CLINICAL PRACTICE GUIDELINES

Anxiety Disorders

MOH Clinical Practice Guidelines 1/2015

Published by Ministry of Health, Singapore
16 College Road,
College of Medicine Building
Singapore 169854

Printed by Oxford Graphic Printers Pte Ltd

ISBN 978-981-07-1411-6

Available on the MOH website: http://www.moh.gov.sg/cpg

Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Such standards are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Contents

		Page
	Executive summary of recommendations	1
1	Introduction	12
2	Clinical evaluation and overview	16
3	Management of Panic Disorder	32
4	Management of Generalised Anxiety Disorder	37
5	Management of Specific Phobia	41
6	Management of Social Anxiety Disorder	43
7	Management of Obsessive-Compulsive Disorder	46
8	Management of Post-Traumatic Stress Disorder	50
9	Management of anxiety disorders in pregnancy	55
10	Cost-effectiveness issues	63
11	Clinical quality improvement	65
	Annexes	66
	References	68
	Self-assessment (MCQs)	90
	Workgroup members	92

Foreword

Anxiety disorders are common and result in considerable burden to sufferers and their families, as well as a high rate of utilisation of medical services. The early detection and appropriate management of anxiety disorders is important, especially in patients who present with a variety of physical symptoms to non-psychiatrists and to primary healthcare facilities. Failure to detect these conditions results in unnecessary investigations, with the primary condition remaining untreated. Fortunately, such conditions are not difficult to diagnose and are highly amenable to treatment. Patients with milder symptoms may be successfully managed in the primary care setting, leaving the more severely ill to specialist services.

Although most patients with anxiety disorders can be managed as outpatients, the majority are still not seeking treatment. This has serious implications. Psychological and physical symptoms contribute to lower quality of life and impairment of social and occupational functioning, which could lower work productivity and even cause unemployment. Untreated or under-treated individuals with anxiety disorders are also at risk of suicide.

The Anxiety Disorders CPG workgroup is to be commended for their painstaking efforts in updating the original 2003 guidelines with new evidence. I trust that readers will find these guidelines useful in the management of their patients.

ASSOCIATE PROFESSOR BENJAMIN ONG
DIRECTOR OF MEDICAL SERVICES

Commonly used abbreviations

The following is a list of abbreviations commonly used in this set of guidelines (arranged in alphabetical order), and a description of what they represent:

- APA: American Psychiatric Association
- DSM: Diagnostic and Statistical Manual of mental disorders
- EMEA: European Medicines Agency
- FDA: Food and Drug Administration
- GAD: Generalised anxiety disorder
- OCD: Obsessive-compulsive disorder
- PTSD: Post-traumatic stress disorder
- SNRI: Serotonin-norepinephrine reuptake inhibitor
- SRI: Serotonergic reuptake inhibitor
- SSRI: Selective serotonin reuptake inhibitor
- TCA: Tricyclic Antidepressant

Executive summary of recommendations

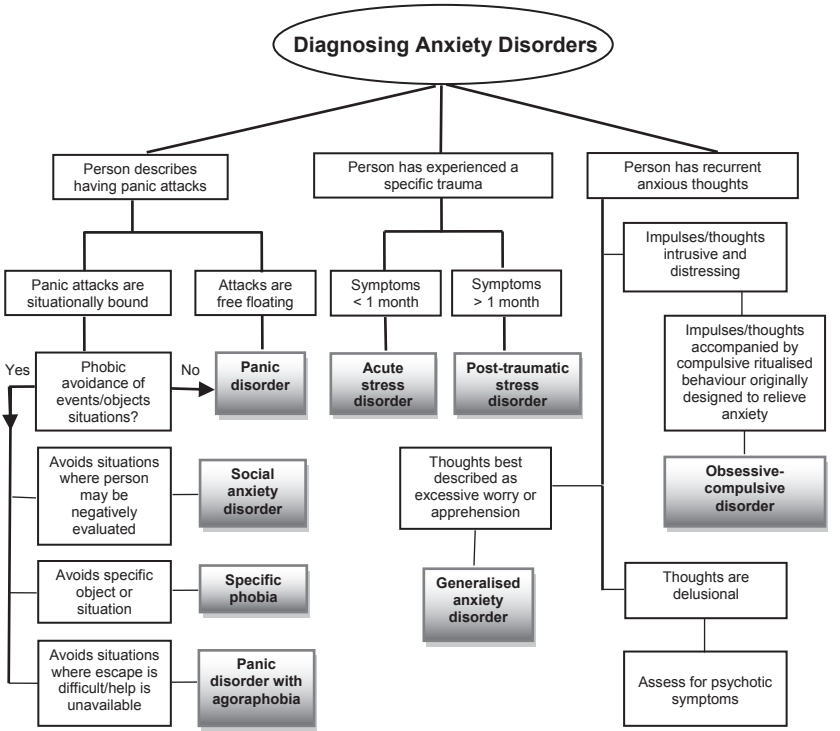
Details of recommendations can be found on the indicated pages. Key recommendations are highlighted in blue.

Clinical Evaluation and Overview

No.	Recommendation	Grade, Level of evidence	CPG Page no.
1	A diagnosis of anxiety disorder should be considered only after appropriate clinical evaluation and investigation to rule out general medical conditions have been done. Figure 1 summarises how the various anxiety disorders are diagnosed.	GPP	16
2	The initial management of anxiety disorders should ideally be instituted at the primary care level. The recommended framework for the management of anxiety disorders in primary care is described in Figure 2.	GPP	22
3	The following may be instituted in primary care immediately after diagnosis: • Educating patient on nature and origin of anxiety symptoms and providing appropriate reassurance, e.g. not having a 'heart attack' or 'going crazy' • Suggestion of lifestyle changes as appropriate, i.e., stress reduction strategies, reducing alcohol and caffeine intake, avoiding nicotine and drug use, regular exercise • Supportive counselling • Symptomatic relief with medication prescribed on a short-term basis • Evaluation and mobilisation of family and social resources • Monitoring and addressing early signs of relapse	Grade D, Level 4	22

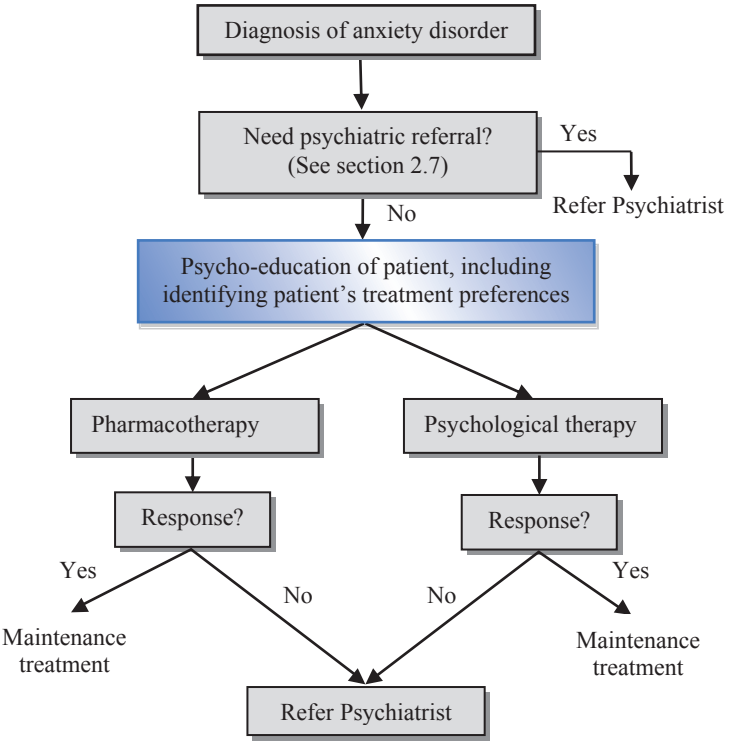
No.	Recommendation	Grade, Level of evidence	CPG Page no.
4	Psychiatric evaluation and treatment is appropriate when there is serious risk of suicide, there are psychotic symptoms, co-occurring drug/alcohol problems exist, symptoms are severe/complex or if symptoms fail to improve on initial treatment and follow-up.	GPP	27
5	Consider transferring patients with anxiety disorders from psychiatric to primary care for long-term management if they have the following characteristics: • Aged 18 or older • Stabilised for the past 3 months • No psychiatric hospitalisation in the past 6 months • No history of forensic or substance abuse • No disruptive personality disorders • Non suicidal • No history of aggressive behaviour • Not currently receiving clozapine, lithium, valproate, hypnotics (including benzodiazepines, zopiclone, zolpidem) or formal psychotherapy treatment	GPP	27
6	All patients should receive education about their disorder, including aetiology, treatment choices, and prognosis.	GPP	28
7	As local patients may show higher propensity for initial side effects of antidepressants (e.g. paradoxical excitation), starting doses for local patients should be lower than those suggested by overseas guidelines.	GPP	30
8	The Clinical Global Impression scales (both severity and improvement sub-scales) may be used to measure illness severity and treatment progress during consultations for anxiety disorders.	Grade B, Level 2++	31

Figure 1. Differentiating Anxiety Disorders



Adapted from "Guidelines for assessing and treating anxiety disorder", National Health Committee, New Zealand, November 1998.

Figure 2. Anxiety Disorders management algorithm



Management of Panic Disorder

No.	Recommendation	Grade, Level of evidence	CPG Page No.
9	Either SSRIs or venlafaxine should be used as first-line agents for the pharmacological treatment of panic disorder.	Grade A, Level 1+	33
10	Imipramine and clomipramine are effective and may be used as second-line treatment of panic disorder.	Grade A, Level 1+	33
11	Benzodiazepines may be added to antidepressants in the short term to produce a more rapid therapeutic response in the treatment of panic disorder. In view of addictive potential, benzodiazepines should be tapered and withdrawn by 4 weeks.	Grade A, Level 1+	35
12	Depending on availability of treatment and patient preference, CBT or combination therapy (i.e. CBT and SSRIs or venlafaxine) may be used for the treatment of panic disorder.	Grade A, Level 1++	36

Management of Generalised Anxiety Disorder (GAD)

No.	Recommendation	Grade, Level of evidence	CPG Page No.
13	Either SSRIs or venlafaxine should be used as first-line pharmacological treatment for patients with GAD.	Grade A, Level 1++	38
14	Imipramine may be considered as a second-line treatment for GAD, in view of the possibility of poor tolerability and the danger of fatal overdosage.	Grade A, Level 1+	38
15	Mirtazapine may be considered as a second-line treatment for GAD due to its anxiolytic effects.	Grade A, Level 1+	38
16	Benzodiazepines should not be used for the long-term treatment of GAD.	Grade B, Level 1+	39
17	Pregabalin may be prescribed for patients with GAD as it has anxiolytic effects which may be more rapid acting. Due caution must be exercised when prescribing to patients who are at risk of abusing substances.	Grade B, Level 2++	39
18	Hydroxyzine may be used as adjunctive treatment together with other anxiolytic agents for treatment of GAD.	Grade C, Level 2+	39
19	Propanolol is not recommended for the long-term treatment of generalised anxiety disorder.	Grade B, Level 1+	39
20	Drug treatment for GAD needs to be continued for at least 32 weeks as high relapse rates were reported after discontinuing medications.	Grade A, Level 1+	40
21	CBT may be used as first-line psychotherapy treatment for GAD.	Grade A, Level 1++	40
22	A specialist's opinion should be sought for patients with complex GAD and/or with marked functional impairment, or at high risk of self-harm.	GPP	40

Management of Specific Phobia

No.	Recommendation	Grade, Level of evidence	CPG Page No.
23	CBT should be used as first-line treatment of specific phobia.	Grade A, Level 1++	41
24	Benzodiazepines may be used on a short-term basis for temporary anxiety relief in specific phobia, pending resolution of symptoms with other forms of treatment.	Grade B, Level 1+	42

Management of Social Anxiety Disorder (SAD)

No.	Recommendation	Grade, Level of evidence	CPG Page No.
25	Either pharmacotherapy or psychotherapy alone may be used as first-line treatment for SAD, depending on patient preferences, values and economic considerations.	Grade A, Level 1++	43
26	Either SSRIs or venlafaxine should be used as first-line pharmacotherapy for SAD.	Grade A, Level 1+	44
27	Moclobemide may be used for the treatment of SAD if treatment with SSRIs or venlafaxine has not been effective.	Grade A, Level 1+	44
28	Benzodiazepines may be used on a short-term basis for temporary anxiety relief pending resolution of phobic symptoms with other forms of treatment.	Grade A, Level 1+	44
29	Beta-blockers (e.g. atenolol, propranolol) are not recommended for the treatment of SAD as they have been found ineffective. However, they may be used for the treatment of performance anxiety (e.g. playing an instrument, giving a speech).	Grade B, Level 2++	45
30	CBT should be used as first-line psychotherapy treatment of SAD.	Grade A, Level 1+	45
31	Pharmacotherapy with SSRIs, venlafaxine, or moclobemide in SAD should be continued for at least 12 months to prevent relapse.	Grade B, Level 2++	45

Management of Obsessive-Compulsive Disorder (OCD)

No.	Recommendation	Grade, Level of evidence	CPG Page No.
32	Either pharmacotherapy or psychotherapy alone may be chosen as first-line treatment for OCD, depending on patient preferences, values and economic considerations.	Grade A, Level 1++	46
33	The first-line pharmacological treatment for OCD should be a 10-12 week trial with an SSRI at adequate doses.	Grade A, Level 1++	47
34	Clomipramine may be used as a treatment for OCD after an adequate trial of SSRI treatment has failed.	Grade A, Level 1++	47
35	An adequate treatment trial in OCD should last for at least 12 weeks. If the patient does not respond to treatment in adequate dosages, the medication may be changed or specialist opinion sought.	Grade D, Level 4	48
36	Venlafaxine may be considered in patients who have not responded to SSRIs and clomipramine. Monitor blood pressure during treatment as venlafaxine at high doses can raise blood pressure.	Grade A, Level 1+	48
37	CBT may be used as first-line treatment for OCD if patients prefer psychological treatment over pharmacotherapy.	Grade A, Level 1+	49
38	CBT augmentation of serotonergic antidepressants (e.g. SSRIs, clomipramine) in the treatment of OCD may be considered for those who are treatment-resistant or partially responsive to medications.	Grade B, Level 1+	49
39	Patients with OCD who respond to antidepressants in the acute phase should be continued on their medication for at least 12 months.	Grade A, Level 1+	49

Management of Post-Traumatic Stress Disorder (PTSD)

No.	Recommendation	Grade, Level of evidence	CPG Page No.
40	Either the SSRIs or venlafaxine may be used as first-line pharmacological treatment for PTSD.	Grade A, Level 1++	51
41	Mirtazapine may be considered as a second-line treatment for PTSD.	Grade B, Level 1+	51
42	Either amitriptyline or imipramine may be considered for PTSD if the first-line and second-line treatments are ineffective or poorly tolerated.	Grade A, Level 1+	52
43	Benzodiazepines should not be used for the treatment of PTSD.	Grade A, Level 1+	52
44	Risperidone, olanzapine, quetiapine, and lamotrigine may be prescribed as adjunctive treatments for PTSD in conjunction with the SSRIs.	Grade B, Level 1+	52
45	Pharmacological treatment for PTSD should be continued for at least 12 months.	Grade D, Level 4	53
46	CBT should be used as the first-line psychological treatment for PTSD.	Grade A, Level 1+	53
47	Eye Movement Desensitisation and Reprocessing therapy may be used as second-line treatment for PTSD.	Grade B, Level 2++	54
48	If CBT or eye movement desensitisation and reprocessing therapy for PTSD are contraindicated or have failed, combination therapy (i.e. CBT plus pharmacotherapy) may be used as an alternative treatment.	Grade B, Level 1+	54

Management of anxiety disorders in pregnancy

No.	Recommendation	Grade, Level of evidence	CPG Page No.
49	If a woman is planning a pregnancy or becomes pregnant while on medication for an anxiety disorder, consider: • stopping medication and starting CBT, if necessary and if not already tried. • switching to a safer drug, if the decision is to maintain her on medication.	Grade D, Level 4	55
50	When prescribing a drug for a woman with an anxiety disorder who is planning a pregnancy, already pregnant, or breastfeeding: • choose drugs with the lowest risk potential for the mother and foetus/infant • start at the lowest effective dose, and slowly titrate upwards • continue for the shortest possible duration • use monotherapy instead of combination treatment	Grade D, Level 4	56
51	Sertraline, paroxetine and citalopram should be avoided during pregnancy.	Grade C, Level 2+	57
52	Benzodiazepines should not be routinely prescribed for pregnant and breastfeeding women, except for the short-term treatment of extreme anxiety and agitation.	Grade D, Level 4	59
53	The risk-benefit ratio of prescribing benzodiazepines should be assessed on a case-by-case basis; use the lowest dose for the shortest time, or avoid prescribing at all during the first trimester.	GPP	59
54	Atypical antipsychotics should be prescribed with caution in patients suffering from or at risk of gestational diabetes.	Grade D, Level 3	59
55	Medication for nursing mothers should be maintained at the lowest effective dose to minimise infant exposure.	Grade D, Level 3	60

No.	Recommendation	Grade, Level of evidence	CPG Page No.
56	When antidepressant treatment is indicated in the postpartum period, women should generally not be advised to discontinue breastfeeding.	Grade D, Level 3	60
57	Treatment with paroxetine or sertraline should be preferred over other SSRIs in treatment-naive breastfeeding women due to the low infant exposure to these drugs.	Grade D, Level 3	61
58	Drugs for which little data exist, such as fluvoxamine, venlafaxine, bupropion and mirtazapine, should not be considered as first-line therapies in breastfeeding women, but they may be used in special cases.	Grade D, Level 4	61
59	If mothers have been successfully treated with a particular SSRI, TCA, or SNRI, this drug should be the first-line treatment if there are no contraindications. An individual risk-benefit assessment should always be done before starting antidepressants.	Grade D, Level 4	61
60	Women on long term treatment with high dose benzodiazepines should continue to breastfeed, as stopping of benzodiazepine may precipitate withdrawal symptoms in the infant. Gradual tapering and stopping of benzodiazepines may be attempted at a later stage when the infant has grown bigger.	GPP	62
61	During maternal treatment with benzodiazepines, infants should be monitored for signs of sedation, lethargy, poor feeding and weight loss.	Grade D, Level 4	62

1 Introduction

Anxiety disorders are known to be one of the most prevalent of psychiatric conditions, yet they often remain under-diagnosed and under-treated.[1-5] Their chronic, disabling symptoms cause considerable burden not only to sufferers but also to their families, and contribute to poorer quality of life and considerable economic burden on society.

