and attention to emotional states. 'Psychoeducation' is essential and includes information about the aetiology and treatment of anxiety disorders. Many patients may require specific psychological treatment interventions. Psychological and pharmacological treatment modalities must be seen as partners, not alternatives, in the treatment of anxiety disorders. The effective treatment of anxiety disorders with cognitive behaviour therapy has been demonstrated in many controlled studies. In particular, exposure therapy (e.g. 'flooding') or response prevention is very effective in specific phobia, agoraphobia, social phobia and OCD. In this treatment modality, patients are confronted *'in vivo'* with a feared situation (e.g. using public transport in agoraphobia). Special cognitive strategies have been developed for symptoms that cannot be treated with exposure, such as spontaneous panic attacks, worrying or obsessive thoughts.
Cognitive behaviour therapy is reputed to maintain its treatment gains over time, which would be a distinct advantage over medications. However, only a few studies could demonstrate the superiority of CBT over a control group (e.g. relaxation) at follow-up, while more studies failed to show a difference (see page 183).
For a detailed analysis of methodological issues regarding the comparisons of psychotherapy and pharmacotherapy, the reader is referred to Hollon (1999) and Klein (1998, 2000).
Psychodynamic therapy is frequently used in the treatment of patients with anxiety disorders. However, there are no published reports of randomised trials in anxiety disorders showing the superiority of this approach to a control condition.
For other psychological treatments, no sufficient proof of efficacy exists.
Like drug treatment, psychological therapy also may show insufficient efficacy. Also, relapses or even a deterioration of the symptoms is possible.
The differential indication for psychopharmacological or psychosocial treatment of the different anxiety disorders depends on the preference of the patient, unwanted side effects, onset of efficacy, co-morbidity (e.g. with depression), economic considerations, time availability and commitment of the patient, availability of psychiatric and psychological treatment resources, and qualification and experience of the therapist.

3 Drug treatment: available compounds

A number of psychopharmacological agents are available for the successful treatment of anxiety disorders; these are briefly reviewed in the following section. These recommendations are based on clinical studies, which are presented in the Chapter 'Special treatment recommendations for the different anxiety disorders'.
For details of the treatment with psychopharmacological drugs, the reader is referred to the special literature (e.g. the 'Clinical Handbook of Psychotropic Drugs', Bezchlibnyk-Butler and Jeffries 2001).

3.1 Tricyclic antidepressants (TCA)

The efficacy of tricyclic antidepressants in many anxiety disorders is well proven, mainly for imipramine and clomipramine (see below for references). Especially at the beginning of treatment, compliance may be hampered by adverse effects such as initially increased anxiety, dry mouth, postural hypotension, tachycardia, sedation, sexual dysfunctions, impaired psychomotor function and car driving safety, and others. Weight gain may be a problem in long-term treatment. In general, the frequency of adverse events is higher for TCAs than for newer antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norperinephrine reuptake inhibitors (SSNRIs). Thus, the latter drugs should be tried first before TCAs are used.
The dosage should be titrated up slowly until dosage levels as high as in the treatment of depression are reached. Patients should be informed that the onset of the anxiolytic effect

of the drug may have a latency of two to four weeks (in some cases up to six weeks, and generally longer in OCD). During the first two weeks, side effects may be stronger. Also, during the first days of treatment, jitteriness or increase in anxiety symptoms may occur.
TCAs have not been investigated thoroughly in social anxiety disorder.

3.2 Selective serotonin reuptake inhibitors (SSRI)

The efficacy of the SSRIs in anxiety disorders (panic disorder, generalised anxiety disorder, social phobia, PTSD and OCD) has been proven in many controlled studies (see below for references). Restlessness, jitteriness, an increase in anxiety symptoms and insomnia in the first days or weeks of treatment may hamper compliance with treatment. Lowering the starting dose of SSRIs may reduce this overstimulation. Sexual dysfunctions may be a problem in long-term treatment, and discontinuation syndromes have been observed (Price et al 1996; Stahl et al 1997). In general, the side effect profile of these drugs is benign. The anxiolytic effect may start with a latency of two to four weeks (in some cases more, and generally longer in OCD). To avoid overstimulation and insomnia, doses should be given in the morning and at midday.

3.3 Selective serotonin noradrenaline reuptake inhibitor (SSNRI) venlafaxine

The efficacy of the antidepressant venlafaxine, a selective serotonin noradrenaline reuptake inhibitor, in generalised anxiety disorder has been shown in several controlled studies (see below for references). At the beginning of treatment, side effects like nausea, restlessness or insomnia may occur and hamper compliance with treatment. The antianxiety effect may occur with a latency of two to four weeks, in some cases even later.

3.4 Reversible inhibitor of monoamine oxidase A (RIMA) moclobemide

Results with moclobemide are inconsistent. The compound was superior to placebo in two studies (IMCTGMSP 1997; Stein et al 2002) and also more effective than placebo and equally effective as phenelzine on most measures (Versiani et al 1992). In a fourth study, the size of its clinical effect was small (Schneier et al 1998), and in fifth study (Noyes et al 1997), no superiority against placebo could be demonstrated.

3.5 Irreversible monoamine oxidase inhibitors (MAOI)

The efficacy of the irreversible MAOI phenelzine in panic disorder and social phobia has been shown in some controlled studies (see below for references). Because of the possibility of severe side effects and interactions with other drugs or food components, the MAO-inhibitors phenelzine and tranylcypromine are not considered first-line drugs and should only be used by experienced psychiatrists when other treatment modalities have been unsuccessful or have not been tolerated. To avoid overstimulation and insomnia, doses should be given in the morning and mid-day.

3.6 Benzodiazepines

The efficacy of benzodiazepines in anxiety disorders (panic disorder, generalised anxiety disorder and social phobia) has been shown in many controlled clinical studies (see below for references). The anxiolytic effects start immediately after oral or parenteral application. In contrast to antidepressants they do not lead to initially increased nervousness. In general they have a good record of safety. Due to CNS depression, benzodiazepine treatment may be associated with sedation, dizziness, prolonged reaction time and other side effects. Cognitive functions and driving skills may be affected. After long-term treatment with benzodiazepines (e.g. over four to eight months), dependency may occur in some patients (Bradwejn 1993; Livingston 1994; Nelson and Chouinard 1999; Rickels et al 1990; Schweizer et al 1990b; Shader and Greenblatt 1993; Smith and Landry 1990), especially in predisposed patients (Schweizer et al 1998). Withdrawal reactions have their peak severity at 2 days for short half-life and 4 to 7 days for long half-life benzodiazepines (Rickels et al 1990). It is claimed that prolonged withdrawal reactions may occasionally occur. Tolerance seems to be rare (Rickels 1982).
Thus the treatment with benzodiazepines requires a careful weighing of risks and benefits. In particular, in patients in whom other treatment modalities were not effective or were not tolerated due to side effects, a year-long treatment with benzodiazepines may be justified. Patients with a history of benzodiazepine abuse should be excluded from treatment. Cognitive-behavioural interventions may facilitate benzodiazepine discontinuation (Otto et al 1993; Spiegel 1999). Benzodiazepines may also be used in combination with antidepressants during the first weeks before the onset of efficacy of the antidepressants (Goddard et al 2001). In depressed patients, drop-out rates were lower when benzodiazepines were added to antidepressant treatment (Furukawa et al 2002).
Benzodiazepines may also be used in the p.r.n. treatment of short-term distress (e.g. airplane travel).
A large number of benzodiazepines have received approval for the treatment of 'anxiety states' or 'anxiety disorders'. However, in the present guideline, recommendations of benzodiazepines are restricted to the ones that have been studied in patients with DSM- or ICD-defined diagnoses.
When treating co-morbid anxiety disorders, one should be aware that benzodiazepines do not treat co-morbid conditions, such as depression or OCD.

