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Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology

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Abstract

This revision of the 2005 British Association for Psychopharmacology guidelines for the evidence-based pharmacological treatment of anxiety disorders provides an update on key steps in diagnosis and clinical management, including recognition, acute treatment, longer-term treatment, combination treatment, and further approaches for patients who have not responded to first-line interventions. A consensus meeting involving international experts in anxiety disorders reviewed the main subject areas and considered the strength of supporting evidence and its clinical implications. The guidelines are based on available evidence, were constructed after extensive feedback from participants, and are presented as recommendations to aid clinical decision-making in primary, secondary and tertiary medical care. They may also serve as a source of information for patients, their carers, and medicines management and formulary committees.

Keywords

Anticonvulsants, antidepressants, antipsychotics, anxiety disorders, anxiolytics, benzodiazepines, cognitive behaviour therapy, evidence-based guidelines, generalised anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, pregabalin, separation anxiety disorder, serotonin-noradrenaline reuptake inhibitor, social anxiety disorder, specific phobia, selective serotonin reuptake inhibitor, treatment.

1. Introduction

The British Association for Psychopharmacology (BAP; www.bap.org.uk) aims to advance education and research in the science and practice of psychopharmacology by arranging scientific meetings, fostering research and teaching, encouraging publication of research results, and providing guidance and information on matters relevant to psychopharmacology. As part of this

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process the BAP has developed and periodically revised a series of consensus statements on the use of psychotropic drugs in patients with psychiatric and other disorders, with an emphasis on making concise and realistic recommendations based on a review of the evidence [IV] (Anderson et al., 2000, 2008; Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology, 2011; Burns and O'Brien., 2006; Goodwin, 2003, 2005; Goodwin et al., 2008; Lingford-Hughes et al., 2004, 2012; National Institute for Health and Clinical Excellence, 2011; O'Brien and Burns, 2010; Nutt et al., 2006; Wilson et al., 2010).

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 recognised or treated. Likely factors in this sub-optimal management include the range of different anxiety disorders, their co-morbidity with other disorders (particularly mood disorders), a widespread lack of awareness of anxiety disorders by affected individuals and health practitioners, and the low confidence of many practitioners in their management. Conversely, some patients with only mild or transient anxiety symptoms receive unnecessary or inappropriate treatment. Given the considerable room for improvement, the BAP previously produced evidence-based guidelines for the pharmacological treatment of anxiety disorders [IV] (Baldwin et al., 2005): this revision of those guidelines provides an update on key steps in diagnosis and treatment.

2. Caveats

Clinical guidelines are systematically derived statements that aim to inform treatment decisions in clinical care. Recommendations are graded according to the strength of evidence, and whenever possible are derived from the findings of systematic reviews and randomised controlled trials. Principal recommendations apply to the management of 'typical' patients and hence apply much of the time: we therefore use expressions such as 'clinicians *should* consider…' in the summary boxes. But there are many patients and many clinical decision points where slavish adherence to guideline recommendations may be unhelpful and possibly harmful. In situations where the evidence is weaker we summarise potential management options, recognising that their implementation depends upon clinician experience, patient clinical features and preference, and local circumstance [IV] (Haynes et al., 2002). Some of our recommendations may be regarded as standards of clinical care that are largely driven by custom and practice: these are 'standards' which are intended to be applied routinely.

There is often a tension between existing established clinical practice and the possible implications of new research findings for changing practice. Existing practice may be accepted on the basis of prolonged clinical experience but limited good quality evidence: new treatments may have proven superiority to placebo in methodologically robust randomised controlled trials, but lack comparator data against 'established' treatments. We attempt to strike a balance between the risks of advocating specific novel treatment recommendations that may prove premature and adhering to established routines when the evidence supporting them is questionable.

3. Process for achieving consensus

The revision of the original BAP guidelines started in February 2011, with a consensus meeting attended by experts in the field and representatives of patient groups (all who attended are named in the acknowledgments). Brief presentations were made on key areas, with an emphasis on systematic reviews and randomised controlled trials. Each presentation was followed by discussion, to identify areas of consensus or uncertainty.

A literature review was then performed to ascertain the validity of the consensus points. Logistical factors made it impossible to perform a systematic review of all possible data from primary sources. Existing systematic reviews and randomised controlled trials were identified from MEDLINE and EMBASE searches and from the Cochrane Database, as well as from recent previous guidelines and reviews [IV] (Baldwin et al., 2011b; Bandelow et al., 2008a; Batelaan et al., 2012; Blanco et al., 2013; Fineberg et al., 2012; Ipser and Stein, 2012), through cross-referencing, and through discussion with experts in the field. We also drew on recent guidelines for generalised anxiety disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder and obsessive-compulsive disorder developed by the National Institute for Health and Clinical Excellence (2005, 2011a, 2011b, 2013).

Particular attention was paid to research findings which had appeared since 2005, the year of publication of the original guidelines. Draft versions of the consensus statement, with recommendations based on the level of supporting evidence, were circulated repeatedly to the presenters and other participants and their comments were 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.

4. Levels of evidence and strength of recommendations

The categories of evidence for causal relationships and the grading of recommendations have their origin in 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 [IV] (Shekelle et al., 1999). Given current debates about their competing merits, we have accorded a similar 'level' ('I') in the hierarchy of evidence to the findings of systematic reviews and to the results of randomised controlled trials, noting the evidence source which is available for each statement and recommendation (Table 1). Weaker levels of recommendations do not necessarily imply a reduced level of clinical importance. As in some previous guidelines we have included a category denoted as 'S' (representing a standard of care), for a recommendation that reflects important consensus on good clinical practice rather than on empirical evidence.

5. Aim and scope of the guidelines

We hope the guidelines will prove relevant to most doctors treating patients with anxiety and related disorders, in primary, secondary and tertiary medical care settings. Each of the principal disorders – generalised anxiety disorder, panic disorder, specific

Table 1. Levels of evidence and strength of recommendations.

Categories of evidence relevant to treatment	
I [M]	Evidence from meta-analysis of randomised double-blind placebo-controlled trials
I [PCT]	Evidence from at least one randomised double-blind placebo-controlled trial
II	Evidence from at least one randomised double-blind comparator-controlled trial (without placebo)
III	Evidence from non-experimental descriptive studies
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Categories of evidence relevant to 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 (either I [M] or I [PCT])
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 other categories
S	Standard of clinical care

(or simple) phobia, social anxiety disorder (also known as social phobia), post-traumatic stress disorder, and obsessive-compulsive disorder – is considered in turn, following key steps in management (acute treatment; longer-term treatment; combination with psychological approaches; treatment resistance). The continued inclusion or otherwise of obsessive-compulsive disorder within the broad category of anxiety disorders is the subject of continuing debate, given evidence of its dissimilarity from other anxiety disorders and its resemblance to other conditions characterised by compulsivity and impulsivity: but the principles of pharmacological treatment of anxiety disorders and obsessive-compulsive disorder share many common features, and so we have chosen to retain obsessive-compulsive disorder within these guidelines. We also include separation anxiety disorder, given its inclusion within anxiety disorders in the *Diagnostic and Statistical Manual* (DSM-5) (American Psychiatric Association, 2013), though evidence relating to its treatment in adults is at present very sparse. We also summarise the evidence for treatment of patients with health anxiety ('illness anxiety disorder'), partly because of the overlap in clinical features with those of generalised anxiety disorder.

We expect the guidelines will be most useful in informing decisions in primary and secondary care, regarding pharmacological treatment in patients aged between 18–65 years. The nature and prevalence of anxiety disorders changes during childhood and adolescence and the mean age of onset in adult patients varies between anxiety disorders. Most adults with anxiety disorders report an onset of symptoms in childhood or adolescence (Jones, 2013; Kessler et al., 2005), and some recommendations (for example those pertaining to obsessive-compulsive disorder and social phobia) will therefore be potentially applicable to adolescent patients. Similarly the recommendations are also likely to be pertinent to elderly patients although we did not specifically review evidence in those aged over 65 years.

6. 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 personal distress, with an associated impairment in everyday function. Most research in the field has been based on the diagnostic categories for anxiety disorders in the fourth edition of the *Diagnostic and Statistical Manual* (DSM-IV) [IV] (American Psychiatric Association, 1994) which are broadly similar to those in the tenth edition of the *International Classification of Diseases* (ICD-10) [IV] (World Health Organisation, 1992). The DSM system has recently been revised, and it is uncertain whether the approach to anxiety disorders within 'ICD-11' will differ substantially from ICD-10 or DSM-5.

We give simplified versions of the principal clinical features of the anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder in Table 2: a simple algorithm for initial delineation of anxiety and depressive symptoms into disorders is suggested in Figure 1.

Epidemiological studies in the general population indicate that when taken together anxiety disorders have a 12-month period prevalence of approximately 14% [I] (Wittchen et al., 2011) (see Table 3), and a lifetime prevalence of approximately 21% [I] (Wittchen and Jacobi, 2005). Individual disorders are less frequent, with estimated 12-month prevalence rates ranging between 0.7% (obsessive-compulsive disorder) and 6.4% (specific phobia), and estimated lifetime prevalence rates between 0.8% (obsessive-compulsive disorder) and 13.2% (specific phobia). 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 in middle age. Despite this variation within 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.

Table 2. Principal clinical features of the anxiety disorders, post-traumatic stress disorder, and obsessive-compulsive disorder.

Generalised anxiety disorder

Generalised anxiety disorder is characterised by excessive and inappropriate worrying that is persistent (lasting more than a few months) 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). Generalised anxiety disorder is often co-morbid with major depression, panic disorder, phobic anxiety disorders, health anxiety and obsessive-compulsive disorder.

Panic disorder (with or without agoraphobia)

Panic disorder is characterised 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 multiple physical or psychological anxiety symptoms. Panic attacks typically reach their peak within 10 min and last around 30–45 min. 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: they are either avoided or endured with significant personal distress.

Social phobia (social anxiety disorder)

Social phobia is characterised by a marked, persistent and unreasonable fear of being observed or evaluated negatively by other people, in social or performance situations, which is 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 distress.

Specific phobia

Specific, simple or isolated phobia is characterised by excessive or unreasonable fear of (and restricted to) single people, animals, objects, or situations (for example, dentists, spiders, lifts, flying, seeing blood) which are either avoided or are endured with significant personal distress.

Separation anxiety disorder

Separation anxiety disorder is characterised by fear or anxiety concerning separation from those to whom an individual is attached: common features include excessive distress when experiencing or anticipating separation from home, and persistent and excessive worries about potential harms to attachment figures or untoward events that might result in separation.

Post-traumatic stress disorder

Post-traumatic stress disorder is characterised 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 intrusive symptoms (such as recollections, flashbacks or dreams), avoidance symptoms (for example efforts to avoid activities or thoughts associated with the trauma), negative alterations in cognitions and mood, and hyper-arousal symptoms (including disturbed sleep, hypervigilance and an exaggerated startle response).

Obsessive-compulsive disorder

Obsessive-compulsive disorder is characterised by recurrent obsessive 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.

Illness anxiety disorder

A somatic symptom related disorder characterised by excessive or disproportionate preoccupations with having or acquiring a serious illness, with excessive health-related behaviours and high levels of alarm about personal health status.

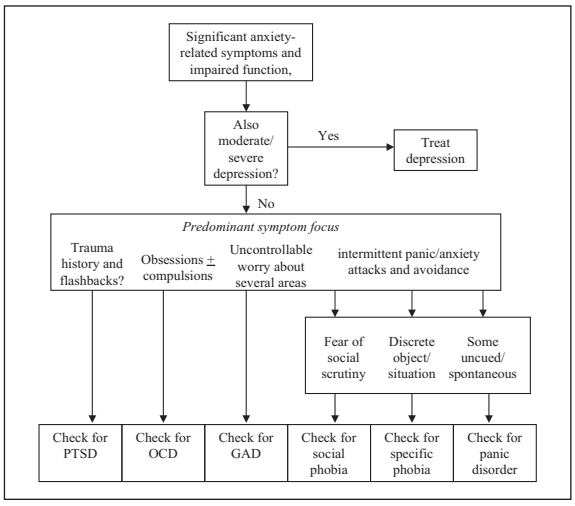

Figure 1. Suggested scheme for exploring a suspected anxiety disorder. GAD: generalised anxiety disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder.

6.1. Course of anxiety symptoms and disorders

Longitudinal studies in community samples indicate that many individuals with anxiety symptoms that are below the threshold for an anxiety disorder diagnosis experience an episodic condition with prolonged periods of remission: reappearance or worsening of symptoms being associated with adverse life events and other psychosocial stressors. By contrast, follow-up studies in patient groups demonstrate that anxiety disorders tend to run a chronic course, often over many years, with symptoms fluctuating in severity between periods of remission and relapse, the course of illness varying between disorders [II] (Bruce et al., 2005).

Generalised anxiety disorder tends to run a waxing and waning course in non-clinical samples [I] (Angst et al., 2009), and a prolonged course in primary care [I] (Rodriguez et al., 2006): but may also 'switch' to other diagnoses particularly depression and somatoform disorders [II] (Rubio and Lopez-Ibor, 2007a). Social anxiety disorder tends to run a chronic course in primary [I] (Beard et al., 2010) and secondary medical care settings [II]

Table 3. Twelve-month prevalence of anxiety disorders within the European Union.

Diagnosis (DSM-IV)	Inter-quartile range (%)	Best estimate (%)	Number affected (millions)[a]
Anxiety disorders	Not applicable[b]	14.0	61.5
Panic disorder	0.4–2.0	1.8	7.9
Agoraphobia	0.4–2.0	2.0	8.8
Social anxiety disorder	1.1–4.4	2.3	10.1
Specific phobias	3.4–7.1	6.4	22.7
Generalised anxiety disorder	0.6–2.2	1.7–3.4[c]	8.9
Obsessive-compulsive disorder	0.5–1.1	0.7	2.9
Post-traumatic stress disorder	0.7–2.5	1.1–2.9[d]	7.7

[a]According to Eurostat Directorate General of European Commission (Eurostat 2010) for the age groups used.
[b]Aggregate data from single study. 95% confidence interval, 13.4–15.6%.
[c]Age range 14–65 years, 1.7%; age 65+ years, 3.4%.
[d]Age range 14–34 years, 2.9%; age range 35–65 years, 1.3%; age 66+ years, 1.1%.
Best estimates represent consensus view of experts on most probable estimate from identified range. Full data available in Wittchen et al. (2011). DSM-IV refers to the *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association (1994).

