PART 2

The South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders

Edited by Robin Emsley and Soraya Seedat
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The South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders

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The South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders have been developed in order to address the local need for guidelines in our unique clinical setting. The need for treatment guidelines has frequently been expressed by South African psychiatrists and other medical practitioners, as well as by other role players such as medical scheme and other funding body advisors and the pharmaceutical industry. While several well-developed international treatment guidelines are readily accessible and are indeed extensively utilised in South Africa, they are not always applicable to our own circumstances. There are often important differences, not only regarding the availability of various psychotropic medications, but also in healthcare settings and availability of resources that need to be considered when selecting particular medications. For example, prescribing compounds that require regular monitoring such as lithium and clozapine may not always be feasible in certain rural settings in South Africa.

It is important to point out that these Guidelines do not aim to provide a comprehensive review of all the pertinent literature comprising the evidence base, and as such, should be utilised in conjunction with other guidelines that do provide that kind of information. We advise readers to use these and other guidelines with a great deal of caution. Prescribing medication for psychiatric disorders comprises a major component of psychiatrists’, and indeed general practitioners’ function. It is therefore necessary for practitioners to maintain a high level of knowledge and expertise in clinical psychopharmacology, and to keep up-to-date with the ever-evolving ‘evidence base’. However, it needs to be remembered that the evidence base in psychiatry is often difficult to interpret. Results of clinical trials are frequently difficult to generalise to clinical practice, and are often inconclusive, inconsistent or even conflicting. Methodological differences in aspects such as selection of patient samples, dosage and duration of treatment administered and outcome measures all make it difficult to interpret findings across studies. This means that ‘the evidence’ may be interpreted in different ways and there is a real risk that it can be selectively applied to support a particular point of view. This has been a point of criticism against the use of guidelines and evidence-based practice in psychiatry. At the end of the day it behoves practitioners to maintain an open and flexible mind, and most of all to apply sound clinical judgement and common sense when interpreting the available evidence.

These Guidelines do not cover all of the psychiatric disorders at this stage, although most of the important ones are covered. We envisage an ongoing process of updating and expanding the Guidelines regularly, as new drugs are introduced and as healthcare settings evolve. The chapters comprise a collection of systematically developed chapters in standardised format that attempt to provide evidence-based recommendations for assessment and treatment of common psychiatric disorders. The aim is to provide guidelines that are of assistance to psychiatrists and other medical practitioners in clinical decision making. It is hoped that policy makers and administrators will also make use of them.

These SASOP Guidelines refer to the current private healthcare setting in South Africa. There are two important considerations here. First, the pending introduction of a National Health Insurance (NHI) in South Africa is likely to have an impact on the Guidelines. However, at present no details of the NHI are available and it has not been possible to take this into account in the current version. Second, a majority of the people in South Africa currently receive healthcare in the public sector and do not have access to many of the medications referred to in the SASOP Guidelines. This is clearly a shortcoming and an issue that needs to be addressed if the NHI is not going to be introduced in the near future. Nevertheless, we hope that the SASOP Guidelines will have some application in the public healthcare sector, and particularly that they may assist decision makers determine the most appropriate and cost-effective treatments in the public sector.
**The process.** In 2009 the SASOP National Executive appointed Prof Robin Emsley to chair a Task-Team to develop the Guidelines. A team of experts was selected and several teleconference meetings were held. The experts were identified, based on both their academic and clinical experience, and they were invited to write one or two chapters. The authors were requested to write their chapters according to the following brief:

- The Guidelines should be specific to South Africa.
- We should aim at what is appropriate in a private practice setting – and what is realistic given our budgetary constraints.
- As far as possible decisions should be evidence-based, and key references should be provided.
- The Guidelines should be clear, concise and user-friendly.
- Authors were encouraged to use the following documents as a point of departure:
  - The partly developed previous SASOP Guidelines, which were available on the SASOP website.

Each of the chapters was subjected to anonymous peer review by at least two reviewers, together with editorial review. Chapter drafts were revised according to these reviews. Finally, the chapters were edited and formatted according to a uniform style. These draft Guidelines were posted on the SASOP website (http://www.sasop.co.za/) and comment was invited. Finally, a SASOP workshop with national representation from both state-employed and private psychiatrists was held in George in April 2013 to finalise the document.


**Conflict of interest disclosures**

Prof. Emsley reports receiving research funding from Janssen, Lundbeck, and AstraZeneca, participating in speakers/advisory boards, and receiving honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, Organon, Pfizer, Servier, Otsuka, and Wyeth.

Dr Colin reports lecturing in continuing medical education programmes of Eli Lilly, Lundbeck, BMS, Janssen, GSK, Cipla, Pfizer, Servier, and AstraZeneca and serving on advisory boards for Janssen, Lundbeck, Lilly, Servier, Cipla, and AstraZeneca. He has also received sponsorships from many pharmaceutical companies for attendance of overseas and local congresses.

Dr Grobler reports attending a Lilly Advisory Board meeting.

Drs Hawkriddle and Potocnik declare no conflict of interest.

Prof. Seedat reports receiving research grants from Lundbeck, GlaxoSmithKline, and Astra-Zeneca and speaking for Pfizer, Servier, Dr. Reddy’s, Sanofi-Aventis and Lilly.

Prof. Stein reports receiving research grants and/or consultancy honoraria from Abbott, AstraZeneca, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikvah and Wyeth.

Dr Swingler reports receiving speaker and consultation fees from Servier and GlaxoSmithKline and speaker fees for Janssen and Lundbeck.

Prof. Szabo reports receiving speaker fees from Lilly, Sanofi, and AspenGSK for continuing professional development meetings that were not product related and participating in advisory board matters for Servier and Lilly.

It is recommended that the guidelines for bipolar disorder and major depressive disorder be considered in conjunction with the annexures for these guidelines (‘The management of psychiatric disorders; evidence-based and consensus treatment guidelines (including protocols and algorithms) for major depression and bipolar disorder; practice guideline for the private sector; Psychiatry Management Group (PsychMg)) that will be posted on the SASOP website (www.sasop.co.za).

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Prof. Dan Stein kindly provided permission for us to make liberal use of the publication ‘Standard treatment guidelines for common mental health conditions’ 2nd edition. South African Psychiatry Review 2007;0(2):106-119) for several of the chapters.

Dr Karen Cloete provided extensive editorial assistance.

Permission to reproduce various Tables, Figures and text was obtained and these acknowledgements are included in the text.
Attention deficit hyperactivity disorder in children and adolescents

A J Flisher, S Hawkridge

1. Introduction
Attention deficit hyperactivity disorder (ADHD), although commonest in childhood and adolescence, can be diagnosed across the age span. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)\(^1\) defines the disorder using the core features of hyperactivity, impulsivity and/or inattention which are inappropriate for developmental stage.

The major aetiological influence for ADHD is genetic, which accounts for 80% of the variability of the disorder.\(^2,3,4\) However, the environment and environment-gene interactions are also significant. Examples of social factors associated with ADHD are low socioeconomic status, low parental education, family conflict and non-intact nuclear families, parental mental disorder, substance abuse, criminality, punitive parenting, severe early deprivation and institutional upbringing.\(^5\) Examples of pre-, peri- and postnatal environmental insults that are associated with ADHD include low birth weight, maternal prenatal smoking, stimulant and alcohol use, obstetric complications, head injury, epilepsy, HIV/AIDS, iron and zinc deficiency, lead exposure, and early and increased television exposure.\(^6\)

The treatment guidelines that follow draw on and are broadly compatible with the following documents, which should be consulted for further information:

- Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit Hyperactivity Disorder of the American Academy of Child and Adolescent Psychiatry\(^3\)
- Treatment guidelines of the National Institute for Health and Clinical Excellence (NICE) on methylphenidate, atomoxetine and dexamphetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents\(^6\)
- European Guidelines for hyperkinetic disorder\(^7,8\)
- Flisher et al.\(^9\) ‘Packages of care for attention deficit hyperactivity disorder in low- and middle-income countries’.

2. Diagnosis and clinical characteristics
2.1 Screening
Screening for ADHD should be included in the psychiatric assessment of every patient, regardless of the main complaint. Questions about the core symptoms of ADHD should be asked to assess whether a diagnosis of ADHD is possibly applicable. If it is, then a complete assessment should be performed. The diagnosis is not appropriate if the symptoms occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or another psychotic disorder, or are better accounted for by another psychiatric disorder. The diagnosis is also inappropriate if the symptoms are better accounted for by a substance use disorder (e.g. intoxication) or a general medical condition such as allergic conditions, sensory deficits, chronic infections, etc. Collateral information is essential, particularly with regard to performance at school.

There are two types of instrument available to detect (and diagnose) ADHD: clinical diagnostic interviews and rating scales. The Diagnostic Interview Schedule for Children (DISC-IV) has been assessed for use in South Africa.\(^10,11\) No specific rating scales for ADHD have been assessed in South Africa, but the Conner’s Parent Rating Scale - Revised (CPRS-R) and the Conner’s Teacher Rating Scale - Revised (CTRS-R)\(^11\) are often used. However, the AD/HD Rating Scale-IV\(^12\) may be a better choice since the symptoms correspond directly to those in DSM-IV-TR.

2.2 Evaluation
Evaluation of the child or adolescent for ADHD should consist of clinical interviews with the caregiver and patient, obtaining information about the patient’s school or day-care functioning, evaluation for comorbid psychiatric disorders, and review of the patient’s medical, developmental, social and family history.

Clinical observation of the patient should occur more than once and if possible in more than one setting. School visits are recommended if there is a discrepancy between reports from home and school or if there is uncertainty about the diagnosis. If possible, school observations should be carried out by a clinician other than those known to the child.

An important initial step is to determine whether the child or adolescent fulfils the criteria for the diagnosis. This involves establishing whether each of the 18 symptoms is present; confirming that at least 6 of the inattentive or at least 6 of the hyperactivity/impulsivity cluster are present more days than not; that there is a chronic course; that onset was before the age of 7 years; and that the symptoms are associated with functional impairment. There is a significant risk of misdiagnosing other psychiatric disorders as ADHD, particularly anxiety disorders, and it is important to explore the child’s emotional symptoms (e.g. worry, anxiety, beliefs, somatic symptoms, etc.). Oppositional defiant disorder can also be misdiagnosed as ADHD, because of some overlap of symptoms.

It is equally necessary to establish whether comorbid disorders are present, the most common of which are oppositional defiant disorder and conduct disorder. Other important comorbid disorders include intellectual disability, depression, mania, anxiety disorders, tic disorders, substance abuse, and specific learning disability. In some cases symptoms of inattention and hyperactivity may be attributable to another disorder, and not ADHD. In other cases, a child may suffer from symptoms that do meet criteria for a disorder and are a direct consequence of ADHD. For example, a child may become depressed owing to social isolation or academic difficulties that are caused by ADHD. Finally, a child may satisfy the criteria for ADHD as well as...
another disorder. In such cases, treatment may be necessary for both disorders.

It is generally helpful to use a symptom scale, which can be completed by the clinician, teacher and parent, although a diagnosis should never be made only on the basis of such a scale. However, extreme scores should raise the index of suspicion. The main use of symptom scales is to monitor response to treatment.

It is important to assess the patient’s family, as untreated ADHD in family members is a common finding. Providing treatment for family members can often have collateral benefits for the child or adolescent who has been referred. Children or adolescents with ADHD function better in structured environments, and an unstructured environment may be the result of parental ADHD.

2.3 Clinical presentation
A thorough mental status and physical examination of the patient is mandatory, during which particular care should be taken to assess whether other psychiatric disorders are present. It is important to note that at the first session, hyperactivity may not be particularly evident as the child may initially be inhibited or making an extra effort to behave well for the occasion, so it is useful to see the child more than once before making a diagnosis of ADHD. Girls in particular may present with predominantly inattentive symptoms and this may not be obvious in the consulting room unless specifically sought.

3. Assessment

3.1 Laboratory or neurological testing
If there is a medical disorder that can account for the symptoms of ADHD, this will almost always be evident from the history and physical examination. Examples of such disorders include brain injury, hyperthyroidism, encephalopathies, lead poisoning and fetal alcohol syndrome. In the absence of any specific indications for such pathology, laboratory or neurological testing is not indicated. However, there is a significant comorbidity of epilepsy with ADHD, and a high index of suspicion should be maintained, bearing in mind that a normal electroencephalogram (EEG) is not necessarily proof of the absence of a seizure disorder, and an evaluation by a neurologist may be helpful.

3.2 Psychometric testing
Psycological and neuropsychological tests are not diagnostic for ADHD, but should be performed if the patient's history suggests low general cognitive ability or low achievement in language or mathematics relative to the patient's intellectual ability. It is common for those with ADHD to perform poorly on testing owing to poor concentration and impulsivity. This should be taken into account when interpreting results, and results should be regarded as conclusive only once the child is being successfully treated for ADHD.

It is not uncommon for children and adolescents with ADHD to have evidence of poor educational attainment. The clinician needs to assess whether the low level of educational attainment is entirely due to the ADHD; whether the symptoms attributable to ADHD are in fact the result of other learning or language problems; or whether ADHD and other problems are both present. In the South African context, tests or norms may not be available for all language and cultural groups, and interpretation of the findings should take this into account.

4. Treatment

4.1 Treatment goals
The aim of treating ADHD is to optimise the child’s cognitive, social and emotional functioning so as to prevent the development of secondary emotional distress or psychiatric disorders, and allow the child to reach his/her full developmental potential. Symptoms of inattentiveness and hyperactivity/impulsivity should be targeted, but the child’s overall functioning, including family and social relationships, leisure activities and self-esteem must also receive attention.

4.2 General aspects of treatment
It is important to develop a treatment plan once the diagnosis has been established. This plan can be changed in the light of responses to treatment options, the emergence of other issues that need to be addressed and changing family circumstances. The treatment plan should always include psycho-education of the patient and their caregivers and educators. It should include information about ADHD, helping parents and teachers to anticipate developmental challenges that are difficult for children and adolescents with ADHD, and general advice to improve the child’s academic, social and behavioural functioning.

4.3 Acute treatment
In recent years, much research attention has been focused on the relative indications for various forms of management, from which a considerable degree of consensus has emerged. Based on the existing guidelines, we propose that behavioural treatments may be applicable as first-line treatment if:
- The ADHD is mild or (perhaps) moderate, with minimal impairment
- The diagnosis is uncertain
- The parents (or patient) reject medication as a treatment option
- There is disagreement between key stakeholders about the diagnosis
- There are no comorbid diagnoses or significant life stressors
- An urgent response is not required.

However, if the patient’s response to behavioural interventions is suboptimal, in that there is still significant impairment, relationships are still affected, or development is held back, then a trial of medication should be instituted. For severe cases, or where the above circumstances do not pertain, a trial of medication is appropriate as a first line of intervention.

Further steps following the initiation of treatment are indicated in the algorithm (Fig. 1).

Comorbid psychiatric conditions should be independently addressed by an appropriate child and adolescent mental health professional.

4.4 Maintenance treatment
Children who are taking stimulant medication require monthly prescriptions (repeat prescriptions are not permitted for Schedule 6 drugs) and at least 6-monthly reviews by a psychiatrist. At each review the following should be recorded:
• Weight and height (recorded on a percentile chart)
• Reported adverse effects
• Efficacy (school and parent reports)
• Pulse rate and blood pressure.

Significant deviation from the child’s usual percentile in terms of weight or height should provoke a review of dosage as well as the institution of a ‘drug holiday’ of at least 4 weeks, preferably during school holidays, so that catch-up growth can occur. Should this not happen, alternative medication or non-pharmacological treatment should be considered. Should failure to gain weight continue, consultation with a paediatrician should be requested.

Adverse effects include headaches and gastric discomfort. These may be transitory, but if they persist, dose reduction should be implemented. If this does not relieve the adverse effects, or if the ADHD symptoms again become troublesome, then a change of medication should be considered.

If efficacy is reduced, an increased dose may be required according to the child’s increasing weight. If this is already optimal or does not improve the situation, examination for developing comorbid conditions (especially mood disorders or substance use disorders) should be carried out.

