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ORIGINAL INVESTIGATION

World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders – Version 3. Part I: Anxiety disorders

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ABSTRACT

Aim: This is the third version of the guideline of the World Federation of Societies of Biological Psychiatry (WFSBP) Task Force for the Pharmacological Treatment of Anxiety, Obsessive–Compulsive and Posttraumatic Stress Disorders (published in 2002, revised in 2008).

Method: A consensus panel of 33 international experts representing 22 countries developed recommendations based on efficacy and acceptability of available treatments. In total, 1007 RCTs for the treatment of these disorders in adults, adolescents, and children with medications, psychotherapy and other non-pharmacological interventions were evaluated, applying the same rigorous methods that are standard for the assessment of medications.

Result: This paper, Part I, contains recommendations for the treatment of panic disorder/agoraphobia (PDA), generalised anxiety disorder (GAD), social anxiety disorder (SAD), specific phobias, mixed anxiety disorders in children and adolescents, separation anxiety and selective mutism. Selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are first-line medications. Cognitive behavioural therapy (CBT) is the first-line

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psychotherapy for anxiety disorders. The expert panel also made recommendations for patients not responding to standard treatments and recommendations against interventions with insufficient evidence.
Conclusion: It is the goal of this initiative to provide treatment guidance for these disorders that has validity throughout the world.

Introduction

Anxiety disorders are the most prevalent mental disorders (Kessler et al. 2007; Bandelow and Michaelis 2015), and considerable burden is associated with these conditions, not only for the individual sufferer, but also for the health care system. However, many patients who might benefit from treatment are not diagnosed or treated (Alonso et al. 2018). Also, the stigma still associated with mental disorders and lack of confidence in psychiatric or psychotherapeutic treatments are likely to contribute to non-recognition and inadequate management. We hope this guideline may contribute to an improvement in the management of patients with anxiety disorders.

This guideline represents the third version of the guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) Task Force for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Posttraumatic Stress Disorders, a consensus panel of international experts on anxiety disorders, obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) (Bandelow et al. 2002). Since the second version in 2008 (Bandelow et al. 2008), many clinical studies have been published and several new treatments have emerged. Therefore, the Task Force deemed it necessary to update the guidelines. In contrast to earlier versions, psychotherapeutic and other non-pharmacological treatments are fully covered in the updated version. Further revisions are planned in the future.

This guidance addresses healthcare professionals in primary, secondary and community care services.

Although in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 and International Classification of Diseases (ICD)-11, OCD and PTSD are no longer classified as anxiety disorders, due to many similarities and psychopathological overlap, it is still appropriate to prepare 'joint' guidelines for anxiety disorders, OCD and PTSD. The latter disorders will be covered in Part II (Bandelow et al. 2022b).

Methods

The recommendations in this guideline were developed by experts from several countries in the world. To be included in the WFSBP Task Force for Anxiety Disorders, OCD, and PTSD, the expert should fulfil the following criteria: (1) has routinely treated patients with these disorders, (2) has good knowledge of psychotherapy and/or psychopharmacology of these disorders, (3) has published clinical studies, meta-analysis or guidelines, (4) has good knowledge of methodology of clinical studies, including statistics, and the principles of evidence-based medicine.

Adhering to the principles of evidence-based medicine, the present guideline is based on evidence from randomised controlled trials (RCTs).

Inclusion criteria were:

- Original articles published in peer-reviewed journals
- Treatment studies in adults, children, and adolescents for the treatment of ICD- or DSM-defined anxiety disorders (panic disorder, generalised anxiety disorder, social anxiety disorder (SAD), specific phobias, separation anxiety disorder, and selective mutism), OCD and PTSD
- Studies fulfilling defined quality criteria (Table 1)
- In the case of drug studies: drugs that are available on the market and are licenced in at least one country

Exclusion criteria were:

- Studies examining mixed populations (e.g. 'anxiety disorders comorbid with substance abuse')
- Studies restricted to certain subgroups (e.g. students only, mild disorders only)
- RCTs with less than 10 evaluable patients in any treatment arm.

Data were extracted from published articles on the MEDLINE Database and the Web of Science (ISI) until 1 March 2022. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement is provided in Figure 1 (Supplementary Appendix). Additional trials were searched for and found manually. A total of 1007 RCTs were included.

Recommendations from recent guideline activities were also considered (Table 1; Supplementary Appendix).

Table 1. Check list for quality of randomised controlled trials (RCTs).

- Use of standard diagnostic criteria (DSM or ICD)
- Use of an adequate randomisation method
- Use of an adequate control group (identical placebo, dummy, sham intervention etc., or use of active control groups (e.g. 'psychological placebo') and
- Assessment of the primary efficacy measure by a 'blind' rater in the case of psychotherapy studies
- In the case of an active comparator: use of a comparator with established efficacy
- Description of withdrawals and dropouts; declaration of evaluation method ('intent to treat'/'according to protocol')
- The only difference between the experimental and the control group is the treatment under investigation. The groups should be identical in all other ways
- Use of parallel groups (instead of cross-over studies, waitlist controls or 'historical' comparisons)
- Adequate sample size, based on *a priori* calculation
- Use of validated and sensitive rating scales addressing the core symptoms of the disorder
- Declaration of the primary efficacy measure or use of a method to correct for multiple testing (e.g. Bonferroni correction)
- Use of appropriate statistical tests (e.g. control for baseline differences etc.); method of management of drop-outs described (e.g. last observation carried forward/LOCF, mixed model repeated measures analysis/MMRM)
- Fulfilment of good clinical practice (GCP) criteria
- Approval by an ethics committee
- A priori registration in a clinical trial registry (does not apply for studies performed before trial registries became available)

The list is based on the Scottish Intercollegiate Guidelines Network (SIGN) statement (Agrawal and Mula 2019) but includes additional items.

Evidence grading in medication studies

To be recommended, a medication must have shown its efficacy in double-blind placebo-controlled (DBPC) studies. In addition to placebo controls, a new drug should be compared to a reference drug – an established standard treatment which has shown efficacy in placebo-controlled trials by itself (comparator trial). However, 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, such comparator trials ('non-inferiority trials') should have very large sample sizes. Ideally, a new treatment should be tested in a 3-arm study against the reference treatment and placebo to ensure assay sensitivity. For the placebo arm, smaller samples are acceptable than for active treatments.

In a substantial number of evaluated studies that compared two or more active treatments, the sample sizes were too small for a non-inferiority comparison. Studies that found no differences between active treatments and had too small sample sizes have been characterised as 'underpowered' in the tables containing the RCTs.

Evidence grading in psychotherapy studies

Inactive control conditions

Inactive controls include 'waitlist' and 'no treatment'. In this guideline, 'no treatment' controls have only been used in a few studies. In this control group, patients who do not receive any treatment at all are followed up for the same period as the patients in the experimental group and are not offered any treatment after this period, while 'waitlist' patients are offered the active treatment after a waiting period. Historically, waitlist controls were introduced into psychotherapy research because it was assumed that even without treatment some improvement occurs in many mental disorders due to spontaneous remission and the tendency of regression to the mean. However, in reality, in waitlist studies, most patients do not show any substantial improvement. For anxiety disorders, the average pre-to-post gain in waitlist arms was Cohen's $d = 0.2$ (defined as a 'small effect' by Cohen (1962)), according to a meta-analysis (Bandelow et al. 2015). In contrast, pill placebo treatment is associated with a large pre-to-post change of around $d = 1.3$. Improvements seen in waitlist arms were even significantly smaller than in 'no treatment' conditions, as was shown in depression trials (Furukawa et al. 2014). Thus, comparisons with waitlist will mostly show a significant difference between the groups. Of the 200 comparisons with waitlists evaluated in this guideline, only 12.5% showed a negative result.

Blinding is an issue in psychotherapy studies. It was found that nonblinded assessors exaggerate the effect size by 68% (Hrobjartsson et al. 2013). In a waitlist study, the patients are not blinded, and even if a 'blind rater' – an investigator who is not informed about the treatment arm a patient is assigned to – is employed to assess the outcomes, these may be influenced by patients' expectations (Bandelow 2021).

Following the principles of the WFSBP grading system (Hasan et al. 2019), full evidence (LoE A) for a psychotherapeutic modality was only accepted when it was shown to be more effective than active control conditions.

Active control groups

If a form of psychotherapy was shown to be superior to waitlist, we still do not know whether this method would produce changes beyond any that might occur because of the non-specific factors of psychotherapy, i.e. rapport, expectation of gain, and sympathetic attention (Seligman 1995). A drug that does not separate from placebo would never come to the market. If medications were approved on the basis of waitlist studies, hundreds of substances with dubious usefulness would flood the market. Likewise, full evidence for efficacy of any form of psychotherapy can only be accepted when it shows superiority to a psychological

placebo or a comparable active control. Active control groups include 'psychological placebo', 'pill placebo', 'supportive therapy', 'relaxation', 'psychoeducation' or 'treatment as usual' (TAU). Not all these active control conditions have a high power of discrimination.

Psychological placebo. This active control consists of talking sessions in which no specific psychotherapeutic techniques are applied, and which are not necessarily conducted by a trained psychotherapist. Table 2 contains a proposal for ideal standards for psychological placebo control. A meta-analysis of RCTs in anxiety disorders (Bandelow et al. 2015) demonstrated that the average pre-to-post effect sizes of such psychological placebos are significantly smaller (Cohen' $d = 0.83$) than those of pill placebos ($d = 1.29$).

Pill placebo. In some studies, in which medications and psychotherapy were compared, a pill placebo arm was included. When a psychotherapeutic method is superior to a pill placebo, this is a strong indicator for efficacy.

'*Supportive therapy*' is often used as an active control group in psychotherapy studies. In some studies, this control group was described as a form of psychological placebo. However, in other studies, supportive therapy included some ingredients of psychotherapy which makes the results difficult to interpret.

'*Relaxation*' is also used as a control and some psychotherapy studies. As pure relaxation programs do not contain elements of talking about psychosocial issues, it is doubtful whether this control condition can replace a psychological placebo.

'*Psychoeducation*'. As psychoeducation is integral to many psychotherapy treatments, it is not appropriate for it to be included as a control because all effective ingredients should be omitted in the control group.

'*TAU*'. This is a very heterogenous control condition, as TAU can mean anything between infrequent and short visits to a mental health service and standard quality psychological and/or pharmacological treatment (Watts et al. 2015). It is hard to account for the differences in time spent with patients receiving either the active intervention or TAU. Therefore, the results of comparisons with TAU are difficult to interpret.

In summary, 'psychological placebo' seems to be the best control method to obtain valid results (see also Zhou et al. 2015).

Table 2. Proposal for standards for 'psychological placebo' control conditions.

- Patients receive talking sessions of the same length and frequency as in the experimental group
- Sessions are performed by staff without any education in psychotherapy
- Talking sessions include psychosocial issues but do not include psychoeducation about the disorder to be treated
- Persons conducting the sessions are allowed to show empathetic involvement and sympathetic attention or provide reassurance
- Specific ingredients of psychotherapies (e.g. transference or correction of catastrophic misinterpretations) that require intensive training in a specific form of psychotherapy must be omitted; psychotherapy manuals should not be used

Study quality in psychological studies

Study quality is often lower in psychotherapy studies than in medication studies, perhaps due to the lack of sufficient financial support, and perhaps because medication studies are under control of drug licencing authorities.

Moreover, there are a number of reasons why the effects of psychotherapy may be overestimated in the available studies. In waitlist studies, the patients are not blinded to the treatment arm (Bandelow 2021). Patients treated in psychotherapy trials were significantly less severely ill than patients in drug trials. In the vast majority of 'pure' psychotherapy studies, patients were not excluded when they were on medication (Bandelow et al. 2015; Skapinakis et al. 2016). Thus, in some patients, the measured pre-post effect is in fact a combination of psychotherapy and medication in a substantial percentage of the participants. Only in half of the psychotherapy studies, intent-to-treat (ITT) analyses were used for missing data. Drug trials were significantly shorter than psychotherapy studies. The longer the trial, the more the treatment effects could be attributable to spontaneous remission. Sample sizes in drug trials were about five times larger than in psychotherapy studies, due to the lack of commercial funding in the latter. Small studies are more prone to publication bias, as journal editors may be reluctant to publish small studies showing no difference from a control group. Publication bias is an issue both in pharmacotherapy and psychotherapy studies (Driessen et al. 2015; Turner et al. 2008).

Lastly, demonstrating efficacy of psychotherapy in a trial conducted at an expert site does not guarantee that the same effect sizes will be obtained in 'real life' conditions (Nutt and Sharpe 2008).

The WFSBP evidence grading system

In this guideline, 'levels of evidence' (LoE) (Table 3) and 'recommendation grades' (RG) (Table 4) are used. A WFSBP working group has developed a new grading system which is mandatory for all new versions of WFSBP guidelines (Hasan et al. 2019). It can also be

Table 3. WFSBP grading system: Levels of evidence (LoE) (Hasan et al. 2019).

Positive evidence		Negative evidence	
A	Strong evidence for the intervention	A-	Strong evidence against the intervention
B	Limited evidence for the intervention	B-	Limited evidence against the intervention
C	Weak evidence for the intervention	C-	Weak evidence against the intervention
D	No evidence		

Table 4. WFSBP grading system: recommendation grades (RG) (Hasan et al. 2019).

Positive recommendation		Negative recommendation	
1	Strong recommendation for the intervention	1-	Strong recommendation against the intervention
2	Limited recommendation for the intervention	2-	Limited recommendation against the intervention
3	Weak recommendation for the intervention	3-	Weak recommendation against the intervention
4	No recommendation possible		

The colors indicate the recommendation levels: RG = 1, dark green; RG = 2, light green; RG = 3, yellow; RG = 4, grey; RG = 1-, dark red; RG = 2-, light red; RG = 3-, orange.

recommended for all other future guidelines in psychiatry or other fields of medicine or psychology. Recommendations should not only be based on efficacy, without regard to the risks of the available treatments. For example, the evidence for the efficacy of benzodiazepines is good (LoE A), but due to their abuse potential they did not receive a recommendation grade 1 (RG 1) but were downgraded to RG 2. 'Risks' were defined as serious adverse events (e.g. addiction potential, metabolic syndrome, serious cardiovascular effects) or critical interactions.

The recommendation grades can be viewed as steps: The first step would be to use a treatment with RG 1. When this treatment fails, other RG 1 options should be tried first before switching to treatments with RG 2.

The evidence grading system also provides negative statements, e.g. an RG of '1-' based on 'A-' evidence characterises a treatment that has been studied in not only one, but several studies with negative results, and the recommendation is 'strongly' against the use of this treatment.

In our recommendations, we have not considered the direct or indirect costs of treatments, as these vary substantially across the different health care systems in the participating countries and change with time. As almost all drugs recommended in this guideline are generic, the costs for pharmacotherapy are generally low.

Levels of evidence (LoE)

The levels of evidence are shown in Table 3. The detailed description of LoEs is given in (Table 2, Supplementary Appendix).

Recommendation grades (RG)

The recommendation grades are shown in Table 4. A detailed description is given in (Table 3, Supplementary Appendix).

When there conflicting opinions among the Task Force members regarding certain decisions about recommendation grades, the decision was put to the vote.