3.7 $5HT_{1A}$-agonist buspirone

The 5 HT_{1A}-agonist buspirone is effective in generalised anxiety, as could be shown in some controlled studies (see below for references). No proof of efficacy is available for other anxiety disorders.

3.8 Antihistamines

The antihistamine hydroxyzine was effective in generalised anxiety disorder in two DBPC studies (see below for references). Because of sedating effects, the antihistamine should only be used when treatment with other drugs has not been successful or these drugs were not tolerated. As experience with long-term treatment is lacking, the drug should not be used for longer than five weeks.

3.9 Barbiturates

Although barbiturates have been used in the treatment of anxiety states, controlled studies are lacking for this indication. Barbiturates should not be used as anxiolytics because they are habit-forming, causing physical dependence, and may have severe withdrawal symptoms. Tolerance develops quickly, requiring increased dosage. Barbiturates have a low margin of safety. They are involved in many drug interactions and may provoke hyperactivity in children or depression in adults. A suicide risk is associated with the use of barbiturates.

3.10 Neuroleptics

In some countries anxiety disorders are sometimes treated with neuroleptics. High or low potency neuroleptics have been used in lower doses than are used in the treatment of schizophrenia. The use of neuroleptics in anxiety disorders should be viewed critically. Studies conducted with neuroleptics in the 1970s and 1980s in patients suffering from 'anxiety neuroses' had some methodological flaws. Moreover, treatment with neuroleptics should not be applied for longer than three months in non-psychotic subjects, as the risk of irreversible tardive dyskinesia may be increased. Longer treatment durations are usually required in the treatment of anxiety disorders. Thus, the use is generally not recommended. However, in some cases of obsessive-compulsive disorders, the addition of typical or atypical antipsychotics is justified by controlled studies.

3.11 Beta blockers

Because beta blockers may influence autonomic anxiety symptoms such as palpitations, tremor, etc., they have been used in the treatment of anxiety disorders. However, available double-blind studies were not able to show efficacy of beta blockers in any anxiety disorder (see below for references). Moreover, patients with anxiety disorders frequently suffer from low blood pressure or postural hypotension, and these conditions may be intensified by beta blockers.
Beta blockers have been shown to improve peripheral symptoms in musicians with performance anxiety, but this condition differs from generalised social anxiety disorder.

3.12 Anticonvulsants

Anticonvulsants, including carbamazepine, valproate, lamotrigine and gabapentin, have shown efficacy in preliminary studies and deserve further research. However, they are not used in routine treatment.

3.13 Homeopathic and herbal preparations

In some countries, herbal preparations such as St. John's wort, kava-kava[1] (piper methysticum) or Valerianae are used in the treatment of anxiety disorders. Sufficient proof of efficacy is not available for these preparations. Also, there is no proof of efficacy for the treatment of anxiety disorders or OCD with homeopathic preparations.
Initial improvement with these compounds may be due to placebo effects, spontaneous remission or tendency of regression to the mean. Herbal and homeopathic preparations are sometimes used in the hope that advantage can be taken of these unspecific effects and adverse events can be minimized. However, placebo effects are usually not long-lasting, and a re-occurrence or deterioration of the symptomatology may result in loss of confidence in the physician. Also, these preparations have not undergone a safety evaluation. The prescription of these compounds may result in considerable costs for the health system.

3.14 Advantages and disadvantages of antianxiety drugs

None of the available drug treatments can be seen as ideal for every patient. In Table 5, risks and benefits of the available compounds are overviewed. The treatment option should be chosen individually for each patient. Also, medication costs have to be taken into account weighing the advantages and disadvantages against each other. Usually, the prices of newer drugs are relatively high before the patents have expired.

4 Special treatment recommendations for the different anxiety disorders

In Table 6, treatment recommendations for the drug treatment of anxiety disorders and OCD are shown.

4.1 Panic disorder and agoraphobia

In acute panic attacks, talking calmly to the patient may be sufficient in most cases. In severe attacks, short-acting benzodiazepines such as lorazepam melting tablets may be needed.

1 Kava kava products have been associated with hepatotoxicity; therefore their licence was withdrawn in Germany

Table 5
Advantages and disadvantages of antianxiety drugs. TCA=tricyclic antidepressants; SSRI=selective serotonin reuptake inhibitors; SSNRI=selective serotonin noradrenaline reuptake inhibitor; SAD=social anxiety disorder

Substance	Advantages	Disadvantages
TCA	No dependency Sufficient evidence from clinical studies (exception: SAD)	Latency of effect 2-6 weeks; anticholinergic effects, cardiac side effects, weight gain and other side effects; may be lethal in overdose
SSRI	No dependency Sufficient evidence from clinical studies for many anxiety disorders Relatively safe in overdose	Latency of effect 2-6 weeks; initial jitteriness, nausea, restlessness, sexual dysfunctions and other side effects
SSNRI	No dependency Sufficient evidence from clinical studies for some anxiety disorders Relatively safe in overdose	Latency of effect 2-6 weeks; nausea and other side effects
Benzodiazepines	Fast onset of action Sufficient evidence from clinical studies for some anxiety disorders Relatively safe in overdose	Dependency possible; sedation, slow reaction time and other side effects
Moclobemide	No dependency Benign side effect; relatively safe in overdose	Latency of effect 2-6 weeks; inconsistent study results in SAD; no efficacy proofs for other anxiety disorders
Buspirone	No dependency Relatively safe in overdose	Latency of effect 2-6 weeks; efficacy proofs only for generalised anxiety disorder; somnolence, nausea and other side effects
Hydroxyzine	No dependency Fast onset of action	Efficacy proofs only for generalised anxiety disorder; sedation and other side effects; no experiences with long-term treatment

Table 6
Recommendations for the drug treatment of anxiety disorders and OCD. Categories of evidence are only based on efficacy without regard to other properties (e.g., side effects). Abbreviations: see text. Category of evidence: see Table 1.

Diagnosis	Treatment	Examples	Category	Recommended Daily Dose for Adults
Panic disorder and agoraphobia	*In acute panic attacks:*			
	Benzodiazepines	Alprazolam	A	0.5 - 2 mg
		Lorazepam melting tablets	B1	1 - 2.5 mg
	Maintenance treatment:			
	SSRIs	Citalopram	A	20 - 60 mg
		Fluoxetine	B1	20 - 40 mg
		Fluvoxamine	A	100 - 300 mg
		Paroxetine	A	20 - 40 mg
		Sertraline	B1	50 - 150 mg
	TCA	Clomipramine	A	75 - 250 mg
		Imipramine	A	75 - 250 mg
	When other treatment strategies are not effective or not tolerated:			
	Benzodiazepines	Alprazolam	A	1.5 - 8 mg
		Clonazepam	A	1 - 4 mg
		Diazepam	A	5 - 20 mg
		Lorazepam	B1	2 - 8 mg
	MAOI	Phenelzine	B1	45 - 90 mg
	SSNRI	Venlafaxine	B1	75 - 225 mg
	SNRI	Reboxetine	B1	4 - 8 mg
	NASSA	Mirtazapine	B2	45 mg
	RIMA	Moclobemide	C	300 - 600 mg

Table 6 cont.

