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Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology

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Abstract

These British Association for Psychopharmacology guidelines cover the range and aims of treatment for anxiety disorders. They are based explicitly on the available evidence and are presented as recommendations to aid clinical decision making in primary and secondary medical care. They may also serve as a source of information for patients and their carers. The recommendations are presented together with a more detailed review of the available evidence. A consensus meeting involving experts in anxiety disorders reviewed the main subject areas and considered the strength of evidence and its clinical implications. The guidelines were constructed after extensive feedback from participants and interested parties. The strength of supporting evidence for recommendations was rated. The guidelines cover the diagnosis of anxiety disorders and key steps in clinical management, including acute treatment, relapse prevention and approaches for patients who do not respond to first-line treatments.

Keywords

anticonvulsants, antidepressants, antipsychotics, anxiety disorders, anxiolytics, benzodiazepines, cognitive behaviour therapy, evidence-based guidelines, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, simple phobia, social phobia, SSRI, treatment, venlafaxine

Introduction

The British Association for Psychopharmacology (BAP) aims to advance education and research in the science of psychopharmacology, by arranging scientific meetings, fostering research and teaching, encouraging publication of research results and providing guidance and information to the public and professions on matters relevant to psychopharmacology (www.bap.org.uk). As an important part of this process the BAP has published a series of evidence-based guidelines for the use of drugs in psychiatric disorders with the emphasis on producing comprehensive but concise and usable guidelines based on a review of the evidence (Anderson *et al.*, 2000; Goodwin and Consensus Group of the BAP, 2003; Lingford-Hughes *et al.*, 2004).

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Anxiety symptoms and disorders are common in community settings, and in primary and secondary medical care. The personal and societal burden associated with anxiety disorders is considerable, but many people who might benefit from treatment are not recognized or treated. Likely factors include the range of anxiety disorders, their comorbidity with other disorders (particularly depression), lack of awareness of anxiety disorders by sufferers and practitioners, poor confidence by many practitioners in their treatment, and the relative lack of research. Conversely, some patients receive unnecessary or inappropriate treatment. Hence there is much room for improvement in the recognition and management of patients with anxiety disorders: we hope these guidelines will contribute to this process.

Methodology

Guidelines are systematically derived statements that aim to inform individual patient and clinician decisions. Recommendations regarding treatment can be graded according to the strength of scientific evidence, and if possible are derived from systematic reviews and randomized controlled trials (RCTs). The principal recommendations apply to the management of *average* patients, and therefore can be expected to apply much of the time: for this reason, we use expressions such as 'clinicians *should* consider. . . .' in the summary tables. We accept that there are many patients and many clinical decision points where unthinking adherence to treatment recommendations may be potentially harmful. In situations where the evidence is weaker we have noted management options, being aware that implementation will depend upon clinician experience, patient clinical features and preference, and local circumstance (Haynes *et al*., 2002). Some of our recommendations may be regarded as standards of clinical care that are driven by ethical considerations or custom and practice: these standards are intended to be applied rigidly.

Guideline process

These guidelines are the final result of a British Association for Psychopharmacology (BAP) consensus meeting on 20–21 May 2004 which included experts in the field and representatives of user groups (all those who attended are listed in the acknowledgements). Brief presentations were made on key areas, with greatest emphasis on systematic reviews and RCTs. This was followed by discussion of important issues, in order to identify areas of consensus or uncertainty. A literature review was then performed to validate the consensus points. This was circulated to the participants and other interested parties, together with a summary of the recommendations and their strength, based on the level of evidence. Wherever possible feedback was incorporated into the final version of the guidelines. Given the range and depth of the subject area it was not possible for all participants in the wider group to achieve full consensus on all points.

Literature search

All the consensus points and the guideline recommendations can be linked to relevant evidence through the literature review. It was not possible to perform a systematic review of all possible data from primary sources. Existing systematic reviews and RCTs were identified from MEDLINE and EMBASE searches and from the Cochrane Database, as well as from recent previous guidelines (Ballenger *et al*., 1998a, 1998b; Ballenger *et al*., 2001; Bandelow *et al*., 2002; Allgulander *et al*., 2003; Greist *et al*., 2003; Pollack *et al*., 2003; Van Ameringen *et al*., 2003; Stein *et al*., 2004; Ballenger *et al*., 2004) through cross-referencing, and by discussion with experts in the field.

Strength of evidence and recommendations for guidelines

As in previous BAP guidelines, the categories of evidence for causal relationships and grading of recommendations are taken from the methodology of the North of England Evidence-Based Guideline Development Project undertaken by the Centre for Health Services Research, University of Newcastle upon Tyne and the Centre for Health Economics, University of York (Shekelle *et al*., 1999).

Evidence categories

Evidence categories are adapted from the US Agency for Health Care Policy and Research Classification (US Department of Health and Human Services, 1992). Six categories are available, when considering causal relationships and treatments, and we have proposed four categories for observational findings and associations (see Table 1).

Strength of recommendations

Recommendations are graded as shown in Table 1. Weaker levels of recommendations (B, C or D) do not necessarily imply a reduced level of clinical importance. As in previous recommendations (Goodwin and Consensus Group of the BAP, 2003) we have included a category S (representing a standard of care), denoting a recommendation that incorporates an important clinical consensus on good practice rather than factual evidence.

Range and aim of the guidelines

We anticipate that the content of the guidelines will be relevant to all doctors treating patients with anxiety disorders, in primary and secondary medical care settings. Each of the principal disorders – generalized anxiety disorder (GAD), panic disorder (PD), social phobia (also known as social anxiety disorder, SAD), post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) – is considered in turn, following key steps in management (acute treatment: continuation treatment: prevention of relapse: combination with psychological approaches: treatment resistance).

We anticipate that the guidelines will prove most useful in informing treatment decisions in primary and secondary care regarding pharmacological management in patients aged between

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Table 1 Categories of evidence and strength of recommendations

Categories of evidence relevant to specific causal relationships and treatments	
Ia	Evidence from meta-analysis of RCTs
Ib	Evidence from at least one RCT
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Proposed categories of evidence for observational findings and associations	
I	Evidence from large representative population samples
II	Evidence from small, well-designed but not necessarily representative samples
III	Evidence from non-representative surveys, case reports
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Strength of recommendations	
A	Directly based on category I evidence
B	Directly based on category II evidence or an extrapolated recommendation from category I evidence
C	Directly based on category III evidence or an extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or an extrapolated recommendation from category I, II or III evidence
S	Standard of clinical care

RCT: randomized controlled trial

18 and 65 years. The type and prevalence of anxiety disorders changes during childhood and adolescence (Costello *et al*., 2003) and the mean age of onset of adult patients with anxiety disorders varies between diagnoses. Nevertheless many adult patients describe an onset of symptoms in childhood or adolescence, and certain recommendations (for example those pertaining to obsessive-compulsive disorder) will be potentially applicable to adolescent patients. Similarly, recommendations that are applicable to adult patients do not necessarily become invalid once they exceed their sixty-fifth birthday.

We have considered those guidelines developed by the National Institute for Clinical Excellence for generalized anxiety disorder, panic disorder, post-traumatic stress disorder and obsessive-compulsive disorder (NICE, www.nice.org.uk), and those from other organizations, such as the recent statements from the World Federation of Societies of Biological Psychiatry (Bandelow *et al*., 2002) and the World Council on Anxiety (Allgulander *et al*., 2003; Greist *et al*., 2003; Pollack *et al*., 2003; Stein *et al*., 2003; Van Ameringen *et al*., 2003).

There is often a tension between existing established clinical practice and the possible implications of new research for changing practice. Existing practice may be accepted on the basis of prolonged clinical experience and by extension of a related proven indication: new treatments may have superior efficacy to placebo in methodologically robust RCTs, but lack comparator data against current treatment. We have highlighted where this tension is greatest, but do not wish to impose specific treatment recommendations that may prove premature.

Epidemiology of anxiety symptoms and disorders

Anxiety symptoms are common in the general population and in primary and secondary medical care. Symptoms may be mild, transient and without associated impairment in social and occupational function, but many patients are troubled by severe and persistent symptoms that cause significant personal distress, impair function and reduce quality of life. To meet the diagnosis of an anxiety disorder, patients have to experience a certain number of symptoms for more than a minimum specified period, the symptoms causing significant distress, with an associated impairment in everyday function. Most research has used the diagnostic categories for anxiety disorders in the Fourth Edition of the Diagnostic and Statistical Manual (DSM-IV) (American Psychiatric Association, 1994), which are broadly similar to those in the Tenth Edition of the International Classification of Diseases (ICD-10) (World Health Organization, 1992): we give simplified versions of the disorders in Table 2.

Epidemiological studies in the general population aged 18–65 years (I) indicate that when taken together anxiety disorders have a 12-month period prevalence of approximately 15%, and a lifetime prevalence of approximately 21% (Wittchen and Jacobi, 2005). Individual disorders are less frequent, with estimated 12-month prevalence rates ranging between 0.7% (OCD) and 7.6% (specific phobia), and estimated lifetime prevalence rates between 0.8% (OCD) and 13.2% (specific phobia) (Table 3). The age and sex distribution of individual disorders varies: for example, specific phobias are markedly more common in women than men across all age bands, whereas panic disorder is almost as frequent in men and women aged 51–65 years. Due to this variation within

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Table 2 Short description of the clinical feature of the anxiety disorders

Derived from the clinical descriptions and diagnostic guidelines in ICD-10 (World Health Organization, 1992) and DSM-IV (American Psychiatric Association, 1994). More detailed descriptions are available in DSM-IV and ICD-10.

Generalized anxiety disorder (GAD)
Generalized anxiety disorder (GAD) is characterized by excessive and inappropriate worrying that is persistent (lasting some months in ICD-10, six months or longer in DSM-IV) and not restricted to particular circumstances. Patients have physical anxiety symptoms and key psychological symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension and disturbed sleep). Can be comorbid with major depression (but not arise solely in its context), panic disorder, phobic anxiety disorders and OCD in DSM-IV, but must not meet full criteria for these in ICD-10.

Panic disorder (with or without agoraphobia)
Panic disorder is characterized by recurrent unexpected surges of severe anxiety ('panic attacks'), with varying degrees of anticipatory anxiety between attacks. Panic attacks are discrete periods of intense fear or discomfort, accompanied by at least four physical or psychological anxiety symptoms. Typically panic attacks reach their peak within ten minutes and last around 30–45 minutes. Most patients develop a fear of having further panic attacks. Around two-thirds of patients with panic disorder develop agoraphobia, defined as fear in places or situations from which escape might be difficult or in which help might not be available, in the event of having a panic attack. These situations include being in a crowd, being outside the home or using public transport (two situations required in ICD-10): they are either avoided or endured with significant personal distress (avoidance at some stage is required for ICD-10 diagnosis).

Social phobia (social anxiety disorder)
Social phobia is characterized by a marked, persistent and unreasonable fear of being observed or evaluated negatively by other people, in social or performance situations, associated with physical and psychological anxiety symptoms. Feared situations (such as speaking to unfamiliar people or eating in public) are either avoided or are endured with significant personal distress (avoidance must be prominent for ICD-10 diagnosis).

Specific phobia
Specific, simple or isolated phobia is characterized by excessive or unreasonable fear of (and restricted to) single people, animals, objects, or situations (for example, flying, dentists, seeing blood, etc.) which are either avoided or are endured with significant personal distress (avoidance must be prominent for ICD-10 diagnosis).

Post-traumatic stress disorder (PTSD)
Post-traumatic stress disorder is characterized by a history of exposure to trauma (actual or threatened death, serious injury, or threats to the physical integrity of the self or others) with a response of intense fear, helplessness or horror: with the later development of re-experiencing symptoms (intrusive recollections, flashbacks or dreams), avoidance symptoms (for example efforts to avoid activities or thoughts associated with the trauma), and hyper-arousal symptoms (including disturbed sleep, hypervigilance and an exaggerated startle response). Must usually be within six months of the exposure to trauma for an ICD-10 diagnosis.

Obsessive–compulsive disorder (OCD)
Obsessive–compulsive disorder is characterized by recurrent obsessional ruminations, images or impulses, and/or recurrent physical or mental rituals, which are distressing, time-consuming and cause interference with social and occupational function. Common obsessions relate to contamination, accidents, and religious or sexual matters: common rituals include washing, checking, cleaning, counting and touching.

individual anxiety disorders, the pattern for all disorders taken together is fairly constant with an overall female:male ratio of approximately 2:1 across the age range. Studies in primary care suggest approximately 50% significantly improve over 6–16 months (II) (Ormel *et al*., 1991; Ormel *et al*., 1993; Ronalds *et al*., 1997) but complete recovery is relative rare. Severity, duration of illness and ongoing social adversity were associated with lack of improvement (II) (Ronalds *et al*., 1997). Long-term follow-up of participants in eight studies of cognitive behaviour therapy (CBT) for anxiety disorders found that 52% had at least one diagnosis, with significant levels of comorbidity and health scores comparable to the lowest 10% of the population (Durham *et al*., 2005). A US longitudinal study indicates that the likelihood of recovery from GAD is significantly less than that of recovering from major depression (II) (Yonkers *et al*., 2000).

Coexisting depressive symptoms are common, particularly in patients with severe anxiety, and many patients simultaneously fulfil diagnostic criteria for anxiety and depressive disorders, this pattern often being named 'comorbidity'. Cross-sectional studies in European community and clinical settings (Fehm *et al*., 2005; Goodwin *et al*., 2005; Lieb *et al*., 2005) and in UK primary medical care (Nease and Aikens, 2003) reveal a significant correlation between measures of anxiety and depressive symptom severity. Epidemiological studies indicate that approximately 62% of subjects with an anxiety disorder fulfil diagnostic criteria for another psychiatric disorder, most commonly depression, which is present in around 33.5% of subjects with any disorder being considerably more common in subjects with GAD and social phobia (I) (Wittchen and Jacobi, 2005). In practice the presence of marked coexisting depressive symptoms is an important

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Table 3 Epidemiology of anxiety disorders in the general population

Diagnostic group	12-month estimate		Lifetime estimate	
	%	(95% CI)	%	(95% CI)
Any anxiety disorder*	12.0	(11.1–13.0)	21.1	(20.5–21.6)
Panic disorder (± agoraphobia)	2.3	(1.9–2.8)	3.8	(3.1–4.5)
Agoraphobia (without panic)	2.0	(1.7–2.5)	3.8	(3.1–4.5)
GAD	1.5	(1.2–1.9)	5.1	(4.3–5.9)
Social phobia	2.0	(1.6–2.5)	5.8	(5.1–6.5)
Specific phobia	7.6	(6.9–8.5)	13.2	(12.8–13.6)
OCD	0.7	(0.5–1.0)	0.8	(0.6–1.1)
PTSD	1.2	(0.9–1.3)	Not established	

*Without PTSD.
GAD: generalised anxiety disorder: OCD: obsessive–compulsive disorder: PTSD: post-traumatic stress disorder.
Based upon community studies reporting either prevalence estimates for established diagnoses of mental disorders (according to DSM-III, DSM-III-R, DSM-IV or ICD-10 criteria) or upon studies employing instruments with explicit diagnostic criteria that allow such inferences. See Wittchen and Jacobi (2005).

Table 4 Distribution of anxiety disorders (12-month prevalence) by age and gender

Diagnostic group	Age 18–34		Age 35–49		Age 50–65		Total	
	M	F	M	F	M	F	M	F
Any anxiety disorder*	7.0	17.0	8.0	15.9	8.4	16.2	7.8	16.3
Panic disorder (± agoraphobia)	1.0	3.4	2.0	3.4	2.1	2.4	1.7	3.0
Agoraphobia (without panic)	0.9	2.0	1.1	2.9	0.9	4.4	1.0	3.1
GAD	0.5	1.1	0.9	2.9	1.8	2.2	1.0	2.1
Social phobia	1.9	3.1	0.7	2.7	1.4	2.2	1.3	2.7
Specific phobia	4.2	11.9	4.7	9.7	4.6	10.7	4.5	10.8
OCD	0.4	1.0	1.0	0.9	0.3	0.8	0.6	0.9
PTSD	0.4	1.6	0.6	1.4	0.4	1.3	0.5	1.5

*Without PTSD.
GAD: generalised anxiety disorder: OCD: obsessive–compulsive disorder: PTSD: post-traumatic stress disorder.
Based upon community studies reporting either prevalence estimates for established diagnoses of mental disorders (according to DSM-III, DSM-III-R, DSM-IV or ICD-10 criteria) or upon studies employing instruments with explicit diagnostic criteria that allow such inferences. See Wittchen and Jacobi (2005).

consideration in treatment decisions in primary and secondary medical care. Where the anxiety symptoms are present within the context of a depressive disorder, drug treatment of the depression is effective in improving anxiety (Anderson *et al*., 2000). Where depression follows or is comorbid with an anxiety disorder it is generally indicative of greater severity and associated with poorer prognosis (II) (Albus and Scheibe, 1993; Brown *et al*., 1995; Cowley *et al*., 1996; Shalev *et al*., 1998; Martinsen *et al*., 1998; Rief *et al*., 2000; Erwin *et al*., 2002). Clinical practice has been to direct treatment towards the depressive disorder in the first instance, choosing treatments that also have action against the symptoms of the anxiety disorder: this has been shown to improve outcome in OCD, with better response to sertraline than desipramine (Ib) (Hoehn-Saric *et al*., 2000).