(Bruce et al., 2005; Ramsawh et al., 2009). For panic disorder, prospective studies reveal high degrees of symptom chronicity [I] (Batelaan et al., 2010b), relapse after remission [I] (Batelaan et al., 2010a), and 'switching' to other diagnoses [II] (Rubio and Lopez-Ibor, 2007b). Childhood separation anxiety disorder often resolves with entry into adolescence [I] (Copeland et al., 2014). Retrospective longitudinal studies in obsessive-compulsive disorder suggest a very poor outcome, though prospective studies in non-clinical [I] (Fineberg et al., 2013) and clinical samples [II] (Eisen et al., 2010; Kempe et al., 2007) indicate a more favourable prognosis. Cohort studies which have examined the course of symptoms following traumatic experiences suggest that post-traumatic stress disorder emerges in only a minority of affected individuals (for example, [II] Mayou et al., 2001) the course of established post-traumatic stress disorder is not established, though a chronic course was seen in almost one-half of adolescents and young adults [I] (Perkonigg et al., 2005).

Recommendations: increased awareness of anxiety disorders

- Become familiar with the main features of the anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: and with the main symptoms which distinguish between them **[S]**
- Develop systematic questions to ask about the nature, severity, duration, distress and associated impairment in patients with anxiety symptoms, to decide whether an anxiety disorder, post-traumatic stress disorder or obsessive-compulsive disorder is present **[S]**
- Become familiar with the fluctuating nature of symptoms in patients with anxiety disorders, and with the tendency for symptoms to change in nature over time **[S]**

6.2. Co-existing psychological symptoms and co-morbid mental disorders

Anxiety symptoms often co-exist with other psychological symptoms, especially depressive symptoms, which are particularly frequent among those individuals with more severe anxiety symptoms. Cross-sectional studies in European community and clinical settings [I] (Fehm et al., 2005; Goodwin, 2005; Lieb et al., 2005) and in UK primary medical care [I] (Nease and Aikens, 2003) reveal a significant correlation between measures of anxiety and depressive symptom severity. Many patients with anxiety disorders also simultaneously fulfil diagnostic criteria for another disorder, this pattern typically being named 'co-morbidity'. High levels of co-morbidity are seen between the anxiety disorders, and with major depression [I] (Wittchen and Jacobi, 2005), bipolar disorder [II] (Gaudiano and Miller, 2005; Henry et al., 2003), schizophrenia (IV) (Buckley et al., 2009) substance misuse (Castle, 2008; Crippa et al., 2009; Robinson et al., 2009; Ziedonis et al., 2008) and physical illness [IV] (Davies et al., 2007; Roy-Byrne et al., 2008).

The presence of a comorbid anxiety disorder is associated with both a longer time to recovery and with a greater risk of ending treatment prematurely in patients with major depression [II] (Brown et al., 1996). An early systematic review found that patients with comorbid conditions generally had worse outcomes than those with anxiety disorder or depressive disorder alone [I] (Emmanuel et al., 1998). This is supported by the findings of the US National Comorbidity Survey which demonstrated that individuals with comorbid generalised anxiety disorder and major depression were significantly more likely to remain symptomatic than individuals with depression or generalised anxiety disorder alone [I] (Kessler et al., 2008).

Detection of co-morbid depression can sometimes lead to simultaneous recognition of an underlying primary anxiety disorder. For example, a French primary care study of the prevalence, recognition and treatment of social phobia found that detection rates were increased in the presence of comorbid depression (66%, compared with 53% in those without depression) [I] (Weiller et al., 1996). However the presence of a seemingly more pressing comorbid condition can result in sub-optimal treatment for the anxiety disorder. Data from a United Kingdom general practice cluster randomised controlled trial of the impact of mental health guidelines, which found that only 54% of patients with a 'common mental disorder' (depression or anxiety) were offered active treatment, revealed that patients with anxiety or mixed anxiety-depression were significantly less likely to be offered

treatment than patients with depression alone [I] (Hyde et al., 2005). Analysis of a Dutch primary care database involving patients with a newly diagnosed anxiety disorder found that benzodiazepines were significantly more frequently prescribed in patients with psychiatric comorbid conditions, and antidepressants significantly more frequently prescribed in patients with comorbid physical illness: in both forms of comorbidity, the prescription pattern of benzodiazepines was inconsistent with current guideline recommendations [I] (Smolders et al., 2007).

The presence of marked co-existing depressive symptoms is an important consideration in treatment decisions. Where anxiety symptoms are present within the context of a depressive disorder, antidepressant drug treatment is often effective in reducing anxiety (IV) (Anderson et al., 2008). 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; Erwin et al., 2002; Martinsen et al., 1998; Rief et al., 2000; Shalev et al., 1998). Clinical practice has usually 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: though some guidance notes that when a patient has an anxiety disorder and comorbid depression or depressive symptoms, treating the anxiety disorder first should also be considered, as effective treatment of the anxiety disorder will often improve the depression or depressive symptoms (National Institute for Health and Clinical Excellence, 2011).

Recommendations: enquiring about coexisting symptoms and comorbid disorders

- Check for anxiety symptoms in patients presenting with symptoms of other mental disorders, including depression, bipolar disorder, psychosis and substance misuse **[A]**
- Remember that coexisting depressive symptoms in patients with anxiety disorders are associated with greater functional impairment and a longer duration of illness **[B]**
- Assess for comorbid depression and treat if depressive symptoms are of more than mild intensity **[S]**

7. Detection of anxiety symptoms in primary medical care settings

Within the setting of primary medical care (general practice), most patients with anxiety or depression have relatively mild and transient symptoms, which tend to resolve without the need for intervention: but many have severe, persistent and disabling symptoms, which are likely to benefit from psychological or pharmacological treatment. However, many patients with anxiety and depressive symptoms do not present to primary medical care services [I] (Andrews and Carter, 2001; Roness et al., 2005). Even when patients do consult their general practitioner, anxiety symptoms are usually not their presenting complaints. The general practitioner therefore faces a significant challenge, in detecting the sample of patients most in need of treatment, from among the wider group, in many of whom intervention may be unnecessary.

The limited detection of anxiety disorders in primary care has been observed in multiple countries over many years. A Dutch study found a low (47%) rate of detection of anxiety and depression, recognition being more likely in anxiety disorders of shorter duration [I] (Ormel et al., 1991). A German study, in which 5.3% of patients fulfilled diagnostic criteria for generalised anxiety disorder, and 1.6% for comorbid major depressive episode and generalised anxiety disorder, found that whilst the majority (over 70%) of affected individuals were recognised as having clinically significant emotional problems, accurate diagnosis was less common (34.4% for generalised anxiety disorder) [I] (Wittchen et al., 2002). A United States investigation of older patients with generalised anxiety disorder found low rates of recording of anxiety symptoms (34%) or anxiety disorder (9%) despite much use of health services [I] (Calleo et al., 2009). A Canadian study found the majority of 'cases' of anxiety disorder diagnosed through a structured clinical interview did not have a recorded diagnosis (generalised anxiety disorder, 71.0%; panic disorder, 85.8%; social anxiety disorder, 97.8%) [I] (Vermani et al., 2011).

Limited recognition is partly related to difficulty in discussing emotional difficulties: many patients do not express emotional symptoms and many doctors find it hard to raise concerns about potential psychological distress. A United Kingdom general practice survey involving patients whose questionnaire scores indicated likely psychiatric 'caseness' found the vast majority had not mentioned emotional problems in the consultation, mainly through fears of either being unable to cope with the ensuing distress or of embarrassment, or through not wishing to trouble their doctor: but many also felt there would be either insufficient time, or the doctors could do nothing to help [II] (Cape and McCulloch, 1999). A United States primary care study found that doctors who were more sensitive to non-verbal communications were more likely to make diagnoses; but those who tended to 'blame' patients made fewer psychological assessments, and were less accurate in detecting distress [II] (Robbins et al., 1994).

Fortunately general practice is structured in such a way that many patients present repeatedly, which provides an opportunity for recognition of symptoms at subsequent consultations, if an anxiety disorder is not detected at the first visit. In a United Kingdom longitudinal study of the detection of depression and anxiety which found that many 'cases' were not detected at the initial appointment, the vast majority of undetected cases of depression or anxiety were recognised at follow-up [I] (Kessler et al., 2002). A Dutch primary care practice survey found that patients with an anxiety disorder were less likely to be diagnosed than patients with a depressive episode, but the likelihood of diagnosis in both conditions increased with the number of consultations, and the expression of more severe psychological symptoms [I] (Verhaak et al., 2006).

Recommendations: increasing skills in detecting anxiety symptoms

- Remember that many patients are either reluctant to present with psychological symptoms or find it hard discuss emotional problems **[A]**

- Be sensitive to non-verbal expression of psychological distress **[B]**
- Use the opportunity provided by repeated consultations in primary care to ask follow-up questions about possible anxiety symptoms when these were suspected but not established at earlier appointments **[A]**
- Routine screening of all patients for the presence of anxiety symptoms is not recommended **[A]**

8. Screening for anxiety disorders in primary care settings

In theory, patients and health professionals might benefit from the use of screening tools for detecting anxiety disorders, which can lead to discussion of psychological symptoms at both the index and subsequent appointments. A Danish primary care study of the potential value of screening for common mental disorders found that disclosure of scores on screening questionnaires increased the recognition of mental disorders by doctors with moderate or low recognition rates; and also resulted in increased discussion of psychological concerns and planned follow-up consultations in patients who had 'screened positive' [I] (Christensen et al., 2005). However, use of screening questionnaires needs to be accompanied by other changes in practice structure, and it is uncertain whether routine screening and disclosure of 'screened positive' patients with anxiety disorders leads to improved clinical outcomes. An educational intervention involving this design, among United States primary care patients found no evidence for an improvement in patient outcomes [I] (Mathias et al., 1994).

The criteria for diagnosing psychiatric disorders are mainly from clinical observations in psychiatric outpatients and inpatients and so may not be appropriate for routine use in screening for common mental disorders, among the more mildly ill patients in primary care. Primary care doctors often have reservations about the usefulness of DSM-IV criteria for diagnosis in primary care, and many of their patients are reluctant to accept any offered diagnoses or undergo psychotropic drug treatment [II] (Van Rijswijk et al., 2009). Although general practitioners sometimes find using screening questionnaires to be troublesome within a standard consultation, patients do not object to completing them [II] (Leydon et al., 2011). The use of questionnaires for detecting and following up patients with depressive symptoms has become part of routine primary care practice in the United Kingdom, suggesting that use of a similar questionnaire for detecting anxiety disorders is feasible in practice [IV] (Buszewicz and Chew-Graham, 2011).

9. Increasing awareness of anxiety disorders in particular patient populations

When compared with the general population, anxiety disorders are more common among patients with other mental disorders, with chronic physical illness, and in certain demographic groups. Patients with long-standing socioeconomic problems, and those from certain ethnic populations, may be at greater risk of receiving sub-optimal care and treatment. A Dutch primary care investigation, which included a nested case-control study of care received by patients with or without psychosocial problems, found that individuals with associated problems were significantly more likely to receive benzodiazepines and less likely to receive antidepressants: which may have contributed to their poorer outcomes [I] (Van Rijswijk et al., 2006). A cross-sectional study of anxiety and depressive symptoms in Australian family practices found that unemployed patients, when compared to employed patients, were significantly more likely to report affective symptoms, to have greater symptom severity, to have previously undergone treatment and to be prescribed psychotropic medication: but were no more likely to be referred to mental health services than were employed patients [I] (Comino et al., 2000).

Data from the United States indicate that black and Hispanic patients were less likely than white patients to receive care for depression and anxiety, or to receive antidepressant prescriptions (and for Hispanic patients, to undergo counselling) in primary care; and black patients were less likely than white patients to receive antidepressant prescriptions from a psychiatrist [II] (Lagomasino et al., 2011). Similar discrepancies were seen in a treatment review among United States primary care patients with anxiety disorders, where 'non-white' individuals were significantly less likely to receive treatment [II] (Weisberg et al., 2007). This situation may not necessarily apply in all countries, as a Dutch general practice study of the quality of care for anxiety and depression across ethnic minority groups found that all groups (with the exception of individuals originating from Surinam and the Antilles) were as likely to receive guideline-concordant medical care [I] (Fassaert et al., 2010).

Recommendations: paying particular attention to certain patient groups

- Remember that anxiety symptoms tend to persist longer in patients who are experiencing long-standing socioeconomic difficulties **[B]**
- Ensure that the presence of socioeconomic disadvantage or membership of a minority ethnic group among patients in your practice is not associated with a reduced chance of their undergoing evidence-based pharmacological or psychological treatment **[S]**

10. Identifying which patients with anxiety disorders should undergo treatment

Many anxious individuals have mild symptoms of recent onset that are associated with stressful life events or troublesome situations, which will often improve without needing specific treatment. However, the chronic nature and significant associated disability of anxiety disorders means that most patients who fulfil the diagnostic criteria for an anxiety disorder – in terms of severity, duration, distress and impairment – are likely to benefit from some form of treatment, whether this is psychological or pharmacological. The need for treatment is influenced by the intensity and duration of illness, the impact of symptoms on everyday life, the presence of co-existing depressive symptoms and comorbid

disorders, and the presence of concomitant medication; together with other features such as a good response to, or poor tolerability of, previous treatments. The choice of a particular treatment should be influenced by the supporting evidence base, by patient characteristics (such as co-morbid physical illness, previous response, or treatment contraindications), the preferences of patients and experience of doctors, and the local availability of any proposed intervention [IV] (Haynes et al., 2002).

However, many patients with anxiety disorders who might benefit from treatment do not receive it. A United States longitudinal primary care study of the use of health services by patients with panic disorder found that 64% had undergone some form of intervention over 4–10 months, but only 22% had been given appropriate pharmacological treatment, and only 12% had received appropriate psychological treatment [II] (Roy-Byrne et al., 1999). The quality of treatment in those who do receive it may be enhanced through making an accurate diagnosis and by regular monitoring of progress. Another United States primary care study of the treatment of patients with panic disorder found that inadequate dosage and insufficient duration of treatment were both common, and suggested that enhanced patient education and an increased frequency of appointments would be more likely to facilitate adequate treatment than would physician education [II] (Roy-Byrne et al., 2002). A study of adherence to evidence-based guidelines for depression and anxiety disorders within the setting of Dutch primary medical care found that only 27% of patients with anxiety disorders received guideline-consistent care: symptom severity had no influence on adherence, but documentation of a diagnosis by the general practitioner significantly increased the likelihood of receiving guideline-consistent care [I] (Smolders et al., 2009).

Media reports in many countries have raised concerns about the 'medicalisation' of anxiety, shyness, worrying and adjustment to trauma, and about the inappropriate prescribing of psychotropic drugs to patients who are experiencing life stresses or situational problems. This may be a factor in some settings, though most studies find a low level of inappropriate prescribing and a high level of unmet need. For example, a Norwegian primary care study involving over 1300 patients found some of evidence of 'overtreatment' (including inappropriate counselling, prescription of psychotropic medication, or specialist referral) in 11% of individuals without a formal psychiatric diagnosis, but also found substantial rates of 'under-treatment' for individuals with the diagnoses of major depressive episode (49%) or generalised anxiety disorder (64%) [I] (Olsson et al., 2006).

