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REVIEW ARTICLE

Guidelines for the pharmacological treatment of anxiety disorders, obsessive–compulsive disorder and posttraumatic stress disorder in primary care

BORWIN BANDELOW[1], LEO SHER[2], ROBERTAS BUNEVICIUS[3], ERIC HOLLANDER[2], SIEGFRIED KASPER[4], JOSEPH ZOHAR[5], HANS-JÜRGEN MÖLLER[6], WFSBP TASK FORCE ON MENTAL DISORDERS IN PRIMARY CARE[a] AND WFSBP TASK FORCE ON ANXIETY DISORDERS, OCD AND PTSD[b]

[1]*Department of Psychiatry and Psychotherapy, University of Göttingen, Göttingen, Germany,* [2]*Albert Einstein College of Medicine and Montefiore Medical Center, New York City, NY, USA,* [3]*Institute of Psychophysiology and Rehabilitation, Lithuanian University of Health Sciences, Palanga, Lithuania,* [4]*Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria,* [5]*Division of Psychiatry, Chaim-Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel, and* [6]*Department of Psychiatry and Psychotherapy, Ludwig Maximilian University, Munich, Germany*

Abstract

Objective. Anxiety disorders are frequently under-diagnosed conditions in primary care, although they can be managed effectively by general practitioners. *Methods.* This paper is a short and practical summary of the World Federation of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety disorders, obsessive–compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) for the treatment in primary care. The recommendations were developed by a task force of 30 international experts in the field and are based on randomized controlled studies. *Results.* First-line pharmacological treatments for these disorders are selective serotonin reuptake inhibitors (for all disorders), serotonin-norepinephrine reuptake inhibitors (for some) and pregabalin (for generalized anxiety disorder only). A combination of medication and cognitive behavior/exposure therapy was shown to be a clinically desired treatment strategy. *Conclusions.* This short version of an evidence-based guideline may improve treatment of anxiety disorders, OCD, and PTSD in primary care.

Key Words: *Anxiety disorders, guidelines, panic disorder, generalized anxiety disorder, social anxiety disorder, pharmacological treatment*

Introduction

Anxiety disorders are frequently under-diagnosed conditions in primary care, although they can be managed effectively by general practitioners. The World Health Organization (WHO) and American Psychiatric Association (APA) developed specific diagnostic guidelines for the mental disorders in primary care. This publication is a complementary tool – a brief and user friendly diagnostic guideline, developed for general practitioners. It is a short and practical summary of the WFSBP guidelines for the anxiety disorders, obsessive–compulsive disorder (OCD) and posttraumatic stress disorder

[a]Chair: Robertas Bunevicius (Lithuania), Co-Chair: Siegfried Kasper (Austria), Secretary: Florence Thibaut (France), Members: Wioletta Baranska-Rybak (Poland), Wieclaw J. Cubala (Poland), David Fiellin (USA), Henry R. Kranzler (USA), Alison Moore (USA), Elmars Rankans (Latvia), Jill Rasmussen (UK), Richard Saitz (USA), Djea Saravane (France), Thomas E. Schlaepfer (Germany), Leo Sher (USA), S.W. Tang (Hong Kong), Leonas Valius (Lithuania), David Wong (Hong Kong), Larisa M Zhitnikova (Russia), Joseph Zohar (Israel).

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Correspondence: Borwin Bandelow, Psychiatry and Psychotherapy, University of Göttingen, von-Siebold-Str. 5, D-37075 Göttingen, Germany. E-mail: Borwin.Bandelow@medizin.uni-goettingen.de

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(PTSD) [1], aiming at providing information about how to use modern medications for managing anxiety disorders in a busy primary care setting.

Although the lifetime prevalence of anxiety disorders has remained stable over the last decade – about 29% – the rate of treatment increased, along with the increased awareness about anxiety disorders, and the desire to improve quality of life. Patients with anxiety disorders are frequent users of emergency and primary medical services and are at a high risk for suicide attempts and substance abuse.

The current conceptualization of anxiety disorders includes an interaction of a specific neurobiological vulnerability (genetic, childhood adversity) and environmental factors (stress, trauma). Anxiety disorders are associated with dysfunction of serotonin, norepinephrine and other neurotransmitter systems.