Meta-analyses

There is an abundance of published meta-analyses of available studies on anxiety disorders, OCD and PTSD, many of which report contradictory findings. There are several methodological issues associated with meta-analyses. Some of the existing meta-analyses did not have the same strict inclusion criteria used in this review (e.g. including a mix of open and controlled studies, mixed diagnoses, or studies with very small sample sizes), and did not make a difference between inactive controls (e.g. waitlist) and active controls (e.g. pill placebo or psychological placebo) despite the large effect size difference between these control conditions. Meta-analyses are prone to bias (e.g. by excluding unsuitable studies with weak supporting arguments). When several studies that show only minimal, insignificant effects are combined in a meta-analysis, the power can be inflated to achieve a significant result. On the other hand, with meta-analysis, larger studies get more weight than smaller ones.

As a first step, the decisions of this guideline was based on a thorough analysis of the available original RCTs. Meta-analyses were only conducted by the Task Force for certain decisions in the case of inconsistent findings, e.g. when there were about as many negative as positive findings. At least 3 studies were required for conducting a meta-analysis for a certain decision.

Meta-analytical procedure. The details of the procedure were taken from (Bandelow et al. 2015). Two reviewers independently extracted all data, with differences resolved following discussion. Interrater

reliability for decisions about whether to include or exclude a study was $\kappa = .86$. In order to limit heterogeneity and to achieve maximum comparability, we preferably used the most commonly applied scales, i.e. the Panic Disorder Severity Scale (PDSS) for PDA, the Penn State Worry Questionnaire (PSWQ) for GAD, the Liebowitz Social Anxiety Scale (LSAS) for SAD, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) for OCD and the Clinician-Administered PTSD Scale (CAPS for PTSD). These were not necessarily defined as primary efficacy measures in the studies. If these scales were not available, we used other specific symptom scales following a hierarchy (Bandelow et al. 2015).

Statistical analysis was done using Comprehensive Meta-Analysis 3. Effect size (ES) (Cohen's d) were calculated as treated vs. control ES (post-test difference between the mean of the treatment condition and the mean of the control condition). Because moderate ($I2 > 50\%$) to high ($>75\%$) heterogeneity was found for most comparisons, the random-effects model was used in all analyses. To assess publication biases, p values for Egger's regression intercept (a method to quantify the bias captured by a funnel plot) for between group ES sizes were calculated, and ES adjusted for publication bias using Duval and Tweedie's 'trim and fill' method, which is used to correct the funnel plot by estimating the number and ES of missing studies, were determined.

We preferably used intent-to-treat (ITT) data based on the last observation carried forward (LOCF) method or mixed modelling statistics, if available.

Cohen's $d \geq 0.2$ is considered a 'small' effect size, ≥ 0.5 represents a 'medium' and ≥ 0.8 a 'large' effect size. A difference between two groups' means less than 0.2 standard deviations is negligible, even if it is statistically significant.

Diagnosis

In Table 5, a short overview of the various disorders is given. There is a marked overlap among the anxiety disorders, OCD and PTSD, and comorbidity with other psychiatric disorders, such as major depression, is common (Bandelow 2003).

Prevalence

Anxiety disorders, OCD, and PTSD are among the most prevalent mental disorders. Prevalence rates of anxiety disorders vary substantially across various large representative surveys from different countries. In Table 6, 12-month and lifetime prevalence rates of these conditions are presented. These figures are based on a review (Bandelow and Michaelis 2015) of large epidemiologic surveys including the Epidemiologic Catchment Area Program ECA (Regier et al. 1993), the National Comorbidity Survey–Replication NCS-R (Kessler, Chiu, et al. 2005; Kessler et al. 2012), the European Study of the Epidemiology of Mental Disorders ESEMeD (Alonso et al. 2007) and an analysis of 27 European studies (Wittchen and Jacobi 2005). Additionally, data from the China Mental Health Survey were included (Huang et al. 2019). The prevalence rates show high heterogeneity, which may be due to several factors, including methods of data collection, interviewer instructions, cultural differences, and others.

Selective mutism is a relatively rare condition, with point prevalence rates ranging between 0.03% and 0.79% (Kopp and Gillberg 1997; Driessen et al. 2020).

Table 5. Short description of anxiety disorders as defined by ICD-10/ICD-11(WHO 1993, 2017) and DSM-5 (APA 2013).

Panic disorder (PD)
Panic disorder is characterised by recurrent panic attacks. Panic attacks are discrete periods of intense fear or discomfort, accompanied by at least four of 14 somatic and psychic symptoms (13 in DSM-V). A panic attack reaches a peak within several minutes and lasts 30–45 min on average. Usually, the patient is afraid that she or 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.
The individual is consistently anxious about these situations due to a fear of specific negative outcomes (e.g. panic attacks, other incapacitating or embarrassing physical symptoms).
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 (GAD)
The main features are excessive anxiety and worry. The worry pertains to a wide variety of concerns (e.g. relationship problems, illness, financial difficulties, job security). The patients suffer from somatic anxiety symptoms as well as restlessness, irritability, difficulty concentrating, muscle tension, sleep disturbances or being easily fatigued.
Social anxiety disorder (SAD)
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 symptoms (including palpitations, trembling, blushing, etc.). The feared situations are avoided or 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.
Specific phobia
Specific phobia is characterised by excessive or unreasonable fear of single objects or situations (e.g. flying, heights, animals, seeing blood, dental treatments, etc.).
Separation anxiety disorder
Individuals experience excessive anxiety about separation from home and/or from people to whom the individual has a strong emotional attachment (e.g. parents, caregivers, siblings, children, romantic partners or significant others).
Selective mutism
Selective mutism is characterised by consistent selectivity in speaking, such that a child demonstrates adequate language competence in specific social situations, typically at home, but consistently fails to speak in others, typically at school.

Table 6. 12-month and lifetime prevalence rates (percent) of anxiety disorders, OCD and PTSD.

Disorder	12-month	Lifetime
Panic disorder	0.5–3.1	0.5–5.2
Agoraphobia	0.4–10.5	0.4–2.6
Generalised anxiety disorder	0.3–4.3	0.3–6.2
Social anxiety disorder	0.6–8.0	0.6–13.0
Specific phobia	2.6–11.1	2.6–13.8
Separation anxiety disorder	1.2	8.7
Obsessive-compulsive disorder	1.2–2.4	2.3–2.4
Posttraumatic stress disorder	0.3–3.7	0.3–5.7

Gender differences

Although gender differences varied widely between studies, all studies found a higher percentage of women for all anxiety disorders. Female-to-male ratios were found to be 1.6–2.3 for panic disorder, 1.6–3.1 for agoraphobia, 1.7–2.6 for GAD, 1.2–2.1 for SAD, and 1.8–2.6 for specific phobia (Bandelow and Michaelis 2015). For separation anxiety disorder, a ratio of 1.6 was found (Kessler et al. 2012), and 1.2–2.0% for selective mutism (Driessen et al. 2020). For OCD, it was 1.5 (Wittchen and Jacobi 2005) and for PTSD 3.22 (Alonso et al. 2004a).

Age of onset and course

A meta-analysis using 24 representative surveys found an average age of onset for separation anxiety disorder of 10.6 years, followed by specific phobia (11.0 years), SAD (14.3 years), agoraphobia without panic disorder (21.1 years), OCD (24.0 years), PTSD (26.6 years), PDA (30.3 years), and GAD (34.9 years) (Lijster et al. 2017). The mean age of onset of selective mutism was reported to be between 2.7 and 4.6 years (Driessen et al. 2020).

A systematic analysis of the mean age of individuals participating in clinical studies (Bandelow and Schuller 2020) found that the mean age for patients with SAD was 35.2 years, 37.5 years for PDA and 40.7 years for GAD. OCD patients had a mean age of 35.6 years, while it was 38.2 years for PTSD. This analysis was based on the assumption that patients would apply for participation in a treatment study when their illness severity had reached its peak.

Anxiety disorders tend to be less common in the fifth decade (Bandelow 2003; Kessler, Berglund, et al. 2005; Rubio and Lopez-Ibor 2007a, 2007b).

Anxiety disorders tend to have a chronic course. A study evaluating the long-term outcomes found that of patients with GAD, 58% still had this diagnoses after 30 years (Tyrer P et al. 2021). Of patients with PDA, 31% showed a persistence of this disorder after this time period.

Burden/health care utilisation

In Europe, the total annual cost for anxiety disorders in 2010 was 74.4 billion €; only the costs for mood disorders (113.4 €) and psychotic disorders (93.9 €) were higher (Olesen et al. 2012).

Patients with anxiety disorders are frequent users of emergency medical services. Anxiety disorders are often underdiagnosed or recognised only years after onset. In a large European study, it was found that only one-fifth of anxiety patients sought help from healthcare services, and of these, one-fifth received no treatment (Alonso et al. 2007).

Aetiology

Hypotheses about the aetiology of anxiety disorders are currently based on a combination of vulnerability factors and stressful exposure, e.g. traumatic experiences during childhood or later in life. The vulnerability may be based on genetic factors associated with neurobiological adaptation of the central nervous system (CNS). Substantial heritability was found in twin studies (Bandelow et al. 2016). Neurobiological abnormalities in anxiety and OCD patients that have been suggested include dysfunctions of serotonin, noradrenaline, dopamine, gamma-aminobutyric acid (GABA), cholecystokinin, glutamate, or endogenous opioid receptors or the hypothalamic-pituitary-adrenal (HPA) axis. Despite the extent and rigour of research on the neurobiology of these disorders, no biomarker has to date proven sufficiently sensitive and specific (Bandelow et al. 2016; Bandelow et al. 2017).

Separation anxiety may not necessarily be caused by actual separation experiences in childhood (Bandelow et al. 2001). This condition has also been associated with neurobiological alterations (Schiele et al. 2020).

Treatment: General principles

Before treatment is initiated, the mechanisms underlying psychic and somatic anxiety should be explained to the patient. Brochures or web sites that explain the typical features of the patient's condition, treatment options, and the risks and benefits associated with these treatments should be offered to the patients. The principles of psychotherapeutic methods should be explained. Compliance with drug treatment can be improved when the advantages and disadvantages of the drugs are explained carefully to the patient.

Indication for treatment

Treatment is indicated in most patients who fulfil the ICD-11 or DSM-5 criteria for an anxiety disorder, OCD or PTSD. The treatment plan is based on the patient's preference, severity of illness, comorbidity, concomitant medical illnesses, complications like substance abuse or suicide risk, the history of previous treatments, cost issues and availability of types of treatment in a given area. Treatment options include psychoactive drug treatment, psychotherapy, exercise, and other interventions. Neurostimulation methods and neurosurgery are covered in the accompanying paper, Part II.

Monitoring treatment efficacy

In order to monitor treatment efficacy, it is useful to use symptom rating scales such as the Panic and Agoraphobia Scale (PAS; Bandelow 1999) for PDA, the Hamilton Anxiety Scale (HAM-A; Hamilton 1959) for GAD, the LSAS (Liebowitz 1987) for SAD, the Y-BOCS (Goodman et al. 1989) for OCD, and the Clinician-Administered PTSD Scale (CAPS-5) (Weathers et al. 2018). As these assessments are time-consuming, global improvement ratings such as the Clinical Global Impression (CGI; NIMH 1976) and self-rated symptom and function scales may suffice in busy practice settings. Alternatively, using disorder-specific self-report measures may be less time-consuming.

Medications

Duration of medication 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 6–12 months to reduce the risk of relapse, and only after all, or almost all, symptoms have disappeared. This recommendation is derived from long-term and relapse prevention studies which are evaluated in the subsequent chapters.

Dosing

Recommended dosages are given in Table 7. In RCTs, approximately 75% of patients respond to the initial (low) dose selective serotonin reuptake-inhibitors (SSRIs)/serotonin norepinephrine reuptake-inhibitors (SNRIs) (with the exception of OCD). In some patients, such as the elderly and those from East Asia, treatment should be started with half the recommended dose or less, to minimise initial adverse drug events, such as nausea, dizziness, headache and a paradoxical increase in anxiety. In particular, patients with PDA may be sensitive to these side effects and may easily discontinue treatment because of initial jitteriness and nervousness. Some patients may not verbalise feelings of anxiety, but instead, may report generalised physical discomfort after initiation with SSRIs/SNRIs. For tricyclic antidepressants (TCAs), initiating the drug at a low dose and increasing dose every 3–5 days is recommended. The antidepressant dose should be increased to the highest recommended therapeutic level if initial treatment with a low or medium dose fails. For OCD, medium to high doses are recommended (for details, see Part II). As PTSD is sometimes associated with poor response, higher doses should also be tried in these cases.

Long-term and relapse prevention studies have usually been conducted with the same dose levels as in the acute studies. It is not known whether lower doses may be sufficient in maintenance treatment (Caldirola

Table 7. Dosing recommendations for medication treatment of anxiety disorders, OCD and PTSD.

Treatment	Examples	Recommended daily dose for adults
SSRIs	Citalopram	20–40 mg[a]
	Escitalopram	10–20 mg[a]
	Fluoxetine	20–40 mg
	Fluvoxamine	100–300 mg
	Paroxetine	20–60 mg
	Sertraline	50–200 mg
SNRIs	Venlafaxine	75–225 mg
	Duloxetine	60–120 mg
TCAs	Amitriptyline	75–150 mg
	Clomipramine	75–250 mg
	Imipramine	75–250 mg
	Desipramine	100–300 mg
	Lofepramine	70–210 mg
Benzodiazepines	Alprazolam	1.5–8 mg
	Bromazepam	1.5–6 mg
	Clonazepam	1–4 mg
	Diazepam	5–20 mg
	Lorazepam	2–8 mg
SSRI/5-HT_{1A} receptor partial agonist	Vilazodone	20–40 mg
SARI	Trazodone	150–600 mg
NaSSA	Mirtazapine	30–60 mg
MAOI	Phenelzine	45–90 mg
RIMA	Moclobemide	300–600 mg
MT_1/MT_2 agonist/5-HT_{2C} antagonist	Agomelatine	25–50 mg
Calcium channel modulators	Pregabalin	150–600 mg
	Gabapentin	600–3600 mg
Atypical antipsychotics	Quetiapine	50–300 mg
	Risperidone	0.5–6 mg
	Olanzapine	2.5–20 mg
Antihistamine	Hydroxyzine	37.5–75 mg
Tricyclic anxiolytic	Opipramol	50–150 mg
Azapirone	Buspirone	15–60 mg
Anticonvulsant	Lamotrigine	25–500 mg
Lavender oil extract	Silexan	80–160 mg
α_1-Antagonist	Prazosin	1–10 mg

[a]Caution should be used when considering prescribing off label dosages of citalopram (exceeding 40 mg/day) and escitalopram (exceeding 20 mg/day) because of the risk of dose dependent QT_C prolongation, particularly when combined with other medicines that can also affect the QT_C interval or when treating patients >65 years. If a decision is made to proceed, periodic ECG monitoring is advisable.

et al. 2020). Therefore, the same dose as in the acute phase is recommended for the maintenance phase.

To increase compliance, it is preferable to prescribe medications in a single dose, if pharmacokinetic data support once-daily dosing.

In elderly patients, lower doses are recommended, especially when using TCAs.

In patients with hepatic impairment, dosage adjustment or use of medications with primarily renal clearance (e.g. pregabalin) may be required.

Licencing of drugs may differ between the various countries of the world. An overview of the licencing status of all medications for anxiety disorders, OCD, and PTSD in the different countries is provided in Table 4, Supplementary Appendix. However, recommendations in this guideline are only based on evidence from RCTs and not on whether a drug is licenced for a certain disorder in one or more countries. Depending on country, medicolegal issues must be considered whenever drugs that have not been approved for the treatment of a certain disorders are given off label.