Abnormalities of pulse rate and/or blood pressure should be retested 10 minutes later and if persistent, stimulant medication should be withdrawn. Should the abnormal cardiovascular parameters persist without medication, a referral to a paediatrician or physician is mandatory. If there is a return to normal parameters, then alternative medication or non-pharmacological treatments should be instituted.

If a patient with ADHD has been symptom-free for at least 1 year, the clinician may consider stopping the medication. Clues that this may be appropriate include: not needing to adjust the dose despite an increase in growth; the lack of obvious symptoms when a dose is accidentally omitted; and observations of adequate concentration during drug holidays. Medication can be tapered or stopped at a time when stressors are absent or minimal, and once the school term is under way. It is important to obtain feedback from the patient, the parents and the educators about the effect of this change. If symptoms recur, it is necessary to reinstitute treatment immediately.

4.5 Pharmacological treatment
Pharmacotherapy of ADHD with psychostimulants is one of the best established and most consistently demonstrated effective treatments in psychiatric medicine. There is consistent evidence of effect in domains such as symptomatic improvement; enhanced cognitive, social, family and academic functioning; and improvement of non-diagnostic symptoms frequently associated with the condition such as irritability, aggressive outbursts and difficulties with fine motor co-ordination.[13-16] Significant and clinically substantial effect sizes (0.8 – 1.1) of methylphenidate have been reported from analyses of clinical studies.[8] Results from the most comprehensive study of ADHD treatment (the Multimodal Treatment Study of Children with ADHD (MTA)) strongly support the use of methylphenidate as a treatment for young people (school age into adolescence).[17]

Dosing should be started as low as possible (usually 5 - 10 mg) in a morning dose of a short-acting formulation. The effect of short-acting methylphenidate lasts approximately 3 hours, and the teacher should be able to give a report as to the efficacy in the first few hours of school. Should this be ineffective, an increased dose (10 - 20 mg) should be
considered. Initial dosing should not exceed 1 mg/kg/day. If a response is obtained, the dose can be repeated at about 11h00, and the outcome documented. Conversion to a long-acting formulation should then be considered. Should insufficient response to an optimal dose be seen, the protocol for partial and non-responders should be followed. Doses greater than 1 mg/kg/day may occasionally be necessary, but should only be considered in consultation with a child and adolescent psychiatrist.

The preferred formulation of methylphenidate is long-acting and removes the necessity for mid-morning doses, which are potentially embarrassing for the child and have become difficult owing to the paucity of school-based medical services and legislation prohibiting the possession or dispensing of scheduled medication by unqualified individuals. Long-acting formulations have the additional benefit of maintaining blood levels of methylphenidate, giving more even efficacy. Adverse effects tend to be less troublesome, and adherence to medication is enhanced. Additional doses of short-acting formulation may be required for specific times of the day, either before the morning dose of long-acting formulation takes effect or to cover a possible afternoon period of rebound hyperactivity as the effect wears off.

Adverse effects of methylphenidate include headache, insomnia, gastric discomfort and decreased appetite (with concomitant weight loss or failure to gain weight appropriately). Anxiety and depression may be worsened by methylphenidate, prompting many clinicians to choose alternative medications for children with comorbid anxiety or mood disorders. Methylphenidate carries a Food and Drug Administration black box warning in respect of a slightly increased danger of sudden death. A family history of cardiovascular disease or sudden death, or an individual history of unexplained fainting or cardiovascular disorders, should cause the treating physician to refer the child to a cardiologist for an opinion before instituting psychostimulant therapy. In the absence of these risk factors, a baseline electrocardiograph is not regarded as mandatory by most authorities.

Children and adolescents with tic disorders may experience worsening of tics on methylphenidate. Some will consider the advantage of their improved school functioning worth the increase in tics; others should be offered other treatment options. Patients with mania or psychosis should not be given methylphenidate. Methylphenidate has been shown to protect against substance use disorders, but for patients with comorbid substance use disorders, alternative medications should be considered, although physical dependence is not a documented risk.

Other medications have also demonstrated positive therapeutic effects in ADHD across the life span, from primary school age to adulthood. The most intensively studied of these is atomoxetine, a noradrenergic reuptake inhibitor. Even though treatment effect sizes are less than for methylphenidate, it can be considered the agent of first choice for patients with an active substance abuse problem, comorbid anxiety, or tics; or if the patient experiences intolerable side-effects to methylphenidate, or if the patient (or caregiver) prefers this agent. Dosing of atomoxetine starts at 0.5 mg/kg/day and can be titrated upwards at minimum 3-day intervals to 1.2 mg/kg/day. Adverse effects tend to be mild but severe liver damage can occur, and cardiovascular monitoring should be routine. Atomoxetine has been included in the group of drugs potentially causing an increase in suicidality in children and adolescents, so informed consent and appropriate psycho-education of patient and caregivers is mandatory.

Less evidence exists for the tricyclic antidepressants (desipramine and imipramine), bupropion and clonidine. These medications may be considered to be second-line pharmacotherapy alternatives because of the proportionally smaller research data base, shorter timeline of clinical experience, a potentially greater frequency of medically significant side-effects and greater expense compared with methylphenidate.

4.6 Non-pharmacological treatment

Behavioural programmes are the first line of treatment in very young children, and in those whose difficulties are mild and where immediate relief is not required. Such programmes can be delivered by non-medical personnel such as mental health nurses or psychologists, provided adequate training has been done. Parent support groups for ADHD may be helpful in the sourcing of such resources.

The successful behavioural programmes consist of between 10 and 20 sessions of 1 - 2 hours each in which parents are given information about the nature of ADHD and learn to:

- Attend more carefully to their child’s behaviour and to notice when their child does or does not comply with requests
- Understand the principles and implementation of behaviour management
- Use time out effectively
- Use a daily school report card
- Anticipate future difficulties.

A systematic literature review and a meta-analysis investigating ADHD treatment studies concluded that behavioural treatment is highly effective.

4.8 Special populations

Data from preschool-age populations are sparse, but those available support use of psychostimulants for the treatment of ADHD with the caveat that psychosocial modalities, especially parent training, should be the initial interventions of first choice. Should consideration be given to treating a preschool child with a stimulant drug, consultation with a child and adolescent psychiatrist should be obtained where possible.

The treatment of adolescents with ADHD is the same as that for children, but special attention must be given to the developmental trajectory of adolescents. Increasing weight will usually require an increased dose. Sporting activities at a high level (where drug testing is carried out) may require a switch to non-stimulant medication, and social changes make it imperative that substance use disorders should be specifically asked about and managed appropriately. Some adolescents may find themselves in a tertiary education environment and others may be in the workplace before they turn 18. These individuals should be managed as adults. Symptoms persist into adulthood in at least one-third of children with ADHD, and ADHD is increasingly diagnosed in adults. Diagnostic criteria and management are modified for the different environment and obligations of adults, and separate guidelines are required.

4.7 Managing partial and non-responders

Partial response may be dose-related, or there may be undiagnosed comorbid conditions which are limiting response. Should there be no
response to therapeutic doses of pharmacological treatment or parent training/behavioural programmes, the diagnosis should be reviewed. Pervasive developmental disorders, mood disorders and anxiety disorders are frequently misdiagnosed as ADHD, and require very different management. An evaluation by, or at least consultation with, a child and adolescent psychiatrist should be obtained.

In ADHD with severe behavioural difficulties, atypical antipsychotic drugs are sometimes prescribed for impulsive aggression or temper outbursts. This should not be done without a complete review of the family and school environments, possible stressors, adequate psychosocial intervention and a clear risk-benefit evaluation of the potential adverse effects of the drug considered. The involvement of child mental health professionals is advised prior to such a step being taken.

5. Summary points

- The most important aspect of treating ADHD is an accurate diagnosis. Making the incorrect diagnosis may render treatment futile or even harmful.
- In mild to moderate ADHD, first-line treatment is a behavioural programme with or without pharmacological modalities.
- In moderate to severe ADHD, first-line treatment is a pharmacological agent plus a behavioural programme.
- Family education and intervention where necessary is mandatory.

References


Dementia

F C V Potocnik

1. Introduction
By definition, dementia is an acquired global impairment in memory, personality and intellect in an alert patient, that is sufficiently severe to interfere with social and/or occupational functioning. In the absence of a stroke or rapidly growing cerebral tumours (among other causes), the onset is usually gradual and the cognitive decline is always progressive. In the absence of a cure for the disease, non-pharmacological inventions and the judicious use of pharmacotherapy may not only help the patient and alleviate the stress on the caregiver, but can also help in delaying institutionalisation.

1.1 Prevalence and burden of disease
The worldwide prevalence of dementia currently approximates 35.6 million people, a figure set to rise to 65.7 million by 2030 and (by doubling every 20 years) to 115.4 million by 2050. Nearly two-thirds of individuals with dementia live in developing countries, where the sharpest increase in numbers is said to occur. The prevalence of dementia is approximately 5 - 7% of the elderly population. Starting at 1% for 60-year-olds, the prevalence doubles every 5.1 years, rising to some 30 - 45% of those aged 85 and older[2,3] in developed countries, while doubling every 7 years in developing countries.[4] Among the South African elderly an estimate would place the number of dementia sufferers at 250 000, with some 35 000 of these suffering from Alzheimer’s disease (AD).

Twenty per cent of AD patients are alive after a 15-year period, the mean duration of illness being some 10 - 12 years.[5] Of the people with late-onset (65 years and older) dementia in developed countries, more than half have AD, some 15% have vascular dementia (VaD), and the remaining 30%, a variety of some 60 other forms of dementia. [6] Many cases of AD exhibit a confluence with cerebrovascular disease (CvD). The total worldwide societal cost of dementia was estimated at US$422 billion in 2009, which included US$142 billion (34%) for informal care. Americans estimate that dementia costs them some US$100 billion per year,[11] and yet a delay in the onset of AD by only 5 years would halve the prevalence of the disease, resulting in enormous savings of human misery and cost to society.[1,3] In all cases there are profound psychosocial effects on the caregiver, in whom the rates of depression, substance abuse, hospitalisation and physical illness are all increased.[9]

1.2 Causes and types of dementia
In the South African population, dementia due to the HIV/AIDS complex (affecting mainly the younger age group) is the most common. Among the elderly the most prevalent is VaD, followed by AD, which is on the increase.[7]

1.2.1 Alzheimer’s disease
The neuropathological hallmarks of AD are amyloid plaques, neurofibrillary tangles, and synaptic and neuronal loss with subsequent brain atrophy. Macroscopically, and with neuro-imaging (magnetic resonance imaging (MRI) and computed tomography (CT) scan), this demonstrates as flattening of gyri, widening of sulci, atrophied medial temporal lobes and enlarged ventricles. Pathology at microvascular level has increasingly been implicated in the aetiology of AD, blurring the boundaries with VaD in many cases. AD and possibly most other dementias tend to follow a sinusoidal course in that the initial slow, progressive deterioration accelerates rapidly before flattening out towards the end – in keeping with the 3 stages of mild, moderate and severe.[9]

The duration of illness may be as short as 6 months or as long as 20 years, with an average of 12 years. Neurochemically there are deficits in neurotransmitters including acetylcholine, noradrenaline, serotonin, and somatostatin. Specific mutations on chromosomes 21, 14 and 1, inherited as familial autosomal dominant traits with full penetrance, are found in some 1% of all AD patients. Here the illness usually presents itself in the 40s or early 50s and is essentially ‘pre-senile’ in onset (i.e. before the age of 65 years). More than 90% of cases of AD occur in individuals older than 60 years. Individuals carrying one or both alleles coding for apolipoprotein E-4 (APOE4) on chromosome 19 bear an elevated risk for late-onset AD, although this gene is not itself a cause of the disorder.[11] Fig. 1 represents the course of AD.

1.2.2 Vascular dementia – with or without stroke
Among the VaDs, multi-infarct dementia associated with multiple areas of cortical infarction, patchy cognitive impairment, focal neurological signs and a ‘step-wise’ rather than a steady, continuous deterioration as in AD is more easily diagnosed than dementia due to vascular damage of the deep white matter.

After each shower of ‘mini strokes’, which produce a sudden deterioration in the individual’s functioning, there is a partial recovery which stabilises within approximately 3 - 12 weeks until the next stroke or ‘step’ occurs several weeks or months later. It is hypothesised that in both vascular and alcohol-induced dementias, temporary vascular spams may result in intermittent or fluctuating intellectual

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**Fig. 1. Course of Alzheimer’s disease (with/out memory enhancer).**[^10]
and personality changes, with unpredictable bouts of irritability and mood swings. In all types of VaDs the risk factors for stroke such as hypertension, arrhythmias, hypercholesterolaemia, diabetes, smoking and alcohol need to be assessed. Fig. 2 represents the course of multi-infarct dementia compared to AD.

1.2.3 Combination of Alzheimer’s disease and vascular dementia
This is referred to as AD with CvD.

1.2.4 Dementia with Lewy bodies
Dementia with Lewy bodies usually exhibits as fluctuations in cognition (mimicking a sub-acute delirium) with pronounced variations in attention and alertness, recurrent well-formed visual hallucinations (especially sun-downing), and motor features of Parkinsonism. The course of the illness tends to be rapidly progressive, interspersed with repeated falls, syncope, transient loss of consciousness, other hallucinations and congruent delusions. These patients tend to be sensitive to the side-effects of neuroleptic agents (requiring utilisation of drugs like clozapine or newer neuroleptic agents). They may be responsive to cholinesterase inhibitors.

1.2.5 Pick’s disease and frontotemporal dementia
Pick’s disease (PD) is a progressive dementia that chiefly affects the frontal cortex. PD most commonly manifests between the ages of 50 and 60 years and is distinguished from frontotemporal dementia by the presence of characteristic intraneuronal argentophilic Pick inclusion bodies found at autopsy. Patients present with prominent personality changes and impaired executive function. In frontotemporal dementia diagnostic criteria range across 4 domains:
1. Behavioural disorder: insidious onset and slow progression; early loss of personal and social awareness; early signs of disinhibition; mental rigidity and inflexibility; and hyperorality, stereotyped and perseverative behaviour.

Fig. 2. Course of (a) Alzheimer’s disease and (b) vascular dementia.

2. Affective symptoms: depression and anxiety; somatic preoccupation; emotional unconcern.
4. Physical signs: early primitive reflexes and incontinence; late akinesia, rigidity and tremor.

1.2.6 Substance-induced persisting dementia
Paramount are deep white-matter changes blurred with alcohol-induced vasculopathy, clinically often indistinguishable from VaDs and with the same risk factors as precipitating and perpetuating causes. Note that both vascular and alcohol-induced dementia patients have relatively well-preserved personalities, compared to the degree of dementia present. Their excellent social skills or verbal ability may be misleading unless one screens for dementia using the Mini Mental State Examination (MMSE).

1.2.7 Huntington’s disease
Huntington’s disease is an inherited disease (autosomal dominant gene on chromosome 4) characterised by degeneration of the basal ganglia and cerebral cortex. Age of onset is between 15 and 50 years, when choreiform movements and progressive dementia are noted. The dementia initially presents as a sub-cortical dementia before affecting the cortex as the illness progresses. No cure is currently available and death results within 15 - 20 years. Psychiatric disorders, especially depression, may be the presenting feature.

1.2.8 Parkinson’s disease
The primary features are tremor, muscular rigidity, hypokinesia and postural abnormality. Although a movement disorder, cognitive impairment occurs in 10 - 40% of patients during the course of the disease, known as Parkinson’s disease dementia.

1.2.9 Creutzfeldt-Jakob’s disease
Creutzfeldt-Jakob’s disease is brought about by a virus-like infective agent called a prion. It causes a rapid progressive dementia also affecting the pyramidal and extrapyramidal systems. A new variant of Creutzfeldt-Jakob’s disease, described in England in 1995, appears to express itself under certain conditions in individuals under the age of 40 years, leading to death within a year. This variant is associated with bovine spongiform encephalopathy or ‘mad cow disease’.

1.2.10 Dementia associated with normal pressure hydrocephalus
Normal pressure hydrocephalus occurs in the elderly and is characterised by a triad of ataxia (wide-based, shuffling gait), urinary incontinence and dementia. CT scans of the brain show prominent enlargement of the ventricles out of keeping with the widening of the sulci. Ventricular peritoneal shunts may improve cognitive functions in 10 - 30% of patients. Usually a demented person only becomes incontinent on attaining an MMSE score of 8 - 10/30.