Generalised anxiety disorder	SSNRI	Venlafaxine extended release	A	75 - 225 mg
	SSRI	Paroxetine	A	20 - 50 mg
	TCA	Imipramine	A	75 - 200 mg
	Azapirone	Buspirone	C	15 - 60 mg
	When other treatment strategies are not effective or not tolerated:			
	Benzodiazepines	Diazepam	A	5 - 15 mg
	Antihistamine	Hydroxyzine	B1	37.5 - 75 mg
Social phobia	SSRI	Fluvoxamine	A	100 - 300 mg
		Paroxetine	A	20 - 50 mg
		Sertraline	A	50 - 150 mg
	MAOI	Phenelzine	A	45 - 90 mg
	RIMA	Moclobemide	C	300 - 600 mg
	When other treatment strategies are not effective or not tolerated:			
	Benzodiazepines	Clonazepam	B1	1.5 - 8 mg
	Anticonvulsant	Gabapentin	B1	600 - 3,600 mg
	SSRI	Citalopram	B2	20 - 60 mg
		Fluoxetine	B2	20 - 40 mg
Obsessive compulsive disorder	TCA	Clomipramine	A	75 - 300 mg
	SSRI	Fluoxetine	A	20 - 80 mg
		Fluvoxamine	A	100 - 300 mg
		Sertraline	A	50 - 200 mg
		Paroxetine	B1	40 - 60 mg
		Citalopram	B1	20 - 60 mg
	When other treatment strategies are not effective or not tolerated:			
	MAOI	Phenelzine	C	45-90 mg
	Augmenting agents for patients with a partial response to antidepressants:			
		Haloperidol	B1	Up to 3 mg
		Risperidone	B1	0.5 - 2.0 mg
		Pindolol	B1	7.5 mg
		Clonazepam	B1	Up to 5 mg
		L-tryptophan	B2	8 - 16 g
		Olanzapine	B2	5 - 15 mg
		Quetiapine	B1	150 - 750 mg
Posttraumatic stress disorder	SSRIs	Fluoxetine	B1	20 - 40 mg
		Sertraline	B1	50 - 100 mg
		Fluvoxamine	B2	100 - 300 mg
		Paroxetine	B1	20 - 40 mg
	TCA	Amitriptyline	B1	75 - 200 mg
		Imipramine	B1	75 - 200 mg
	When other treatment strategies are not effective or not tolerated:			
	MAOI	Phenelzine	B1	45 - 90 mg
	Anticonvulsant	Lamotrigine	B1	25 - 500 mg

These recommendations are based on randomised, double-blind clinical studies published in peer-reviewed journals. Not all of the recommended drugs are licensed for these indications in every country.

4.1.1 *Selective serotonin reuptake inhibitors (SSRI)*

For continuous treatment, SSRIs are the first-line drugs. Efficacy has been shown for *citalopram* in a placebo- and comparator-controlled trial (Wade et al 1997) and one comparison with fluoxetine (Amore et al 1999b), for *fluvoxamine* in a number of DBPC studies (Black et al 1993; den Boer and Westenberg 1990; Hoehn-Saric et al 1993; Sandmann et al 1998) and one placebo- and comparator-controlled trial (Bakish et al 1996), for *fluoxetine* in a DBPC (Michelson et al 1998) and some comparator-controlled trials (Amore et al 1999a, b; Bystritsky et al 1994), for

paroxetine in DBPC (Ballenger et al 1998c; Oehrberg et al 1995) and comparator-controlled studies (Bakker et al 1999; Lecrubier et al 1997), and *sertraline* in DBPC studies (Londborg et al 1998; Pohl et al 1998; Pollack et al 1998).

4.1.2 *Tricyclic antidepressants (TCA)*

Treatment with TCAs has been shown to improve panic disorder. This was shown for *imipramine* in DBPC (Klein 1964; Zitrin et al 1980; Zitrin et al 1983) and comparator-controlled studies (CNCPS 1992; Sheehan et al 1990; Uhlenhuth et al 1989) and for *clomipramine* in DBPC (Bandelow et al 2000; Johnston et al 1988) and comparator-controlled studies (Cassano et al 1988; Lecrubier et al 1997; Modigh et al 1992; Wade et al 1997).

4.1.3 *Benzodiazepines*

Alprazolam was superior to placebo and as equally effective as comparator drugs in a number of studies (Andersch et al 1991; Ballenger et al 1988; CNCPS 1992; Lydiard et al 1992; Noyes et al 1996; Uhlenhuth et al 1989). *Clonazepam* was investigated in DBPC studies (Beauclair et al 1994; Dyukova et al 1992; Moroz and Rosenbaum 1999; Rosenbaum et al 1997) and one placebo- and comparator-controlled trial (Tesar et al 1991). *Lorazepam* was equally effective as alprazolam in two studies (Charney and Woods 1989; Schweizer et al 1990a). *Diazepam* was evaluated in a placebo- and comparator-controlled (Noyes et al 1996) and comparator-controlled trial (Dunner et al 1986).

4.1.4 *Monoamine oxidase inhibitors (MAOI) and reversible inhibitor of monoamine oxidase A (RIMA)*

Despite the wide-spread use of *phenelzine* in panic disorder, only one study showed superiority to placebo and equal efficacy to imipramine (Sheehan et al 1980).

The reversible inhibitor of monoamine oxidase (RIMA) *moclobemide* was equally effective as fluoxetine (Tiller et al 1999) or clomipramine (Krüger and Dahl 1999). However, it was not superior to placebo in a double-blind study (Loerch et al 1999). In another study, superiority to placebo could only be established for the more ill patients, but not for the whole group (Uhlenhuth et al 2002).

4.1.5 *Buspirone*

Buspirone was not superior to placebo (Sheehan et al 1990; Sheehan et al 1993) and less effective than imipramine (Sheehan et al 1990), clorazepate (Schweizer and Rickels 1988) and alprazolam (Sheehan et al 1993).

4.1.6 *Beta blockers*

The beta blocker *propranolol* was not superior to placebo (Munjack et al 1989) and less effective than comparator drugs (Munjack et al 1989; Noyes et al 1984). In an underpowered DBPC study, propranolol was not different from alprazolam, although alprazolam showed a more rapid onset of efficacy (Ravaris et al 1991).

4.1.7 *Other agents*

The SSNRI venlafaxine has demonstrated efficacy for panic disorder in a small DBPC study (Pollack et al 1996). Also, the efficacy of the norepinephrine reuptake inhibitor *reboxetine* was shown in DBPC studies (Schatzberg 1999; Versiani 2000; Versiani et al 2002). The anticonvulsant *valproate* (valproic acid) was effective in one very small DBPC cross-over study (Lum et al 1990). The intracellular second-messenger precursor *inositol* showed superiority to placebo in a small DBPC study (Benjamin et al 1995).

Open trials with other compounds are listed in Table 7.

4.1.8 *Comparisons of antipanic drugs*

In studies comparing the efficacy of TCAs and SSRIs, no differences in terms of efficacy could be found between the two classes of drugs (Amore et al 1999a; Bakish et al 1996; Bakker et al 1999; Bystritsky et al 1994; Lecrubier and Judge 1997; Wade et al 1997). However, in all of these studies, the SSRIs were better tolerated than the TCAs.