Treatment resistance

A substantial number of patients with anxiety disorders do not meet response criteria after initial standard treatment. While no universally accepted criteria exist, a commonly used threshold for response is a $>$ 50% improvement in the total score of a commonly used rating scale (e.g. the Hamilton Anxiety Rating Scale [HAMA]). However, this definition is somewhat arbitrary and not fully supported by clinical data (Bandelow 2006; Bandelow et al. 2006). For OCD, it has been suggested that a successful treatment response is a Y-BOCS score reduction of $\geq$ 35% and a CGI-I score of 1 or 2 (Mataix-Cols et al. 2016).

Before considering a patient to be treatment-refractory, the diagnosis should be reviewed, the patient should be assessed for compliance with therapy, the dosage should be confirmed as being within the therapeutic range, and the trial period should be adequate. Concurrent prescription drugs (or traditional medicines) may interfere with efficacy, e.g. as metabolic enhancers or inhibitors. Poor therapeutic alliance and several psychosocial stress factors may also diminish response, along with concomitant personality disorders. Depression and substance abuse need to be considered as complicating factors. Past treatment history may be used as guide to practice.

When initial treatment fails, the physician should consider changing the dose or switching to another medication. Controlled data on switching medications are lacking for the anxiety disorders. Study data showed that in GAD and SAD, a trial of at least 4 weeks is worthwhile before considering further intervention (Baldwin et al. 2009). If partial response is seen after 4 weeks, it is still possible that the patient will respond within the next 4–6 weeks of therapy. Elderly patients may take longer to respond.

Although 8–12 weeks remain as the optimal duration of an initial trial in OCD, two meta-analyses have demonstrated a significant improvement of OCD severity within the first 2 weeks of treatment with SSRIs, with the greatest incremental gains occurring early in the course of treatment (Issari et al. 2016; Varigonda et al. 2016). Likewise, an open-label trial of fluoxetine in treatment-naive patients indicated that a reduction of at least 20% of OCD symptom severity at week 4 was the best predictor of treatment response at 12 weeks (da Conceicao Costa et al. 2013). Altogether, these findings suggest that, in the absence of early improvement, modifications in the treatment plan may be considered before 8–12 weeks.

Although double-blind 'switching studies' are lacking, experienced clinicians report that many treatment-resistant patients respond to a different class of medication (e.g. switching from SSRI/SNRIs to TCAs or *vice versa*). Another strategy for treatment-unresponsive cases is to 'augment' an ongoing treatment with a second drug. However, this strategy has the disadvantage that should an improvement occur after augmentation, it is unclear whether it is due to the second drug or to the combination. Also, the combination may be associated with increased rates of adverse effects or interactions. Therefore, switching should be tried before augmentation. Some augmentation strategies, like adding benzodiazepines to an SSRI/SNRI for anxiety disorders or an antipsychotic to an SSRI for OCD are supported by controlled studies.

Special recommendations for the various anxiety disorders, OCD and PTSD are provided in the respective sections.

Medications: available compounds

Several psychopharmacological agents are available for the treatment of anxiety disorders. These are briefly reviewed in the following section. These recommendations are based on RCTs which are presented in the Chapter 'Special treatment recommendations for the different disorders'.

For a detailed description of psychopharmacological agents, including their adverse effects, interactions and precautions, the readers are referred to the relevant literature (e.g. (Procyshyn et al. 2019).

The currently used nomenclature for psychotropics is outdated, as it is based on certain indications, while many medications are used for more than one disorder, e.g. we prescribe antidepressants for anxiety disorders, or antipsychotics for OCD. The new 'Neuroscience-based nomenclature (NbN)' was proposed which provides more logical descriptions of psychotropic medications (Zohar et al. 2014). According to NbN, the term 'TCAs' should be changed to 'monoamine enhancers', 'benzodiazepines' to 'GABA enhancers', 'atypical antipsychotics' to 'dopamine serotonin blockers', 'anxiolytics' to 'medications for anxiety', 'antidepressants' to 'medications for depression', and 'antipsychotics' to 'medications for psychosis'. However, as many readers maybe not yet familiar with NbN, we used the classical nomenclature in this text.

Selective serotonin reuptake inhibitors (SSRIs). SSRIs are first-line drugs for the treatment of anxiety disorders, OCD and PTSD.

Although treatment with SSRIs is usually well tolerated, restlessness, jitteriness, an increase in anxiety symptoms, insomnia, or headache in the first days or weeks of treatment may jeopardise compliance with treatment. Lowering the starting dose may reduce this overstimulation. Other side effects include fatigue, dizziness, nausea, anorexia, or weight gain. Gastrointestinal bleeding may occur. Sexual dysfunction (mainly reduced libido and delayed or impaired orgasm) may be a problem in both sexes, particularly in long-term treatment. Discontinuation symptoms (dizziness, vertigo, light-headedness, nausea/vomiting, fatigue, irritability, headaches) may occur during SSRI discontinuation and can sometimes be hard to distinguish from a reoccurrence of the pre-existing anxiety disorder. Gradual reduction in the dose is recommended before ceasing the medication. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may be a problem mainly in elderly patients (Bouman et al. 1998).

The anxiolytic effect may start with a delay of 2–4 weeks (in some cases up to 6 or 8 weeks). To avoid overstimulation and insomnia, doses can be given in the morning or at mid-day, except in patients reporting daytime sedation.

Serotonin norepinephrine reuptake inhibitors (SNRIs). The efficacy of the SNRIs venlafaxine and duloxetine in certain anxiety disorders has been shown in several controlled studies (see below for references). At the beginning of treatment, side effects like nausea, restlessness, insomnia or headache may pose a threat to compliance with treatment. Also, sexual dysfunctions, SIADH, gastrointestinal bleeding and other adverse events have been reported.

Likewise, discontinuation of SNRIs has frequently been associated with withdrawal symptoms.

The antianxiety effect of SNRIs may have a latency of two to four weeks, and in some cases this latency may even be longer.

Tricyclic antidepressants/monoamine enhancers. The efficacy of the TCAs amitriptyline, clomipramine, imipramine in anxiety disorders, OCD and PTSD is well established (see below for references). Desipramine and lofepramine were effective in one DBPC study each. TCAs have not been investigated systematically in the treatment of SAD.

Especially at the beginning of treatment, compliance may be reduced by adverse effects such as initially increased anxiety symptoms, dry mouth, amblyopia, postural hypotension, tachycardia, sedation, impaired psychomotor function/car driving safety, and others. Weight gain and sexual dysfunction may be a problem in long-term treatment. Stopping TCAs abruptly can also cause withdrawal symptoms. Due to the broad receptor profiles of these drugs, many pharmacokinetic interactions can limit their use in patients taking concomitant medication. Elderly patients should be monitored for cardiovascular side effects. TCAs should be avoided in patients considered at risk of suicide, due to their potential cardiac and CNS toxicity after overdose (Nutt 2005). In general, the frequency and burden of adverse events is higher for TCAs than for the SSRIs or SNRIs. 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 prominent.

NaSSA mirtazapine. Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). There is only on DBPC study supporting the use of mirtazapine in SAD. Common side effects include sedation, constipation, drowsiness, hyperlipidaemia, weight gain, fatigue, insomnia, increased or decreased appetite and dry mouth.

Serotonergic drug vilazodone. *Vilazodone* is a serotonin reuptake inhibitor and 5-hydroxytryptamine –

serotonin (5-HT_{1A}) partial agonist which is licenced for the treatment of major depression in Canada and the US but not for anxiety disorders. It has shown efficacy in GAD. Common adverse effects include diarrhoea, nausea, vomiting, and insomnia.

Calcium channel modulator pregabalin. Pregabalin was found to be effective in several studies in GAD and in a few trials in SAD. The anxiolytic, analgesic, and antiepileptic effects of the drug are attributed to its binding to the α_2-δ-subunit protein of voltage-gated calcium channels in the CNS. Main side effects of pregabalin include dizziness, sedation, dry mouth, amblyopia, impaired coordination, and impaired psychomotor and cognitive function. Withdrawal symptoms have been reported, including nausea, diarrhoea, headache, seizures spasticity, nightmares, sleep disturbances, numb or tingling feelings, dizziness, anxiety, diaphoresis, tachycardia, hallucinations and others. According to case reports, pregabalin has been used in very high doses by individuals with multi-substance abuse, including snorting (Gahr et al. 2013; Schwan et al. 2010). There are only a few case reports of persons who misused pregabalin alone but were not addicted to other substances (Driot et al. 2016; Halaby et al. 2015). A recent review of all available studies has shown that when misused to 'self-medicate', the gabapentinoids gabapentin and pregabalin can produce desirable effects alone, but are also often used concomitantly with other drugs, and that opioid use disorder is the greatest risk factor for gabapentinoid abuse (Evoy et al. 2021). Therefore, prescribing pregabalin to patients with a history of substance abuse is not recommended.

Reversible inhibitor of monoamine oxidase A (RIMA) moclobemide. The reversible inhibitor of monoamine oxidase A (RIMA) moclobemide has shown efficacy in SAD, however, the overall effect was small (see below for an analysis of the RCTs).

To avoid overstimulation and insomnia, doses should be given in the morning and mid-day.

Irreversible monoamine oxidase inhibitor (MAOI) phenelzine. The efficacy of the irreversible MAOI phenelzine has been shown in some controlled studies in PDA, SAD and PTSD (see below for references). Because of the possibility of severe side effects and interactions with other drugs or food components, phenelzine is not considered a first-line drug. It is used mostly by experienced psychiatrists when other treatment modalities have been unsuccessful or have not been tolerated. However, in these cases, it may be very useful (Chamberlain and Baldwin 2021). To avoid overstimulation and insomnia, doses should be given in the morning and mid-day. MAOIs should be used only after giving the patient proper explanation about the dietary restrictions and interactions with other medications. Phenelzine has not received regulatory approval for treatment of the anxiety disorders in any country.

RCTs with tranylcypromine and other MAOIs which fulfilled the criteria of this guideline were not found.

Benzodiazepines. The efficacy of benzodiazepines in anxiety disorders has been shown in many controlled clinical studies (see below for references). The anxiolytic effect starts within 30–60 min after oral or parenteral application. In contrast to antidepressants, they do not lead to initially increased anxiety or agitation. In patients with suicidal ideation, they may provide fast symptom control. They have a good record of safety and have important uses in medicine (Tyrer et al. 2010; Allgulander 2022; Silberman et al. 2021). Benzodiazepine treatment initiation may be associated with sedation, dizziness, and prolonged reaction time. Cognitive functions may be affected initially. These effects are aggravated by concurrent alcohol intake. Atypical (paradoxical) reactions in elderly patients treated with benzodiazepines are rare (around 1%) (Mancuso et al. 2004). They include increased talkativeness, agitation, excessive movement, hostility, psychosis and others. After long-term treatment with benzodiazepines (e.g. over 2–8 months), tolerance to the therapeutic dose may occur in some patients (Nelson and Chouinard 1999). This is probably more common in predisposed patients, e.g. with a history of alcohol or drug abuse or personality disorders (Romach et al. 1995; Schweizer et al. 1998). Discontinuation symptoms 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). Prolonged withdrawal reactions may occur, but they are difficult to distinguish from pre-treatment symptoms and 'nocebo' effects. Tolerance to anxiolytic or other effects seems to be rare, according to long-term controlled trials (Rickels 1982; Nagy et al. 1989; Pollack et al. 1993; Worthington et al. 1998).

Treatment with benzodiazepines is usually safe and effective for short-term use. However, maintenance treatment requires a careful weighing of risks and benefits. Long-term treatment with benzodiazepines may be justified in patients who did not respond to other treatment modalities or did not tolerate them.

Withdrawal of benzodiazepines is often challenging (Baldwin 2022). Patients with a history of benzodiazepine, alcohol or other psychoactive substance abuse or dependence should generally not be administered benzodiazepines. When this is not possible, such patients should be closely monitored in specialised care settings. Individuals with substance use disorders may use benzodiazepines to potentiate the effects of illicit opioids, or to cope with CNS stimulant withdrawal (May et al. 2020).

In a study with 73 patients receiving the benzodiazepine clonazepam for at least 3 years, it was found that clonazepam could be successfully discontinued (decreasing by 0.5 mg per 2-week period until 1 mg/day was reached, followed by a decrease of 0.25 mg per week) without any major discontinuation symptoms (Nardi et al. 2010). Cognitive-behavioural interventions may facilitate benzodiazepine discontinuation (Otto et al. 1993; Spiegel 1999).

Benzodiazepines may also be used in combination with serotonergic medications during the first weeks of treatment to accelerate onset of action or suppress increased anxiety sometimes seen when serotonergic therapy is initiated (Goddard et al. 2001). In depressed patients, drop-out rates were lower when benzodiazepines were added to antidepressant treatment (Furukawa et al. 2019).

In general, benzodiazepines should be used with a regular dosing regimen and not on a p.r.n. basis. P.r.n. use may only be justified in the treatment of short-term distress (e.g. before MRT scans, air travel or dental procedures).

Many benzodiazepines have received approval for the treatment of 'anxiety states' prior to the DSM-III nosology based on specified diagnostic criteria. However, in the present guideline, recommendations of benzodiazepines are restricted to those that have been studied in patients with DSM- or ICD-defined diagnoses.

When treating anxiety disorders, one should be aware that benzodiazepines were not found to be effective for frequently occurring comorbid conditions, such as depression or OCD. Although benzodiazepines are often used to treat acute stress reactions, studies in PTSD are lacking.

5HT$_{1A}$-agonist buspirone. The partial 5 HT$_{1A}$-agonist (azapirone) buspirone may be effective for symptoms of GAD, as shown in some controlled studies (see below for references). Buspirone is not effective in PDA. Side effects include headache, dizziness, light-headedness, restlessness, fatigue, paresthesias and others.

Opipramol. Opipramol is a tricyclic anxiolytic that has many similarities with TCAs. There is only one DBPC study supporting its use in GAD. Side effects include fatigue, drowsiness, dry mouth, orthostatic hypotension, and nasal congestion.

Antihistamine hydroxyzine. The antihistamine hydroxyzine was effective in GAD in several DBPC studies (see below for references). Because of sedating effects, the antihistamine should only be used when treatment with other medications was not successful or not tolerated. Experience with long-term treatment is lacking. There is no antidepressant effect. Side effects include sedation, anticholinergic effects at high doses, blurred vision, confusion, delirium and others. The drug does not generally play a role in the current pharmacotherapy of GAD.

Atypical antipsychotics (dopamine serotonin blockers). In the 1970s and 1980s, anxiety disorders were frequently treated with typical high or low potency antipsychotics (dopamine blockers) such as haloperidol, fluspirilene, flupentixol, sulpiride, chlorprothixene, melperone and others at lower doses than those that are used in the treatment of schizophrenia. However, studies carried out with antipsychotics in patients suffering from 'anxiety neuroses' had some methodological flaws. Moreover, there were concerns regarding tardive side effects after year-long treatment, which is often required in the treatment of anxiety disorders. Therefore, use of typical antipsychotics was abandoned, as alternative medications emerged for the treatment of anxiety disorders.

Quetiapine was found effective as a monotherapy for GAD and PTSD. However, there have been concerns about the metabolic syndrome and a potential for lethal arrhythmia associated with the drug.

Olanzapine and risperidone were effective in treatment-unresponsive patients with PTSD.

In several studies, atypical antipsychotics (including aripiprazole, olanzapine, and risperidone) have been used as add-on treatment for non-responsive cases of anxiety disorders, OCD and PTSD.

Side effects of atypical antipsychotics include sedation, orthostatic hypotension, sexual dysfunctions, metabolic syndrome, arrythmias, extrapyramidal effects and others.