In many instances, there is a delay in seeking treatment and in some cases such delay may stretch up to nearly ten years.[5] This may result from ignorance of the condition, fear of taking medications, and the stigma of receiving a psychiatric diagnosis, and or having to accept psychiatric treatment.

The anxiety disorders include panic disorder with or without agoraphobia, social anxiety disorder, specific phobia, obsessive-compulsive disorder, generalised anxiety disorder, acute stress disorder, and post-traumatic stress disorder. In the clinical evaluation of anxiety disorders, it is important to ascertain the type of anxiety disorder present. This would allow treatment to be targeted at the specific type of disorder.

These guidelines are developed to provide practical, evidence-based recommendations to primary care physicians and specialists in psychiatry for the diagnosis and management of the anxiety disorders.

The first edition of the guidelines[6] was published in 2003. In this edition, we present data from newer research as well as older data not previously reported in the earlier guidelines.

For example, we examine the efficacy of combining medications with psychological therapy over medications alone, or psychological therapy alone. In view of the majority of anxiety sufferers being female we have made recommendations for pharmacotherapy during pregnancy and breastfeeding. As these guidelines are intended for use in the Singapore context, we have omitted treatments that are currently not available in Singapore.

1.1 Aim

These guidelines are developed to facilitate the diagnosis and assessment of the anxiety disorders, and to ensure that their management is appropriate and effective.

1.2 Scope

These guidelines will cover the management of anxiety disorders in adults and address the issues of medication use during pregnancy and breastfeeding.

1.3 Target group

The content of the guidelines will be useful for all doctors treating patients with anxiety disorders. Efforts have been made to ensure that the guidelines are particularly useful for primary care physicians and specialists in psychiatry, including all those involved in the assessment and management of patients with anxiety disorders in the community. The doctor treating the patient is ultimately responsible for clinical decisions made after reviewing the individual patient's history, clinical presentation and treatment options available.

1.4 Development of guidelines

These guidelines have been produced by a committee of psychiatrists, a clinical psychologist, pharmacist, patient representative, and family practitioners appointed by the Ministry of Health. They were developed by revising the existing guidelines, reviewing relevant literature, including overseas clinical practice guidelines and by expert clinical consensus of professionals with experience in treating patients in the local setting.

The following principles underlie the development of these guidelines:

- Treatment recommendations are supported by scientific evidence whenever possible (randomised controlled clinical trials represent the highest level of evidence) and expert clinical consensus is used when such data are lacking.
- Treatment should maximise therapeutic benefits and minimise side effects.

1.5 What's new in the revised guidelines

This edition of the guidelines contains updated recommendations based on latest evidence, as well as detailed discussions and recommendations on the management of anxiety disorders in adult populations.

The following represent changes to the revised guidelines

- An extensive review of the literature including new evidence. This involved the re-writing and extensive revision of the chapters.
- Length of treatment, which provides answers to a pertinent question.
- Use of medications during pregnancy and breastfeeding. Given that females are more likely to be at risk of being diagnosed with anxiety disorders, this is an important subject.

We are aware that the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) was released in 2013. In DSM-5, post-traumatic stress disorder and obsessive-compulsive disorder have been removed and classified separately from the rest of the anxiety disorders. If we were to adhere strictly to DSM-5 this would entail omitting discussion on post-traumatic stress disorder and obsessive-compulsive disorder. As it is our aim to provide an update on the 2003 guidelines, post-traumatic stress disorder and obsessive-compulsive disorder have been included in this edition of the guidelines.

In addition, anxiety conditions in children are included in DSM-5. Since the present guidelines are meant to address only adult anxiety disorders, guidelines on children's anxiety conditions are not included here.

Hence, for purposes of these guidelines we will continue to use classifications based on the International Classification of Diseases-10 (ICD-10)[7] and DSM-IV-TR[8] criteria.

1.6 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review five years after publication, or when new evidence appears that requires substantive changes to the present recommendations.

2 Clinical Evaluation and Overview

2.1 Diagnosis and Assessment

Patients with anxiety disorders often present with mainly somatic symptoms in primary care and emergency settings. A diagnosis of anxiety disorder should be made only after appropriate clinical evaluation and investigation to rule out general medical conditions have been carried out.

> **GPP** A diagnosis of anxiety disorder should be considered only after appropriate clinical evaluation and investigation to rule out general medical conditions have been done.
>
> **GPP**

Many patients do not seek professional help for psychiatric problems because of their attitudes and beliefs about mental health and mental disorder — embracing the concept that one needs to be 'strong enough' to cope alone, for instance. Yet, as most people have regular contact with primary care health services, patients with anxiety disorder are likely to consult their primary health care doctor even though psychiatric problems may not be the main reason for the consultation.

Early recognition of these disorders facilitates early intervention. This reduces distress, disability and burden of illness, with potential for reducing the downstream need for secondary mental health services.

2.2 Comprehensive Assessment

A comprehensive general medical and psychiatric assessment is the basis for the formulation of a good treatment plan. It is important to determine if there are comorbid general medical or drug/substance-induced conditions that may cause anxiety symptoms, complicate treatment or require specific interventions (Table 1, page 17). This is especially so if a patient develops new symptoms that have yet to be medically evaluated.

Table 1. Conditions which may aggravate or mimic anxiety symptoms

Type of physical condition	Examples
Endocrine	▪ hyperthyroidism ▪ hypoglycaemia ▪ adrenal insufficiency ▪ hyperadrenocorticism ▪ phaeochromocytoma
Cardiovascular	▪ congestive heart failure ▪ pulmonary embolism ▪ arrhythmia ▪ mitral valve prolapse
Respiratory	▪ asthma ▪ chronic obstructive lung disease ▪ pneumonia
Metabolic	▪ diabetes mellitus
Neurologic	▪ vestibular dysfunction ▪ migraine ▪ neoplasm ▪ temporal lobe epilepsy
Gastrointestinal	▪ irritable bowel syndrome ▪ peptic ulcers
Haematologic	▪ anaemia ▪ vitamin B12 deficiency
Medication induced	▪ some medications, e.g. specific SSRIs are associated with an increase in anxiety in the first 2 weeks
Others	▪ excessive stimulant intake (including caffeine and nicotine), alcohol or drug withdrawal

Appropriate laboratory investigations and diagnostic studies may be necessary.

Basic screening tests to identify medical conditions might include:

- a full blood count
- serum urea, electrolytes, calcium, creatinine
- thyroid function tests
- electrocardiogram (ECG)
- chest X-ray

A psychosocial assessment would include elucidating the nature of developmental factors, life stressors and conflicts, social support/resources, and the present general living situation.

2.3 Types of Anxiety Disorder

A brief description of the anxiety disorders, based on the ICD-10[7] and DSM-IV-TR[8] criteria is appended.

2.3.1 Generalised anxiety disorder

The main features of generalised anxiety disorder are excessive anxiety and worry. The patients suffer from somatic anxiety symptoms, as well as from restlessness, irritability, difficulty concentrating, muscle tension, sleep disturbances and from being easily fatigued.

2.3.2 Panic disorder

Panic disorder is characterised by recurrent panic attacks which consist of discrete periods of intense fear, accompanied by at least four of 14 somatic and psychological symptoms (13 in DSM-IV).[8] A panic attack reaches a peak within 10 minutes and lasts 30-45 minutes on average. Usually, the patient is afraid that he has a serious medical condition, and fears he is going to die or is going crazy.

2.3.3 Specific phobia

Specific phobia is characterised by excessive or unreasonable fear of specific objects or situations (e.g. flying, heights, animals, seeing blood). Exposure to the feared object, situation or phobic stimulus elicits an anxiety response and is usually

avoided or endured with dread. This may affect and even compromise the daily functioning of a person.

2.3.4 Social anxiety disorder

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

2.3.5 Obsessive-compulsive disorder

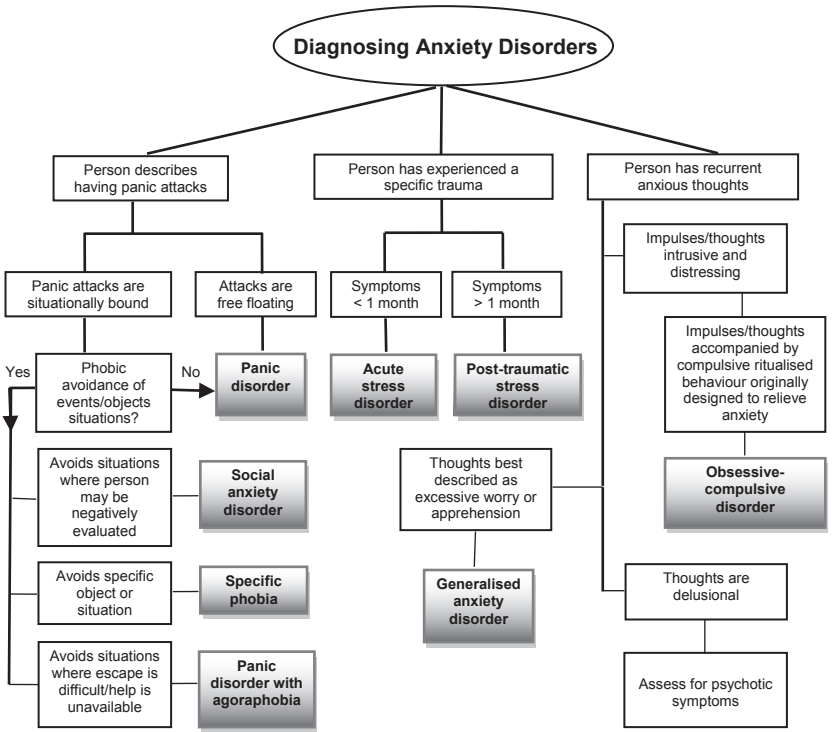
Obsessive-compulsive disorder is characterised by recurrent obsessions, compulsions, or both, that cause impairment in terms of distress, time, or interference with functioning. Concerns involving contamination, harm, and sexual, somatic and religious preoccupations are the most common obsessions. Compulsions include washing, checking, repeating, ordering, counting, and hoarding.

2.3.6 Post-traumatic stress disorder

Post-traumatic stress disorder develops after a terrifying ordeal that involved physical harm or the threat of physical harm. The condition is characterised by recurrent and intrusive distressing recollections of the event, nightmares, a sense of reliving the experience with illusions, hallucinations, or dissociative flashback episodes, intense psychological or physiological distress at exposure to cues that resemble the traumatic event, avoidance of stimuli associated with the trauma, inability to recall important aspects of the trauma, loss of interest, estrangement from others, sleep disturbances, irritability, difficulty concentrating, hypervigilance, and exaggerated startle response. The symptom picture must be present for more than one month.

Identifying the key features which characterise the disorder enables classification of the type of anxiety disorder according to a diagnostic algorithm (see Figure 1).

Figure 1. Differentiating Anxiety Disorders



Adapted from "Guidelines for assessing and treating anxiety disorder", National Health Committee, New Zealand, November 1998.

2.4 Comorbid Medical and Psychiatric Disorders

Anxiety disorders often present together with other psychiatric or physical conditions.[3,8] Alternatively, physical and psychiatric disorders may present with anxiety as a prominent feature without an anxiety disorder being present.

Up to 75% of those diagnosed with an anxiety disorder have at least one other comorbid psychiatric condition.[9] Common comorbid conditions include another anxiety disorder, depressive disorder (e.g. major depression or dysthymic disorder), alcohol and substance abuse, personality disorders, and bipolar disorder.[3, 9]

The Singapore National Mental Health Survey of 2002-2003 found comorbidity between generalised anxiety disorder and other psychiatric disorders with 85% of recently diagnosed generalised anxiety disorder sufferers and 93% persons with lifetime generalised anxiety disorder having a comorbid psychiatric condition.[10]

Anxiety disorders were also significantly associated with chronic medical conditions. For example, coronary artery disease, asthma, chronic obstructive pulmonary disease, diabetes, hyperthyroidism and arthritis were significantly associated with primary anxiety disorders,[9-14] and the individual effects of medical and psychiatric morbidity on functional status and quality of life were considerably worse when both were present in the same individual.[15]

2.5 Overview of management

Anxiety disorders are mostly managed in the outpatient setting and rarely require hospital admission. Initial management can ideally be instituted at the primary care level.[16]

GPP The initial management of anxiety disorders should ideally be instituted at the primary care level. The recommended framework for the management of anxiety disorders in primary care is described in Figure 2.

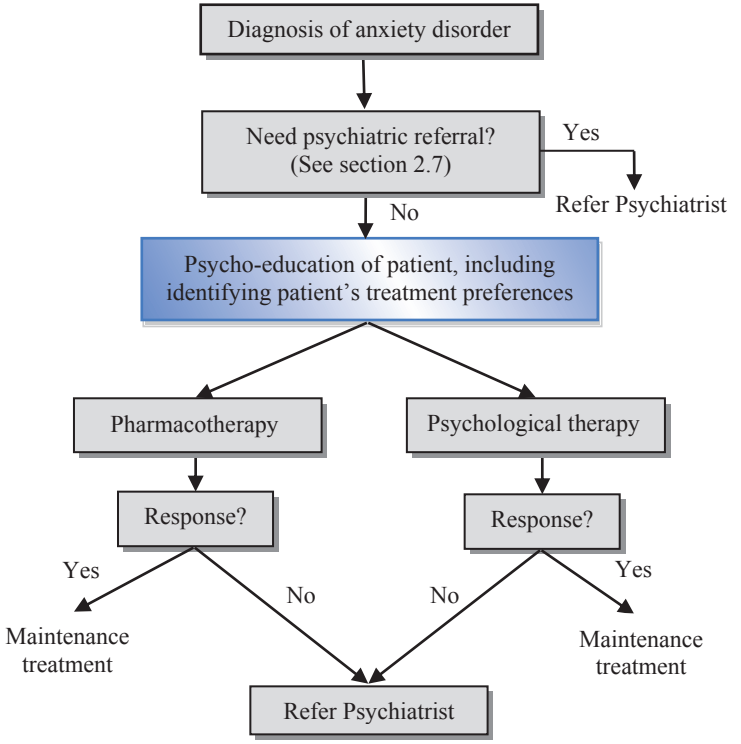
GPP

D The following may be instituted in primary care immediately after diagnosis:[17]

- Educating patient on nature and origin of anxiety symptoms and providing appropriate reassurance, e.g. not having a 'heart attack' or 'going crazy'
- Suggestion of lifestyle changes as appropriate:
  - Stress reduction strategies
  - Reducing alcohol and caffeine intake
  - Avoiding nicotine and drug use
  - Regular exercise
- Supportive counselling
- Symptomatic relief with medication prescribed on a short-term basis
- Evaluation and mobilisation of family and social resources
- Monitoring and addressing early signs of relapse

Grade D, Level 4

Figure 2 Anxiety Disorders management algorithm



2.6 Diagnostic and Screening Instruments

This section provides information on various diagnostic and screening instruments for anxiety disorders and how they are used.

2.6.1 Panic Disorder

2.6.1.1 *Panic Disorder Severity Scale*

Treatment response in panic disorder can be quantified and documented with the Panic Disorder Severity Scale (PDSS),[18] a clinician-rated instrument assessing 7 dimensions of PD on 4-point scales (a self-report version is also available).

The PDSS consists of seven items, each rated on a 5-point scale, which ranges from 0 to 4. The items assess 7 dimensions e.g. panic frequency, distress during panic, panic-focused anticipatory anxiety, phobic avoidance of situations, phobic avoidance of physical sensations, impairment in work functioning, and impairment in social functioning.

The overall score is derived by summing the scores for all seven items. The total scores range from 0 to 28.

The PDSS-self report version is used as a screening tool and a score of 9 and above suggests the need for a formal diagnostic assessment.

2.6.1.2 *Panic and Agoraphobic Scale (PAS)*

The Panic and Agoraphobic Scale (PAS)[19] is a measure of the severity of illness in patients with panic disorder (with or without agoraphobia). It is available in both clinician-administered and self-rating formats. It contains 5 sub-scales: panic attacks, agoraphobic avoidance, anticipatory anxiety, disability, and functional avoidance (health concerns).

This questionnaire is designed for people suffering from panic attacks and agoraphobia. First, respondents are asked to read the definition of “panic attacks” and then rate the severity of their symptoms over the past week.

2.6.2 Generalised anxiety disorder

Generalised Anxiety Disorder 7-item (GAD-7) scale

The Generalised Anxiety Disorder 7-item (GAD-7) scale[20] is a self-reported questionnaire for screening and severity measuring of generalised anxiety disorder. GAD-7 has seven items, which measure severity of various signs of generalised anxiety disorder according to reported response categories of "not at all," "several days," "more than half the days," and "nearly every day." The total score is obtained by adding the scores for all seven items.

2.6.3 Social Phobia

Social Phobia Inventory

The Social Phobia Inventory[21] (abbreviated as SPIN) is a 17-item questionnaire. It is effective in screening for, and measuring the severity of social anxiety disorder. Item scores are added to produce a total score. Higher scores indicate more severe symptoms. A cut-off value of 19 may be used to distinguish between patients with and without social phobia.