There are no direct comparisons between SSRIs and benzodiazepines in the treatment of panic disorder. In a meta-analysis, the effect sizes for the SSRIs were higher than for the benzodiazepine alprazolam (Boyer 1995).

In a number of studies, alprazolam was compared with the tricyclic antidepressant imipramine (Andersch et al 1991; Charney et al 1986; CNCPS 1992; Lepola et al 1990; Rizley et al 1986; Taylor et al 1990; Uhlenhuth et al 1989). No differences could be found between the two drugs in terms of global improvement.

4.1.9 *Treatment-resistant panic disorder*

Only a few studies with treatment-resistant panic patients exist. In the only existing preliminary DBPC study, it was demonstrated that *pindolol* has an augmenting effect on fluoxetine in patients with treatment-resistant panic disorder (Hirschmann et al 2000). In a small open study an augmentation strategy in which those patients taking a TCA had fluoxetine added and those patients taking fluoxetine had a TCA added was very successful (Tiffon et al 1994). *Sodium valproate* and *clonazepam* were combined in the treatment of four patients with panic disorder who were resistant to several antipanic drug treatments (Ontiveros and Fontaine 1992). In a single case, the addition of *lithium* to clomipramine treatment was successful (Cournoyer 1986).

4.1.10 *Non-pharmacological treatment*

Among non-pharmacological treatments, cognitive behaviour therapy has been investigated. Exposure therapy is used to treat agoraphobia, and cognitive therapy including interoceptive exposure was developed for treating spontaneous panic attacks (Barlow 1997; Marks et al

Table 7
Open trials. OCD = obsessive compulsive disorder, PTSD= posttraumatic stress disorder

Anxiety Disorder	Drugs	Authors	Efficacy
Panic disorder	5-HT_2 antagonist nefazodone	Bystritsky et al 1999; DeMartinis et al 1996; Papp et al 2000	yes
	α_2/5-HT_2/5-HT_3 blocker mirtazapine	Carpenter et al 1999	yes
	5-HT_3 antagonist ondansetron	Schneier et al 1996	yes
	Anticonvulsant valproate (valproic acid)	Keck et al 1993; Primeau et al 1990; Woodman and Noyes 1994	yes
Generalised anxiety disorder	Paroxetine vs. imipramine vs. chlordemethyldiazepam	Rocca et al 1997	all equally effective
Social phobia	SSRI citalopram	Bouwer and Stein 1998	yes
	SSRI fluoxetine	Gorman et al 1987; van Ameringen et al 1993	yes
OCD, treatment-resistant	SSRI citalopram	Marazziti et al 2001	yes
	Addition of clomipramine to an SSRI	Pallanti et al 1999	yes
	Addition of an SSRI to clomipramine	Ravizza et al 1996	yes
	Addition of buspirone to an SSRI	Jenike et al 1991; Markovitz et al 1990	yes
	Addition of atypical antipsychotics olanzapine, quetiapine or risperidone to SSRI or clomipramine	Agid and Lerer 1999; Atmaca et al 2002; Bogetto et al 2000; Francobandiera 2001; Kawahara et al 2000; Koran et al 2000; Marazziti and Pallanti 1999; Mohr et al 2002; Pfanner et al 2000; Ravizza et al 1996; Saxena et al 1996; Stein et al 1997; Weiss et al 1999	yes
	Addition of L-tryptophan to clomipramine or to SSRI+pindolol	Blier and Bergeron 1996; Rasmussen 1984	yes
	Addition of lithium to clomipramine	Rasmussen 1984	yes
OCD in children, treatment-resistant	Adding clonazepam or risperidone to an SSRI	Fitzgerald et al 1999; Leonard et al 1994	yes
PTSD	SSRI paroxetine	Marshall et al 1998	yes
	SSRI fluvoxamine	Davidson et al 1998; Marmar et al 1996	yes
	Anticonvulsant carbamazepine	Lipper et al 1986	moderate
	Anticonvulsant valproate	Fesler 1991	moderate
PTSD, treatment-resistant	SSNRI venlafaxine	Hamner and Frueh 1998	yes

1993). As this review is focused on drug therapy, the reader is referred to the relevant literature for a detailed description of cognitive behaviour therapy (Barlow 1994; Beck et al 1985; Clark 1994). Cognitive behavioural techniques were superior to waiting list control condition in a number of studies in panic disorder and/or agoraphobia (Barlow et al 1989; Gould and Clum 1995; Klosko et al 1990; Lidren et al 1994; Margraf et al 1993; Swinson et al 1995; Telch et al 1993, 1995; Williams and Falbo 1996), with one exception (Gould et al 1993). Superiority to a pill placebo or a psychological placebo was demonstrated in some studies (Barlow et al 2000; Beck et al 1992; Klosko et al 1990; Marks et al 1983, 1993; Mavissakalian and Michelson 1983), while others found no difference to the control condition (Bakker et al 1999; Black et al 1993; Mavissakalian and Michelson 1986a; Michelson et al 1988; Shear et al 1994).
In direct comparisons of cognitive behaviour or exposure therapy with psychopharmacological treatment, drugs were superior in three studies (Bakker et al 1999; Black et al 1993; Mavissakalian and Michelson 1986a). No differences were found in five studies (Clark et al 1994; Klosko et al 1990; Marks et al 1983; Sharp et al 1997; Telch et al 1985), and one study showed inconsistent results (Marks et al 1993).
As the aetiology of the anxiety disorder is multifactorial, the combination of drug treatment and cognitive behaviour therapy seems rational. The combination was superior to psychological therapy alone in the vast majority of studies (Barlow et al 2000; Cottraux et al 1995; de Beurs et al 1995; Marks et al 1993; Mavissakalian and Michelson 1986a; Oehrberg et al 1995; Stein et al 2000b; Telch et al 1985; Zitrin et al 1980, 1983), whereas only two studies showed no difference between combined treatment and psychological therapy (Marks et al 1983; Sharp et al 1997). Despite statements implying the contrary, there is no methodologically sound study showing that drugs lessen the gains with CBT. The combination of CBT or psychodynamic treatment with a drug was superior to drug therapy alone in two studies (Mavissakalian et al 1983; Wiborg and Dahl 1996), whereas three studies

failed to show a difference between the combination and CBT alone (Barlow et al 2000; Marks et al 1983; Sharp et al 1997). Altogether, there is enough evidence to recommend the combination. Other psychological treatments cannot be recommended due to lack of proof of efficacy. Psychodynamic treatment of agoraphobia was less effective than a combination of exposure and psychodynamic therapy, which only demonstrates the efficacy of exposure, but not of psychodynamic therapy (Hoffart and Martinsen 1990). Eye Movement Desensitisation and Reprocessing (EMDR) has been used for panic disorder with disappointing results (Feske and Goldstein 1997; Goldstein et al 2000).
In one study, aerobic exercise (jogging) was more effective than a pill placebo, but less effective than clomipramine (Bandelow et al 2000).