Agomelatine. According to several studies, the melatonin MT$_1$ and MT$_2$ receptor agonist and 5-HT$_{2C}$ receptor antagonist agomelatine was effective in the treatment of GAD. A risk of liver toxicity is associated

with the drug; liver function tests are required before starting and regularly during treatment. It is only licenced by the European Medicines Agency (EMA), the Chinese National Medical Products Administration (NMPA) and in Australia for the treatment of depression and not for GAD or other anxiety disorders.

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

Trazodone. Trazodone is a serotonin antagonist and reuptake inhibitor (SARI). Side effects include sedation, fatigue, orthostatic hypotension, blurred vision, dizziness, dry mouth, nausea, headache, and others. Only one study supports the efficacy of trazodone in GAD.

Ketamine. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist primarily used for anaesthesia. It was shown to be effective as a rapid-acting antidepressant, although its effect may be transient. There is only on DBPC study supporting the use of ketamine in SAD. Adverse effects include nausea, vomiting, dizziness, diplopia, dysphoria, confusion, dreamlike states, hallucinations, sedation, loss of memory, decreased attention, hypertonia, and slowed breathing. Non-medical use of ketamine as a recreational drug is not uncommon, due to its hallucinogenic properties. Therefore, ketamine should not be prescribed to patients with substance abuse.

Advantages and disadvantages of antianxiety drugs. None of the available drug treatments can be considered as 'ideal' for every patient. In Table 8, the risks and benefits of the available compounds are reviewed. The treatment option should be chosen individually for each patient.

Psychological treatments

All patients with anxiety disorders require supportive interviews and attention to emotional states. 'Psychoeducation' – provision of information about the aetiology and treatment of anxiety disorders, OCD, and PTSD helps the affected patients understand the causes of their disorder and how treatments work. Many patients prefer specific psychological treatment interventions to pharmacotherapy.

Forms of psychotherapy

Cognitive behavioural therapy (CBT). The most studied psychotherapy is CBT. Forms of CBT, such as exposure therapy (e.g. gradual exposure *in vivo*) were found to be very effective for specific phobia, agoraphobia, and SAD. In this treatment modality, patients are confronted *in vivo* with a feared situation (e.g. using public transport in agoraphobia). For symptoms that cannot be treated with exposure alone, such as

Table 8. Advantages and disadvantages of drugs for anxiety disorders, OCD and PTSD.

Substance	Advantages	Disadvantages
SSRIs	Not addictive Sufficient evidence from clinical studies for all anxiety disorders Relatively safe in overdose	Latency of effect 2–6 weeks, initial jitteriness, nausea, restlessness, sexual dysfunction and other side effects. Some risk of withdrawal symptoms.
SNRIs	Not addictive Sufficient evidence from clinical studies Relatively safe in overdose	Latency of effect 2–6 weeks, nausea, possible increase in blood pressure at high doses (with venlafaxine) and other side effects. Some risk of withdrawal symptoms.
Pregabalin	Sufficient evidence from clinical studies Rapid onset of effect	Dizziness, sedation and other side effects Possible discontinuation symptoms; possible overdosing, abuse or dependence mainly in patients with substance abuse.
TCAs	Sufficient evidence from clinical studies	Latency of effect 2–6 weeks, anticholinergic effects, cardiac side effects, weight gain and other side effects, may be lethal in overdose
Benzodiazepines	Rapid onset of action Evidence from clinical studies Relatively safe in overdose	Sedation, slow reaction time and other side effects. Potentially addictive; discontinuation symptoms may occur after prolonged use. Rare paradoxical reactions in elderly patients. Non-medical use in subjects with other substance use disorders.
Moclobemide	Not addictive Benign side effects; relatively safe in overdose	Latency of effect 2–6 weeks, inconsistent study results in SAD, no efficacy proofs for other anxiety disorders
MAOIs	Not addictive	Few supporting studies in PD and SAD; latency of effect 2–6 weeks; potentially dangerous side effects and interactions
Buspirone	Not addictive Relatively safe in overdose	Latency of effect 2–6 weeks; efficacy proofs only for symptoms of GAD; light-headedness, nausea and other side effects
Agomelatine	Not addictive	Latency of effect 2–6 weeks; efficacy proofs only for symptoms of GAD; risk of liver toxicity
Hydroxyzine	Not addictive	Efficacy proofs only for GAD; sedation and other side effects; no experience with long-term treatment

spontaneous panic attacks or worrying in GAD, various cognitive strategies have been proposed.

CBT for OCD comprises two components: cognitive reappraisal and exposure with response prevention (ERP). The latter is the psychological treatment of choice for OCD and involves gradual and prolonged exposure to fear-provoking stimuli combined with instructions to abstain from engaging in compulsive behaviour.

CBT for PTSD most often is trauma-focused and comprises imaginary or *in vivo* exposure to the traumatic memory, cognitive processing and several other effective ingredients.

Psychodynamic (psychoanalytic) therapy (PDTh). Psychodynamic therapy is a traditional method of treating anxiety disorders and PTSD. For OCD, it has never been seen as an adequate treatment. Controlled studies of psychodynamic therapy started to emerge only a few decades ago.

Applied relaxation (AR). Applied relaxation (AR) is a form of relaxation treatment. The goal of AR is the ability to relax whenever anxiety symptoms occur. In its original form, AR does not contain elements often used in psychotherapy such as discussing psychological problems or helping with problem solving. AR has often been used as a control condition in psychotherapy research.

Internet psychotherapeutic interventions (IPI). Internet psychotherapeutic interventions have been developed in the last decades. Usually, participants have to work through computerised modules specially developed for anxiety disorders, which are based on standard psychotherapeutic techniques (mostly CBT-oriented approaches) and can be modified to accommodate the special requirements of individual patients. To be eligible, participants have to complete diagnostic tests on the website. Some programs include structured diagnostic interviews administered over the telephone or video link. The modules require about as much patient time as personal (face-to-face) psychotherapy and often involve 'homework', e.g. self-exposure to threatening stimuli in phobic disorders. In most studies, patients can contact therapists via E-mail. However, the time therapists spend communicating with patients is usually limited because saving therapist time is one of the goals of IPIs.

'Blended care' refers to a mixture of online therapy and in-person treatment.

Eye movement desensitization and reprocessing therapy (EMDR). EMDR was originally developed for the treatment of PTSD but was also investigated in PDA studies. In an EMDR session, the client is instructed to focus on an image of the traumatic memory. Then the therapist moves his fingers from one end to the other of the patient's field of vision, while the patient moves her/his eyes to follow the therapist's fingers. Some therapists use alternating side-to-side sounds, tapping, or tactile stimulations in addition to, or instead of using hand movements.

Doubts have been expressed whether such extraneous movements can cause changes in brain circuits. Argument has revolved around whether the eye movements or other distraction elements in the EMDR protocol or the exposure to traumatic memories are a necessary condition to treatment outcome (Cahill et al. 1999). Studies comparing EMDR with or without eye movements did not find a difference (Boudewyns and Hyer 1996; Devilly et al. 1998).

Dose-response relationship for psychotherapies

Usually, psychotherapeutic interventions are provided on a weekly basis. Regarding 'dosing' of psychotherapy, empirical data are almost lacking completely. Most RCTs with psychotherapy have a duration of around 12 weeks of weekly sessions. There are only a few studies comprising more than 30 sessions. According to a review, the optimum duration of psychotherapy (all forms) is between 4 and 24 sessions (Robinson et al. 2020).

An analysis of treatment duration of psychotherapies for anxiety disorders did not find evidence from controlled studies that longer therapies (e.g. 24 sessions) are more effective than shorter ones (e.g. 12 sessions) (Bandelow et al. 2022a).

Comparisons of massed vs. spaced CBT found equal efficacy (Ehlers et al. 2014; Foa et al. 2018).

Relationship of psychotherapy and pharmacotherapy

Psychotherapeutic and pharmacological treatment modalities should be seen as partners, not alternatives, in the treatment of anxiety disorders.

When comparing medications and psychotherapy, some methodological issues must be considered. Direct comparisons of psychotherapeutic and pharmacological interventions or their combination in randomised parallel group designs are rare. Some of these did not use, as a comparison, drugs that were

consistently shown to be effective in RCTs, and some did not use drugs in the recommended dose range.

In 70% of available studies, psychological treatments have been compared to a waitlist which is not an adequate control condition (see Section 'Evidence grading in psychotherapy studies'). Most meta-analyses comparing drugs and CBT examined treated-vs.-control effect sizes instead of pre-to-post effect sizes. This will result in a large treated vs. control effect size difference of Cohen's $d = 1.1$. In contrast, medications are usually compared with placebo, resulting in an effect size difference of only 0.7, which makes CBT appear superior. However, as waitlists produce only an average pre-post effect size of 0.2, while placebo has an effect of 1.3, this is not an adequate comparison.

A large meta-analysis using pre-to-post effect sizes found that the effect sizes of medications are substantially higher than those achieved with psychotherapy (Bandelow et al. 2015), demonstrating that only 60% of the improvement with medications can be achieved with psychotherapy.

In 85% of the psychotherapy studies for anxiety disorders, patients were not excluded when they were on ongoing medication (Bandelow et al. 2015), i.e. in a substantial number of participants of these studies, it is not possible to disentangle whether the improvement was due to the psychological treatment or to the additional drug treatment. It is problematic to give recommendations for psychotherapy as sole treatment when most of the studies have included medicated patients.

Pharmacotherapy is associated with many possible adverse effects. Psychotherapy may also have side effects (Moritz et al. 2019). Techniques like exposure and response prevention have high rates of therapy refusal and attrition due to unpleasant feelings during sessions and related anticipatory anxiety. Overreliance on the therapist has also been observed. Also, a relapse or deterioration in the symptoms is possible after or during psychological therapy. When a trial with a drug fails, there are several alternative medications that can be used so that the patient can achieve remission after 2, 3, or 4 drugs. However, when CBT fails, there are few alternative psychotherapy options.

Response to psychotherapy may be delayed and occurs usually later than with drug treatment. A prolonged course of treatment may be needed to maintain initial treatment response.

CBT is reputed to maintain its treatment gains over time, which would be a distinct advantage over medications and would also justify its higher treatment costs. However, a meta-analysis of follow-up studies revealed that not only psychotherapy, but also medications and, to a lesser extent, placebo can produce enduring effects after termination (Bandelow et al. 2018). Long-lasting treatment effects observed in the follow-up period may be confounded by effects of spontaneous remission or regression to the mean.

The choice between medications and CBT is determined by a number of factors, particularly the patient's preference, treatment options at hand, adverse drug effects, onset of efficacy, comorbidity (e.g. with depression), economic considerations, time availability and commitment of the patient, accessibility of psychiatric and psychological treatment resources, and qualification and experience of the clinician. Unfortunately, in many regions of the world, the availability of psychotherapy is often limited. Even in affluent countries, patients seeking treatment often must wait for many months to start psychotherapy. In many cases, patients who have started drug treatment while waiting for psychotherapy may already be in remission before they commence psychotherapy. By using internet psychotherapeutic interventions, waiting time may be reduced.

In everyday clinical practice, both treatments are often combined. In Europe, 57% of patients receiving psychotherapy are also on medication (Alonso et al. 2004b).

As psychotherapy and pharmacotherapy likely target different brain circuits, from a theoretical point of view, it can be assumed that they have additive effects. This is corroborated by the finding that evidence for the combination of both modalities is stronger than against it (for evidence from RCTs, see below).

Medication adherence can be improved by using psychotherapeutic and psychoeducational methods (Zomahoun et al. 2017).

Special treatment recommendations for the each disorder

In the following chapter, a systematic review of all available RCTs for the various anxiety disorders is presented. Tables containing all these studies can be found in the Supplementary Appendix.

How to read the tables with evidence information

For the recommendations in the following chapters, all available RCTs for the different treatment modalities have been analysed and tabulated. The decision on whether a treatment was effective or not was only

based on the acute treatment phase (endpoint scores or LOCF). Superiority or inferiority was indicated as '>' or '<', and equal efficacy as '='. In some cases, the statements regarding evidence for a certain treatment may differ from the statements in the original article, for example when a statistical re-evaluation led to a different conclusion. Usually, the decision regarding efficacy was based on the primary efficacy measure of a study. If many scales were used in a trial, a primary efficacy measure was not identified and there were no corrections for multiple testing, a *post hoc* Bonferroni-Holm correction was applied. Thus, in some cases, a statement that a certain treatment was superior to a control, was changed to 'no difference' after applying the Bonferroni correction. When equal efficacy of two treatments was found, although the sample size was not large enough for a non-inferiority trial, the comparison was marked as 'underpowered'. Studies comparing two active treatments ('non-inferiority comparisons') with ≤50 evaluable patients per treatment arm were considered underpowered.

In the evidence tables, the studies were marked as 'long-term' if the study duration was >20 weeks. 'Relapse prevention trials' were studies in which patients were first randomised to an active drug or placebo. In a second step, the responders to the active drug were again randomised to the active drug or placebo in order to determine how many participants in each group experienced a relapse during a period of 26–52 weeks.

Panic disorder and agoraphobia (PDA)

The summary of recommendations for the treatment of PDA is presented in Table 9. This table contains a reference to tables in the Supplementary Appendix in which all included RCTs are evaluated.

Medications

SSRIs and *SNRI venlafaxine* are considered to be first-line drugs for this disorder (LoE A/RG 1) (Table 9).

The TCAs clomipramine and imipramine are as effective as the SSRIs/SNRIs. However, the frequency of adverse events is higher for TCAs than for newer antidepressants, such as the SSRIs (Bystritsky et al. 1994; Bakish et al. 1996; Lecrubier and Judge 1997; Wade et al. 1997; Lepola et al. 1998; Amore et al. 1999; Bakker, van Dyck, et al. 1999) (LoE A/RG 2). For *desipramine* and *lofepramine*, only one DBPC study exists (LoE B/RG 3).

Benzodiazepines have shown sufficient evidence of efficacy for PDA; however, they are potentially addictive (LoE A/RG 2). In clinical practice, benzodiazepines are often combined with SSRIs, SNRIs or TCAs. In a study examining this combination, patients were treated with paroxetine and clonazepam or with paroxetine and placebo. Combined treatment with paroxetine and clonazepam resulted in more rapid response than with the SSRI alone, but there was no differential benefit beyond the initial few weeks of therapy (Pollack et al. 2003). Similar placebo-controlled studies involved a combination of imipramine and alprazolam (Woods et al. 1992) or of sertraline and clonazepam (Goddard et al. 2001). Both studies showed a faster response to these combinations than to imipramine or sertraline plus placebo, respectively.

In acute panic attacks, reassurance of the patient may be sufficient in most cases. In severe attacks, fast-acting benzodiazepines may be needed.

The *irreversible monoamine oxidase inhibitor phenelzine* was only studied in one trial; due to possible severe interactions with food components or other drugs the drug should only be used when treatments with a higher recommendation grade have failed (LoE B/RG 3).

The evidence for the *RIMA moclobemide* is inconsistent. DBPC studies did not show superiority to placebo; however, two adequately powered studies showed equal efficacy to standard treatments (LoE D/RG 4). It can be tried when other standard treatments were ineffective or not tolerated.

For *mirtazapine*, only one underpowered comparison trial exists (LoE D/RG 4).

No efficacy in the treatment of PDA was found for *buspirone*, *propranolol* and *trazodone* (LoE A-/RG 1-).

Long-term treatment. Typically, panic disorder has a waxing and waning course. After remission, treatment should continue for at least several months to prevent relapse. Several studies have investigated the long-term value of drug treatments. Relapse prevention studies can also be used to estimate the necessary length of treatment.