Recommendations: deciding when and which treatment is required

- Assess the severity and duration of anxiety symptoms, and the associated distress and impairment, when deciding which patients should be offered pharmacological or psychological treatment **[S]**
- Remember to ask about coexisting depressive symptoms and other potential comorbid disorders **[S]**
- Consider other factors such as the presence of physical illness, current concomitant medication, and a history of good response to, or poor tolerability of, previous treatments **[S]**
- Record the diagnosis and review this at subsequent appointments **[A]**
- The choice of a particular treatment should be influenced by the supporting evidence base, by clinical characteristics (such as treatment contraindications and expected impact of potential side effects), the preferences of patients, personal experience, and the local availability of any proposed intervention **[S]**

11. Anticipating common concerns about potential adverse effects of psychotropic drugs

Many patients experience unwanted and distressing adverse effects of psychotropic drug treatment, such as sexual dysfunction with selective serotonin reuptake inhibitors (SSRIs), excessive perspiration with serotonin-noradrenaline reuptake inhibitors (SNRIs), drowsiness with pregabalin and the benzodiazepines, or weight gain with antipsychotic drugs. Others fear developing a tolerance or becoming dependent on medication, and so are reluctant to start, let alone continue, pharmacological treatment. In addition, many patients and health professionals and some commentators consider pharmacological intervention to be a merely symptomatic and not a definitive treatment. For these reasons, many of those who might benefit from treatment do not receive it, and many of those who do undergo treatment stop it early because of the emergence of unwanted effects.

Opinions about the potential value and drawbacks of psychotropic drug treatment vary widely. A United States cross-sectional study of patients with panic disorder attending primary care found high levels of willingness to see a psychiatrist or psychotherapist, or to undergo pharmacological treatment [III] (Johnson et al., 2000). However a United Kingdom primary care qualitative study of patients' views on anxiety and depression found marked preferences regarding their perceived health needs, and much scepticism about the value of pharmacological treatments [II] (Kadam et al., 2001). Certain patient groups may be particularly reticent about starting or continuing psychotropic drug treatment. For example, in a United States study of beliefs about psychotherapy and psychotropic drug treatment for an anxiety disorder which found few differences between diagnostic groups, coexisting depression was associated with more favourable views regarding drug treatment, whereas individuals from black and minority ethnic groups were less favourably inclined towards pharmacological or psychological treatments [II] (Wagner et al., 2005).

Adherence to prescribed treatment may be enhanced by providing relevant information about treatment and minimising administrative challenges. A qualitative study of experiences of care among groups of treatment-adherent and non-adherent economically disadvantaged patients with panic disorder found that providing information was empowering and reduced a sense of isolation; that patients used a continuing process to evaluate the benefits and risks of treatment; and that barriers to treatment were primarily logistical [II] (Craske et al., 2005). Another investigation of perceived barriers to care suggested that difficulties in the continuing treatment of panic disorder were primarily administrative, such as being uncertain where to seek help, worrying

about potential costs, a lack of health insurance cover, and a delay in receiving appointments [II] (Mukherjee et al., 2006).

Recommendations: ascertaining attitudes to care and treatment

- Explore attitudes and expectations about pharmacological and psychological treatment and correct any misconceptions with patients prior to making a specific treatment recommendation **[S]**
- Review patient attitudes and experiences periodically during the course of treatment **[B]**
- Consider the administrative aspects of practice organisation to see whether these facilitate the care and treatment of patients with anxiety disorders **[S]**

12. Pharmacological treatments in patients with anxiety disorders

It has often proved difficult to demonstrate the benefit of antidepressant drug treatment in patients with mild depressive symptoms and the same difficulty is likely to be seen in patients with milder forms of anxiety disorders. Randomised controlled trials across a range of anxiety disorders also often demonstrate a high placebo response [IV] (Baldwin et al., 2011b; Batelaan et al., 2012; Blanco et al., 2013; Fineberg et al., 2013, 2012; Ipser and Stein, 2012) which suggests that non-specific effects of assessment and monitoring can play a large part in overall improvement. It should be emphasised that treatment response is not immediate; that a transient worsening of symptoms can sometimes occur; that prolonged courses are needed to maintain an initial treatment response; and that psychotropic medications and psychological treatments can have additive effects in some disorders.

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 [IV] (Aquilina et al., 2007; Baldwin and Kosky, 2007; Royal College of Psychiatrists, 2007). The presence of coexisting depressive symptoms of moderate or greater severity should guide treatment choice towards the prescription of antidepressant drugs rather than benzodiazepines.

12.1. SSRIs and SNRIs

SSRIs have 'broad spectrum' efficacy in both short-term and long-term treatment, and are generally well tolerated; and for these reasons are widely considered to be the first-line pharmacological approach in patients with anxiety disorders or obsessive-compulsive disorder. However SSRIs have potentially troublesome adverse effects, including initial increased nervousness, insomnia, nausea and sexual dysfunction [I (M)] (Gartlehner et al., 2011; Serretti and Chiesa, 2009; Sinclair et al., 2009). Fluoxetine and paroxetine are inhibitors of some cytochrome P450 enzymes and hence may interact with some other psychotropic drugs and treatments for physical illness [IV] (Muscatello et al., 2012). When stopped abruptly, and even when tapered slowly, SSRIs can produce a discontinuation syndrome characterised by dizziness, insomnia and flu-like symptoms [I (M)] (Baldwin et al., 2007; Schatzberg et al., 2006): this seems more likely with paroxetine and least likely with fluoxetine [II] (Tint et al., 2008).

The SNRIs duloxetine and venlafaxine have proven efficacy in short-term and long-term treatment of generalised anxiety disorder [IV] (Baldwin et al., 2011b), and placebo-controlled trials indicate that venlafaxine is also efficacious in the acute treatment and prevention of relapse in panic disorder [IV] (Batelaan et al., 2012). Although the tolerability profiles of SSRIs and SNRIs in patients with anxiety disorders are not established fully, systematic reviews of studies in depressed patients suggest that duloxetine and venlafaxine may be less well tolerated than the SSRIs [I (M)] (Cipriani et al., 2012; Schueler et al., 2011). Both duloxetine and venlafaxine have been associated with discontinuation symptoms after abrupt withdrawal [I(M)] (Baldwin et al., 2007; Perahia et al., 2005) in adult patients, data being limited in children and adolescents [IV] (Hosenbocus and Chahal, 2011). Although evidence is mixed (Harrison et al., 2004; Mbaya et al., 2007; Thase, 1998) venlafaxine is sometimes associated with an increase in blood pressure, and monitoring is recommended with higher daily doses [IV] (Joint Formulary Committee, 2012). A systematic review [I (M)] (McIntyre et al., 2008) and the findings of pharmacoepidemiological studies [I (M)] (Strombom et al., 2008; Wernicke et al., 2008a, 2008b) provide no consistent evidence of an increased risk of hepatotoxicity with duloxetine, but it is recommended that duloxetine is avoided in patients with known liver disease and patients considered to be at risk of hepatic dysfunction [IV] (Joint Formulary Committee, 2012).

12.2. Other antidepressant drugs

Certain tricyclic antidepressants (TCAs) [IV] (Baldwin et al., 2011b; Bandelow et al., 2008a; Batelaan et al., 2012; Blanco et al., 2013; Fineberg et al., 2012; Ipser and Stein, 2012) are efficacious in some anxiety disorders, but TCAs are associated with a greater burden of adverse effects than either SSRIs or SNRIs [IV] (Anderson et al., 2008), and for this reason should be generally be reserved for use after a non-response to or poor tolerance of initial treatment with an SSRI or SNRI. TCAs should be avoided in patients considered to be at risk of suicide, due to their potential fatal toxicity after overdose [IV] (Thanacoody and Thomas, 2005; Woolf et al., 2007). As with some SSRIs, many possible pharmacokinetic interactions limit their use in patients taking concomitant medication (listed in Appendix 1 of the *British National Formulary*, Joint Formulary Committee, 2012). As with other antidepressants, stopping TCAs abruptly can cause a discontinuation syndrome [IV] (Schatzberg et al., 2006).

The traditional irreversible monoamine oxidase inhibitor (MAOI) phenelzine has proven efficacy in panic disorder and social phobia: but side effects and the need to follow dietary restrictions limit its use, so it should generally be reserved for when patients have not responded to, or proved intolerant of, other treatment approaches. Phenelzine overdose is potentially fatal [III] (White et al., 2008), and it should usually be avoided in patients considered to be at risk of suicide. Interactions involving

traditional MAOIs and serotonergic antidepressants such as SSRIs and clomipramine can be hazardous (Lane and Baldwin, 1997). Moclobemide, a reversible inhibitor of mono-amine oxidase A (RIMA) has proven efficacy in social phobia [IV] (Blanco et al., 2013) and some evidence of benefit in panic disorder [I (PCT)] (Ross et al., 2010): the reversibility of its action reduces the need for dietary restrictions at lower daily doses though avoidance of tyramine-containing foods is advisable at higher dosage [I (PCT)] (Dingemanse et al., 1998).

Agomelatine has proven efficacy in acute treatment (Stein et al., 2008a) and prevention of relapse (Stein et al., 2012) in generalised anxiety disorder: sexual dysfunction is less likely than with SSRI or SNRI antidepressants [I (M)] (Serretti and Chiesa, 2009), as are discontinuation symptoms [I (PCT)] (Goodwin et al., 2009; Montgomery et al., 2004): elevations of hepatic enzymes occur in more than 1% of treated patients and regular monitoring of liver function tests is required in the early months of treatment [IV] (McAllister-Williams et al., 2010). The evidence for the efficacy of mirtazapine in patients with anxiety disorders is limited and inconsistent (Andrisano et al., 2013; Muehlbacher et al., 2005; Schutters et al., 2010), but in depressed patients treatment-emergent sexual dysfunction is probably less frequent than with SSRIs [I (M)] (Watanabe et al., 2011).

12. 3. Benzodiazepines

Some benzodiazepines have proven efficacy in the treatment of patients with panic disorder, generalised anxiety disorder and social anxiety disorder [IV] (Baldwin et al., 2011b; Bandelow et al., 2008b; Batelaan et al., 2012; Blanco et al., 2013). However benzodiazepines can cause troublesome sedation and cognitive impairment in both short-term and long-term treatment, and tolerance and dependence can occur (especially in predisposed patients) with prolonged use: and it is hard to identify those patients at risk of developing long-term problems [IV] (Dell'Osso and Lader, 2012). It is uncertain whether benzodiazepines are efficacious in relieving depressive symptoms in patients with anxiety disorders but there is no evidence of efficacy for benzodiazepines in the acute treatment of patients with minor depression [I (M)] (Barbui et al., 2011) and antidepressants should therefore be preferred in patients with significant coexisting depressive symptoms. Benzodiazepines will usually be reserved for the further treatment of patients who have not responded to at least three previous treatments (such as after non-response to both an SSRI and an SNRI and a psychological intervention); but it has been argued that concerns about potential problems in long-term use should not prevent their use in patients with persistent, severe, distressing, and impairing anxiety symptoms, when other treatments have proved ineffective [IV] (Baldwin and Talat, 2012; Nutt, 2005).

12. 4. Pregabalin

Pregabalin has proven efficacy in both acute treatment and prevention of relapse in generalised anxiety disorder [IV] (Baldwin et al., 2011b) and social anxiety disorder. In generalised anxiety disorder, it is efficacious in relieving depressive symptoms of mild to moderate intensity [I (M)] (Stein et al., 2008a), and in reducing the severity of sleep disturbance (Holsboer-Trachsler and Prieto, 2013). Common adverse effects include drowsiness and dizziness though it may be better tolerated than other medications in the acute treatment of generalised anxiety disorder [I (M)] (Baldwin et al., 2011a). Long-term treatment is accompanied by weight gain in approximately 20% of patients [III] (Montgomery et al., 2013). It is not subject to hepatic metabolism and is excreted unchanged in the urine, which is a potential advantage in patients with hepatic impairment and in patients taking other drugs metabolised by the liver, but potentially disadvantageous in patients with renal disease. There is no known untoward interaction with lithium. Spontaneous reports of adverse sexual side effects are uncommon but the incidence of treatment-emergent sexual dysfunction with pregabalin is uncertain [IV] (Baldwin et al., 2013). Discontinuation symptoms after abrupt withdrawal of pregabalin have been reported, as has the abuse of pregabalin generally in individuals with a history of other substance abuse: but the relative potential for developing tolerance and abuse, when compared to with medications, is not established [IV] (Baldwin et al., 2013).

12. 5. Other agents

Antipsychotic drugs are often prescribed to patients with anxiety disorders, but the strongest evidence for benefit is restricted to acute treatment and prevention of relapse with quetiapine in generalised anxiety disorder [IV] (Baldwin et al., 2011b), and the augmentation of SSRI antidepressants in patients with obsessive-compulsive disorder [IV] (Fineberg et al., 2012). The tolerability profile of antipsychotic drugs is such that they should generally be reserved for treatment after a non-response to other interventions [IV] (National Institute for Health and Clinical Excellence, 2011). The azapirone drug buspirone is efficacious in the acute treatment of generalised anxiety disorder [I (M)] (Chessick et al., 2006), as is the anti-histamine drug hydroxyzine [I (M)] (Guaiana et al., 2010), though neither has published evidence of efficacy in the prevention of relapse.

Recommendations: general aspects of pharmacological treatment

- Discuss the anticipated balance of potential benefits and potential risks of specific psychotropic medications with patients before starting treatment **[S]**
- Consider a SSRI for first-line treatment, as SSRIs are effective across the anxiety and related disorders, in both the short-term and long-term, and are generally well tolerated **[A]**
- Remain familiar with the evidence base for other classes of medication, as many patients do not respond to or are intolerant of SSRI treatment, but may respond to other classes of psychotropic drug **[S]**
- Discuss potential adverse effects early in treatment, including increased nervousness, worsened agitation, and review patient progress carefully over the first few weeks of treatment **[A]**
- Remember that benzodiazepines can be effective in many patients with anxiety disorders **[A]**, but recognise that their use should generally only be short-term:

and only considered beyond this in patients who have not responded to a succession of other treatment approaches **[S]**
- Discuss the potential for experiencing discontinuation or withdrawal symptoms during unforeseen abrupt interruptions to treatment and after the planned end of pharmacological treatment **[S]**

13. Psychological treatments in patients with anxiety disorders

Many patients with anxiety disorders or obsessive-compulsive disorder have a marked preference for psychological treatment approaches [II] (Patel and Simpson, 2010; Zoellner et al., 2009). Certain forms of psychotherapy, such as exposure therapy, cognitive therapy and cognitive behavioural therapy (CBT), have largely consistent evidence of efficacy in the treatment of anxiety disorders [I (M)] (Hofmann and Smits, 2008). An early 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 [I (M)] (Bower et al., 2001): though a subsequent meta-analysis suggests that short-term counselling is less beneficial than longer-term treatment with other psychological interventions [I (M)] (Cape et al., 2010). Some psychological interventions – such as psychodynamic psychotherapy - have not been subject to extensive controlled investigations (Leichsenring, 2005; Lewis et al., 2008). Psychodynamic psychotherapy was reported to be superior to applied relaxation in patients with panic disorder (Leichsenring et al., 2009; Milrod et al., 2007), but has been found less beneficial than CBT in generalised anxiety disorder (Durham et al., 1999) . Many evaluations of the efficacy of psychological treatments have not employed an optimal psychological placebo control treatment: the use of waiting list controls is inadequate to demonstrate potential efficacy.