1.2.11 Dementia secondary to head injury
This is lesion-location- and severity-specific, and diagnosed and treated accordingly. It may manifest with 2 distinct symptom clusters, namely cognitive impairment (i.e. decreased information processing speed, decreased attention, increased distractibility) and behavioural
disturbances. The behavioural disturbances may involve personality changes, impulsivity and depression, all of which can be exacerbated by substance misuse.

1.2.12 AIDS dementia complex/HIV dementia
HIV infection currently affects 5 million people in South Africa and is set to reach a steady state of 32% within less than a decade. The course of the illness may vary considerably but in general the patient converts to AIDS after 9 years of illness and dies a year later from systemic complications. Nearly 90% of AIDS brains are histopathologically abnormal, more than half of them uniquely due to HIV infection. Referred to as the AIDS dementia complex, this condition contributes significantly to the morbidity of HIV patients, causing varying degrees of cognitive, motor or behavioural impairment, known as HIV-associated neurocognitive disorders (HAND).

1.2.13 Other less common causes of dementia
• Endocrine states (hypo- or hyperthyroidism, hyperparathyroidism)
• Deficiency states (B complex vitamins)
• Intracranial space-occupying lesions (subdural haematomas, tumours)
• Post-irradiation dementia
• Demyelinating disorders
• Neurosyphilis

2. Diagnosis, clinical characteristics and course
The diagnostic criteria for AD are outlined in Table 1.[11] Clinical features include the following:
• Memory impairment: Poor memory must interfere with daily functioning. Initially, short-term memory is affected, with the later involvement of long-term memory.
• Personality and behavioural changes: Emotions are shallow and easily influenced by environmental factors; irritability and bouts of anger are common. Usually premorbid traits become more accentuated. There is a loss of initiative and the person becomes increasingly apathetic and withdrawn. Emotional blunting ensues, and may be mistaken for depression.
• Intellectual impairment: Thinking becomes more concrete. There are word-finding and other language difficulties (dysphasia), the person may no longer recognise familiar faces or objects (agnosia) and may be unable to carry out simple manual tasks such as fixing a plug or dressing themselves (apraxia). A key feature is the instrumental impairment of activities of daily living (e.g. ability to use telephone, shop, handle finances).
• Physical changes: As the disease progresses, the patient appears unduly frail and weak, is stooped in posture with slow, shuffling gait and mild tremor of the hands. There is weight loss, regardless of appetite, increasing bouts of restlessness and confusion, and reduced sphincter control.

2.1 Course
This may give an indication of aetiology. Patients with vascular (especially multi-infarct) dementia and to some extent alcohol-induced dementia will present with patchy memory loss and fluctuating disturbances in language and behaviour with a relatively well-preserved personality in the earlier phases, characterised by appropriate social interaction.
• A step-wise deterioration rather than a steady even pattern
• A more abrupt deterioration rather than slow, insidious onset
• Attacks of dizziness, frequent falls and fainting spells, nocturnal confusion
• Bouts of urinary urgency, particularly at night.

Table 1. Diagnostic criteria for dementia of the Alzheimer’s type[11]*

| A. The development of multiple cognitive deficits manifested by both: |
| 1. Memory impairment (impaired ability to learn new information or to recall previously learned information) |
| 2. One (or more) of the following cognitive disturbances: |
| a. aphasia (language disturbance) |
| b. apraxia (impaired ability to carry out motor activities despite intact motor function) |
| c. agnosia (failure to recognise or identify objects despite intact sensory function) |
| d. disturbance in executive functioning (i.e., planning, organising, sequencing, abstracting) |

| B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning. |
| C. The course is characterised by gradual onset and continuing cognitive decline. |
| D. The cognitive deficits in criteria A1 and A2 are not due to any of the following: |
| 1. Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g. cerebrovascular disease, Parkinson’s disease, Huntington’s disease, subdural hematoma, normal-pressure hydrocephalus, brain tumour) |
| 2. Systemic conditions that are known to cause dementia (e.g. hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcaemia, neurosyphilis, HIV infection) |
| 3. Substance-induced conditions |
| E. The deficits do not occur exclusively during the course of a delirium. |
| F. The disturbance is not better accounted for by another Axis I disorder (e.g. major depressive disorder, schizophrenia). |

3. Assessment and differential diagnosis

3.1 Mild cognitive impairment

Of note is that up to one-quarter of elderly present as ‘dodderly’, falling into the realm of mild cognitive impairment (MCI), also known as age-associated cognitive decline. Here the MMSE score is around 27/30. Cognitive function is not impaired to the point where it interferes significantly with daily social or occupational functioning, but may well do so over the next 2 - 5 years, when an estimated 30% of this category are known to go on to exhibit dementia. These patients need to be re-evaluated at regular intervals.

3.2 Depression and delirium

At this stage of diagnostic screening dementia must be distinguished from depression (primarily a mood disorder with very little disturbance in cognition), and delirium (a transient organic disorder hallmarked by a global cognitive impairment as well as disturbance in consciousness and attention/concentration deficit). In addition there is a reversal of the sleep-wake cycle. In the elderly, depression and delirium may frequently coexist with AD or herald its presence, and both require management in their own right. Delirium constitutes a medical emergency. Good collateral information from a reliable family member, friend or caregiver is crucial. A detailed history and thorough physical examination including blood (‘organic work-up’) and urine tests not only distinguish AD from depression and delirium, but also help to differentiate AD from other types of dementia. A review of all current prescribed medications and over-the-counter preparations, with particular emphasis on those impacting on central nervous system functions, is essential.

3.3 Assessment of neuropsychiatric symptoms

This is discussed below.

3.3.1 Cognitive assessment: the Mini Mental State Examination

Ascertain the degree of cognitive impairment by administering the MMSE,[13] which was designed to distinguish dementia from depressive pseudodementia. While one or two mistakes are allowed, the nature of these mistakes is of importance (e.g. an accountant failing to do the serial sevens). An MMSE score of 27 generally indicates MCI. In mild AD (MMSE range 21 - 26) there is short-term memory impairment, often accompanied by symptoms of anxiety and depression. Moderate AD (MMSE range 11 - 20) is characterised by neuropsychiatric phenomena such as visual hallucinations, false beliefs, restlessness and disturbed sleep patterns. Severe AD (MMSE range 0 - 10) is characterised by prominent cognitive decline, motor signs and the onset of loss of sphincter control.

While depressed patients will still obtain a high MMSE score, an MMSE score of 26 or less out of 30 is strongly indicative of dementia, where the patient has had at least 7 years of schooling. AD patients lose on average some 2 - 3 points on the MMSE per year, and progress can thus be tracked by re-administration of the test at 3 - 6-monthly intervals. There is no time limit for the completion of the test.

Note that a person with dementia may achieve an MMSE score of 30 out of 30 with some difficulty, while still holding a high position in working life. This function is support-staff dependent.

3.3.2 Functional assessment: activities of daily living

Cognition and behaviour also impact on the patient’s level of function.[15] This determines whether patients can still perform more complicated tasks such as taking their medication, difficult household chores, shopping, cooking and finances (instrumental activities of daily living (IADL)) or only wash, dress, feed and toilet themselves (basic activities of daily living (BADL)).[16] The watershed between IADL and BADL usually occurs at an MMSE of 16 out of 30,[16] while urinary incontinence occurs at a score of around 8.

3.3.2.1 Driving

Driving a car relies on implicit memory, praxis and executive functioning. In the early stages of the illness patients can still drive a car because these abilities are still relatively intact. With time, however, they are unable to pay attention to all aspects of driving and often become impulsive or exercise the wrong options. Note that if the dementia renders the person incapable of driving and controlling a vehicle safely, he/she is medicolegally disqualified from driving. Doctors have a legal obligation under the National Road Traffic Act 1996 (Act 93 of 1996) to report such individuals to the traffic authorities.[16]

In general:

- Assess all cases on individual merit.
- Patients must drive in conditions affording good visibility and then in day time only, on non-busy suburban roads and always accompanied by a caregiver.
- Their MMSE should be at least 20-22/30 or above and they must still be able to do the pentagon test (which tests for visuospatial ability) or trail-making B.
- Re-assess at 3-monthly intervals.

3.3.2.2 Firearms

Similarly gun licenses should be revoked for the same reasons.

3.3.2.3 Financial affairs and wills

Should the patient be incapable of handling her/his own financial affairs, urge a reliable and trustworthy member of the family to take control of the situation. Transfer of authority by means of power of attorney works well in early dementia where competency is still preserved. Failing this, or where no family members are available, curatorship should be sought. The forms are obtainable from the court who will appoint a curator honsi to attend to the patient’s affairs based on the recommendations of a psychiatrist and medical officer/general practitioner. Social workers and occupational therapists who are well-versed in these matters may have to be called in for advice and help with these cases. A patient who has not yet written a will or testament but now wishes to do so should be referred to a psychiatrist in order to establish testamentary capacity.[16]

3.3.2.4 Social assessment

A thorough social evaluation is of the utmost importance when assessing a dementia patient. The social assessment includes information regarding where the person lives, living circumstances, relevant family members and caregivers, and the extent of coping of both patient and caregivers, employment (if relevant) and economic...
resources, and degree of additional social support, as well as medicolegal matters.

3.3.2.5 Elder abuse
Awareness of abuse in the area of financial resources and the administration of the patient's affairs is of paramount importance. It should be determined who draws, administers and dispenses the patient's financial resources and pension.

Elder abuse includes physical abuse as well as 'acts of omission' or negligence leading to the detriment of the health and well-being of the person. This would include physical, psychological, financial and material aspects. Examples would be the denial of food, visits, medication, clothing and other essentials. Note that sexual abuse and incest also occur.

Cases must be reported to Halt Elder Abuse Line (toll free 0800 003081) for investigation and management.

3.4 Comorbid medical conditions
Patients with dementia commonly have comorbid medical conditions such as depression, cardiovascular and pulmonary diseases, infections, arthritis, sleep disturbances, falls, incontinence and drug-related adverse events, among others. There is a strong association between medical conditions and impaired cognition in AD. [17]

People with dementia, particularly those who live alone, are at risk of inadequate nutrition and dehydration. Both of these factors can contribute to the development of neuropsychiatric symptoms (NPS). The propensity to develop subsequent bronchopneumonia or urinary tract infection is very high.

Comorbid medical conditions need to be optimally managed, especially vascular risk factors which may be contributing to the dementia by exacerbating any vascular disease. Regular medication review is mandatory as is the supervision of medication by a responsible caregiver.

3.5 Investigations
Cost restraints and other practicalities often dictate the number of investigations that can be performed. Generally, in a typical or advanced case of dementia, investigations have little to offer towards treatment. A ‘positive’ result is more likely to be obtained when:
- The patient is less than 65 years of age
- Onset has been recent and the course rapid
- Course of disease fluctuates markedly
- Physical examination reveals a neurological deficit.

Special investigations help to improve or rule out treatable contributory and exacerbating causes of dementia. The full ‘organic work-up’ entails a full blood count, plasma viscosity, urea and electrolytes; thyroid, liver and parathyroid function tests, random blood sugar, niacin, vitamin B12, red cell folate and lipogram. C-reactive protein (CRP) levels may be indicated. Additional tests include syphilis serology and urine dipsticks.

Assessment by a trained neuropsychologist may be required when the cognitive impairment is very mild or does not conform to an expected pattern.

The trimmed-down version of the ‘organic work-up’ consists of the following only: haemoglobin, mean cell volume, white cell count and platelets; glucose; potassium, sodium and urea/creatinine; thyroid-stimulating hormone; albumin and gamma-glutamyl transferase (γGT); calcium; vitamin B12; total cholesterol; syphilis serology and urine dipsticks. [10]

4. Treatment
Patients with dementia almost invariably display neuropsychiatric symptoms (NPS), such as disturbances in mood with psychotic and vegetative symptoms among other phenomena. [16] Hitherto the focus with cognitive enhancers has been on cognitive improvement, overlooking the fact that these medications will often improve the NPS, especially in the early phases of the illness. Amelioration of these symptoms may be insufficient later on, at which stage treatment with more conventional psychotropic agents will be required.

4.1 Treatment goals
- Re-establishing the homeostasis, correcting for both internal and external factors by correcting influences such as dehydration, urinary tract infection, and disruptions in day/night rhythm.
- Stabilising the NPS to promote patient well-being and reduce caregiver burden.
- Maintaining the quality of life and highest level of patient functioning for as long as possible, in order to delay institutional care.

4.2 General aspects of treatment
As with the assessment process, treatment is holistic, by its nature multifaceted and, more often than not, multidisciplinary. Of necessity, the treatment involves caregivers and family. Team-work is essential and should utilise as many members from the community (helpful family members, religious groups) and medical resources (social worker, occupational therapist, community nurse) as possible. Patient target symptoms include declining cognition and impairment in daily functioning, among various associated symptoms that manifest during the course of the disorder. Treatment aims at maximising functional performance and quality of life, while reducing the period of disability.

4.2.1 Imparting the diagnosis
Ensure that key family members and caregivers are present. Be compassionate, honest and leave sufficient time available for questions and answers in order to contain the situation. Keep hope alive in that there are treatments available for some dementias, and potential benefits from psycho-education, social support and medication trials. Apart from the diagnosis, include prognosis and management strategies. Keep an open-door policy, link up with the family physician and refer to the local support organisation. [19] Additional issues that need to be addressed include genetics and other practical and medicolegal decisions such as driving, firearms, power of attorney, financial controls, curatorship and wills, and capacity assessments (discussed above). Note that the detection of elder abuse, incapacity to drive and/or ownership of a firearm is notifiable by law. [16]
4.2.2 Accommodation and level of supervision
The situation in South Africa mirrors the global move away from residential institutions. Fewer beds are available at ever-rising cost. Patients, their families and caregivers increasingly have to rely on their own resources. To help them in this task are the primary-care facilities, social clubs, seniors centres, daycares centres and respite-care facilities. Welfare organisations and non-profit organisations (NPOs) offering support, counselling and psycho-education are invaluable.

4.3 Pharmacological treatment
4.3.1 Acetylcholinesterase inhibitors and memantine
Based on the cholinergic hypothesis of AD, cognitive deterioration is associated with progressive loss of cholinergic neurons and decreasing levels of acetylcholine in the brain. Both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) have been found to play an important role in the degradation of acetylcholine. Table 2 outlines these medications.

The 3 acetylcholinesterase inhibitors (AChEIs) differ in their pharmacological action: donepezil selectively inhibits AChE; rivastigmine affects both AChE and BuChE; and galantamine selectively inhibits AChE and also affects nicotinic receptors. To date, these differences have not been shown to result in differences in efficacy and tolerability.[20]

An alternative strategy is the inhibition of excitotoxic amino-acid neurotransmitters (e.g. glutamate, aspartate, homocysteine) which play an important role in the pathophysiology of dementia. Memantine is an N-methyl-D-aspartate receptor antagonist which regulates calcium flux across membranes and may protect against neuronal death.