Detection and diagnosis of anxiety disorders

In drawing up the guidelines we are aware that there are often practical and conceptual difficulties in delineating specific anxiety disorders, ranging from overlap with milder degrees of depression ('mixed anxiety and depression') to comorbidity between anxiety disorders. The diagnosis of some anxiety disorders has also been criticized, with comments relating to potential legal implications (e.g. PTSD) or so-called medicalization of normal variation (e.g. social phobia). Nevertheless the current diagnostic classification provides a useful clinical delineation of distressing and debilitating symptom clusters that, crucially for an evidence-based approach, has been used for patient selection in treatment trials and therefore allows assessment of clinical benefit.

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From relatively sparse evidence, the detection of a mental health problem in patients with anxiety disorders in primary care varies between studies, but is probably similar to that for depression with values ranging from 56% to 92%, the differing disorders varying in recognition rates (I) (Ormel *et al*., 1990; Tiemens *et al*., 1996; Ronalds *et al*., 1997; Wittchen *et al*., 2003). Comorbidity of anxiety with depression improves the detection of mental health problems (Sartorius *et al*., 1996; Wittchen *et al*., 2002). However correct identification of which anxiety disorder is present and subsequent active treatment may be less good for anxiety disorders than for depression (Wittchen *et al*., 2002).

Screening questions and self-report questionnaires are fairly sensitive but not very specific, making the value of routine screening for anxiety disorders questionable (Goldberg and Bridges, 1987; Dowell *et al*., 1990; Lewis and Wessely, 1990; Parkerson and Broadhead, 1997; Wittchen and Boyer, 1998; Bjelland *et al*., 2002). The Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) is a widely used brief self-report scale with anxiety and depression sub-scales (seven items each): it has sensitivity and specificity of about 0.8 for both sub-scales using a cut-off of eight or above (Bjelland *et al*., 2002) making it reasonable for use in high risk populations. The World Health Organization has recently published guidance on the identification and management of mental health problems in primary health care (World Health Organization, 2004). A simple algorithm for initial delineation of anxiety disorder subtypes is suggested in Fig. 1.

General issues in the treatment of anxiety disorders

When to treat

Anxiety symptoms exist on a continuum and many people with milder degrees of anxiety, particularly of recent onset and associated with stressful life events but with little disability will experience an improvement without specific intervention (II) (Mann *et al*., 1981). In milder forms of depression the benefit of antidepressant treatment over placebo is difficult to demonstrate (Ia) (Khan *et al*., 2005) and the same is likely to be true of anxiety disorders. Randomized controlled trials across a range of anxiety disorders often demonstrate a high placebo response (e.g. Oosterbaan *et al*., 2001; Huppert *et al*., 2004) indicating that non-specific effects can play a large part in improvement. However the chronic nature and associated disability of many disorders means that most patients who fulfil diagnostic criteria for an anxiety disorder are likely to benefit from some form of treatment.

This need for treatment is determined by the severity and persistence of symptoms, the presence of comorbid mental disorder or physical illness, the level of disability and impact on social functioning, concomitant medication, and a history of good response to, or poor tolerability of, previous treatment approaches. As randomized controlled trials are generally performed in rather restricted patient groups with little comorbidity or other features commonly seen in conventional clinical samples, and because

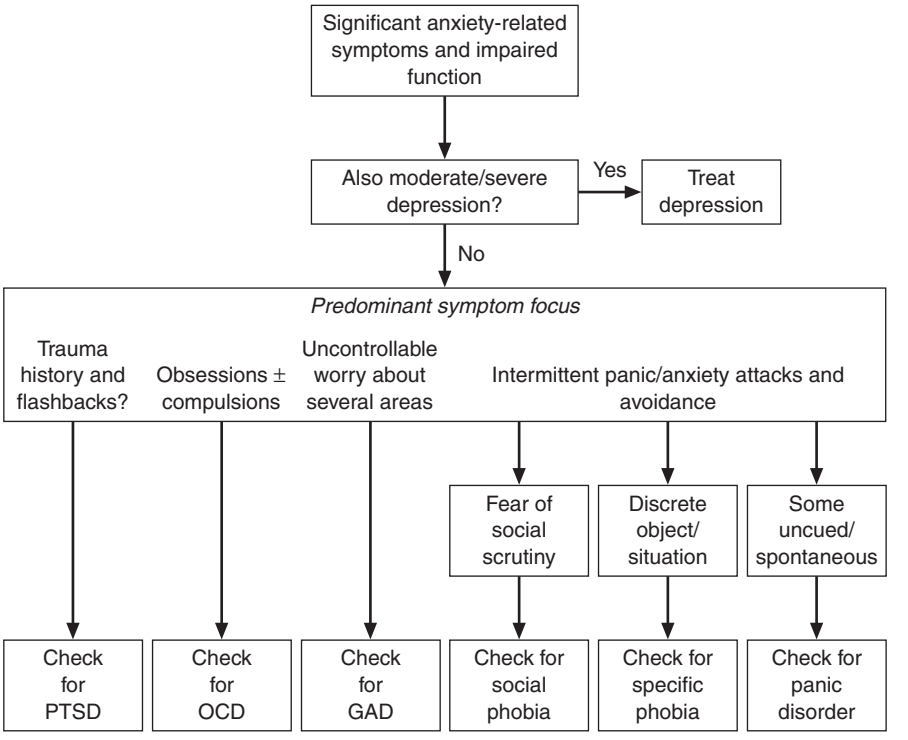

Figure 1 Suggested scheme for exploration of a suspected anxiety disorder

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many RCTs have major methodological flaws, study findings may not necessarily simplify treatment decisions in primary or secondary care. Choice of treatment is affected by the patient characteristics (such as previous response or contraindications), the evidence base supporting its use, patient and physician preference, and the local availability of that proposed intervention (IV) (Haynes *et al*., 2002). Although there is considerable overlap between effective therapies for the different anxiety disorders there are also differences (discussed in the individual sections) and separate evidence bases for treating each disorder (Ib). For this reason identifying individual disorders is helpful.

Recommendations: detection and decision to treat

- Check for significant anxiety symptoms in patients presenting with depression or other psychological problems (S)
- Become familiar with the main features of different anxiety disorders and distinguish between them (B)
- Assess for comorbid depression and treat if depressive symptoms are moderate or severe (A)
- In milder, recent-onset anxiety disorders consider 'watchful waiting' (support, addressing social factors and monitoring) (D)

The principal options include a range of pharmacological treatments, psychological therapies based on exposure and cognitive methods, and self-help strategies.

Pharmacological treatments

Many patients are cautious about starting psychotropic drug treatment, fearing problems such as unwanted sedation or the development of physical or psychological dependence, and doctors should discuss the relative benefits and risks of proposed interventions before initiating a treatment prescription. It should be emphasized that response is not immediate, that transient worsening of symptoms can sometimes occur; that prolonged courses are needed to maintain an initial treatment response and minimize the risk of relapse; and that antidepressants (when used) are not 'addictive' (Nutt, 2003).

The selection of a particular drug class (and of a specific drug within that class) should be determined principally by the evidence base supporting its use, and also by whether the patient has previous experience of treatment with that compound. The absence of a licensed indication does not necessarily mean an absence of evidence for the proposed treatment intervention. Conversely it should not be assumed that all drugs within a class are likely to be efficacious in the treatment of a particular anxiety disorder, when one member of that class has proven efficacy. The presence of significant coexisting depressive symptoms should guide treatment choice towards prescription of antidepressant drugs rather than benzodiazepines. The major adverse effects and problems associated with prescription of psychotropic drugs mentioned in the sections on treatment of individual anxiety disorders are summarized in Table 5.

Selective serotonin reuptake inhibitors and venlafaxine

Selective serotonin reuptake inhibitors (SSRIs) have broad spectrum anxiolytic efficacy and are generally well tolerated, and for this reason generally represent the first-line pharmacological treatment approach in anxiety disorders. However SSRIs have potentially troublesome adverse effects, including initial increased nervousness, insomnia, nausea (Ib) (Baldwin and Birtwistle, 1998) and sexual dysfunction (Ib) (Baldwin, 2004). When stopped abruptly, most SSRIs can produce a discontinuation syndrome characterized by dizziness, insomnia and flu-like symptoms (Ib) (Schatzberg *et al*., 1997). The serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine is also associated with discontinuation symptoms after abrupt withdrawal (Ib) (Silverstone and Ravindran, 1999).

The United Kingdom Committee on Safety of Medicines (CSM) recommends that patients are monitored frequently and carefully when starting or increasing the dosage of SSRI and other antidepressant treatments (CSM, 2004), and recent guidance from the National Institute of Clinical Excellence (NICE, 2004) on the treatment of panic disorder and generalized anxiety disorder recommends that patients are reviewed at fortnightly intervals in the first six weeks of treatment. Due to concerns about its potential safety in overdose, the CSM currently recommends that venlafaxine treatment should only be initiated by specialist mental health practitioners, requires pre-treatment ECG and blood pressure measurement, and is avoided in patients with cardiac disease, electrolyte imbalances or hypertension (IV) (CSM, 2004). Current advice regarding the relative safety of antidepressants after overdose has however been questioned (Nutt, 2005a).

Recommendations: general issues for pharmacotherapy

- Discuss the benefits and risks of specific drug treatments with patients before treatment (S)
- SSRIs are effective across the range of anxiety disorders and are generally suitable for first-line treatment (A)
- Benzodiazepines are effective in many anxiety disorders but their use should be short term and only considered beyond this in treatment-resistant cases because of problems with side effects and dependence (C)
- The use of other drugs such as tricyclic antidepressants, MAOIs, antipsychotics and anticonvulsants needs to be considered in relation to their evidence-base for specific conditions and their individual risks and benefits (S)
- With all antidepressants, especially SSRIs and venlafaxine, there should be specific discussion and monitoring of possible adverse effects early in treatment (initial worsening of anxiety/agitation or rarely the emergence of suicidal ideation) (S)
- With antidepressants and benzodiazepines there should be specific discussion and monitoring of adverse effects on stopping the drugs after a week of treatment (discontinuation symptoms and, with benzodiazepines, rebound anxiety and withdrawal/dependence) (S)

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Table 5 Summary of potential adverse effects, interactions and other specific problems of named psychotropic drugs used in the treatment of anxiety disorders*

Class	Examples	Potential adverse effects							Specific problems	Inhibition of hepatic enzymes	Toxicity in overdose	Withdrawal symptoms
		'Anti-Ch'	Sedation	Insomnia	↓bp	Nausea	Sexual problems	Weight gain				
Selective serotonin reuptake inhibitors	citalopram	−	−	+	−	+	+	−	All SSRIs:	−	low	+
	escitalopram	−	−	+	−	+	+	−	a. can increase	−	low	+
	fluoxetine	−	−	+	−	+	+	−	nervousness in first few	++	low	?
	fluvoxamine	−	−	+	−	+	+	−	days of treatment:	++	low	+
	paroxetine	−	−	+	−	+	+	+		++	low	++
	sertraline	−	−	+	−	+	+	−	b. possible increased risk of suicide attempts in depressed children and adolescents.	−	low	+ Usually only transient, when present.
Serotonin-noradrenaline reuptake inhibitors	duloxetine	+	−	+	−	+	+	−	−	−	?	?
	venlafaxine	+	−	+	−	+ (more at higher doses)	+	−	Hypertension. BP and ECG monitoring suggested.	−	medium	++
Selective noradrenaline reuptake inhibitors	maprotiline	+	+	−	−	−	+	++	Seizures	?	high	+
	reboxetine	+	−	−	−	−	−	−	−	−	low	?
Tricyclic antidepressants	amitriptyline	++	++	−	++	−	+	++	All TCAs:	++	high	+
	clomipramine	++	++	+	++	+	++	+	Potentially cardiotoxic	++	high	+
	desipramine	+	+	+	+	−	+	−	in therapeutic dosage	++	high	+
	imipramine	++	+	+	++	−	+	+	and in overdose.	++	high	+
Monoamine oxidase inhibitors	phenelzine	+	−	+	++	+	+	+	Phenelzine:	−	high	++
	moclobemide	−	−	+	−	+	−	−	Hypertensive crisis with sympathomimetics. Need to follow restricted diet.	−	low	−
Receptor antagonists	mirtazapine	+	++	−	−	−	−	++	Blood dyscrasia (as common as with TCAs)	?	low	−
Benzodiazepines	alprazolam	−	++	−	−	−	−	−	All benzodiazepines:	Minimal	Medium.	++
	bromazepam	−	++	−	−	−	−	−	a. can impair attention	effects on	Can be	++
	clonazepam	−	++	−	−	−	−	−	and memory	hepatic	reversed	+
	diazepam	−	++	−	−	−	−	−		enzymes;	with	+
	lorazepam	−	++	−	−	−	−	−	b. tolerance and dependence may occur	pharmaco-dynamic interactions with sedative drugs.	flumazenil.	++ May persist for long periods.

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Conventional neuroleptics	haloperidol	−	+	−	+	−	+	+	Risk of development of acute and delayed movement disorders.	Many drug interactions.	high	+
	trifluoperazine	+	++	−	+	−	+	+			high	+
Atypical antipsychotics	olanzapine	+	+	−	+	−	+	++	All atypicals:	+	low	?
	quetiapine	+	++	−	+	−	−	+	Risk of hyperglycaemia and induction of diabetes mellitus.	+	low	?
	risperidone	+	+	−	+	−	+	+		+	low	?
Anticonvulsants	gabapentin	+	+	−	?	+	−	+	Potential for the development of tolerance or dependence is not established.	−	?	Abrupt withdrawal may possibly precipitate seizures.
	pregabalin	−	++	−	−	−	−	?			?	
	tiagabine	−	+	−	−	−	−	−			?	
Mood stabilizer	lithium	−	−	−	−	+	(−)	++	Narrow therapeutic window necessitates regular blood level monitoring.	−	Acute: medium Chronic intoxication: high.	Abrupt withdrawal may precipitate mania.
Beta-blockers	pindolol	+	+	−	+	−	+	+	Avoid in patients with asthma, heart failure, and peripheral vascular disease.	Many drug interactions.	medium	Abrupt withdrawal may precipitate hypertension.
	propranolol	−	+	−	+	−	+	+				
Antihistamines	hydroxyzine	+	+ Fast tolerance	−	−	−	?	+	Little information on benefits and risks.	?	low–medium	?
5-HT_{1A} agonist	buspirone	+	−	+	−	+	−	−	Little information on benefits and risks.	Some interactions	low	−

Annotations

'Anti-Ch', anticholinergic: refers to symptoms commonly caused by muscarinic receptor blockade (including dry mouth, sweating, blurred vision, constipation and urinary retention), although one or more of these symptoms may be caused by other mechanisms and does not necessarily imply that the drug binds to muscarinic receptors: ↓bp, postural hypotension: ++, relatively common or strong: +, may occur or moderately strong: −, absent or weak: ?, unknown or insufficient information.

*Only those psychotropic drugs that are named in the text and currently available for clinical use are considered: naming a drug in this table does not indicate that it has proven efficacy or a license for the treatment of anxiety. The side-effect profiles given are not comprehensive and provide approximate comparison only. Details of drugs and potential cautions and interactions should be looked up in a reference book such as the *British National Formulary* (2005).

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Tricyclic antidepressants and monoamine oxidase inhibitors Certain tricyclic antidepressants (TCAs) are efficacious in some anxiety disorders, but are associated with a greater burden of adverse effects than either SSRIs or venlafaxine, and for this reason TCAs should only be used after non-response to or poor tolerance of SSRI or SNRI treatment. TCAs should be avoided in patients considered at risk of suicide, due to their potential cardiac and CNS toxicity after overdose (Nutt, 2005a). Stopping TCAs abruptly can also cause a discontinuation syndrome, and pharmacokinetic interactions can limit their use in patients taking concomitant medication. The irreversible monoamine oxidase inhibitor (MAOI) phenelzine has proven efficacy in panic disorder and SAD, but side effects and the need to follow dietary restrictions limit its use, and it should only be considered when patients have not responded to or proved intolerant of other treatment approaches. Moclobemide has some efficacy in panic disorder and social phobia, and the reversibility of its action reduces the need for dietary restrictions.

Benzodiazepines Some benzodiazepines have proven efficacy in panic disorder, GAD and social phobia, but they can cause troublesome sedation in acute treatment, and dependence can occur (especially in predisposed patients) with longer-term use (Royal College of Psychiatrists, 2005). Discontinuation symptoms have their peak severity at two days for short half-life and 4–7 days for long-half life benzodiazepines (Rickels *et al*., 1990). As they have limited efficacy in relieving depressive symptoms (Ib) (Rickels *et al*., 1991), antidepressants should be preferred in patients with significant comorbid depression. Benzodiazepines will usually be reserved for the treatment of patients who have not responded to at least two treatments (such as after non-response to both an SSRI and a psychological treatment) but concerns about potential problems in long-term use should not prevent their use in patients with persistent, severe, distressing and impairing anxiety symptoms (Nutt, 2005b).

Other agents The side-effect burden and currently limited evidence base for antipsychotic drugs in the treatment of anxiety disorders (with efficacy mainly for certain antipsychotics after non-response to SSRI treatment in OCD) means they have only a limited role in overall patient management (El-Khayat and Baldwin, 1998). Certain non-benzodiazepine anticonvulsant drugs have proven efficacy in some anxiety disorders (principally GAD and social phobia) but there have been few randomized controlled trials and the potential for development of tolerance or dependence with prolonged use in anxiety disorders is not certain (Ashton and Young, 2003): for these reasons, anticonvulsants would normally be restricted for use in patients who have not responded to or proved intolerant of treatments with a more substantial evidence base.