The efficacy of psychological and pharmacological approaches is broadly 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 [IV] (Haynes et al., 2002). In most anxiety disorders (generalised anxiety disorder, social anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder) it is uncertain whether combining psychological and pharmacological treatments is associated with greater long-term benefit than that which is seen with either treatment approach when given alone. However, previous concerns that prescription of psychotropic drugs might reduce the efficacy of psychological treatment are probably unfounded: in some anxiety disorders systematic reviews suggest that psychotropic drug administration can enhance the short-term efficacy of cognitive-behavioural interventions. As with pharmacological approaches, it should be emphasised that response to psychological treatment 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.

Given uncertainty about the value of combination treatment and widespread constraints in the availability of mental health services, it may be best to plan sequential steps in patient management [IV] (National Institute for Health and Clinical Excellence, 2005, 2011). 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 [IV] (National Institute for Health and Clinical Excellence, 2005). The potential effectiveness of initiatives designed to increase the uptake of psychological interventions for patients with common mental health problems – such as the Improving Access to Psychological Therapies programme [IV] (Brown et al., 2010; Clark, 2011) in the United Kingdom – has not been established through formal randomised controlled trials.

A general range of 8–20 h of sessions of CBT may be needed in the treatment of anxiety disorders. In generalised anxiety disorder and panic disorder, a typical treatment course consists of approximately 16–20 h, up to half of which can be conducted by the patient in supervised 'homework' sessions, over a period of approximately four months [IV] (National Institute for Health and Clinical Excellence, 2011). In social anxiety disorder a standard course should consist of up to 14 sessions of 90 min duration over the course of four months [IV] (National Institute for Health and Care Excellence, 2013). In post-traumatic stress disorder, a standard course of psychological treatment might involve 8–12 sessions of trauma-focused CBT, delivered at weekly intervals [IV] (National Institute for Clinical Excellence (NICE), 2005). In obsessive-compulsive disorder, a typical initial treatment course might include approximately 16 h of intervention based on exposure and response prevention, with longer and more intensive treatment in housebound patients [IV] (National Institute for Health and Clinical Excellence, 2005).

Recommendations: general aspects of psychological treatment

- Remember that the efficacy of psychological and pharmacological approaches is broadly similar in the acute treatment of patients with anxiety disorders **[A]**
- Discuss the anticipated balance of potential benefits and potential risks of specific psychological interventions with patients before starting treatment **[S]**
- Ensure that psychological treatments are only delivered by suitably trained and supervised staff, able to demonstrate that their clinical practice adheres to evidence-based treatment protocols **[A]**
- Remind patients that response to psychological treatment is not immediate and that a prolonged course is usually needed to maintain an initial treatment response **[S]**
- Plan sequential steps in patient management rather than combining treatments from the start, as it is uncertain whether combining is associated with greater long-term benefit **[D]**

14. The role of self-help and complementary approaches in anxiety disorders

Patient preference and the often sub-optimal effects of 'standard' pharmacological or psychological treatment approaches have encouraged the development of a range of self-help techniques and therapies in anxiety disorders; some undertaken as individuals, often through internet-based resources, and others in groups. Many patients and their carers derive considerable practical and emotional support from local self-help groups and national self-help organisations (such as the United Kingdom organisations Anxiety-UK and Obsessive Action): though formal evaluations of the effectiveness of participation in such groups are sparse [I (M)] (Pistrang et al., 2008).

There have been relatively few randomised controlled trials of the efficacy and acceptability of self-help approaches undertaken as individuals, and few studies have been conducted in diagnostically homogenous groups, with reliable outcome measures and robust statistical analysis. An early systematic review of six randomised controlled trials found evidence for the efficacy of self-help in primary care patients with mixed anxiety disorders, greater efficacy being seen with more detailed instruction in use of self-help manuals [I (M)] (Van Boeijen et al., 2005). The findings of a systematic review of 21 studies in patients with depression or anxiety disorders suggest that guided self-help has similar effectiveness to face-to-face psychotherapy [I (M)] (Cuijpers et al., 2010): a subsequent systematic review of 31 randomised controlled trials in anxiety disorders indicates that self-help interventions are more effective than being placed on a waiting list, but less effective than therapist-administered treatments [I (M)] (Lewis et al., 2012). In addition, the evidence base for self-help approaches in young people with anxiety disorders is limited [IV] (Parslow et al., 2008; Rickwood and Bradford, 2012). In 2006, the UK National Institute for Clinical Excellence concluded that there was insufficient evidence to recommend the general introduction of computerised CBT for anxiety symptoms or disorders (National Institute for Health and Clinical Excellence, 2006): however the findings of a systematic review of 26 studies in individuals with depression or anxiety disorders suggest that internet-based interventions offer promise, in overall management [I (M)] (Griffiths et al., 2010); though there is a need to further investigate factors associated with beneficial outcomes (Andersson, 2012).

Many patients with anxiety disorders wonder whether taking herbal preparations or nutritional supplements might prove beneficial, either instead of or in conjunction with standard pharmacological or psychological treatments. Systematic reviews find some evidence for the potential effectiveness of a number of 'phytomedicines', including *Passiflora* species extracts, Kava (*Piper methysticum*), and combinations of l-lysine and l-arginine (Lakhan and Vieira, 2010; Sarris et al., 2011b; Van der Watt et al., 2008). There is no current convincing evidence for the effectiveness of homoeopathic preparations in the treatment of patients with anxiety disorders [I (M)] (Davidson et al., 2011; Pilkington et al., 2006). Kava preparations appeared to have some beneficial effects in patients with generalised anxiety disorder but have been withdrawn in many countries due to potential hepatotoxic effects [IV] (Sarris et al., 2011a).

Other complementary approaches include regular exercise and interventions drawing on meditation techniques. A systematic review indicates that exercise training reduces anxiety symptoms in sedentary patients with long-term medical conditions [I (M)] (Herring et al., 2010); and regular walking may enhance the efficacy of group CBT, across a range of anxiety disorders [II] (Merom et al., 2008). In panic disorder, regular exercise is marginally superior to relaxation [I (PCT)] (Wedekind et al., 2010); but less effective than either the TCA clomipramine [I (PCT)] (Broocks et al., 1998) or group CBT [II] (Hovland et al., 2012). Preliminary evidence suggests that exercise training may be effective in obsessive-compulsive disorder (Abrantes et al., 2009), generalised anxiety disorder (Herring et al., 2012) and social anxiety disorder (Jazaieri et al., 2012).

Meditation and yoga practices are often advocated, as part of the overall management of patients with anxiety disorders. Early systematic reviews found only minimal evidence for the effectiveness of meditation therapy [I (M)] (Krisanaprakornit et al., 2006) or mindfulness-based meditation [I (M)] (Toneatto and Nguyen, 2007). However another systematic review indicated that relaxation training (which often includes components of meditation) is effective in reducing anxiety symptoms in non-clinical and clinical groups [I (M)] (Manzoni et al., 2008): and the findings of two recent systematic reviews suggest that meditative therapies are effective in reducing anxiety symptoms (though their effect in anxiety disorders is uncertain) [I (M)] (Chen et al., 2012), and that mindfulness- and acceptance-based interventions are effective in reducing anxiety and co-existing depressive symptoms in patients with anxiety disorders [I (M)] (Vøllestad et al., 2012).

Recommendations: self-help and complementary approaches

- Remember that self-help approaches, such as use of internet-based educational resources, are potentially beneficial in patients with mild anxiety and depressive symptoms **[A]**
- Keep patients who use such resources under review as many will not improve, and so will need to undergo other forms of treatment **[S]**
- Enquire about the use by patients of herbal preparations or nutritional supplements, but remember that the evidence base for their use is relatively slight, when compared to the substantial evidence supporting the use of pharmacological and psychological interventions **[S]**

15. Costs of illness and cost-effectiveness of treatment

Anxiety disorders are associated with a substantial economic burden: both in health care systems (mainly direct costs of assessment, investigation, treatment and care), and in the wider society (including premature mortality, unemployment, reduced productivity losses) [I] (Andlin-Sobcki and Wittchen, 2005; Gustavsson et al., 2011; Wittchen et al., 2011). Using estimates to calculate the size of the population in the European Union that would be affected (69.1 million people), it was estimated that, in 2010, anxiety disorders (excluding post-traumatic stress disorder) cost close to €66

billion [I] (Gustavsson et al., 2011). Treatment costs account for a small proportion of the overall costs of health care, and it has been argued that the increased costs of strategies to increase the recognition and evidence-based treatment in patients that would otherwise remain undetected and untreated would be small, compared to the saving arising from unemployment and reduced productivity at work [IV] (Baldwin et al., 2010; Issakidis et al., 2004). However there have been relatively few randomised controlled trials or systematic evaluations of the cost-effectiveness of pharmacological, psychological or self-help interventions across the broad range of anxiety disorders (Joesch et al., 2012; Konnopka et al., 2009; Lewis et al., 2012; Poirier-Bisson et al., 2010).

Investigations of the costs of illness and cost-effectiveness of individual anxiety disorders are limited. The cost-effectiveness of Improving Access to Psychological Therapies (IAPT) services within the UK is not established [III] (McCrone, 2013; Mukuria et al., 2013). For generalised anxiety disorder, cost-effectiveness studies provide evidence for the value of CBT, certain antidepressants, and pregabalin (Bereza et al., 2009; Heuzenroeder et al., 2004; Iskedjian et al., 2008; Jorgensen et al., 2006; Vera-Llonch et al., 2010). Cost-effectiveness studies in panic disorder provide evidence for the value of CBT (Heuzenroeder et al., 2004; Roberge et al., 2008) [II]; SSRI or tricyclic antidepressants (Heuzenroeder et al., 2004; McHugh et al., 2007); lifestyle approaches (Lambert et al., 2010) [III]; computerised interventions (Klein et al., 2009; McCrone et al., 2009; Mihalopoulos et al., 2005) and early intervention (Smit et al., 2009). Brief interventions (Klein et al., 2009), monotherapies (McHugh et al., 2007) and self-directed approaches (McCrone et al., 2009) may be more cost-effective than longer, combination treatment, or clinician-led approaches, respectively. Treatment studies in social anxiety disorder provide some evidence for the cost-effectiveness of internet-delivered approaches [II] (Hedman et al., 2011c; Titov et al., 2009), group CBT [II] (Hedman et al., 2011a), and for long-term treatment with the SSRI escitalopram in the prevention of relapse [I (PCT)] (Francois et al., 2008). The cost-effectiveness of treatments for obsessive-compulsive disorder has been investigated only rarely, with limited evidence for the greater cost-effectiveness of 'stepped care' compared to standard CBT [II] (Tolin et al., 2011) and group CBT in children and adolescents [III] (Farrell et al., 2012). In post-traumatic stress disorder, there is only modelled or limited evidence, for the cost-effectiveness of trauma-focused CBT in the treatment of sexually abused children, which may be enhanced when combined with an SSRI [III] (Gospodarevskaya and Segal, 2012); and for virtual reality graded exposure therapy in combat-related trauma [III] (Wood et al., 2009).

16. Management of generalised anxiety disorder

16. 1. Recognition and diagnosis

Generalised anxiety disorder is amongst the most common of mental disorders in primary medical care, and is associated with increased use of health services. However it is often not recognised, possibly because only a minority of patients present with anxiety symptoms (most present with physical symptoms), and doctors tend to overlook anxiety unless it is a presenting complaint [I] (Munk-Jorgensen et al., 2006). The degree of functional impairment associated with generalised anxiety disorder is similar to that with major depression [I] (Wittchen et al., 2000). Patients with 'co-morbid' depression and generalised anxiety disorder have a more severe and prolonged course of illness and greater functional impairment (Tyrer et al., 2004). Patients with co-morbid depression are more likely to be recognised as having a mental health problem, though not necessarily as having generalised anxiety disorder [I] (Weiller et al., 1998; Wittchen et al., 2002).

16.2. Acute treatment

The findings of systematic reviews [I (M)] (Baldwin et al., 2011b; National Institute for Health and Clinical Excellence, 2011) and randomised placebo-controlled trials of acute treatment of patients with generalised anxiety disorder together provide substantial evidence for the efficacy of many antidepressant drugs – including SSRIs (citalopram, escitalopram, paroxetine, sertraline), SNRIs (duloxetine, venlafaxine), the tricyclics imipramine and opipramol, trazodone, and agomelatine [IV] (Baldwin et al., 2011a). Other compounds with efficacy in placebo-controlled acute treatment studies include pregabalin [I (M)] (Wensel et al., 2012), some benzodiazepines (alprazolam, diazepam, lorazepam) [I (M)] (Martin et al., 2007), buspirone [I (M)] (Chessick et al., 2006), some antipsychotic drugs (quetiapine, trifluoperazine) [I (M)] (Lalonde and Van Lieshout, 2011) and the antihistamine hydroxyzine [I (M)] (Guaiana et al., 2010). Beta-blockers are often used in primary medical management of physical symptoms of anxiety but placebo-controlled evidence of efficacy in acute treatment of patients with generalised anxiety disorder is minimal [I (PCT)] (Meibach et al., 1987).

There have been relatively few randomised comparator-controlled studies of acute treatment in generalised anxiety disorder [I (M)] (Baldwin et al., 2011b; National Institute for Health and Clinical Excellence, 2011) and most reveal no significant differences in overall efficacy between active compounds. An early analysis of randomised controlled trials of acute treatment found an overall mean effect size of 0.39: medications with higher effect sizes were pregabalin, hydroxyzine and SNRIs; and with lower effect sizes were benzodiazepines, SSRIs and buspirone [I (M)] (Hidalgo et al., 2007). The tentative findings of a mixed treatment comparison suggest fluoxetine, sertraline and pregabalin have some advantages over other medications: among currently licensed treatments in the United Kingdom, duloxetine, escitalopram and pregabalin may have some advantages over paroxetine and venlafaxine [I (M)] (Baldwin et al., 2011b). It is uncertain whether antidepressant drugs, pregabalin and benzodiazepines differ in their relative efficacy in reducing the severity of psychological or somatic anxiety symptoms [IV] (Baldwin et al., 2011a). The findings of fixed-dose randomised placebo-controlled trials provide some evidence of a dose-response relationship for pregabalin [I (M)] (Bech, 2007; Lydiard et al., 2010), but studies with antidepressant drugs provide no consistent evidence for a dose-relationship [IV] (Baldwin et al., 2011a). Although not an antidepressant, a post hoc pooled analysis of randomised placebo-controlled trials with pregabalin indicate that it is efficacious in reducing depressive symptom severity in patients with mild to moderate intensity of depressive symptoms [I (M)] (Stein et al., 2008b).