A combination of an AChEI with memantine appears to be more effective than either agent on its own and is well tolerated, there being no pharmacokinetic or pharmacodynamic interactions between the two.[20,21]

Most indications for the above agents are AD-specific but may also benefit those AD patients with cerebrovascular disease. Other indications include MCI, diffuse Lewy body (DLB) dementia, and Parkinson’s disease dementia. These indications are, however, country-specific as is their range of applications for the mild, moderate and severe stages of AD. The mode of administration (slow-release capsules, transdermal patches) further impacts more positively on tolerability, compliance and efficacy; as do ease of titration, price of product and familiarity with the medication. Under ideal circumstances, treatment should start in the prodromal/symptomatic/MCI phase of AD, bearing in mind that patients only tolerate the minimum effective dose in the early stages. The earlier diagnosis would involve the testing of cerebrospinal fluid biomarkers for AD, which is currently being standardised.[21] Patients respond with both improved cognitive and behavioural changes. Studies tend not to capture the more subtle changes in the dementing patient, such as the return of personality, spontaneity, insight and interest in their surroundings. The relief in caregiver stress burden is observed immediately, and this in turn enhances the well-being of the caregiver. Improvement in the mild to moderate AD patient is usually above baseline for the first 9 months; then it slowly declines as the illness relentlessly progresses. Data obtained at the 3-year mark show that patients are still functioning at above their expected level of deterioration when compared to untreated patients observed over the past decades.[23,24]

4.3.1.1 Adverse effects
Excess cholinergic stimulation with the use of AChEIs may lead to transitory nausea, vomiting, dizziness, insomnia and diarrhoea. A lowering of dosage, short pause or even rechallenge (if treatment is re-initiated after a prolonged period) is usually successful in overcoming these events should they occur. Urinary incontinence, abdominal muscle cramps and excessive sweating may occur and usually indicate the need for a ‘switch’ to another agent. There appear to be no important differences between drugs in respect of type or frequency of adverse events.[20]

AChEIs may potentially have vagotonic effects on heart rate (i.e. bradycardia), of importance in patients with ‘sick sinus syndrome’
or other supraventricular cardiac conduction disturbances such as sinoatrial or atrioventricular block. These medications should therefore be used with caution in patients with cardiovascular disease or those taking concurrent medicines that reduce heart rate. Bradycardic drugs include beta-blockers, digoxin, amiodarone and calcium channel antagonists. Recent reviews show that the incidence of cardiovascular side-effects is low and that serious adverse effects are rare. Interestingly, the value of pretreatment screening and routine electrocardiograms (ECG) is questionable and these are not currently recommended by the National Institute for Health and Clinical Excellence.[20,31]

Common (usually transient) side-effects of memantine include confusion, dizziness, headache and tiredness. Uncommon are anxiety, hypertonia and vomiting. Note that, being an amantadine derivative memantine may enhance the action of L-dopa and dopaminergic agonists.[20]

Generally, all the above interact with anticholinergic drugs and cholinomimetics to a variable extent.

### 4.3.1.2 Recommended dosages

It is also important to optimise the dose and duration of cholinesterase inhibitor treatment. It is thought that the higher the dose tolerated by the patient, the better the result. A minimal trial period of between 3 and 6 months is indicated.

AD patients are given a once-daily dose of 5 mg donepezil at night, increasing to 10 mg after 4 weeks. Medication is given at night to obviate side-effects which may occur 4 hours after ingestion coinciding with peak plasma levels. The half-life of donepezil is 70 hours and steady state is usually obtained in 14 - 21 days. As with the other medications, should side-effects become intolerable, one skips the medication for a day or two.[20] Elimination of the drug is through both renal excretion of intact drug and bio-transformation via the cytochrome P450 system. The latter is only partially saturated by the drug, and hence drug-drug interactions tend not to be a problem. Rivastigmine is initiated at 1.5 mg twice daily, and increased by 1.5 mg twice daily every 2 - 4 weeks to a maximum of 12 mg daily. Rivastigmine has almost no potential for interaction since it is metabolised at the site of action and does not affect hepatic cytochromes. Galantamine is initiated at 8 mg daily, and the dose is then increased by 8 mg every 4 weeks to a maximum of 24 mg daily. Metabolism is via the cytochrome P450 system. Memantine is given in the morning with a starting dose of 5 mg, then raised in increments of 5 mg on a weekly basis to a maximum of 20 mg per day. Metabolism is primarily non-hepatic (Table 3).[19,20,32-34]

### 4.3.1.3 Follow up

It is important to determine the patient's response to medication, and as such it may be useful to complete a scale such as the MMSE or ADL.[15] or the Neuropsychiatric Inventory (NPI) for NPS[35] in order to help quantify the treatment response.

### 4.3.1.4 Neuropsychiatric symptoms

NPS, also formally known as BPSDL, rather than cognitive decline, prompt entry into long-term care. Over 90% of subjects with dementia will exhibit at least one NPS that needs specific management at some point in the course of their illness.[16,36] These symptoms may wax and wane over time while some symptoms (e.g. visual hallucinations in DLB dementia) are more common in some dementias than in others. Another frequent mistake made by both caregivers and physicians alike is to assume that there are no hallucinations or delusions, since patients may objectively not display these phenomena which are only elicited on very careful mental state examination or behavioural assessment. The behavioural domains are best assessed by using the NPI.[19] The diffuse nature of the NPS means that each patient needs an individual assessment and treatment strategy.[19,32,35-37]

In general, on-treatment medical causes for NPS have been addressed or eliminated, psychosocial intervention follows with or without psychotropic medication. The latter consists of the use of AChEIs or memantine on their own or in combination followed by antidepressant, antipsychotic or other medication as indicated.

The general treatment principles follow those for younger adults. Except that half to two-thirds of the adult dose is given. 'Start low, go slow, review frequently' is the standard watchword, as the elderly are more sensitive to medication side-effects than the younger adult. Note that polypharmacy may be necessary in the form of a non-sedating (high-potency) neuroleptic by day and a sedating (low-potency) neuroleptic at night. Psycho-education about the illness and supervision of medication is essential, keeping in mind that data on medication are, in general, controversial (Table 4).[32,36]

### 4.3.2 Antidepressants

While symptoms of anxiety or depression are common in the premonitory stages of dementia, e.g. their occurrence at 50 years of age may herald dementia 10 - 20 years later, once the dementia is established, apathy is the most common NPS (frequently misinterpreted as 'depression').[15] Though major depression may precede the onset of AD, it occurs less frequently as the disease progresses, while minor depression, mild depressive symptoms or bouts of dysphoria become much more common in the early course of AD. If in doubt about the coexistence of depression with AD, a trial of antidepressant medication should be given. Note that antidepressants also have anxiolytic, and in the case of some newer-generation antidepressants, sedating if not hypnotic qualities. Symptomatic treatment of neuropsychiatric disturbances will afford both the patient and caregiver much relief. By and large the elderly require smaller dosages (about half to two-thirds) of antidepressant medication than that of the young adult population, and in most cases the 'sedating' antidepressants are preferred. Higher dosages may be required for more resistant cases where the diagnosis of coexistent depression is certain. Exercise caution with regard to side-effects and patient tolerance. AD patients with an MMSE of below 20/30 tend not to benefit from an antidepressant in terms of its antidepressant effect. AD patients on an AChEI, however, may experience depressive symptoms in both the mild and moderate stages of AD.[16] In these patients the depression appears in part to be coupled to the renewed insight afforded the patient by the drug, and is usually transient in nature. When it persists, treatment with an antidepressant is indicated.[19]

Avoid tricyclics in therapeutic doses on account of anticholinergic side-effects, and ECG QTc problems, especially when combined with other medication, e.g. antipsychotics.

Dementia patients fare better on ‘sedating’ antidepressants such as citalopram (20 mg), sertraline (30 - 150 mg), mirtazapine (15 - 30 mg)
and agomelatine (25 - 50 mg) at night. Escitalopram (2.5 - 5 mg) and venlafaxine (75 - 225 mg) are given in the mornings. The latter should only be used as second-line treatment. Augmentation usually involves neuroleptics, while electroconvulsive therapy may only be effective during the prodromal phase of the disorder.

### 4.3.3 Antipsychotics

Table 5 outlines a treatment schedule for restlessness, psychotic symptoms, agitation and insomnia. Note that haloperidol (a potent antipsychotic, with little sedation, but prone to extrapyramidal side-effects) acts synergistically with chlorpromazine (a less potent antipsychotic, sedating, and prone to postural hypotension as side-effect). The drugs in combination usually allow for a lower dose of either agent, with fewer side-effects, affording better tolerability and targeting of symptoms. Some caregivers prefer one drug only, an even lower dosage of either agent, or different timing. Good caregivers will experiment with different regimens, tell you what their AD patient needs, and should be accommodated, for at the end of the day it is they who have to live with the consequences.[10,38]

When aggression, psychosis, resistance to care or restlessness is prominent, low-dose risperidone/haloperidol at 0.25/0.5 mg twice daily is the drug of choice. Reinforce the day-night cycle by adding a sedative antipsychotic such as quetiapine/chlorpromazine 25 - 50 mg at night (Table 5).[10] Titrate up as indicated. For acute sedation 1 - 2 mg lorazepam orally or intramuscularly is the drug of choice (Table 6).[10]

---

### Table 3: Description of cognitive enhancers. Adapted from Taylor et al.,[32] Ihl et al.[33] and Rossiter.[34]

<table>
<thead>
<tr>
<th>Name</th>
<th>Derivative</th>
<th>Therapeutic class</th>
<th>Therapeutic dose</th>
<th>Starting dose</th>
<th>Presentation</th>
<th>Interval between dose increases</th>
<th>Common adverse effects (often transient)</th>
<th>Half-life (h)</th>
<th>Metabolism</th>
<th>Drug-drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donepezil</strong></td>
<td>Piperidine</td>
<td>Acetylcholinesterase inhibitors</td>
<td>5 - 10 mg at night</td>
<td>5 mg at night</td>
<td>5 mg, 10 mg tablets</td>
<td>4 weeks</td>
<td>Nausea, vomiting, diarrhea, fatigue, insomnia, muscle cramps, anorexia, headache, vivid dreams</td>
<td>70</td>
<td>CYP 2D6</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Rivastigmine</strong></td>
<td>Carboxamate</td>
<td>Acetylcholinesterase inhibitors</td>
<td>3 - 6 mg 2 x daily</td>
<td>1.5 mg 2 x daily</td>
<td>1.5 mg, 3 mg, 4.5 mg, 6 mg capsules</td>
<td>4 weeks</td>
<td>Nausea, vomiting, diarrhea, confusion, headache, somnolence, muscle cramps</td>
<td>12</td>
<td>Non-hepatic</td>
<td>Interaction unlikely</td>
</tr>
<tr>
<td><strong>Galantamin</strong></td>
<td>Tertiary alkaloid</td>
<td>Acetylcholinesterase inhibitors</td>
<td>16 - 24 mg daily</td>
<td>8 mg daily</td>
<td>8 mg, 16 mg, 24 mg CR capsules</td>
<td>4 weeks</td>
<td>Nausea, vomiting, diarrhea, abdominal pain, anorexia, fatigue, dizziness, headache, somnolence</td>
<td>7 - 8</td>
<td>CYP 2D6</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Memantine</strong></td>
<td>NMDA receptor antagonist</td>
<td></td>
<td>5 - 10 mg 2 x daily</td>
<td>5 mg daily</td>
<td>10 mg tablets/oral drops</td>
<td>1 week weighted mornings</td>
<td>Confusion, dizziness, headache, tiredness, constipation</td>
<td>60 - 100</td>
<td>Primarily non-hepatic</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Therapeutic dose** - The therapeutic dose is indicated for each drug. **Starting dose** - The starting dose for each drug is provided. **Presentation** - The presentation of the drug is given. **Interval between dose increases** - The interval between dose increases is provided. **Common adverse effects** - Common adverse effects of the drug are listed. **Half-life (h)** - The half-life of the drug is provided. **Metabolism** - The metabolism of the drug is indicated. **Drug-drug interactions** - The drug-drug interactions of the drug are indicated.

### Table 4. Approach to neuropsychiatric symptoms/behavioural and psychological symptoms of dementia. Adapted from Ames et al.[36] and Taylor et al.[34]

Take a routine history (patient and key informants) focusing on mental state (including MMSE) and assess interpersonal and environmental factors. Key questions around symptoms exhibited, the circumstances under which they arose and management strategies utilised to date.

Exclude physical illness potentially precipitating NPS/BPSD, e.g. constipation, infection (e.g. urinary tract infections especially from dehydration) and pain.

Target the symptom requiring treatment.

Consider non-pharmacological methods.

Psycho-educate the patient (if they have the capacity) and family/caregiver.

Carry out a risk/benefit analysis prior to selecting medication. Ideally start with an AChEI or memantine prior to other psychotropic medication. Discuss the use and side-effect profile fully with patient/family/caregiver.

Titrate medication from a low starting dose and maintain the lowest dose possible for the shortest period of time necessary.

Review medication regularly, monitoring for compliance, efficacy and adverse events.

Ensure support and ongoing psycho-education, monitoring and dealing with problems as they arise. Create awareness of local support group.

**NPS** = neuropsychiatric symptoms; **BPSD** = behavioural and psychological symptoms of dementia; **AChEi** = acetylcholinesterase inhibitors.
Ultimately, it is the treatment with which one is familiar and comfortable that works best. First-generation antipsychotics (FGAs) are probably as effective as second-generation antipsychotics (SGAs) but owing to their side-effect profile less well tolerated. As a rule of thumb, the ‘non-sedating’ antipsychotics have extrapyramidal symptoms as side-effects, the sedating antipsychotics have oversedation, hypotension and dizziness as their chief side-effect. There is no significant difference between treatment groups.[32,36]

In 2004 increased mortality with antipsychotics in dementia raised warnings for risperidone and olanzapine, which over the years were extended to include all SGAs as well as FGAs. The risk of developing both serious and non-serious cerebrovascular adverse events (CVAEs) such as stroke and mortality increases threefold with the use of antipsychotics. To date the mechanism by which the risk of such CVAEs is raised remains obscure, and patients with poorly controlled cardiac arrhythmias, hypertension, diabetes and previous stroke are more at risk.[32]

4.3.4.1 Hypnotics

Avoid benzodiazepines on account of the frequent occurrences of oversedation, hypotension and dizziness as their chief side-effects.

- Benzodiazepine-related: zolpidem 5 mg or zopiclone 3.75 – 7.5 mg
- Antidepressants: Sedating agents such as citalopram 10 - 20 mg, trazodone 50 mg, mirtazapine 7.5 - 15 mg or agomelatine 25 mg at night.

4.3.4 Other medications/strategies

4.3.4.1 Hypnotics

Avoid benzodiazepines on account of the frequent occurrences of daytime somnolence, emotional lability, confusion, incoordination, ataxia, memory impairment and incontinence. Implementation of measures of sleep hygiene is a prerequisite.

If medication is required for insomnia (preferably short-term) the following may be useful:

- Benzodiazepine-related: zolpidem 5 mg or zopiclone 3.75 – 7.5 mg
- Antidepressants: Sedating agents such as citalopram 10 - 20 mg, trazodone 50 mg, mirtazapine 7.5 - 15 mg or agomelatine 25 mg at night.

### Table 5. Example of a neuroleptic regimen[10]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (Serenace)</td>
<td>0.5 mg/0.25 - 0.5 mg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>0.5 mg/0.25 - 0.5 mg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Chlorpromazine (Largactil)</td>
<td>25 mg</td>
<td>at night</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>25 mg</td>
<td>at night</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>2.5 - 5 mg</td>
<td>at 17h00</td>
</tr>
</tbody>
</table>

4.3.4.2 Mood stabilisers/anticonvulsants

Trials with anticonvulsants (carbamazepine, sodium valproate, lamotrigine, topiramate and gabapentin) have not produced convincing evidence upon which to advocate their routine use.[32]

4.3.4.3 Restless legs syndrome

Clonazepam 0.5 mg may be taken at bedtime. Failing this, a dopamine agonist may be indicated: pramipexole, 0.125 mg at night.