Treatment

The WFSBP Task Force conducted a computer-based literature research in order to identify all relevant studies showing superiority to placebo and superiority or equivalent efficacy compared with established comparator treatments. The studies had to fulfill certain quality requirements. The categories of evidence are shown in Table I and are based on a systematic analysis of 510 randomized controlled studies. Recommendation grades are based on a synthesis of evidence and the risks of a drug (for example, benzodiazepines have category of evidence A, but only a recommendation grade of 2, due to their addiction potential).

Treatment is indicated in the majority of patients who fulfill the WHO International Classification of Diseases (ICD-10) or APA Diagnostic and Statistical Manual (DSM-IV-TR) criteria for an anxiety disorder, OCD or PTSD (Table II). The treatment plan is based on the patient's preference, severity of illness, co-morbidity, concomitant medical illnesses, complications like substance abuse or suicide risk, the history of previous treatments, cost issues and availability of types of treatment in a given area. Treatment options include drug treatment and psychological therapy. Before drug treatment is initiated, it is strongly recommended that the mechanisms underlying psychic and somatic anxiety be explained to the patient (brochures that explain the typical features of the patient's condition, treatment options, and adverse drug effects might be useful). Compliance with drug treatment can be improved when the advantages and disadvantages of the drugs are explained carefully.

Treatment should continue for at least 6–24 months after remission has occurred, in order to reduce the risk of relapse, and may be stopped only if all, or almost all, symptoms disappear.

Drug treatment: available compounds

Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and pregabalin are recommended as first-line drugs due to their favorable risk-benefit ratio, with some differentiation regarding the various anxiety disorders (Table III).

SSRIs. SSRIs are indicated for the anxiety disorders, OCD, and PTSD. Although treatment with SSRIs is

Table I. Categories of evidence and recommendation grades (Table III gives the categories of evidence for all recommended drugs). For a detailed definition of the evidence and recommendation grades, see [1].

Category of evidence	Description
A	Full evidence from controlled studies
B	Limited positive evidence from controlled studies
C	Evidence from uncontrolled studies or case reports/expert opinion
C1	Uncontrolled studies
C2	Case reports
C3	Based on the opinion of experts in the field or clinical experience
D	Inconsistent results
E	Negative evidence
F	Lack of evidence
Recommendation grade	**Based on:**
1	Category A evidence *and* good risk-benefit ratio
2	Category A evidence *and* moderate risk-benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence

Table II. Short description of anxiety disorders as defined by ICD-10 [2] and DSM-IV-TR [3].

Panic disorder (PD)

Panic disorder is characterized by recurrent panic attacks. Panic attacks are discrete periods of intense fear or discomfort, accompanied by at least four somatic and psychic symptoms (palpitations, sweating, trembling, dyspnoea, choking sensations, chest pain, nausea, abdominal distress, dizziness, feeling of unreality, fear of dying, etc.). A panic attack reaches a peak within 10 min and lasts 30–45 min on average. Usually, the patient is afraid that he has a serious medical condition such as myocardial infarction.

Agoraphobia

About two-thirds of all patients with panic disorder suffer from agoraphobia, which is defined as fear in places or situations from which escape might be difficult or in which help may not be available in the event of having an unexpected panic attack. These situations include being in a crowd or standing in a line, being outside the home alone, or traveling in a bus, train or automobile. These situations are avoided or endured with marked distress.

Generalized anxiety disorder (GAD)

The main features of generalized anxiety disorder are excessive anxiety and worry. The patients suffer from somatic anxiety symptoms as well as from restlessness, irritability, difficulty concentrating, muscle tension, sleep disturbances and being easily fatigued. Patient may express constant worry that the patient or a relative will shortly become ill or have an accident.

Specific phobia

Specific phobia is characterized by excessive or unreasonable fear of single objects or situations (e.g., flying, heights, animals, seeing blood, etc.).

Social phobia (social anxiety disorder; SAD)

This disorder is characterized by marked, persistent, and unreasonable fear of being observed or evaluated negatively by others in social performance or interaction situations and is associated with somatic and cognitive symptoms. The feared situations are avoided or else are endured with intense anxiety or distress. These situations include fear of speaking in public, speaking to unfamiliar people or being exposed to possible scrutiny by others.