16.3. Longer term treatment

The findings of acute treatment studies indicate that the proportion of responding patients steadily increases over time [IV] (Baldwin et al., 2011a). Continuing with SSRI or SNRI treatment is associated with an increase in overall response rates: from 8–24 weeks with escitalopram or paroxetine [II] (Bielski et al., 2005); from 4–12 weeks with sertraline [I (PCT)] (Allgulander et al., 2004a) and from 8–24 weeks with venlafaxine [I (PCT)] (Montgomery et al., 2002). However, the findings of post hoc analyses of data from randomised double-blind placebo-controlled studies with duloxetine [I (M)] (Pollack et al., 2008), escitalopram [I (M) (Baldwin et al., 2009), and with alprazolam, pregabalin and venlafaxine [I (M) (Baldwin et al., 2011a) all suggest that response is likely only if there is an onset of effect within four weeks of treatment. The findings of randomised placebo-controlled relapse-prevention studies in patients who have responded to previous 'open' acute treatment of varying lengths reveal a significant advantage for staying on active medication (agomelatine, duloxetine, escitalopram, paroxetine, pregabalin, quetiapine, venlafaxine, vortioxetine), when compared with switching to placebo, for periods of between 6–18 months (Baldwin et al., 2011b, 2012; Katzman et al., 2011; Rickels et al., 2010).

16.4. Comparative efficacy of psychological, pharmacological, and combination treatments

Pharmacological or psychological treatments, when delivered singly, have broadly similar efficacy in acute treatment [I (M)] (Bandelow et al., 2007a; National Institute for Health and Clinical Excellence, 2011). The efficacy of CBT and applied relaxation appears superior to that of other psychological interventions (National Institute for Health and Clinical Excellence, 2011). A randomised controlled trial found that augmentation of venlafaxine with CBT conferred no additional benefit, when compared with venlafaxine alone [II] (Crits-Christoph et al., 2011) but it is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than is seen with either treatment, when given alone [I (M)] (Bandelow et al., 2007a), and a 'stepped care' approach is recommended [IV] (National Institute for Health and Clinical Excellence, 2011). Anxiety symptom severity at follow-up after initial treatment is lower with CBT than with other forms of psychological treatment [III] (Durham et al., 2005): but the comparative efficacy of pharmacological and psychological approaches over the long-term is not established.

16. 5. Further management after non-response to initial treatment

Many patients do not respond to first-line pharmacological or psychological interventions. There is only inconsistent evidence for a dose-response relationship with antidepressant drugs, but some patients who have not responded to an initial low dosage may respond to a higher daily dose. The efficacy of pregabalin when compared with placebo is more marked at higher daily doses (200 mg or higher) [I (M)] (Bech, 2007; Lydiard et al., 2010). Switching between pharmacological and psychological treatments with proven efficacy may be helpful [IV] (National Institute for Health and Clinical Excellence, 2011).

The addition of pregabalin to SSRI or SNRI antidepressant drugs is superior to continued treatment with antidepressants alone [I (PCT)] (Rickels et al., 2012). The findings of small randomised placebo-controlled augmentation studies suggest that augmentation of antidepressants with antipsychotic drugs (olanzapine, quetiapine, risperidone) may be beneficial [I (PCT)] (Brawman-Mintzer et al., 2005; Pollack et al., 2006; Altamura et al., 2011), but the evidence for quetiapine augmentation is inconsistent [I (PCT)] (Khan et al., 2011; Simon et al., 2008), and uncertain for ziprasidone augmentation [I (PCT)] (Lohoff et al., 2010).

Alternative treatments which have been found helpful in some patients include multi-faith spiritually based intervention [II] (Koszycki et al., 2010); *Galphimia glauca* ('thyrallis') [I (PCT)] (Herrera-Arellano et al., 2007), *Matricaria recutita* extract (chamomile) [I (PCT)] (Amsterdam et al., 2009), 'Silexa' lavender oil preparation [I (PCT)] (Woelk and Schlaefke, 2010), 'relaxing room therapy' [III] (Sherman et al., 2010), yoga-based breathing programme [III] (Katzman et al., 2012) and 'balneotherapy' (hydrotherapy with message) [III] (Dubois et al., 2010): but more investigation of these approaches is needed before they can be recommended.

Recommendations: managing patients with generalised anxiety disorder

Detection and diagnosis

- Become familiar with the symptoms and signs of generalised anxiety disorder **[S]**
- Ask about the presence of coexisting depressive symptoms **[A]**
- Ask about long-standing anxiety in patients with depressive or unexplained physical symptoms **[S]**
- Assess any comorbid physical illness and enquire about excess alcohol consumption **[S]**

Acute treatment

- Choose an evidence-based acute treatment **[A]**
  - pharmacological: most SSRIs (citalopram, escitalopram, paroxetine, sertraline), duloxetine, venlafaxine, pregabalin, agomelatine, quetiapine, some benzodiazepines (alprazolam, diazepam, lorazepam), imipramine, buspirone, hydroxyzine and trazodone **[A]**
  - psychological: cognitive-behaviour therapy, applied relaxation **[A]**
- 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 **[A]**
- SNRIs and pregabalin may be considered as alternative initial treatments if SSRIs are judged to be unsuitable **[A]**
- Remember that higher daily doses of pregabalin may be associated with greater response rates **[A]**

- Advise the patient that treatment periods of up to 12 weeks may be needed to assess efficacy **[S]** but recognise that an absence of clinical benefit within four weeks warns that a response to unchanged treatment is unlikely **[A]**

Longer-term treatment

- Continue drug treatment for up to 18 more months in patients who have responded to treatment **[A]**
- Use a treatment approach that is known to be efficacious in preventing relapse **[S]**
- Recommend CBT over other forms of psychological treatment as it may reduce relapse rates better than other psychological treatments **[C]**
- Monitor effectiveness and acceptability regularly over the course of treatment **[S]**
- When stopping treatment, reduce the dose gradually over an extended period to avoid discontinuation and rebound symptoms **[A]**: 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 **[A]**

When initial treatments fail

- Consider raising the dosage of pregabalin if the current dosage is well tolerated **[A]**
- Consider switching to another evidence-based treatment **[D]**
- Consider combining evidence-based treatments only when there are no contraindications **[S]**
- Consider pregabalin augmentation after a non-response to initial SSRI or SNRI treatment **[A]**
- Consider use of benzodiazepines after a non-response to SSRI, SNRI, pregabalin and buspirone treatment **[S]**
- Consider combining drug treatment and cognitive-behaviour therapy **[D]**
- Consider referral to regional or national specialist services in treatment refractory patients **[S]**

17. Management of panic disorder

17.1. Recognition and diagnosis

Accurate diagnosis of panic disorder is dependent upon establishing the presence of recurring panic attacks (i.e. short-lived periods of severe psychological and physical symptoms of anxiety, typically peaking within 10 min and resolving within 30 min), at least some of which are, or have been, unexpected. There should be intervening periods of comparative freedom from anxiety between attacks; but the presence of associated concern, worry or change in behaviour due to an anticipated risk of having further panic attacks [IV] (Roy-Byrne et al., 2006). There is substantial overlap between panic disorder and agoraphobia, in community and clinical samples [I] (Goodwin et al., 2005; Wittchen et al., 2010). Patients with panic disorder are often not recognised or accurately diagnosed in primary [IV] (National Collaborating Centre for Mental Health, 2011) or secondary medical care [I] (Burton et al., 2011; Deacon et al., 2008), despite their considerable use of emergency, cardiac, gastrointestinal, neurological and mental health services [IV] (Roy-Byrne et al., 2006). There is considerable co-morbidity with other mental disorders, including anxiety disorders, bipolar disorder and major depression [IV] (Roy-Byrne et al., 2006): co-morbid panic and depression is particularly common, and associated with greater disability and impairment, and increased use of health services [I] (Roy-Byrne et al., 2000).

17.2. Acute treatment

Systematic reviews demonstrate that a range of pharmacological [IV] (Andrisano et al., 2013, Batelaan et al., 2012;), psychological [IV] (Schmidt and Keough, 2010) and combination [I (M)] (Furukawa et al., 2007; Watanabe et al., 2007) interventions are effective in the acute treatment of patients with panic disorder. Little is known about the efficacy of pharmacological or psychological treatment in patients with agoraphobia but without panic attacks (Perna et al., 2011). The findings of randomised double-blind placebo-controlled trials of antidepressants indicate that all SSRIs (escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); the SNRI venlafaxine; the selective noradrenaline reuptake inhibitor reboxetine; some TCAs (clomipramine, desipramine, imipramine, lofepramine); the MAOI phenelzine; some benzodiazepines (alprazolam, clonazepam, diazepam, lorazepam); and some anticonvulsants (gabapentin, sodium valproate) are all efficacious in acute treatment [IV] (Batelaan et al., 2012).

The findings of randomised comparator-controlled studies provide some evidence for beneficial effects with mirtazapine [II] (Ribeiro et al., 2001) and moclobemide [II] (Kruger and Dahl, 1999; Tiller et al., 1999). The relative efficacy and tolerability of differing pharmacological treatments is uncertain, but there may be efficacy advantages for venlafaxine, and tolerability disadvantages for fluvoxamine and reboxetine [I (M)] (Andrisano et al., 2013). A post hoc analysis of findings from a randomised placebo-controlled trial suggests that escitalopram is superior to citalopram [I (PCT)] (Bandelow et al., 2007b); and randomised controlled trials suggest that some SSRIs (fluvoxamine, paroxetine) are more effective than some noradrenaline reuptake inhibitors (maprotiline, reboxetine) [II] (Bertani et al., 2004; Den Boer and Westenberg, 1988). Medications with a lack of efficacy in the acute treatment of patients with panic disorder include the antidepressant bupropion [I (PCT)] (Sheehan et al., 1983), the beta-blocker propranolol [I (PCT)] (Munjack et al., 1989); and buspirone[I (PCT)] (Sheehan et al., 1988). The potential value of antipsychotic drug monotherapy in acute treatment is unknown [I (M)] (Depping et al., 2010).

17.3. Longer term treatment

The findings of acute treatment studies indicate that the proportion of responding patients steadily increases over time [IV] (Batelaan et al., 2012). Double-blind studies indicate that continuing SSRI or clomipramine treatment from 12–52 weeks is associated with an increase in overall treatment response rates [I (PCT)] (Ballenger, 1998; Lecrubier and Judge, 1997; Lepola et al., 1998). The relative effectiveness and acceptability of

differing medications over long-term treatment is uncertain, but a 12-month comparison of the efficacy and tolerability of differing SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine) suggests that fluvoxamine is less likely to be associated with weight gain or sexual adverse effects [III] (Dannon et al., 2007); and the findings of a randomised naturalistic parallel-group study of 34 months of continuation treatment with clonazepam or paroxetine suggest that clonazepam is marginally more effective and better tolerated [II] (Nardi et al., 2012).

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, imipramine, paroxetine, sertraline, venlafaxine), compared to switching to placebo, for periods of up to six months: but the optimal duration of continuation treatment is uncertain [I (M)] (Donovan et al., 2010).

17.4. Comparative efficacy of psychological, pharmacological, and combination treatments

The findings of pooled analyses and randomised controlled trials together indicate that pharmacological and psychological treatments, when delivered singly, have broadly similar efficacy in acute treatment [I (M)] (Bandelow et al., 2007b; McHugh et al., 2009). In acute treatment, the combination of psychotherapy with antidepressants is superior to psychotherapy or an antidepressant, when either is given alone (Furukawa et al., 2007; Koszycki et al., 2011; Van Apeldoorn et al., 2010): the advantage over monotherapies persists as long as the antidepressant is continued, but combination treatment is more effective than antidepressant treatment alone, though no different to psychological treatment alone, in preventing relapse [I (M)] (Furukawa et al., 2007). Based on limited data, the combination of psychotherapy with a benzodiazepine is probably superior to a benzodiazepine when given alone during acute treatment, but the relative efficacy of combination treatment and monotherapies in the prevention of relapse is uncertain [I (M)] (Watanabe et al., 2007). However combination treatment appears no more cost-effective than antidepressant or CBT monotherapy [II] (McHugh et al., 2007). Exploratory placebo-controlled studies suggest that the addition of d-cycloserine may hasten the onset of effect [I (PCT)] (Siegmund et al., 2011) or increase overall effectiveness [I (PCT)] (Otto et al., 2010) of CBT in the acute treatment of patients with panic disorder.

17. 5. Further management after non-response to initial treatment

Many patients do not respond to first-line pharmacological or psychological interventions. The findings of randomised fixed-dose placebo-controlled studies suggest that higher daily doses of some antidepressants [I (PCT)] (paroxetine, fluoxetine: Ballenger et al., 1998; Michelson et al., 1998) but not others [I (PCT)] (citalopram, venlafaxine: Pollack et al., 2007; Wade et al., 1997) may be superior in efficacy to lower doses. However, the evidence to support dose escalation after an initial lack of response to lower doses is only limited [I (PCT)] (Michelson et al., 2001) or negative [I (PCT)] (Simon et al., 2009).

Switching between pharmacological and psychological treatments with proven efficacy may be helpful [IV] (National Institute for Health and Clinical Excellence, 2011). A single-blind crossover study in non-responders suggests that switching between citalopram and reboxetine may be worthwhile [II] (Seedat et al., 2003). A randomised placebo-controlled study found that pindolol augmentation of fluoxetine was superior to continued fluoxetine alone [I (PCT)] (Hirschmann et al., 2000). A small open study involving the addition of fluoxetine in patients taking a TCA, or vice versa, found some evidence of benefit [III] (Tiffon et al., 1994). Combined treatment with sodium valproate and clonazepam may be beneficial in patients who have not responded to several previous medications [III] (Ontiveros and Fontaine, 1992); as has the addition of olanzapine to other medications [III] (Sepede et al., 2006). Addition of lithium to clomipramine was found successful in a single case report [III] (Cournoyer, 1986).