4.3.4.4 Hypersexuality

Cypionate acetate 150 mg given every 2 - 4 weeks IMI is effective in combating paraphilia in non-dementing patients and those with dementia. Sexual disinhibition or hypersexuality will diminish within a few days. The strategy is to administer the medication for 6 months, then withhold treatment, and should symptoms re-emerge, another 3 months of treatment is indicated. Very occasionally a further 3-month course may be necessary.[19]

4.3.4.5 Treatment-resistant psychoses and disruptive vocalisers

In these situations the clozapine/amisulpiride regimen (taking into account white cell count measurements) may be useful:

- Initiate: clozapine
  - Start with 12.5 mg (in very frail patients, prone to extrapyramidal side-effects)
  - Increase in 12.5 mg increments
  - Start with 25 mg (in more robust patients)
  - Increase in 25 mg increments
  - If response is good, continue to near-intolerance level
  - Split dose with night-time weighting, then drop one level
  - Total daily dose 125 - 300 mg
  - Watch out for: sedation, hypotension, urinary incontinence and drooling
- Add: amisulpiride
  - Start with 50 mg
  - Increase in 50 mg increments
  - Split dose with night-time weighting
  - Total daily dose 150 - 200 mg
  - Watch out for sedation and dystonia

4.4 Non-pharmacological treatment

4.4.1 The patient

A complex interaction of biological, psychosocial and environmental factors contribute to the development of NPS in AD.[14] It is therefore important to observe for environmental triggers that influence behaviour, and get feedback from those around the patient. This has led to the A-B-C approach, whereby Antecedents to the behaviour are noted, as well as details of the Behaviour (description, time, duration), and the Consequences. A disruptive patient may thus get much more attention from nursing staff than when they are quiet, which inadvertently reinforces their disruptive behaviour.[18]

Environmental factors implicated in triggering NPS include excessive noise and stimulation, lack of daily structure and routine, confusing surroundings, excessive demands, loneliness and boredom.[18] Specific

### Table 6. Psychotropics for acute sedation[10]

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Range</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam (Ativan)</td>
<td>1 - 2 mg po/IMI</td>
<td>0.5 - 1.5 mg IVI</td>
</tr>
<tr>
<td>Haloperidol (Serenace)</td>
<td>2.5 mg IMI/IVI</td>
<td>Do not exceed 8 mg over 24 hours</td>
</tr>
</tbody>
</table>

- Neuroleptics: Sedating agents such as chlorpromazine 25 mg, olanzapine 2.5 mg (given at 17h00) or quetiapine 25 mg at night.

4.4.4.2 Mood stabilisers/anticonvulsants

Trials with anticonvulsants (carbamazepine, sodium valproate, lamotrigine, topiramate and gabapentin) have not produced convincing evidence upon which to advocate their routine use.[32]
non-pharmaceutical interventions that enjoy success are validation therapy, positive reinforcement, reminiscence therapy, reality orientation and creative diversions, among others.

4.4.2 The caregiver

A most vital link in the pharmacotherapy and general care of AD is the caregiver. Caregivers are estimated to spend an average of 70 - 100 hours per week on providing care. Caregivers utilise 45% more physician visits and 70% more prescription drugs than non-caregivers, and are more likely to be hospitalised. More than 50% of caregivers are at risk for clinical depression.[40,41] A recent study[42] showed that, in general, there was a six-fold risk of dementia in spouses of patients with dementia. Where husbands looked after spouses suffering from dementia the risk was twelve-fold. Judicious use of pharmacotherapy, therefore, not only alleviates the stress on the caregiver but also delays the institutionalisation of the AD patient.

All caregivers should be referred to NPOs such as Dementia SA in the Western Cape and Alzheimer’s South Africa, elsewhere. Not only do these organisations assist in supporting caregivers and monitoring their well-being but they also explain how to care for the patient, provide support services – such as home help or respite care – wherever possible, provide counselling and medicolegal advice, and continually update the caregiver by means of newsletters, meetings or workshops, on the latest developments.

4.5 Preventative measures

It is estimated that the neurodegeneration in AD starts some 20 - 30 years before the appearance of the first clinical symptoms,[43] reflecting the need for earlier intervention while minimal brain damage has occurred.

Note that the preventative measures mentioned below offer no benefit to people whose preclinical AD pathology is sufficiently advanced to produce dementia symptoms within very few years and especially once the dementia is clinically evident:

- Hormone replacement therapy (oestrogen with or without progesterone) is only effective if initiated at the time of menopause where a deficiency in female sex hormones has clearly been established.[44]
- Vitamin E (≤400 IU) and C (400 mg) daily, preferably in combination.[45] Note that high-dose vitamin E (+400 IU daily) supplementation is associated with an increased mortality risk.[46]
- Red wine (Bordeaux blend 250 - 500 ml daily). Ascribed to resveratrol and other aliphatic compounds.[47]
- Non-steroidal anti-inflammatory drugs (NSAIDs). Conventional NSAIDs such as ibuprofen and voltaren[48] as well as naproxen used for as little as 2 - 3 years[49] may protect against AD.
- Coffee. Consuming 3 - 5 cups of coffee (not decaffeinated or instant) a day decreases the risk of dementia/AD later in life.[50-52] Currently, there is interest in establishing a ‘risk score’ as early as midlife, similar to that of the risk of cardiovascular disease. It is hoped that these lifestyle changes, antioxidant supplementation and treatment of medical conditions may then decrease the risk of AD and other dementias in persons at risk.[53] A diet rich in vitamins B, C, D and E (fruit and vegetables) and omega 3 fatty acids (fish) and low in high trans-fat (processed foods) reflects in beneficial blood nutrient biomarker patterns influencing both cognitive function and brain volume.[54]
- Physical exercise
- Weight reduction
- Control of hypertension
- Control of hypercholesterolaemia
- Dietary antioxidants
- Intellectual activity
- Leisure activities and hobbies
- Social networks
- Red wine
- Fish and other sources of omega 3
- Folate-rich food or low-dose vitamin B supplementation

5. Algorithm

Fig. 3 shows the treatment algorithm for dementia.

For further reading on the biological treatment of AD, please refer to Ihl et al.[55] Rossiter[56] and Daoud.[57]
14. For hyperactivity or agitation, a low-dose first- or second-citalopram should not be used in doses greater than 20 mg per day in patients with depression, consider antidepressants that have mood or anxiety symptoms.

15. Rule out underlying or coexisting medical conditions and CvD by addressing its risk factors.

The most promising approach to VaD is secondary prevention of treatment of AD, VaD, DLB dementia, dementia in Parkinson’s and tolerability. These medications are effective in the symptomatic constellation of symptoms, the stage of the disease, the side-effect profile, and caregiver availability.

— GUIDELINE —

6. Summary points

- Treatment with antideementia medication combined with non-pharmacological measures provides the most benefits in patients with dementia.
- Medication must be individualised taking into account the constellation of symptoms, the stage of the disease, the side-effect profile, and caregiver availability.
- Titrate medication from a low starting dose.
- Target daily doses of first-line antideementia medication are as follows: donepezil 10 mg, rivastigmine 12 mg, galantamine 24 mg, and memantine 20 mg. This should, however, be guided by response and tolerability. These medications are effective in the symptomatic treatment of AD, VaD, DLB dementia, dementia in Parkinson’s disease and certain frontotemporal dementias.
- Patients should be closely monitored for the first month after commencing treatment.
- The most promising approach to VaD is secondary prevention of CvD by addressing its risk factors.
- Rule out underlying or coexisting medical conditions and psychosocial environmental factors in patients with behavioural, mood or anxiety symptoms.
- In patients with depression, consider antidepressants that have more sedative effects, such as citalopram, sertraline, mirtazapine, and agomelatine. In view of the potential for QT prolongation, citalopram should not be used in doses greater than 20 mg per day in adults older than 60 years.
- For hyperactivity or agitation, a low-dose first- or second-generation antipsychotic medication may be used for a short period of time.

References


Schizophrenia

D Swingler

1. Introduction
Schizophrenia is a major mental disorder that imposes a significant burden on the individual including poor quality of life\(^\text{[1]}\) and increased morbidity\(^\text{[2]}\) and mortality\(^\text{[3]}\) it disrupts interpersonal relationships and family structures, and has significant economic costs to society. While there are substantial limitations to current treatments\(^\text{[5]}\), an integrated package of biopsychosocial interventions is essential to alleviate the negative impact of the disorder and enhance quality of life.\(^\text{[5,6]}\) Active early intervention, in particular, can improve long-term outcomes.\(^\text{[6]}\)

2. Diagnosis and clinical characteristics
Schizophrenia is a heterogeneous cluster of psychotic conditions characterised by positive (delusions, hallucinations) and negative or 'deficit' (blunting of affect, avolition) symptoms, disorganised speech and behaviour, as well as mood (depressive) and cognitive impairments.

Diagnosis in terms of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)\(^\text{[7]}\) requires the presence for at least 1 month (or less if successfully treated) of 2 or more of the following characteristic symptoms (in the context of the disturbance persisting for at least 6 months which includes 1 month of symptoms) (criterion A):
- Delusions
- Hallucinations
- Disorganised speech
- Grossly disorganised or catatonic behaviour
- Negative symptoms.

Further, the disorder must cause social and/or occupational dysfunction, and cannot be better accounted for by:
- Schizoaffective or mood disorders
- Substance-related disorders
- General medical conditions.

3. Assessment
3.1 Diagnostic
A detailed clinical history, mental state and careful physical examinations must inform a diagnosis made rigorously in terms of available resources. Pharmacological treatment remains the mainstay of therapy, while psychosocial interventions are crucial in promoting recovery and improving quality of life.\(^\text{[6]}\)

While both the classification and relative efficacies of the so-called 'typical' first-generation antipsychotic (FGA) agents, such as haloperidol and chlorpromazine, and 'atypical' second-generation antipsychotic (SGA) compounds, such as risperidone and olanzapine, remain controversial, current evidence supports the following:
- Drugs from both groups are equally effective in alleviating psychosis\(^\text{[6]}\)
- SGAs may have benefit in negative syndromes, and with mood and cognitive impairments\(^\text{[6]}\)
- Where differences exist, the effect sizes are small to modest, except for clozapine which is more effective in treatment resistance and reducing suicide risk\(^\text{[4]}\)
- SGAs, largely because of less severe extrapyramidal side-effects (EPS), are more tolerable\(^\text{[9]}\)
- Each drug has a unique side-effect profile
- The choice of drug is informed by\(^\text{[8]}\)
  - Access and availability
  - Shared patient-centred decision making
  - Previous experience (efficacy and side-effects), if any
  - Tailoring the side-effect profile to the individual patient
  - Choice of mode of administration (oral or parenteral)

3.2 Pre-treatment
Clinically indicated baseline investigations prior to initiating antipsychotic treatment are directed by the clinical process and choice of initial drug therapy, and include body mass index (BMI) and waist:hip ratio (cardiovascular (CV) risk), fasting blood glucose and lipogram (metabolic risk), and full blood count and liver function tests (depending on drug selection).

A baseline electrocardiogram (ECG) is indicated before treatment if required by the product's package insert. If there is a personal history of CV disease or evidence of CV risk on physical examination, an ECG should be considered for inpatients.\(^\text{[9]}\)

4. Treatment
4.1 Treatment goals
Therapeutic goals are to relieve symptoms, prevent relapse, promote recovery and improve quality of life.\(^\text{[6]}\) More specifically, this includes:
- Achieving and maintain symptom alleviation
- Achieving and maintain treatment adherence
- Minimising treatment side-effects
- Monitoring physical health and drug-specific adverse event risks, e.g.
  - White cell count (WCC) (acute neutrophil count) with clozapine
  - Metabolic syndrome risk factors with olanzapine
  - Tardive dyskinesia with haloperidol
  - Managing smoking and substance abuse
  - Managing risk of harm to self and others.

4.2 General aspects of treatment
At the outset of management, an integrated treatment plan including pharmacological, psychological and social interventions should be formulated in terms of available resources. Pharmacological treatment remains the mainstay of therapy, while psychosocial interventions are crucial in promoting recovery and improving quality of life.\(^\text{[6]}\)

Management of initial drug therapy, and include body mass index (BMI) and waist:hip ratio (cardiovascular (CV) risk), fasting blood glucose and lipogram (metabolic risk), and full blood count and liver function tests (depending on drug selection).

A baseline electrocardiogram (ECG) is indicated before treatment if required by the product's package insert. If there is a personal history of CV disease or evidence of CV risk on physical examination, an ECG should be considered for inpatients.\(^\text{[9]}\)
• Recommended dosage is in the range of 300 - 1 000 mg chlorpromazine (CPZ) equivalents.[6]

Oral therapy is advised. Should parenteral therapy be considered for maintenance on the basis of patient preference or convenience or to manage non- adherence, this can be planned in the acute phase. It is logical to convert from an effective oral agent to its parenteral equivalent, and a test dose of the oral equivalent of the agent should be used before administering a long-acting injectable antipsychotic agent.

Monotherapy is recommended. There is no advantage to combining antipsychotics, which should only be done for short periods when switching agents, or in treatment-resistant settings.[4,6] Doses should not exceed 1 000 mg CPZ equivalents and/or the manufacturer’s instruction as there is no additional therapeutic benefit in doing so, with added cost and side-effects.[4,6]

Loading doses or ‘rapid neuroleptisation’ is ill-advised as it confers no therapeutic benefit with added risks.[6] Adjunctive benzodiazepines (the evidence supports lorazepam[10]) can be used liberally to attenuate disruptive behaviour in the acute setting.[6]

Continuous dosing is advised, as intermittent or targeted dosing leads to increased risk of relapse.[4] A trial of 4 - 6 weeks is required before considering another agent.[4,6,11]

4.3 Acute pharmacological treatment

4.3.1 First episode

A recent meta-analysis[12] found no differences between FGAs and SGAs in efficacy in this population, but a clear difference in side-effect profile. In view of the vulnerability of drug-naïve first-episode psychosis patients to develop EPS and tardive dyskinesia, the drug of choice is an SGA other than clozapine. Risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and amisulpride are supported by the evidence base.[4,6,13] Dosing should start low with incremental upward titration, with the target dosage at the lower end of the therapeutic range for each agent according to the package insert.[6]

4.3.2 Multi-episode/relapse

The drug of choice will be influenced by any prior agents’ efficacy and tolerability. If SGAs are available, they are generally preferred and risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and amisulpride are supported by the evidence base.[4,6,13] Haloperidol and chlorpromazine are FGA alternatives.

4.3.3 Second-line treatment

If response to the first-line agent above is unsatisfactory, then a second trial should be considered after review of potential contributors to non-response.[4]

This second-trial agent can be another SGA or an FGA, but should be an SGA if there was a failed response to an FGA in the first trial.[4,6] Switching strategies include cross-titration, overlap-and-taper, and abrupt change. Other than for switching to clozapine (see below), there is no evidence of difference in efficacy or tolerability.[14]

Oral monotherapy at doses not exceeding 1 000 mg CPZ equivalents and/or the manufacturer’s recommendation in a continuous dosing strategy is advised for a further 4 - 6 weeks before considering the third line of treatment.[4,6,11]

4.3.4 Third-line treatment

Clozapine oral monotherapy is the next treatment of choice, at the highest tolerable dose (≤900 mg daily) for 6 months.[11] Switching requires tapering and stopping the extant agent prior to initiating clozapine, to minimise haematological risk.

Because of a non-dose-dependent risk of agranulocytosis, WCCs – absolute neutrophil counts in particular – should be monitored prior to treatment, weekly for the first 18 weeks and monthly thereafter. Considering the risk of dose-related seizures, caution and careful monitoring should be exercised at doses above 450 mg daily.[15]

4.4 Long-term maintenance

Half of all patients stopping medication will relapse within 6 - 10 months, compared to one-fifth on treatment.[6] Long-term antipsychotic treatment reduces the risk of relapse over several years by two-thirds.[6]

Continuation of pharmacological treatment that was effective in the acute and stabilisation phases is advised. While many practitioners attempt dose reduction during maintenance, the evidence suggests that even gradually decreasing doses increases the risk of relapse.[17] Continuous dosing is advised as intermittent or targeted dosing leads to increased risk of relapse.[4]

Oral therapy is usual, but long-acting intramuscular preparations should be considered for maintenance on the basis of patient preference or convenience, or to manage non-adherence.

The minimum duration of treatment for first-episode patients is 1 year symptom-free if the episode is of mild severity and responds well to treatment, and 2 years symptom-free in severe cases or those slow to respond initially.[17] Second-episode patients require at least 2 and up to 5 years symptom-free before drug withdrawal can be considered. Indefinite treatment is advised after a third episode.[17]

4.5 Non-pharmacological treatment

4.5.1 Psychological interventions

These are focused on the individual (cognitive behaviour therapy, psycho-education, supportive psychotherapy) and the family (psycho-education, family therapy). These can be introduced during the acute phase of illness, but are more usually commenced in the stabilisation period.[8]

4.5.2 Social interventions

Long-term goals of treatment adherence and symptom reduction, limitation of injurious behaviours (smoking, substance abuse, suicide risk) and improved quality of life are supported by social interventions, including assertive community programmes, social skills training, appropriate housing, supported employment and adaptation to life in the community. These may be required during the acute phase of illness, but are more usually commenced in the stabilisation period.[9]

4.6 Special populations

4.6.1 First-episode psychosis

In view of the vulnerability of drug-naïve first-episode psychosis patients to develop EPS and tardive dyskinesia, the drug of choice is an SGA other than clozapine. Dosing should start low with incremental upward titration, with the target dosage at the lower

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end of the therapeutic range of each agent according to package insert. Oral therapy is recommended.