Severity	None	Mild	Moderate	Severe	Very Severe
Score	Less than 20	21 - 30	31 - 40	41 - 50	51 or more

2.6.4 Post-Traumatic Stress Disorder

Short PTSD Rating Interview (SPRINT)

The SPRINT[22] provides a brief global assessment for post-traumatic stress disorder and each of the individual symptom clusters associated with the disorder (i.e. intrusion and re-experiencing, avoidance and numbing, hyperarousal). The SPRINT is responsive to symptom change over time and correlates with comparable symptom measures. In victims of trauma, a score of 14-17 is associated with 96% diagnostic accuracy, whereas in those with post-traumatic stress disorder, highest efficiency corresponded to a range of 11-13. The SPRINT demonstrates solid psychometric properties and is a reliable, valid and homogeneous measure of post-traumatic stress disorder illness severity and of global improvement.

Note: The SPIN and SPRINT are not in the public domain and permission for use should be obtained from the copyright holder, Dr. Davidson, at david011@mc.duke.edu.

2.6.5 Obsessive-Compulsive Disorder

Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

The Yale–Brown Obsessive Compulsive Scale[23] is a tool to rate the severity of obsessive–compulsive disorder symptoms. It is used extensively in research and clinical practice to both determine severity of the disorder and to monitor improvement during treatment. It measures obsessions separately from compulsions, specifically measuring the severity of symptoms of obsessive–compulsive disorder without being biased towards the type of content of obsessions or compulsions present.

The scale is clinician-rated, comprising 10-items, with each item rated from 0 (no symptoms) to 4 (extreme symptoms), yielding a total possible score ranging from 0 to 40. The scale includes questions about the amount of time the patient spends on obsessions, how much impairment or distress they experience, and how much resistance and control they have over these thoughts. The same types of questions are asked about compulsions (e.g., time spent, interference) as well. The results can be interpreted based on the total score:

- 0–7 sub-clinical;
- 8–15 mild;
- 16–23 moderate;
- 24–31 severe;
- 32–40 extreme.

Patients scoring in the mild range or higher are likely experiencing a significant negative impact on their quality of life and should consider professional help in alleviating obsessive–compulsive symptoms. A self-rated version of the Yale-Brown Obsessive-Compulsive Scale has also been developed.

2.7 Psychiatric Referral and Siting of Care

GPP Psychiatric evaluation and treatment is appropriate when:

- there is serious risk of suicide
- there are psychotic symptoms
- co-occurring drug/alcohol problems exist
- symptoms are severe/complex or
- symptoms fail to improve on initial treatment and follow-up

GPP

It is important for the treating clinician to assess the symptoms, establish the psychiatric diagnosis and associated comorbidities, and provide psycho-education and treatment choices.

The option of psychological or pharmacological treatment depends on patient preference and motivation, the skills and experience of the clinician, availability of resources, response to prior treatment, and the presence of comorbidities.[25]

To optimise siting of care, patients with anxiety disorders who are receiving specialist psychiatric care could be well-managed in primary care if they have suitable characteristics.

GPP Consider transferring patients with anxiety disorders from psychiatric to primary care for long-term management if they have the following characteristics:

- Aged 18 or older
- Stabilised for the past 3 months
- No psychiatric hospitalisation in the past 6 months
- No history of forensic or substance abuse
- No disruptive personality disorders
- Non suicidal
- No history of aggressive behaviour
- Not currently receiving clozapine, lithium, valproate, hypnotics (including benzodiazepines, zopiclone, zolpidem) or formal psychotherapy treatment

GPP

2.8 Psychological treatment: General principles

GPP All patients should receive education about their disorder, including aetiology, treatment choices, and prognosis.

GPP

Causative factors (predisposing, precipitating and perpetuating) should be identified, and wherever possible attempts made to tackle these. Helpful reading materials e.g. information brochures for each anxiety condition, with contact details of agencies catering to the counselling and the support of persons with psychiatric problems (including anxiety disorders) are recommended. Psychological treatments play an important role in the management of anxiety disorders; however, patient preference and motivation determines choice of treatment.

General practitioners and nurses can be trained to deliver a range of specific anxiety management strategies, including breathing control, relaxation, and problem solving techniques. However, extensive training is essential before specific interventions such as cognitive behaviour therapy can be done safely and effectively.

2.8.1 Therapeutic relationship

The effectiveness of therapy depends on a good therapeutic relationship, with a fundamental agreement on the goals and tasks of therapy and commitment to the working relationship between therapist and patient. The duration, frequency, and nature of treatment should be collaboratively agreed upon at the outset. Social, cultural and religious/spiritual issues of the patient should be respected by the therapist or treating clinician.

2.8.2 Cognitive Behaviour Therapy

Cognitive behaviour therapy is a pragmatic combination of concepts and techniques from cognitive and behaviour therapies. Cognitive techniques (e.g. identification and modification of negative automatic thoughts and dysfunctional assumptions and schemas/core beliefs) in combination with behavioural techniques

(e.g. exposure to feared situations/objects) are used with the aim of achieving symptom relief and relapse prevention.

2.8.3 Exposure-based approaches

Phobias and obsessional fears tend to persist when there is avoidance of the feared situation. In exposure therapy, the patient is gradually exposed to a graded set of feared situations/ objects/ thoughts until fears spontaneously reduce (termed "habituation"). Exposure must be of sufficient duration for habituation to occur. Repeated exposure brings about further reductions of anxiety and a concomitant increase in a sense of mastery over the fear.

The efficacy of cognitive behaviour therapy has been demonstrated in meta-analytic studies[26] but there is insufficient evidence to recommend other therapies such as hypnotherapy, interpersonal, supportive, and dynamic psychotherapies for anxiety disorders.[25]

2.9 Pharmacological treatment: General principles

2.9.1 Antidepressants

2.9.1.1 *Selective serotonin reuptake inhibitors (SSRIs)*

SSRIs are recommended as first-line treatments for most anxiety disorders. Although SSRIs are usually well tolerated there are problems of initial excitation upon starting treatment. This may be experienced as generalised discomfort, headache, fatigue and nausea. For this reason, after-food dosing is advised.[27] Initiation dosages should be kept low to avoid overstimulation. Anxiolytic effects can be expected after 2-4 weeks. Generally it is advisable to start low and go slow, especially for elderly patients.

2.9.1.2 *Serotonin-norepinephrine reuptake inhibitors (SNRIs)*

Low starting doses are also recommended for SNRIs (e.g. venlafaxine) to avoid excitatory side effects. There is also a delay of 2-4 weeks before beneficial effects are evident. Patients and caregivers are encouraged to be patient and to continue with treatment despite not experiencing appreciable anxiolysis in the first few weeks of starting treatment.

2.9.1.3 *Tricyclic Antidepressants (TCAs)*

Although TCAs have demonstrated efficacy, they are less well tolerated due to their propensity for anticholinergic side effects e.g. dry mouth, blurred vision. In the event of overdosage, the resulting cardiac arrhythmias could be fatal. Hence, TCAs should be avoided in persons with a serious risk for suicide.

2.9.2 Benzodiazepines

Benzodiazepines may be effective for treating many anxiety disorders.[27] The onset of action is within a few minutes. Side effects include sedation, dizziness, prolonged reaction time and cognitive dysfunction.[27] Benzodiazepines may be successfully combined with SSRIs or SNRIs to offset the initial excitatory effects of antidepressants but dependency arises in a substantial number of patients after weeks to months of continuous use.[27]

2.9.3 Antihistamines

The antihistamine hydroxyzine has mildly sedating effects and is an effective agent for generalised anxiety disorder. Without the potential for dependency, it is preferred over benzodiazepines.

2.9.4 Atypical antipsychotics

Atypical antipsychotics have been used as monotherapy or as add-on treatment for some anxiety disorders.[32] However they are usually not licensed for these disorders, and side effects include sedation, orthostatic hypotension, and extrapyramidal effects. Therefore, treatment with atypical antipsychotics is best instituted in a specialist setting.

2.10 Pharmacological treatment: Dosage guidelines

GPP As local patients may show higher propensity for initial side effects of antidepressants (e.g. paradoxical excitation), starting doses for local patients should be lower than those suggested by overseas guidelines.[25]

GPP

A list of medications used (and their dosages) for anxiety disorders (as recommended by overseas guidelines) is included in Annex B. The dosages are meant as a guide and prescribers are advised to exercise clinical judgement when prescribing.

2.11 Monitoring of outcomes

The Clinical Global Impression (CGI) rating scales[24] are commonly used measures of symptom severity, treatment response and treatment efficacy in studies of patients with mental disorders. The scales are suitable for use by primary care physicians as they are quick to administer and enable clinicians to monitor patient progress in a consistent manner.[24]

The scales have two components: the Clinical Global Impression - Severity scale (CGI-S) and the Clinical Global Impression - Improvement scale (CGI-I).

The Clinical Global Impression - Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis.

The Clinical Global Impression - Improvement scale (CGI-I) is a 7- point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state (i.e. at initiation of treatment).

B The Clinical Global Impression scales (both severity and improvement sub-scales; refer to Annex A) may be used to measure illness severity and treatment progress during consultations for anxiety disorders.

Grade B, Level 2++

3 Management of Panic Disorder

3.1 Epidemiology

The estimated one-month prevalence of panic disorder is about 2%,[33] one-year prevalence of 2.7% and lifetime prevalence of 4.7%.[1, 33] It is estimated that about one-third to one-half of patients with panic disorder also have symptoms of agoraphobia.[2] Panic disorder and agoraphobia are more common in women than in men[2, 34] and their illness generally begins in late adolescence, or early adulthood.[35]

Patients with panic disorder have levels of mental health and daily functioning that are substantially lower than those of patients with other major chronic medical illnesses, such as diabetes, heart disease, and arthritis.[36] Comorbid depression is common and has a negative impact on outcomes.[37, 38] Individuals with panic disorder have more than double the risk of suicidal ideation and suicide attempts, compared with those with other psychiatric disorders, and almost 20 times the risk compared with those with no psychiatric disorder.[39]

3.1.1 Agoraphobia

About one-third to one-half of all patients with panic disorder suffer from agoraphobia, which is defined as fear in enclosed places or situations from which escape might be difficult or in which help may not be readily available. These situations include being in a crowd or standing in a queue, being outside the home alone, or travelling in a bus, train or car. These situations are avoided, or are endured with marked distress.

3.2 Pharmacological treatments

3.2.1 SSRIs

SSRIs reduce the frequency and intensity of panic attacks, reduce anticipatory anxiety, and improve associated depressive mood.

There is no difference in efficacy between individual SSRIs. For instance, sertraline and paroxetine were found to be equally effective.[40] Sertraline was also found to be more effective than placebo at preventing relapses,[41] and was as effective as imipramine in patients with panic disorder with comorbid depression.[42]

3.2.2 SNRIs

Venlafaxine was more effective than placebo in double-blind placebo controlled trials[48,49] and was as efficacious as paroxetine.[50] Venlafaxine was also more effective than placebo at preventing relapses.[51]

KEY RECOMMENDATION

A Either SSRIs or venlafaxine should be used as first-line agents for the pharmacological treatment of panic disorder.

Grade A, Level 1+

3.2.3 TCAs

TCAs have well-established efficacy data for panic symptoms, but their side effects are less well tolerated than the SSRIs and may lead to early treatment discontinuation.

There was no difference in efficacy between paroxetine and clomipramine in panic suppression and relapse prevention,[52] although paroxetine had an earlier onset of action than clomipramine.[53]

A Imipramine and clomipramine are effective and may be used as second-line treatment of panic disorder.[54, 55]

Grade A, Level 1+

3.2.4 Benzodiazepines

Studies have demonstrated that Alprazolam,[56-60] Clonazepam,[61,62] diazepam[59,63] and lorazepam[64,65] are more effective than placebo.

In terms of relapse prevention, alprazolam was superior to placebo, and equal in efficacy to imipramine.[66]

Several studies suggest that the short-term (4–6 week) addition of benzodiazepines to antidepressants produces a more rapid therapeutic response.[67-69]

Notwithstanding its efficacy, benzodiazepine monotherapy cannot be recommended due to the potential for dependency and abuse.[67,68] Instead, if benzodiazepines are used, they should be added to antidepressants.

3.2.4.1 *Benzodiazepine-antidepressant combinations*

Patients are often given benzodiazepine-antidepressant combinations. Patients treated with combined paroxetine and clonazepam responded quicker than patients treated with paroxetine monotherapy.[69] However, beyond the initial few weeks, the advantages of the combination therapy were lost. Other benzodiazepine-antidepressant combinations have yielded similar findings.[67, 68]

Major concerns about benzodiazepine tolerance and withdrawal have been raised. However, according to the report of the American Psychiatric Association (APA) Task Force on Benzodiazepine Dependence, Toxicity, and Abuse,[70] "there are no data to suggest that long-term therapeutic use of benzodiazepines by patients commonly leads to dose escalation or to recreational abuse."[57]

Studies of long-term alprazolam treatment for panic disorder show that the doses patients use at 32 weeks of treatment are similar to doses used at 8 weeks, indicating that as a group, patients with panic disorder do not escalate their alprazolam doses or display tolerance to alprazolam's therapeutic effects, at least in the first 8 months of treatment.[71]

Although numerous reports warn of the dependency potential of benzodiazepines, there is no evidence from long-term studies to suggest that patients develop tolerance and require dose escalation. Notwithstanding, studies have shown that there were difficulties in weaning patients off once they have been taking benzondiazepines on a long-term basis.[71]

A Benzodiazepines may be added to antidepressants in the short term (up to 4 weeks) to produce a more rapid therapeutic response in the treatment of panic disorder.[67-69] In view of their addictive potential, benzodiazepines should be tapered and withdrawn by 4 weeks.[67, 68]

Grade A, Level 1+

3.2.5 Length of treatment

There is limited and mixed data about whether patients who remit during treatment benefit more from over a year of subsequent treatment, compared with 6 months of continued pharmacotherapy.[72-74]

One study that compared imipramine treatment for 12–30 months with 6 months of maintenance treatment after remission found nearly identical rates of reported relapse for the two groups.[74] This suggests that achieving remission before treatment discontinuation may be a more critical determinant in preventing relapse than the subsequent duration of maintenance therapy.[61]

3.3 Psychotherapies

The goal of psychotherapy treatment is to eliminate panic attacks, anticipatory anxiety, and avoidance.

Psycho-education for patients with anxiety disorders involves teaching patients about the disorder, discussing treatment options, modalities of treatment, and coping strategies. The support of family members, friends, support groups, and voluntary organisations would also benefit the patient.

Psycho-education has been shown to improve quality of life, reduce symptoms, and improve treatment outcomes.

Cognitive behaviour therapy is the only type of psychotherapy shown to be efficacious in the treatment of panic disorder, with or without agoraphobia.[75]

The treatment components of cognitive behaviour therapy may include:

- psycho-education
- in-vivo exposure to feared situations
- interoceptive exposure
- cognitive restructuring
- continuous panic monitoring
- breathing retraining

3.4 Combination therapy

Pharmacotherapy and psychotherapy can be used in combination for treatment of panic disorder, with or without agoraphobia.[76-81]

Although monotherapy with SSRIs is effective, meta-analytic studies have demonstrated the superiority of combined cognitive behaviour therapy with pharmacological treatment over monotherapy.[82]

KEY RECOMMENDATION

A Depending on availability of treatment and patient preference, cognitive behaviour therapy or combination therapy (i.e. cognitive behaviour therapy and SSRIs or venlafaxine) may be used for the treatment of panic disorder.[75]

Grade A, Level 1++

4 Management of Generalised Anxiety Disorder

4.1 Epidemiology

The lifetime prevalence of generalised anxiety disorder ranges from 0.9% to 3.3%.[10,83] Generalised anxiety disorder affects more females more than males,[10] with the unemployed more likely to be diagnosed.[10,83] The median age of onset was 20 years.[83] Persons with medical comorbidities e.g. coronary artery disease, chronic obstructive pulmonary disease, asthma and arthritis were also more likely to be diagnosed.[10] Higher odds of association were also found in those who were divorced and in those experiencing life events.[10]

Generalised anxiety disorder was significantly associated with other psychiatric co-morbidities, e.g. major depressive disorder, dysthymia, panic disorder, agoraphobia, and social phobia.[10]

4.2 Treatment

4.2.1 Pharmacological treatment

Generalised anxiety disorder is associated with chronicity, functional impairment, high health care use, and relatively poor treatment response. Although antidepressants work more slowly, they are as effective as benzodiazepines, have a broader spectrum of action, are easier to discontinue, and are less subject to misuse.

4.2.1.1 *SSRIs and venlafaxine*

There is strong evidence from randomised, placebo-controlled trials that SSRIs, including paroxetine,[85, 86] escitalopram[87, 88] and sertraline[85,89] should be used as first-line treatment of generalised anxiety disorder.

There is also strong evidence to support the efficacy of venlafaxine in patients with generalised anxiety disorder.[90-93]

KEY RECOMMENDATION

A Either SSRIs or venlafaxine should be used as first-line pharmacological treatment for patients with generalised anxiety disorder.

Grade A, Level 1++

4.2.1.2 *TCAs*

Imipramine has demonstrated superiority over placebo in the treatment of generalised anxiety disorder. [94-96]

A Imipramine may be considered as a second-line treatment option for generalised anxiety disorder, in view of the possibility of poor tolerability and the danger of fatal overdosage.

Grade A, Level 1+

4.2.1.3 *Mirtazapine*

A Mirtazapine may be considered as a second-line treatment for generalised anxiety disorder due to its anxiolytic effects.[97, 98]

Grade A, Level 1+

4.2.1.4 *Benzodiazepines*

There is evidence that the benzodiazepines, e.g. alprazolam, bromazepam, lorazepam, diazepam, are effective in the short term acute treatment of generalised anxiety disorder.[91,99-101] While demonstrating rapid onset of action,[95, 102] however, after 4-6 weeks, their effectiveness may not significantly differ from that of placebo.[102-104] Consequently few patients achieve and sustain remission on benzodiazepine monotherapy in the long term.[105]

B Benzodiazepines should not be used for the long-term treatment of generalised anxiety disorder.