Augmentation of CBT with paroxetine may be superior to continuing with CBT alone, in patients who did not previously respond over 15 sessions [I (PCT)] (Kampman et al., 2002); and addition of group CBT may be beneficial in non-responders to pharmacological approaches [III] (Heldt et al., 2003; Otto et al., 1999; Pollack et al., 1994). However a small study in multiply treatment-resistant patients found no difference in effectiveness between the augmentation of medication with CBT or 'medication optimisation' (SSRI plus clonazepam) [I (PCT)] (Simon et al., 2009).

Recommendations: managing patients with panic disorder

Detection and diagnosis

- Become familiar with the symptoms and signs of panic attacks and panic disorder **[S]**
- Ask about the presence of coexisting depressive symptoms **[A]**
- Assess the level of agoraphobic avoidance to help judge the severity of the condition **[S]**
- Ask about panic attacks and agoraphobia in patients with medically unexplained physical symptoms **[D]**

Acute treatment

- Choose an evidence-based acute treatment **[A]**
  - pharmacological: all SSRIs, some TCAs (clomipramine, desipramine, imipramine, lofepramine) venlafaxine, reboxetine, some benzodiazepines (alprazolam, clonazepam, diazepam, lorazepam), some anticonvulsants (gabapentin, sodium valproate) **[A]**
  - psychological: cognitive-behaviour therapy **[A]**
- Avoid prescribing propranolol, buspirone and bupropion **[A]**
- 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 remember that the evidence for a dose-response relationship with SSRIs and venlafaxine is inconsistent **[A]**
- Initial side effects can be minimised by slowly increasing the dose or by adding a benzodiazepine for a few weeks **[D]**
- Advise the patient that treatment periods of up to 12 weeks may be needed to assess efficacy **[A]**

Longer-term treatment

- Continue drug treatment for at least six months in patients who have responded to treatment **[A]**
- Use an approach that is known to be efficacious in preventing relapse **[S]**
- Monitor effectiveness and acceptability regularly over the course of treatment **[S]**
- When stopping treatment, reduce the dose gradually over an extended period to avoid discontinuation and rebound symptoms **[A]**: in the absence of evidence a minimum of three months is recommended for this taper period **[D]**

Combination of drugs and psychological treatment

- Consider combining cognitive therapy with antidepressants as this has greater efficacy and may reduce relapse rates better than drug treatment alone **[A]**
- Consider combining cognitive therapy with benzodiazepines (being mindful of potential long-term problems) as this probably has greater efficacy than drug treatment alone **[A]**

When initial treatments fail

- Consider raising the dosage if the current dosage is well tolerated **[A]**
- Consider switching to another evidence-based treatment **[D]**
- Consider combining evidence-based treatments only when there are no contraindications **[S]**
- Consider combining evidence-based pharmacological and psychological treatments **[A]**
- Consider referral to regional or national specialist services in treatment refractory patients **[S]**

18. Management of specific phobia (also known as simple or isolated phobia)

18.1. Recognition and diagnosis

Specific fears of objects, animals, people or situations are widespread in children, adolescents and adults, but only a minority of affected individuals reach the full diagnostic criteria for specific phobia. Specific (or simple or isolated) phobia has an estimated 12-month prevalence of 6.4% [I] (Wittchen et al., 2011), and had a lifetime prevalence of 9.4% in the United States National Epidemiologic Survey on Alcohol and Related Conditions [I] (Stinson et al., 2007). Many affected individuals have multiple fears, whose presence is associated with an earlier onset, greater severity and impairment, and more frequent psychiatric comorbidity [I] (Burstein et al., 2012; Stinson et al., 2007). Most individuals with specific phobia do not present for treatment of that condition, presentation being more likely with comorbid anxiety or mood disorders [I] (Mackenzie et al., 2012).

18.1 Treatment

The effectiveness and acceptability of psychological or pharmacological treatments for specific phobia has been relatively under-researched when compared to other anxiety disorders. The findings of a meta-analytic review of 33 randomised controlled treatment studies indicate that exposure-based therapies (particularly those involving in vivo exposure) are more effective than other psychological interventions: effectiveness being seen regardless of the nature of the specific phobia, and being somewhat greater with multiple rather than single sessions [I (M)] (Wolitzky-Taylor et al., 2008).

Most patients respond to psychological approaches, but some may benefit from pharmacological treatment. The findings of small randomised placebo-controlled trials provide evidence for the efficacy of escitalopram [I (PCT)] (Alamy et al., 2008) and paroxetine [I (PCT)] (Benjamin et al., 2000). The findings of small randomised placebo-controlled studies suggest that the efficacy of exposure therapy can be enhanced through prior administration of d-cycloserine [I (PCT)] (Nave et al., 2012; Ressler et al., 2004): but not all evidence is consistent [I (PCT)] (Guastella et al., 2007), and its administration after a session is not associated with enhanced efficacy [I (PCT)] (Tart et al., 2013). Prior administration of naltrexone may reduce the effectiveness of exposure therapy [I (PCT)] (Kozak et al., 2007). It is unclear whether concomitant use of benzodiazepines enhances or reduces the efficacy of behavioural approaches.

Recommendations: managing patients with specific (or simple) phobia

- Become familiar with the symptoms and signs of specific phobia **[S]**
- Assess the number of fears, the level of anxiety, and the degree of impairment to judge severity **[A]**
- Ask about symptoms of comorbid disorders in treatment-seeking patients **[A]**
- Use psychological treatments based on exposure techniques as first-line treatment **[A]**
- Consider SSRI treatment for patients who have not responded to psychological interventions **[A]**

19. Management of social anxiety disorder (also known as social phobia)

19.1. Recognition and diagnosis

Social anxiety disorder is often not recognised in primary medical care [I] (Weiller et al., 1996) but detection can be enhanced through the use of screening questionnaires in psychologically distressed primary care patients [I] (Donker et al., 2010; Terluin

et al., 2009). Social anxiety disorder is often misconstrued as mere 'shyness' but can be distinguished from shyness by the higher levels of personal distress, more severe symptoms and greater impairment [I] (Burstein et al., 2011; Heiser et al., 2009). The generalised sub-type (where anxiety is associated with many situations) is associated with greater disability and higher comorbidity, but patients with the non-generalised subtype (where anxiety is focused on a limited number of situations) can be substantially impaired [I] (Aderka et al., 2012; Wong et al., 2012). Social anxiety disorder is hard to distinguish from avoidant personality disorder, which may represent a more severe form of the same condition [IV] (Reich, 2009). Patients with social anxiety disorder often present with symptoms arising from comorbid conditions (especially depression), rather than with anxiety symptoms and avoidance of social and performance situations [I] (Stein et al., 1999). There are strong, and possibly two-way, associations between social anxiety disorder and dependence on alcohol and cannabis [I] (Buckner et al., 2008; Robinson et al., 2011).

19.2. Acute treatment

The findings of meta-analyses and randomised placebo-controlled treatment studies indicate that a range of approaches are efficacious in acute treatment [IV] (Blanco et al., 2013). CBT is efficacious in adults [I (M)] (Hofmann and Smits, 2008) and children [I (M)] (James et al., 2005): cognitive therapy appears superior to exposure therapy [I (M)] (Ougrin, 2011), but the evidence for the efficacy of social skills training is less strong [IV] (Ponniah and Hollon, 2008).

Antidepressant drugs with proven efficacy include most SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), the SNRI venlafaxine, the MAOI phenelzine, and the RIMA moclobemide: nefazodone is not efficacious and the evidence for mirtazapine is inconsistent [I (M)] (De Menezes et al., 2011). The potential efficacy of tricyclic antidepressants is unknown. Some benzodiazepines (bromazepam and clonazepam, but not alprazolam) and anticonvulsants (gabapentin and pregabalin, but not levatiracetam), and the antipsychotic olanzapine also appear efficacious in acute treatment [IV] (Blanco et al., 2013). Neither the 5-hydroxytryptamine (5-HT_{1A}) partial agonist buspirone, nor the beta-blocker atenolol are efficacious in generalised social anxiety disorder [IV] (Blanco et al., 2013), although a number of small single-dose placebo-controlled cross-over studies together suggest that beta-blockers can be beneficial in reducing anxiety symptoms in individuals with 'performance anxiety' (for example, when speaking in public), which overlaps with mild non-generalised social anxiety disorder) [IV] (Blanco et al., 2013).

There have been relatively few randomised comparator-controlled studies of acute treatment and most reveal no significant differences in overall efficacy or tolerability between active compounds. In randomised placebo- and comparator- controlled studies, phenelzine was superior to placebo, but atenolol was not [I (PCT)] (Liebowitz et al., 1992); phenelzine was superior to placebo, but alprazolam was not [I (PCT)] (Gelernter et al., 1991); and escitalopram was found superior to paroxetine [I (PCT)] (Lader et al., 2004); venlafaxine and paroxetine had similar overall efficacy in two placebo-controlled studies [I (PCT)] (Allgulander et al., 2004b; Liebowitz et al., 2005).

19.3. Longer term treatment

The findings of acute treatment studies indicate that the proportion of responding patients increases steadily over time [IV] (Blanco et al., 2013). Double-blind studies indicate that continuing SSRI or SNRI treatment from 12–24 weeks is associated with an increase in overall treatment response rates [I (M)] (Lader et al., 2004; Stein et al., 2002a, 2003). A post hoc analysis of the clinical trial database for escitalopram indicates that response is unlikely if there is no onset of clinical effect within the first four weeks of treatment [I (PCT)] (Baldwin et al., 2009): however a post hoc analysis of the clinical trial database with paroxetine indicates that many non-responders to treatment at eight weeks become responders with a further four weeks of double-blind treatment [I (PCT)] (Stein et al., 2002a). The findings of randomised 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, pregabalin, sertraline) for up to six months [IV] (Blanco et al., 2013).

19.4. Comparative efficacy of pharmacological, psychological and combination treatments

Pharmacological and psychological treatments, when delivered singly, have broadly similar efficacy in acute treatment [I (M)] (Canton et al., 2012). However, acute treatment with cognitive therapy (group or individual) is associated with a reduced risk of symptomatic relapse at follow-up [I (M)] (Canton et al., 2012). It is unlikely that the combination of pharmacological with psychological treatments is associated with greater overall efficacy than with either treatment, when given alone, as only one in four studies of the relative efficacy of combination treatment found evidence for superior efficacy [I (PCT)] (Blanco et al., 2010). The findings of small randomised placebo-controlled studies suggest that the efficacy of psychological treatment may be enhanced through prior administration of d-cycloserine [I (PCT)] (Guastella et al., 2008; Hofmann et al., 2006) or cannabidiol [I (PCT)] (Bergamaschi et al., 2011).

19.5. Further management after non-response to initial treatment

The findings of fixed-dose randomised controlled trials do not provide consistent evidence of a dose-response relationship with antidepressant drugs: but a fixed-dose study of pregabalin found that only the higher daily dosage was efficacious [I (PCT)] (Pande et al., 2004). A double-blind randomised controlled dosage escalation trial found no advantage for increasing to a higher daily dosage (120 mg) of duloxetine, when compared to continuing treatment with a lower (60 mg) dosage [II] (Simon et al., 2010). Switching between treatments with proven efficacy may be helpful [IV] (Blanco et al., 2013). An uncontrolled study of augmentation of SSRI treatment with buspirone found some evidence of beneficial effects [III] (Van Ameringen et al., 1996); but a placebo-controlled crossover-study of the augmentation of paroxetine with pindolol found no evidence of efficacy [I (PCT)] (Stein et al., 2001). A small

placebo-controlled study of the augmentation of paroxetine with clonazepam found the combination was marginally short of superiority, when compared to paroxetine alone [I (PCT)] (Seedat and Stein, 2004).

Recommendations: managing patients with social anxiety disorder

Detection and diagnosis

- Become familiar with the symptoms and signs of social anxiety disorder **[S]**
- Assess the level of distress and disability to help distinguish social anxiety disorder from shyness **[A]**
- Ask about the presence of coexisting depressive symptoms **[A]**
- Ask about social anxiety symptoms when patients present with depression, panic attacks restricted to social situations, or alcohol and cannabis 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
- Avoid prescribing atenolol or buspirone in generalised social anxiety disorder **[A]**
- 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 **[A]**
- 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 may be needed to assess efficacy **[A]**

Longer-term treatment

- Use an approach that is known to be efficacious in preventing relapse **[S]**
- Continue drug treatment for at least six months in patients who have responded to treatment **[A]**
- Consider cognitive therapy with exposure as this may reduce relapse rates better than drug treatment **[A]**
- Consider cognitive therapy after response to drug treatment, in patients with a high risk of relapse **[D]**
- Monitor effectiveness and acceptability regularly over the course of 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 when given alone **[A]**

When initial treatments fail

- Consider raising the dosage if the current dosage is well tolerated **[D]**
- Consider switching to another evidence-based treatment **[D]**
- Consider combining evidence-based treatments only when there are no contraindications **[S]**
- Consider adding buspirone after partial response to an SSRI **[C]**
- Consider combining evidence-based pharmacological and psychological treatments **[A]**
- Consider benzodiazepines in patients who have not responded to other approaches **[D]**
- Consider referral to regional or national specialist services in treatment refractory patients **[S]**

20. Management of post-traumatic stress disorder

20.1. Recognition and diagnosis

Exposure to potentially life-damaging traumatic events is common, in both genders, during childhood, adolescence and adult life [IV] (Nemeroff et al., 2006): but only a proportion of those exposed to trauma develop psychological sequelae. For example, the US National Comorbidity Survey found that 60.7% of men and 51.2% of women reported exposure to at least one traumatic event, but post-traumatic stress disorder had a lifetime prevalence of 7.8% [I] (Kessler et al., 1995). In the UK, post-traumatic stress disorder was present in only a minority of individuals exposed to motor vehicle accidents, at three-month (11%) and 12-month (5%) follow-up [I] (Mayou et al., 2001). The 12-month prevalence of post-traumatic stress disorder is estimated to be 1.1–2.9%, being more common in younger than older adults [I] (Wittchen et al., 2011).

Post-traumatic stress disorder shows considerable co-morbidity with other mental disorders [I] (Loewe et al., 2011). Suicidal thoughts are common but the increased risk of completed suicide is probably due to the presence of comorbid depression [I (M)] (Krysinska and Lester, 2010). Post-traumatic stress disorder is associated with increased use of health services, but is often not recognised in primary or secondary care [I] (Liebschutz et al., 2007). Diagnosis can be established through eliciting the 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; and the presence of 're-experiencing symptoms' (such as intrusive recollections, flashbacks or dreams); avoidance symptoms (such as efforts to avoid activities or thoughts associated with the trauma); and hyper-arousal symptoms (including disturbed sleep, hypervigilance and an exaggerated startle response).