4.6.2 Electro-convulsive therapy (ECT)
While ECT is considered a last-line treatment in uncomplicated schizophrenia, it has a role in early acute treatment in the context of extreme psychomotor agitation, catatonia, pregnancy, or when life is at risk.

4.7 Managing partial and non-responders
4.7.1 Non/partial response
If response to any line of treatment is unsatisfactory, then a further line of intervention should be considered after review of potential contributors to non-response. This includes:
- Review of the diagnosis
- Review of treatment adherence
  - Drug choice
  - Dosage
  - Duration
- Adequacy of psychosocial interventions
- Presence of comorbid:
  - Substance abuse
  - Psychiatric illness
  - Physical illness
  - Pharmacotherapy.

4.7.2 Treatment resistance
While there are many definitions of treatment-resistant schizophrenia, for the purposes of this guideline it is taken to mean ‘insufficient improvement in target symptoms despite treatment at the recommended dosage for at least 6 weeks with at least 2 antipsychotic agents, one of which was an SGA other than clozapine.’

In addition to a review of potential contributors to non-response as above, a multidimensional assessment of positive, negative, affective and cognitive symptoms, as well as social and vocational function and quality of life, is indicated.

With ongoing insufficient response to maximum dose clozapine, the options (for which there is only limited evidence) are:
- Combining clozapine with another SGA that does not compound its side-effects
- Augmentation with mood stabilisers
- Lamotrigine has some evidence for utility
- Valproate when hostility is a problem
- Lithium when depression is troublesome
- Benzodiazepines can be added in cases of agitation, for short-term use
- ECT is a last-line treatment

5. Summary points
Both typical FGA agents and atypical SGA agents are effective in schizophrenia. Any differences in efficacy between these agents are small to modest. There are, however, clear differences in side-effect profiles.

- Monotherapy is recommended as there is no advantage to combining antipsychotics.
- A loading dose (‘rapid neuroleptisation’) is ill-adviced, as it confers no therapeutic benefit with added risks.
- Risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and amisulpride are effective in first-episode psychosis patients.
- For multi-episode patients, consider risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and amisulpride. Haloperidol and chlorpromazine may be considered as alternatives to FGAs.
- A trial of 4 - 6 weeks is required before considering an alternative agent.
- A second trial agent may be another SGA or an FGA, but should be an SGA if...

Fig. 1. Treatment algorithm. FGA = first-generation antipsychotic; HPL = haloperidol; CPZ = chlorpromazine; CPZ/E = chlorpromazine equivalents; SGA = second-generation antipsychotics; RIS = risperidone; OLA = olanzapine; QUE = quetiapine; ARI = aripiprazole; AMI = amisulpride; CLO = clozapine; BZP = benzodiazepines; LAM = lamotrigine; VAL = valproate; Li = lithium.
there was a failed response to an FGA in the first trial. Third-line treatment is clozapine.

- Clozapine is more effective than other FGA and SGA agents in treatment resistance and reduction of suicide risk.
- If there is an insufficient response to a maximum dose clozapine, consider combining clozapine with another SGA, or augmenting with a mood stabiliser, ECT, or adding a benzodiazepine in the short-term to control agitation or disruptive behaviour.
- Half of all patients stopping medication will relapse within 6 - 10 months, compared to one-fifth on treatment.
- Minimum treatment duration for first episode patients is 1 year symptom-free if the episode is of mild severity and responds well to treatment, and 2 years symptom-free in severe cases or those slow to respond initially.
- Second-episode patients require at least 2 - 5 years of medication to respond initially.
- Patients who have had 3 or more episodes should be treated indefinitely.

References
1. Jones PB, Barnes TRE, Davies L, et al. Randomised control trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost utility of the latest antipsychotic drugs in schizophrenia study (CULASS 1). Arch Gen Psychiatry 2006;63:1079-1086. [http://dx.doi.org/10.1001/archpsyc.63.10.1079]
1. Introduction

This treatment guideline draws on several international guidelines: (i) Practice Guidelines of the American Psychiatric Association (APA) for the Treatment of Patients with Major Depressive Disorder, Second Edition;[1] (ii) Clinical Guidelines for the Treatment of Depressive Disorders by the Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT);[2] (iii) National Institute for Clinical Excellence (NICE) guidelines;[3] (iv) Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression (RANZCAP);[4] (v) Texas Medication Algorithm Project (TMAP) Guidelines;[5] (vi) World Federation of Societies of Biological Psychiatry (WFSBP) Treatment Guideline for Unipolar Depressive Disorder;[6] and (vii) British Association for Psychopharmacology Guidelines.[7]

Major depressive disorder (MDD) is frequently associated with comorbid psychiatric and medical conditions and carries with it a high risk of morbidity and mortality. For many an initial episode of depression evolves into a recurrent and debilitating chronic illness with significant and pervasive impairments in psychosocial functioning.[8-11] The recent Global Burden of Disease Study estimated that unipolar major depression is the fourth largest contributor to the global burden of disease (premature mortality and disability).[12] By the year 2020, unipolar MDD is projected to be the second largest contributor to the global burden of disease, after heart disease.[13]

1.1 Prevalence and risk factors

MDD has a median lifetime prevalence of 16.1% (range 4.4 - 18%).[14] Twelve-month prevalence ranges from 5% to 10% in adults, with women at higher risk than men (ratio is approximately 2:1).[15,16] In South Africa, the lifetime prevalence of MDD documented in the South African Stress and Health (SASH) survey, the first nationally representative epidemiological survey of common mental disorders in South Africa,[17] was 9.8% across all age groups, with the highest prevalence (14.6%) in the Free State. The survey, conducted between 2003 and 2004 was a three-stage, area probability sample of 4 351 adults of all races and ethnic groups living in households and single-sex migrant labourer group quarters in South Africa. The 12-month prevalence rate of MDD during this period was 4.9%. The aforementioned SASH study found that females were 1.75 more likely to develop MDD than males.

The age of onset of MDD is difficult to assess because the first episode is frequently mild and untreated, and may be determined and treated retrospectively many years after first onset. MDD can begin at any age, even in childhood and adolescence, but there are two peaks, in the twenties and forties.[18,19] The mean age of onset of MDD has been estimated around the age of 30.[20] Family and twin studies have indicated that MDD is a complex genetic disorder being 1.5 - 3 times more common among first-degree biological relatives of persons with this disorder than among the general population.[21,22]

Female gender, a previous episode of major depression and a positive first-degree family history of depression are the most consistently described risk factors.

1.2 Comorbidity and consequences

Anxiety disorders are highly comorbid, occurring in about 58% of patients with MDD.[23] In addition, anxiety symptoms are highly prevalent in MDD, occurring in up to 80% of patients.[24] Studies investigating the effects of depression on health-related quality of life have demonstrated detrimental effects that equal or exceed those of patients with chronic medical illnesses, such as ischaemic heart disease or diabetes mellitus.[25-28] The most serious sequela of MDD is suicide. It has been estimated that about 50% of depressed patients make at least one suicide attempt during their lifetime.[29] It is well established that patients with mood disorders suffer a higher risk of suicide relative to the general population.[30] However, no risk factor or classification of diagnostic subtype has been shown to reliably predict suicide.[31] In a recent meta-analysis, the lifetime prevalence of suicide was estimated, on the basis of the intensity of the treatment setting. The analysis showed that clinically depressed patients who had been hospitalised for suicidality had a lifetime risk of suicide of 8.6%. Patients with affective disorders, who had been hospitalised without specification of suicidality, had a lifetime suicide rate of 4.0%. The lifetime suicide prevalence for mixed inpatient/outpatient populations was 2.2%, and less than 0.5% for the non-affectively ill population.[32] Depression also substantially increases the risk of death by cardiovascular disease.[33]

In addition to the personal suffering of individuals and their families, depression imposes significant costs on society.[34] These include both direct total healthcare costs and indirect costs (the latter have been estimated to be much higher than direct costs). Direct costs include mental health treatment costs and all other healthcare costs. Indirect costs include such varied factors as lost productivity associated with morbidity and mortality.[35] As depression is often not properly diagnosed and/or undertreated,[36,37] and as it can affect many individuals at a relatively early age, the impact on cost can be cumulative over time.

2. Diagnosis and clinical characteristics

MDD is characterised by single or recurrent major depressive episodes. The essential feature of a major depressive episode is a period of at least 2 weeks of depressed mood with abnormalities of neurovegetative functions (e.g. appetite, weight loss, sleep disturbances), psychomotor activity (e.g. loss of energy and interests, agitation or retardation), cognition (feelings of worthlessness, hopelessness or inappropriate guilt), as well as anxiety and suicidal ideation.[1] Table 1 summarises the diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[38] as well as the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).[39]
Depressive symptoms and pathology lie on a spectrum in terms of duration, severity and comorbid pathology.

2.1 Course and prognosis

An untreated depressive episode typically lasts about 6 months or longer. Modern pharmacotherapy alleviates suffering during acute episodes, and placebo-controlled trials show response and remission occurring more quickly in actively treated groups. A 27-year prospective study of 186 unipolar depressed patients meeting DSM-III criteria for major depression found shorter episodes and cycles with increasing episode number. However, a 10-year prospective study of 258 subjects treated for unipolar MDD showed that the duration of recurrent mood episodes remained relatively uniform over time and averaged approximately 20 weeks.

MDD is typically a recurrent disorder and 50 - 85% of the patients who have an episode will eventually have another episode. There is also increasing evidence that some who experience a major depressive episode will have a lifelong course of illness characterised by recurrent major depressive episodes or the development of chronicity, e.g. recurrent MDD without full inter-episodic recovery, or a chronic major depressive episode, or ‘double depression’ (concurrent major depression and dysthymic disorder). Between 9% and 24% of patients with the initial diagnosis of a major depressive episode will undergo a change in diagnosis over time, mostly to bipolar disorder.

Although the prognosis for a depressive episode is good, with most patients returning to normal functioning once the episode is over, in 20 - 30% of cases depressive symptoms will persist.

3. Assessment

A thorough diagnostic evaluation to determine both the presence of MDD and comorbid psychiatric or general medical conditions is key. This should include a review of the history of the illness including symptoms of current illness, past psychiatric and treatment history (with attention to current treatment and response to past treatment); general medical history; history of psychoactive substance abuse; personal developmental history and response to life transitions and major life events; social, occupational, and family history; mental status examination; physical examination; and laboratory investigations, as indicated.

Careful assessment of the patient's suicidal as well as homicidal risk is paramount. The APA guidelines propose evaluation of the following:
- Presence of suicidal or homicidal ideation, intent, or plans
- Access to means for suicide and the lethality of those means
- Presence of psychotic symptoms, command hallucinations in particular, or severe anxiety
- Presence of alcohol or substance use disorder(s)
- History and seriousness of previous attempts
- Family history of, or recent exposure to, suicide.

<table>
<thead>
<tr>
<th>Table 1. Criteria and classification of a depressive episode and major depressive disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Classification of Diseases, Tenth Revision code</td>
</tr>
<tr>
<td><strong>A. Depressive episode</strong></td>
</tr>
<tr>
<td>Severe (F32.2): all 3 typical symptoms plus at least 4 other common symptoms; some severe symptoms</td>
</tr>
<tr>
<td>Moderate (F32.1): at least 2 typical symptoms plus at least 3 common symptoms; some marked symptoms</td>
</tr>
<tr>
<td>Mild (F32.0): at least 2 typical symptoms plus at least 2 other common symptoms; no intense symptoms</td>
</tr>
<tr>
<td><strong>B. Recurrent depressive disorder (F33): recurrent depressive episodes</strong></td>
</tr>
<tr>
<td>Minimum duration of episode: about 2 weeks</td>
</tr>
<tr>
<td>Typical symptoms</td>
</tr>
<tr>
<td>Reduced energy, increased fatigability</td>
</tr>
<tr>
<td>Loss of interest and enjoyment</td>
</tr>
<tr>
<td>Depressed mood</td>
</tr>
<tr>
<td>Other common symptoms</td>
</tr>
<tr>
<td>Diminished appetite</td>
</tr>
<tr>
<td>Disturbed sleep</td>
</tr>
<tr>
<td>Ideas or acts of self-harm or suicide</td>
</tr>
<tr>
<td>Agitation or retardation</td>
</tr>
<tr>
<td>Ideas of guilt and unworthiness</td>
</tr>
<tr>
<td>Reduced self-esteem and self confidence</td>
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<tr>
<td>Reduced concentration and attention</td>
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</tbody>
</table>

Measurement-based diagnostic tools can aid in the assessment of depression severity, presence of co-occurring disorders, and suicide risk, but should always be accompanied by a clinical diagnostic assessment incorporating a differential diagnosis. Conditions that need to be excluded before making a definitive diagnosis of MDD include bipolar disorder, an adjustment disorder with depressed mood, mood disorder due to a general medical condition and a substance-induced mood disorder.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[49] and the Mini-International Neuropsychiatric Interview (MINI)[50] are clinician-rated diagnostic instruments, while the 9-item Patient Health Questionnaire (PHQ-9)[51] and the PRIME-MD[52] are commonly used patient-rated tools. For monitoring of depressive symptoms on treatment, the Hamilton Depression Rating Scale (HAM-D)[53] and the Montgomery-Åsberg Depression Rating Scale (MADRS)[54] are gold-standard clinician-rated scales. Other measures include the Quick Inventory of Depressive Symptomatology (QIDS)[55] which is available in both clinician-rated and patient-rated formats and the patient-rated Beck Depression Inventory (BDI).[56]

Diagnostic assessment and evaluation of patient safety, as well as that of others, should be followed by an evaluation of functional impairment and determination of the treatment setting (inpatient or outpatient).

4. Treatment
4.1 Treatment goals
Definitions of response, remission, and recovery[1] are summarised in Table 2.[57] In depression, full remission is defined as the virtual elimination of symptoms which in most clinical trials refers to depression scores within the normal range. This is most consistently defined as a score of 7 or less on the 17-item Hamilton Depression Rating Scale (HDRS-17). The term ‘response’ generally indicates a 50% reduction in depression score. Recovery from depression is often equated with remission in the literature. It is also variably defined as remission for an extended period of time or the complete absence of symptoms and improved work and psychosocial functioning.

Evidence for the benefits of treating remission in depression is clear: remitted patients are more likely to regain full functional recovery and to suffer fewer relapses and recurrences.[58] Remission has become the accepted treatment goal in MDD, as seen in many recent clinical trials. In the current National Institutes for Mental Health Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, for example, anything less than remission was viewed as treatment failure.[59,60]

4.2 General aspects of treatment
Treatment consists of an acute phase (during which remission of all symptoms is induced); a continuation phase, during which remission is preserved; and a maintenance phase during which susceptible patients are protected against the recurrence of subsequent major depressive episodes.[31]

4.3 Acute treatment
Initial management of MDD should entail: the establishment and maintenance of a therapeutic alliance; education of the patient and the family about the disorder with provision of information about treatment options; a review of the possible adverse effects of medications and potential drug-drug interactions; emphasis of the importance of taking medication as prescribed; and addressing the early signs of relapse.[61] The appropriate treatment setting (inpatient or outpatient) should be selected and the treatment plan should be individualised to the patient’s needs.[62]

Treatment decisions should also importantly take into account depression severity. A mild depressive episode, according to the DSM-IV-TR,[35] is characterised by 5 or 6 symptoms or less and mild disability (social, occupational and other important areas of functioning), a moderate depressive episode by 6 or more symptoms and moderate disability, and a severe depressive episode by most of the symptoms (as per the DSM-IV-TR symptom list) and observable disability. According to the DSM-IV-TR, subthreshold depression comprises fewer than 5 symptoms.[37]

Guidelines differ in their opinion on the management of mild depression. The APA guidelines[1] advise psychotherapy or antidepressant monotherapy based on patient preference. Similarly the CANMAT guidelines[2] recommend either cognitive-behavioural therapy (CBT), cognitive therapy, interpersonal therapy (IPT), or antidepressants as a first-line treatment, while the BAP guidelines[63] recommend CBT, behavioural therapy with activity scheduling, IPT or an antidepressant.