In summary, the SSRIs citalopram, fluoxetine, paroxetine, and sertraline, the SNRI venlafaxine, the TCAs clomipramine and imipramine, and the benzodiazepine alprazolam have shown long-term efficacy in these studies (see Table 5, Supplementary Appendix) which had a duration between 24 and 104 weeks. These studies suggest that after remission, an additional 6–12 months of treatment is recommended. In some individuals, many years of treatment may be warranted.

Table 9. Summary of recommendations for the treatment of panic disorder (PDA).

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 5
SSRIs	Citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline are first-line treatments	A	1	
SNRI	Venlafaxine is a first-line treatment	A	1	
TCAs	Clomipramine and imipramine are effective, but are less well tolerated than the SSRIs/SNRIs	A	2	
	Desipramine and lofepramine were effective in one DBPC each	B	3	
Benzodiazepines	Alprazolam, clonazepam, diazepam and lorazepam may be used in treatment-resistant cases, when the patient does not have a history of substance use disorder. They may also be used in patients with severe somatic disorder, when standard treatments are not effective or contraindicated, and in suicidal patients.	A	2	
	Benzodiazepines can be combined with antidepressants in the first weeks of treatment before the onset of efficacy of the antidepressants.	B	2	
MAOI	Phenelzine was effective in one DBPC. Due to adverse effects and possible serious interactions, it should only be used as third-line treatment	B	3	
RIMA	The evidence for moclobemide is inconsistent. It can be tried when other standard treatments were ineffective or not tolerated	D	4	
NaSSA	For mirtazapine, only one underpowered comparison trial exists	D	4	
Azapirone (5-HT_{1A} agonist)	Buspirone is not effective	A-	−1	
Beta Blocker	Propranolol is not effective	A-	−1	
SARI	Trazodone is not effective	A-	−1	
Psychotherapy				Table 6
Cognitive behavioural therapy (CBT)	CBT/exposure therapy for PDA is more effective than a waitlist condition but shows inconsistent results in comparison to active controls, with more studies showing no difference than showing superiority. A meta-analysis found only a small difference between CBT and active controls. CBT also shows inconsistent results in comparison to drug treatment, with more studies showing inferiority than showing equal efficacy	A	1	
Internet interventions based on CBT (iCBT)	iCBT was superior to waitlist in most studies, more effective than relaxation and as effective as personal CBT. Internet interventions are only recommended for bridging the waiting period for personal CBT or as add-on to standard treatments	B	2	
Applied relaxation (AR)	The evidence for AR is inconclusive. AR was superior an active control, progressive muscle relaxation. Some underpowered studies show equal efficacy in comparison to CBT, while others show inferiority to CBT and imipramine	D	4	
Psychodynamic therapy (PdTh)	PdTh was not tested against a waitlist condition. In comparison to active controls, it was not superior or even less effective. In comparison to CBT, it was less effective	A-	1-	
EMDR	EMDR was not superior to waitlist or psychological placebo	A-	1-	
Combination of psychotherapy and medication				Table 7
CBT vs. drug	Evidence is inconclusive whether CBT is as effective as medications. Most studies showed no difference, however, most of these studies were underpowered. 5 studies showed superiority of drug treatment and 2 showed superiority of CBT	D	4	
Combination vs. CBT alone	The combination of CBT + drug is more effective than CBT alone	A	1	
Combination vs. drug alone	The combination of CBT + drug is not more effective than drug alone	B-	2-	
Augmentation of CBT with D-cycloserine	Data on combining D-cycloserine with CBT/exposure are inconclusive, with 2 studies showing superiority to placebo and 3 studies showing no effect	D	4	Table 9
Exercise	Exercise was superior to pill placebo, but less effective than clomipramine. In another study, it was no more effective than an active control (relaxation). It should not be used as monotherapy, but as add-on to standard treatments.	B	2	Table 10

LoE: Level of evidence; RG: recommendation grade; RCTs (suppl.): tables showing randomised controlled studies in Supplementary Appendix; SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin-norepinephrine reuptake inhibitor; TCA: tricyclic antidepressant; RIMA: Reversible inhibitor of monoamine oxidase A; CBT: cognitive behavioural therapy; iCBT: internet interventions based on CBT; AR: applied relaxation; PdTh: psychodynamic therapy; EMDR: eye movement desensitisation therapy; DBPC: double-blind placebo-controlled study.
The colors indicate the recommendation levels (see Table 4, Part I): RG = 1, dark green; RG = 2, light green; RG = 3, yellow; RG = 4, grey; RG = 1-, dark red; RG = 2-, light red.

Regarding SSRIs, the same doses are usually prescribed in the maintenance treatment of panic disorder as in the acute treatment phase. There are no studies examining reduced doses of SSRIs in maintenance treatment. In an open study with the TCA imipramine, patients stabilised on imipramine who received further treatment with half their previous dose of imipramine did not show relapse or sustained worsening (Mavissakalian and Perel 1992).

Comparisons of antipanic drugs. In studies comparing TCAs and SSRIs, no differences in terms of efficacy were found between the two classes of drugs (Bystritsky et al. 1994; Bakish et al. 1996; Lecrubier and

Judge 1997; Wade et al. 1997; Amore et al. 1999; Bakker, Spinhoven, et al. 1999; Cavaljuga et al. 2003), with the exception of the tetracyclic antidepressant maprotiline, which had no effect in contrast to fluvoxamine (Den Boer and Westenberg 1988). In most of these studies, the SSRIs were better tolerated than the TCAs, although one analysis did not find a difference in tolerability between SSRIs and imipramine (Otto et al. 2001). Also, in patients with comorbid panic disorder and major depressive disorder, sertraline and imipramine were equally effective, but sertraline showed significantly greater tolerability and compliance than imipramine (Lepola et al. 2003).

Some comparisons among the SSRIs did not reveal differences with regard to efficacy (Perna et al. 2001; Bandelow et al. 2004), while escitalopram showed evidence of superiority over citalopram on some outcome measures (Bandelow et al. 2007).

There are no direct double-blind comparisons between SSRIs and benzodiazepines in the treatment of panic disorder. In open comparisons of clonazepam and paroxetine, clonazepam demonstrated a faster onset of action and greater clinical improvement than paroxetine, and in both short-term and long-term treatment, clonazepam was better tolerated (Nardi et al. 2011; Nardi et al. 2012; Freire et al. 2017). According to a meta-analysis, the effect sizes for the SSRIs were higher than for the benzodiazepine alprazolam (Boyer 1995).

Another meta-analysis found that in acute (short-term) treatment of panic disorder, SSRIs were associated with more adverse effects than benzodiazepines (Quagliato et al. 2019).

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

In a meta-analysis of all available studies for the treatment of anxiety disorders, pre-to-post effect sizes were used, making it possible to compare all medications with regard to their efficacy across the studies (Bandelow et al. 2015). In this study, large differences were found between the various drugs. Drugs that show high efficacy in this meta-analysis and have a recommendation grade of 1, included escitalopram, paroxetine, and venlafaxine.

Medications for treatment-resistant panic disorder. When initial treatments have failed and after the doses were increased to the maximum tolerated doses, patients should first be switched to other first-line standard treatments, e.g. from an SSRI to an SNRI or *vice versa*. As the SSRIs are chemically different compounds, a switch from one SSRI to another is also justified. As the next step, second-line drugs should be tried. Lastly, drugs or drug combinations that were effective in open studies and case reports may be an option (see also Chen and Tsai 2016)).

Psychotherapy

In Table 9, levels of evidence and recommendation grades for psychotherapies for PDA are provided. The table contains references to lists of the included RCTs in the Supplementary Appendix.

Cognitive behavioural therapy. CBT has been investigated thoroughly in PDA. Exposure therapy is used to treat agoraphobia, and cognitive techniques including interoceptive exposure were developed for treating spontaneous panic attacks. Although CBT is the psychotherapeutic modality with the best body of evidence for PDA, it was mostly tested against waitlist controls. When CBT was tested against active control groups, e.g. psychological placebo, pill placebo, relaxation, self-exposure or TAU, no significant difference was found in the majority of studies. Therefore, a metaanalysis was performed accrding to the principles of this guideline.

Meta-analysis. Our meta-analysis of studies comparing CBT with active controls showed a significant but small difference between CBT and active controls (Cohen's $d = 0.23$; CI 0.02–0.44; $p = .035$; Figure 2, Supplementary Appendix) (LoE A/RG 1).

A previous meta-analysis has shown that CBT is markedly less effective than medications in (Bandelow et al. 2015) and had an average pre-post effect size on the same level as pill placebos.

In some direct comparisons, CBT was as effective as medications, and in one study it was even more effective. However, some of those comparison studies showing equal efficacy were underpowered and therefore not reliable. On the other hand, several studies showed superiority of drug treatment over CBT.

CBT was shown to be more effective than psychodynamic psychotherapy in a number of studies. However, as the evidence for psychodynamic therapy is negative, these results cannot be used as proof for the efficacy of CBT.

Applied relaxation. AR for PDA has only been shown to be more effective than progressive muscle

relaxation as a control. Studies comparing AR with CBT are inconclusive. Also, studies comparing AR with psychodynamic therapy show diverging results, as they have shown inferiority, superiority or equal efficacy to psychodynamic therapy, which itself cannot be regarded as effective treatment (LoE D/RG 4).

Internet interventions based on CBT (iCBT). Cognitive behavioural interventions delivered via Internet (iCBT) by using computers, tablets or smartphones were superior to waitlist in most studies, more effective than an active control in one study (relaxation) and as effective as personal CBT. Internet interventions are only recommended for bridging the waiting period for personal CBT or as add-on to standard treatments (LoE B/RG 2).

According to a meta-analysis using pre-to post effect sizes, iCBT was marginally less effective than face-to-face CBT. In comparison to medication, iCBT was less effective (Bandelow and Wedekind 2022). There were concerns that the effect sizes of iCBT interventions may be overestimated in the available studies mainly because most of the studies were not based on blinded assessments. In only 15% of the studies, diagnoses were made in personal contact with a psychiatrist or psychologist. There were also concerns regarding the representativity of the studies, as the majority of participants had an academic background.

Therefore, iCBT for PDA should only be used in patients waiting for face-to-face CBT or as an add-on to face-to-face CBT or drug treatment.

Psychodynamic psychotherapy (PdTh). For PDA, there are no comparisons of PdTh against waitlist. In comparison to 'no treatment' or active controls, no differences were found. In one study, psychodynamic therapy was even less effective than the control treatment, relaxation. In comparison to CBT, the majority of studies showed inferiority of PdTh. Because of this strong evidence for non-efficacy, there is advice against the use of psychodynamic therapy in PDA (LoE A-/RG 1-).

Eye movement desensitization and reprocessing (EMDR). EMDR for PDA showed negative results (LoE A-, RG 1-).

Comparisons of psychotherapeutic and pharmacological interventions and their combination

Most trials that have compared psychotherapy (mostly CBT) and various medications did not find a difference; however, most of these studies were underpowered (Table 7; Supplementary Appendix). Five studies found superiority of medication, while two studies found superiority of CBT (LoE D/RG 4).

A meta-analysis that used pre-post effects found superiority of drug treatment over psychotherapy (Bandelow et al. 2015).

The majority of studies showed that the combination of psychotherapy plus medication was superior to psychotherapy alone (LoE A/RG 1). While three studies did not demonstrate superiority of the combination over medication alone, one small study found that the combination was more effective than imipramine alone (LoE B-/RG 2-).

In studies without control condition, patients having residual symptoms despite being on an adequate dose of medication showed improvement after the introduction of CBT (Pollack et al. 1994; Heldt et al. 2003).

Enduring effects. It is often contended that gains from CBT are maintained after termination of treatment, while patients on drugs immediately have a relapse of anxiety symptoms after medication is stopped. This, if true, would suggest a considerable advantage of CBT over drug treatment. However, follow-up studies directly comparing the durability of CBT with drug therapy did not clearly show longer 'durability' of CBT. Two studies showed an advantage for CBT, one showed superiority of medication and three studies showed no difference (LoE D) (Table 8, Supplementary Appendix).

As there are only few follow-up studies that directly compare enduring effects of psychotherapy with those in a control group, a meta-analysis of all studies in which patients were followed up after treatment termination was conducted which compared pre-to-post effect size differences, allowing the inclusion of many more studies (Bandelow et al. 2018). In this analysis, it was found that gains with CBT and other psychotherapies were maintained for up to 24 months. However, medications, and, to a lesser extent, placebo conditions also demonstrated enduring effects in the meta-analysis. The problem in follow-up studies is that the outcome is confounded by other treatments. In the case of a relapse, patients will utilise all kinds of treatments outside the study protocol, and many will resume the treatment that was helpful in the treatment period. Also, the long-lasting treatment effects observed in the follow-up period may be superimposed on the effects of spontaneous remission or regression to the mean.

Enhancing CBT/exposure with D-cycloserine. Several studies examined whether D-cycloserine, a partial NMDA receptor agonist, might facilitate fear extinction and exposure therapy by either enhancing NMDA receptor function during extinction or by reducing NMDA receptor function during fear memory consolidation (Table 9). However, results were inconsistent, with the majority of studies showing no effect of the combination (LoE D/RG 4).

Exercise

Only two controlled studies have been performed to assess the usefulness of exercise for PDA (Table 9). In the first controlled study examining the role of exercise in an anxiety disorder, patients with PDA were randomly assigned to three treatment modalities: running, clomipramine or placebo. Both exercise and clomipramine led to a significant decrease of symptoms in comparison to placebo; however, exercise was significantly less effective than clomipramine. In a second study, a combination of drug treatment and exercise was investigated. Patients received paroxetine or placebo in a double-blind manner. Additionally, patients in both groups were randomly allocated to exercise or a control group doing relaxation training. Whereas paroxetine was superior to placebo, exercise did not differ from the control group, perhaps due to the high effect sizes attained in the latter treatment modality. Taking the results of both studies together, exercise seems to have some effect in panic disorder, however, this effect seems to be less pronounced than the effect of medication. Exercise should not be used as the sole treatment for PDA, but it can be combined with other standard treatments such as medication or psychotherapy (LoE B/RG 2).

Generalised anxiety disorder (GAD)

Recommendations for the treatment of GAD are summarised in Table 10.

Medications

Drug treatment recommendations for GAD are listed in Table 10. First-line drugs for GAD include *SSRIs (escitalopram, paroxetine, and sertraline)* and *SNRIs (duloxetine, venlafaxine)*. (LoE A/RG 1). *Citalopram* was only evaluated in a study with elderly patients, in which it was superior to placebo (LoE B/RG 2 for elderly patients).

The melatonin agonist/5-HT_{2C} antagonist *agomelatine* was effective in several DBPC and comparator studies and a relapse prevention study (LoE A/RG 1).

Three studies showed the efficacy of *vilazodone* in GAD. However, GAD studies comparing vilazodone with reference drugs are lacking, and so are long-term studies (LoE A/RG 2).

The *TCA imipramine* is also effective, but less well tolerated than SSRIs and SNRIs (LoE B/RG 2).

Pregabalin has a good record of evidence but is only recommended as second line due to abuse potential which was mainly observed in individuals with substance abuse (LoE A/RG 2).

The *benzodiazepines alprazolam, bromazepam, diazepam* and *lorazepam* are effective, but are only recommended if first-line treatment with an SSRI or SNRI is ineffective or not tolerated (LoE A/RG 2). In a meta-analysis of GAD studies, benzodiazepines had somewhat greater efficacy than SSRIs/SNRIs (Gomez et al. 2018).