Psychological treatments

Many patients have a preference for psychological treatments over pharmacological approaches. Certain forms of psychotherapy, such as exposure therapy, cognitive therapy and cognitive-behaviour therapy (CBT), have proven efficacy in the treatment of anxiety disorders: but others, such as psychodynamic psychotherapy, have not been found superior to control interventions, or have not been subject to controlled investigations. Many evaluations of the efficacy of psychological treatments have not employed an adequate psychological placebo-control treatment: the use of waiting list controls is suboptimal. As with pharmacological approaches, it should be emphasized that response is not immediate: that transient worsening of symptoms can sometimes occur: that prolonged courses are often needed to maintain an initial treatment response: that dependence on the therapist may occur, with problems when treatment is stopped: and that encouraging short-term outcomes are no guarantee of good outcomes over the longer term.

In general, the efficacy of psychological and pharmacological approaches is similar in the acute treatment of anxiety disorders. In some studies, relapse rates are lower after an initial response to cognitive therapy with exposure than after response to drug treatment. For these reasons, patients should be offered a choice of treatment approaches, selection being affected by patient clinical features, needs and preference, and by the local availability of services able to offer evidence-based psychological interventions. It is uncertain whether combining psychological and pharmacological treatments is associated with greater efficacy, than either treatment given alone. As such it may be best to plan sequential steps in patient management (NICE, 2004). Previous concerns that prescription of psychotropic drugs might reduce the efficacy of psychological treatment are probably unfounded (Lader and Bond, 1998).

When psychological treatment is recommended, it should only be delivered by suitably trained and supervised staff, able to demonstrate that their clinical practice adheres to evidence-based treatment protocols (NICE, 2004). The relative scarcity of such individuals reduces the range of treatment options open to patients and doctors.

Recommendations: general issues for psychotherapy and self-help

- Discuss the benefits and risks of specific treatments with patients before treatment (S)
- Selection of a particular psychological treatment should be determined by the evidence-base supporting its use, the clinical features of the patient, patient preference and the local availability of that service (S)
- Psychological treatments should only be delivered by suitably trained and supervised staff, able to demonstrate their clinical practice adheres to evidence-based treatment protocols (S)
- Patients with more than mild symptoms are unlikely to improve significantly through self-help approaches alone (S)

A general range of 8–20 hours of sessions of CBT may be needed in the treatment of anxiety disorders. In GAD and panic disorder, a typical treatment course consists of approximately 16–20 hours, up to half of which can be conducted by the patient

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in supervised 'homework' sessions, over a period of approximately four months (NICE, 2004). In PTSD, a standard course of psychological treatment might involve 8–12 sessions of trauma-focused CBT, delivered at weekly intervals (NICE, 2005). In OCD, a typical initial treatment course might include approximately 16 hours of intervention based on exposure and response prevention, with longer and more intensive treatment in house-bound patients (NICE, 2005).

The role of self-help and other approaches in anxiety disorders

Patient preference and the sub-optimal effects of pharmacological or psychological treatment approaches have encouraged the development of a range of self-help techniques and therapies in anxiety disorders. Many patients and their carers derive considerable support from local self-help groups and national self-help organizations (such as the United Kingdom organizations: the National Phobics Society, No Panic, and Obsessive Action). However, there have been relatively few randomized controlled trials of the efficacy and acceptability of self-help approaches and few studies have been conducted in diagnostically homogenous groups, with reliable outcome measures and robust statistical analysis.

A systematic review of six randomized controlled trials indicates that self-help is efficacious in primary care patients with mixed anxiety disorders, greater efficacy being seen with more detailed instruction in use of self-help manuals (Ia) (van Boeijen *et al*., 2005). Bibliotherapy (use of self-help books) appears efficacious in patients with 'clinically significant emotional disorders', but the efficacy of self-help groups in this population is not established (Ia) (den Boer *et al*., 2004). A systematic review of complementary therapies finds some evidence for the efficacy of bibliotherapy (in specific phobia), relaxation training (in GAD and panic disorder), exercise (in GAD) and use of Kava [now withdrawn due to hepatotoxicity] (in GAD) (Ia) (Jorm *et al*., 2004). A systematic review of counselling for primary care patients with emotional problems (including anxiety, depression, and 'stress') indicates that the short-term (but not long-term) efficacy of counselling was greater than that of standard general practitioner care, with or without antidepressant treatment (Ia) (Bower *et al*., 2001).

In discrete anxiety disorders, there is some evidence for the efficacy of a broad range of interventions, including bibliotherapy (Ib) (Lidren *et al*., 1994), exercise therapy (Ib) (Broocks *et al*., 1998) and Internet-based computerized cognitive therapy (Ib) (Carlbring *et al*., 2003) in panic disorder: and computer-guided behaviour therapy (Ib) (Greist *et al*., 2002) and possibly yogic meditation (Ib) (Shannahoff-Khalsa *et al*., 1999) in OCD. The efficacy of self-help techniques in other anxiety disorders has not been examined extensively: it was no more efficacious than repeated assessment in post-traumatic stress disorder (Ehlers *et al*., 2003). The UK National Institute for Clinical Excellence concluded that there was insufficient evidence to recommend the general introduction of computerized cognitive behaviour therapy for anxiety symptoms or disorders (Ia) (NICE, 2002).

Cost-effectiveness of treatment

Anxiety disorders are associated with a substantial economic burden, both for the health system and (especially) for wider society in terms of productivity losses (I) (Souetre *et al*., 1994; Salvador-Carulla *et al*., 1995; Rice and Miller, 1998; Greenberg *et al*., 1999; Andlin-Sobocki and Wittchen, 2005), but there have been few evaluations of the cost-effectiveness of treatment in anxiety disorders. Treatment costs account for a small proportion of the overall costs of health care (Durham *et al.*, 2005). An economic evaluation of the cost-effectiveness of differing forms of secondary care provision for Vietnam veterans with PTSD found higher levels of patient satisfaction, reduced overall costs and reduced likelihood of symptomatic relapse with short-stay, compared to long-stay inpatient provision (Ib) (Fontana and Rosenheck, 1997). A randomized controlled trial of a collaborative care intervention (education, surgery visits from a psychiatrist) in United States primary care patients with panic disorder found that patients subject to such intervention experienced proportionately more anxiety-free days over 12 months at reduced overall costs compared to a 'treatment as usual' control group (Ib) (Katon *et al*., 2002). A randomized controlled trial of computerized CBT versus standard care in United Kingdom primary care patients with depression and/or anxiety disorders found that outcomes were improved (Ib) (Proudfoot *et al*., 2004), service costs were higher but lost employment costs lower in the intervention group (Ib) (McCrone *et al*., 2004). The computerized CBT appeared to be cost-effective by broad (health system-wide and societal) criteria. Decision modelling indicates that venlafaxine is more cost-effective than diazepam in the treatment of generalized anxiety disorder (IIb)(Guest *et al.,* 2005). In general, economic models suggest that evidence-based treatment of anxiety disorders would produce greater population health gain at a similar cost to current care (II) (e.g. Patel *et al*., 2002; Issakidis *et al*., 2004; NICE, 2005) – consequences which are likely to be seen as a cost-effective use of resources.

Generalized anxiety disorder (GAD)

Recognition and diagnosis

Although generalized anxiety disorder (GAD) is amongst the most common mental disorders in primary care, and is associated with increased use of health services, it is often not recognized (I): possibly because only a minority of patients present with anxiety symptoms (most patients with present physical symptoms), and doctors tend to overlook anxiety unless it is a presenting complaint (I) (Ormel *et al*., 1990). The disability associated with GAD is similar to that with major depression (I) (Wittchen *et al.*, 2000). Patients with 'comorbid' depression and GAD have a more severe and prolonged course of illness and greater functional impairment (I) (Kessler *et al*., 1999), and a greater chance of being recognized as having mental health problems, though not necessarily as having GAD (Weiller *et al*., 1998; Wittchen *et al.*, 2002).

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Table 6 Generalized anxiety disorder: treatment approaches supported by placebo-controlled studies

	SSRIs	TCAs	Benzodiazepines	Others
Acute efficacy	Escitalopram Paroxetine Sertraline	Imipramine	Alprazolam Diazepam	Venlafaxine CBT Buspirone Hydroxyzine Pregabalin Trifluoperazine (Abercarnil) (Opipramol)
Long-term efficacy	Escitalopram Paroxetine			CBT Venlafaxine
Relapse prevention	Paroxetine Escitalopram			CBT
Enhances the efficacy of psychological treatment After non-response			Diazepam	

Empty cell indicates current absence of published placebo-controlled data. Brackets indicate drug is not available for clinical use.

Acute treatment

Systematic reviews and placebo-controlled RCTs indicate that some SSRIs (escitalopram, paroxetine and sertraline), the SNRI venlafaxine, some benzodiazepines (alprazolam and diazepam), the tricyclic imipramine, and the 5-HT_{1A} partial agonist buspirone are all efficacious in acute treatment (Ia) (Kapczinski *et al*., 2003; NICE, 2004; Baldwin and Polkinghorn, 2005; Mitte *et al*., 2005). Other compounds with proven efficacy (Ib) include the antipsychotic trifluoperazine (Mendels *et al*., 1986), the antihistamine hydroxyzine (Lader and Scotto, 1998; Llorca *et al*., 2002), the anticonvulsant pregabalin (Feltner *et al*., 2003), and the sigma-site ligand opipramol (Möller *et al*., 2001). Treatments with unproven efficacy in GAD include the beta-blocker propranolol (Ib) (Meibach *et al*., 1987).

There have been few comparator-controlled studies, and most reveal no significant differences in efficacy between active compounds (Mitte *et al*., 2005): however, escitalopram (20 mg/day) has been found significantly superior to paroxetine (20 mg/day) (Ib) (Baldwin *et al*., 2004), and venlafaxine (75–225 mg/day) superior to fluoxetine (20–60 mg/day) on some outcome measures in patients with comorbid GAD and major depression (Ib) (Silverstone and Salinas, 2001). Psychological symptoms of anxiety may respond better to antidepressant drugs than to benzodiazepines (Meoni *et al*., 2004; Baldwin and Polkinghorn, 2005). Fixed-dose RCTs provide some evidence of a dose-response relationship with escitalopram, paroxetine and venlafaxine (Ib) (Rickels *et al*., 2000; Allgulander *et al*., 2001; Rickels *et al*., 2003; Baldwin *et al*., 2004).

Long-term treatment

Double-blind studies indicate that continuing with SSRI or SNRI treatment is associated with an increase in overall response rates (Ib): from eight to 24 weeks with escitalopram or paroxetine (Bielski *et al*., 2004); from four to 12 weeks with sertraline (Allgulander *et al*., 2004) and from eight to 24 weeks with venlafaxine (Montgomery *et al*., 2002). Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication (escitalopram or paroxetine), compared to switching to placebo, for up to six months (Ib) (Stocchi *et al*., 2003; Allgulander *et al*., 2005).

Comparative efficacy of psychological, pharmacological, and combination treatments

Drug or psychological treatments, delivered singly, have broadly similar efficacy in acute treatment (Ia) (Gould *et al*., 1997; NICE, 2004). Relapse rates are lower with cognitive behaviour therapy than with other forms of psychological treatment (Ib) (Fisher and Durham, 1999; Durham *et al*., 2003), but the comparative efficacy of drug and psychological approaches over the long term is not established. It is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment, given alone (Ib) (Durham and Turvey, 1987; Lader and Bond, 1998; Power *et al*., 1990).

When initial treatments prove unhelpful

There is no clear evidence for an increase in response with dose escalation after an initial non-response to a lower dose. Switching between treatments with proven efficacy may be helpful (NICE, 2004).

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Recommendations: treatment of generalized anxiety disorder

Detection and diagnosis

- Become familiar with the symptoms and signs of generalized anxiety disorder (S)
- Assess the level of disability to help determine the threshold for treatment (A)
- Ask about long-standing anxiety symptoms when patients present with depression or unexplained physical symptoms (A)

Acute treatment

- Choose an evidence-based acute treatment (A):
  - *pharmacological*: some SSRIs (escitalopram, paroxetine, sertraline), venlafaxine, some benzodiazepines (alprazolam, diazepam), imipramine, buspirone, hydroxyzine
  - *psychological*: cognitive-behaviour therapy
- Take account of patient clinical features, needs and preference and local service availability when choosing treatment, as pharmacological and psychological approaches have broadly similar efficacy in acute treatment (S)
- Consider an SSRI for first-line pharmacological treatment (D)
- Higher doses of SSRIs or venlafaxine may be associated with greater response rates (A)
- Advise the patient that treatment periods of up to 12 weeks are needed to assess efficacy (A)

Longer-term treatment

- Continue drug treatment for a further six months in patients who are responding at 12 weeks (A)
- In longer-term pharmacological treatment use an approach known to be efficacious in preventing relapse: the best evidence is for SSRIs (escitalopram, paroxetine) (A)
- Consider cognitive-behaviour therapy as it may reduce relapse rates better than drug treatment (S)
- Monitor efficacy and tolerability regularly during long-term treatment (S)

Combination of drugs and psychological treatment

- Routinely combining drug and psychological approaches is not recommended for initial treatment in the absence of consistent evidence for enhanced efficacy over each treatment given alone (A)

When initial treatments fail

- Consider switching to another evidence-based treatment after non-response to initial treatment (C):
  - Consider switching to venlafaxine or imipramine in non-responders to acute treatment with an SSRI (C)
  - Consider use of benzodiazepines after non-response to SSRI and SNRI treatment (C)
  - Consider combining drug treatment and cognitive-behaviour therapy (D)
  - Consider combining evidence-based treatments only when there are no contraindications (D)
  - Consider referral to regional or national specialist services in refractory patients (S)

Panic disorder (with and without agoraphobia)

Recognition and diagnosis

Patients with panic disorder are often not recognized in primary or secondary medical care, despite their considerable use of emergency, cardiac, gastrointestinal, neurological and mental health services (I) (Roy-Byrne *et al*., 1999). There is considerable comorbidity with other anxiety disorders, bipolar disorder and major depression: comorbid panic and depression being associated with greater disability and impairment, and increased use of health services (I) (Roy-Byrne *et al*., 2000). Accurate diagnosis is dependent upon establishing the presence of initially unexpected panic attacks (with comparative freedom from anxiety between attacks) and the associated concern, worry or change in behaviour due to the anticipated risk of further attacks. In primary and secondary medical care, very few patients fulfil diagnostic criteria for agoraphobia without panic disorder: in coexisting panic and agoraphobia, some (II) (Goisman *et al*., 1995; Langs *et al*., 2000) but not all (II) (Lelliott *et al*., 1989; Amering *et al*., 1997) studies suggest agoraphobia is a consequence of the severity of a primary panic disorder.

Acute treatment

Systematic reviews demonstrate that a range of pharmacological, psychological and combination interventions are effective in panic disorder (Ia) (Van Balkom *et al*., 1997; Bakker *et al*., 1998). Randomized double-blind placebo-controlled trials of antidepressants indicate that all SSRIs (Ia) (escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), some TCAs (Ia) (clomipramine, imipramine) and some benzodiazepines (Ia) (alprazolam, clonazepam, diazepam and lorazepam) are efficacious in acute treatment (Den Boer, 1998; Otto *et al*., 2001). Other antidepressants with proven efficacy include the SNRI venlafaxine (Ib) (Pollack *et al*., 2004), the selective noradrenaline reuptake inhibitor reboxetine (Ib) (Versiani *et al*., 2002) and the MAOI brofaromine (no longer in development) (Ib) (van Vliet *et al*., 1993).

Comparator-controlled studies provide some evidence for efficacy of mirtazapine (Ib) (Ribeiro *et al*., 2001) and moclobemide (Ib) (Tiller *et al*., 1999) and suggest that escitalopram is superior to citalopram (Ib) (Stahl *et al*., 2003), and some SSRIs (paroxetine, fluvoxamine) to some noradrenaline reuptake inhibitors (reboxetine, maprotiline) (Ib) (Den Boer *et al*., 1988; Bertani *et al*., 2004). The side-effect burden associated with SSRI treatment in panic disorder is somewhat less than that with other classes of psychotropic drug (Ib) (Baldwin and Birtwistle, 1998). Treatments with unproven efficacy in panic disorder include the beta-blocker

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Table 7 Panic disorder: treatment approaches supported by placebo-controlled studies

	SSRIs	TCAs	Benzodiazepines	Others
Acute panic attack			Alprazolam Lorazepam	
Acute efficacy	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Clomipramine Imipramine	Alprazolam Clonazepam Diazepam Lorazepam	CBT Phenelzine Moclobemide* Mirtazapine* Venlafaxine Reboxetine Navalproate (Brofaromine) (Nefazodone)
Long-term efficacy	Citalopram Fluoxetine Paroxetine Sertraline	Clomipramine Imipramine	Alprazolam	Moclobemide* CBT
Relapse prevention	Fluoxetine Paroxetine Sertraline	Imipramine		CBT
Enhances the efficacy of psychological treatment (meta-analysis)	Paroxetine Buspirone	Antidepressants (meta-analysis)		Benzodiazepines
After non-response	Paroxetine (prior CBT)			Pindolol Group-CBT

*Comparator-controlled study only.
Empty cell indicates current absence of published placebo-controlled data.

propranolol (Ib) (Munjack *et al*., 1989), buspirone (Ib) (Sheehan *et al*., 1988) and antihistamines or antipsychotics (IV) (NICE, 2004). Fixed-dose RCTs with SSRIs provide only limited evidence of a dose-response relationship, for fluoxetine (Ib) (Michelson *et al*., 1998) and for paroxetine (Ib) (Ballenger *et al*., 1998).

Long-term treatment

Double-blind studies indicate that continuing SSRI or clomipramine treatment from 12 weeks to 52 weeks is associated with an increase in overall treatment response rates (Ib) (Lecrubier and Judge, 1997; Lepola *et al*., 1998), (IV) (Ballenger *et al*., 1998). Placebo-controlled and other relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication (fluoxetine, paroxetine, sertraline, imipramine), compared to switching to placebo for up to six months (Ib) (Mavissakalian and Perel, 1999; Michelson *et al*., 1999; Rapaport *et al*., 2001; Dannon *et al*., 2004).