Obsessive-compulsive disorder (OCD)

OCD is characterized by recurrent obsessions or compulsions, or both, that cause impairment in terms of distress, time, or interference with functioning. Concerns involving contamination, harm, hoarding, and sexual, somatic and religious preoccupations are the most common obsessions. Compulsions include washing, checking, repeating, ordering, counting, hoarding and touching (rare).

Post-traumatic stress disorder (PTSD)

PTSD develops after a terrifying ordeal that involved physical harm or the threat of physical harm. The person who develops PTSD may have been the one who was harmed, the harm may have happened to a loved one, or the person may have witnessed a harmful event that happened to loved ones or strangers. The condition is characterized by recurrent and intrusive distressing recollections of the event, nightmares, a sense of reliving the experience with illusions, hallucinations, or dissociative flashback episodes, intense psychological or physiological distress at exposure to cues that resemble the traumatic event, avoidance of stimuli associated with the trauma, inability to recall important aspects of the trauma, loss of interest, estrangement from others, sleep disturbances, irritability, difficulty concentrating, hypervigilance, and exaggerated startle response. The full symptom picture must be present for more than 1 month.

usually well tolerated, restlessness, jitteriness, an increase in anxiety symptoms, insomnia or headache in the first days or weeks of treatment may jeopardize compliance with treatment. Lowering the starting dose of SSRIs may reduce this overstimulation. Other side effects include nausea (and therefore the recommendation is to take it after a meal), headache, fatigue and dizziness. The anxiolytic effect may start with a delay of 2–4 weeks (in some cases up to 6 or 8 weeks). Long term side effects include sexual dysfunctions and weight gain.

SNRIs. The anti-anxiety effect of SNRIs may have a latency of 2–4 weeks. Like SSRIs, at the beginning of treatment, side effects like nausea, restlessness, insomnia or headache may pose a threat to compliance with treatment. Also, sexual dysfunctions, discontinuation syndromes, increased blood pressure, and other adverse events have been reported. There is no sufficient evidence to support the use of SNRIs in OCD.

Pregabalin. The calcium channel modulator pregabalin has been found to be effective in GAD. The anxiolytic effects of the drug are attributed to its binding at the α_2-δ-subunit protein of voltage-gated calcium channels in central nervous system tissues. Such binding reduces calcium influx at nerve terminals and modulates the release of neurotransmitters. The main side effects include dizziness and somnolence. The onset of efficacy occurs in the first days of treatment, which is an advantage over treatment with antidepressants.

TCAs. The efficacy of TCAs in panic disorder and generalized anxiety disorder is well proven, mainly for imipramine and clomipramine. However, TCAs have not been investigated systematically in social anxiety disorder. Compliance may be reduced by adverse effects such as sedation, prolonged reaction time, dry mouth, constipation and weight gain. Pharmacokinetic interactions can limit their use in patients taking concomitant medication. However, the major consideration is their potential lethality in case of overdose, due to their potential cardiac and CNS toxicity. Hence, TCAs should be avoided in patients at risk of suicide. Moreover, in general, the frequency of adverse events is higher for TCAs than for newer antidepressants, such as the SSRIs or SNRIs. Thus, the latter drugs should be tried first before TCAs are used.

Table III. Recommendations for drug treatment of anxiety disorders and OCD. Daily dose in mg (in brackets: categories of evidence and recommendation grade: see Table I.