Grade B, Level 1+

4.2.1.5 *Other drugs*

A randomised placebo-controlled double blind study which compared pregabalin with venlafaxine and placebo in patients with moderate to severe generalised anxiety disorder found that pregabalin was as effective as venlafaxine, and that both drugs were superior to placebo.[106]

The 2012 World Federation of Biological Psychiatry (WFSBP) guidelines also recommended pregabalin for generalised anxiety disorder.[27] Caution is, however, advised in prescribing pregabalin to susceptible populations, in view of its potential for abuse and misuse.[107, 108]

B Pregabalin may be prescribed for patients with generalised anxiety disorder as it has anxiolytic effects which may be more rapid acting. Due caution must be exercised when prescribing to patients who are at risk of abusing substances.

Grade B, Level 2++

C Hydroxyzine may be used as adjunctive treatment together with other anxiolytic agents for treatment of generalised anxiety disorder.[109]

Grade C, Level 2+

The beta blocker propranolol was not found to have significantly better efficacy than placebo after 3 weeks of treatment in a randomised controlled trial.[110]

B Propranolol is not recommended for the long-term treatment of generalised anxiety disorder.

Grade B, Level 1+

A Drug treatment for generalised anxiety disorder needs to be continued for at least 32 weeks as high relapse rates were reported after discontinuing medications.[86]

Grade A, Level 1+

4.2.2 Psychotherapies

Cognitive behaviour therapy administered by experienced therapists shows good evidence of efficacy in generalised anxiety disorder.[111-114]

KEY RECOMMENDATION

A Cognitive behaviour therapy may be used as first-line treatment for generalised anxiety disorder.

Grade A, Level 1++

4.2.3 Combination therapy

Cognitive behaviour therapy or pharmacotherapy as monotherapy are both efficacious in the treatment of generalised anxiety disorder.[111,115] However, combination therapy is not demonstrably superior to either cognitive behaviour therapy or pharmacotherapy alone[78,111,116,117] and may add significantly to costs for the patient. While combination therapy (addition of medication to cognitive behaviour therapy) will enhance short term outcomes, there is no evidence to support, at present, that combination therapy will improve long term outcomes.

GPP A specialist's opinion should be sought for patients with complex generalised anxiety disorder and/or with marked functional impairment, or at high risk of self-harm.

GPP

5 Management of Specific Phobia

5.1 Epidemiology

Although the life-time prevalence of specific phobia ranges from 8.8%-12.5%[1,118,119] there are no data of its prevalence in Singapore. Specific phobia is about twice as common in women, with age of onset ranging from 5 to 12 years (mean 7 years).[1]

Evidence suggests animal and blood-injection-injury phobia generally begin in childhood and situational phobia (e.g. thunder phobia) begins in late adolescence or early adulthood.[120-122]

5.2 Treatment

The goals of treatment of specific phobia are the mastery of fear and the recovery of function. Components of cognitive behaviour therapy for specific phobia may include systematic desensitisation, imaginal exposure and in-vivo exposure.

KEY RECOMMENDATION

A Cognitive behaviour therapy should be used as first-line treatment of specific phobia.

Grade A, Level 1++

As much as 70-85% of specific phobias could be effectively treated by exposure therapy.[123, 124] Medications alone are of little benefit in specific phobia, except in cases where there has been substantial reductions in quality of life.[125]

B Benzodiazepines may be used on a short-term basis for temporary anxiety relief in specific phobia, pending resolution of symptoms with other forms of treatment.[126, 127]

Grade B, Level 1+

However, relapse was usual after cessation of short-acting benzodiazepine use.

Combination therapy did not result in improvements. One long-term follow-up study suggested that relapse was common after successful treatment with combination imipramine and psychotherapy.[128, 129]

5.3 Length of treatment

There are no data to suggest how long treatment of specific phobia should be continued for.

6 Management of Social Anxiety Disorder

6.1 Epidemiology

Social anxiety disorder, also known as social phobia, is one of the most common mental disorders.[118]

Different surveys suggest differing prevalence rates for social anxiety disorder, ranging from 3%[130] to 12.8%.[1] Persons with social phobia are more likely to be female, single, and have lower income and educational levels.[132] In clinical populations, the condition is equally distributed among males and females.[133] The age of onset is usually earlier than other anxiety disorders,[134] and mean age of onset is between mid-teens to early 20s.[118]

6.2 Treatment

Both psychological and pharmacological treatments have been found to be effective in the treatment of social anxiety disorder.

KEY RECOMMENDATION

A Either pharmacotherapy or psychotherapy alone may be used as first-line treatment for social anxiety disorder, depending on patient preferences, values and economic considerations.[78, 115, 135]

Grade A, Level 1++

However, combination therapy was not demonstrably superior to either cognitive behaviour therapy alone or pharmacotherapy alone.[78, 115, 135]

6.2.1 Pharmacotherapy

6.2.1.1 *SSRIs and venlafaxine*

SSRIs have demonstrated efficacy and favourable side-effect profile in the treatment of social anxiety disorder. There are no differences in efficacy among the different SSRIs.[136]

Venlafaxine has also demonstrated comparable efficacy to SSRIs in the treatment of social anxiety disorder.[137-140]

KEY RECOMMENDATION

A Either SSRIs or venlafaxine should be used as first-line pharmacotherapy for social anxiety disorder.

Grade A, Level 1+

6.2.1.2 *Moclobemide*

A Moclobemide may be used for the treatment of social anxiety disorder if treatment with SSRIs or venlafaxine has not been effective.[141]

Grade A, Level 1+

6.2.1.3 *Benzodiazepines*

In randomised controlled trials and a meta-analysis, the efficacy of the benzodiazepine clonazepam was superior to that of placebo and comparable to SSRIs or cognitive behaviour therapy.[145] Alprazolam[146] and bromazepam[147] have also demonstrated efficacy for the treatment of social anxiety disorder.

A Benzodiazepines may be used on a short-term basis for temporary anxiety relief pending resolution of phobic symptoms with other forms of treatment.[145-147]

Grade A, Level 1+

6.2.1.4 *Beta-blockers*

B Beta-blockers (e.g. atenolol,[148] propranolol[149]) are not recommended for the treatment of social anxiety disorder as they have been found ineffective. However, they may be used for the treatment of performance anxiety (e.g. giving a speech).[150]

Grade B, Level 2++

6.3 Psychotherapies

KEY RECOMMENDATION

A Cognitive behaviour therapy should be used as first-line psychotherapy treatment of social anxiety disorder.[75, 151-153]

Grade A, Level 1+

Exposure to feared situations is a crucial component of cognitive behaviour therapy. Group cognitive behaviour therapy approaches are also useful and often include elements of social skills training.

Cognitive behaviour therapy interventions include in-vivo exposure, cognitive restructuring, relaxation training and self-control desensitisation, of which exposure-based interventions are the most efficacious for social anxiety disorder.[154]

6.4 Length of treatment

Discontinuation of pharmacotherapy is associated with high rates of relapse.[155-157] Conversely, the effects of cognitive behaviour therapy are associated with lower relapse rates following cessation of therapy.[158,159]

B Pharmacotherapy with SSRIs, venlafaxine or moclobemide in social anxiety disorder should be continued for at least 12 months to prevent relapse.[155-157, 160]

Grade B, Level 2++

7 Management of Obsessive-Compulsive Disorder

7.1 Epidemiology

The estimated lifetime prevalence of obsessive-compulsive disorder in Singapore is 3% with a median age of onset of 19 years.[83] There is a tendency for obsessive-compulsive disorder to be more prevalent in women than in men.[161] Obsessive-compulsive disorder is a chronic illness.

A study that followed up patients for 40 years found that 20% had complete recovery, although most showed some improvement in terms of clinical symptoms and functioning.[162] Even with pharmacotherapy, up to 40-60% of patients did not have a satisfactory response to serotonergic antidepressants (which include SSRIs and clomipramine) and these patients have significant disability, morbidity, and poor quality of life.[133]

7.2 Treatments

Meta-analytic reviews suggest either psychotherapy or pharmacotherapy could be administered as first-line treatment for obsessive-compulsive disorder.[163-166]

KEY RECOMMENDATION

A Either pharmacotherapy or psychotherapy alone may be chosen as first-line treatment for obsessive-compulsive disorder, depending on patient preferences, values and economic considerations.[163-166]

Grade A, Level 1++

7.2.1 Pharmacological treatments

7.2.1.1 *Selective serotonin reuptake inhibitors (SSRIs)*

There is strong evidence for the use of SSRIs (e.g. fluvoxamine, fluoxetine, citalopram, escitalopram, sertraline, paroxetine[167, 168]) in the treatment of obsessive-compulsive disorder.

KEY RECOMMENDATION

A The first-line pharmacological treatment for obsessive-compulsive disorder should be a 10-12 week trial with an SSRI at adequate doses.[167, 168]

Grade A, Level 1++

7.2.1.2 *Tricyclic antidepressants*

Clomipramine has been shown to be efficacious in the treatment of obsessive-compulsive disorder,[169] which may be related to its marked potency for blocking serotonin reuptake. However, due to safety concerns (convulsions, cardiotoxicity, cognitive impairment, anticholinergic side effects, drug interactions, and lethality in overdose) clomipramine should only be used after an adequate trial of SSRI treatment has failed.[170]

A Clomipramine may be used as a treatment for obsessive-compulsive disorder after an adequate trial of SSRI treatment has failed.

Grade A, Level 1++

7.2.1.3 *Antidepressant Dosing for obsessive-compulsive disorder*

Some fixed-dose trials of SSRIs indicate that higher doses are significantly superior to lower doses in the treatment of obsessive-compulsive disorder.[27]

D An adequate treatment trial in obsessive-compulsive disorder should last for at least 12 weeks. If the patient does not respond to treatment in adequate dosages, the medication may be changed or specialist opinion sought.

Grade D, Level 4

7.2.1.4 *SNRIs and mirtazapine*

The efficacy of SSRIs and clomipramine in the treatment of obsessive-compulsive disorder has led to the hypothesis that dual acting SNRIs may be of even greater benefit. However the evidence for this is contradictory.

Open label studies[171-173] and two small double blind studies[174, 175] suggest that venlafaxine may be effective in the treatment of obsessive-compulsive disorder. A double-blind crossover study[176] suggested that venlafaxine may actually be less effective than paroxetine in the treatment of refractory patients.

Based on current available evidence venlafaxine cannot be recommended as monotherapy for uncomplicated obsessive-compulsive disorder, but may be considered for patients who have not responded to SSRIs and clomipramine.

A Venlafaxine may be considered in patients who have not responded to SSRIs and clomipramine. Monitor blood pressure during treatment as venlafaxine at high doses can raise blood pressure.

Grade A, Level 1+

There is preliminary evidence suggesting that duloxetine[177] and mirtazapine[178] could be efficacious in the treatment of obsessive-compulsive disorder. However, more research needs to be done before these can be considered as monotherapy for uncomplicated obsessive-compulsive disorder.

7.2.2 Psychotherapies

Cognitive behaviour therapy substantially reduces obsessive compulsive symptomatology.[75]

KEY RECOMMENDATION

A Cognitive behaviour therapy may be used as first-line treatment for obsessive-compulsive disorder if patients prefer psychological treatment over pharmacotherapy.

Grade A, Level 1+

7.2.3 Combination therapy

The combination of cognitive behaviour therapy and serotonergic reuptake inhibitors (SRIs) has not been found to be clearly superior in efficacy to cognitive behaviour therapy alone, or pharmacotherapy alone.[166, 179-182]

B Cognitive behaviour therapy augmentation of serotonergic antidepressants (e.g. SSRIs, clomipramine) in the treatment of obsessive-compulsive disorder may be considered for those who are treatment-resistant or partially responsive to medications.

Grade B, Level 1+

7.3 Length of treatment

Patients who respond to antidepressants in the acute phase and then switch to a placebo may relapse. Hence it is important to continue antidepressants after clinical improvement has occurred.[196-200]

A Patients with obsessive-compulsive disorder who respond to antidepressants in the acute phase should be continued on their medication for at least 12 months.[196-200]

Grade A, Level 1+

8 Management of Post-Traumatic Stress Disorder

8.1 Epidemiology

There are no local prevalence data of post-traumatic stress disorder, although a nationally representative estimate of life-time risk in the United States is 7.8%.[1]

Approximately 20% of women and 8% of men who have been exposed to significant traumatic events eventually develop symptoms of post-traumatic stress disorder, with the lifetime prevalence approximately 10-14% for women and 5-6% for men.[201, 202] There is data to suggest that some people are more likely to develop post-traumatic stress disorder after a traumatic event. Risk factors include severe or prolonged trauma, trauma/abuse during childhood, pre-existing history of psychiatric illness, comorbid substance abuse, poor social support and female gender.[203]

8.2 Treatments

There is strong evidence suggesting that both pharmacotherapy[204-218] and psychotherapy[75,219] alone are effective for treating post-traumatic stress disorder.

8.2.1 Pharmacological treatments

8.2.1.1 *Selective serotonin reuptake inhibitors (SSRIs)*

The efficacy of SSRIs has been demonstrated in multiple studies.

Fluoxetine was shown to be effective in double–blind placebo controlled studies.[204 -208] In a relapse prevention study, fluoxetine was also found to be superior to placebo.[209, 210]

Paroxetine was shown to be effective in double-blind placebo controlled studies.[211, 212]

Sertraline was effective in several double-blind placebo controlled studies.[213-216] A relapse-prevention study also found significantly lower relapse rates for the sertraline group.[220] In an open-label trial, patients who had completed 12-weeks[220] of a trial of sertraline versus placebo received sertraline for an additional 24 weeks. Responders to the initial study sustained their initial response, and patients who failed in the initial study eventually became responders.[221]

Fluvoxamine also improved sleep and hyper-arousal in a small uncontrolled study.[222]

8.2.1.2 *Selective serotonin-norepinephrine reuptake inhibitors (SNRIs)*

The SNRI venlafaxine was found to be more effective than placebo in double-blind placebo-controlled studies.[217, 218]

KEY RECOMMENDATION

A Either the SSRIs or venlafaxine may be used as first-line pharmacological treatment for post-traumatic stress disorder.

Grade A, Level 1++

8.2.1.3 *Mirtazapine*

In a small double-blind placebo controlled study, mirtazapine was found to be effective.[223]

B Mirtazapine may be considered as a second-line treatment for post-traumatic stress disorder.

Grade B, Level 1+

8.2.1.4 *Tricyclic antidepressants (TCAs)*

Double-blind studies found amitriptyline to be superior to placebo.[224, 225]

Imipramine was also found to be superior to placebo,[226] but compared to SSRIs, TCAs are associated with a higher incidence of side-effects, risk of fatal overdose, and poor compliance.

A Either amitriptyline or imipramine may be considered for post-traumatic stress disorder if the first-line and second-line treatments are ineffective or poorly tolerated.

Grade A, Level 1+

8.2.1.5 *Benzodiazepines*

Several small controlled studies suggested that alprazolam and clonazepam were no better than placebo.[227-229]

A Benzodiazepines should not be used for the treatment of post-traumatic stress disorder.

Grade A, Level 1+

8.2.1.6 *Other medications*

Adjunctive antipsychotics may be effective in treating psychotic symptoms present in patients with post-traumatic stress disorder.[230, 231]

Risperidone monotherapy[232] and adjunctive risperidone[233, 234] were found to be effective for women with post-traumatic stress disorder related to sexual assault and domestic abuse.

Adjunctive olanzapine improved post-traumatic stress disorder symptoms, mood and sleep in nonresponders to SSRIs.[235]

A small study showed that lamotrigine showed a higher response rate than placebo, particularly against flashbacks and avoidance reactions.[236]

B Risperidone, olanzapine, quetiapine, and lamotrigine may be prescribed as adjunctive treatments for post-traumatic stress disorder in conjunction with the SSRIs.

Grade B, Level 1+

8.2.1.7 *Length of treatment*

Post-traumatic stress disorder often needs long-term treatment for at least 12-24 months. Long-term efficacy was demonstrated for fluoxetine, sertraline[213-216] and venlafaxine.[217, 218]

The importance of long-term treatment of post-traumatic stress disorder is suggested by the continued improvement of symptoms following acute treatment with paroxetine, but not placebo.[211] Short-term treatment with fluoxetine[209] and sertraline[220] may be insufficient to prevent relapses. These findings support consensus recommendations that duration of treatment should last from 6-12 months for acute post-traumatic stress disorder,[203] and for at least 12 months in the case of chronic post-traumatic stress disorder to prevent relapse.[203, 237]

D Pharmacological treatment for post-traumatic stress disorder should be continued for at least 12 months.[238]

Grade D, Level 4

8.2.2 Psychotherapies

8.2.2.1 *Cognitive behaviour therapy*

Evidence suggests that cognitive behaviour therapy is an effective treatment for post-traumatic stress disorder.[75,219,239] The components of cognitive behaviour therapy include prolonged exposure to memories of the traumatic event.

KEY RECOMMENDATION

A Cognitive behaviour therapy should be used as the first-line psychological treatment for post-traumatic stress disorder.[75, 219]

Grade A, Level 1+

8.2.2.2 *Eye Movement Desensitisation and Reprocessing therapy*

Eye movement desensitisation and reprocessing therapy involves recalling the traumatic event while watching the fingers of the therapist move from one end to the other of the patient's visual field. Alternative methods (e.g. tapping sounds) are also effective.

Eye movement desensitisation and reprocessing therapy has been found to be effective in the treatment of post-traumatic stress disorder,[240-245] but a meta-analysis showed that it had a smaller effect size compared to cognitive behaviour therapy.[240]

However a review of 6 randomised controlled trials and 3 quasi-experimental studies concluded that evidence for the use of eye movement desensitisation and reprocessing therapy for post-traumatic stress disorder was sparse and equivocal.[246]

B Eye Movement Desensitisation and Reprocessing therapy may be used as second-line treatment for post-traumatic stress disorder.