For moderate depression, all guidelines accept the use of an antidepressant or evidence-based psychotherapy as a first-line choice, with the exception of the NICE guideline which recommends antidepressants as the only first-line choice.[37] In view of their superior tolerability and safety, the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or the norepinephrine-dopamine reuptake inhibitors (NDRIs), and mirtazapine are encouraged over the use of the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs). However, the following considerations apply in deciding on the most appropriate medication: availability, safety

<table>
<thead>
<tr>
<th>Table 2. Response, remission, and recovery definitions[57]</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Recovery</td>
</tr>
<tr>
<td>Remission</td>
</tr>
<tr>
<td>Residual symptoms</td>
</tr>
<tr>
<td>Response</td>
</tr>
<tr>
<td>Partial response</td>
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<tr>
<td>No response</td>
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</table>


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and tolerability, patient preference and patient needs, and cost.\(^\text{60}\) Newer antidepressant classes such as a melatonin agonist may also be employed. Moderate depression may necessitate a combination of both an antidepressant and psychotherapy (either CBT or IPT); the APA guidelines recommend a combination of antidepressants and psychotherapy for patients with significant psychosocial problems or Axis II disorders and/or poor compliance.\(^\text{1}\)

For severe depression, the guidelines concur that the following first-line treatment options apply: (i) a combination of an antidepressant and psychotherapy (either CBT or IPT); (ii) electroconvulsive therapy (ECT) (6 to 10 treatments, maximum of 20, WFSBP guidelines recommend bilateral rather than unilateral ECT); or (iii) a combination of an antidepressant with an antipsychotic agent for a major depressive episode with psychotic features.\(^\text{60}\) In addition to using SSRIs as first-line agents, the WFSBP guidelines\(^\text{4}\) also recommend TCAs and SNRIs as first-line options for severe depression. The RANZCAP guidelines\(^\text{62}\) suggest a TCA or venlafaxine, an SNRI, as first-line treatment with lesser evidence for use of the SSRIs as first-line therapy. The RANZCAP guidelines also recommend the use of phenelzine or CBT for depression with atypical features. The BAP guidelines\(^\text{63}\) do not consider psychotherapy alone as adequate for acute severe depression and recommend the use of an antidepressant as a first line. The aforementioned guidelines do not consider repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS), hypericum extract (St John's wort) or omega 3 supplementation as first-line treatments for severe depression, but consider light therapy as first-line treatment for seasonal affective disorder (SAD).

4.4 Pharmacological treatment

Dosage ranges for antidepressant medications are summarised in Table 3.\(^\text{1}\) In order to improve tolerability, it may be necessary to initiate the patient on a subtherapeutic dose of an antidepressant (e.g. 10 mg fluoxetine) with gradual titration up to therapeutic dose levels. A medication trial should be of adequate dose and duration (i.e. 8 - 12 weeks). Cognisance should be taken of pharmacodynamic and pharmacokinetic properties of the selected antidepressant, and the expectation that efficacy may only be achieved following several weeks of treatment. The principle of ‘what gets you well, keeps you well’ should be kept in mind.

The patient should be monitored at regular intervals (fortnightly) to assess clinical status, response, side-effects, and safety, including worsening or emergence of suicidal ideation. Response can be assessed using a measurement-based tool such as the Clinical Global Impressions Scale (CGI). In addition to monitoring response of depressive symptoms, overall change in functioning, disability and subjective well-being should also be ascertained. If side-effects are intolerable, the patient should be switched to an alternative. Mirtazapine and bupropion, for example, may be useful in patients who experience SSRI-induced sexual dysfunction.

In general benzodiazepines (which do not have specific antidepressant effects) are not recommended as monotherapy and should be used judiciously as short-term adjunctive therapy (i.e. not longer than 4 weeks) to manage symptoms of anxiety, insomnia, and agitation on an as-needed basis. Benzodiazepines should be avoided in patients with comorbid substance-use disorders.

### Table 3. Dosage ranges for antidepressant medications\(^\text{1}\)

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Starting dosage (mg/day)</th>
<th>Usual dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics and tetracyclics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>25 - 50</td>
<td>100 - 300</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>25</td>
<td>100 - 250</td>
</tr>
<tr>
<td>Doxepin</td>
<td>25 - 50</td>
<td>100 - 300</td>
</tr>
<tr>
<td>Imipramine</td>
<td>25 - 50</td>
<td>100 - 300</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>25 - 50</td>
<td>100 - 300</td>
</tr>
<tr>
<td><strong>Secondary amine tricyclics (not available in SA)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>25 - 50</td>
<td>100 - 300</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25</td>
<td>50 - 150</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>10</td>
<td>15 - 60</td>
</tr>
<tr>
<td><strong>Tetracyclics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxapine</td>
<td>50</td>
<td>100 - 400</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>50</td>
<td>100 - 225</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors (SSRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>20</td>
<td>20 - 40</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20</td>
<td>20 - 60</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>50</td>
<td>50 - 300</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20</td>
<td>20 - 50</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50</td>
<td>50 - 200</td>
</tr>
<tr>
<td><strong>Dopamine-norepinephrine reuptake inhibitors (NDRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>150</td>
<td>150 - 300</td>
</tr>
<tr>
<td>Bupropion, sustained release</td>
<td>150</td>
<td>150 - 300</td>
</tr>
<tr>
<td>Bupropion, extended release</td>
<td>150</td>
<td>150 - 300</td>
</tr>
<tr>
<td><strong>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>40</td>
<td>40 - 60</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5</td>
<td>75 - 375</td>
</tr>
<tr>
<td>Venlafaxine, extended release</td>
<td>37.5</td>
<td>75 - 225</td>
</tr>
<tr>
<td><strong>Serotonin modulators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>50</td>
<td>75 - 400</td>
</tr>
<tr>
<td><strong>Monoamine oxidase inhibitors (MAOIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Irreversible, nonselective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenelzine</td>
<td>15</td>
<td>15 - 90</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>10</td>
<td>30 - 60</td>
</tr>
<tr>
<td><strong>Reversible MAO-I-A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moclobemide</td>
<td>300</td>
<td>300 - 600</td>
</tr>
<tr>
<td><strong>Melatonergic agonist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agomelatine</td>
<td>25</td>
<td>25 - 50</td>
</tr>
</tbody>
</table>

4.5 Continuation and maintenance treatment

According to APA guidelines, the continuation phase is defined as the 16 - 20-week period that precedes sustained and complete remission from the acute phase. To prevent relapse, antidepressant medication should be continued at the same dose used during the acute phase. The aforementioned guidelines recommend that the frequency of visits be dictated to by the patient's condition and the specific treatment. Frequency can vary from once every 2 - 3 months to a few times per week.

On average, 50 - 85% of patients with a single episode of MDD will have at least one more episode. Therefore, following the continuation phase, maintenance phase treatment should be considered to prevent episodic recurrences. The following issues need to be borne in mind when considering maintenance treatment:

- The risk of recurrence (based on the number of previous episodes, presence of comorbid conditions, and residual symptoms between active episodes)
- The severity of episode(s) (based on the presence of suicidality, psychotic features, level of functional impairment)
- Side-effects associated with continuous treatment
- Patient preference.

The precise timing and methods of discontinuing psychotherapy and pharmacotherapy for depression have not been systematically evaluated. The decision to discontinue maintenance treatment should be based on the same factors guiding the decision to initiate maintenance treatment, including the probability of recurrence, the frequency and severity of past episodes, the persistence of depressive symptoms after recovery, the presence of comorbid disorders, and patient preference.

4.6 Non-pharmacological treatment

Non-pharmacological alternatives include psychotherapy (e.g. CBT, IPT) and newer alternatives that work on the basis of electric currents or magnetic impulses such as ECT, rTMS, VNS, and deep brain stimulation (DBS). Both CBT and IPT have been shown to be effective in acute depression (as monotherapy in mild depression and as augmentation in moderate and severe depression), and in preventing relapse and recurrence.[63] ECT should be considered in patients with severe depression, in patients with depression with psychotic features, and in special circumstances or emergency situations.[67] rTMS, VNS and DBS are not recommended as first- or second-line treatments in MDD.

4.7 Special populations

4.7.1 Subtypes

MDD may present with melancholia, with psychotic features, with atypical features, with catatonia, or as SAD. MDD with melancholic features is characterised by anhedonia, lack of reactivity to pleasurable stimuli and typical neurovegetative features such as worsening of mood in the morning, early morning waking, and marked weight loss.[43] Although data are inconsistent, there is some evidence that venlafaxine and TCA's may be more effective than SSRIs for this depressive subtype. As mentioned previously, depression with psychotic features responds to the addition of an antipsychotic; however ECT is also an effective first-line option.[60]

Atypical depression is characterised by mood reactivity, significantly decreased energy or leaden feelings in the limbs (leaden paralysis), heightened sensitivity to interpersonal rejection, and a reversal of neurovegetative symptoms (increased sleep and appetite). SSRIs are considered first-line agents but monoamine oxidase inhibitors (MAOIs) are also effective (the latter have demonstrated superior efficacy to the TCAs).[64] In these patients, it is important to consider medication that has a lower propensity for sedation or weight gain or a switch to mania. SAD, a subtype characterised by autumn/winter depressive episodes and spring/summer hypomanic episodes, responds to both antidepressants (e.g. SSRIs) and light therapy. Both of the aforementioned treatments may be used as first-line, either separately or in combination.[64] The extended release formulation of bupropion is US Food and Drug Administration (FDA) approved for use in patients with this subtype (i.e. seasonal MDD). In patients with catatonia, ECT has been shown to be effective.[76] Intravenous administration with a benzodiazepine (e.g. lorazepam, diazepam) may also induce rapid relief.[71]

4.7.2 Comorbidity

Patients with coexisting dysthymic disorder usually have a better response to a combination of an antidepressant and psychotherapy than to either treatment alone. In patients with comorbid anxiety disorders, SSRIs or SNRIs are a good first choice.[72] In addition, short-term augmentation with a benzodiazepine may be warranted and may also assist in enhancing compliance. In patients with comorbid panic disorder, it is prudent to start off with lower dose of an SSRI; in patients with comorbid obsessive-compulsive disorder (OCD) a serotonergic agent (SSRI or clomipramine) is advised; and in patients with comorbid social anxiety disorder, an SSRI or venlafaxine but not a TCA should be used.[73,74] Psychotherapies such as CBT, behavioural therapy, and IPT may also be used to treat anxiety disorders and symptoms in this setting. Substance use disorders are often comorbid with MDD and in these patients an SSRI would be a good option although it may be necessary to detoxify these patients and then treat the substance use disorder first. For patients with comorbid borderline personality disorder, an SSRI or SNRI, should be considered. The behavioural impulsivity and dyscontrol can also be treated with a low-dose antipsychotic, lithium, or an antiepileptic medication.[75]

In patients with comorbid medical disorders, the choice of antidepressant medication and the potential for multiple interactions with other medications need careful consideration; for example, in patients with cardiac disease TCAs should be avoided while in patients with stroke or epilepsy an SSRI is preferred.[76] In HIV-infected patients, SSRIs are a preferred choice and are better tolerated than TCAs. For those patients on antiretroviral treatment, it is important to check for potential drug-drug interactions when choosing an antidepressant.[77]

4.7.3 Suicidality

 Debate about the risks of suicidal ideation and attempts following the initiation of antidepressant treatment continues. It is well known that as mood begins to improve on antidepressant treatment, so too do neurovegetative symptoms, energy and psychomotor activity. Patients may, therefore, act on pre-existing suicidal intent.[79] Recent meta-analyses of data from clinical trials have shown a statistically
significant increase in suicidal thoughts or behaviours in depressed individuals aged 25 years or younger treated with antidepressant medications, compared with placebo, with a 1.5- to 2.5-fold increase in the relative risk. In contrast, no change in risk was detected for adults aged 25 to 64 years, while older adults (aged 65 years or older) on antidepressant treatment showed a decrease in the risk of suicidal thinking or behaviours. All antidepressants, in accordance with an FDA directive, carry a black-box warning that advises of the increased risk of suicidal thinking and behaviour pertaining to children, adolescents, and young adults.

4.7.4 Pregnancy and lactation

Both antidepressant use and untreated depression in pregnancy carry their own set of risks. Any decision to commence, continue, or discontinue an antidepressant needs to weigh up the risks and the benefits to mother and infant. Furthermore, it is important to bear in mind that relapse rates for women with a history of MDD are high during pregnancy, especially when antidepressants are discontinued. The risk of teratogenicity with antidepressants following first-trimester exposure appears to be low overall. However, some rare birth defects have been observed to occur at higher rates with the use of specific SSRIs. For example first-trimester paroxetine exposure has been associated with cardiac malformations, a finding that resulted in changes in FDA labelling for paroxetine. Although most earlier reports suggested that SSRIs were not associated with a greater risk of congenital malformation, Chambers et al. have since shown that SSRIs can adversely affect fetal development. Antidepressant use in late pregnancy has been shown in some, but not all, studies to result in medical complications such as prematurity and transient neonatal withdrawal/adaptation syndrome.

ECT is both safe and effective during pregnancy and should be considered in pregnant women with moderate to severe depression who are unresponsive to, or unsuitable for, pharmacotherapy, for pregnant patients with psychotic features, and for pregnant patients who prefer this modality. MDD with postpartum onset is defined, in the DSM-IV-TR, as a major depressive episode with onset within 4 weeks of delivery. Antidepressants can be prescribed for postpartum depression, in accordance with the same treatment principles delineated for other types of MDD.

While long-term evidence on the risks and benefits of antidepressant use during lactation are as yet not available, existing data suggest that antidepressants are compatible with breastfeeding. There have been case reports of adverse effects in breastfeeding infants exposed to maternal antidepressants but most studies have indicated low levels of exposure via breast milk with the SSRIs. The exception to this is fluoxetine, which appears to have a dose-related risk for detectable levels in infant sera.

4.8 Managing partial and non-response

Medication response may take 6 - 8 weeks or longer. If a first-line treatment has not worked after 8 weeks at an optimal dose (i.e. there is no response), most guidelines recommend a re-evaluation of symptoms and adverse effects before switching to another antidepressant from another class; for example, if a patient has had a trial of an SSRI then one should consider switching to an SNRI or to mirtazapine or bupropion. If a first-line treatment has partially worked (i.e. there is a partial response), then it is important to ensure that the patient is adherent and not experiencing intolerable side-effects. In this instance, the dose should be increased. If there is still no response after 4 - 6 weeks, it is prudent to consider combining the existing antidepressant with another antidepressant with a different mechanism of action (e.g. combining bupropion or mirtazapine with an SSRI, combining an SSRI with a TCA, combining venlafaxine with mirtazapine). Alternatively, augmentation strategies can be tried. These include the addition of lithium, an atypical antipsychotic, triiodothyronine (T3) or mianserin.

5. Summary points

- First-line treatment for mild to moderate depression should consist of psychotherapy (CBT or IPT) either alone or in combination with an SSRI, an SNRI (e.g. venlafaxine), bupropion, mirtazapine or agomelatine.
- For severe depression, always consider an antidepressant as first-line (an SSRI, venlafaxine (SNRI), bupropion or mirtazapine) in combination with CBT or IPT, or alternatively consider ECT.
- Severe major depression with psychotic features warrants a combination of an antidepressant with an antipsychotic. ECT should also be considered. Consider a combination of either a tertiary amine tricyclic antidepressant with an antipsychotic agent (either a first- or second-generation antipsychotic); an SSRI in combination with an antipsychotic; or venlafaxine in combination with an antipsychotic.
- Choice of medication should be based on patient profile, side-effect profile, medication availability, nature of prior response to medication, comorbid psychiatric and medical conditions, patient preference, potential drug interactions and cost.
- If a patient presents without comorbidities and has had a previous satisfactory response to an SSRI, consider initiating treatment with a SSRI. If a patient presents with a comorbid anxiety or pain disorder, consider initiating treatment with an SSRI, SNRI or mirtazapine.
- Monitor patients initially at least fortnightly and continue medication treatment for 4 - 6 weeks.
- If remission is achieved, continuation treatment is warranted.
- With partial responders but not full remitters, increase the dose and continue for a further 4 - 6 weeks and reassess.
- With no response, choose to: (i) switch to another first-line medication from a different pharmaceutical class; (ii) augment with any one of the following: lithium, triiodothyronine (T3), an antipsychotic agent, an anticonvulsant/mood stabiliser; or (iii) combine an SSRI with a TCA, an SSRI with bupropion, an SSRI with mirtazapine, or venlafaxine with mirtazapine.