	Panic disorder	Generalized anxiety disorder	Social anxiety disorder	Obsessive-compulsive disorder	Post-traumatic stress disorder
Selective Serotonin Reuptake Inhibitors (SSRIs)					
Citalopram	20–60 (A; 1)		20–40 (B; 3)		
Escitalopram	10–20 (A; 1)	10–20 (A; 1)	10–20 (A; 1)	10–20 (A; 1)	
Fluoxetine	20–40 (A; 1)		20–40 (D; 5)	20–60 (A; 1)	20–40 (A; 1)
Fluvoxamine	100–300 (A; 1)		100–300 (A; 1)	100–300 (A; 1)	
Paroxetine	20–60 (A; 1)	20–50 (A; 1)	20–50 (A; 1)	20–60 (A; 1)	20–40 (A; 1)
Sertraline	50–150 (A; 1)	50–150 (A; 1)	50–150 (A; 1)	50–200 (A; 1)	50–100 (A; 1)
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)					
Venlafaxine	75–225 (A; 1)	75–225 (A; 1)	75–225 (A; 1)		75–225 (A; 1)
Duloxetine		60–120 (A; 1)			
Tricyclic Antidepressants					
Amitriptyline					75–200 (B; 3)
Clomipramine	75–250 (A; 2)			75–300 (A; 2)	
Imipramine	75–250 (A; 2)				75–200 (B; 3)
Calcium Channel Modulators					
Pregabalin		150–600 (A; 1)			
Gabapentin			600–3,600 (B; 3)		
MAO Inhibitors					
Phenelzine	45–90 mg (B; 3)		45–90 (A; 2)	45–90 (D; 5)	45–90 (D; 5)
Reversible Inhibitor of Monoaminoxidase A (RIMA)					
Moclobemide			300–600 mg (D; 5)		
Benzodiazepines					
Alprazolam	1.5–8 (A; 2)				
Clonazepam	1–4 (A; 2)		1.5–8 mg (B; 3)		
Diazepam	5–20 (A; 2)	5–15 (A; 2)			
Lorazepam	2–8 (A; 2)	2–8 (A; 2)			
Atypical Antipsychotics					
Quetiapine		50–300 (A; 1)			
Risperidone					0.5–6 (B; 3)
Tricyclic Anxiolytic					
Opipramol	50–150 (B;3)				
Azapirone					
Buspirone		15–60 (D; 5)			
Noradrenergic and specific serotoninergic antidepressant (NasSA)					
Mirtazapine				30–60 (B; 3)	30–60 (B; 3)
Antihistamine					
Hydroxyzine		37.5–75 (A;2)			

Abbreviations: see text. Not all drugs are currently approved in all countries for these indications; refer to local prescribing information.

Benzodiazepines. The anxiolytic effect starts within minutes after oral or parenteral application. In general, they have a good record of safety. Due to CNS depression, benzodiazepine treatment may be associated with sedation, dizziness, and prolonged reaction time. Accordingly, cognitive functions and driving skills are affected. After a couple of weeks or months of continuous treatment with benzodiazepines, low-dose dependency may occur in a substantial number of patients. Patients with a history of benzodiazepine, alcohol or other psychoactive substance abuse should generally be excluded from treatment, or be closely monitored in specialized care settings. Benzodiazepines may also be used in combination with serotonergic medications during the first weeks of treatment to suppress increased anxiety. In general, benzodiazepines should be used with a regular dosing regimen. Only in the treatment of short-term distress (e.g., air travel or dental phobia), p.r.n. (when necessary) use may be justified. One should be aware that benzodiazepines were not found to be effective in acute stress disorder and in conditions with depression comorbidity, or OCD.

Antihistamines. The antihistamine hydroxyzine is effective in generalized anxiety dis order. Because of sedating effects, the antihistamine should only be

used when other medications have not been successful or not tolerated. Side effects include sedation, anticholinergic effects at high doses, blurred vision, confusion, delirium and others. When sedating effects are wanted, the antihistamine would be a better option than benzodiazepines.

Atypical antipsychotics. In a number of studies, atypical antipsychotics such as quetiapine have been used as monotherapy in GAD or 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, extrapyramidal effects and others. However, in most countries atypical antipsychotics are not licensed for these disorders. Therefore, treatment with these medications should probably be reserved only to a specialist setting.

Dosing

Approximately 75% of patients respond to the initial low dose of antidepressants (with the exception of OCD). In some patients, such as the elderly, treatment should be started with half the recommended dose or less in order to minimize initial adverse drug events. In particular, patients with panic disorder may be sensitive to serotonergic stimulation and may easily discontinue treatment because of initial jitteriness and nervousness. For tricyclic antidepressants (TCAs), it is recommended to initiate the drug at a low dose and increase the dose every 3–5 days. The antidepressant dose should be increased to the highest recommended therapeutic level if the initial treatment with a low or medium dose fails. For OCD, medium to high doses are recommended. If pharmacokinetic data support once daily dosing, taking medications in a single dose may increase compliance. In patients with hepatic impairment, a dosage adjustment or use of medications with primarily renal clearance (e.g., pregabalin) may be required.