20.2. Prevention of post-traumatic disorder after experiencing trauma

There is some scope for preventing the emergence of psychological post-traumatic symptoms in people subject to major trauma. Early administration of benzodiazepines after trauma may not

prevent the emergence of post-traumatic symptoms [III] (Gelpin et al., 1996). A small randomised placebo-controlled study found that acute administration of propranolol (160 mg/day) was superior to placebo in reducing subsequent post-traumatic symptoms and physiological hyper-activity to reminders of trauma, but not the emergence of post-traumatic stress disorder, at one month [I (PCT)] (Pitman et al., 2002). A naturalistic study suggests acute administration of propranolol (120 mg/day) prevented the emergence of syndromal post-traumatic stress disorder at two months [III] (Vaiva et al., 2003): but not all evidence is consistent [I (PCT)] (Nugent et al., 2010, Stein et al., 2007b). Intravenous administration of hydrocortisone has been found superior to placebo in preventing post-traumatic symptoms, in intensive care adult patients with septic shock (median interval, 31 months) [I (PCT)] (Schelling et al., 2001), in patients undergoing cardiac surgery (interval, six months) [I (PCT)] (Schelling et al., 2004), and in patients experiencing acute stress reactions following a range of traumatic experiences [I (PCT)] (Zohar et al., 2011). The findings of small randomised placebo-controlled treatment studies find evidence for the efficacy for sertraline [I (PCT)] (Stoddard et al., 2011), but not for gabapentin [I (PCT)] (Stein et al., 2007b) or escitalopram [I (PCT)] (Shalev et al., 2012), in preventing post-traumatic symptoms. The findings of systematic reviews suggest that trauma-focused CBT is potentially beneficial in preventing chronic post-traumatic symptoms, when provided within six months of the incident [I (M)] (Roberts et al., 2009); but approaches with limited efficacy include single-session 'debriefing' [I (M)] (Van Emmerik et al., 2002) and multiple-session early intervention [I (M)] (Roberts et al., 2009).

20.3. Acute treatment of post-traumatic disorder

The findings of randomised placebo-controlled treatment studies indicate that there is evidence for the efficacy of a range of antidepressants including some SSRIs (fluoxetine, paroxetine, sertraline), amitriptyline, imipramine, mirtazapine, nefazodone, phenelzine and venlafaxine (Ipser and Stein, 2011). There is also evidence for the efficacy of the antipsychotics risperidone (Padala et al., 2006), olanzapine (Carey et al., 2012) and the anticonvulsant topiramate; (Yeh et al., 2011). Medications which have not been found efficacious in placebo-controlled trials include citalopram, alprazolam, and the anticonvulsants tiagabine and divalproex. However when 37 randomised placebo-controlled trials are subject to meta-analysis (restricted to comparisons of outcome data using validated scales), only paroxetine, sertraline and venlafaxine were found to have superiority over placebo [I (M)] (Ipser and Stein, 2011). Probably due to the small size of certain patient sub-groups (men vs women, civilians vs military veterans) neither paroxetine nor sertraline have been found consistently beneficial across all patient groups: though a post hoc analysis suggests that venlafaxine is potentially efficacious in reducing post-traumatic symptom severity in men and women, and across all trauma types [I (PCT)] (Rothbaum et al., 2008a). There have been few controlled comparisons of the effectiveness and acceptability of differing medications, though venlafaxine was found superior to placebo, when sertraline was not [I (PCT)] (Davidson et al., 2006b); reboxetine had similar effectiveness but lower overall tolerability than fluvoxamine [II] (Spivak et al., 2006); and mirtazapine had somewhat greater than effectiveness than sertraline, in a randomised but 'open' trial [II] (Chung et al., 2004).

20.4. Longer term treatment

Although many patients with post-traumatic stress disorder experience a prolonged illness, there is some uncertainty about the course of the condition, as most longitudinal studies in post-traumatic stress disorder are retrospective in design. Few prospective studies have been published, although the findings of a prospective study in adolescents and young adults with post-traumatic stress disorder or sub-threshold post-traumatic stress disorder indicate that around 50% will experience a chronic course of illness [I] (Perkonigg et al., 2005). The findings of acute and continuation treatment studies indicate that the proportion of responding patients increases steadily over time (Davidson et al., 2006a; Ipser and Stein, 2011; Londborg et al., 2001). A small number of randomised double-blind placebo-controlled relapse prevention studies find evidence for the efficacy of longer-term treatment, for fluoxetine [I (PCT)] (Martenyi et al., 2002) and sertraline [I (PCT)] (Davidson et al., 2005), but not tiagabine [I (PCT)] (Connor et al., 2006).

20.5. Comparative efficacy of pharmacological, psychological and combination treatments

Meta-analyses demonstrate that trauma-focused CBT and eye movement desensitisation and reprocessing (EMDR) are both efficacious and superior to 'stress management' [I (M)] (Bisson and Andrew, 2007), and appear to have similar overall efficacy [I (M)] (Seidler and Wagner, 2006). There have been very few direct comparisons of the efficacy of psychological and pharmacological treatments, in either acute or long-term treatment of patients with post-traumatic stress disorder. A small unblinded 12-week comparison of paroxetine and trauma-focused CBT [III] (Frommberger et al., 2004) suggested that CBT may have certain advantages, in reducing the severity of post-traumatic and depressive symptoms. A systematic review of four studies of the combination of pharmacological with psychological treatments could find insufficient evidence to draw conclusions about the relative efficacy of combination treatment compared to monotherapy [I (M)] (Hetrick et al., 2010), although a more recent randomised placebo-controlled trial found evidence that paroxetine could enhance the effectiveness of prolonged (10 sessions) exposure therapy [I (PCT)] (Schneier et al., 2012). The findings of two randomised placebo-controlled studies of the potential augmentation of exposure therapy through administration of d-cycloserine could find no evidence of increased efficacy [I (PCT)] (De Kleine et al., 2012; Litz et al., 2012). The findings of two small exploratory randomised placebo-controlled trials in patients with treatment-resistant post-traumatic stress disorder suggest that the short-term efficacy of psychological treatment may be enhanced through concurrent administration of 3,4-methylenedioxymethamphetamine (MDMA) [I (PCT)] (Mithoefer et al., 2011; Oehen et al., 2013): with some evidence of persisting improvement at two-year follow-up [III] (Mithoefer et al., 2013).

20.6. Further management after non-response to initial treatment

Many patients with post-traumatic stress disorder do not respond to initial pharmacological or psychological treatment. Switching between treatments with proven efficacy may be beneficial [IV] (National Institute for Clinical Excellence (NICE), 2005). The findings of small randomised placebo-controlled augmentation studies provide evidence for the efficacy of the alpha-adrenergic agonist prazosin in reducing nightmares and other PSTD symptoms [I (PCT)] (Raskind et al., 2003), for olanzapine in reducing post-traumatic and depressive symptoms and sleep disturbance [I (PCT)] (Stein et al., 2002b) and risperidone in reducing comorbid 'psychotic symptoms' [I (PCT)] (Hamner et al., 2003), in reducing irritable aggression [I (PCT)] (Monnelly et al., 2003), and in reducing overall post-traumatic symptoms [I (PCT)] (Bartzokis et al., 2005; Rothbaum et al., 2008b). However a large randomised placebo-controlled trial found no evidence of benefit for risperidone augmentation of a range of pharmacological and psychological treatments [I (PCT)] (Krystal et al., 2011).

Recommendations: managing patients with post-traumatic stress disorder

Detection and diagnosis

- Ask about a history of traumatic events when patients present with psychological symptoms **[S]**
- Become familiar with the symptoms and signs of post-traumatic stress disorder **[S]**
- Ask about the presence of coexisting depressive symptoms **[A]**

Prevention of post-traumatic symptoms

- After major trauma, discuss the potential for preventing the emergence of post-traumatic symptoms, and providing there are no contra-indications, consider preventive treatment with propranolol or sertraline **[A]** or trauma-focused CBT **[A]**
- Do not recommend routine single-session or multiple-session 'debriefing' **[A]**

Acute treatment of chronic post-traumatic stress disorder

- Choose an evidence-based acute treatment **[A]**
  - pharmacological: paroxetine, sertraline, venlafaxine **[A]**
  - psychological: trauma-focused individual CBT or EMDR **[A]**
- Consider an SSRI for first-line pharmacological treatment **[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]**
- Advise the patient that treatment periods of up to 12 weeks may be needed to assess efficacy **[A]**.

Longer-term treatment

- Use an approach that is known to be efficacious in preventing relapse **[S]**
- Continue drug treatment for at least 12 months in patients who have responded to treatment **[A]**
- Monitor effectiveness and acceptability regularly over the course of treatment **[S]**

Combination of drugs with 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 when given alone **[A]**: but paroxetine may enhance the effectiveness of exposure therapy **[A]**

When initial treatments fail

- Consider raising the dosage if the current dosage is well tolerated **[D]**
- Consider switching to another evidence-based treatment **[D]**
- Consider combining evidence-based treatments only when there are no contraindications **[S]**
- Consider combining evidence-based pharmacological and psychological treatments **[A]**
- Consider augmentation of antidepressants with olanzapine [A] risperidone **[A]** or prazosin **[A]**
- Consider referral to regional or national specialist services in treatment refractory patients **[S]**

21. Management of obsessive-compulsive disorder

21.1. Recognition and diagnosis

Obsessive-compulsive disorder has an estimated 12-month prevalence of 0.7–1.0% [I] (Kessler et al., 2012; Wittchen et al., 2011), and an estimated lifetime morbid risk of 2.7% [I] (Kessler et al., 2012). The female preponderance, early age of onset and typical presence of coexisting obsessions and compulsions are common features across societies, but the content of obsessions varies between cultures [I (M)] (Fontenelle et al., 2004). The disorder usually follows a chronic course, waxing and waning in severity; and has substantial co-morbidity with major depression and anxiety disorders [IV] (Zaudig, 2011), and with tic disorders [I] (Fibbe et al., 2012). Distinguishing obsessive-compulsive disorder from obsessive-compulsive personality disorder is difficult, and patients often fulfil diagnostic criteria for both conditions: their comorbidity is associated with greater illness severity [I] (Coles et al., 2008; Garyfallos et al., 2010; Lochner et al., 2011). Patients often present with symptoms arising from the co-morbid conditions, rather than with obsessional ruminations and compulsive rituals [I] (Torres et al., 2007).

21.2. Acute treatment of obsessive-compulsive disorder

The findings of systematic reviews and meta-analyses of randomised double-blind placebo-controlled trials indicate that the TCA antidepressant clomipramine, and the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) [I (M)] (Soomro et al., 2008) are all efficacious in acute treatment, in reducing symptom severity and in improving health-related quality

of life [IV] (Fineberg et al., 2012). Pharmacological approaches are efficacious in treating children and adolescents with obsessive-compulsive disorder [I (M)] (Watson and Rees, 2008).

There have been few evaluations of the relative efficacy and tolerability of differing pharmacological treatments. The findings of meta-analysis suggest that the efficacy of clomipramine is on the margins of superiority over that of SSRIs [I (M)] (Ackerman and Greenland, 2002; National Institute for Health and Clinical Excellence, 2005) but in randomised controlled trials the tolerability of SSRIs is generally superior [IV] (Fineberg and Gale, 2005). The findings of a randomised comparator controlled trial suggest that paroxetine and venlafaxine had comparable effectiveness and acceptability [II] (Denys et al., 2003). Fixed-dose randomised controlled studies provide inconsistent evidence for a dose-response relationship with SSRIs, higher doses being associated with greater overall efficacy in some but not all studies: however the findings of meta-analysis of nine treatment studies involving SSRIs finds some evidence for greater efficacy (though poorer tolerability) with higher daily dosages [I (M)] (Bloch et al., 2010).

Meta-analyses of controlled studies involving psychological treatment approaches find evidence for the efficacy of behaviour therapy based on exposure with response prevention alone, for cognitive restructuring alone, and for exposure with response prevention plus cognitive restructuring [I (M)] (Rosa-Alcazar et al., 2008). Internet-delivered CBT is superior to online supportive therapy [I (PCT)] (Andersson et al., 2012), though therapist-led CBT appears more effective than computerised CBT [I (M)] (Tumur et al., 2007). The relative effectiveness of individual and group CBT approaches is uncertain [I (M)] (Jonsson and Hougaard, 2009). Psychological approaches are efficacious in treating children and adolescents with obsessive-compulsive disorder [I (M)] (Watson and Rees, 2008).

21.3. Longer term treatment

The findings of acute treatment studies indicate that the proportion of responding patients increases steadily over time. Long-term (up to 12 months) double-blind randomised controlled studies demonstrate an advantage for continuing with medication, in patients who have responded to acute treatment [I (PCT)] (Greist et al., 1995; Katz et al., 1990; Tollefson et al., 1994). A randomised placebo-controlled trial with paroxetine as an active comparator found that a low dosage of escitalopram only became efficacious in the second half of a 24-week study [I (PCT)] (Stein et al., 2007a). 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 (escitalopram, fluoxetine at higher daily doses, paroxetine, sertraline), compared with switching to placebo, for up to 12 months [I (PCT)] (Fineberg et al., 2007), but the optimal duration of continuation treatment is uncertain [I (M)] (Donovan et al., 2010).

21.4. Comparative efficacy of pharmacological, psychological and combination treatments

It is probable, but not certain, that the combination of pharmacological and psychological treatment is superior to psychological approaches or medication, when either is given alone. The evidence for enhanced efficacy of exposure therapy with clomipramine compared with exposure alone is inconsistent (Foa et al., 2005; Marks et al., 1988; Rachman et al., 1979), though fluvoxamine has been shown to enhance the efficacy of exposure therapy [I (PCT)] (Cottraux et al., 1990) and multi-modal CBT [I (PCT)] (Hohagen et al., 1998). The combination of exposure and response prevention with varying SSRIs has been found superior to SSRI treatment alone [II] (Simpson et al., 2008); the addition of behaviour therapy after completion of acute treatment was superior to continuing with SSRI treatment alone in another study [II] (Tenneij et al., 2005); and the addition of CBT (but not CBT instructions) to SSRI treatment was found superior to medication management alone, in children and adolescents [II] (Franklin et al., 2011). However the value of combination treatment over psychological or pharmacological treatments given alone over the long term is uncertain. A series of small randomised placebo-controlled studies suggest that administration of d-cycloserine may hasten the response to CBT, but provide no evidence that the overall effectiveness of CBT is enhanced [I (PCT)] (Kushner et al., 2007; Storch et al., 2010; Wilhelm et al., 2008).

21.5. Further management after non-response to initial treatment

Many patients do not respond to first-line pharmacological or psychological interventions. Switching between pharmacological or psychological treatments with proven efficacy is helpful in some patients. Increasing the dose of an SSRI, sometimes beyond formulary limits, may be beneficial (Ninan et al., 2006; Pampaloni et al., 2010). A placebo-controlled study found that intravenous clomipramine infusion was efficacious after non-response to oral clomipramine, but the necessary arrangements limit its usefulness in practice [I (PCT)] (Fallon et al., 1998).