Efficacy of the antihistamine *hydroxyzine* was established in some RCTs. However, long-term studies are lacking with this drug (LoE A/RG 3). Day-time sedation may be a problem. The medication is not used frequently.

The atypical antipsychotic *quetiapine* is usually prescribed in the treatment of schizophrenia or bipolar disorder in doses between 150 and 800 mg/d (Falkai et al. 2005). For the treatment of GAD, lower doses (50–300 mg/day) are adequate. There are concerns regarding the side effect profile, including e.g. metabolic syndrome in long-term therapy and arrhythmias (LoE A/RG 3).

Opipramol is a tricyclic anxiolytic that is widely used in some countries in Europe. However, only one RCT exists (LoE B/RG 3).

Trazodone was superior to placebo and as effective as imipramine and diazepam in one RCT. Long-term studies are lacking (LoE B/RG 3).

The anticonvulsant *valproate* was shown to be effective in a DBPC study (LoE B/RG 3).

A *lavender oil extract* was effective in GAD. Long-term studies are missing (LoE B/RG 3).

The 5 HT_{1A}-agonist *buspirone* was superior to placebo in 6 studies, but 3 studies failed to show a significant difference to placebo. Some comparisons with established anxiolytic drugs showed lesser efficacy. Long-term and relapse prevention studies are lacking (LoE D/RG 4).

The antidepressant *vortioxetine* is a serotonin transporter (SERT) inhibitor also acting as a 5-HT_{1B} partial agonist, a 5-HT_{1A} agonist and a 5-HT_3 and 5-HT_7 antagonist. Although two adequately powered DBPC studies have been positive in GAD (one study was for acute treatment and one was for relapse prevention), three other adequately powered

Table 10. Summary of recommendations for the treatment of GAD.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 11
SSRIs	The SSRIs escitalopram, paroxetine, and sertraline are first-line treatments for GAD	A	1	
SNRIs (venlafaxine, duloxetine)	The SNRIs venlafaxine and duloxetine are first-line treatments for GAD	A	1	
MT_1/MT_2 agonist/5-HT_{2C} antagonist agomelatine	Results with agomelatine were positive	A	1	
TCA imipramine	Imipramine is effective in GAD, but its potential lethality in case of overdose, as well as its lower tolerability, puts it as a second-line option	A	2	
Calcium modulator pregabalin	Pregabalin has consistently shown efficacy for GAD, however, it should only be used as a second-line option due to its abuse potential	A	2	
SSRI/5-HT_{1A} receptor partial agonist vilazodone	Vilazodone was shown to be effective in double-blind studies, however, comparator studies and long-term studies are lacking	A	2	
Benzodiazepines	The benzodiazepines alprazolam, bromazepam, diazepam, and lorazepam may be used in treatment-resistant cases, when the patient does not have a history of substance use disorder. Also, they can be combined with antidepressants in the first couple of weeks of treatment before the onset of efficacy of the antidepressants	A	2	
Antihistamine hydroxyzine	Hydroxyzine was effective in placebo- and comparator-controlled studies. Long-term studies are lacking	A	3	
Antipsychotic quetiapine	Results with quetiapine were positive; however, there are concerns regarding the side effect profile (e.g. metabolic syndrome)	A	3	
Tricyclic anxiolytic opipramol	For opipramol, limited positive evidence is available (only one placebo- and comparator-controlled study). Long-term studies are lacking	B	3	
SARI trazodone	Trazodone was superior to placebo and as effective as imipramine and diazepam in one RCT. Long-term studies are lacking	B	3	
Anticonvulsant valproate	Valproate was shown to be effective in a double-blind placebo-controlled study	B	3	
Lavender oil extract	For lavender oil, limited positive evidence is available (only one placebo and comparator-controlled study). Long-term studies are lacking	B	3	
Azapirone buspirone	Buspirone was superior to placebo in 7 studies, but 3 studies failed to show a significant difference to placebo. Some comparisons with established anxiolytic drugs showed lesser efficacy. Long-term and relapse prevention studies are lacking	D	4	
Serotonergic drug vortioxetine	Vortioxetine was superior to placebo in 2 studies, but 3 studies were negative	B-	2-	
Medications for treatment-refractory GAD				Table 12
Olanzapine as add-on to fluoxetine	In treatment-refractory GAD patients, olanzapine as add-on to fluoxetine may be used	B	3	
Pregabalin as add-on to antidepressants	In treatment-refractory GAD patients, pregabalin may be used as add-on to antidepressants (SSRIs/SNRIs)	B	3	
Psychotherapy				Table 13
Cognitive behavioural therapy (CBT)	CBT was more effective than waitlist controls but did not show a significant difference to active controls in the meta-analysis	B	2	
Internet interventions based on CBT (iCBT)	iCBT was superior to waitlist in most studies. However, comparisons to active controls are lacking. Internet interventions are only recommended for bridging the waiting period for face-to-face CBT or as add-on to standard treatments	D	4	
Applied relaxation (AR)	AR showed inconsistent data when compared to waitlist psychological placebos, and there is inconsistent evidence whether it is as effective as CBT	B-	2-	
Psychodynamic therapy (PdTh)	For PdTh, evidence is lacking that it is more effective than waitlist or psychological placebo controls, and it seems to be less effective than CBT	B-	2-	
Internet psychodynamic therapy	Internet psychodynamic therapy did not differ from a waitlist condition in the only available study	B-	2-	
Combination of psychotherapy and medication				
Combination of CBT and medication	Data on the combination of CBT and drug treatment are inconclusive. CBT + diazepam is more effective than diazepam alone, but not more effective than CBT alone. Adding CBT to venlafaxine treatment was not superior to venlafaxine alone	D	4	Table 14

RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.
The colors indicate the recommendation levels (see Table 4, Part I): RG = 1, dark green; RG = 2, light green; RG = 3, yellow; RG = 4, grey; RG = 2-, light red.

RCTs have been negative. Therefore, the evidence does not support vortioxetine for use in GAD (LoE B-/RG 2-).

Long-term treatment. GAD is generally a chronic disorder and requires long-term treatment. In many patients, GAD has a waxing and waning course. After remission, treatment should continue for at least several months to prevent relapse. According to relapse prevention studies, treatment with escitalopram, paroxetine, venlafaxine, duloxetine, pregabalin, agomelatine, quetiapine and vortioxetine was more

effective in preventing relapses than placebo (Table 11, Supplementary Appendix).

Benzodiazepines can only be used for long-term treatment when other drugs have failed. Such failure should be clearly documented in the notes.

Medications for treatment-resistant GAD. A few studies investigated the addition of atypical antipsychotics and other drugs in patients remaining symptomatic despite initial standard medication treatment (Table 10). Only the addition of *olanzapine* or *pregabalin* to an SSRI was shown to be effective in treatment-refractory cases.

Psychotherapy

Levels of evidence and recommendation grades for psychotherapeutic interventions for GAD are summarised in Table 10.

Cognitive behavioural therapy. Several studies showed that CBT for GAD was superior to waitlist conditions; however, CBT did not consistently demonstrate superiority over active controls.

Meta-analysis. Our meta-analysis of studies with active controls showed only a trend for a significant difference between CBT and active controls (small effect size: Cohen's $d = 0.44$ (−0.08–0.96); $p = .098$) (Figure 3; Supplementary Appendix) (LoE B/RG 2).

Also, another meta-analysis showed that CBT exerted greater effects than waitlist groups but did not have greater effects compared with psychological placebo (Chen et al. 2019).

Internet interventions based on CBT. Several studies showed that iCBT was superior to waitlist; only in one study, it was not significantly different from this control condition. One study showing equal efficacy to face-to-face CBT was underpowered. More adequately powered studies comparing iCBT with active controls have to be undertaken (LoE D/RG 4).

Applied relaxation. AR was more effective than waitlist in one study, but not better than waitlist in another study. One study showed similar efficacy as CBT, but two studies showed superiority of CBT (LoE B-/RG 2-).

Psychodynamic therapy. The evidence for PdTh is weak. One GAD study showed it was less effective than CBT. Another study that was underpowered for a non-inferiority comparison did not report a significant difference of the primary efficacy measure between PdTh and CBT; however, there were large numerical differences in all scale scores in favour of CBT which perhaps did not reach significance because of the small sample size. Studies showing that PdTh is more effective than waitlist or psychological placebo are lacking. Thus, PdTh cannot be recommended for GAD (LoE B-/RG 2-).

Internet psychodynamic therapy for GAD did not differ from a waitlist condition as demonstrated in the only available study (LoE B-/RG 2-).

Comparisons of psychotherapy and pharmacotherapy and their combination

Only two studies compared the combination of CBT and drug treatment with the monotherapies. One found that the combination of CBT and diazepam is more effective than diazepam alone, but not more effective than CBT alone.

Another study found that adding CBT to venlafaxine did not differ from venlafaxine alone.

Altogether, due to the lack of conclusive evidence, no recommendations regarding the combination of medications and psychotherapy can be given (LoE D/RG 4).

Exercise

In a small study, two forms of exercise, weightlifting and cycling, were compared with a waitlist control in women who were treated with pharmacotherapy for GAD (Herring et al. 2012). There were no significant differences between both exercise conditions and waitlist.

GAD, separation anxiety disorder and mixed anxiety disorders in children and adolescents

Some fears children express are a natural, transient phenomenon and do not have to be treated at all.

For example, 1-year-old children are afraid of strangers, heights or loud noises. Two- to four-year-olds are afraid of certain animals and of the dark. Four- to six-year-olds often may have a fear of ghosts or of thunder and lightning. In the first school years, blood/injury phobias and separation anxiety are common. From the age of eight, fears of failure in sports or at school are also common. Simple phobias such as fears of animals are also found at this age. From the age of twelve, the first social fears appear. However, 'major' anxiety disorders such as PDA or GAD are rare in childhood and adolescence.

While there are some RCTs for the treatment of children and adolescents with GAD, there are no studies in which children or adolescents with pure GAD have been treated with psychotherapy, perhaps because of the difficulty in differentiating the various anxiety disorders in children and the considerable overlap of these conditions. There are almost no studies which exclusively included individuals with separation anxiety disorder. However, several studies have been conducted with mixed samples which included children and adolescents with GAD, SAD, and separation anxiety disorders. Therefore, we did not abide by the general principle of this guideline to exclude studies in individuals with mixed diagnoses when assessing efficacy of treatments for this population.

The recommendations for the treatment of mixed anxiety disorders are summarised in Table 11.

Medications for children and adolescents with GAD, separation anxiety disorder and mixed anxiety disorders

The SSRIs *fluvoxamine* and *sertraline* were effective in treating GAD/mixed anxiety disorders in children and adolescents (Table 11) (LoE A/RG 1). For the SSRIs *escitalopram* and *fluoxetine* and the SNRIs *duloxetine* and *venlafaxine*, one placebo-controlled study each is available (LoE B/RG 2).

Alprazolam was not superior to placebo in a DBPC study (LoE B-/RG 2-).

Regarding an increased risk of suicidal ideation and behaviour associated with antidepressant treatment of young people aged less than 25 years, see Section 'Treating children and adolescents'.

Despite the sufficient evidence for treatment with antidepressants, some clinicians think that it may be preferable to reserve pharmacological treatments only for patients who do not respond to psychotherapeutic approaches.

Psychotherapies for children and adolescents with separation anxiety disorder and mixed anxiety disorders

The evidence for CBT for children and adolescents with separation anxiety disorder and mixed anxiety disorders is inconclusive, as several studies did not show its superiority to waitlist, and the majority of comparisons with active controls did not show better efficacy (Table 11).

Meta-analysis

Our meta-analysis of studies with active controls did not show a significant difference between CBT and active controls (Cohen's $d = 0.15$; −0.05–0.35); $p = .13$; N.S.) (Figure 7; Supplementary Appendix) (LoE D/RG 4).

Combination of psychotherapies and medications for children and adolescents with mixed anxiety disorders

One study compared a combination of CBT and sertraline. The combination was superior to both monotherapies, and both monotherapies were superior to placebo (Table 11).

In a DBPC study with children with separation anxiety disorder who failed to respond to CBT, both *imipramine* and placebo lead to improvements, with no significant difference (Klein et al. 1992).

Table 11. Summary of recommendations for the treatment of GAD, separation anxiety disorder and mixed anxiety disorders in children and adolescents.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 15
SSRI fluvoxamine and sertraline	Fluvoxamine demonstrated efficacy in DBPC studies	A	1	
SSRIs escitalopram and fluoxetine	Fluoxetine and sertraline showed efficacy in one DBPC study each	B	2	
SNRIs duloxetine and venlafaxine	Duloxetine and venlafaxine showed efficacy in one DBPC study each	B	2	
Benzodiazepine alprazolam	Alprazolam was not superior to placebo in one study	B-	2-	
Psychotherapy				Table 16
Cognitive behavioural therapy (CBT)	The evidence for CBT/exposure therapy is inconclusive. CBT was more effective than a waitlist condition in some, but not all studies, and showed inconsistent results in comparison to active control conditions, with most studies showing no difference. CBT was as effective as sertraline in one study. The meta-analysis revealed no significant difference between CBT and active controls.	D	4	
Combination of psychotherapy and medication				Table 15
Combination of CBT and sertraline	In one study, the combination was superior to both monotherapies, and both monotherapies were superior to placebo	B	2	

RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.
The colors indicate the recommendation levels (see Table 4, Part I): RG = 1, dark green; RG = 2, light green; RG = 4, grey; RG = 2-, light red.

Separation anxiety disorder in adults

For separation anxiety disorders in adults, no recommendation can be given due to the lack of studies. In a DBPC study with a very small sample size, *vilazodone* for adult separation anxiety disorder did not differ from placebo (Schneier et al. 2017).

Social anxiety disorder (social phobia; SAD)

Recommendations for the treatment of SAD are summarised in Table 12.

Medications

The recommendations for drug treatment of SAD are shown in Table 12.

The SSRIs *escitalopram, fluvoxamine, paroxetine, sertraline* are first-line drugs for the treatment of SAD (LoE A/RG 1). For *citalopram*, only one DBPC study exists (LoE B/RG 2). The evidence for *fluoxetine* is inconclusive (LoE D/RG 4).

The SNRI *venlafaxine* is a first-line drug for the treatment of SAD (LoE A/RG 1). The SNRI *desvenlafaxine* did not differ from placebo in one study (LoE B-/RG 2-).

The calcium channel modulator *pregabalin* was effective in RCTs (LoE A/RG 2). *Gabapentin* was also effective in one study (LoE B/RG 2).

The MAOI *phenelzine* was shown to be effective; however, due to its unfavourable adverse effects profile and possible interactions with certain types of food and medications, the drug should only be used in otherwise treatment unresponsive patients (LoE A/RG 2).

The results with the reversible inhibitor of monoamine oxidase A (RIMA) *moclobemide* were inconsistent. The compound was superior to placebo in some studies, while it failed to separate from placebo in two studies. It showed similar efficacy to phenelzine.

Meta-analysis. A meta-analysis of studies comparing moclobemide with placebo showed a significant difference between moclobemide and placebo (small effect size: Cohen's $d = 0.33$; CI 0.17–0.50; $p < .0001$; Figure 6; Supplementary Appendix) (LoE B/RG 2).

The benzodiazepines *bromazepam* and *clonazepam* were effective in one placebo-controlled study each; however, due to possible discontinuation symptoms, these medications should only be used second in line (LoE B/RG 2).

The antidepressant *mirtazapine* was effective in one study (LoE B/RG 2).

The NMDA receptor antagonist *ketamine* (i.v.) was effective in one DBPC study (LoE B/RG 3).