Grade B, Level 2++

8.2.3 Combination therapy

A systematic review of combined pharmacotherapy and psychological therapies for post-traumatic stress disorder (based on 4 randomised controlled trials) concluded that there was not enough evidence to either support or refute the effectiveness of combined pharmacotherapy and psychological therapy compared to either of these interventions alone.[247]

B If cognitive behaviour therapy or eye movement desensitisation and reprocessing therapy for post-traumatic stress disorder are contraindicated or have failed, combination therapy (i.e. cognitive behaviour therapy plus pharmacotherapy) may be used as an alternative treatment.

Grade B, Level 1+

9 Management of Anxiety Disorders in Pregnancy

9.1 Overview of drug treatment during pregnancy

The use of antidepressants during pregnancy is of a concern because of the risks of adverse perinatal and postnatal outcomes. All psychotropic medications cross the placenta, and are present in amniotic fluid, and breast milk.

No drug has been approved by the European Medicines Agency (EMEA) or the Food and Drug Administration (FDA) for use during pregnancy; thus no risk-free decision can be made with regard to treatment during pregnancy.[248]

The risk of drug treatment during pregnancy must be weighed against the risk of a relapse of anxiety disorder if treatment is withheld, and the possible adverse effects of maternal anxiety on foetal development (namely birth weight, gestational duration, neurocognitive changes).[27] If clinically indicated, antidepressants may be prescribed after assessing and discussing the risk- benefit ratio with patients.

To minimise the risk of harm to the foetus or child, drugs should be prescribed cautiously for women who are planning a pregnancy, who are already pregnant, or who are breastfeeding.[249]

D If a woman is planning a pregnancy or becomes pregnant while on medication for an anxiety disorder, consider:[249]

- stopping medication and starting cognitive behaviour therapy, if necessary and if not already tried.
- switching to a safer drug, if the decision is to maintain her on medication.

Grade D, Level 4

D When prescribing a drug for a woman with an anxiety disorder who is planning to become pregnant, already pregnant, or is breastfeeding:[249]

- choose drugs with the lowest risk potential for the mother and the foetus/infant
- start at the lowest effective dose, and slowly titrate upwards
- continue for the shortest possible duration[250]
- use monotherapy instead of combination treatment[250]

Grade D, Level 4

9.2 SSRIs and SNRIs

When choosing an antidepressant for pregnant or breastfeeding women, prescribers should bear in mind that the safety of these drugs is not well understood, and take into account that:

- fluoxetine is the SSRI with the lowest known risk during pregnancy, and sertraline is present in breast milk at relatively low levels
- citalopram and fluoxetine are present in breast milk at relatively high levels
- SSRIs taken after 20 weeks' gestation may be associated with an increased risk of persistent pulmonary hypertension in the neonate
- paroxetine taken in the first trimester may be associated with foetal heart defects
- venlafaxine may be associated with increased risk of high blood pressure at high doses, higher toxicity in overdose than SSRIs and some tricyclic antidepressants, and increased difficulty in withdrawal
- all antidepressants carry the risk of withdrawal or toxicity in neonates but in most cases, the effects are mild and self-limiting.

The combined prevalence of major malformations or non-cardiac malformations was not significantly higher among exposed children, but SSRI use was associated with an increased prevalence of septal heart defects in a Danish study that

evaluated associations between SSRIs and major malformations during the first trimester.[251]

The largest prevalence was found in women who were on more than one type of SSRI during the first trimester. There is no association between exposure to SSRIs during pregnancy and stillbirth or neonatal mortality.[252]

The use of fluoxetine was associated with an increased risk of ventricular septal defects.[253, 254] Paroxetine was associated with right ventricular outflow tract defects.[253] Sertraline and citalopram during pregnancy were associated with neural tube defects[253] and septal heart defects.[255]

The risk of persistent pulmonary hypertension of the newborn is low but use of SSRIs in late pregnancy after gestational week 20 increases the risk more than twofold. Specific SSRIs have similar increased risks of persistent pulmonary hypertension of the newborn which suggests a class effect.[256, 257] These findings should be taken into account in decisions as to whether to continue the use of SSRIs during pregnancy.

The risk of cardiovascular and other congenital malformations may be higher with paroxetine than other antidepressants.[258-260]

C Sertraline, paroxetine[258-260] and citalopram[253,255] should be avoided during pregnancy.

Grade C, Level 2+

A study which[261] used population-based health data to determine venlafaxine or other serotonergic reuptake inhibitor (SRI) monotherapy exposure during the first trimester found no increased risk of birth defects overall compared to women unexposed to SSRIs, other SNRIs, and benzodiazepines. SRI monotherapy exposure was only associated with an increased incidence of atrial septal defects.[261]

The American Congress of Obstetricians and Gynecologists (ACOG) recommended that therapy with SSRIs or SNRIs during pregnancy be individualised.[262] For further information, readers are advised to refer to the paper.

9.3 Tricyclic Antidepressants

TCA use in pregnancy was associated with pre-term birth and persistent pulmonary hypertension of the newborn (PPHN).[263]

9.4 Other Antidepressants

Some studies suggest a possible risk of congenital cardiovascular malformations such as ventricular septal defects and left outflow tract heart defects following bupropion exposure during pregnancy,[264] while others have found no increased risk for all forms of congenital malformations.[265]

The Health Sciences Authority has advised that if bupropion is considered for women of child-bearing potential, healthcare professionals are encouraged to inform patients of the potential risk of congenital cardiovascular malformations associated with its use and to emphasise the importance of using an effective birth control method.[266]

9.5 Benzodiazepines

Pooled data from cohort studies showed no apparent association between benzodiazepine use and the risk for major malformations or oral cleft alone. There was, however, a small but significantly increased risk for oral cleft according to data from the available case-control studies.[267]

Data published after 2000 did not indicate an absolute contraindication in prescribing benzodiazepines during the first trimester. Currently available evidence suggests that benzodiazepine exposure during pregnancy is not associated with an increasing risk of congenital major malformation but is associated with a high rate of spontaneous abortion.[268]

Data concerning the risk of major malformation following exposure to alprazolam and nitrazepam are still too scarce to draw firm conclusions on their safety profile in early pregnancy.

Iqbal et al (2002) suggested that diazepam and chlordiazepoxide should be preferred if a benzodiazepine needs to be prescribed in

early pregnancy. Caution should be exercised in prescribing clonazepam and lorazepam in the first trimester, owing to reports of higher risk of major malformations after in-utero exposure.[269]

KEY RECOMMENDATION

D Benzodiazepines should not be routinely prescribed for pregnant and breastfeeding women, except for the short-term treatment of extreme anxiety and agitation.[269]

Grade D, Level 4

GPP The risk-benefit ratio of prescribing benzodiazepines should be assessed on a case-by-case basis; use the lowest dose for the shortest time, or avoid prescribing at all during the first trimester.

GPP

9.6 Atypical antipsychotics

Data suggests that olanzapine and clozapine do not appear to increase teratogenic risk during pregnancy.[270,271] Although there is a lack of information on the risks of intra-partum ingestion of risperidone and quetiapine,[270,272] cases of gestational diabetes have been reported with the use of atypical antipsychotics. These medications are secreted in breast milk, and adverse effects have been reported in infants.[273]

D Atypical antipsychotics should be prescribed with caution in patients suffering from or at risk of gestational diabetes.

Grade D, Level 3

9.7 Drug treatment in breastfeeding

Serum levels are not indicated on a regular basis except in the case of clinical indication or concern.[274]

Strategies used to decrease infant exposure, but for which there is little evidence, include medication administration immediately after feeds, and pumping and discarding the breast milk obtained during peak serum levels.[274]

D Medication for nursing mothers should be maintained at the lowest effective dose to minimise infant exposure.[274]

Grade D, Level 3

9.7.1 Antidepressants

The available evidence on the effects of antidepressants during lactation largely consists of case reports, case series, and studies of small samples. Controlled studies on the use of antidepressants during lactation are still lacking.

Most antidepressants are excreted in breast milk, although the effects on the infant are not well understood. Antidepressants generally have long or intermediate half-life, and are usually suspected to accumulate in the nursing infant.

However the advantages of breastfeeding are likely to outweigh the minimal risk of side-effects of maternal drug use to the infant.[275, 276]

D When antidepressant treatment is indicated in the postpartum period, women should generally not be advised to discontinue breastfeeding.[275]

Grade D, Level 3

9.7.1.1 *SSRIs and SNRIs*

Among the SSRIs, paroxetine, fluvoxamine and sertraline produce undetectable infant plasma levels. Fluoxetine and venlafaxine are present in breast milk at relatively high levels and produce the highest infant plasma concentrations. Citalopram levels have been measurable in some infants, even though mostly relatively low. Minimising the maternal dose may be helpful with citalopram. Escitalopram has been detected at extremely low concentration in infant plasma.[276, 277]

KEY RECOMMENDATION

D Treatment with paroxetine or sertraline should be preferred over other SSRIs in treatment-naive breastfeeding women due to the low infant exposure to these drugs.

Grade D, Level 3

D Drugs for which little data exist, such as fluvoxamine, venlafaxine, bupropion and mirtazapine, should not be considered as first-line therapies in breastfeeding women, but they may be used in special cases.[274, 275, 278, 279]

Grade D, Level 4

9.7.1.2 *Tricyclic antidepressants (TCAs)*

The risks of taking TCAs during pregnancy and when breastfeeding are better established than those of newer drugs, although the issues of tolerability and risk in overdose remain.

The majority of the available data for infant serum level for TCAs includes nortriptyline and imipramine, which in most cases are undetectable and have not been associated with adverse events.[279]

KEY RECOMMENDATION

D If mothers have been successfully treated with a particular SSRI, TCA, or SNRI, this drug should be the first-line treatment if there are no contraindications.[274] An individual risk-benefit assessment should always be done before starting antidepressants.

Grade D, Level 4

9.7.1.3 *Other drugs/drug combinations*

GPP Women on long term treatment with high dose benzodiazepines should continue to breastfeed, as stopping of benzodiazepine may precipitate withdrawal symptoms in the infant. Gradual tapering and stopping of benzodiazepines may be attempted at a later stage when the infant has grown bigger.

GPP

D During maternal treatment with benzodiazepines, infants should be monitored for signs of sedation, lethargy, poor feeding and weight loss.[27]

Grade D, Level 4

10 Cost-effectiveness issues

Anxiety disorders are associated with increased economic burden through the loss of productivity and increased medical costs through the inappropriate use of general medical services.[281, 282]

There are few cost effectiveness studies on anxiety disorders. Two studies estimated the total annual costs of anxiety disorders in the US. The Dupont et al study[283] in 1996 estimated that the annual cost of anxiety disorders was US$47 billion. In 1999, Greenberg et al[284] estimated that this cost was US$42.3 billion. This study also found that more than $23 billion of these costs were associated with repeated use of health care services as patients with anxiety disorders sought relief of symptoms that mimic physical illnesses.

There is also a gap in the treatment of anxiety disorders in Singapore, as shown by the Singapore National Mental Health Survey.[84] Early identification and effective evidence-based treatment would likely reduce economic and societal costs.

Issakidis[285] found that adopting an evidence-based approach to the treatment of anxiety disorders would result in greater population health gain at similar cost to that of current care, resulting in substantial gains in the cost-effectiveness of treatment.

When the impact of mental health interventions in a primary care setting were estimated,[286] the single most cost-effective strategy for panic disorder is the scaled-up use of older antidepressants (due to their lower cost but similar efficacy compared with newer antidepressants).

However, as the price difference between older and newer generic antidepressants diminishes, generic SSRIs which have milder side effects and are more likely to be taken at a therapeutic dose can be expected to be at least as cost-effective and be the pharmacological treatment of choice.

A comprehensive systematic literature review[287] of all cost-of-illness studies and cost-effectiveness analyses of anxiety disorders concluded that anxiety disorders resulted in considerable economic burden because of its high prevalence. This burden (at least from the payer's and societal perspective) could be reduced by adequate treatment.

In terms of total costs to society (both indirect and direct) panic disorder seems to be the most expensive anxiety disorder to treat. From the studies analysed, neither pharmacological nor psychological treatments were found to be more cost-effective.

11 Clinical Quality Improvement

The following clinical and audit parameters, based on recommendations in these guidelines, are proposed:

1. Percentage of patients with an anxiety disorder, who are assessed using the clinical global impression scales (both severity and improvement component scales) during consultations (see pg 31).

2. Percentage of patients with panic disorder who receive treatment with an SSRI or venlafaxine, if pharmacological treatment is given (see pg 33).

3. Percentage of patients with generalised anxiety disorder who receive treatment with an SSRI or venlafaxine, if pharmacological treatment is given (see pg 38).

4. Percentage of patients with social anxiety disorder (social phobia) who receive treatment with an SSRI or venlafaxine, if pharmacological treatment is given (see pg 44).

Annex A Clinical Global Impression (CGI) scale

Considering your total clinical experience with this particular population, how would you rate this patient's mental condition at this time?

1) Severity of Illness

1 = Normal (not at all mentally ill)
2 = Borderline mentally ill
3 = Mildly mentally ill
4 = Moderately mentally ill
5 = Markedly mentally ill
6 = Severely mentally ill
7 = Extremely mentally ill

2) Global Improvement

0 = Not assessed
1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

Annex B Anxiety medication doses recommended by other guidelines (see section 2.10)

Drug	Initial Daily Dose (mg)	Max Daily Dose (mg)
SSRIs		
Citalopram[25]	20	40
Escitalopram[25]	5	20
Fluoxetine[25]	20	80
Fluvoxamine[25]	50	300
Paroxetine[25]	20	60
Paroxetine CR[25]	25	62.5
Sertraline[25]	50	200
SNRIs		
Duloxetine[288-290]	30	120
Venlafaxine XR[25]	37.5	225
Other antidepressants		
Bupropion SR[25]	150	300
Mirtazapine[25]	15	45
TCAs		
Clomipramine[25]	25	200
Imipramine[25]	25	150
Benzodiazepines		
Alprazolam[25]	0.25	1.5
Bromazepam[25]	6	30
Chlordiazepoxide[288-290]	15	100
Clobazam[289, 290]	20	80
Clonazepam[25]	0.25	4
Diazepam[25]	2.5	10
Lorazepam[25]	0.5	3
Atypical antipsychotics		
Olanzapine[25]	5	20
Risperidone[25]	0.5	6
Quetiapine[25]	50	800

References

1 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):593-602.

2 Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):617-27.

3 Antony M, Swinson R. Anxiety disorders and their treatment: a critical review of the evidence-based literature. Ottawa (ON): Health Canada; 1996.

4 Stein MB, Sherbourne CD, Craske MG, Means-Christensen A, Bystritsky A, Katon W, et al. Quality of care for primary care patients with anxiety disorders. Am J Psychiatry. 2004 Dec;161(12):2230-7.

5 Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):603-13.

6 Ministry of Health. Clinical Practice Guidelines: Anxiety Disorders. Singapore: Ministry of Health; 2003.

7 World Health Organisation. International classification of diseases and related health problems, 10th rev. Geneva: Author; 1992.

8 American Psychiatric Association. Diagnostic and statistical manual of mental disorders Fourth Edition – Text Revision (DSM-IV-TR). 4 ed. Washington, DC: American Psychiatric Publishing, Inc.; 2000.

9 Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. J Affect Disord. 2002 Feb;68(1):1-23.

10 Lim L, Ng TP, Chua HC, Chiam PC, Won V, Lee T, et al. Generalised anxiety disorder in Singapore: prevalence, co-morbidity and risk factors in a multi-ethnic population. Soc Psychiatry Psychiatr Epidemiol. 2005 Dec;40(12):972-9.

11 Goldberg R, Posner D. Anxiety in the medically ill. In: Stoudemire A, Fogel B, editors. Psychiatric care of the medically ill patient. New York: Oxford University Press; 1993. p. 155-206.

12 Harter MC, Conway KP, Merikangas KR. Associations between anxiety disorders and physical illness. Eur Arch Psychiatry Clin Neurosci. 2003 Dec;253(6):313-20.

13 Katon W. Panic disorder: relationship to high medical utilization, unexplained physical symptoms, and medical costs. J Clin Psychiatry. 1996;57 Suppl 10:11-8.

14 Bunevicius R, Prange AJ, Jr. Psychiatric manifestations of Graves' hyperthyroidism: pathophysiology and treatment options. CNS Drugs. 2006;20(11):897-909.

15 Lim L, Jin AZ, Ng TP. Anxiety and Depression, Chronic Physical Conditions, and Quality of Life in an Urban Population Sample Study. Social Psychiatry and Psychiatr Epidemiol. 2012;47:1047–53.

16 Culpepper L. Use of algorithms to treat anxiety in primary care. J Clin Psychiatry. 2003;64 Suppl 2:30-3.

17 Practice guideline for the treatment of patients with panic disorder. Work Group on Panic Disorder. American Psychiatric Association. Am J Psychiatry. 1998 May;155(5 Suppl):1-34.

18 Shear M, Brown T, Barlow D, Money R, Sholomskas D, Woods S, et al. Multicenter collaborative Panic Disorder Severity Scale. American Journal of Psychiatry. 1997;154:1571-5.

19 Bandelow B. Panic and Agoraphobia Scale (PAS). Seattle, WA: Hogrefe & Huber Publications; 1999.

20 Spitzer R, Kroenke K, Williams J, Lowe B. A brief measure for assessing generalized anxiety disorder. Arch Intern Med. 2006;166:1092-7.

21 Connor K, Davidson J, Churchill L, Sherwood A, Foa E, RH W. Psychometric properties of the Social Phobia Inventory (SPIN). Br J Psychiatry. 2000;176:379-86.

22 Connor K, Davidson J. SPRINT: a brief global assessment of post-traumatic stress disorder. International Clinical Psychopharmacology. 2001;16:279-84.