Comparative efficacy of psychological, pharmacological and combination treatments

Pooled analyses and randomized controlled trials indicate that drug and psychological treatments, delivered singly, have broadly similar efficacy in acute treatment, and suggest CBT may be superior to TCAs in preventing symptomatic relapse (Ia) (van Balkom *et al*., 1997). Overall, it is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment, given alone (Ia) (Ib) (van Balkom *et al*., 1997; Barlow *et al*., 2000). An early study found that combination treatment with exposure was superior to imipramine given alone (Mavissakalian *et al.,* 1983). Combination treatment with paroxetine was superior to psychological treatment alone, in studies of bibliotherapy (Ib) (Dannon *et al*., 2002), 'very brief' CBT (Ib) (Stein *et al*., 2000) and basic CBT (Ib) (Oehrberg *et al*., 1995): and buspirone may enhance the short-term efficacy of CBT (Ib) (Cottraux *et al*., 1995).

When initial treatments prove unhelpful

There is no clear evidence for the benefit of dose escalation after an initial non-response to low doses. Switching between treatments with proven efficacy may be helpful (NICE, 2004). Augmentation of CBT with paroxetine may be superior to continuing with CBT alone, in patients who did not previously respond over 15 sessions (Kampmann *et al*., 2002), and augmentation of fluoxetine with pindolol was superior to continued monotherapy with fluoxetine (Hirschmann *et al*., 2000). The addition of group CBT may be beneficial in non-responders to pharmacological approaches (Pollack *et al*., 1994; Otto *et al*., 1999; Heldt *et al*.,

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2003). There is only limited evidence for augmentation strategies involving benzodiazepines, mood stabilizers or antipsychotic drugs.

Recommendations: treatment of panic disorder

Detection and diagnosis

- Become familiar with the diagnostic criteria for panic disorder (S)
- Assess the level of agoraphobic avoidance to help judge the severity of the condition (B)
- Ask about panic attacks and agoraphobia when patients present with depression or medically unexplained physical symptoms such as chest pain or shortness of breath (A)

Acute treatment

- Choose an evidence-based acute treatment (A):
  - *pharmacological*: all SSRIs, some TCAs (clomipramine, imipramine), some benzodiazepines (alprazolam, clonazepam, diazepam, lorazepam), venlafaxine, reboxetine
  - *psychological*: cognitive-behaviour therapy
- Take account of patient clinical features, needs and preference and local service availability when choosing treatment, as pharmacological and psychological approaches have broadly similar efficacy in acute treatment (S)
- Consider an SSRI for first-line pharmacological treatment (S)
- Consider increasing the dose if there is insufficient response, but there is only limited evidence for a dose-response relationship with SSRIs (A)
- Initial side-effects can be minimized by slowly increasing the dose (D)
- Advise the patient that treatment periods of up to 12 weeks are needed to assess efficacy (A)

Longer-term treatment

- Consider cognitive therapy with exposure as this may reduce relapse rates better than drug treatment (A)
- Continue drug treatment for a further six months in patients who are responding at 12 weeks (A)
- In longer-term drug treatment use an approach known to be efficacious in preventing relapse (S): first line drug choice is an SSRI (A), imipramine is a second-line choice (B)
- Monitor efficacy and tolerability regularly during long-term treatment (S)
- When stopping treatment, reduce the dose gradually over an extended period to avoid discontinuation and rebound symptoms (D). In the absence of evidence a minimum of three months is recommended for this taper period (D)

Combination of drugs and psychological treatment

- Routinely combining drug and psychological approaches is not recommended for initial treatment in the absence of consistent evidence for enhanced efficacy over each treatment given alone (D)

When initial treatments fail

- Consider switching to another evidence-based treatment after non-response at 12 weeks (C)
- Consider combining evidence-based treatments only when there are no contraindications (D)
- Consider adding paroxetine or buspirone to psychological treatments after partial response (A)
- Consider adding paroxetine, whilst continuing with CBT, after initial non-response (A)
- Consider adding group-CBT in non-responders to pharmacological approaches (A)
- Consider referral to regional or national specialist services in refractory patients (S)

Social phobia (also known as social anxiety disorder)

Recognition and diagnosis

Social phobia is often not recognized in primary medical care (I), where it is often misconstrued as shyness (Weiller *et al*., 1996). It can be distinguished from shyness by the levels of personal distress and associated social and occupational impairment (I) (Stein *et al*., 2000). The generalized subtype is associated with greater disability and higher comorbidity but patients with the non-generalized form can also be substantially impaired (I) (Kessler *et al.*, 1998; Eng *et al.*, 2000). Distinguishing social phobia from avoidant personality disorder is difficult and many patients fulfil diagnostic criteria for both conditions (I) (McGlashan *et al*., 2000). Patients can present with symptoms arising from comorbid conditions (especially depression), rather than with characteristic social anxiety and avoidance (IV) (Lecrubier *et al.*, 2000). Many patients use alcohol and drugs of misuse in an attempt to relieve symptoms (I) (Patel *et al.*, 2002).

Acute treatment

Systematic reviews and placebo-controlled RCTs indicate that a range of treatment approaches are efficacious, including CBT (Ia) (Heimberg, 2002), SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), the SNRI venlafaxine, the MAOI phenelzine and the RIMA moclobemide. Some benzodiazepines (bromazepam and clonazepam), anticonvulsants (gabapentin and pregabalin) and the antipsychotic olanzapine are also efficacious in acute treatment (Ia) (Blanco *et al*., 2003), (Ib) (Pande *et al*., 2004; Davidson *et al.*, 2004a; Davidson *et al.*, 2004b; Lader *et al.*, 2004). Treatments with unproven efficacy in generalized social phobia include the TCA imipramine, buspirone and the beta-blocker atenolol (Ib) (Blanco *et al*., 2003). There have been few comparator-controlled studies: escitalopram (20 mg/day) has been found superior to paroxetine (20 mg/day) (Lader *et al.*, 2004),

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Table 8 Social phobia: treatment approaches supported by placebo-controlled studies

	SSRIs	TCAs	Benzodiazepines	Others
Acute efficacy	Escitalopram		Bromazepam	CBT
	Fluoxetine		Clonazepam	Phenelzine
	Fluvoxamine		Moclobemide	
	Paroxetine		Venlafaxine	
	Sertraline		Gabapentin	
				Pregabalin
				Olanzapine
				(Brofaromine)
Long-term efficacy	Escitalopram			CBT
	Fluvoxamine			Phenelzine
	Paroxetine			Moclobemide
	Sertraline			Venlafaxine
Relapse prevention	Escitalopram	Clonazepam	CBT	
	Paroxetine			
	Sertraline			
Enhances the efficacy of psychological treatment	Sertraline			
After non-response				

Empty cell indicates current absence of published placebo-controlled data.

whereas venlafaxine (75–225 mg/day) and paroxetine (20–50 mg/day) had similar efficacy in two placebo-controlled studies (Allgulander *et al.*, 2004; Liebowitz *et al*., 2005). Fixed-dose RCTs do not provide convincing evidence of a dose-response relationship (Ib) (Liebowitz *et al.*, 2002; Lader *et al.*, 2004). *Post hoc* analysis of the RCT database with paroxetine indicates that many non-responders to treatment at eight weeks become responders with four further weeks of double-blind treatment (Stein *et al.*, 2002).

Long-term treatment

Double-blind studies indicate that continuing SSRI or SNRI treatment from 12 weeks to 24 weeks is associated with an increase in overall treatment response rates (Ib) (Stein *et al.*, 2003; Lader *et al.*, 2004; Stein *et al*., 2005). Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication (clonazepam, escitalopram, paroxetine, sertraline), compared with switching to placebo for up to six months (Ib) (Blanco *et al*., 2003).

Comparative efficacy of pharmacological, psychological and combination treatments

Drug and psychological treatments, delivered singly, have broadly similar efficacy in acute treatment (Ia) (Heimberg *et al.*, 1998; Otto *et al.*, 2000; Blomhoff *et al*., 2001; Davidson *et al.*, 2004). However, acute treatment with cognitive therapy (group or individual) may be associated with reduced risk of symptomatic relapse at follow-up (Ib) (Liebowitz *et al*., 1999; Clark *et al*., 2003; Haug *et al*., 2003). It is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment, given alone (Ib) (Blomhoff *et al*., 2001; Clark *et al*., 2003; Davidson *et al*., 2004).

When initial treatments prove unhelpful

There is no clear evidence for the benefit of dose escalation after an initial non-response. Switching between treatments with proven efficacy may be helpful (IIb) (Altamura *et al.*, 1999). Open-label augmentation of SSRI treatment with buspirone has been reported as beneficial (IIb) (Van Ameringen *et al.*, 1996), but a placebo-controlled pindolol augmentation study with paroxetine treatment indicates that the addition of pindolol was not associated with greater treatment efficacy (Ib) (Stein *et al*., 2001).

Simple phobia (also known as specific [or isolated] phobia)

Recognition and diagnosis

Specific fears of objects, animals, people or situations are widespread (having a lifetime prevalence of 49.5% in the National Comorbidity Survey), but only a minority (24.2%) of affected individuals reach diagnostic criteria for simple phobia (I) (Kessler *et al*., 1994). The presence of multiple fears is associated with increasing impairment, and comorbidity with other anxiety disorders (I) (Kessler *et al*., 1994). Many patients with specific fears only present for treatment at the time of changes in domestic or occupational responsibilities.

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Recommendations: treatment of social phobia

Detection and diagnosis

- Become familiar with the diagnostic criteria for social phobia (S)
- Assess the level of disability to help distinguish social phobia from shyness (A)
- Ask about social anxiety symptoms when patients present with depression, panic attacks restricted to social situations, or alcohol misuse (A)

Acute treatment

- Choose an evidence-based acute treatment (A):
  - *pharmacological*: most SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), venlafaxine, phenelzine, moclobemide, some benzodiazepines (bromazepam, clonazepam) and anticonvulsants (gabapentin, pregabalin) and olanzapine
  - *psychological*: cognitive-behaviour therapy
- Take account of patient clinical features, needs and preference and local service availability when choosing treatment, as pharmacological and psychological approaches have broadly similar efficacy in acute treatment (S)
- Consider an SSRI for first-line pharmacological treatment (D)
- Routine prescription of higher doses of SSRIs is not recommended (A), but individual patients may benefit from higher doses (D)
- Advise the patient that treatment periods of up to 12 weeks are needed to assess efficacy (A)

Longer-term treatment

- Continue drug treatment for a further six months in patients who are responding at 12 weeks (A)
- Consider cognitive therapy with exposure as this may reduce relapse rates better than drug treatment (A)
- In longer-term treatment use an approach known to be efficacious in preventing relapse (S): consider an SSRI or CBT first-line (A): clonazepam may be considered as a second-line choice (D)
- Consider cognitive therapy after response to drug treatment, in patients with a high risk of relapse (D)
- Monitor efficacy and tolerability regularly during long-term treatment (S)

Combination of drugs and psychological treatment

- Routinely combining drug and psychological approaches is not recommended for initial treatment in the absence of consistent evidence for enhanced efficacy over each treatment given alone (A)

When initial treatments fail

- Consider switching to venlafaxine after non-response to acute treatment with an SSRI (C)
- Consider adding buspirone after partial response to an SSRI (C)
- Consider benzodiazepines in patients who have not responded to other approaches (D)
- Consider combining evidence-based treatments only when there are no contraindications (D)
- Consider combining drug treatment and CBT (D)
- Consider referral to regional or national specialist services in refractory patients (S)

Treatment

Most specific fears respond to simple psychological approaches, based on exposure techniques. *In vivo* exposure with participant modelling appears superior to imaginal exposure (Ib) (Ost *et al*., 1997). Most patients respond to psychological approaches, and only few will require other treatment interventions (D). Limited data suggest that paroxetine (Ib) (Benjamin *et al*., 2000) and some benzodiazepines (III) (Uhlenhuth *et al*., 1999) are efficacious in acute treatment of simple phobia. It is unclear whether concomitant use of benzodiazepines enhances or reduces the efficacy of behavioural approaches.

Recommendations: treatment of simple phobia

Detection and diagnosis

- Assess the number of fears, impairment and comorbidity to judge severity (S)
- Ask about anxiety symptoms when patients present with specific fears or phobias (A)

Treatment

- Use psychological approaches based on exposure techniques as first-line treatment (D)
- Consider paroxetine or benzodiazepines when patients with distressing and impairing phobias have not responded to psychological approaches (C)

Post-traumatic stress disorder (PTSD)

Recognition and diagnosis

The findings of the US National Comorbidity Survey indicate that exposure to traumatic events was common (60.7% of men and 51.2% of women reported exposure to at least one traumatic event) but post-traumatic stress disorder (PTSD) had a lower lifetime prevalence (7.8%) indicating that many are resilient to traumatic adversity (I) (Kessler *et al*., 1995). PTSD shows considerable comorbidity with other anxiety disorders, depression and alcohol abuse or dependence, and is associated with increased use of health services, but is often not recognized in primary or secondary care, possibly due to unfamiliarity with the diagnostic criteria. Diagnosis can be established through a history of exposure to trauma (actual or threatened death, serious injury, or threats to the physical integrity of the self or others): a response of intense fear, helplessness or horror: re-experiencing symptoms (commonly intrusive recollections, flashbacks or dreams): avoidance symptoms (such as efforts to avoid activities or thoughts

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Table 9 Post-traumatic stress disorder: treatment approaches supported by placebo-controlled studies

	SSRIs	TCAs	Benzodiazepines	Others
Prevention of post-traumatic symptoms?				Hydrocortisone Propranolol Trauma-focused CBT
Acute efficacy	Fluoxetine	Amitriptyline	Alprazolam	Trauma-focused CBT
	Paroxetine	Imipramine		EMDR
	Sertraline			Brofaromine Phenelzine Lamotrigine Mirtazapine Venlafaxine
Long-term efficacy	Sertraline			
Relapse prevention	Fluoxetine Sertraline			CBT?
Enhances the efficacy of psychological treatment				
After non-response				Olanzapine* Risperidone*

*Placebo-controlled augmentation study.
Empty cell indicates current absence of published placebo-controlled data.

associated with the trauma): and hyper-arousal symptoms (including disturbed sleep, hypervigilance and an exaggerated startle response).

Prevention of post-traumatic symptoms

There is theoretical scope for preventing the emergence of post-traumatic symptoms in people subject to major trauma. Acute administration of propranolol (160 mg/day) was superior to placebo in reducing subsequent post-traumatic symptoms and physiological hyperactivity to reminders of trauma, but not the emergence of PTSD, at 1 month (Ib) (Pitman *et al*., 2002), and a naturalistic study suggests acute administration of propranolol (120 mg/day) prevented the emergence of syndromal PTSD at two months (IIa) (Vaiva *et al*., 2003). Acute intravenous administration of hydrocortisone was superior to placebo in preventing emergence of post-traumatic symptoms, both in intensive care patients with septic shock (median interval, 31 months), and in patients undergoing cardiac surgery (interval, six months) (Ib) (Schelling *et al*., 2001; Schelling *et al*., 2004). By contrast, early administration of benzodiazepines after trauma may not prevent the emergence of post-traumatic symptoms (IIa) (Gelpin *et al.*, 1996). The psychological approach with best evidence of efficacy in prevention of chronic post-traumatic symptoms is trauma-focused CBT, when provided within six months of the incident (Ia), approaches with limited efficacy include debriefing, relaxation and supportive psychotherapy (NICE, 2004).

Acute treatment of chronic PTSD

Systematic reviews demonstrate that a range of pharmacological and psychological approaches are efficacious in acute treatment of PTSD (Ia) (Van Etten and Taylor, 1998; Friedman *et al*., 2000; Stein *et al*., 2004; NICE, 2005). Randomized placebo-controlled trials provide evidence for the efficacy of some antidepressants (the SSRIs fluoxetine, paroxetine and sertraline: the TCAs amitriptyline and imipramine: the MAOIs phenelzine and brofaromine: and mirtazapine) on some outcome measures (Ia), but the clinical relevance of drug–placebo differences is debatable (NICE, 2005). In addition, there is evidence for the efficacy of venlafaxine (Ib) (Davidson *et al*., 2004), nefazodone (Davis *et al.*, 2004) and the anticonvulsant lamotrigine (Ib) (Hertzberg *et al*., 1999). A comparator- and placebo-controlled study suggests phenelzine was superior to imipramine, in relieving avoidance symptoms (Ib) (Kosten *et al*., 1991). It is uncertain whether there is a dose-response relationship with any of the compounds with evidence of efficacy. Psychological approaches with proven efficacy include individual trauma-focused CBT and eye movement desensitization and reprocessing (EMDR) (Ia) (Van Etten and Taylor, 1998; NICE, 2005). Non trauma-focused psychological treatments and group therapies have not been shown to have proven efficacy, but neither have they been shown to be harmful (Ia) (NICE, 2005).

Long-term treatment

After a response to acute treatment, continuing with venlafaxine (Ib) (Davidson *et al.*, 2004) or sertraline (IIb) (Londborg *et al*.,

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2001) treatment over six months is associated with a gradual increase in overall treatment response. Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication, for fluoxetine (Ib) (Martenyi *et al*., 2002; Davidson *et al.*, 2005) and sertraline (Ib) (Davidson *et al*., 2001).

Comparative efficacy of psychological and drug treatments

There have been very few direct comparisons of the efficacy of psychological and pharmacological treatments, in either acute or long-term treatment. A small unblinded 12-week comparison of paroxetine and trauma-focused CBT (IIa) (Frommberger *et al*., 2004) suggested that CBT may have certain advantages, in reducing post-traumatic and depressive symptoms.