4.1.11 *Long-term treatment*

Three studies have investigated the long-term feasibility of SSRI and TCA treatment. In one long-term study, citalopram and clomipramine maintained their effects for up to one year (Lepola et al 1998). In another study, paroxetine and clomipramine were given for a total of 48 weeks and maintained their effects (Lecrubier and Judge 1997). In a 50-week comparison of fluoxetine and imipramine, high remission rates were found, with no differences between these two drugs (Amore et al 1999a).
In the long-term treatment of panic disorder the same doses are usually prescribed as in the acute treatment phase.
Cognitive behavioural therapy is reputed to maintain its treatment gains over time, which would be a distinct advantage over medications. However, not many studies have compared the effects of CBT with a control group (e.g. relaxation) at follow-up. Only two studies could demonstrate that CBT continues to be effective over a follow-up period, although the results were modest in comparison to the control groups (Barlow et al 2000; Marks et al 1993). Other studies failed to show a difference between CBT and a control group or showed inconsistent results (Clark et al 1994; Cohen et al 1984; Craske et al 1991; Loerch et al 1999; Marks et al 1983; Mavissakalian and Michelson 1986b; Shear et al 1994). It has to be taken into account that many follow-up studies have methodological flaws (Nadiga et al, submitted).

4.1.12 *Summary of recommendations for the treatment of panic disorder*

In summary, SSRIs are the first-line treatment for panic disorder. TCAs are equally effective, but they are less well tolerated than the SSRIs. In treatment-resistant cases, benzodiazepines like alprazolam may be used when the patient does not have a history of dependency and tolerance. Also, they can be combined with antidepressants in the first weeks of treatment before the onset of efficacy of the antidepressants.
Due to possible serious side effects and interactions with other drugs and food components, the irreversible MAOI phenelzine should only be prescribed when other first-line drugs have failed or not been tolerated. As the efficacy results with the RIMA moclobemide are inconsistent, it may only be a third-line treatment option.
In treatment-resistant cases, augmentation of SSRI treatment with pindolol or TCAs, augmentation of TCA treatment with SSRIs, or a combination of valproate and clonazepam may be tried, according to preliminary studies.
When first-line treatment strategies have failed, drugs that have been investigated in preliminary, mostly open studies may be tried. These drugs include nefazodone, ondansetron and valproate. The respective studies were not conducted with treatment-resistant patients.
According to existing studies, a combination of pharmacological treatment with psychological therapy (cognitive behaviour therapy) can be recommended.

4.2 Generalised anxiety disorder (GAD)

4.2.1 *Selective serotonin noradrenaline reuptake inhibitor (SSNRI) venlafaxine*

The SSNRI *venlafaxine* was superior to placebo (Allgulander et al 2001; Gelenberg et al 2000; Rickels et al 2000b), equally effective as pregabalin (Kasper et al 2002a) and more effective than another comparator drug, buspirone (Davidson et al 1999), in patients with generalised anxiety disorder. However, in the latter study, scores were only significantly lower for HAM-A psychic anxiety, anxious mood and tension, but not for HAM-A total and CGI for venlafaxine-treated patients than for placebo-treated patients.
Generally, the extended release preparation of venlafaxine is preferred in order to reduce side effects.

4.2.2 *Selective serotonin reuptake inhibitors (SSRI)*

The SSRI *paroxetine* was effective in one DBPC study (Pollack et al 2001). A small study in children aged 5-17 years demonstrated superiority of *sertraline* over placebo (Rynn et al 2001).

4.2.3 *Tricyclic antidepressants (TCA)*

The TCA *imipramine* was superior to placebo and as effective as reference drugs (Hoehn-Saric et al 1988; Rickels et al 1993).

4.2.4 *Buspirone*

The azapirone *buspirone* was superior to placebo in some studies (Davidson et al 1999; Enkelmann 1991; Pollack et al 1997) and equally effective as the benzodiazepines (Feighner et al 1982; Jacobson et al 1985; Rickels et al 1982; Ross and Matas 1987; Strand et al 1990). However, it was less effective than venlafaxine (Davidson et al 1999) or hydroxyzine (Lader and Scotto 1998).

4.2.5 *Benzodiazepines*

Alprazolam showed positive results in placebo-

and comparator-controlled studies (Elie and Lamontagne 1984; Enkelmann 1991; Hoehn-Saric et al 1988; Lydiard et al 1997; Möller et al 2001).
Also, *diazepam* was effective in studies containing a placebo condition (Ansseau et al 1991; Boyer and Feighner 1993; Fontaine et al 1983; Rickels et al 1993, 1997, 2000a) as well as studies using a comparator with established efficacy (Elie and Lamontagne 1984; Feighner et al 1982; Jacobson et al 1985; Ross and Matas 1987).

4.2.6 *Antihistamine*
Efficacy of the antihistamine *hydroxyzine* was established in a DBPC study (Ferreri et al 1994). In a comparator study, only hydroxyzine, but not buspirone, was superior to placebo (Lader and Scotto 1998). However, long-term and dose-finding studies are lacking with this drug, so that it can only be recommended as second or third line treatment.

4.2.7 *Other drugs*
Pregabalin was superior to placebo and equally effective as venlafaxine in a double-blind study (Kasper et al 2002a).
Opipramol showed efficacy in a placebo- and comparator-controlled study (Möller et al 2001). However, this drug is not available in most countries.

4.2.8 *Long-term treatment*
Controlled long-term studies for the treatment of GAD are scarce (Mahe and Balogh 2000). Efficacy of venlafaxine was established in two six-month studies (Allgulander et al 2001; Gelenberg et al 2000).

4.2.9 *Treatment-resistant GAD*
There have been no systematic investigations of treatment-refractory patients with generalised anxiety disorder.

4.2.10 *Non-pharmacological treatment*
As a psychological treatment strategy, cognitive behaviour therapy has been used in generalised anxiety disorder (Harvey and Rapee 1995). For an overview, the reader is referred to the relevant literature (Borkovec and Whisman 1996; Wells 1997). When GAD is co-morbid with depression, which is very common, pharmacotherapy is increasingly indicated (Ballenger et al 2001).
Data on the advantage of combining drugs and psychological therapy are almost completely lacking. One study found no gains in combining buspirone and CBT (Lader and Scotto 1998), however, the statistical power of this study may have been too low. In another study, the combination of CBT and diazepam was more effective than diazepam alone (Power et al 1990).

4.2.11 *Summary of recommendations for the treatment of GAD*
The drugs recommended as the first-line treatment for GAD are the SSNRI venlafaxine and the SSRI paroxetine. The efficacy of the azapirone buspirone was shown in a number of studies, with only two studies making the picture inconsistent. The TCA imipramine is effective in GAD, however, due to the more unfavourable side effect profile as compared with venlafaxine and the SSRIs (see above), this drug stays second in line. In treatment-resistant cases, benzodiazepines like alprazolam may be used when the patient does not have a history of dependency and tolerance. Also, they can be combined with antidepressants in the first weeks of treatment before the onset of efficacy of the antidepressants. The antihistamine hydroxyzine was more effective than buspirone in one study. However, experiences with this drug in the treatment of GAD are limited, and the sedating effects of this drug may be seen as a disadvantage.
In general, long-term studies in GAD are lacking, with the exception of venlafaxine.
If first-line drugs like venlafaxine, paroxetine or imipramine fail, a trial with second-choice drugs such as buspirone, diazepam or hydroxyzine is warranted.
Due to the lack of studies, it remains unclear whether a combination of CBT and drug therapy is advantageous.

4.3 Social phobia (social anxiety disorder)

4.3.1 *Selective serotonin reuptake inhibitors (SSRI)*
For the treatment of social phobia, SSRIs such as *fluvoxamine* (Stein et al 1999; van Vliet et al 1994), *paroxetine* (Allgulander 1999; Baldwin et al 1999; Stein et al 1998) and *sertraline* (Blomhoff et al 2001; Katzelnick et al 1995; van Ameringen et al 2001) have been shown to be effective in DBPC studies. Comparator trials are lacking as no drug is established as a mainstay in the treatment of social phobia.
Escitalopram, the S-enantiomer of citalopram, was effective in a DBPC study in social anxiety disorder, but this study has not yet been published (Kasper et al 2002b).
Although a number of small, open-label trials of fluoxetine have suggested potential efficacy in social anxiety disorder (Table 7), *fluoxetine* failed to separate from placebo in a trial with 60 patients (Kobak et al 2002).