23 Goodman WK, Price LH, Rasmussen SA. The Yale-Brown Obsessive-Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 1989;46:1006-11.

24 Zaider TI, Heimberg RG, Fresco DM, Scheneier FR, Liebowitz MR. Evaluation of the clinical global impression scale among individuals with social anxiety disorder. Psychol Med. 2003;33:611-22.

25 Canadian Psychiatric Association. Clinical practice guidelines: Management of anxiety disorders. The Canadian Journal of Psychiatry. 2006;51:1S-92S.

26 Norton P, Price E. A meta-analytic review of adult cognitive-behavioral treatment outcome across the anxiety disorders. J Nerv Ment Dis. 2007;195:521-31.

27 Bandelow B, Sher L, Bunevicius R, Hollander E, Kasper S, Zohar J, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. Int J Psychiatry Clin Pract. 2012 Jun;16(2):77-84.

28 Health Sciences Authority. Risk of dose-dependent QT prolongation with citalopram. 2012: Availablefrom: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/Safety_Alerts_2012/risk_of_dose-dependent.html

29 US Food and Drug Administration. Abnormal heart rhythms associated with high doses of celexa (citalopram hydrobromide). 2011 [28 Sep 2013]; Available from : http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm269481.html.

30 US Food and Drug Administration. Celexa (citalopram hydrobromide) drug safety communication: revised recommendations, potential risk of abnormal heart rhythms. 2012 [cited 2013 28 Sep]; Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm297624.htm.

31 Health Sciences Authority. Risk of dose-dependent QT prolongation with citalopram. 2012 [cited 2013 28 Sep]; Available from: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/Safety_Alerts_2012/risk_of_dose-dependent.html

32 Komossa K, Depping AM, Meyer M, Kissling W, Leucht S. Second-generation antipsychotics for obsessive compulsive disorder. Cochrane Database Syst Rev. 2010(12):CD008141.

33 Fones CS, Kua EH, Ng TP, Ko SM. Studying the mental health of a nation: a preliminary report on a population survey in Singapore. Singapore Med J. 1998 Jun;39(6):251-5.

34 Eaton WW, Kessler RC, Wittchen HU, Magee WJ. Panic and panic disorder in the United States. Am J Psychiatry. 1994 Mar;151(3):413-20.

35 Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, et al. The cross-national epidemiology of panic disorder. Arch Gen Psychiatry. 1997 Apr;54(4):305-9.

36 Ramage-Morin PL. Panic disorder and coping. Health Rep. 2004;15 Suppl:31-43.

37 Sherbourne CD, Wells KB, Judd LL. Functioning and well-being of patients with panic disorder. Am J Psychiatry. 1996 Feb;153(2):213-8.

38 Roy-Byrne PP, Stang P, Wittchen HU, Ustun B, Walters EE, Kessler RC. Lifetime panic-depression comorbidity in the National Comorbidity Survey. Association with symptoms, impairment, course and help-seeking. Br J Psychiatry. 2000 Mar;176:229-35.

39 Coryell W, Endicott J, Andreasen NC, Keller MB, Clayton PJ, Hirschfeld RM, et al. Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. Am J Psychiatry. 1988 Mar;145(3):293-300.

40 Bandelow B, Behnke K, Lenoir S, Hendriks GJ, Alkin T, Goebel C, et al. Sertraline versus paroxetine in the treatment of panic disorder: an acute, double-blind noninferiority comparison. J Clin Psychiatry. 2004 Mar;65(3):405-13.

41 Rapaport MH, Wolkow R, Rubin A, Hackett E, Pollack M, Ota KY. Sertraline treatment of panic disorder: results of a long-term study. Acta Psychiatr Scand. 2001 Oct;104(4):289-98.

42 Lepola U, Arato M, Zhu Y, Austin C. Sertraline versus imipramine treatment of comorbid panic disorder and major depressive disorder. J Clin Psychiatry. 2003 Jun;64(6):654-62.

43 Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. Am J Psychiatry. 2001 Dec;158(12):1989-92.

44 Ballenger JC, Wheadon DE, Steiner M, Bushnell W, Gergel IP. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry. 1998 Jan;155(1):36-42.

45 Oehrberg S, Christiansen PE, Behnke K, Borup AL, Severin B, Soegaard J, et al. Paroxetine in the treatment of panic disorder. A randomised, double-blind, placebo-controlled study. Br J Psychiatry. 1995 Sep;167(3):374-9.

46 Pollack MH, Doyle AC. Treatment of panic disorder: focus on paroxetine. Psychopharmacol Bull. 2003 Spring;37 Suppl 1:53-63.

47 Sheehan DV, Burnham DB, Iyengar MK, Perera P. Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. J Clin Psychiatry. 2005 Jan;66(1):34-40.

48 Bradwejn J, Ahokas A, Stein DJ, Salinas E, Emilien G, Whitaker T. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. Br J Psychiatry. 2005 Oct;187:352-9.

49 Pollack MH, Worthington JJ, 3rd, Otto MW, Maki KM, Smoller JW, Manfro GG, et al. Venlafaxine for panic disorder: results from a double-blind, placebo-controlled study. Psychopharmacol Bull. 1996;32(4):667-70.

50 Pollack M, Mangano R, Entsuah R, Tzanis E, Simon NM, Zhang Y. A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. Psychopharmacology (Berl). 2007 Oct;194(2):233-42.

51 Ferguson JM, Khan A, Mangano R, Entsuah R, Tzanis E. Relapse prevention of panic disorder in adult outpatient responders to treatment with venlafaxine extended release. J Clin Psychiatry. 2007 Jan;68(1):58-68.

52 Lecrubier Y, Bakker A, Dunbar G, Judge R. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. Collaborative Paroxetine Panic Study Investigators. Acta Psychiatr Scand. 1997 Feb;95(2):145-52.

53 Bakker A, van Dyck R, Spinhoven P, van Balkom AJ. Paroxetine, clomipramine, and cognitive therapy in the treatment of panic disorder. J Clin Psychiatry. 1999 Dec;60(12):831-8.

54 Drug treatment of panic disorder. Comparative efficacy of alprazolam, imipramine, and placebo. Cross-National Collaborative Panic Study, Second Phase Investigators. Br J Psychiatry. 1992 Feb;160:191-202.

55 Mavissakalian MR, Perel JM. Imipramine dose-response relationship in panic disorder with agoraphobia. Preliminary findings. Arch Gen Psychiatry. 1989 Feb;46(2):127-31.

56 Andersch S, Rosenberg NK, Kullingsjo H, Ottosson JO, Bech P, Bruun-Hansen J, et al. Efficacy and safety of alprazolam, imipramine and placebo in treating panic disorder. A Scandinavian multicenter study. Acta Psychiatr Scand Suppl. 1991;365:18-27.

57 Ballenger JC, Burrows GD, DuPont RL, Jr., Lesser IM, Noyes R, Jr., Pecknold JC, et al. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. I. Efficacy in short-term treatment. Arch Gen Psychiatry. 1988 May;45(5):413-22.

58 Lydiard RB, Lesser IM, Ballenger JC, Rubin RT, Laraia M, DuPont R. A fixed-dose study of alprazolam 2 mg, alprazolam 6 mg, and placebo in panic disorder. J Clin Psychopharmacol. 1992 Apr;12(2):96-103.

59 Noyes R, Jr., Burrows GD, Reich JH, Judd FK, Garvey MJ, Norman TR, et al. Diazepam versus alprazolam for the treatment of panic disorder. J Clin Psychiatry. 1996 Aug;57(8):349-55.

60 Uhlenhuth EH, Matuzas W, Glass RM, Easton C. Response of panic disorder to fixed doses of alprazolam or imipramine. J Affect Disord. 1989 Nov-Dec;17(3):261-70.

61 Beauclair L, Fontaine R, Annable L, Holobow N, Chouinard G. Clonazepam in the treatment of panic disorder: a double-blind, placebo-controlled trial investigating the correlation between clonazepam concentrations in plasma and clinical response. J Clin Psychopharmacol. 1994 Apr;14(2):111-8.

62 Moroz G, Rosenbaum JF. Efficacy, safety, and gradual discontinuation of clonazepam in panic disorder: a placebo-controlled, multicenter study using optimized dosages. J Clin Psychiatry. 1999 Sep;60(9):604-12.

63 Dunner DL, Ishiki D, Avery DH, Wilson LG, Hyde TS. Effect of alprazolam and diazepam on anxiety and panic attacks in panic disorder: a controlled study. J Clin Psychiatry. 1986 Sep;47(9):458-60.

64 Charney DS, Woods SW. Benzodiazepine treatment of panic disorder: a comparison of alprazolam and lorazepam. J Clin Psychiatry. 1989 Nov;50(11):418-23.

65 Schweizer E, Rickels K, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. II. Effects of gradual taper. Arch Gen Psychiatry. 1990 Oct;47(10):908-15.

66 Curtis GC, Massana J, Udina C, Ayuso JL, Cassano GB, Perugi G. Maintenance drug therapy of panic disorder. J Psychiatr Res. 1993;27 Suppl 1:127-42.

67 Woods SW, Nagy LM, Koleszar AS, Krystal JH, Heninger GR, Charney DS. Controlled trial of alprazolam supplementation during imipramine treatment of panic disorder. J Clin Psychopharmacol. 1992 Feb;12(1):32-8.

68 Goddard AW, Brouette T, Almai A, Jetty P, Woods SW, Charney D. Early coadministration of clonazepam with sertraline for panic disorder. Arch Gen Psychiatry. 2001 Jul;58(7):681-6.

69 Pollack MH, Simon NM, Worthington JJ, Doyle AL, Peters P, Toshkov F, et al. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. J Psychopharmacol. 2003 Sep;17(3):276-82.

70 American Psychiatric Association. Benzodiazepine Dependence, Toxicity, and Abuse: A Task Force Report of the American Psychiatric Association. Washington, DC: American Psychiatric Association; 1990.

71 Soumerai SB, Simoni-Wastila L, Singer C, Mah C, Gao X, Salzman C, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. Psychiatr Serv. 2003 Jul;54(7):1006-11.

72 Mavissakalian MR, Perel JM. Long-term maintenance and discontinuation of imipramine therapy in panic disorder with agoraphobia. Arch Gen Psychiatry. 1999 Sep;56(9):821-7.

73 Mavissakalian MR, Perel JM. 2nd year maintenance and discontinuation of imipramine in panic disorder with agoraphobia. Ann Clin Psychiatry. 2001 Jun;13(2):63-7.

74 Mavissakalian MR, Perel JM. Duration of imipramine therapy and relapse in panic disorder with agoraphobia. J Clin Psychopharmacol. 2002;22:294–9.

75 Stewart RE, Chambless DL. Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: a meta-analysis of effectiveness studies. J Consult Clin Psychol. 2009 Aug;77(4):595-606.

76 Gould R, Otto M, Pollack M. A meta-analysis of treatment outcome for panic disorder. Clin Psychol Rev. 1995;15(8):819-44.

77 Furukawa TA, Watanabe N, Churchill R. Psychotherapy plus antidepressant for panic disorder with or without agoraphobia: Systematic review. British Journal of Psychiatry. 2006;188:305-12.

78 Hoffmann SG, Sawyer AT, Korte KJ, Smits JA. Is it Beneficial to Add Pharmacotherapy to Cognitive-Behavioral Therapy when Treating Anxiety Disorders? A Meta-Analytic Review. International Journal of Cognitive Therapy. 2009;2:160-75.

79 Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. JAMA. 2000 May 17;283(19):2529-36.

80 Clum GA, Surls R. A meta-analysis of treatments for panic disorder. J Consult Clin Psychol. 1993 Apr;61(2):317-26.

81 Stein MB, Ron Norton G, Walker JR, Chartier MJ, Graham R. Do selective serotonin re-uptake inhibitors enhance the efficacy of very brief cognitive behavioral therapy for panic disorder? A pilot study. Psychiatry Res. 2000 Jul 17;94(3):191-200.

82 Bandelow B, Seidler–Brandler U, Becker A. Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders. World J Biol Psychiatry. 2007;8:175-87.

83 Chong SA, Abdin E, Vaingankar JA, Heng D, Sherbourne C, Yap M, et al. A population-based survey of mental disorders in Singapore. Ann Acad Med Singapore. 2012 Feb;41(2):49-66.

84 Chong SA, Abdin E, Sherbourne C, Vaingankar J, Heng D, Yap M, et al. Treatment gap in common mental disorders: the Singapore perspective. Epidemiol Psychiatr Sci. 2012 Jun;21(2):195-202.

85 Ball S, Kuhn A, Wall D, Shekhar A, Goddard A. Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. J Clin Psychiatry. 2005;66:94-9.

86 Stocchi F, Nordera G, Jokinen RH, Lepola UM, Hewett K, Bryson H, et al. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. J Clin Psychiatry. 2003 Mar;64(3):250-8.

87 Davidson J, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. Depress Anxiety. 2004;19:234-40.

88 Goodman W, Bose A, Wang Q. Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J Affect Disord 2005;87:161-7.

89 Allgulander C, Dahl A, Austin C. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. Am J Psychiatry. 2004;161:1642-9.

90 Kapczinski F, Lima MS, Souza JS, Schmitt R. Antidepressants for generalized anxiety disorder. Cochrane Database Syst Rev. 2003(2):CD003592.

91 Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. J Clin Psychopharmacol. 2005;25:141-50.

92 Davidson J, Du Pont R, Hedges D, Haskins J. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry. 1990;60:528-35.

93 Nimatoudis I, Zissis N, Kogeorgos J. Remission rates with venlafaxine extended release in Greek outpatients with generalized anxiety disorder. A double-blind, randomized, placebo controlled study. Int Clin Psychopharmacol. 2004;19:331-6.

94 Hoehn-Saric R, McLeod D, Zimmerli W. Differential effects of alprazolam and imipramine in generalized anxiety disorder: somatic versus psychic symptoms. J Clin Psychiatry. 1988;49:293-301.

95 Rickels K, Downing R, Schweizer E, Hassman H. Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry. 1993 Nov;50(11):884-95.

96 Rickels K, DeMartinis N, Garcia-Espana F, Greenblatt DJ, Mandos LA, Rynn M. Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. Am J Psychiatry. 2000 Dec;157(12):1973-9.

97 Gambi F, De Berardis D, Campanella D, Carano A, Sepede G, Salini G, et al. Mirtazapine treatment of generalized anxiety disorder: a fixed dose, open label study. J Psychopharmacol. 2005 Sep;19(5):483-7.

98 Ribeiro L, Busnello J, Kauer-Sant'Anna M, Madruga M, Quevedo J, Busnello E, et al. Mirtazapine versus fluoxetine in the treatment of panic disorder. Braz J Med Biol Res. 2001;34(10):1303-7.

99 Lydiard RB, Ballenger JC, Rickels K. A double-blind evaluation of the safety and efficacy of abecarnil, alprazolam, and placebo in outpatients with generalized anxiety disorder. Abecarnil Work Group. J Clin Psychiatry. 1997;58 Suppl 11:11-8.

100 Moller HJ, Volz HP, Reimann IW, Stoll KD. Opipramol for the treatment of generalized anxiety disorder: a placebo-controlled trial including an alprazolam-treated group. J Clin Psychopharmacol. 2001 Feb;21(1):59-65.

101 Rickels K, Pollack MH, Feltner DE, Lydiard RB, Zimbroff DL, Bielski RJ, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry. 2005 Sep;62(9):1022-30.

102 Gorman J. Treatment of generalized anxiety disorder. J Clin Psychiatry. 2002;63(Suppl 8):17-23.

103 Shader R, Greenblatt D. Use of benzodiazepines in anxiety disorders. N Engl J Med. 1993;328:1398-405.

104 Ross CA, Matas M. A clinical trial of buspirone and diazepam in the treatment of generalized anxiety disorder. Can J Psychiatry. 1987 Jun;32(5):351-5.

105 Hoffman E. Pharmacotherapy for Generalized Anxiety Disorder. In: Antony M, Strein M, editors. Oxford Handbook of anxiety and related Disorders. New York: Oxford U Press; 2009.

106 Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. J Clin Psychiatry. 2006 May;67(5):771-82.

107 Canadian Agency for Drugs and Technologies in Health. Abuse and misuse potential of pregabalin: A review of the clinical evidence. : Canadian Agency for Drugs and Technologies in Health; 2012.

108 Schwan S, Sundström A, Stjernberg E, Hallberg E, Hallberg P. A signal for an abuse liability for pregabalin--results from the Swedish spontaneous adverse drug reaction reporting system. Eur J Clin Pharmacol. 2010;66(9):947-53.

109 Llorca PM, Spadone C, Sol O, Danniau A, Bougerol T, Corruble E, et al. Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study. J Clin Psychiatry. 2002 Nov;63(11):1020-7.

110 Meibach RC, Dunner D, Wilson LG, Ishiki D, Dager SR. Comparative efficacy of propranolol, chlordiazepoxide, and placebo in the treatment of anxiety: a double-blind trial. J Clin Psychiatry. 1987 Sep;48(9):355-8.

111 Davidson JR. First-line pharmacotherapy approaches for generalized anxiety disorder. Journal of Clinical Psychiatry. 2009;20(2):25-31.

112 Cottraux J. Recent developments in the research on generalized anxiety disorder. Current Opinion in Psychiatry. 2004;17:49-52.

113 Borkovec TD, Ruscio AM. Psychotherapy for generalized anxiety disorder. J Clin Psychiatry. 2001;62 Suppl 11:37-42; discussion 3-5.

114 Fisher PL, Durham RC. Recovery rates in generalized anxiety disorder following psychological therapy: An analysis of clinically significant chance in the STAI-T across outcome studies since 1990. Psychol Med. 1999;29(6):1425-34.

115 Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: A review of meta-analyses. Clin Psychol Rev. 2006;26:17-31.