Buspirone was not effective in the only DBPC study (LoE B-/RG 2-).

The beta blocker *atenolol* failed to show efficacy in two DBPC studies with SAD patients (LoE A-/RG 1-).

Long-term treatment. SAD is generally a persistent condition and requires long-term treatment. Controlled maintenance studies with a duration of 6–12 months also suggest treatment to be continued for this period, as significantly more relapses occurred in the patients treated with placebo. Escitalopram, paroxetine, sertraline, venlafaxine, phenelzine and moclobemide were more effective than placebo in preventing relapses (Table 16, Supplementary Appendix).

Medications for treatment-resistant SAD. In one study, non-responders to sertraline were randomised to ongoing sertraline (plus placebo), sertraline plus clonazepam, or venlafaxine. While there was a numerical advantage for the addition of clonazepam relative to a switch to venlafaxine or continuation on sertraline (plus placebo), the difference between clonazepam and placebo augmentation was not statistically significant, nor was the difference between venlafaxine and sertraline plus placebo (Pollack et al. 2014).

Psychotherapy

Evidence for psychotherapies is summarised in Table 12. *CBT* for SAD was more effective than waitlist conditions. However, of 14 comparisons with active control conditions, only two showed a significant difference. CBT was less effective than drug treatment in one study.

Meta-analysis. Our meta-analysis of studies with active controls showed a significant difference between CBT and active controls, however, the difference is small (Cohen's $d = 0.27$; CI 0.10–0.43; $p = .001$) (Figure 5; Supplementary Appendix) (LoE A/RG 1).

Internet psychotherapeutic interventions based on CBT (iCBT) were superior to waitlist in most studies. Comparisons with active controls are lacking. In several studies, iCBT was as effective as face-to-face CBT. Internet interventions are only recommended for bridging the waiting period for personal CBT or as add-on to standard treatments (LoE B/RG 2).

Virtual reality exposure therapy was superior to waitlist in 2 of 3 studies. In comparison to *in vivo* exposure, it was equally effective in one underpowered study, and less effective in another (LoE D/RG 4).

Table 12. Summary of recommendations for the treatment of SAD.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 17
SSRIs	Escitalopram, fluvoxamine, paroxetine, and sertraline are first-line treatments for SAD	A	1	
SNRI venlafaxine	Venlafaxine is a first-line treatment for SAD	A	1	
Calcium modulator pregabalin	Pregabalin was effective in some double-blind placebo-controlled studies, however, it should only be used as a second-line option due to its possible abuse potential	A	2	
Irreversible MAOI phenelzine	The efficacy of phenelzine has been shown in RCTs, however, due to possible adverse effects and interactions with other drugs and foods, the drug should only be used when standard treatments have failed or were not tolerated	A	2	
SSRI citalopram	One double-blind placebo-controlled study showed efficacy of citalopram	B	2	
Benzodiazepines	The benzodiazepines bromazepam and clonazepam were effective in one DBPC study each. In treatment-resistant cases, the benzodiazepines may be used in patients without a history of substance use disorder. They may also be used in patients with severe somatic disorder when standard treatments are not effective or contraindicated: The have a role in the acute treatment of suicidality. Also, they can be combined with antidepressants in the first weeks of treatment before the onset of efficacy of the antidepressants	B	2	
RIMA moclobemide	The evidence for moclobemide is inconsistent, with two studies showing no difference to placebo. Meta-analysis showed only a small effect size difference to placebo	B	2	
NaSSA mirtazapine	One DBPC study showed efficacy of mirtazapine	B	2	
Calcium modulator gabapentin	One DBPC study showed efficacy of gabapentin	B	2	
NMDA receptor antagonist ketamine	One DBPC study showed efficacy of ketamine	B	3	
SSRI fluoxetine	One DBPC study showed efficacy of fluoxetine, while two studies were negative	D	4	
SNRI desvenlafaxine	A DBPC study did not show efficacy of desvenlafaxine	B-	2-	
Azapirone buspirone	A DBPC study did not show efficacy of buspirone	B-	2-	
Beta blocker atenolol	Two DBPC studies did not show efficacy of atenolol	A-	1-	
Psychotherapy				Table 18
Cognitive behavioural therapy/exposure (CBT)	CBT therapy for SAD was more effective than waitlist conditions. However, of 14 comparisons with active control conditions, only 2 showed a significant difference. A meta-analysis showed a significant difference between CBT and active controls; however, the difference is small. CBT was less effective than drug treatment in one study	A	1	
Internet interventions based on CBT (iCBT)	iCBT was superior to waitlist in most studies, however, comparisons to active controls are lacking. It was as effective as personal CBT. Internet interventions are only recommended for bridging the waiting period for personal CBT or as add-on to standard treatments	B	2	
Virtual reality therapy	Virtual reality therapy was superior to waitlist in 2 of 3 studies. In comparison to *in vivo* exposure, it was equally effective in an underpowered study, and less effective in another study	D	4	
Internet intervention based on PdTh (iPdTh)	iPdTh was superior to waitlist in one study. Comparisons with active controls are lacking. iPdTh is only recommended for bridging the waiting period for face-to face psychotherapy or as add-on to standard treatments when other forms of psychotherapy have failed, including iCBT	D	4	
Psychodynamic therapy (PdTh)	PdTh has not been tested against a waitlist condition. In comparison with an active control, it was not superior. In comparison with CBT, it was less effective	A-	1-	
Combination of psychotherapy and medication				Table 19
CBT + anxiolytic drugs	Data on combining CBT and various medications for SAD are inconclusive	D	4	
Enhancing CBT with D-cycloserine				Table 20
CBT + d-cycloserine	Evidence for enhancing CBT with D-cycloserine is inconsistent, with two studies showing an effect and one showing no added benefit	D	4	

RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.
The colors indicate the recommendation levels (see Table 4, Part I): RG = 1, dark green; RG = 2, light green; RG = 3, yellow; RG = 4, grey; RG = 1-, dark red; RG = 2-, light red.

PdTh has not been tested against a waitlist condition. In comparison to an active control, it was not superior. In comparison to CBT, it was less effective. Therefore, psychodynamic therapy cannot be recommended for SAD (LoE A-/RG 1-).

Comparisons of psychotherapy and pharmacotherapy and their combination

Data on combining CBT and drugs for SAD are inconclusive (Table 18, Supplementary Appendix). Some of the comparison studies have been conducted with

drugs that are not first-line medications for SAD, including phenelzine, moclobemide and clonazepam. The combination of phenelzine with CBT was superior to both monotherapies. Sertraline combined with CBT was not more effective than both monotherapies. Combining moclobemide with CBT is not superior to CBT alone but more effective than moclobemide alone. Adding psychodynamic therapy to clonazepam was not more effective than monotherapy with clonazepam.

Enhancing CBT/exposure with D-cycloserine

Some studies have evaluated the potential of *D-cycloserine* for enhancing the effects of exposure therapy or CBT for SAD (Table 19). Altogether, the data are inconsistent, with two studies showing an effect and one showing no added benefit (LoE D/RG 4).

Social anxiety disorder in children and adolescents

Recommendations for the treatment of SAD are summarised in Table 13.

Medications for children and adolescents with SAD

The SNRI *venlafaxine* and the SSRI *paroxetine* were effective in one placebo-controlled study each (LoE B/RG 2). One DBPC study showed efficacy of *fluoxetine*; however, it was less effective than CBT (LoE B/RG 3).

Regarding an increased risk of suicidal ideation and behaviour associated with drug treatment of young people aged less than 25 years, see Section 'Treating children and adolescents').

Psychotherapies for children and adolescents

Cognitive behavioural therapy. CBT was more effective than a waitlist condition in some, but not all studies, and showed inconsistent results in comparison to active control conditions, with some studies showing no difference (Table 13). CBT was more effective than fluoxetine in one study.

Meta-analysis. Our meta-analysis of studies with active controls showed a medium significant difference between CBT and active controls (Cohen's $d = 0.61$; 0.27–0.97); $p = .001$) (Figure 6; Supplementary Appendix) (LoE A/RG 1).

Also, another meta-analysis found that CBT for children and adolescents with SAD was superior to active control conditions (Yang et al. 2019).

Internet CBT-based interventions (iCBT). Some studies showed superiority over waitlist, and one study showed that iCBT differed from a psychological placebo (LoE B/RG 2).

Comparisons of psychological and pharmacological interventions and their combination in children and adolescents. Comparison studies are lacking, except for one study showing superiority of CBT over fluoxetine.

In a meta-analysis on treatments for children with SAD, symptoms of social anxiety and impairment were reduced by both CBT and SSRI treatment, with higher effect sizes for SSRIs (Segool and Carlson 2008).

Specific phobias

Usually, patients with specific phobia do not consult psychiatrists, psychologists or other medical professionals, especially if they can cope with their phobia by avoiding the specific feared situations or objects. Only when experiencing significant restrictions in their quality of life, the affected individuals will seek professional advice.

Recommendations for the treatment of specific phobias are summarised in Table 14.

Table 13. Summary of recommendations for the treatment of SAD in children and adolescents.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 21
SSRI paroxetine	One DBPC study showed efficacy of paroxetine.	B	2	
SNRI venlafaxine	One DBPC study showed efficacy of venlafaxine	B	2	
SSRI fluoxetine	One DBPC study showed efficacy of fluoxetine; however, it was less effective than CBT	B	3	
Psychotherapy				Table 22
Cognitive behavioural therapy (CBT)	CBT therapy for SAD was more effective than a waitlist condition in some, but not all studies, and showed inconsistent results in comparison to active control conditions, with some studies showing no difference. Meta-analysis of studies comparing CBT with active controls revealed a medium effect size. CBT was more effective than fluoxetine in one study.	A	1	
Internet interventions based on CBT (iCBT)	iCBT was superior to waitlist and more effective than a psychological placebo	B	2	

RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.
The colors indicate the recommendation levels (see Table 4, Part I): RG = 1, dark green; RG = 2, light green; RG = 3, yellow.

Table 14. Summary of recommendations for the treatment of specific phobias.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Fear of spiders/small animals				Table 23
Psychotherapies				
Exposure	Exposure is a first-line treatment for fear of spiders/small animals	A	1	
Virtual reality exposure	Virtual reality exposure was superior to psychological placebo, while studies comparing virtual reality with *in vivo* exposure show conflicting results	D	4	
Fear of heights				Table 23
Psychotherapies				
Virtual reality exposure	Virtual reality exposure was superior to wait list; evidence that it is as effective as *in vivo* exposure is only based on one underpowered study	D	4	
Fear of flying				Table 23
Psychotherapies				
Exposure	Exposure is a first-line treatment for fear of flying. Exposure was superior to 'no treatment' and psychological placebo	A	1	
Virtual reality exposure	Virtual exposure was superior to waitlist and active controls	A	1	
Dental phobia				Table 23
Psychotherapy				
CBT	CBT was only superior to waitlist but not to active control groups (psychological placebo and applied relaxation). However, it was superior to general anaesthesia.	B	2	
Virtual reality exposure	Virtual reality exposure was superior to waitlist; comparisons with active controls are lacking	D	4	
EMDR	EMDR was superior to waitlist; comparisons with active controls are lacking	D	4	
Medications				Table 24
Midazolam	Midazolam was superior to placebo and placebo acupuncture and as effective as nitrous oxide	A	1	
Alprazolam	Alprazolam was superior to placebo and as effective as pregabalin	B	2	
Pregabalin	Pregabalin was superior to placebo and as effective as alprazolam	B	2	
Various specific phobias				Table 24
SSRI paroxetine	Paroxetine was superior to placebo in a small DBPC study	B	2	
D-cycloserine + psychotherapy				Table 25
	All studies evaluating D-cycloserine for enhancing the effects of exposure or CBT were negative	A-	1-	

RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.
The colors indicate the recommendation levels (see Table 4, Part I): RG = 1, dark green; RG = 2, light green; RG = 4, grey; RG = 1-, dark red.

Medications for specific phobias

Psychopharmacological drugs are not recognised as a standard treatment for uncomplicated cases of specific phobia. However, when specific phobia leads to substantial restrictions in quality of life, e.g. in severe fear of dental treatments, drug treatment should be seen as an option.

Paroxetine was effective in a small DBPC study in individuals with various specific phobias (LoE B/RG 2) (Table 14). *Midazolam* (LoE A/RG 1), *alprazolam* (LoE B/RG 2) and *pregabalin* (LoE B/RG 2) can be used a p.r.n. treatment in dental phobia.

Psychotherapies for specific phobias

Exposure to the feared situation is considered the standard psychotherapy for specific phobias (Table 14). A review of exposure treatments has shown that only a few sessions with an overall treatment length of 1–5 h was sufficient to treat certain specific phobias (Bandelow et al. 2022a).

Fear of spiders/small animals. Exposure is a first-line treatment (LoE A/RG 1). Virtual reality exposure therapy was more effective than active controls but less effective than *in vivo* exposure (LoE D/RG 4).

Fear of heights. Virtual reality exposure therapy was superior to wait list; evidence that it is as effective as *in vivo* exposure is only based on one underpowered study (LoE D/RG 4).

Fear of flying. For exposure therapy, only one waitlist study exists (LoE D/RG 4). Virtual reality exposure was superior to active controls (LoE A/RG 1).

Dental phobia. CBT was only superior to waitlist but not to active control groups (psychological placebo and AR). However, it was superior to general anaesthesia. It was also superior to hypnosis, which is not a validated treatment (LoE B/RG 2).

Comparisons of psychotherapy and medications

Studies comparing psychotherapy and medications for specific phobias are lacking.

The advantage of a short-term as-needed treatment with benzodiazepines or pregabalin is that it can be applied directly before the patient enters the feared situation, e.g. before MRI scans, dental treatment or air travel. The risk of developing benzodiazepine addiction can be disregarded in occasional use. In contrast,

Table 15. Summary of recommendations for the treatment of selective mutism.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Psychotherapy				
Cognitive behavioural therapy (CBT)	The evidence for CBT for selective mutism is inconsistent. CBT did not clearly separate from waitlist in the available studies; one study showed superiority to psychoeducation.	D	3	Table 26
Medications				
SSRIs, phenelzine	According to small RCTs, case series and single case reports, the SSRIs citalopram, escitalopram, fluoxetine, sertraline and phenelzine showed some effect in the treatment of children with selective mutism	C	3	

RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.
The colors indicate the recommendation levels (see Table 4, Part I): RG = 3, yellow.

it takes several weeks for psychotherapy to show sufficient effects.

Enhancing CBT/exposure with D-cycloserine. Some studies have evaluated the potential of *D-cycloserine* for enhancing the effects of exposure or CBT for specific phobias. No effect of this combination could be demonstrated (LoE A-/RG 1-).

Selective mutism

There is a lack of high-quality, adequately powered studies for the treatment of selective mutism (Table 15).

Psychotherapy

The evidence for *CBT* for selective mutism is inconsistent. It did not clearly separate from waitlist in the available studies; one study showed superiority to psychoeducation (LoE D/RG 3).

Medication

Small DBPC studies which do not fulfil the criteria of this guideline because of small sample sizes showed some effect of *fluoxetine* and *sertraline* (Barterian et al. 2018; Black and Uhde 1994; Carlson et al. 1999). According to a review of open and controlled studies, medications, including the SSRIs citalopram, escitalopram, fluoxetine, sertraline and the MAOI phenelzine can be tried in debilitating cases of selective mutism (Manassis et al. 2016).

Regarding an increased risk of suicidal ideation and behaviour associated with antidepressant treatment of young people aged less than 25 years, see Section 'Treating children and adolescents'.