4.3.2 *Reversible inhibitor of monoamine oxidase A (RIMA) moclobemide*
Results with *moclobemide* are inconsistent. The compound was superior to placebo in one study (IMCTGMSP 1997), and also more effective than placebo and equally effective as phenelzine on most measures (Versiani et al 1992). In a third study, the size of its clinical effect was small (Schneier et al 1998), and in another study (Noyes et al 1997) no superiority against placebo could be demonstrated.
In a meta-analysis, response rates and effect sizes

for RIMAs were smaller than those seen for SSRIs (van der Linden et al 2000).

4.3.3 *Irreversible monoamine oxidase inhibitors (MAOI)*

The irreversible MAOI *phenelzine* was superior to placebo, atenolol and moclobemide (Heimberg et al 1998; Liebowitz et al 1988; Versiani et al 1992). Phenelzine was less well tolerated than moclobemide (Versiani et al 1992).
In an open study, *tranylcypromine* was associated with improvement of social anxiety disorder; however, side effects were frequent (Versiani et al 1988).

4.3.4 *Benzodiazepines*

The benzodiazepine *clonazepam* was superior to placebo or a waiting list condition in two studies (Davidson et al 1993; Munjack et al 1990).

4.3.5 *Beta blockers*

Despite their wide-spread use in social anxiety, the only existing studies do not show superiority of the beta blocker *atenolol* over placebo (Liebowitz et al 1988; Turner et al 1994). Findings with the treatment of performance anxiety in musicians (James and Savage 1984; James et al 1983) should not be generalised to social anxiety disorder.

4.3.6 *Other compounds*

The anticonvulsant *gabapentin* and an analogous substance, *pregabalin*, were effective in a DBPC studies in social anxiety disorder (Feltner et al 2000; Pande et al 1999).
The results of another DBPC study do not support the efficacy of the azapirone anxiolytic *buspirone* in social anxiety disorder (van Vliet et al 1997).
For open trials with other compounds, see Table 7.

4.3.7 *Long-term treatment*

Few controlled long-term studies exist for the treatment of social anxiety disorder. In one 24-week DBPC study (Blomhoff et al 2001) and a 24-week relapse prevention study (Walker et al 2000) following a 20-week DBPC study (van Ameringen et al 2001) the efficacy of *sertraline* could be demonstrated.
In the extension of a 12-week single-blind treatment with paroxetine, responders were randomised to a further 24 weeks of paroxetine or placebo. Relapse rates were significantly lower in the paroxetine group (Hair et al 2000).
In a 24-week study, both *phenelzine* and *moclobemide* were superior to placebo (Versiani et al 1992).

4.3.8 *Treatment-resistant social phobia*

Buspirone augmentation may be a useful clinical strategy in social phobia patients who show a partial response to an SSRI (van Ameringen et al 1996).
Open treatment with venlafaxine was effective in 12 patients who were non-responders to SSRIs (Altamura et al 1999).

4.3.9 *Non-pharmacological treatment*

Among psychological therapies, exposure therapy and cognitive therapy have been shown to be effective (Heimberg 1995; Heimberg et al 1998). The reader is referred to detailed reviews of CBT in social phobia (Clark and Wells 1995).
In one study comparing the efficacy of phenelzine and CBT, phenelzine was superior to CBT in the acute and maintenance treatment phase, but phenelzine patients showed a trend toward greater relapse during treatment-free follow-up (Heimberg et al 1998; Liebowitz et al 1999). In another placebo-controlled study, sertraline, exposure therapy, and their combination were compared. Sertraline-treated patients improved significantly more than non-sertraline-treated patients. No significant difference was observed between exposure- and non-exposure-treated patients. Although the combination showed higher effect sizes than both treatment modalities alone, the difference was not statistically significant (Blomhoff et al 2001).

4.3.10 *Summary of recommendations for social phobia*

SSRIs have been shown to be superior to placebo in a number of studies. Comparator trials are lacking, as no drug was appropriate as a reference drug at this stage. Thus, the SSRIs may be regarded as first-line drugs in social phobia. The MAOI phenelzine shows robust results in terms of efficacy. However, this drug is less well tolerated than alternative treatments. The results with moclobemide are inconsistent to some extent, and the effect sizes observed in clinical studies were only moderate.
The database for benzodiazepines is small. Benzodiazepines are not recommended as first-line agents in treating social phobia because they are associated with abuse and long-term dependence. However, they may play a role as an adjunctive agent or for patients who are refractory to other treatments. They may be used as an adjunct to antidepressant therapy during the first period of two to three weeks before the onset of efficacy of these drugs.
Social phobia patients refractory to treatment with SSRIs may benefit from second-line drugs, such as phenelzine, moclobemide or clonazepam. Moreover, compounds that are in an early stage of evaluation may be tried, such as venlafaxine, nefazodone, gabapentin or tranylcypromine, although this stratagem is not yet supported by controlled large-scale studies.
From the available studies on the combination of drugs and CBT, the preliminary conclusion may be drawn that a combination of both treatment modalities may be advantageous.

4.4 Specific phobia

Patients with specific phobia rarely consult psychiatrists or other medical professionals, as they can cope with the disorder by avoiding the specific feared situations or objects without significant restrictions in the quality of life.

Exposure therapies are effective to treat specific phobia (Marks 1987). Psychopharmacological drugs are not recognized as a standard treatment for specific phobia, despite its apparent similarities to other kinds of phobia. In a small, preliminary DBPC study, paroxetine was superior to placebo (Benjamin et al 2000).

4.5 Obsessive compulsive disorder (OCD)

This short overview is mainly focused on the treatment of 'pure' OCD and does not cover OCD-spectrum disorders such as tic disorders, Gilles-de-la-Tourette syndrome, trichotillomania and others.

The treatment of obsessive compulsive disorder is usually associated with lower response rates than the treatment of other anxiety disorders. Sometimes only partial remission is achieved.

4.5.1 *Selective serotonin reuptake inhibitors (SSRI)*

A number of studies have been performed to assess the efficacy of SSRIs in the treatment of OCD. *Fluvoxamine* was investigated in DBPC studies (Goodman et al 1989b, 1996; Hohagen et al 1998) and in clomipramine-controlled trials (Milanfranchi et al 1997; Mundo et al 2000). *Paroxetine* was significantly more effective than placebo, and of comparable efficacy as clomipramine (Zohar and Judge 1996). *Sertraline* was effective in DBPC (Chouinard et al 1990; Kronig et al 1999) and clomipramine-controlled (Bisserbe et al 1997) studies.

Fluoxetine was superior to placebo in double-blind studies (Montgomery et al 1993; Tollefson et al 1994; Zitterl et al 1999). In a comparison with clomipramine, efficacy for both drugs was comparable, with a minor advantage for clomipramine (Lopez-Ibor et al 1996).

For *citalopram* (Montgomery et al 2001) only a DBPC study but no comparator trials exist.

Dosage recommendations are overviewed in Table 6. As a rule, higher doses of the antidepressants are used in OCD as compared to other anxiety disorders or major depression (Greist et al 1995a; Montgomery et al 1993, 2001).