When initial treatments prove unhelpful

There is no clear evidence for dose escalation after an initial non-response. Switching between treatments with proven efficacy may be helpful although there is little evidence (NICE, 2005). In placebo-controlled augmentation studies in patients who have not responded to antidepressant treatment, there is evidence for the efficacy of the atypical antipsychotic drugs olanzapine (Ib) (Stein *et al*., 2002) and risperidone (in patients with coexisting psychotic symptoms, or aggression) (Ia) (Hamner *et al*., 2003; Monelly *et al*., 2003). An uncontrolled small study suggests that augmentation with the anticonvulsant tiagabine may be beneficial, after initial non-response (IIb) (Taylor, 2003).

Obsessive-compulsive disorder (OCD)

Recognition and diagnosis

Obsessive-compulsive disorder has a lifetime prevalence of approximately 2.0% (I) (Weissman *et al*., 1994). The content of obsessions varies little between countries or cultures (I) (Sasson *et al.*, 1997). The disorder typically follows a chronic course, waxing and waning in severity: and substantial comorbidity with major depression and anxiety disorders(I) (Rasmussen and Eisen, 1990) and tic disorders (I) (Zohar *et al*., 1992). Distinguishing OCD from obsessive-compulsive personality disorder is difficult and patients may fulfil diagnostic criteria for both conditions (I) (Albert *et al*., 2004). Patients can present with symptoms arising from comorbid conditions (especially bipolar disorder and major depression), rather than with obsessional ruminations and compulsive rituals (IV) (Angst *et al.*, 2000).

Acute treatment

Systematic reviews and meta-analyses of randomized placebo-controlled trials indicate that the TCA clomipramine and the SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) are efficacious in acute treatment. Psychological approaches

Recommendations: treatment of post-traumatic stress disorder

Detection and diagnosis

- Ask about a history of trauma when patients present with psychological symptoms (S)
- Become familiar with the diagnostic criteria for post-traumatic stress disorder (S)

Prevention of post-traumatic symptoms

- After major trauma, and providing there are no contra indications, consider preventive treatment of post-traumatic symptoms with propranolol (A). Routine debriefing is not indicated (A)
- Trauma-focused CBT can prevent the emergence of chronic PTSD in individuals with post-traumatic symptoms lasting one month or longer after a traumatic event (A)

Acute treatment of chronic PTSD

- Choose an evidence-based acute treatment (A):
  - *pharmacological*: some SSRIs (fluoxetine, paroxetine, sertraline), some TCAs (amitriptyline, imipramine), phenelzine, mirtazapine, venlafaxine, lamotrigine
  - *psychological*: trauma-focused individual CBT and EMDR (A)
- Take account of patient clinical features, needs and preference and local service availability when choosing treatment, as the comparative efficacy of drug and psychological approaches is not established (S)
- Routinely prescribing higher doses of SSRIs is not recommended (A) but individual patients may benefit from higher doses (D)
- Advise the patient that treatment periods of up to 12 weeks are needed to assess efficacy (A)

Longer-term treatment

- Continue drug treatment for a further 12 months in patients who are responding at 12 weeks (C)
- In longer-term treatment use an approach known to be efficacious in preventing relapse (S): among pharmacological treatments the best evidence is for SSRIs (A)
- Monitor efficacy and tolerability regularly during long-term treatment (S)

Combination of drugs with psychological treatment

- Routinely combining drug and psychological approaches is not recommended because of the lack of evidence of enhanced efficacy over each treatment given alone (A)
- Antidepressants should be used in patients with co-existing severe depressive symptoms (A)

When initial treatments fail

- Consider switching to other evidence-based treatments, after non-response to first treatment (C)
- Consider combining evidence-based treatments only when there are no contraindications (D)
- Consider combining drug and psychological treatment (D)
- Consider augmentation of antidepressants with an atypical antipsychotic after initial non-response (C)
- Consider referral to regional or national specialist services in refractory patients (S)

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Table 10 Obsessive–compulsive disorder: treatment approaches supported by placebo-controlled studies

	SSRIs	TCAs	Benzodiazepines	Others
Acute efficacy	Citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Clomipramine Imipramine	Clonazepam?	CBT
Long-term efficacy	Fluoxetine Sertraline	Clomipramine		CBT
Relapse prevention	Fluoxetine Paroxetine Sertraline			
Enhances the efficacy of psychological treatment	Fluvoxamine	Clomipramine		
After non-response			Clonazepam	Another SSRI Haloperidol* Risperidone* Quetiapine* Pindolol*

*Placebo-controlled augmentation study.
Empty cell indicates absence of placebo-controlled data.

with proven efficacy in acute treatment include behaviour therapy based on exposure techniques and cognitive therapy (Ia) (Kobak *et al*., 1998).

The efficacy of clomipramine appears marginally superior to that of SSRIs in meta-analysis (Ia) (Ackerman and Greenland, 2002): though not in randomized controlled trials, in which the tolerability of SSRIs is generally superior (Ia) (Fineberg and Gale, 2005).

Fixed-dose comparator studies provide inconsistent evidence for a dose-response relationship with SSRIs, higher doses being associated with greater efficacy in some (Ib) (Montgomery *et al.*, 1993; Wheadon *et al.*, 1993; Hollander *et al.*, 2003) but not all evaluations (Ib) (Tollefson *et al.*, 1994; Greist *et al.*, 1995; Montgomery *et al.*, 2001).

Long-term treatment

Long-term (up to 12 months) double-blind studies demonstrate an advantage for continuing with medication, in patients who have responded to acute treatment (Ib) (Katz *et al*., 1990; Tollefson *et al*., 1994; Greist *et al*., 1995). Most (but not all) placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication (clomipramine, paroxetine, sertraline and fluoxetine, at higher dose), compared to switching to placebo (Ia) (Fineberg and Gale, 2005).

Comparative efficacy of psychological and drug treatments

There is some evidence that combination treatment is superior to psychological approaches or serotonergic antidepressant treatment, when given alone. The evidence for enhanced efficacy of exposure therapy with clomipramine compared to exposure alone is inconsistent (Ib) (Marks *et al*., 1988; Foa *et al*., 2005), but fluvoxamine has been shown to enhance the efficacy of exposure therapy (Ia) (Cottraux *et al*., 1993) and multi-modal CBT (Ia) (Hohagen *et al*., 1998). Some studies have suggested that relapse rates are greater after initial treatment with a pharmacological rather than with a psychological intervention (Ib) (Simpson *et al*., 2004).

When initial treatments prove unhelpful

Switching between pharmacological or psychological treatments with proven efficacy may be helpful in some patients, as may increasing dosage, tolerability permitting. Randomized double-blind or single-blind (Atmaca *et al*., 2002) placebo-controlled augmentation studies indicate that haloperidol (Ib) (McDougle *et al*., 1994), risperidone (Ib) (McDougle *et al*., 2000; Hollander *et al*., 2003; Erzegovesi *et al*., 2005) and quetiapine (Ib) (Atmaca *et al*., 2002; Denys *et al*., 2004) are all efficacious in patients who have not responded to initial treatment with SSRIs: the evidence for augmentation with pindolol is mixed (Ib) (Blier and Bergeron, 1996; Dannon *et al*., 2000). Intravenous infusion of clomipramine also appears efficacious after non-response to oral clomipramine, but the necessary arrangements for monitoring limit its usefulness in clinical practice (Fallon *et al*., 1998). By contrast, placebo-controlled or comparator-controlled (Pigott *et al*., 1991) studies indicate that augmentation treatment with lithium (Ib) (McDougle *et al*., 1991; Pigott *et al*., 1991), buspirone (Ib) (Pigott *et al*., 1992; Grady *et al*., 1993), liothyronine (Ib) (Pigott *et al*., 1991), desipramine (Ib) (Barr *et al*., 1997) or inositol (Ib)

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Recommendations: treatment of obsessive–compulsive disorder

Detection and diagnosis

- Become familiar with the diagnostic criteria for obsessive-compulsive disorder (S)
- Assess the time engaged in obsessive-compulsive behaviour, the associated distress and impairment, and the degree of attempted resistance to confirm the diagnosis
- Ask about obsessive-compulsive symptoms when patients present with depression (A)

Acute treatment

- Choose an evidence-based acute treatment (A):
  - *pharmacological*: clomipramine and SSRIs
  - *psychological*: exposure therapy and cognitive-behaviour therapy
- Take account of patient clinical features, needs and preference and local service availability when choosing treatment (S): drug and psychological approaches have broadly similar efficacy in acute treatment but relapse rates after response may be higher with pharmacological than with psychological treatment approaches (A)
- Consider an SSRI for first-line pharmacological treatment (D)
- Increase the dose of SSRIs if there is insufficient response (C), but be aware that this approach has not always been associated with greater response rates (A)
- Advise the patient that treatment periods of up to 12 weeks are needed to assess efficacy (A)

Longer-term treatment

- Continue drug treatment for a further 12 months in patients who are responding at 12 weeks (A)
- In longer-term treatment use an approach known to be efficacious in preventing relapse (S): consider SSRIs as first choice (A) as there is best evidence for this group
- Monitor efficacy and tolerability regularly during long-term treatment (S)

Combination of drugs with psychological treatments

- Routinely combining drug and psychological approaches is not recommended for initial treatment (B) but consider adding an SSRI or clomipramine to psychological treatment when efficacy needs to be maximized (C)

When initial treatments fail

- Consider increasing the dose of clomipramine or SSRI after initial non-response to standard doses (A)
- Consider switching between proven treatments after initial non-response (A)
- Consider combining evidence-based treatments only when there are no contraindications (S)
- Consider combining drug treatment and exposure therapy or CBT (B)
- Consider augmentation with antipsychotics or pindolol after initial SSRI non-response (A)
- Consider referral to regional or national specialist OCD services in refractory patients (S)

(Fux *et al*., 1999) is not efficacious. Potential but as yet not fully proven approaches in treatment-resistant OCD include higher-dose SSRI monotherapy; combination SSRI-clomipramine treatment; augmentation with other atypical antipsychotics, CNS-penetrating triptans, immunoglobulins and plasmapharesis (IV) (Husted and Shapira, 2004). Other potential approaches include deep brain stimulation (IIb) (Nuttin *et al*., 2003); and neurosurgical approaches, including anterior capsulotomy, limbic leucotomy and cingulotomy (III) (Royal College of Psychiatrists, 2000).

Special considerations

Children and adolescents

Certain anxiety disorders (social phobia and obsessive-compulsive disorder) have a typical age of onset of symptoms in adolescence, and many young people are substantially disabled by distressing, persistent and severe anxiety symptoms (I) (Rasmussen and Eisen, 1990; Faravelli *et al*., 2000; Weissman *et al*., 1994). There have been comparatively few controlled evaluations of the benefits and risks of psychotropic drug treatment in young people, but randomized placebo-controlled trials in children and adolescents indicate that SSRIs and clomipramine are efficacious in OCD (Ib) (Geller *et al*., 2003), and paroxetine in social phobia (Ib) (Wagner *et al*., 2004). The treatment response in OCD is similar in adult (18–65 years) and younger (6–17 years) clinical samples (Ia) (Fineberg *et al*., 2004).

The United Kingdom Committee on Safety of Medicines has stated that the balance of risks and benefits for the treatment of depressive illness in people under the age of 18 years is judged to be unfavourable for some SSRIs (escitalopram, citalopram, paroxetine and sertraline), mirtazapine and venlafaxine (IV) (Committee on Safety of Medicines, 2004), and has advised caution when treating adults aged 18–30 years with SSRIs. These recommendations do not apply to the treatment of children and adolescents with anxiety disorders, because the risk of self-harm is less and the therapeutic benefits greater. Nevertheless, careful monitoring is advisable, due to possible diagnostic uncertainty, the presence of comorbid depression, problems associated with estimating the optimal dosage and the difficulties young people might have in describing untoward effects of psychotropic drug treatment. It may be preferable to reserve pharmacological treatments for patients who do not respond to evidence-based psychological approaches.

Elderly patients

Many elderly patients are troubled by anxiety symptoms, though anxiety disorders in those over 65 years may be less common than in younger samples (I) (Flint, 1994; Schaub and Linden, 2000), and there have been few controlled investigations in this patient group. Placebo-controlled studies indicate that venlafaxine is efficacious in elderly patients with GAD (Ia) (Katz *et al*., 2002), and citalopram in patients with a range of anxiety disorders (Ib) (Lenze *et al*., 2005).

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Pharmacological treatment of anxiety disorders in patients with cardiac disease or epilepsy

TCAs are best avoided in patients with cardiac disease: they can increase heart rate, induce orthostatic hypotension, slow cardiac conduction and have significant quinidine-like effects on conduction within the myocardium. Other type 1A antiarrhythmics (quinidine, moricizine) carry an increased risk of mortality in patients with ventricular arrhythmias and ischaemic heart disease, and TCAs should be regarded as relatively contraindicated in these situations: by contrast, the SSRIs have minimal effects on cardiovascular function and may have potentially beneficial effects on platelet aggregation (Davies *et al*., 2004; Roose, 2003). The UK CSM currently recommends that venlafaxine is avoided in patients with cardiac disease, electrolyte imbalances or hypertension (IV) (Committee on Safety of Medicines, 2004).

Most antidepressants can lower the seizure threshold. The antidepressants amoxapine and maprotiline (and bupropion, marketed in the US as an antidepressant) probably have the most marked proconvulsant properties and should be avoided in epileptic patients (Kanner, 2003): the lack of evidence of efficacy in anxiety disorders means prescription of these drugs should be avoided. Pharmacokinetic interactions between antidepressants and anticonvulsants are not uncommon – for example, carbamazepine can increase the metabolism of TCAs, whereas fluoxetine can inhibit the metabolism of some anticonvulsants: it is always advisable to establish the potential for untoward drug–drug interactions when treating epileptic patients with anxiety disorders.

Pregnant and breastfeeding women

In general, most doctors would consider withdrawing psychotropic drugs in pregnant women (particularly in the first trimester), but it is sometimes necessary to continue treatment in patients with severe anxiety disorders. Many studies have indicated that TCAs and fluoxetine may be safe when taken during the first trimester, but their potential teratogenicity and effects on development after delivery is less certain. The findings of a prospective controlled study suggest that long-term pre-natal exposure to fluoxetine or TCAs does not adversely affect cognition, language development or temperament (II) (Nulman *et al*., 2002). A recent systematic review and pooled analysis indicates that plasma levels of paroxetine and sertraline (and the TCA nortriptyline) in breast-fed infants are usually undetectable, whereas citalopram and fluoxetine produce infant plasma levels that are above 10% of the maternal plasma level (in 22% and 17% of infants, respectively) (II) (Weissman *et al.*, 2004). The principal concern when treating parents with responsibility for infants is probably to avoid the use of excessively sedating compounds (principally TCAs, but also mianserin, mirtazapine and trazodone).

Referral to secondary care mental health services

Patients should be referred to secondary care mental health services when the primary care practitioner feels insufficiently experienced to manage the patient's condition; when two or more attempts at treatment have not resulted in sustained improvement; when there are severe coexisting depressive symptoms or a risk of suicide; when comorbid physical illness and concomitantly prescribed treatments could interact with prescribed psychotropic medication; and when proposed interventions are not available within primary care services.

Recommendations: special considerations

Children and adolescents

- Reserve pharmacological treatments for children and adolescents who have not responded to psychological treatments, and in whom the potential benefits are likely to outweigh potential risks (B)
- If drug treatment is considered choose from the same range of treatments as with adults: SSRIs are a first-line choice from limited evidence (A), but avoid benzodiazepines and tricyclic antidepressants because of potential adverse effects (D)
- Consider dosages carefully in relation to age and size, starting with low doses (D)
- Carefully monitoring for potential adverse effects, being aware that children and adolescents may find it difficult to describe them (S)

Elderly patients

- Treat as for patients younger than 65 years being mindful of the possibility of drug interactions, physical comorbidity, the need for lower doses due to reduced metabolism, or increased sensitivity to adverse effects (D)

Cardiac disease and epilepsy

- Avoid tricyclic antidepressants in cardiac disease (C)
- The relative safety of venlafaxine is unclear at the time of writing (August 2005) and it is not possible to make a consensus recommendation. Current recommendations advise against use of venlafaxine in patients with cardiac disease
- Avoid antidepressants that lower the seizure threshold in epilepsy (C)
- Consider pharmacokinetic interactions between antidepressants and other drugs, e.g. anticonvulsants (S)

Pregnancy and breastfeeding

- Consider carefully the potential risks and benefits of pharmacological treatment and alternative evidence-based psychological treatments, avoiding drugs if possible (S)
- Fluoxetine or tricyclic antidepressants are considered first-line if drug treatment is used in pregnancy, as there is most evidence with these drugs (C)
- Consider SSRIs (apart from fluoxetine and citalopram) and tricyclic antidepressant in breast-feeding mothers as secretion into breast milk is low (C)

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Referral to secondary care mental health services

- Patients should be referred (S) if any of the following apply:
  - the primary care practitioner feels insufficiently experienced to manage the patient's condition
  - two or more attempts at treatment have not resulted in sustained improvement
  - there are severe coexisting depressive symptoms or a risk of suicide
  - comorbid physical illness and concomitantly prescribed treatments could interact with prescribed psychotropic medication
  - proposed interventions are not available within primary care services

Note

Enquiries about data held by pharmaceutical companies and referenced here should be directed to the medical department of the relevant company.

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The patient organizations National Phobics Society and No Panic were represented at the meeting. Observers were also present from the Janssen, Roche, Lundbeck and Wyeth pharmaceutical companies.

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No Panic: www.nopanic.org.uk.