If the patient does not respond to treatment in an adequate dose after 4–6 weeks (8–12 weeks in OCD or PTSD), medication should be changed or a referral to a psychiatrist should be considered. For patients who do not improve with standard treatments, a number of alternative options exist, including the addition of antipsychotics to the antidepressant medication in OCD (for details see [1].

In patients unresponsive to medications, the addition of cognitive behavioral therapy (CBT) may be successful.

Non-pharmacological treatment

All patients with anxiety disorders require supportive therapy. Psychological and pharmacological treatments are often concomitant therapies, rather than alternative therapies. Exposure therapy (e.g., gradual exposure in vivo, "flooding") and response prevention were found to be very effective in specific phobia, agoraphobia, social phobia and OCD. However, techniques like exposure and response prevention have high rates of therapy refusal and attrition due to unpleasant experience during sessions and related anticipatory anxiety. As a rule, patients should be transferred to experienced psychotherapists for formal psychotherapy; however, physicians in primary care also can help their patients with supportive talks, by providing psychoeducational advice, and by encouraging them not to avoid feared situations. Choosing 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), financial considerations, time availability and commitment of the patient, accessibility of psychiatric and psychological treatment resources, and qualification and experience of the clinician.

Special treatment recommendations for the different anxiety disorders

The treatment recommendations for the different anxiety disorders are summarized in Table III. Some antianxiety drugs are effective in all anxiety disorders, whereas some drugs have only been studied in specific anxiety disorders and thus should be reserved for use in these particular disorders.

Panic disorder and agoraphobia. In acute panic attacks, reassurance of the patient may be sufficient in most cases. In severe attacks, short-acting benzodiazepines may be needed (e.g., melting tablets). SSRIs and venlafaxine are the first-line treatments for panic disorder. After remission, treatment should continue for at least several months in order to prevent relapses. SSRIs, venlafaxine, TCAs, benzodiazepines and other drugs have shown long-term efficacy in these studies. Regarding SSRIs and SNRIs, the same doses are usually prescribed in the maintenance treatment as in the acute treatment phase.

A combination of CBT and medication treatment has been shown to have the best treatment outcomes. Exposure therapy is used to treat agoraphobia, and CBT was developed for treating spontaneous panic attacks. Exercise seems to have some effect in panic

disorder; however, this effect seems to be less pronounced than the effect of medication.

Generalized anxiety disorder (GAD). The first-line treatments for GAD are SSRIs, SNRIs and pregabalin. Other treatment options include buspirone and hydroxyzine. Benzodiazepines should only be used for long-term treatment when other drugs or CBT have failed.

As a psychological treatment strategy, CBT and associated techniques have been used in generalized anxiety disorder. CBT is based on cognitive models stressing the role of worrying, cognitions, and avoidance behavior.

Social anxiety disorder (SAD). First-line treatments include SSRIs and venlafaxine. Benzodiazepines have not been studies extensively in SAD, and there is no evidence for the use of tricyclic antidepressants in SAD. The irreversible monoamineoxidase inhibitor phenelzine may be an option in treatment-unresponsive cases. SAD is generally a chronic disorder and requires long-term treatment.

Among psychological therapies, exposure therapy and CBT have been shown to be effective.

Specific phobia. Usually, patients with specific phobia do not consult medical professionals, especially if they can cope with their phobia by avoiding the specific feared situations or objects. Exposure therapy is effective to treat specific phobia. Psychopharmacological drugs are not recognized as a standard treatment in simple cases of specific phobia. In severe cases, SSRIs can be tried.

Obsessive–compulsive disorder (OCD). First-line treatments are the SSRIs and the TCA clomipramine. It is recommended to use the medium to upper dose range (although the evidence regarding a dose-response relationship for SSRIs and clomipramine in OCD is mixed). OCD requires long-term treatment at an effective dose-level ("The dose that makes you well, keeps you well"). If patients do not respond, consultation with a psychiatrist might be considered. In severe OCD cases, where all other available therapeutic approaches have been tried without success, deep brain stimulation may be a treatment option.

Post-traumatic stress disorder (PTSD). First-line treatments include the SSRIs and venlafaxine. PTSD is often a chronic disorder and needs long-term treatment for at least 12–24 months. Long-term efficacy was proven for the SSRIs fluoxetine and sertraline and the SNRI venlafaxine.