116 Durham RC, Chambers JA, MacDonald RR, Power KG, Major K. Does cognitive-behavioural therapy influence the long-term outcome of generalized anxiety disorder? An 8-14 year follow-up of two clinical trials. Psychol Med. 2003 Apr;33(3):499-509.

117 Power KG, Simpson RJ, Swanson V, Wallace LA. Controlled comparison of pharmacological and psychological treatment of generalized anxiety disorder in primary care. Br J Gen Pract. 1990 Jul;40(336):289-94.

118 Magee W, Eaton J, Wittchen H-U. Agoraphobia, simple phobia and social anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1996;53:159-68.

119 Reiger D, Boyd J, Burke J. One-month prevalence of mental disorders in the United States. Arch gen Psychiatry. 1988;45:977-86.

120 Lipsitz J, Barlow D, Mannuzza S. Clinical features of four DSM-IV-specific phobia subtypes. J Nerv Ment Dis. 2002;190:471-8.

121 Craske MG, Barlow DH, Clark D, Curtis G, Hill EM, Himle J. Specific (simple) phobia. In: T. A. Widiger AF, H. Pincus, R. Ross, M. First, & W.

Davis, editor. DSM-IV sourcebook, Vol 2. Washington, DC: American Psychiatric Association; 1996. p. 473–506.

122 Antony MM, Brown TA, Barlow DH. Heterogeneity among specific phobia types in DSM-IV. Behav Res Ther. 1997 Dec;35(12):1089-100.

123 Dupont R. Phobia: a comprehensive summary of modern treatments. New York: Brunner/Mazel; 1982.

124 Park JM, Mataix-Cols D, Marks IM, Ngamthipwatthana T, Marks M, Araya R, et al. Two-year follow-up after a randomised controlled trial of self- and clinician-accompanied exposure for phobia/panic disorders. Br J Psychiatry. 2001 Jun;178:543-8.

125 Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, Allgulander C, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. World J Biol Psychiatry. 2008;9(4):248-312.

126 Marks I, Viswanathan R, Lipsedge M. Enhanced relief of phobias by flooding during waning diazepam effect. Br J Psychiatry. 1972;121:493-506.

127 Marks I, Swinson R, Başoğlu M, Kuch K, Noshirvani H, O'Sullivan G, et al. Alprazolam and exposure alone and combined in panic disorder with agoraphobia. A controlled study in London and Toronto. Br J Psychiatry. 1993;162:776-87.

128 Choy Y, Fyer A, Lipsitz J. Treatment of specific phobia in adults. Clin Psychology Rev. 2007;27:266-86.

129 Lipsitz J, Mannuzza S, Klein D, Ros D, Fyer A. Specific phobia 10-16 years after treatment. Depression and Anxiety. 1999;10:105-11.

130 ESEMeD/MHEDEA 2000 Investigators. Prevalence of mental disorders in Europe: Results from the European study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatrica Scand. 2004;109(Suppl 420):21-7.

131 Fehm L, Pelissolo A, Furmark T, Wittchen H-U. Size and burden of social anxiety disorder in Europe. European Neuropsychopharmacology 2005;15.

132 Wells J, Tien A, Garrison R. Risk factors for the incidence of social anxiety disorder as determined by the Diagnostic Interview Schedule in a population-based study. Acta Psychiatrica Scand. 1994;90:84-90.

133 Degonda M, Angst J. The Zurich Study XX: social anxiety disorder and agoraphobia. Eur Arch Psychiatry Clin Neurosci. 1993;243:95-102.

134 Scheibe G, Albus M. Age at onset, precipitating events, sex distribution, and co-occurrence of anxiety disorders. Psychopathology 1992;25:11-8.

135 Muller JE, Koen L, Seedat S, Stein DJ. Social anxiety disorder: Current treatment recommendations. CNS Drugs. 2005;19:377-91.

136 Blanco C, Schneier F, Schmidt A, Blanco-Jerez C, Marshall R, Sánchez-Lacay A, et al. Pharmacological treatment of social anxiety disorder: a meta-analysis. Depress Anxiety. 2003;18:29-40.

137 Stein MB, Pollack MH, Bystritsky A, Kelsey JE, Mangano RM. Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: A 6-month randomized controlled trial. Psychopharmacology. 2004;177:280-8.

138 Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. Journal of clinical psychopharmacology. 2004;24:488-96.

139 Allgulander C, Mangano R, Zhang J. Efficacy of venlafaxine ER in patients with social anxiety disorder: a double-blind, placebo-controlled, parallel-group comparison with paroxetine. Hum Psychopharmacol. 2004;19:387-96.

140 Liebowitz M, Gelenberg A, Munjack D. Venlafaxine extended release vs. placebo and paroxetine in social anxiety disorder. Arch Gen Psychiatry. 2005;62:190-8.

141 Stein DJ, Cameron A, Amrein R, Montgomery SA. Moclobemide is effective and well tolerated in the long-term pharmacotherapy of social anxiety disorder with or without comorbid anxiety disorder. Int Clin Psychopharmacol. 2002 Jul;17(4):161-70.

142 Ten A, Malaya L, Dancourt C. Quetiapine versus risperidone in treatment of anxiety/panic disorder. American Psychiatric Association New Research Abstracts, Annual Meeting of the American Psychiatric Association. Washington (DC): American Psychiatric Association; 2003.

143 Schutters S, van Megen H, Westenberg HG. Efficacy of quetiapine in generalized social anxiety disorder: results from an open-label study [letter]. J Clin Psychiatry. 2005;66:540-2.

144 Barnett SD, Kramer ML, Casat CD, Connor KM, Davidson JR. Efficacy of olanzapine in social anxiety disorder: a pilot study. J Psychopharmacol. 2002 Dec;16(4):365-8.

145 Otto M, Pollack M, Gould R. A comparison of the efficacy of clonazepam and cognitive-behavioral group therapy for the treatment of social anxiety disorder. J Anxiety Disord. 2000;14:345-58.

146 Gelernter C, Uhde T, Cimbolic P. Cognitive-behavioral and pharmacological treatments of social anxiety disorder. A controlled study. Arch Gen Psychiatry. 1991;48:938-45.

147 Versiani M, Nardi A, Figuera I, Marques C. Double-blind placebo controlled trial with bromazepam in social anxiety disorder. J Bras Psiquiatr. 1997;46:167-71.

148 Liebowitz M, Schneier F, Campeas R. Phenelzine vs atenolol in social anxiety disorder. A placebo-controlled comparison. Arch Gen Psychiatry. 1992;49:290-300.

149 Falloon I, Lloyd G, Harpin R. The treatment of social anxiety disorder. Real-life rehearsal with nonprofessional therapists. J Nerv Ment Dis. 1981;169:180-4.

150 Tyrer P. Current status of beta-blocking drugs in the treatment of anxiety disorders. Drugs 1988;36:773-83.

151 Stangier U, Heidenreich T, Peitz M, Lauterbach W, Clark DM. Cognitive therapy for social phobia: Individual versus group treatment. Behaviour Research and Therapy. 2003;41:991-1007.

152 Clark DM, Ehlers A, Hackmann A, McManus F, Fennell M, Grey N. Cognitive therapy versus exposure and applied relaxation in social phobia: A randomized controlled trial. Journal of Consulting and Clinical Psychology. 2006;74:569-78.

153 Davidson JRT, Foa EB, Huppert JD, Keefe FJ, Franklin ME, Compton JS. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. Archives of General Psychiatry. 2004;61:1005-13.

154 Borgeat F, Stankovic M, Khazaal Y, Rouget BW, Baumann MC, Riquier F, et al. Does the form or the amount of exposure make a difference in the cognitive-behavioral therapy treatment of social phobia? J Nerv Ment Dis. 2009 Jul;197(7):507-13.

155 Versiani M, Amrein R, Montgomery S. Social anxiety disorder: long-term treatment outcome and prediction of response-a moclobemide study. Int Clin Psychopharmacol. 1997;12:239-54.

156 Stein D, Versiani M, Hair T, Kumar R. Efficacy of paroxetine for relapse prevention in social anxiety disorder: a 24-week study. Arch Gen Psychiatry. 2002;59:1111-8.

157 Walker JR, Van Ameringen MA, Swinson R, Bowen RC, Chokka PR, Goldner E, et al. Prevention of relapse in generalized social phobia: results of a 24-week study in responders to 20 weeks of sertraline treatment. J Clin Psychopharmacol. 2000 Dec;20(6):636-44.

158 Clark D, Ehlers A, McManus F. Cognitive therapy versus fluoxetine in generalized social anxiety disorder: a randomized placebo-controlled trial. J Consult Clin Psychol. 2003;71:1058-67.

159 Haug T, Blomhoff S, Hellstrom K. Exposure therapy and sertraline in social anxiety disorder: 1-year follow-up of a randomised controlled trial. Br J Psychiatry 2003. 2003;182:312-8.

160 Allgulander C, Bandelow B, Hollander E, Montgomery SA, Nutt DJ, Okasha A, et al. WCA recommendations for the long-term treatment of generalized anxiety disorder. CNS Spectr. 2003 Aug;8(8 Suppl 1):53-61.

161 Kolada J, Bland R, Newman S. Obsessive-compulsive disorder. Acta Psychiatrica Scandinavica. 1994;376:24-35.

162 Skoog G, Skoog I. A 40-year follow-up of patients with obsessive-compulsive disorder. Arch Gen Psychiatry. 1999 Feb;56(2):121-7.

163 Abramowitz J. Effectiveness of psychological and pharmacological treatments for obsessive-compulsive disorder: A quantitative review. Journal of Consulting and Clinical Psychology. 1997;65:44-52.

164 Kobak K, Greist J, Jefferson J, Katzelnick D, Henk H. Behavioral versus pharmacological treatments of obsessive compulsive disorder: A meta-analysis. Psychopharmacology. 1998;136:205–16.

165 Stein DJ, Spadaccini E, Hollander E. Meta-analysis of pharmacotherapy trials for obsessive-compulsive disorder. International Clinical Psychopharmacology. 1995;10:11-8.

166 Van Oppen P, de Haan E, van Balkom AJLM, Spinhoven P, Hoogduin K, van Dyck R. Cognitive therapy and exposure in vivo in the treatment of obsessive compulsive disorder. Behavior Research and Therapy. 1995;33:379–90.

167 Greist JH, Jefferson JW, Kobak KA, Katzelnick DJ, Serlin RC. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. Arch Gen Psychiatry. 1995 Jan;52(1):53-60.

168 Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane Database Syst Rev. 2008(1):CD001765.

169 Piccinelli M, Pini S, Bellantuono C, Wilkinson G. Efficacy of drug treatment in obsessive-compulsive disorder. A meta-analytic review. Br J Psychiatry. 1995;166:424-43.

170 Fineberg N, Gale T. Evidence-based pharmacotherapy of obsessive-compulsivedisorder. . Int J Neuropsychopharmacol 2005;8:107-29.

171 Rauch S, O'Sullivan R, Jenike M. Open treatment of obsessive-compulsive disorder with venlafaxine: a series of 10 cases. J Clin Psychopharmacol. 1996;16:81-4.

172 Sevincok L, Uygur B. Venlafaxine open-label treatment of patients with obsessive-compulsive disorder. Aust N Z J Psychiatry. 2002;36:817.

173 Yaryura-Tobias J, Neziroglu F. Venlafaxine in obsessive-compulsive disorder. Arch Gen Psychiatry. 1996;53:653-4.

174 Denys D, van der Wee N, van Megen H, Westenberg H. A double blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. J Clin Psychopharmacol. 2003;23:568-75.

175 Denys D, van Megen H, van der Wee N, Westenberg H. A double-blind switch study of paroxetine and venlafaxine in obsessive-compulsive disorder. J Clin Psychiatry. 2004;65:37-43.

176 Hollander E, Friedberg J, Wasserman S. Venlafaxine in treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry. 2003;64:546-50.

177 Dell'osso B, Mundo E, Marazziti D. Switching from serotonin reuptake inhibitors to duloxetine in patients with resistant obsessive-compulsive disorder: a case series. J Psychopharmacol. 2008;22(2):210-13.

178 Koran L, Gamel N, Choung H. Mirtazapine for obsessive compulsive disorder: an open trial followed by double-blind discontinuation. J Clin Psychiatry. 2005;66(4):515-20.

179 Marks IM, Lelliott P, Basoglu M, Noshirvani H, Monteiro W, Cohen D, et al. Clomipramine, self-exposure and therapist-aided exposure for obsessive-compulsive rituals. Br J Psychiatry. 1988 Apr;152:522-34.

180 Marks IM, Stern RS, Mawson D, Cobb J, McDonald R. Clomipramine and exposure for obsessive-compulsive rituals: i. Br J Psychiatry. 1980 Jan;136:1-25.

181 Cottraux J, Mollard E, Bouvard M, Marks I, Sluys M, Nury AM, et al. A controlled study of fluvoxamine and exposure in obsessive-compulsive disorder. Int Clin Psychopharmacol. 1990 Jan;5(1):17-30.

182 Foa EB, Franklin ME, Moser J. Context in the clinic: how well do cognitive-behavioral therapies and medications work in combination (Structured abstract). Biological Psychiatry [serial on the Internet]. 2002; (10): Available from: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12002006727/frame.html.

183 Dold M, Aigner M, Lanzenberger R, Kasper S. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. Int J Neuropsychopharmacol. 2013;16(3):557-74.

184 Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. Molecular Psychiatry. 2006;11(7):622-32.

185 Skapinakis P, Papatheodorou T, Mavreas V. Antipsychotic augmentation of serotonergic antidepressants in treatment-resistant obsessive-compulsive disorder: a meta-analysis of the randomized controlled trials. Eur Neuropsychopharmacol. 2007;17(2):79-93.

186 McDougle C, Goodman W, Leckman J, Lee N, Heninger G, Price L. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry. 1994;51(4):302-8.

187 McDougle C, Walsh K. Treatment for refractory OCD. In: Fineberg N, Marazitti D, Stein D, editors. Obsessive Compulsive Disorder; A Practical Guide. London: Martin Dunitz; 2001.

188 Li X, May R, Tolbert L, Jackson W, Flournoy J, Baxter L. Risperidone and haloperidol augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder: a crossover study. J Clin Psychiatry. 2005;66(6):736-43.

189 Matsunaga H, Hayashida K, Maebayashi K, Mito H, Kiriike N. A case series of aripiprazole augmentation of selective serotonin reuptake inhibitors in treatment-refractory obsessive compulsive disorder. Int J Psychiatry Clin Pract. 2011;15(4):263-9.

190 Higuma H, Kanehisa M, Maruyama Y. Aripiprazole augmentation in 13 patients with refractory obsessive-compulsive disorder: a case series. World J Biol Psychiatry. 2012;13(1):14-21.

191 Muscatello M, Bruno A, Pandolfo G. Effect of aripiprazole augmentation of serotonin reuptake inhibitors or clomipramine in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. J Clin Psychopharmacol. 2011;31(2):174-9.

192 Sayyah M, Boostani H, Ghaffari S, Hoseini A. Effects of aripiprazole augmentation in treatment-resistant obsessive-compulsive disorder (a double blind clinical trial). Depress Anxiety. 2012;29(10):850-4.

193 Koran L, Ringold A, Elliott M. Olanzapine augmentation for treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry. 2000;61(7):514-7.

194 Bogetto F, Bellino S, Vaschetto P, Ziero S. Olanzapine augmentation of fluvoxamine-refractory obsessive-compulsive disorder (OCD): a 12-week open trial. Psychiatry Res. 2000;96(2):91-8.

195 Maina G, Pessina E, Albert U, Bogetto F. 8-week, single-blind, randomized trial comparing risperidone versus olanzapine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder. Eur Neuropsychopharmacol. 2008;18(5):364-72.

196 Donovan MR, Glue P, Kolluri S, Emir B. Comparative efficacy of antidepressants in preventing relapse in anxiety disorders - a meta-analysis. J Affect Disord. 2010 Jun;123(1-3):9-16.

197 Fineberg NA, Pampaloni I, Pallanti S, Ipser J, Stein DJ. Sustained response versus relapse: the pharmacotherapeutic goal for obsessive-compulsive disorder. Int Clin Psychopharmacol. 2007 Nov;22(6):313-22.

198 Greist JH, Bandelow B, Hollander E, Marazziti D, Montgomery SA, Nutt DJ, et al. WCA recommendations for the long-term treatment of obsessive-compulsive disorder in adults. CNS Spectr. 2003 Aug;8(8 Suppl 1):7-16.

199 Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson JR, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2005 Nov;19(6):567-96.

200 National Collaborating Centre for Mental Health. Obsessive compulsive disorder (OCD) and body dysmorphic disorder (BDD). London WC1V

6NA: The British Psychological Society and The Royal College of Psychiatrists; 2006. Available from: www.nice.org.uk/CG31.

201 Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995 Dec;52(12):1048-60.

202 Yehuda R. Post-traumatic stress disorder. New England Journal of Medicine. 2002;346:106-14.

203 Foa EB, Davidson J, Frances A. Treatment of posttraumatic stress disorder. J Clin Psychiatry. 1999;60(S16):6-74.

204 Connor K, Sutherland S, Tupler LA, Malik M, Davidson JR. Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study. Br J Psychiatry. 1999;175:17-22.

205 Martenyi F, Brown E, Zhang H, Prakash A, SC K. Fluoxetine versus placebo in posttraumatic stress disorder. J Clin Psychiatry. 2002;63:199-206.

206 Meltzer-Brody S, Connor K, Churchill E, Davidson J. Symptom-specific effects of fluoxetine in post-traumatic stress disorder. Int Clin Psychopharmacol. 2000;15:227-31.

207 van der Kolk B, Dreyfuss D, Michaels M, Shera D, Berkowitz R, Fisler R. Fluoxetine in posttraumatic stress disorder. J Clin Psychiatry. 1994;55:517-22.

208 van der Kolk B, Spinazzola J, Blaustein M, Hopper J, Hopper E, Korn D. A randomized clinical trial of eye movement desensitization and reprocessing (EMDR), fluoxetine, and pill placebo in the treatment of posttraumatic stress disorder: treatment effects and long-term maintenance. J Clin Psychiatry. 2007;68:37-46.