References

Ackerman D L, Greenland S (2002) Multivariate meta-analysis of controlled drugs studies for obsessive compulsive disorder. J Clin Psychopharmacol *22*: 309–317

Albus M, Scheibe G (1993) Outcome of panic disorder with or without concomitant depression: A 2-year prospective follow-up study. Am J Psychiatry *150*: 1878–1880

Allgulander C, Hackett D, Salinas E (2001) Venlafaxine extended release (ER) in the treatment of generalized anxiety disorder: twenty-four week placebo-controlled dose-ranging study. Br J Psychiatry *179*: 15–22

Allgulander C, Huusom A K T, Florea I (2005) Escitalopram for relapse prevention in generalized anxiety disorder (GAD). Poster presentation, ADAA meeting, March

Allgulander C, Mangano R, Zhang J, Dahl A A, Lepola U, Sjodin I, Emilien G. (2004) Efficacy of venlafaxine ER in patients with social anxiety disorder: a double-blind, placebo-controlled, parallel-group comparison with paroxetine. Human Psychopharmacology *19*: 387–396

Allgulander C, Bandelow B, Hollander E, Montgomery S A, Nutt D J, Okasha A, Pollack M H, Stein D J, Swinson R P: World Council of Anxiety (2003) WCA recommendations for the long-term treatment of generalized anxiety disorder. CNS Spectrums *8* (Suppl. 1): 53–61

Allgulander C, Dahl A A, Austin C (2004) Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. Am J Psychiatry *161*: 1642–1649

Altamura A C, Pioli R, Vitto M, Mannu P (1999) Venlafaxine in social phobia: a study in selective serotonin reuptake inhibitor non-responders. Int Clin Psychopharmacol *14*: 239–245

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th edn. American Psychiatric Association, 1994. Washington, DC

Amering M, Katschnig H, Berger P, Windhaber J, Baischer W, Dantendorfer K (1997) Embarrassment about the first panic attack predicts agoraphobia in panic disorder patients. Behav Res Ther *35*: 517–521

Anderson I M, Nutt D J, Deakin J F (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British Association for Psychopharmacology. J Psychopharmacol *14*: 3–20

Andlin-Sobocki P, Wittchen H U (2005) Cost of anxiety disorders in Europe. Eur J Neurol *12* (Suppl. 1): 39–44

Angst J, Gamma A, Endrass J, Hantouche E, Goodwin R, Ajdacic V, Eich D, Rossler W (2005) Obsessive-compulsive syndromes and disorders: Significance of comorbidity with bipolar and anxiety syndromes. Eur Arch Psychiatry Clin Neurosci *255*: 65–71

Ashton H, Young A H (2003) GABA-ergic drugs: exit stage left, enter stage right. J Psychopharmacol *17*: 174–178

Atmaca M, Kuloglu M, Tezcan E, Gecici O (2002) Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. Int Clin Psychopharmacol *17*: 115–119

Bakker A, van Balkom A J, Spinhoven P, Blaauw B M, van Dyck R (1998) Follow-up on the treatment of panic disorder with or without agoraphobia: a quantitative review. J Nerv Ment Dis *186*: 414–419

Baldwin D S (2004) Sexual dysfunction associated with antidepressant drugs. Expert Opinion on Drug Safety *3*: 457–470

Baldwin D S, Birtwistle J (1998) The side effect burden associated with drug treatment of panic disorder. J Clin Psychiatry *59* (Suppl. 8): S39–S44

Baldwin D S, Polkinghorn C (2005) Evidence-based pharmacotherapy of generalized anxiety disorder. Int J Neuropsychopharmacol *8*: 293–302

Baldwin D S, Huusom A K T, Maehlum E (2004) Escitalopram and paroxetine compared to placebo in generalised anxiety disorder. Eur Neuropsychopharmacol *14*: (Suppl. 3): S311–S312

Ballenger J C, Wheadon D E, Steiner M, Bushnell W, Gergel I P (1998) Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry *155*: 36–42

Ballenger J C, Davidson J R, Lecrubier Y, Nutt D J, Baldwin D S, den Boer J A, Kasper S, Shear M K (1998) Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry *59* (Suppl. 8): 47–54

Ballenger J C Davidson J R, Lecrubier Y, Nutt D J, Bobes J, Beidel D C, Ono Y, Westenberg H G (1998) Consensus statement on social anxiety

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disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry *59* (Suppl. 17): 54–60

Ballenger J C, Davidson J R, Lecrubier Y, Nutt D J, Borkovec T D, Rickels K, Stein D J, Wittchen H U (2001) Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry *62* (Suppl. 11): 53–58

Ballenger J C, Davidson J R, Lecrubier Y, Nutt D J, Marshall R D, Nemeroff C B, Shalev A Y, Yehuda R (2004) Consensus statement update on posttraumatic stress disorder from the international consensus group on depression and anxiety. J Clin Psychiatry *65* (Suppl. 1): 55–62

Bandelow B, Zohar J, Hollander E, Kasper S, Möller H J, World Federation of Societies of Biological Psychiatry Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Posttraumatic Stress Disorders (2002) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders. World J Biol Psychiatry *3*: 171–199

Barlow D H, Gorman J M, Shear M K, Woods S W (2000). Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. JAMA *283*: 2529–2536

Barr L C, Goodman W K, Anand A, McDougle C J, Price L H (1997). Addition of desipramine to serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder. Am J Psychiatry *154*: 1293–1295

Benjamin J, Ben-Zion I Z, Karbofsky E, Dannon P (2000) Double-blind placebo-controlled pilot study of paroxetine for specific phobia. Psychopharmacology (Berl.) *149*: 194–196

Bertani A, Perna G, Migliarese G, Di Pasquale D, Cucchi M, Caldirola D, Bellodi L (2004) Comparison of the treatment with paroxetine and reboxetine in panic disorder: a randomized, single-blind study. Pharmacopsychiatry *37*: 206–210

Bielski R J, Bose A, Chang C-C (2004) A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology, December 7–11, San Juan, Puerto Rico

Bjelland I, Dahl A A, Haug T T, Neckelmann D (2002) The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res *52*: 69–77

Blanco C, Raza M S, Schneier F, Liebowitz M R (2003) The evidence-based pharmacotherapy of social anxiety disorder. Int J Neuropsychopharmacol *6*: 427–442

Blier P, Bergeron R (1996) Sequential administration of augmentation strategies in treatment-resistant obsessive-compulsive disorder: preliminary findings. Int Clin Psychopharmacol *11*: 37–44

Blomhoff S, Haug T T, Hellstrom K, Holme I, Humble M, Madsbu H P, Wold J E (2001) Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. Br J Psychiatry *179*: 23–30

Bower P, Richards D, Lovell K (2001) The clinical and cost-effectiveness of self-help treatments for anxiety and depressive disorders in primary care: a systematic review. Br J Gen Pract *51*: 838–845

Broocks A, Bandelow B, Pekrun G, George A, Meyer T, Bartmann U, Hillmer-Vogel U, Ruther E (1998) Comparison of aerobic exercise, clomipramine, and placebo in the treatment of panic disorder. Am J Psychiatry *155*: 603–609

Brown T A, Antony M M, Barlow D H (1995) Diagnostic comorbidity in panic disorder: effect on treatment outcome and course of comorbid diagnoses following treatment. J Consult Clin Psychol *63*: 408–418

Carlbring P, Ekselius L, Andersson G (2003) Treatment of panic disorder via the Internet: a randomized trial of CBT vs. applied relaxation. J Behav Ther Exp Psychiatry *34*: 129–140

Clark D M, Ehlers A, McManus F, Hackmann A, Fennell M, Campbell H, Flower T (2003) Cognitive therapy versus fluoxetine in generalized social phobia: a randomized placebo-controlled trial. Journal of Consulting and Clinical Psychology *71*: 1058–1067

Committee on Safety of Medicines (2004). Safety of selective serotonin reuptake inhibitor antidepressants. 6 December

Costello E J, Mustillo S, Erkanli A, Keeler G, Angold A (2003) Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry *60*: 837–844

Cottraux J, Mollard E, Bouvard M, Marks I (1993) Exposure therapy, fluvoxamine, or combination treatment in obsessive-compulsive disorder: one-year follow-up. Psychiatry Res *49*: 63–75

Cottraux J, Note I D, Cungi C, Legeron P, Heim F, Chneiweiss L, Bernard G, Bouvard M (1995) A controlled study of cognitive behaviour therapy with buspirone or placebo in panic disorder with agoraphobia. Br J Psychiatry *167*: 635–641

Cowley D S, Flick S N, Roy-Byrne P P (1996) Long-term course and outcome in panic disorder: a naturalistic follow-up study. Anxiety *2*: 13–21

Dannon P N, Iancu I, Grunhaus L (2002) Psychoeducation in panic disorder patients: effect of a self-information booklet in a randomized, masked-rater study. Depress Anxiety *16*: 71–76

Dannon P N, Sasson Y, Hirschmann S, Iancu I, Grunhaus L J, Zohar J (2000) Pindolol augmentation in treatment-resistant obsessive compulsive disorder: a double-blind placebo controlled trial. Eur Neuropsychopharmacol *10*: 165–169

Dannon P N, Iancu I, Cohen A, Lowengrub K, Grunhaus L, Kotler M (2004) Three year naturalistic outcome study of panic disorder patients treated with paroxetine. BMC Psychiatry *4*: 16

Davidson J, Pearlstein T, Londborg P, Brady K T, Rothbaum B, Bell J, Maddock R, Hegel M T, Farfel G (2001) Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. Am J Psychiatry *158*: 1974–1981

Davidson J R, Baldwin D S, Stein D J (2004) Treatment of Posttraumatic Stress Disorder With Venlafaxine Extended Release: A 6-Month Randomized, Controlled Trial. Presented at American College of Neuropsychopharmacology, Puerto Rico, December

Davidson J R (2005) Maintenance therapy with fluoxetine in posttraumatic stress disorder: a placebo-controlled discontinuation study. J Clin Psychopharmacology *25*: 166–169

Davidson J R T, Foa E B, Huppert J, Keefe F J, Franklin M E, Compton J S, Zhao N (2004) Fluoxetine, comprehensive cognitive behavioral therapy (CCBT) and placebo in generalized social anxiety disorder. Arch Gen Psychiatry *61*: 1005–1013

Davies S J C, Jackson R P, Potokar J, Nutt D J (2004) Treatment of anxiety and depressive disorders in patients with cardiovascular disease. BMJ *328*: 939–943

Davis L L, Jewell M E, Ambrose S, Farley J, English B, Bartolucci A, Petty F (2004) A placebo-controlled study of nefazodone for the treatment of chronic posttraumatic stress disorder: a preliminary study. J Clin Psychopharmacol *24*: 291–297

Den Boer J A, Westenberg H G (1988) Effect of a serotonin and noradrenaline uptake inhibitor in panic disorder: a double-blind comparative study with fluvoxamine and maprotiline. Int Clin Psychopharmacol *3*: 59–74

Den Boer J A (1998) Pharmacotherapy of panic disorder: differential efficacy from a clinical viewpoint. J Clin Psychiatry *59* (Suppl. 8): 30–36

Den Boer P C, Wiersma D, Van den Bosch R J (2004) Why is self-help

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neglected in the treatment of emotional disorders? A meta-analysis. Psychol Med *34*: 959–971

Denys D, de Geus F, van Megen H J, Westenberg H G (2004) A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors. J Clin Psychiatry *65*: 1040–1048

Dowell A C, Biran L A (1990) Problems in using the hospital anxiety and depression scale for screening patients in general practice. Br J Gen Pract *40*: 27–28

Durham R C, Turvey A A (1987). Cognitive therapy versus behaviour therapy in the treatment of chronic generalised anxiety. Behav Res Ther *25*: 229–234

Durham R C, Chambers J A, MacDonald R R, Power K G, Major K (2003) Does cognitive-behavioural therapy influence the long-term outcome of generalized anxiety disorder? An 8–14 year follow-up of two clinical trials. Psychol Med *33*: 499–509

Durham R C, Chambers J A, Power K G, Sharp D M, Macdonald R, Makor K A, Dow M G T, Gumpley A I (in press) Long-term outcome of cognitive behavior therapy clinical trials in central Scotland. Health Technology Assessment

Ehlers A, Clark D M, Hackmann A, McManus F, Fennell M, Herbert C, Mayou R (2003) A randomized controlled trial of cognitive therapy, a self-help booklet, and repeated assessments as early interventions for posttraumatic stress disorder. Arch Gen Psychiatry. *60*: 1024–1032

El-Khayat R, Baldwin D S (1998) Antipsychotic drugs for non-psychotic patients: assessment of the benefit/risk ratio in generalized anxiety disorder. J Psychopharmacol *12*: 323–329

Eng W, Heimberg R G, Coles M E, Schneier F R, Liebowitz M R (2000) An empirical approach to subtype identification in individuals with social phobia. Psychol Med *30*: 1345–1357

Erwin B A, Heimberg R G, Juster H, Mindlin M (2002) Comorbid anxiety and mood disorders among persons with social anxiety disorder. Behav Res Ther *40*: 19–35

Erzegovesi S, Guglielmo E, Siliprandi F, Bellodi L (2005) Low-dose risperidone augmentation of fluvoxamine treatment in obsessive-compulsive disorder: a double-blind, placebo-controlled study. Eur Neuropsychopharmacol *15*: 69–74

Fallon B A, Liebowitz M R, Campeas R, Schneier F R, Marshall R, Davies S, Goetz D, Klein D F (1998) Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. Arch Gen Psychiatry *55*: 918–924

Faravelli C, Zucchi T, Viviani B, Salmoria R, Perone A, Paionni A, Scarpato A, Vigliaturo D, Rosi S, D'adamo D, Bartolozzi D, Cecchi C, Abrardi L (2000) Epidemiology of social phobia: a clinical approach. Eur Psychiatry *15*: 17–24

Fehm L, Pelissolo A, Furmark T, Wittchen H U (2005) Size and burden of social phobia in Europe. Eur Neuropsychopharmacol *15*: 453–462

Feltner D E, Crockatt J G, Dubovsky S J (2003) A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. J Clin Psychopharmacol *23*: 240–249

Fineberg N A, Gale T M (2005) Evidence-based pharmacotherapy of obsessive-compulsive disorder. Int J Neuropsychopharmacol *8*: 107–129

Fineberg N A, Heyman I, Jenkins R, Premkumar P, Veale D, Kendall T, Freeston M (2004) Does childhood and adult obsessive compulsive disorder (OCD) respond the same way to treatment with serotonin reuptake inhibitors? Eur Neuropsychopharmacol *14* (Suppl. 3): 191–192

Fisher P L, Durham R C (1999) Recovery rates in generalized anxiety disorder following psychological therapy: an analysis of clinically significant change in the STAI-T across outcome studies since 1990. Psychol Med *29*: 1425–1434

Flint A J (1994) Epidemiology and comorbidity of anxiety disorders in the elderly. Am J Psychiatry *151*: 640–649

Foa E B, Liebowitz M R, Kozak M J, Davies S, Campeas R, Franklin M E, Huppert J D, Kjernisted K, Rowan V, Schmidt A B, Simpson H B, Tu X (2005) Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. Am J Psychiatry *162*: 151–61

Fontana A, Rosenheck R (1997) Effectiveness and cost of the inpatient treatment of posttraumatic stress disorder: comparison of three models of treatment. Am J Psychiatry *154*: 758–765

Friedman M J, Davidson J R T, Mellman T A (2000) Pharmacotherapy. In Foa E B, Keane T M, Friedman M J (eds) Effective Treatments for PTSD: Practice Guidelines from the International Society for Stress Studies. Guilford Press, New York, pp. 84–105

Frommberger U, Stieglitz R D, Nyberg E (2004) Comparison between paroxetine and behaviour therapy in patients with posttraumatic stress disorder (PTSD): a pilot study. Int J Psychiatry Clin Pract *8*: 19–23

Fux M, Benjamin J, Belmaker R H (1999) Inositol versus placebo augmentation of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder: a double-blind cross-over study. Int J Neuropsychopharmacol *2*: 193–195

Geller D A, Biederman J, Stewart S E, Mullin A, Spencer T, Faraone S V (2003) Which SSRI? A meta-analysis of pharmacotherapy trials in paediatric obsessive-compulsive disorder. Am J Psychiatry *160*: 1919–1928

Gelpin E, Bonne O, Peri T, Brandes D, Shalev A Y (1996) Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin Psychiatry *57*: 390–394

Goisman R M, Warshaw M G, Steketee G S, Fierman E J, Rogers M P, Goldenberg I, Weinshenker N J, Vasile R G, Keller M B (1995) DSM-IV and the disappearance of agoraphobia without a history of panic disorder: new data on a controversial diagnosis. Am J Psychiatry *152*: 1438–1443

Goldberg D, Bridges K (1987) Screening for psychiatric illness in general practice: the general practitioner versus the screening questionnaire. J R Coll Gen Pract *37*: 15–18

Goodwin G M: Consensus Group of the British Association for Psychopharmacology (2003) Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. J Psychopharmacol *17*: 149–173

Goodwin R D, Faravelli C, Rosi S, Cosci F, Truglia E, de Graaf R, Wittchen H U (2005) Size and burden of panic disorder and agoraphobia in Europe. Eur Neuropsychopharmacol *15*: 435–443

Gould R A, Otto M W, Pollack M H (1997) Cognitive behavioural and pharmacological treatment of generalised anxiety disorder: a preliminary meta-analysis. Behav Ther *28*: 285–305

Grady T A, Pigott T A, L'Heureux F, Hill J L, Bernstein S E, Murphy D L (1993) Double-blind study of adjuvant buspirone for fluoxetine-treated patients with obsessive-compulsive disorder. Am J Psychiatry *150*: 819–821