4.5.2 *Tricyclic antidepressants (TCA)*

Efficacy has been shown for the TCA *clomipramine* in DBPC studies (Clomipramine Collaborative Study Group 1991; DeVeaugh Geiss et al 1989; Thoren et al 1980) as well as in comparator trials (Milanfranchi et al 1997) (see also Piccinelli et al 1995 for a review).

4.5.3 *Other compounds*

The second messenger precursor *inositol* was superior to placebo in a cross-over trial with 13 patients, but these results have to be regarded as preliminary due to the low sample size in the study (Fux et al 1996).

The MAOI phenelzine was equally effective as clomipramine in one small study (Vallejo et al 1992), but less effective than fluoxetine and no better than placebo in another (Jenike et al 1997).

4.5.4 *Long-term treatment*

In a number of one-year DBPC studies, the SSRIs fluoxetine (Romano et al 2001) and sertraline (Rasmussen et al 1997) and the TCA clomipramine (Katz et al 1990) demonstrated the same efficacy as in short-term trials.

4.5.5 *Treatment-resistant obsessive-compulsive disorder*

Patients with OCD are often refractory to treatment, and many treatments have been tried in these sometimes desperate cases.

In double-blind studies, *intravenous clomipramine* was more effective than oral clomipramine (Fallon et al 1998; Koran et al 1997).

Augmentation of antidepressant treatment may be tried for patients with a partial response or intolerance to higher doses of antidepressant. Some studies have investigated augmentation of antidepressant treatment with neuroleptics. In DBPC studies, adding *haloperidol* to an SSRI (McDougle et al 1994) appeared to provide an improved response particularly in patients with co-morbid chronic tic disorders. Independently of the presence of tics, *risperidone* augmentation of an SSRI was successful (McDougle et al 2000). However, these studies have been short-term, and long-term side-effects have not been studied. A DBPC study did not demonstrate any additional effect for buspirone augmentation to clomipramine (Pigott et al 1992). The addition of *pindolol* to paroxetine treatment was successful in a DBPC study (Dannon et al 2000), but the addition of pindolol to fluvoxamine had no effect (Mundo et al 1998). In a double-blind cross-over study, patients who were resistant to clomipramine treatment improved with the benzodiazepine *clonazepam* (Hewlett et al 1992).

In a DBPC study a statistically significant reduction in symptoms was noted after *lithium* augmentation of ongoing fluvoxamine treatment, although most patients did not have a clinically meaningful response, according to the authors (McDougle et al 1991).

A number of other augmentation strategies were studied in open-label trials (Table 7).

4.5.6 *Non-pharmacological treatment*

Cognitive behaviour therapy, including exposure and response prevention techniques for compulsions and imaginal exposure for treatment of intrusive obsessive thoughts, is the first choice in the psychological treatment of OCD (Marks 1994, 1997).

A combination of an SSRI, fluvoxamine, with CBT was associated with a higher response rate than CBT alone (Hohagen et al 1998).

Electroconvulsive therapy has been tried in patients with OCD (Facorro and Gomez Hernandez 1997), but its use remains limited to cases co-morbid with severe depression and suicidal ideation. In severe OCD cases, where all

available therapeutic approaches have been tried without success, neurosurgery may be a treatment option (Greist and Jefferson 1998; Mindus et al 1994).

4.5.7 *OCD in children and adolescents*

As in the treatment of adults, the efficacy of the SSRIs fluvoxamine (Riddle et al 1996, 2001), fluoxetine (Geller et al 2001; Riddle et al 1992), and sertraline (March et al 1998) could be confirmed in studies with children and adolescents suffering from OCD. Likewise, clomipramine efficacy could be demonstrated in DBPC studies (DeVeaugh-Geiss et al 1992; Flament et al 1985).

One DBPC study examined the long-term treatment (up to 52 weeks) with fluoxetine (Romano et al 2001). Patients who received fluoxetine had numerically lower relapse rates compared with those who received placebo, although the difference was not significant. However, in patients receiving the highest dose, 60 mg per day, fluoxetine performed better than placebo.

Augmentation strategies have been tried in treatment resistant cases (Table 7).

Non-pharmacological treatment of OCD in children is based on psychosocial interventions such as family education and cognitive behavioural therapy. Behavioural treatment strategies involving exposure and relapse prevention are considered most effective (Rapoport and Inoff-Germain 2000).

4.5.8 *Summary of recommendations for the treatment of OCD*

Serotonin reuptake inhibition seems to be a necessary condition for a drug to be effective in OCD. In direct comparisons compounds with predominant norepinephrine reuptake inhibition, such as desipramine (Hoehn-Saric et al 2000; Leonard et al 1989) or nortriptyline (Thoren et al 1980) were less effective than drugs with a serotonin reuptake component.

The SSRIs are the first-line drugs in the treatment of adult and childhood OCD. Also, clomipramine showed robust study results. As the available research evidence is not conclusive, opinions differ as to whether clomipramine has greater anti-obsessional efficacy than do the SSRIs (Abramowitz 1997; Bisserbe et al 1997; Greist et al 1995b; Piccinelli et al 1995; Pigott and Seay 1999; Todorov et al 2000). Some direct comparisons suggest that SSRIs are better tolerated than clomipramine while having the same efficacy (Bisserbe et al 1997; Milanfranchi et al 1997; Mundo et al 2000; Zohar and Judge 1996).

The onset of efficacy of the antidepressants may be delayed for more than four or six weeks. As a rule, maintenance treatment duration should be longer than in other anxiety disorders, i.e. 12 to 24 months or more. Dosages are used that exceed the dosage usually applied in the treatment of depression or other anxiety disorders.

4.6 Posttraumatic stress disorder (PTSD)

4.6.1 *Selective serotonin reuptake inhibitors (SSRI)*

SSRIs have been regarded as first-line drugs in PTSD. Efficacy has been shown in DBPC studies for *sertraline* (Brady et al 2000; Davidson et al 2001b; Zohar et al 2002), *paroxetine* (Tucker et al, 2001) and *fluoxetine* (Connor et al 1999; van der Kolk et al 1994). In one placebo-controlled study with 12 patients, no effect of fluoxetine could be shown, but the study did not have enough power to be conclusive (Hertzberg et al 2000). For open-label studies, see Table 7.

4.6.2 *Tricyclic antidepressants (TCA)*

One double-blind study found *amitriptyline* to be superior to placebo (Davidson et al 1990). In a comparison with phenelzine, the TCA *imipramine* was superior to placebo. It was equally effective as phenelzine on the CGI, but less effective on another scale (Kosten et al 1991). Another small study showed equal efficacy for phenelzine and imipramine (Frank et al 1988). In a small cross-over study, response to the tricyclic desipramine was only with respect to depression, but not for anxiety and PTSD symptoms (Reist et al 1989).

In comparison to the SSRIs, TCAs are associated with a higher incidence of side effects, risk of overdose, and poor compliance rates.

4.6.3 *Monoamine oxidase inhibitors (MAOI)*

Phenelzine has been studied in the above-mentioned comparisons with imipramine (Frank et al 1988; Kosten et al 1991). It was shown to be effective. One study that failed to show a difference between phenelzine and placebo was underpowered, and the treatment duration (4 weeks) was too short (Shestatzky et al 1988).