209 Davidson J, Connor K, Hertzberg M, Weisler R, Wilson W, Payne V. Maintenance therapy with fluoxetine in posttraumatic stress disorder: a placebo-controlled discontinuation study. J Clin Psychopharmacol. 2005;25:166-9.

210 Martenyi F, Brown E, Zhang H, Koke S, Prakash A. Fluoxetine v. placebo in prevention of relapse in post-traumatic stress disorder. Br J Psychiatry. 2002;181:315-20.

211 Marshall R, Beebe K, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed dose, placebo-controlled study. Am J Psychiatry. 2001;158:1982-8.

212 Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Dillingham K, Pitts C. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry. 2001;62:860-8.

213 Brady K, Pearlstein T, Asnis G, Baker D, Rothbaum B, Sikes C. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. Am Med Assoc. 2000;283:1837-44.

214 Davidson J, Rothbaum B, van der Kolk B, Sikes C, Farfel G. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. Arch Gen Psychiatry. 2001;58:485-92.

215 Stein D, van der Kolk B, Austin C, Fayyad R, Clary C. Efficacy of sertraline in posttraumatic stress disorder secondary to interpersonal trauma or childhood abuse. Ann Clin Psychiatry. 2006;18:243-9.

216 Zohar J, Amital D, Miodownik C, Kotler M, Bleich A, Lane R. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. J Clin Psychopharmacol. 2002;22:190-5.

217 Davidson J, Baldwin D, Stein D, Kuper E, Benattia I, Ahmed S. Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. Arch Gen Psychiatry. 2006;63:1158-65.

218 Davidson J, Rothbaum B, Tucker P, Asnis G, Benattia I, Musgnung J. Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. J Clin Psychopharmacol. 2006;26:259-67.

219 Bisson J, Andrew M. Psychological treatment of post-traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2007(3):CD003388.

220 Davidson J, Pearlstein T, Londborg P, Brady K, Rothbaum B, Bell J. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week doubleblind, placebo-controlled study. Am J Psychiatry. 2001;158:1974-81.

221 Londborg P, Hegel M, Goldstein S, Goldstein D, Himmelhoch J, Maddock R. Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. J Clin Psychiatry. 2001;62:325-31.

222 Tucker P, Smith K, Marx B. Fluvoxamine reduces physiologic reactivity to trauma scripts in posttraumatic stress disorder. Journal of Clinical Psychopharmacology. 2000;20:367-72.

223 Davidson J, Weisler R, Butterfield M, Casat C, Connor K, Barnett S. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. . Biol Psychiatry. 2003;53:188-91.

224 Davidson J, Kudler H, Smith R, Mahorney S, Lipper S, Hammett E. Treatment of posttraumatic stress disorder with amitriptyline and placebo. Arch Gen Psychiatry. 1990;47:259-66.

225 Davidson J, Kudler H, Saunders W, Erickson L, Smith R, Stein R. Predicting response to amitriptyline in posttraumatic stress disorder. Am J Psychiatry. 1993;150:1024-9.

226 Kosten T, Frank J, Dan E. Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. J Nerv Ment Dis. 1991;179:366-70.

227 Gelpin E, Bonne O, Peri T. Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin Psychiatry. 1996;57:390-4.

228 Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. J Clin Psychiatry. 1990;51:236-8.

229 Cates M, Bishop M, Davis L. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Ann Pharmacother. 2004;38:1395-9.

230 Hamner M, Frueh B, Ulmer H, Arana G. Psychotic features and illness severity in combat veterans with chronic posttraumatic stress disorder. Biol Psychiatry. 1999;45:846-52.

231 Ivezic S, Oruc L, Bell P. Psychotic symptoms in post-traumatic stress disorder. Mil Med 1999;164:73-5.

232 Padala P, Madison J, Monnahan M, Marcil W, Price P, Ramaswamy S. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. Int Clin Psychopharmacol. 2006;21:275-80.

233 Monnelly E, Ciraulo D, Knapp C, Keane T. Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. J Clin Psychopharmacol. 2003;23:193-6.

234 Hamner M, Faldowski R, Ulmer H, Frueh B, Huber M, Arana G. Adjunctive risperidone treatment in posttraumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. . Int Clin Psychopharmacol. 2003;18:1-8.

235 Stein M, Kline N, Matloff J. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo controlled study. Am J Psychiatry. 2002;159:1777-9.

236 Hertzberg M, Butterfield M, Feldman M, Beckham J, Sutherland S, Connor K. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. Biol Psychiatry. 1999;45:1226-9.

237 Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Foa EB, Kessler RC, et al. Consensus statement on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 2000;61 Suppl 5:60-6.

238 Ballenger JC. Clinical guidelines for establishing remission in patients with depression and anxiety. J Clin Psychiatry. 1999;60 Suppl 22:29-34.

239 Roth A, Fonagy P. What Works for Whom: A Critical Review of Psychotherapy Research (2nd ed.). New York: Guilford; 2005.

240 Van Etten M, Taylor S. Comparative efficacy of treatments for post-traumatic stress disorder: a meta-analysis. Clin Psychol Psychother. 1998;5:126-44.

241 Bradley R, Greene J, Russ E. A multidimensional meta-analysis of psychotherapy for PTSD. Am J Psychiatry. 2005;162:214-27.

242 Davidson PR, Parker KC. Eye movement desensitization and reprocessing (EMDR): a meta-analysis. J Consult Clin Psychol. 2001 Apr;69(2):305-16.

243 Devilly G, Spence S. The relative efficacy and treatment distress of EMDR and a cognitive-behavior trauma treatment protocol in the amelioration of posttraumatic stress disorder. J Anxiety Disord. 1999;13:131-57.

244 Taylor S, Thordarson D, Maxfield L. Comparative efficacy, speed, and adverse effects of three PTSD treatments: exposure therapy, EMDR, and relaxation training. J Consult Clin Psychol. 2003;71:330-8.

245 Taylor S. Efficacy and outcome predictors for three PTSD treatments: exposure therapy, EMDR, and relaxation training. In: Taylor S, editor. Advances in the treatment of posttraumatic stress disorder: cognitive-behavioral perspectives. New York: Springer Publishing Co; 2004. p. 13-37.

246 Albright D, Thyer B. Does EMDR reduce post-traumatic stress disorder symptomatology in combat veterans? Behavioral Interventions. 2010;25:1-19.

247 Hetrick SE, Purcell R, Garner B, Parslow R. Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2010(7):CD007316.

248 Kruger S. Psychopharmacological treatment of mood and anxiety disorders during pregnancy. Handb Exp Pharmacol. 2012(214):279-305.

249 National Institute for Health and Clinical Excellence. Antenatal and postnatal mental health: clinical management and service guidance: National Institute for Health and Clinical Excellence; 2007.

250 Armstrong C. ACOG guidelines on psychiatric medication use during pregnancy and lactaction. Am Fam Physician. 2008;78(6):772-8.

251 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ. 2009;339:b3569.

252 Jimenez-Solem E, Andersen JT, Petersen M, Broedbaek K, Lander AR, Afzal S, et al. SSRI use during pregnancy and risk of stillbirth and neonatal mortality. Am J Psychiatry. 2013 Mar 1;170(3):299-304.

253 Malm H, Artama M, Gissler M, Ritvanen A. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. Obstet Gynecol. 2011;118:111-20.

254 Riggin L, Frankel Z, Moretti M, Pupco A, Koren G. The fetal safety of fluoxetine: a systematic review and meta-analysis. J Obstet Gynaecol Can. 2013;35(4):362-9.

255 Pedersen L, Henriksen T, Vestergaard M, Olsen J, Bech B. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ. 2009;339:b3569.

256 Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med. 2006 Feb 9;354(6):579-87.

257 Kieler H. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. British Medical Journal. 2011;344:d8012.

258 Källén BAJ, Otterblad Olausson P. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Research Part A: Clinical and Molecular Teratology. 2007;79(4):301-8.

259 Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Gen Hosp Psychiatry. 2009 Sep-Oct;31(5):403-13.

260 Bar-Oz B, Einarson T, Einarson A, Boskovic R, O'Brien L, Malm H, et al. Paroxetine and congenital malformations: meta-Analysis and consideration of potential confounding factors. Clin Ther. 2007 May;29(5):918-26.

261 Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Effects of timing and duration of gestational exposure to serotonin reuptake inhibitor antidepressants: population-based study. Br J Psychiatry. 2008 May;192(5):338-43.

262 Yonkers K, Wisner K, Stewart D, Oberlander T, Dell D, Stotland N. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Gen Hosp Psychiatry. 2009;31(5):403-13.

263 Reis M, Kallen B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med. 2010 Oct;40(10):1723-33.

264 Alwan S, Reefhuis J, Botto L, Rasmussen S, Correa A, Friedman J. Maternal use of bupropion and risk for congenital heart defects. . Am J Obstet Gynecol. 2010;203(1):52.

265 Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. Pharmacoepidemiology and drug safety. 2007 May;16(5):474-84.

266 Health Sciences Authority. Bupropion and possible increased risk of congenital cardiovascular malformations. 2013 [cited 2014 1 Aug]; Available from: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/Safety_Alerts_2013/bupropion_and _possible.html.

267 Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ. 1998 Sep 26;317(7162):839-43.

268 Bellantuono C, Tofani S, Di Sciascio G, Santone G. Benzodiazepine exposure in pregnancy and risk of major malformations: a critical overview. Gen Hosp Psychiatry. 2013 Jan;35(1):3-8.

269 Iqbal MM, Sobhan T, Ryals T. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. Psychiatr Serv. 2002 Jan;53(1):39-49.

270 Gentile S. Clinical utilization of atypical antipsychotics in pregnancy and lactation. Ann Pharmacother. 2004;38:1265–71.

271 Ernst C, Goldberg J. The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. J Clin Psychiatry. 2002;63(S4):42-55.

272 Sivertz K, Kostaras X. The use of psychotropic medications in pregnancy and lactation. B C Med J. 2005;47:135-8.

273 American Academy of Pediatrics Commitee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108(3):776-89.

274 The Academy of Breastfeeding Medicine Protocol Committee. ABM clinical protocol #18: use of antidepressants in nursing mothers. Breastfeed Med. 2008;3(1):44-52.

275 Dodd S, Buist A, Norman TR. Antidepressants and breast-feeding: a review of the literature. Paediatric drugs. 2000;2(3):183-92.

276 Llewellyn A, Stowe ZN. Psychotropic medications in lactation. J Clin Psychiatry. 1998;59 Suppl 2:41-52.

277 Weissman A, Levy B, Hartz A, Bentler S, Donohue M, Ellingrod V, et al. Pooled Analysis of Antidepressant Levels in Lactating Mothers, Breast Milk, and Nursing Infants. Am J Psychiatry. 2004;161(6):1066-78.

278 Berle J, Spigset O. Antidepressant use during breastfeeding. Current Women's Health Reviews. 2011;7(1):28-34.

279 di Scalea T, Wisner K. Antidepressant Medication Use during Breastfeeding. Clin Obstet Gynecol. 2009;52(3):483-97.

280 American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. . Pediatrics. 2001;108:776-89.

281 Kessler R, Greenberg P. Chapter 67: The Economic Burden of anxiety and stress disorders. In: Davis KL, Charney D, Coyle JT, Nemeroff C, editors. Neuropsychopharmacology: The Fifth Generation of Progress. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002.

282 Deacon B, Lickel J, Abramowitz JS. Medical utilization across the anxiety disorders. J Anxiety Disord. 2008;22(2):344-50.

283 DuPont RL, Rice DP, Miller LS, Shiraki SS, Rowland CR, Harwood HJ. Economic costs of anxiety disorders. Anxiety. 1996;2(4):167-72.

284 Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, et al. The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry. 1999 Jul;60(7):427-35.

285 Issakidis C, Sanderson K, Corry J, Andrews G, Lapsley H. Modelling the population cost-effectiveness of current and evidence-based optimal treatment for anxiety disorders. Psychol Med. 2004 Jan;34(1):19-35.

286 Hyman S, Chisholm D, Kessler R, Patel V, Whiteford H. Mental Disorders In Disease control priorities in developing countries. World Health Organisation; 2006.

287 Konnopka A, Leichsenring F, Leibing E, Konig HH. Cost-of-illness studies and cost-effectiveness analyses in anxiety disorders: a systematic review. J Affect Disord. 2009 Apr;114(1-3):14-31.

288 Lacy CF, Armstrong LL, Goldman MP, Lance LL, editors. Drug Information Handbook: A Comprehensive Resource for All Clinicians and Healthcare Professionals. 20 ed. Hudson, Ohio: Lexi-Comp; 2011.

289 BMJ group and the Royal Pharmaceutical Society of Great Britain. British National Formulary No. 612011.

290 Micromedex Healthcare Series. DRUGDEX System. Greenwood Village, CO: Truven Health Analytics; 2013 [cited 2013]; Available from: http://www.thomsonhc.com/.

Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning – Verifiable Self-Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: http://sma.org.sg/publications/index.aspx?ID=26 (the link will only be available once the June 2015 issue of the SMJ becomes available). The answers will be published in the SMJ August 2015 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

Instruction: Choose True or False for each statement.

		True	False
1.	After diagnosis of an anxiety disorder in the outpatient setting, the following immediate steps should be instituted at the primary care level:		
	A) Reassurances and psycho-education about the nature and origin of anxiety.	☐	☐
	B) Lifestyle changes, such as regular exercise.	☐	☐
	C) Treat psychotic symptoms if present.	☐	☐
	D) Refer to a psychiatrist.	☐	☐
2.	Psychiatric referral is appropriate when:		
	A) Risk of suicide is serious.	☐	☐
	B) Anxiety disorder is first diagnosed.	☐	☐
	C) Pharmacological treatment for anxiety disorder is needed.	☐	☐
	D) Anxiety symptoms have stabilised.	☐	☐

		True	False
3.	For panic disorder:		
	A) Treatment response can be quantified and documented with the Panic Disorder Severity Scale (PDSS).	☐	☐
	B) About two-thirds of patients with panic disorder suffer from agoraphobia.	☐	☐
	C) Combination therapy is as efficacious as monotherapy.	☐	☐
	D) Cognitive behaviour therapy is not useful.	☐	☐
4.	For post-traumatic stress disorder:		
	A) Alprazolam and clonazepam have been found to be superior to placebo.	☐	☐
	B) Amitriptyline may be considered as first-line treatment.	☐	☐
	C) Risperidone and lamotrigine may be prescribed as adjunctive treatments.	☐	☐
	D) Combination therapy is superior to trauma-focused cognitive behaviour therapy.	☐	☐
5.	Evaluate the following statements:		
	A) Beta-blockers have been shown to be often useful in the treatment of social phobia.	☐	☐
	B) Moclobemide should be used as first line treatment for social anxiety disorder.	☐	☐
	C) Phobic symptoms respond best to exposure therapy to the feared situation or object.	☐	☐
	D) Cognitive behaviour therapy components such as systematic desensitisation, imaginal exposure, and in-vivo exposure are useful in the treatment of specific phobia.	☐	☐

Workgroup Members

The members of the workgroup, who were appointed in their personal professional capacity, are:

Chairman

A/Prof Leslie Lim
Senior Consultant
Department of Psychiatry
Singapore General Hospital

Members

Dr Chan Hong Ngee
Senior Principal Clinical Pharmacist
Singapore General Hospital

Dr Chua Sze Ming
Consultant
Department of Community Psychiatry
Institute of Mental Health

A/Prof Lee Tih Shih
Associate Professor
Duke-NUS Graduate Medical School

Dr Chew Peng Hoe
Medical Director
Aviation Medicine & Psychiatry
Parkway Health Primary Care Network (The Arcade)

Ms Carolyn Ho
Manager (Mental Health Policy)
Primary & Community Care
Ministry of Health

Dr Daniel Seow Khee
Senior Consultant
Department of Medicine
Ng Teng Fong General Hospital
Jurong Health Services

Ms Patricia Loh
Patient Representative

Dr Alvin Lum
Family Physician
Shenton Family Medical Clinic

Dr Tan Yong Hui, Colin
Family Physician, Consultant
Deputy Director
Clinical Services
National Healthcare Group Polyclinics

Dr Wan Yi Min
Associate Consultant
Department of Psychiatry
Ng Teng Fong General Hospital
Jurong Health Services

Members

A/Prof Matthew Woo
Principal Consultant Psychologist
Riverlife Psychology

Dr Yap Hwa Ling
Chief & Senior Consultant
Department of Psychological Medicine
Changi General Hospital

Acknowledgements

The workgroup is grateful for, and would like to acknowledge the contributions of the following independent reviewers, who have provided important comments on the draft of these guidelines:

Dr Helen Chen
Head & Senior Consultant
Department of Psychological Medicine
KK Women's and Children's Hospital

Mr Ng Boon Tat
Principal Pharmacist (Clinical)
Department of Pharmacy
Institute of Mental Health

The workgroup would also like to thank the following:

Subsidiary editors:

Dr Pwee Keng Ho
Consultant (Health Technology Assessment)
Performance & Technology Assessment Division
Ministry of Health

Mr Raymond Huang
Manager (Health Technology Assessment)
Performance & Technology Assessment Division
Ministry of Health

Dr Edwin Chan Shih-Yen
Head, Epidemiology
Singapore Clinical Research Institute
Assoc Professor, Duke-NUS Graduate Medical School, Singapore
Director, Singapore Branch, Australasian Cochrane Centre;
Head (Evidence-based Medicine)
Performance & Technology Assessment Division
Ministry of Health

These organisations have commented on and endorsed the guidelines (in alphabetical order):

Chapter of General Physicians, College of Physicians, Singapore
Chapter of Psychiatrists, Academy of Medicine, Singapore
College of Family Physicians, Singapore
Singapore Medical Association, Singapore
Singapore Psychiatric Association, Singapore