Greenberg P E, Sisitsky T, Kessler R C, Finkelstein S N, Berndt E R, Davidson J R, Ballenger J C, Fyer A J (1999) The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry *60*: 427–435

Greist J H, Marks I M, Baer L, Kobak K A, Wenzel K W, Hirsch M J, Mantle J M, Clary C M (2002) Behavior therapy for obsessive-compulsive disorder guided by a computer or by a clinician compared with relaxation as a control. J Clin Psychiatry *63*: 138–145

Greist J H, Bandelow B, Hollander E, Marazziti D, Montgomery S A, Nutt D J, Okasha A, Swinson R P, Zohar J, World Council of Anxiety (2003) WCA recommendations for the long-term treatment of obsessive-compulsive disorder in adults. CNS Spectrums *8* (Suppl. 1): 7–16

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Greist J H, Jefferson J W, Kobak K A, Chouinard G, DuBoff E, Halaris A, Kim S W, Koran L, Liebowtiz M R, Lydiard B (1995) A 1 year double-blind placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol *10*: 57–65

Guest J, Russ J, Lenox-Smith A (2005) Cost effectiveness of venlafaxine XL compared with diazepam in the treatment of generalised anxiety disorder in the United Kingdom. Eur J Health Econom *6*: 136–145

Hamner M B, Faldowski R A, Ulmer H G, Frueh B C, Huber M G, Arana G W (2003) Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. Int Clin Psychopharmacol *18*: 1–8

Haug T T, Blomhoff S, Hellstrom K, Holme I, Humble M, Madsbu H P, Wold J E (2003) Exposure therapy and sertraline in social phobia: 1-year follow-up of a randomised controlled trial. Br J Psychiatry *182*: 312–318

Haynes R B, Devereaux P J, Guyatt G H (2002) Physicians' and patients' choices in evidence based practice. BMJ *324*: 1350

Heimberg R G (2002) Cognitive-behavioral therapy for social anxiety disorder: current status and future directions. Biol Psychiatry *51*: 101–108

Heimberg R G, Liebowitz M R, Hope D A, Schneier F R, Holt C S, Welkowitz L A, Juster H R, Campeas R, Bruch M A, Cloitre M, Fallon B, Klein D F (1998) Cognitive behavioral group therapy vs phenelzine therapy for social phobia: 12-week outcome. Arch Gen Psychiatry *55*: 1133–1141

Heldt E, Manfro G G, Kipper L, Blaya C, Maltz S, Isolan L, Hirakata V N, Otto M W (2003) Treating medication-resistant panic disorder: predictors and outcome of cognitive-behavior therapy in a Brazilian public hospital. Psychother Psychosom *72*: 43–48

Hertzberg M A, Butterfield M I, Feldman M E, Beckham J C, Sutherland S M, Connor K M, Davidson J R (1999) A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. Biol Psychiatry *45*: 1226–1229

Hirschmann S, Dannon P N, Iancu I, Dolberg O T, Zohar J, Grunhaus L (2000) Pindolol augmentation in patients with treatment-resistant panic disorder: A double-blind, placebo-controlled trial. J Clin Psychopharmacol *20*: 556–559

Hoehn-Saric R, Ninan P, Black D W, Stahl S, Greist J H, Lydiard B, McElroy S, Zajecka J, Chapman D, Clary C, Harrison W (2000) Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. Arch Gen Psychiatry. *57*: 76–82

Hohagen F, Winkelmann G, Rasche-Ruchle H, Hand I, Konig A, Munchau N, Hiss H, Geiger-Kabisch C, Kappler C, Schramm P, Rey E, Aldenhoff J, Berger M (1998) Combination of behaviour therapy with fluvoxamine in comparison with behaviour therapy and placebo. Results of a multicentre study. Br J Psychiatry *35* (Suppl.): 71–78

Hollander E, Baldini Rossi N, Sood E, Pallanti S (2003) Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. Int J Neuropsychopharmacol *6*: 397–401

Hollander E, Allen A, Steiner M, Wheadon D E, Oakes R, Burnham D B, Paroxetine OCD Study Group (2003) Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. J Clin Psychiatry *64*: 1113–1121

Hoyer J, Wittchen H U (2003) Generalized anxiety disorders in primary medical care. Versicherungsmedizin *55*: 127–135

Huppert J D, Schultz L T, Foa E B, Barlow D H, Davidson J R, Gorman J M, Shear M K, Simpson H B, Woods S W (2004) Differential response to placebo among patients with social phobia, panic disorder, and obsessive-compulsive disorder. Am J Psychiatry *161*: 1485–1487

Husted D S, Shapira N A (2004) A review of the treatment for refractory obsessive-compulsive disorder: from medicine to deep brain stimulation. CNS Spectr *9*: 833–847

Issakidis C, Sanderson K, Corry J, Andrews G, Lapsley H (2004) Modelling the population cost-effectiveness of current and evidence-based optimal treatment for anxiety disorders. Psychol Med *34*: 19–35

Jorm A F, Christensen H, Griffiths K M, Parslow R A, Rodgers B, Blewitt K A (2004) Effectiveness of complementary and self-help treatments for anxiety disorders. Med J Aust *181* (Suppl.): S29–S46

Kampman M, Keijsers G P, Hoogduin C A, Hendriks G J (2002) A randomized, double-blind, placebo-controlled study of the effects of adjunctive paroxetine in panic disorder patients unsuccessfully treated with cognitive-behavioral therapy alone. J Clin Psychiatry *63*: 772–777

Kapczinski F, Schmitt R, Lima M S (2003) The use of antidepressants for generalized anxiety disorder. Cochrane Database of Systematic Reviews

Katon W J, Roy-Byrne P, Russo J, Cowley D (2002) Cost-effectiveness and cost offset of a collaborative care intervention for primary care patients with panic disorder. Arch Gen Psychiatr *95*: 1098–1104

Katz R J, DeVeaugh-Geiss J, Landau P (1990) Clomipramine in obsessive-compulsive disorder. Biol Psychiatry *28*: 401–414

Katz I R, Reynolds C F 3rd, Alexopoulos G S, Hackett D (2002) Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: pooled analysis of five randomized placebo-controlled clinical trials. J Am Geriatr Soc *50*: 18–25

Kessler R C, Stein M B, Berglund P (1998) Social phobia subtypes in the National Comorbidity Survey. Am J Psychiatry *155*: 613–619

Kessler R C, Sonnega A, Bromet E, Hughes M, Nelson C B (1995) Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry *52*: 1048–1060

Kessler R C, McGonagle K A, Zhao S, Nelson C B, Hughes M, Eshleman S, Wittchen H U, Kendler K S (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry *51*: 8–19

Kessler R C, DuPont R L, Berglund (1999) Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. Am J Psychiatry *156*: 1915–1923

Khan A, Brodhead A E, Kolts R L, Brown W A (2005) Severity of depressive symptoms and response to antidepressants and placebo in antidepressant trials. J Psychiatr Res *39*: 145–150

Kobak K A, Greist J H, Jefferson J W, Katzelnick D J, Henk H J (1998) Behavioral versus pharmacological treatments of obsessive compulsive disorder: a meta-analysis. Psychopharmacology (Berl) *136*: 205–216

Lader M H, Bond A J (1998) Interaction of pharmacological and psychological treatments of anxiety. Br J Psychiatry *173* (Suppl. 34): 42–48

Lader M, Scotto J C (1998) A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. Psychopharmacol *139*: 402–406

Lader M, Stender K, Burger V, Nil R (2004) Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. Depression and Anxiety *19*: 241–248

Langs G, Quehenberger F, Fabisch K, Klug G, Fabisch H, Zapotoczky H G (2000) The development of agoraphobia in panic disorder: a predictable process? J Affect Disord *58*: 43–50

Lecrubier Y, Judge R (1997) Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Collaborative Paroxetine Panic Study Investigators. Acta Psychiatr Scand *95*: 153–160

Lecrubier Y, Wittchen H U, Faravelli C, Bobes J, Patel A, Knapp M (2000) A European perspective on social anxiety disorder. Eur Psychiatry *15*: 5–16

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Lelliott P, Marks I, McNamee G, Tobena A (1989) Onset of panic disorder with agoraphobia. Toward an integrated model. Arch Gen Psychiatry *46*: 1000–1004

Lenze E J, Mulsant B H, Shear M K, Dew M A, Miller M D, Pollock B G, Houck P, Tracey B, Reynolds C F 3rd (2005) Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial. Am J Psychiatry *162*: 146–150

Lepola U M, Wade A G, Leinonen E V, Koponen H J, Frazer J, Sjodin I, Penttinen J T, Pedersen T, Lehto H J (1998). A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. J Clin Psychiatry *59*: 528–534

Lewis G, Wessely S (1990) Comparison of the General Health Questionnaire and the Hospital Anxiety and Depression Scale. Br J Psychiatry *157*: 860–864

Lidren D M, Watkins P L, Gould R A, Clum G A, Asterino M, Tulloch H L (1994) A comparison of bibliotherapy and group therapy in the treatment of panic disorder. Consult Clin Psychol *62*: 865–869

Lieb R, Becker E, Altamura C (2005) The epidemiology of generalized anxiety disorder in Europe. Eur J Neuropsychopharmacol *15*: 445–452

Liebowitz M R, Gelenberg A J, Munjack D (2005) Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. Arch Gen Psychiatry *62*: 190–198

Liebowitz M R, Stein M B, Tancer M, Carpenter D, Oakes R, Pitts C D (2002) A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. J Clin Psychiatry *63*: 66–74

Liebowitz M R, Heimberg R G, Schneier F R, Hope D A, Davies S, Holt C S, Goetz D, Juster H R, Lin S H, Bruch M A, Marshall R D, Klein D F (1999) Cognitive-behavioral group therapy versus phenelzine in social phobia: long-term outcome. Depress Anxiety *10*: 89–98

Lingford-Hughes A R, Welch S, Nutt D J: British Association for Psychopharmacology (2004) Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology. J Psychopharmacol *18*: 293–335

Llorca P M, Sapdone C, Sol O (2002) Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a three-month double-blind study. J Clin Psychiatry *63*, 1020–1027

Londborg P D, Hegel M T, Goldstein S, Goldstein D, Himmelhoch J M, Maddock R, Patterson W M, Rausch J, Farfel G M (2001) Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. J Clin Psychiatry *62*: 325–331

McCrone P, Knapp M, Proudfoot J, Ryden C, Cavanagh K, Shapiro D A, Ilson S, Gray J A, Goldberg D, Mann A, Marks I, Everitt B, Tylee A (2004) Cost-effectiveness of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. Br J Psychiatry *185*: 55–62

McDougle C J, Price L H, Goodman W K, Charney D S, Heninger G R (1991) A controlled trial of lithium augmentation in fluvoxamine-refractory obsessive-compulsive disorder: lack of efficacy. J Clin Psychopharmacol *11*: 175–184

McDougle C J, Goodman W K, Leckman J F, Lee N C, Heninger G R, Price L H (1994) Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry *51*: 302–308

McDougle C J, Epperson C N, Pelton G H, Wasylink S, Price L H (2000) A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry *57*: 794–801

McGlashan T H, Grilo C M, Skodol A E, Gunderson J G, Shea M T, Morey L C, Zanarini M C, Stout R L (2000) The Collaborative Longitudinal Personality Disorders Study: baseline Axis I/II and II/II diagnostic co-occurrence. Acta Psychiatr Scand *102*: 256–264

Mann A H, Jenkins R, Belsey E (1981) The twelve-month outcome of patients with neurotic illness in general practice. Psychol Med *11*: 535–550

Marks I M, Lelliott P, Basoglu M, Noshirvani H, Monteiro W, Cohen D, Kasvikis Y (1988) Clomipramine, self-exposure and therapist-aided exposure for obsessive-compulsive rituals. Br J Psychiatry *152*: 522–534

Martenyi F, Brown E B, Zhang H, Koke S C, Prakash A (2002) Fluoxetine v. placebo in prevention of relapse in post-traumatic stress disorder. Br J Psychiatry *181*: 315–320

Martinsen E W, Olsen T, Tonset E, Nyland K E, Aarre T F (1998) Cognitive-behavioral group therapy for panic disorder in the general clinical setting: a naturalistic study with 1-year follow-up. J Clin Psychiatry 59: 437–442

Mavissakalian M, Michelson L, Dealy R S (1983) Pharmacological treatment of agoraphobia: Imipramine versus imipramine with programmed practice. Br J Psychiatry *143*: 348–355

Mavissakalian M R, Perel J M (1999) Long-term maintenance and discontinuation of imipramine therapy in panic disorder with agoraphobia. Arch Gen Psychiatry *56*: 821–827

Meibach R C, Dunner D, Wilson L G (1987) Comparative efficacy of propranolol, chlordiazepoxide, and placebo in the treatment of anxiety: a double-blind trial. J Clin Psychiatry *84*: 355–358

Mendels J, Krajewski T F, Huffer V (1986) Effective short-term treatment of anxiety: a double-blind trial. J Clin Psychiatry *47*: 170–174

Meoni P, Hackett D, Lader M (2004) Pooled analysis of venlafaxine WXR efficacy on somatic and psychic symptoms of anxiety in generalized anxiety disorder. Depress Anx *19*: 127–132

Michelson D, Pollack M, Lydiard R B, Tamura R, Tepner R, Tollefson G (1999) Continuing treatment of panic disorder after acute response: randomised, placebo-controlled trial with fluoxetine. The Fluoxetine Panic Disorder Study Group. Br J Psychiatry *174*: 213–218

Michelson D, Lydiard R B, Pollack M H, Tamura R N, Hoog S L, Tepner R, Demitrack M A, Tollefson G D (1998) Outcome assessment and clinical improvement in panic disorder: evidence from a randomized controlled trial of fluoxetine and placebo. The Fluoxetine Panic Disorder Study Group. Am J Psychiatry *155*: 1570–1577

Mitte K, Noack P, Steil R, Hautzinger M (2005) A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. J Clin Psychopharmacol *25*: 141–150

Möller H-J, Volz V P, Reimann I W (2001) Opipramol for the treatment of generalized anxiety disorder: a placebo-controlled trial including an alprazolam-treated group. J Clin Psychopharmacol *21*: 59–65

Monnelly E P, Ciraulo D A, Knapp C, Keane T (2003) Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. J Clin Psychopharmacol *23*: 193–196

Montgomery S A, Kasper S, Stein D J, Bang Hedegaard K, Lemming O M (2001) Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. Int Clin Psychopharmacol *16*: 75–86

Montgomery S A, McIntyre A, Osterheider M, Sarteschi P, Zitterl W, Zohar J, Birkett M, Wood A J (1993) A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. The Lilly European OCD Study Group. Eur Neuropsychopharmacol *3*: 143–152

Montgomery S A, Sheehan D V, Meoni P (2002) Characterization of the longitudinal course of improvement in generalized anxiety disorder

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during long-term treatment with venlafaxine XR. J Psychiatric Res *36*: 209–217

Mundo E, Guglielmo E, Bellodi L (1998) Effect of adjuvant pindolol on the antiobsessional response to fluvoxamine: a double-blind, placebo-controlled study. Int Clin Psychopharmacol *13*: 219–224

Munjack D J, Crocker B, Cabe D, Brown R, Usigli R, Zulueta A, McManus M, McDowell D, Palmer R, Leonard M (1989) Alprazolam, propranolol, and placebo in the treatment of panic disorder and agoraphobia with panic attacks. J Clin Psychopharmacol *9*: 22–27

National Institute for Clinical Excellence (2002) Guidance on the use of computerised cognitive behavioural therapy for anxiety and depression. Health Technology Appraisal Guidance 51. London

National Institute for Clinical Excellence (2004) Depression. Management of depression in primary and secondary care. Clinical Guideline 23. National Collaborating Centre for Mental Health, London. December

National Institute for Clinical Excellence (2004) The management of panic disorder and generalised anxiety disorder in primary and secondary care. National Collaborating Centre for Mental Health, London. December

National Institute for Clinical Excellence (2004) Obsessive compulsive disorder: core interventions in the treatment of obsessive compulsive disorder and body dysmorphophobic disorder. Draft for consultation, February

National Institute for Clinical Excellence (2005) Post-traumatic stress disorder. The management of PTSD in adults and children in primary and secondary care. National Clinical Practice Guideline number 26. The Royal College of Psychiatrists and the British Psychological Society, London

Nease D E Jr, Aikens J E (2003) DSM depression and anxiety criteria and severity of symptoms in primary care: cross sectional study. BMJ *327*: 1030–1031

Nulman I, Rovet J, Stewart D E (2002) Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry *159*: 1889–1895

Nutt D J (2003) Death and dependence: current controversies over the selective serotonin reuptake inhibitors. J Psychopharmacol *17*: 355–364

Nutt D J (2005a) Death by tricyclic: the real antidepressant scandal? J Psychopharmacol *19*: 123–124

Nutt D J (2005b) Overview of diagnosis and drug treatments of anxiety disorders. CNS Spectrums *10*: 49–56

Nuttin B J, Gabriels L A, Cosyns P R, Meyerson B A, Andreewitch S, Sunaert S G, Maes A F, Dupont P J, Gybels J M, Gielen F, Demeulemeester H G (2003) Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery *52*: 1263–1274

Oehrberg S, Christiansen P E, Behnke K, Borup A L, Severin B, Soegaard J, Calberg H, Judge R, Ohrstrom J K, Manniche P M (1995) Paroxetine in the treatment of panic disorder. A randomised, double-blind, placebo-controlled study. Br J Psychiatry *167*: 374–379

Oosterbaan D B, van Balkom A J, Spinhoven P, van Dyck R (2001) The placebo response in social phobia. J Psychopharmacol *15*: 199–203