Only a minority (10–20%) of persons subject to severe traumatic events develop PTSD. The current recommendation in the first month is summarized by three Ps: *Don't Pathologize* ("this is a normal response to an abnormal situation"), *Don't Psychologize* (don't facilitate emotional reaction via group therapy, or stressful debriefing), and *Don't Pharmacologize* (there is no evidence that prophylactic medication treatment may prevent the development of PTSD). CBT is indicated only several months after exposure to trauma and for individuals who have developed PTSD. "Debriefing" (a therapeutic conversation with an individual who has just experienced a traumatic event in order to prevent PTSD) and benzodiazepines in the first few hours after exposure is contraindicated, as they might interfere with the potent spontaneous recovery process.

Treatment under special conditions

Pregnancy. The risks of drug treatment during pregnancy must be weighed against the risk of withholding treatment for an anxiety disorder. According to the majority of studies, the use of SSRIs and TCAs in pregnancy imposes no increased risk for malformations. It is recommended to avoid paroxetine alprazolam use among pregnant women or women planning to become pregnant.

Breast-feeding. SSRIs and TCAs are excreted into breast milk, and low concentrations have been found in infants' serum. Plasma levels of the SSRIs paroxetine and sertraline in breast-fed infants are usually undetectable. In mothers receiving SSRIs and TCAs (with the exception of doxepine), it seems unwarranted to recommend that breast-feeding should be discontinued. During maternal treatment with benzodiazepines, infants should be observed for signs of sedation, lethargy, poor suckling, and weight loss, and if high doses have to be used and long-term administration is required, breast feeding should probably be discontinued.

Treating children and adolescents. Regarding the pharmacological treatment of anxiety disorders, experience in children and adolescents suggests that SSRIs should be the first-line treatment. However, there have been warnings against their use due to concerns about increased risk of suicidal ideation and behavior. Careful monitoring is advisable, due to possible diagnostic uncertainty and the presence of comorbid depression.

Treating the elderly. Factors that should be regarded in the treatment of the elderly include an increased

sensitivity for anticholinergic properties, an increased risk for orthostatic hypotension, ECG changes during treatment with TCAs, and possible paradoxical reactions to benzodiazepines, which include depression, with or without suicidal tendencies, phobias, aggressiveness, or violent behavior. Thus, treatment with TCAs or benzodiazepines is less favorable, while SSRIs appear to be safe.

Treatment of patients with severe somatic disease. 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 compound the management and the prognosis of chronic obstructive pulmonary disease, coronary artery disease or myocardial infarction, diabetes mellitus or brain injury. Anxiety symptoms may also be a consequence of medical conditions, such as hyperthyroidism.

TCAs are best avoided in patients with cardiac disease. By contrast, the SSRIs have modest effects on cardiovascular function (although higher doses of citalopram and escitalopram have been associated with QT_C prolongation) and may have potentially beneficial effects on platelet aggregation. Venlafaxine is usually well tolerated, but blood pressure should be monitored in patients with hypertension.

When should a patient be referred to specialist care?

When a patient has been unresponsive after two trials with first-line medications, when the anxiety disorder is complicated by alcohol or substance abuse, when the disorder substantially interferes with social and occupational functioning of a patient or when secondary depression or suicidality occur, the patient should be referred to specialist care.

Conclusion

Patients with anxiety disorders, obsessive–compulsive disorder and posttraumatic stress disorder may be effectively treated in primary care. With adequate treatment, the quality of life of patients with these disorders may substantially be improved. A combination of CBT and medication treatment was shown to have better treatment outcomes.

These principles of practice are considered guidelines only. Adherence to them will not ensure a successful outcome in every case. The recommendations are based on randomized controlled studies, which do not always reflect clinical reality. The individual treatment of a patient should be planned in the light of clinical features presented by the patient and the diagnostic and treatment options available.

Key points

- This short version of an evidence-based guideline may improve treatment of anxiety disorders, OCD, and PTSD in primary care
- First-line pharmacological treatments for these disorders are selective serotonin reuptake inhibitors (for all disorders), serotonin-norepinephrine reuptake inhibitors (for some) and pregabalin (for generalized anxiety disorder only)
- A combination of medication and cognitive behavior/exposure therapy was shown to be a clinically desired treatment strategy
- The recommendations are based on randomized controlled studies, which do not always reflect clinical reality

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