The findings of some, but not all, randomised double-blind placebo-controlled augmentation studies indicate that the addition of the antipsychotics aripiprazole, haloperidol, olanzapine, quetiapine or risperidone to continuing antidepressant treatment can be efficacious in patients who have not responded to initial treatment with clomipramine or SSRIs, the evidence currently being most strong for augmentation with risperidone [I (M)] (Dold et al., 2011). The findings of small randomised placebo-controlled augmentation studies with 5-HT_3 antagonists provide evidence for the efficacy of the addition of ondansetron to fluoxetine [I (PCT)] (Soltani et al., 2010) and for the addition of granisetron to fluvoxamine [I (PCT)] (Askari et al., 2012). Three relatively small randomised placebo-controlled anticonvulsant augmentation studies indicate that the addition of topiramate to SSRIs reduces the severity of compulsions [I (PCT)] (Berlin et al., 2011), and of obsessive-compulsive symptoms [I (PCT)] (Mowla et al., 2010); and the addition of lamotrigine to SSRIs reduces the severity of obsessive-compulsive and affective symptoms [I (PCT)] (Bruno et al., 2012). The evidence for augmentation with pindolol is mixed, but placebo-controlled or comparator-controlled augmentation studies find no evidence for the efficacy of augmentation with buspirone, clonazepam, desipramine, inositol, liothyronine, lithium, naltrexone or oxytocin [IV] (Fineberg and Gale, 2005).

The findings of a randomised comparator-controlled trial of dextroamphetamine or caffeine augmentation of SSRI or SNRI antidepressants suggest both compounds were beneficial in reducing symptom severity [II] (Koran et al., 2009). Other potential but as yet unproven approaches in the management of patients with treatment-resistant obsessive-compulsive disorder include monotherapy with once-weekly morphine [I (PCT)] (Koran et al., 2005); and the glutamate-modulating compounds riluzole [III] (Coric et al., 2005; Pittenger et al., 2008), memantine [III] (Stewart et al., 2010), and glycine [I (PCT)](Greenberg et al., 2009). Some patients with treatment-refractory obsessive-compulsive disorder may benefit from deep brain stimulation and other neurosurgical approaches [IV] (Blomstedt et al., 2012; De Koning et al., 2011; Greenberg et al., 2010).

Recommendations: managing patients with obsessive-compulsive disorder

Detection and diagnosis

- Become familiar with the symptoms and signs of 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 **[S]**
- Ask about obsessive-compulsive symptoms when patients present with depression **[S]**
- Ask about the presence of coexisting depressive symptoms **[A]**

Acute treatment

- Choose an evidence-based acute treatment **[A]**
  - pharmacological: clomipramine and all SSRIs **[A]**
  - psychological: exposure therapy, cognitive-behaviour therapy, cognitive therapy **[A]**
- 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
- Consider an SSRI for first-line pharmacological treatment **[D]**
- Consider increasing the daily dosage of SSRIs if there is insufficient response at lower dosage **[A]**
- Advise the patient that initial treatment periods beyond 12 weeks may be needed to assess efficacy **[A]**

Longer-term treatment

- Use an approach that is known to be efficacious in preventing relapse **[S]**
- Continue drug treatment for at least 12 months in patients who have responded to treatment **[A]**
- Monitor effectiveness and acceptability regularly over the course of treatment **[S]**

Combination of drugs with psychological treatments

- Consider combining an SSRI or clomipramine with an evidence-based psychological treatment when efficacy needs to be maximised **[D]**

When initial treatments fail

- Consider raising the dosage if the current dosage is well tolerated **[A]**
- Consider switching to another evidence-based treatment **[D]**
- Consider combining evidence-based treatments only when there are no contraindications **[S]**
- Consider combining evidence-based pharmacological and psychological treatments **[A]**
- Consider augmentation of an SSRI or clomipramine with an antipsychotic drug **[A]**
- Consider augmentation of an SSRI or clomipramine with a 5-HT_3 antagonist **[A]**
- Consider augmentation of an SSRI with topiramate **[A]** or lamotrigine **[A]**
- Consider augmentation of an SSRI with morphine [A]
- Consider augmentation of an SSRI with riluzole **[C]**
- Consider referral to regional or national specialist obsessive-compulsive disorder services in treatment refractory patients **[S]**

22. Management of other anxiety disorders

22.1. Marked health anxiety ('illness anxiety disorder')

The DSM-5 ((American Psychiatric Association, 2013) includes 'illness anxiety disorder' within the group of 'somatic symptom and related disorders'. The condition is characterised by excessive concern over health, constant fear of undiagnosed disease that physicians may have missed, and the characteristic behaviours of repeated checking and need for medical reassurance. Pharmacological treatment is not normally acceptable to patients, as those with marked health anxiety are typically very sensitive to adverse effects of medication: but fluoxetine showed some benefit over placebo, though this was not pronounced and occurred late in treatment (8–12 weeks [I (PCT)] (Fallon et al., 2008). Psychological treatments have been found beneficial [I (M)] (Thomson and Page, 2007), and include behavioural stress management (Clark et al., 1998) ([II]), cognitive behaviour therapy, in both face-to-face and internet format (Hedman et al., 2011b; Seivewright et al., 2008; Sørensen et al., 2011) ([II]), and mindfulness –based CBT (McManus et al., 2012) ([II]). A recent large randomised controlled trial found efficacy for an adapted form of CBT in medical patients, in which significant benefits over standard care were still present two years after therapy had ended [II] (Tyrer et al., 2014).

22.2 Separation anxiety disorder in adults

Though traditionally regarded as having an onset in childhood, separation anxiety disorder is now recognised as both continuing into and having an onset during adult life: and as such is grouped with other anxiety disorders within the DSM-5 (American Psychiatric Association, 2013). The efficacy of psychological or pharmacological treatment in adults with separation anxiety

disorder has not been studied extensively, and treatment studies in children have often involved mixed diagnostic groups [IV] (Bögels et al., 2013). Psychological treatment studies in children find some evidence of benefit with CBT, parent-child interaction training, and 'summer camp' programmes [IV] (Ehrenreich et al., 2008). The findings of randomised placebo-controlled trials of pharmacological treatment in children with separation anxiety disorder provide no convincing evidence of benefit for any medication, although fluvoxamine (Walkup et al., 2001) and sertraline have been found efficacious among the separation anxiety disorder subgroup within mixed diagnostic samples (Walkup et al., 2008).

Recommendations: treatment of children and adolescents

- Reserve pharmacological treatments for children and teenagers who have not responded to psychological interventions, and in whom the anticipated benefits are expected to outweigh any potential risks **[S]**
- Choose from the same range of treatments as considered for adult patients, considering an SSRI for first-line pharmacological treatment: fluoxetine may be the SSRI with the best balance of potential benefit and risk **[B]**
- Ensure that the daily dosage takes account of the age and weight of the patient, and start with low dosage, recognising that more rapid metabolism may lead to the need for 'adult' doses **[S]**
- Monitor patients carefully, especially for any evidence of increased anxiety and agitation, and remember that many children and adolescents find it hard to describe emotional states and possible psychological adverse effects **[D]**

23. Special considerations in particular patient groups

23.1. Children and adolescents

When compared with investigations in individuals aged between 18–65 years, there have been relatively few randomised placebo-controlled studies of the potential benefits and risks of psychotropic drug treatment in younger people, and little is known about the value of long-term treatment [I (M)] (Ipser et al., 2009). The findings of randomised placebo-controlled trials in children and adolescents indicate that SSRI treatment can be effective in children and adolescents with generalised anxiety disorder, separation anxiety disorder or social anxiety disorder [I (M)] (Dieleman and Ferdinand, 2008), and also in post-traumatic stress disorder [IV] (Strawn et al., 2010), and obsessive-compulsive disorder [IV] (Gentile, 2011). Psychological treatments also have evidence of efficacy [I (M)] (Gillies et al., 2012; James et al., 2005; Kircanski et al., 2011; Kowalik et al., 2011) but the relative efficacy of pharmacological and psychological treatment approaches, alone and in combination, is not established: although combination treatment was found optimal in obsessive-compulsive disorder (March et al., 2004).

In 2004, the United Kingdom Committee on Safety of Medicines stated that the balance of risks and benefits for the treatment of depressive illness in people under the age of 18 years was judged to be unfavourable for some SSRIs (escitalopram, citalopram, paroxetine and sertraline), mirtazapine and venlafaxine [IV] (Committee on Safety of Medicines, 2004), and advised caution when treating depressed adults aged 18–30 years with SSRIs. A recent meta-analysis cautiously concluded that the balance of benefit and risk in the treatment of depressed children and adolescents may be most favourable with fluoxetine [I (M)] (Hetrick et al., 2012).

The balance of risks of harm and benefit in the treatment of children and adolescents with anxiety disorders, when compared to the treatment of depression, is more favourable [IV] (Holtkamp and Herpertz-Dahlmann, 2008). However careful monitoring is advisable, due to possible diagnostic uncertainty, the presence of co-morbid 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.

23.2. Elderly patients and patients with cardiac or neurological disease

Many elderly patients are troubled by anxiety symptoms, but anxiety disorders in those over 65 years may be less common than in younger age groups [IV] (Wolitzky-Taylor et al., 2010). When compared with investigations in individuals aged between 18–65 years, there have been relatively few randomised controlled studies of the potential benefits and risks of psychological or pharmacological treatment for anxiety disorders in older people [IV] (Oude Voshaar, 2013), and little is known about the relative effectiveness and acceptability of differing treatments, or about the value of long-term treatment [I (M)] (Goncalves and Byrne, 2012; Gould et al., 2012; Pinquart and Duberstein, 2007; Thorp et al., 2009). Clearance of many drugs is slower in the elderly, so lower doses may be required than in younger patients.

Tricyclic antidepressants and some antipsychotic drugs are best avoided in patients with cardiac disease, as they can increase heart rate, induce orthostatic hypotension, slow cardiac conduction and have significant quinidine-like effects on conduction within the myocardium [IV] (Vieweg et al., 2009). 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. SSRIs have relatively minor effects on cardiovascular function and may have potentially beneficial effects on platelet aggregation (Bismuth-Evenzal et al., 2012; Lopez-Vilchez et al., 2009). Higher doses (more than 40 mg per day) of citalopram may be associated with a slightly increased risk of QT interval prolongation on the electrocardiogram, and should be avoided in patients with known cardiac risk factors including hypokalaemia and hypomagnesaemia [IV] (US Food and Drug Administration, 2012): though a recent large pharmacoepidemiological study found no evidence of elevated risks of ventricular arrhythmia or all-cause, cardiac or non-cardiac mortality associated with higher citalopram dosages [I] (Zivin et al., 2013).

Anxiety symptoms and disorders have an increased prevalence in patients with common neurological conditions, including migraine [IV] (Buse et al., 2012), epilepsy [IV] (Beyenburg et al., 2005), and in the aftermath of stroke [I (M)] (Campbell Burton

et al., 2012). SSRI and SNRI antidepressants should be used with caution in patients with migraine undergoing prophylaxis with triptans [IV] (Evans et al., 2010). Despite widespread belief that antidepressant drugs can lower the seizure threshold, systematic review of data from placebo-controlled trials with psychotropic drugs, submitted to the United States Federal Drug Administration, indicates that that the frequency of seizures is significantly lower with most antidepressants than with placebo [I (M)] (Alper et al., 2007). Pharmacokinetic interactions between medications used for treating anxiety disorders and anticonvulsants are not uncommon and it is always advisable to establish the potential for untoward drug-drug interactions when treating epileptic patients with anxiety disorders [IV] (Muscatello et al., 2012). SSRI treatment may improve overall recovery after stroke [I (M)] (Mead et al., 2012), but little is known about the potential efficacy of psychological or pharmacological interventions in the treatment of anxiety disorders in the aftermath of stroke [I (M)] (Campbell Burton et al., 2011).

Recommendations: treatment in elderly and physically ill patients

- Remember that anxiety symptoms and disorders are common in elderly and physically ill patients, and that many individuals will benefit from evidence-based pharmacological or psychological treatments **[S]**
- Manage elderly patients in a broadly similar way to younger patients, being mindful of the possibility of drug interactions, the potential need for lower doses in patients with renal or hepatic impairment, and the risk of worsening any pre-existing cognitive impairment through the use of medications with sedative effects **[S]**
- Avoid prescribing tricyclic antidepressants to patients with cardiovascular disease **[D]**

23.3. Pregnant and breastfeeding women

Anxiety disorders are not uncommon during pregnancy and in the post-partum period [I (M)] (Ross and McLean, 2006). Symptoms will remit during pregnancy in some women [III] (George et al., 1987). Many doctors consider the scope for withdrawing psychotropic drugs in pregnant women (particularly in the first trimester), and using psychological rather than pharmacological treatments, but in practice it is sometimes necessary to continue pharmacological treatment, in patients with severe anxiety disorders. The findings of a recent systematic review indicate that antidepressant drugs are associated with increased risk of spontaneous abortions, stillbirths, preterm deliveries, respiratory distress, endocrine and metabolic disturbance, with some evidence of a discontinuation syndrome and of an increased risk of cardiac defects; antipsychotics are associated with increased gestational weight and diabetes and with increased risk of preterm birth [I (M)] (Oyebode et al., 2012). However the overall evidence on the balance of risks and benefits of psychotropic drug treatment during pregnancy evolves over time and it is wise to seek advice from respected information sources. The BAP is producing guidance on the management of patients during the perinatal period (McAllister-Williams et al., in development).

Recommendations: women of child-bearing age

- Remember that anxiety disorders are common among women who wish to become pregnant **[S]**
- Keep familiar with the changing evidence base about the potential hazards of treatment of pregnant and breast-feeding women with psychotropic drugs **[S]**
- Consider carefully the anticipated benefits and risks of pharmacological and psychological treatments of anxiety disorders in pregnant women, including the potential relative and actual risks of harm to a developing child **[S]**

23.4. Referral to secondary and tertiary care mental health services

Despite the availability of many evidence-based pharmacological and psychological treatments, a substantial proportion of patients will not respond fully to initial treatments, provided in primary medical care. The criteria for referral to secondary care mental health services should be sufficiently flexible to ensure that patients with disabling and treatment-resistant anxiety disorders can have equitable access to mental health specialists. Consensus between primary and secondary care about when referral of patients with anxiety disorders is advisable should be an explicit component of service commissioning procedures. Potential criteria for referral to secondary care mental health services include 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. Some patients with complex, severe, enduring and treatment-resistant anxiety disorders do not respond to the range of treatment options delivered in secondary care mental health services, and these patients should be referred to tertiary care specialist services for patients with affective disorders.

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Conflict of interest

All participants were asked to provide information about potential conflict of interest at the time of the consensus meeting

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