Ormel J, Koeter M W, van den Brink W, van de Willige G (1991) Recognition, management, and course of anxiety and depression in general practice. Arch Gen Psychiatry *48*: 700–706

Ormel J, Oldehinkel T, Brilman E, van den Brink W (1993) Outcome of depression and anxiety in primary care. A three-wave 3 1/2-year study of psychopathology and disability. Arch Gen Psychiatry *50*: 759–766

Ormel J, Van Den Brink W, Koeter M W, Giel R, Van Der Meer K, Van De Willige G, Wilmink F W (1990) Recognition, management and outcome of psychological disorders in primary care: a naturalistic follow-up study. Psychol Med *20*: 909–923

Ost L G, Ferebee I, Furmark T (1997) One-session group therapy of spider phobia: direct versus indirect treatments. Behav Res Ther *35*: 721–732

Otto M W, Pollack M H, Penava S J, Zucker B G (1999) Group cognitive-behavior therapy for patients failing to respond to pharmacotherapy for panic disorder: a clinical case series. Behav Res Ther 37: 763–770

Otto M W, Tuby K S, Gould R A, McLean R Y, Pollack M H (2001) An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. Am J Psychiatry *158*: 1989–1992

Otto M W, Pollack M H, Gould R A, Worthington J J 3rd, McArdle E T, Rosenbaum J F (2000) A comparison of the efficacy of clonazepam and cognitive-behavioral group therapy for the treatment of social phobia. J Anxiety Disord *14*: 345–358

Pande A C, Feltner D E, Jefferson J W, Davidson J R, Pollack M, Stein M B, Lydiard R B, Futterer R, Robinson P, Slomkowski M, DuBoff E, Phelps M, Janney C A, Werth J L (2004) Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. J Clin Psychopharmacol *24*: 141–149

Parkerson G R Jr, Broadhead W E (1997) Screening for anxiety and depression in primary care with the Duke Anxiety-Depression Scale. Fam Med *29*: 177–181

Patel A, Knapp M, Henderson J, Baldwin D S (2002) The economic consequences of social phobia. J Affect Disord *68*: 221–233

Pigott T A, L'Heureux F, Hill J L, Bihari K, Bernstein S E, Murphy D L (1992) A double-blind study of adjuvant buspirone hydrochloride in clomipramine-treated patients with obsessive-compulsive disorder. J Clin Psychopharmacol *12*: 11–18

Pigott T A, Pato M T, L'Heureux F, Hill J L, Grover G N, Bernstein S E, Murphy D L (1991) A controlled comparison of adjuvant lithium carbonate or thyroid hormone in clomipramine-treated patients with obsessive-compulsive disorder. J Clin Psychopharmacol *11*: 242–248

Pitman R K, Sanders K M, Zusman R M, Healy A R, Cheema F, Lasko N B, Cahill L, Orr S P, Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiatry. *51*: 189–192

Pollack M H, Whitaker T, Mangano R, Tzanis E (2004) A comparison of venlafaxine XR and paroxetine in the treatment of outpatients with panic disorder. Presented at American College of Neuropsychopharmacology, December

Pollack M H, Otto M W, Kaspi S P, Hammerness P G, Rosenbaum J F (1994) Cognitive behavior therapy for treatment-refractory panic disorder. J Clin Psychiatry *55*: 200–205

Pollack M H, Allgulander C, Bandelow B, Cassano G B, Greist J H, Hollander E, Nutt D J, Okasha A, Swinson R P, World Council of Anxiety (2003) WCA recommendations for the long-term treatment of panic disorder. CNS Spectrums *8* (Suppl. 1): 17–30

Power K G, Simpson R J, Swanson V (1990) Controlled comparison of pharmacological and psychological treatment of generalized anxiety disorder in primary care. Br J Gen Pract *40*: 289–294

Proudfoot J, Ryden C, Everitt B, Shapiro D A, Goldberg D, Mann A, Tylee A, Marks I, Gray J A (2004) Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. Br J Psychiatry *185*: 46–54

Rapaport M H, Wolkow R, Rubin A, Hackett E, Pollack M, Ota K Y (2001) Sertraline treatment of panic disorder: results of a long-term study. Acta Psychiatr Scand *104*: 289–298

Rasmussen S A, Eisen J L (1990) Epidemiology of obsessive compulsive disorder. J Clin Psychiatry *51* (Suppl.): 10–14

Ribeiro L, Busnello J V, Kauer-Sant'Anna M, Madruga M, Quevedo J, Busnello E A, Kapczinski F (2001) Mirtazapine versus fluoxetine in the treatment of panic disorder. Braz J Med Biol Res *34*: 1303–1307

Rice D P, Miller L S (1998) Health economics and cost implications of

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anxiety and other mental disorders in the United States. Br J Psychiatry *34* (Suppl.): 4–9

Rickels K, Schweizer E, Case W G, Greenblatt D J (1990) Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. Arch Gen Psychiatry *47*: 899–907

Rickels K, London J, Fox I, Hassman H, Csanalosi I, Weise C (1991) Adinazolam, diazepam, imipramine, and placebo in major depressive disorder: a controlled study. Pharmacopsychiatry *24*: 127–131

Rickels K, Pollack M H, Sheehan D V (2000) Efficacy of extended-release venlafaxine in non-depressed outpatients with generalized anxiety disorder. Am J Psychiatry *157*: 968–974

Rickels K, Zaninelli R, McCafferty J P (2003) Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. Am J Psychiatry *160*: 749–756

Rief W, Trenkamp S, Auer C, Fichter M M (2000) Cognitive behavior therapy in panic disorder and comorbid major depression. A naturalistic study. Psychother Psychosom 69: 70–78

Ronalds C, Creed F, Stone K, Webb S, Tomenson B (1997) Outcome of anxiety and depressive disorders in primary care. Br J Psychiatry. *171*: 427–433

Royal College of Psychiatrists (2000) Neurosurgery for mental disorder. Report from the Neurosurgery Working Group of the Royal College of Psychiatrists. Council Report CR89

Royal College of Psychiatrists (2005) Benzodiazepines: risks, benefits or dependence. A re-evaluation. Council Report CR 59

Roy-Byrne P P, Stang P, Wittchen H U, Ustun B, Walters E E, Kessler R C (2000) Lifetime panic-depression comorbidity in the National Comorbidity Survey. Association with symptoms, impairment, course and help-seeking. Br J Psychiatry *176*: 229–235

Roy-Byrne P P, Stein M B, Russo J, Mercier E, Thomas R, McQuaid J, Katon W J, Craske M G, Bystritsky A, Sherbourne C D (1999) Panic disorder in the primary care setting: comorbidity, disability, service utilization, and treatment. J Clin Psychiatry *60*: 492–499

Salvador-Carulla L, Segui J, Fernandez-Cano P, Canet J (1995). Costs and offset effects in panic disorders. Br J Psychiatry 166 (Suppl. 27): 23–28

Sartorius N, Ustun T B, Lecrubier Y, Wittchen H U (1996) Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. Br J Psychiatry *30* (Suppl.): 38–43

Sasson Y, Zohar J, Chopra M, Lustig M, Iancu I, Hendler T (1997) Epidemiology of obsessive-compulsive disorder: a world view. J Clin Psychiatry *58* (Suppl. 12): 7–10

Schatzberg A F, Haddad P, Kaplan E M, Lejoyeux M, Rosenbaum J F, Young A H, Zajecka J (1997) Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. Discontinuation Consensus panel. J Clin Psychiatry *58* (Suppl. 7): 5–10

Schaub R T, Linden M (2000) Anxiety and anxiety disorders in the old and very old – results from the Berlin Aging Study (BASE). Compr Psychiatry *41* (Suppl. 1): 48–54

Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhausler H B, Kapfhammer H P (2001) The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biol Psychiatry *50*: 978–985

Schelling G, Kilger E, Roozendaal B, de Quervain D J, Briegel J, Dagge A, Rothenhausler H B, Krauseneck T, Nollert G, Kapfhammer H P (2004) Stress doses of hydrocortisone, traumatic memories, and symptoms of posttraumatic stress disorder in patients after cardiac surgery: a randomized study. Biol Psychiatry *55*: 627–633

Shalev A Y, Freedman S, Peri T, Brandes D, Sahar T, Orr S P, Pitman R K (1998) Prospective study of posttraumatic stress disorder and depression following trauma. Am J Psychiatry *155*: 630–637

Shannahoff-Kalsa D S, Ray L E, Levine S (1999) Randomised controlled trial of yogic meditation techniques for patients with obsessive-compulsive disorder. CNS Spectrums *4*: 34–47

Sheehan D V, Raj A B, Sheehan K H, Soto S (1988) The relative efficacy of buspirone, imipramine and placebo in panic disorder: a preliminary report. Pharmacol Biochem Behav *29*: 815–817

Shekelle P G, Woolf S H, Eccles M, Grimshaw J (1999) Clinical guidelines: developing guidelines. BMJ *318*: 593–596

Silverstone P H, Salinas E (2001) Efficacy of venlafaxine extended release in patients with major depressive disorder and comorbid generalized anxiety disorder. J Clin Psychiatry *62*: 523–539

Simpson H B, Liebowitz M R, Foa E B, Kozak M J, Schmidt A B, Rowan V, Petkova E, Kjernisted K, Huppert J D, Franklin M E, Davies S O, Campeas R (2004) Post-treatment effects of exposure therapy and clomipramine in obsessive-compulsive disorder. Depress Anxiety *19*: 225–233

Souetre E, Lozet H, Cimarosti I (1994) Cost of anxiety disorders: impact of comorbidity. J Psychosom Res *38*: 151–160

Stahl S M, Gergel I, Li D (2003) Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry *64*: 1322–1327

Stein D J, Ipser J C, Balkom A J (2004) Pharmacotherapy for social phobia. Cochrane Database Syst Rev Oct 18 (4): CD001206

Stein D J, Stein M B, Pitts C D, Kumar R, Hunter B (2002) Predictors of response to pharmacotherapy in social anxiety disorder: an analysis of 3 placebo-controlled paroxetine trials. J Clin Psychiatry *63*: 152–155

Stein D J, Westenberg H G, Yang H, Li D, Barbato L M (2003) Fluvoxamine CR in the long-term treatment of social anxiety disorder: the 12- to 24-week extension phase of a multicentre, randomized, placebo-controlled trial. Int J Neuropsychopharmacol 6: 317–323

Stein D J, Zungu-Dirwayi N, Van der Linden G J H (2004) Pharmacotherapy for post traumatic stress disorder (PTSD). (Cochrane Review). In Cochrane Library, Issue 2. John Wiley & Sons, Ltd, Chichester, UK

Stein M B, Kline N A, Matloff J L (2002) Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry *159*: 1777–1779

Stein M B, Torgrud L J, Walker J R (2000) Social phobia symptoms, subtypes, and severity: findings from a community survey. Arch Gen Psychiatry *57*: 1046–1052

Stein M B, Sareen J, Hami S, Chao J (2001) Pindolol potentiation of paroxetine for generalized social phobia: a double-blind, placebo-controlled, crossover study. Am J Psychiatry *158*: 1725–1727

Stein M B, Pollack M H, Bystritsky A, Kelsey J E, Mangano R M (2005) Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: a 6-month randomized controlled trial. Psychopharmacology (Berl) *177*: 280–288

Stein M B, Ron Norton G, Walker J R, Chartier M J, Graham R (2000) Do selective serotonin re-uptake inhibitors enhance the efficacy of very brief cognitive behavioral therapy for panic disorder? A pilot study. Psychiatry Res *94*: 191–200

Stocchi F G, Nordera G, Jokinen R H (2003) Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. J Clin Psychiatry 64: 250–258

Taylor F B (2003) Tiagabine for posttraumatic stress disorder: a case series of 7 women. J Clin Psychiatry *64*: 1421–1425

Tiemens B G, Ormel J, Simon G E (1996) Occurrence, recognition, and outcome of psychological disorders in primary care. Am J Psychiatry *153*: 636–644

Tiller J W, Bouwer C, Behnke K (1999) Moclobemide and fluoxetine for panic disorder. International Panic Disorder Study Group. Eur Arch Psychiatry Clin Neurosci *249* (Suppl. 1): S7–S10

Tollefson G D, Birkett M, Koran L, Genduso L (1994) Continuation treat-

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ment of OCD: double-blind and open-label experience with fluoxetine. J Clin Psychiatry *55* (Suppl.): 69–76

Tollefson G D, Rampey A H Jr, Potvin J H, Jenike M A, Rush A J, Kominguez R A, Koran L M, Shear M K, Goodman W, Genduso L A (1994) A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry *51*: 559–67

Uhlenhuth E H, Balter M B, Ban T A, Yang K (1999) Benzodiazepines and other psychotherapeutic medications: VI. Trends in recommendations for the pharmacotherapy of anxiety disorders, 1992–1997. Depress Anxiety *9*: 107–116

US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research (1992) Acute pain management: operative or medical procedures and trauma. Agency for Health Care Policy and Research Publications, Rockville, MD

Vaiva G, Ducrocq F, Jezequel K, Averland B, Lestavel P, Brunet A, Marmar C R (2003) Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. Biol Psychiatry *54*: 947–949

Van Ameringen M, Mancini C, Wilson C (1996) Buspirone augmentation of selective serotonin reuptake inhibitors (SSRIs) in social phobia. J Affect Disord *8*: 115–121

Van Ameringen M, Allgulander C, Bandelow B, Greist J H, Hollander E, Montgomery S A, Nutt D J, Okasha A, Pollack M H, Stein D J, Swinson R P, World Council of Anxiety (2003). WCA recommendations for the long-term treatment of social phobia. CNS Spectrums *8* (Suppl. 1): 40–52

van Balkom A J, Bakker A, Spinhoven P, Blaauw B M, Smeenk S, Ruesink B (1997) A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. J Nerv Ment Dis *185*: 510–516

van Boeijen C A, van Balkom A J, van Oppen P, Blankenstein N, Cherpanath A, van Dyck R (2005) Efficacy of self-help manuals for anxiety disorders in primary care: a systematic review. Fam Pract *22*: 192–196

Van Etten M L, Taylor S (1998) Comparative efficacy of treatments for post-traumatic stress disorder: a meta-analysis. Clin Psychol Psychother *5*: 126–145

van Vliet I M, Westenberg H G, Den Boer J A (1993) MAO inhibitors in panic disorder: clinical effects of treatment with brofaromine. A double blind placebo controlled study. Psychopharmacology (Berl) *112*: 483–489

Versiani M, Cassano G, Perugi G, Benedetti A, Mastalli L, Nardi A, Savino M (2002) Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. J Clin Psychiatry *63*: 31–37

Wagner K D, Berard R, Stein M B, Wetherhold E, Carpenter D J, Perera P, Gee M, Davy K, Machin A (2004) A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. Arch Gen Psychiatry *61*: 1153–1162

Weiller E, Bisserbe J C, Maier W, Lecrubier Y (1998) Prevalence and recognition of anxiety syndromes in five European primary care settings. A report from the WHO study on Psychological Problems in General Health Care. Br J Psychiatry *34* (Suppl.): 18–23

Weiller E, Bisserbe J C, Boyer P, Lepine J P, Lecrubier Y (1996) Social phobia in general health care: an unrecognised undertreated disabling disorder. Br J Psychiatry *168*: 169–174

Weissman A M, Levy B T, Hartz A J (2004) Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. Am J Psychiatry *161*: 1066–1078

Weissman M M, Bland R C, Canino G J, Greenwald S, Hwu H G, Lee C K, Newman S C, Oakley-Browne M A, Rubio-Stipec M, Wickramaratne P J (1994) The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. J Clin Psychiatry *55*: 5–10

Wheadon D, Bushnell W, Steiner M (1993) A fixed dose comparison of 20, 40 or 60 mg paroxetine to placebo in the treatment of obsessive compulsive disorder. Poster presented at Annual Meeting of the American College of Neuro psychopharmacology, Honolulu, Hawaii, USA

Wittchen H U, Boyer P (1998) Screening for anxiety disorders. Sensitivity and specificity of the Anxiety Screening Questionnaire (ASQ-15). Br J Psychiatry *34* (Suppl.): 10–17

Wittchen H U, Jacobi F (2005) Size and burden of mental disorder in Europe: a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol *15*: 357–376

Wittchen H U, Mühlig S, Beedso K (2003) Mental disorders in primary care. Dial Clin Neurosci *5*: 115–128

Wittchen H U, Kessler R C, Pfister H, Lieb M (2000a) Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. Acta Psychiatr Scand *406* (Suppl.): 14–23

Wittchen H U, Carter R M, Pfister H, Montgomery S A, Kessler R C (2000b) Disabilities and quality of life in pure and comorbid generalized anxiety disorder and major depression in a national survey. Int Clin Psychopharmacol *15*: 319–328

Wittchen H U, Kessler R C, Beesdo K, Krause P, Hofler M, Hoyer J (2002) Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry *63* (Suppl. 8): 24–34

World Health Organization (1992) The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization, Geneva

World Health Organization (2004) WHO Guide to Mental and Neurological Health in Primary Care, 2nd edn. World Health Organization, Geneva. Accessible through www.mentalneurologicalprimarycare.org

Yonkers K A, Dyck I R, Warshaw M, Keller M B (2000) Factors predicting the clinical course of generalised anxiety disorder. Br J Psychiatry *176*: 544–549

Zigmond A S, Snaith R P (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand *67*: 361–370

Zohar A H, Ratzoni G, Pauls D L, Apter A, Bleich A, Kron S, Rappaport M, Weizman A, Cohen D J (1992) An epidemiological study of obsessive-compulsive disorder and related disorders in Israeli adolescents. J Am Acad Child Adolesc Psychiatry *31*: 1057–1061

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