Drug treatment under special conditions

Pregnancy and breastfeeding

The risks of drug treatment during pregnancy must be weighed against the risk of withholding treatment for an anxiety disorder, OCD or PTSD. For a detailed overview, the reader is referred to the Consensus Guidance on the Use of Psychotropic Medication Preconception, in Pregnancy and Postpartum of the British Association for Psychopharmacology (McAllister-Williams et al. 2017). The conclusions are shortly summarised here:

- Antidepressants may have a small effect on some pregnancy outcomes but these may be due to residual confounding issues and in addition may not be clinically significant
- Antidepressants that block serotonin uptake may be associated with an increased risk of postpartum haemorrhage, but the magnitude and clinical significance of this risk is uncertain
- There have been concerns about antidepressant (mainly SSRIs and possibly particularly paroxetine) exposure *in utero* being associated with cardiac malformations. However, this may not be the case once all confounders are considered
- The risk of persistent pulmonary hypertension of the newborn seems to be only increased in infants exposed to SSRIs in late pregnancy, with no significant increase subsequent to exposure to SSRIs in early pregnancy. Nonetheless clinically the absolute risk of persistent pulmonary hypertension in the newborn remained very low even in the context of late exposure to SSRIs (Grigoriadis et al. 2014)
- There is some evidence of neonatal effects following late pregnancy exposure to SSRIs, particularly respiratory distress and neonatal behavioural syndrome
- Some studies have reported an association between exposure to antidepressants *in utero* and an increased risk of autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) later in childhood. However, the data are mixed, with other studies suggesting the association may be due to confounding
- Zolpidem may increase the risk of adverse pregnancy outcomes including preterm delivery and low birthweight of infants, though the magnitude of this risk if it exists is uncertain

- There is no convincing evidence in the available data of an increased risk of birth defects associated with benzodiazepines or 'Z-drugs'
- There are limited data suggesting benzodiazepine exposure *in utero* may be associated with delayed psychomotor development
- There are very limited data regarding the risks of gabapentin, pregabalin and buspirone exposure *in utero*
- Sertraline has a low rate of reported adverse effects on breastfed babies and may be appropriate for new episodes of depression
- Hypnotics and anxiolytics cross into breast milk so close monitoring of babies is required in mothers who are breastfeeding and taking these medications.

During pregnancy and the breastfeeding period, alternative treatments like CBT should be considered.

Treating children and adolescents

SSRIs are effective medications for treating anxiety disorders and OCD in children and adolescents. The use of SSRIs in young people aged less than 25 years has been debated, and there have been warnings against their use due to concerns about increased risk of suicidal ideation and behaviour (Scahill et al. 2005; Hetrick et al. 2007). In 2003, the Food and Drug Administration (USA) (FDA) issued a public health warning stating that preliminary evidence showed SSRIs (with the exception of fluoxetine) and related antidepressants might be associated with excess reports of suicidality (suicidal thinking and behaviour), but not verified suicides. Later, the FDA tempered the warning with a statement that both untreated depression and treatments for depression might lead to suicidality. Some analyses found that SSRIs exhibited efficacy for treatment of depression in children and adolescents (Sharp and Hellings 2006) and found no significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs (Simon et al. 2006). However, the FDA warning may have been off-set by reduced antidepressant prescriptions conducive to verified suicides in children and adolescents (Gibbons et al. 2007). Moreover, concerns regarding suicidal ideation in depressive children and youths may not apply to anxiety disorders, OCD and PTSD, as they were not studied. Nevertheless, careful monitoring is advisable, due to possible diagnostic uncertainty and the presence of co-morbid depression. Risks must be balanced with the clinical need for these drugs. This review has shown that evidence for the efficacy of psychotherapies for children and adolescents is not unequivocal for some disorders.

Still, some clinicians think that it may be preferable to reserve pharmacological treatments for patients who do not respond to evidence-based psychological approaches.

Treatment of the elderly

Treatment recommendations for anxiety disorders in older patients are summarised in Table 16.

Medications for treating older patients

A few RCTs have been performed with elderly patients (Table 16). These have found that the SSRIs *citalopram* and *sertraline* were effective, as well as *pregabalin* and *quetiapine* (LoE B/RG 2). *Paroxetine* was as effective as CBT and more effective than waitlist in elderly patients with PDA. Studies comparing paroxetine with placebo are lacking.

However, when treating elderly patients, possible adverse effects and interactions with other medications have to be considered. Factors that should be regarded in the treatment of the elderly include

- increased sensitivity to anticholinergic properties of TCAs
- increased risk for SIADH (SSRIs/SNRIs)
- increased sensitivity to extrapyramidal symptoms (medications for psychosis)
- increased somnolence and dizziness (benzodiazepines, pregabalin)
- an increased risk for orthostatic hypotension and ECG changes, including QT_C prolongation
- rare paradoxical reactions to benzodiazepines (including depression, with or without suicidal tendencies, phobias, aggressiveness, violent behaviour and symptoms misdiagnosed as psychosis)
- increased risk of drug interactions (e.g. additive anticholinergic effects, additive CNS depression, additive effects on orthostatic hypotension, interactions in the cytochrome P450 system and others).

Psychotherapy for treating older patients with GAD

CBT for elderly patients with GAD was only superior to waitlist in two of three studies, not superior to a psychological placebo and less effective than sertraline. A study showing that CBT was as effective as paroxetine was underpowered (LoE D/RG 4) (Table 16).

Table 16. Summary of Recommendations for the treatment of anxiety disorders in older patients.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 27
SSRIs citalopram and sertraline	The SSRIs citalopram and sertraline were effective in one RCT each in elderly patients with GAD	B	2	
Pregabalin	Pregabalin was effective in elderly patients with GAD. However, due to possible side effects like somnolence and dizziness, the drug is only a third-line option	B	3	
Quetiapine	Quetiapine was effective in elderly patients with GAD. However, due to possible side effects like metabolic syndrome or arrhythmias and other contraindications for patients with somatic disease, the drug is only a third-line option	B	3	
SSRI paroxetine	Paroxetine was as effective as CBT in an underpowered study and more effective than waitlist in elderly patients with PDA. DBPC studies are lacking	D	4	
Psychotherapy				Table 28
CBT	CBT for elderly patients with anxiety disorders was only superior to waitlist in two of three studies, not superior to a psychological placebo and less effective than sertraline. A study showing that CBT was as effective as paroxetine was underpowered	D	4	

The colors indicate the recommendation levels (see Table 4, Part I): RG = 3, yellow; RG = 4, grey; RG = 2-, light red.

Treatment of patients with severe somatic disease

Since patients with severe somatic disease are usually excluded from RCTs, controlled studies that show robust benefit of recommended medications on vital variables of the somatic condition (e.g. haemoglobin A1c test for diabetes, pulmonary function tests) are lacking.

TCAs are best avoided in patients with cardiac disease, as they can increase heart rate, increase QT_C interval, induce orthostatic hypotension and slow cardiac conduction, and have significant quinidine-like effects on conduction within the myocardium. By contrast, the SSRIs have minimal effects on cardiovascular function and may potentially have beneficial effects on platelet aggregation (Roose 2003; Davies et al. 2004). Potential cardiovascular side effects from venlafaxine and duloxetine must be considered. In a study with depressed patients aged 60 and older, venlafaxine was well tolerated. However, undesirable cardiovascular effects occurred in some of the participants, including increase in blood pressure, orthostatic hypotension, increase in QT_C interval and others (Johnson et al. 2006). Another study of depressed patients on high dose venlafaxine (mean 346 mg; range 225–525 mg) did not demonstrate any clinical or statistically significant effects on electrocardiographic (ECG) parameters (Mbaya et al. 2007). For depressed patients with recent myocardial infarction or unstable angina, sertraline was found to be safe (Glassman et al. 2002).

Patients with cardiovascular, cerebrovascular and endocrine disease may have adequate and reasonable anxiety reactions associated with their somatic disease state. They may also suffer from comorbid primary anxiety disorders. Such anxiety disorders are believed to complicate the management and prognosis of chronic obstructive pulmonary disease (Brenes 2003), coronary artery disease or myocardial infarction (Bankier et al. 2004; Shen et al. 2008; Frasure-Smith and Lesperance 2008; Holt et al. 2013; Allgulander 2016), diabetes mellitus (Anderson et al. 2002) or brain injury (Rogers and Read 2007). An anxiety factor based on four scales measuring psychasthenia, social introversion, phobia, and manifest anxiety independently and prospectively predicted the incidence of myocardial infarction in a study of older men (Shen et al. 2008). A diagnosis of GAD incurred an odds ratio of 2.09 of a major cardiac event within a 2-year period (Frasure-Smith and Lesperance 2008). Survivors of a traumatic brain injury are susceptible to GAD and PTSD (Rogers and Read 2007). A review of studies of anxiolytic treatments in patients with chronic obstructive pulmonary disease (COPD) and comorbid GAD or panic disorder indicate that such treatment may improve both the physical and mental health (Mikkelsen et al. 2004).

Anxiety symptoms may also be a consequence of medical conditions, such as hyperthyroidism (Bunevicius and Prange 2006) or autoimmune thyroiditis (Siegmann et al. 2018).

Future research

For several 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,

Table 17. Putative new anxiolytics in an advanced stage of development.

Target	Putative anxiolytics
Serotonin	Gepirone
	Psilocybin
	±3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy')
Glutamate	Ketamine
	Lanicemine
Neuropeptides	Oxytocin
	Vasopressin V_{1a} antagonist SRX246
	Orexin-1 antagonist suvorexant
	Neuropeptide Y
	Neuropeptide S
GABA	Zuranolone
Cannabinoids	Cannabidiol
Voltage-dependent ion channels	Riluzole
	Troriluzole
Vomeronasal receptor cells	Pherin 4-androstadienol (PH94B/aloradine)
Other	Curcumin
	Galphimine B
	Xenon gas

Modified from Bandelow (2020).

glutamate receptor agonists and antagonists, neuropeptide Y agonists, CRH receptor antagonists, GABA-A sub-unit selective ligands, natriuretic peptide, cannabinoids, and nitroflavanoids (Sartori and Singewald 2019; Bandelow 2020). In Table 17, some novel anxiolytic mediations are listed that are in an advanced stage of development.

There are also unmet needs regarding psychotherapeutic methods for anxiety disorders. 'Dismantling research' is needed to differentiate which ingredients of psychotherapy are necessary to improve the efficacy of these treatments. With internet psychotherapeutic interventions and virtual/augmented reality exposure therapy, it will be possible to reduce the costs for psychotherapy and increase the availability of these interventions for individuals suffering from these disorders.

Conclusions

In summary, due to increased efforts on the systematic clinical evaluation of treatments for anxiety disorders, OCD and PTSD in recent years, a comprehensive database has accrued, so that more solid recommendations can be provided for treating these conditions. In most cases, treatment with psychotherapy and medication may substantially improve quality of life of patients with these disorders.

Regrettably, in the 14 years since the appearance of the second version of this guideline, only a few new medications for these disorders have emerged. The main reason may be that many efficacious and well-tolerated drugs are already available for the treatment of anxiety disorders, OCD, and PTSD. It presents a great financial risk for pharmaceutical manufacturers to develop new drugs that would have to compete with the available, inexpensive generic medications.

However, there is still room for improvement in current pharmacological treatments. Drugs that have a faster onset of action, have less adverse effects and higher response rates are needed. There is also a gap for drugs that can specifically augment psychotherapy.

This guideline has applied the same strict methodological criteria for medications, psychotherapy and other treatments. Following the principles of the WFSBP grading system (Hasan et al. 2019), the results of waitlist studies were given low priority for the decisions on levels of evidence and recommendations. For GAD and mixed anxiety disorders in children and adolescents, no clear superiority to non-specific control treatments could be determined. Also, for the remaining disorders, a large number of studies did not show a significant difference between the treatment and active controls, and a significant effect was only found when combining all studies in meta-analyses. This does not mean that patients receiving CBT do not show substantial improvement, as the pre-post effect sizes of CBT are still large (Bandelow et al. 2015). However, patients suffering from anxiety disorders might expect that sophisticated psychotherapy programs used by experienced psychotherapists perform significantly better than unspecific relaxation exercises or talks with lay therapists or general practitioners without psychotherapeutic training. Quality standards of trials investigating the efficacy of psychotherapy that need to be improved include the use of a 'psychological placebo' instead of a waitlist as a control condition, adequate sample sizes, adequate blinding, intent-to-treat analysis, and inclusion of medication-free patients.

The lower power of psychological therapies for children to separate from waitlist and active control conditions – as compared to the treatment of adults – may be partly explained by the effects of spontaneous remission. As certain fears in children have the tendency to disappear in relatively short time due to natural development phenomena in childhood, this spontaneous improvement will occur both in the treatment group and in the control group, making it difficult to obtain a significant difference.

In recent years, internet psychotherapeutic interventions (IPIs) have moved more into focus. At present, there is not sufficient evidence for their use as a monotherapy; however, they may be useful as adjunctive therapy together with standard treatments.

Virtual reality exposure therapy, or its newest form, augmented reality exposure therapy, has shown some promise for the treatment of mental disorders.

Although the evidence for combining psychotherapy and pharmacotherapy is inconsistent, there are more arguments in favour than against using both modalities. Psychotherapy and pharmacotherapy have completely different modes of action and can therefore complement each other. There is no evidence for the negative effects of combining both treatments. Moreover, in clinical reality, the combination is used more often than psychotherapy alone.

However, patient preference is important to consider, given the potential risks of interactions and side effects with pharmacotherapy.

It may be a limitation that this review included only published studies, as publication biases have been found in medication (Jones et al. 2013) and psychotherapy trials (Flint et al. 2015).

The recommendations in this guideline are primarily based on randomised, controlled, double-blind trials. However, such studies do not always reflect clinical reality and have their shortcomings, e.g. the exclusion of comorbid, suicidal, or medically ill patients. Moreover, some interventions that could be potentially effective in treating anxiety disorders, OCD and PTSD have not yet been investigated in well-controlled trials because no financial support is available. There is a real need for pragmatic trials, and for collaborative care trials (Stein et al. 2019). In the future, hybrid trial methodology combining the best parts of traditional RCTs and observational study designs with real-world data may produce adequate scientific evidence for decision-making (Baumfeld Andre et al. 2020).

The Task Force members hope that this guideline will be useful to improve the care of patients and to help clinicians and service commissioners in providing and planning high quality care.

This international initiative has shown that guidelines do not have to be different in various countries in the world. The discussion among the international experts was far from controversial. Altogether, the Task Force members showed a high degree of agreement even on controversial issues. Ideally, in the future, the treatment of anxiety disorders, OCD and PTSD in the whole world will be based on internationally accepted standards, following the principles of evidence-based medicine.

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Disclosure statement

The authors have worked to ensure that all information, concerning drug dosages, schedules, routes of administration and licencing in this guideline is accurate and consistent with general psychiatric and medical standards at the time of publication. However, due to changing government regulations, continuing research, and changing information concerning drug therapy and reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage, or for added precautions. Moreover, specific situations may require a specific therapeutic response not included in this guideline. For these reasons and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of physicians directly involved in their care or the care of a member of their family. The authors and publisher disclaim any responsibility for any consequences which may follow from the use of information presented in this guideline.

The preparation of these guidelines has not been financially supported by any commercial organisation. This practice guidelines have 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 medicines discussed in this guideline. A number of mechanisms are in place to minimise the potential for producing biased recommendations due to conflicts of interest.

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Note

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 in the light of clinical features presented by the patient and the diagnostic and treatment options available.

Some of the medications 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 a variety of factors, this guideline is exclusively based on the available evidence.

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