4.6.4 *Benzodiazepines*

In the only placebo-controlled trial of benzodiazepines in PTSD, improvement in anxiety symptoms was significantly greater with *alprazolam* than with placebo but modest in extent. Symptoms specific to PTSD were not significantly altered. However, the sample size of this study (ten patients, cross-over) was too small to draw definite conclusions (Braun et al 1990).

4.6.5 *Anticonvulsants and other compounds*

The anticonvulsant *lamotrigine* has been studied in a small study and showed a higher response rate in comparison to placebo (Hertzberg et al 1999). However, side effects of this drug include potentially serious skin rash. For open trials, see Table 7.

4.6.6 *Long-term treatment*

In a relapse-prevention study, patients who had responded to 24 weeks of open-label treatment with *sertraline*, were randomised to either

sertraline or placebo for an additional 28 weeks. Relapse rates were significantly lower in the sertraline group (Davidson et al 2001a). In an open-label study, patients who had completed 12-week DBPC studies of sertraline vs. placebo received sertraline for an additional 24 weeks. Responders to the DBPC study sustained their initial response, and patients who failed in the initial study could be turned into responders (Londborg et al 2001).

4.6.7 *Treatment-resistant posttraumatic stress disorder*

Controlled trials with treatment-resistant PTSD patients are lacking. According to one case report, venlafaxine may be useful (Table 7).

4.6.8 *Non-pharmacological treatment*

As this review is focused on drug therapy, the reader is referred to the relevant literature for a detailed description of cognitive-behaviour therapy (e.g. Foa 2000). *Cognitive therapy* was shown to be effective in the treatment of PTSD. *Exposure therapy* showed positive results in some, but a deterioration in some other studies (Shalev et al 1996). Imaginal exposure has been applied to treat recollections of traumatic events.
In one study, *psychodynamic therapy* was superior to a waiting-list condition and equally effective as desensitisation (Brom et al 1989).
The efficacy of 'Eye Movement Desensitisation and Reprocessing therapy (EMDR)', a psychological treatment option, which is sometimes applied to treat posttraumatic stress reactions, has not been proven by directly comparing it with an independently validated treatment for posttraumatic stress disorder (e.g. cognitive therapy) (Cahill et al 1999).
Direct comparisons of CBT and pharmacological treatments are lacking (Stein et al 2000a).

4.6.9 *Summary of recommendations for the treatment of posttraumatic stress disorder*

For the pharmacological treatment of PTSD, SSRIs are the first-line therapy. Other treatment options include TCAs and the MAOI phenelzine, but these drugs are inferior to the SSRIs in terms of safety and tolerability. Cognitive-behaviour was effective in controlled studies, and the results with exposure therapy were inconsistent. The magnitude of effect of treatments for PTSD is often limited, and remission is rarely achieved.

5 Treatment under special conditions

5.1 Pregnancy

According to the majority of reviews, the use of SSRIs and TCAs in pregnancy imposes no increased risk for the infant that is detectable during the newborn period, although minor anomalies, prematurity and neonatal complications have been reported with the use of these drugs. However, intrauterine death or major foetal malformations and exposure to SSRIs or TCAs during pregnancy and lactation do not appear to be associated (Altshuler et al 2001; Austin and Mitchell 1998; Emslie and Judge 2000; Ericson et al 1999; Misri et al 2000a, 2000b). According to case reports, direct drug effects and withdrawal syndromes occurred in some neonates whose mothers were treated with antidepressants near term (Nordeng et al 2001; Wisner et al 1999). Preschool age children exposed to fluoxetine *in utero* show no significant neurobehavioural changes (Goldstein and Sundell 1999).
Anticonvulsants were associated with an increased rate of congenital anomalies as well as neonatal problems (Austin and Mitchell 1998). An association between the use of benzodiazepines and congenital malformations has been reported (Laegreid et al 1990). However, there has been no consistent proof that benzodiazepines may be hazardous. The available literature suggests that it is safe to take diazepam or chlordiazepoxide during pregnancy. It has been suggested that it would be prudent to avoid alprazolam during pregnancy (Iqbal et al 2002). To avoid the potential risk of congenital defects, physicians should use the benzodiazepines that have long safety records.

5.2 Breast feeding

SSRIs and TCA are excreted into breast milk, and low levels have been found in infant serum (Misri et al 2000b; Simpson and Noble 2000; Spigset and Hagg 1998). In mothers receiving TCAs (with the exception of doxepine), it seems unwarranted to recommend that breast feeding should be discontinued. Fluoxetine should probably be avoided during lactation (Spigset and Hagg 1998). Treatment with other SSRIs (citalopram, fluvoxamine, paroxetine or sertraline) seems to be compatible with breast feeding, although this view should be considered as preliminary due to the lack of data (Spigset and Hagg 1998).

Regarding anxiolytic benzodiazepines, adverse drug reactions in infants have been described during maternal treatment with diazepam. During maternal treatment with all anxiolytic benzodiazepines, infants should be observed for signs of sedation, lethargy, poor suckling and weight loss, and if high doses have to be used and long-term administration is required, breast feeding should probably be discontinued (Iqbal et al 2002; Spigset and Hagg 1998).

5.3 Treating children and adolescents

Experience with the pharmacological treatment of anxiety disorders in children and adolescents derives mainly from the clinical studies conducted in patients with OCD (see Chapter 'OCD in Children and Adolescents'). These data suggest that SSRIs should be first line treatment in children and adolescents (see also Emslie & Judge 2000).

5.4 Treatment of the elderly

Factors that have to be regarded in the treatment of the elderly include an increased sensitivity for anticholinergic properties of drugs, an increased sensitivity for extrapyramidal symptoms, an increased risk for orthostatic hypotension and ECG changes, and possible paradoxical reactions to benzodiazepines. Thus, treatment with TCAs or benzodiazepines is less favourable, while SSRIs, SSNRIs, buspirone and moclobemide appear to be safe.

However, very few studies exist that investigate the treatment of anxiety in the elderly.

6 Future research

For a number of putative anxiolytic compounds currently under development only preclinical or preliminary data exist. These include 5-HT_{1A}-agonists, 5-HT_{2C}-agonists, 5-HT_2-antagonists, 5-HT_3-antagonists, beta-carbolines, sigma ligands, tachykinin receptor antagonists, glutamate receptor agonists, neuropeptide Y agonists, CRH receptor antagonists, natriuretic peptide and nitroflavanoids.

7 Conclusions

The recommendations in this guideline are almost exclusively based on randomised, controlled, double-blind trials. However, controlled studies do not always reflect clinical reality and have their shortcomings, e.g. the exclusion of co-morbid, suicidal or medically ill patients. The vast majority of controlled pharmacological trials are short-term, whereas most of the medications will be used on a long-term basis. Moreover, it must be seen critically that some treatment modalities that may be effective in treating anxiety disorders have not yet been investigated in well-controlled trials only because no financial support is available. Absence of evidence is not the same as evidence of absence of an effect. Nevertheless, without controlled trials as gold standard, any treatment recommendation would be arbitrary.

In summary, due to increased efforts in the systematic clinical evaluation of psychopharmacological agents in the treatment of anxiety in the recent years, a comprehensive database has been collected so that precise recommendations can be provided for treating the anxiety disorders. In most cases, drug treatment, preferably in combination with non-pharmacological treatments such as cognitive behaviour therapy, may substantially improve quality of life in patients with these disorders.

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This practice guideline has mainly been developed by psychiatrists and psychotherapists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavours. It is possible that through such activities some contributors have received income related to drugs discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest.

Some drugs recommended in the present guideline may not be available in all countries.

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