References

Bipolar disorder

F Colin

1. Introduction
Bipolar disorder (BD) presents in different phases over time and is often complicated by comorbid conditions such as substance-use disorders and anxiety disorders. Treatment usually involves pharmacotherapy with combinations of different classes of medications and frequent medication revisions.

Since practice recommendations or treatment guidelines cannot fully summarise the myriad of presentations, they need to be used flexibly, taking into account the individual patient, the sociocultural context and the availability of treatment resources. The Medicines Control Council (MCC) in South Africa often lags behind other international regulatory agencies regarding the registration of medications with confirmed efficacy for indications in BD and therefore clinicians have to prescribe certain drugs off-label in the treatment of routine, difficult and treatment-resistant cases of BD.

In this guideline, levels of evidence derived from studies will be explored.\[3,4\] Evidence criteria include:

- Level 1: meta-analysis or replicated double-blind (DB), randomised controlled trial (RCT) with a placebo condition
- Level 2: at least one DB-RCT with active comparison condition or placebo
- Level 3: prospective uncontrolled trial with at least ≥10 participants
- Level 4: anecdotal reports or expert opinion.

This guideline makes treatment recommendations\[5\]

- First line: level 1 or level 2 evidence plus clinical support for safety and efficacy
- Second line: level 3 evidence or higher plus clinical support for safety and efficacy
- Third line: level 4 evidence or higher plus clinical support for safety and efficacy
- Not recommended: level 1 or level 2 evidence for lack of efficacy.

1.1 Epidemiology of bipolar disorder pertinent to the treatment guideline[2-8]

1.1.1 Epidemiological statistics
For bipolar I disorder, the mean reported age of the first mood episode is 18.2 years, while the lifetime prevalence is 1%. For bipolar II disorder, the mean reported age of first mood episode is 20.3 years, while the lifetime prevalence is 1.1%. Bipolar I disorder affects men and women equally, while bipolar II disorder is more common in women.\[3,4\]

1.1.2 Illness characteristics
The first symptoms of BD often present at 15 - 19 years of age. The most likely first episode, and also predominant phase in the later stages of the illness, is depression. Suicide is 15 times more likely in BD patients compared to the general population, with as many as 7 - 15% of all bipolar sufferers committing suicide. Suicide is most likely to occur during mixed or depressive episodes.\[5\]

2. Diagnosis and clinical characteristics
The diagnosis should be made with rigour. As the full spectrum of the disorder does not present itself at one point in time only, the diagnosis should be made over time. Table 1 summarises the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)\[6,7\] classification of bipolar subtypes.\[7,8\]

The International Society for Bipolar Disorders (ISBD) Diagnostic Guidelines Task Force made the following recommendations for the DSM-V and International Classification of Diseases 11th Revision (ICD-11) for BD.\[1\] For BD I, the DSM-V criteria for mania should remain similar, but for bipolar depression, the criteria should include a probabilistic approach acknowledging the presence of: (i) atypical depressive symptoms (hyperphagia, hypersomnia, or leaden paralysis); (ii) psychomotor disturbance; (iii) pathological guilt or psychotic features; and (iv) a positive family history of BD. It was suggested that the rapid-cycling specifier for BD I should be extended to BD II and BD not otherwise specified (NOS)(now known as Other Specified Bipolar and Related Disorder in the DSM-V. The Task Force also suggested modifications to the diagnostic criteria for BD II and BD NOS to improve the identification of bipolar spectrum disorders to include the following: (i) subthreshold hypomanic episodes, and (ii) other signs of bipolarity without manic or hypomanic episodes (also known as bipolar spectrum disorder). These include:

- Family history (BD, alcohol and substance use, mental illnesses, suicides)
- Depressive symptoms (atypical, psychomotor slowing, psychosis, seasonal)
- Course of illness (early age of onset, short duration of episodes, greater number of episodes).

Separating major depressive disorder (MDD) and BD, particularly BD II, can be a challenge.\[12\] Several reports have found that BD, in contrast to MDD, is associated with:

- A significantly earlier age of onset
- More recurrences

Table 1. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) classification of bipolar subtypes[6,7,11]

<table>
<thead>
<tr>
<th>Bipolar I disorder</th>
<th>Bipolar II disorder</th>
<th>Cyclothymic disorder</th>
</tr>
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<tbody>
<tr>
<td>Characterised by one or more episodes of mania with or without major depressive episodes.</td>
<td>Characterised by one or more episode of hypomania as well as at least one major depressive episode with no psychotic features.</td>
<td>Characterised by a low grade cycling of mood with the presence or history of hypomanic episodes and periods of depression that do not meet the criteria for major depressive episodes.</td>
</tr>
<tr>
<td>Bipolar disorder not otherwise specified is characterised by bipolar symptoms that do not meet the criteria for previous subtypes.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Atypical and mixed depressions
• A family history of BD or completed suicide.

A BD diagnosis is highly predicted by mixed states, especially BD II, which has been linked with an increased lifetime risk for comorbid psychiatric disorders, more mood episodes, higher rates of treatment contacts, and lower rates of full-time employment compared to pure states.

Once a BD diagnosis has been made, the diagnostic formulation should identify the episode type and the longitudinal course of illness. Valuable clinical tools that inform assessment and assist in monitoring and quantifying treatment response include the following rating scales:

- Bipolar Inventory of Symptoms Scale (BISS)
- Structured Clinical Interview for Mood Spectrum (SCI-MOOD)
- Young Mania Rating Scale (YMRS) for mania
- Bipolar Depression Rating Scale (BDRS) for bipolar depression
- Mood Disorders questionnaire.

Once the diagnosis of BD has been confirmed, a comprehensive risk assessment should be completed on an ongoing basis throughout treatment. Ensuring the safety of patients with acute mania is essential, since there is an increased risk of aggression, excessive spending and disinhibited behaviour, decreased judgement and insight, and an increased risk of suicidal thoughts immediately after admission to, and immediately following discharge from, hospital. The risk to others, including to children or other family members, should also be considered. The appropriate venue for treatment, i.e. inpatient or outpatient, voluntary or involuntary, should then be determined.

3. Recommended baseline investigations for BD

The recommended investigations should assist clinicians in management and are not diagnostic in nature. The list below represents a list of possibilities to be considered where clinically appropriate and does not represent an exhaustive list of tests to be performed in every patient with suspected BD.

Baseline investigations:
• Extrapyramidal side-effects: clinical assessment of abnormal involuntary movements
• Cataracts: ocular examination (quetiapine only)
• Metabolic syndrome:
  - Waist circumference
  - Body mass index
  - Blood pressure
  - Fasting lipid profile (triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL))
  - Fasting blood sugar
• Screen/test:
  - Full blood count
  - Blood chemistry:
    - (i) Electrolytes
    - (ii) Serum creatinine
    - (iii) Thyroid-stimulating hormone
    - (iv) Liver function tests
  - Prolactin levels (if indicated)
  - Substance use: urine toxicology (if indicated)
• Polycystic ovarian syndrome: reproductive endocrine abnormalities (if prescribing valproate to females of child-bearing potential)
• Pregnancy test (if indicated, especially if bearing potential)
• For acute symptoms of mania, taper and cease any antidepressants or agents with mood-elevating properties (e.g. stimulants)
• While some antibipolar agents are efficient in the acute phase, others are more efficient in the maintenance phase.

The treatment of BD can be divided into the following components:
• Acute treatment of mania and hypomania
• Acute treatment of depression
• Maintenance treatment
• Bipolar II disorder
• Treatment of complex bipolar presentations (i.e. rapid cycling and mixed states)
• Partial or no treatment response
• Treatment of comorbidities (i.e. anxiety disorders and substance-use disorders (not included in this guideline)).

4. Treatment

4.1 Pharmacological treatment

Malhi and co-authors[2] have used specific terminology to categorise the pharmacological agents for BD treatment. As illustrated in Fig. 1 these terms have been chosen based on the intended therapeutic action rather than on the traditional medication class.[2]

Medications efficacious in the treatment of mania or hypomania include antimanic agents. Maintenance agents include those administered in the euthymic phase of BD with proven prophylactic efficacy. Bipolar depression agents, which should not be confused or used interchangeably with the term antidepressants, include effective medications for the treatment of bipolar depression.

Some medications have indications for multiple phases of the illness. Since there are very few drugs that truly meet the full definition of a mood stabiliser (i.e. effective for all phases of the illness), the term mood stabiliser has largely fallen into disfavour. While some antibipolar agents are efficient in the acute phase, others are more efficient in the maintenance phase.

4.2 Acute treatment: bipolar mania

For acute symptoms of mania, taper and cease any antidepressants or agents with mood-elevating properties (e.g. stimulants) and introduce general measures where possible:

![Fig. 1. Phases of bipolar illness with matching treatment terminology.[2]](image_url)
• Reduce stimulation
• Lower activity level
• Delay individual from making important decisions
• Maintain a structured routine.

Commence treatment with an antimanic agent (level 1). When selecting an agent, its antimanic efficacy and tolerability, as well as the likelihood of continuing acute treatment into maintenance phase, should be considered. Recommendations for the pharmacological treatment of acute mania are summarised in Table 2.[3]

4.2.1 Monotherapy[2]
Antimanic agents with evidence for efficacy in acute mania include:
• Lithium
• Valproate – the speed of action for valproate can be accelerated using dose-loading
• Olanzapine
• Aripiprazole
• Quetiapine
• Ziprasidone
• Paliperidone
• Haloperidol – haloperidol is efficacious but longer-term use carries an increased risk of extrapyramidal side-effects (e.g. tardive dyskinesia). Haloperidol is not recommended unless other options have failed, as it lacks efficacy in maintenance treatment.
• To a lesser extent, carbamazepine.

4.2.2 Combination treatment[2]
In comparison to monotherapy with either lithium or valproate alone, recent studies have shown superior efficacy of lithium or valproate in combination with the short-term administration of an atypical antipsychotic. If symptoms and/or behavioural disturbances are severe or protracted, electroconvulsive therapy (ECT) (level 3) should be considered. During ECT, discontinue lithium and anticonvulsants. Although recent studies have indicated that anticonvulsants may be continued during ECT without losing therapeutic efficacy of ECT, it is advisable to discontinue anticonvulsants during ECT.

Gabapentin, lamotrigine, topiramate, phenytoin and oxcarbamazepine are not recommended for the treatment of acute mania.

• Behavioural disturbance:[2]
• Acute behavioural disturbance can be managed by either the short-term use of a benzodiazepine (e.g. lorazepam) or an antipsychotic; the concurrent use of two antipsychotics is not recommended.
• Oral administration is preferable.
• It is advisable to use an injectable atypical or a combination of an injectable typical antipsychotic and a benzodiazepine if intramuscular (IM) administration is necessary. RCT data support the use of IM aripiprazole or IM olanzapine (level 2) in the treatment of acute agitation.[1]
• IM aripiprazole (9.75 mg and 15 mg) (not available in South Africa) is superior to placebo and comparable with IM lorazepam (2 mg).[10] In a DBRCT, IM olanzapine 10 mg was superior to placebo and has shown a trend toward greater improvement than IM lorazepam 2 mg.[11]
• In view of the risk of respiratory failure, olanzapine should not be used in combination with benzodiazepines.

Psychotic mania:
• Psychosis is common and occurs in approximately 60% of acute manic episodes.
• For acute psychotic symptoms, an antipsychotic may be employed as adjunctive treatment, if not already being administered as an antimanic agent.
• Atypical antipsychotics are preferred to typical antipsychotics since they have enhanced tolerability.

4.2.3 Psychotherapy for mania
Psycho-education (PE) and family-focused therapy (FFT) are efficacious in the prevention of mania/hypomania (and possibly depression).[11] To prevent bipolar episodes, interpersonal social rhythm therapy (IPSRT) and cognitive-behavioural therapy (CBT) are probably efficacious.[11]

4.3 Acute treatment: bipolar depression
4.3.1 Pharmacotherapy for bipolar depression
In patients with bipolar depression, any agents that could exacerbate depressive symptomatology (e.g. typical antipsychotics such as chlorpromazine, antihypertensive agents and corticosteroids) should be ceased.[12]

Table 2. Recommendations for pharmacological treatment of acute bipolar II depression[1]

<table>
<thead>
<tr>
<th>Category</th>
<th>First Line</th>
<th>Second Line</th>
<th>Third Line</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>Quetiapine*</td>
<td>Lithium</td>
<td>Antidepressant monotherapy (particularly for those with infrequent hypomanias), switch to alternate antidepressant</td>
<td>Risk-benefit ratio for antidepressant use in BD II is still an unresolved issue</td>
</tr>
<tr>
<td>Second line</td>
<td>Lithium</td>
<td>Lamotrigine</td>
<td>Lithium or divalproex + antidepressants</td>
<td>Switch rates with antidepressants are lower in patients with BD II compared with those with BD I</td>
</tr>
<tr>
<td></td>
<td>Divalproex*</td>
<td>Lithium + divalproex</td>
<td>Atypical antipsychotics + antidepressants</td>
<td></td>
</tr>
<tr>
<td>Third line</td>
<td></td>
<td>Lithium + divalproex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not recommended</td>
<td></td>
<td></td>
<td>Antipsychotic monotherapy (particularly for those with infrequent hypomanias), switch to alternate antidepressant</td>
<td></td>
</tr>
</tbody>
</table>

*New
First-line monotherapy treatment options for bipolar depression include:
- Quetiapine 300 - 600 mg/day
- Lamotrigine 200 - 500 mg/day
- Olanzapine 5 - 15 mg/day
- Lithium
- Valproate.

Second-line options for bipolar depression include the following adjunctive or combination therapies:
- Adjunctive risperidone 2 - 4 mg/day
- Lithium and antidepressant combinations
- Olanzapine and fluoxetine combination
- Valproate and lithium
- Lamotrigine as an add-on to lithium.

For concurrent psychotic symptoms, atypical antipsychotics can be used as augmentation (level 2), but combining two antipsychotic medications should best be avoided.

The benefits of conventional antidepressants such as the tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and noradrenaline reuptake inhibitors (SNRIs) in the treatment of bipolar depression is currently unclear. If a conventional antidepressant is employed for bipolar depression, it should be concurrently administered with an antimanic maintenance agent to diminish the possibility of switching. The antidepressant should then gradually be tapered after 2 - 3 months of sustained recovery. In addition, antidepressants should not be prescribed in rapid-cycling BD. Also, venlafaxine (13 - 15%) and the TCAs (7 - 11%) are associated with a relatively higher risk of inducing a manic switch than SSRIs (0 - 4%). While other agents can also precipitate switching (e.g. psychostimulants).

ECT should be considered if the risk to self or others is high, if psychotic features are present, or if there has been a previous response to ECT (level 3).

4.3.2 Psychotherapy for bipolar depression
As there is no definitive evidence for the efficacy of psychological therapies as BD monotherapy, these therapies are best administered as adjunctive treatments to pharmacotherapy. There is also limited evidence for psychological treatments in acute bipolar depression compared to evidence for their use as maintenance-phase treatments.

CBT and FFT are efficacious, with IPSRT possibly efficacious, as adjuncts to medication, in the treatment of bipolar depression.

If a patient has severe psychomotor impairment or psychotic features, psychological treatments are not recommended during the acute phase.

4.4 Maintenance treatment
Maintenance treatment is important once a diagnosis of BD has been made. Indications for maintenance treatment include:
- A mood episode in the past 5 years
- Two previous mood episodes over any time period
- Severe acute episodes with psychotic features, or a suicide risk
- Ongoing functional disability (level 5).

The treatment plan should be re-evaluated and attention should be paid to factors that may increase the risk of relapse, including comorbid conditions and psychosocial stressors. A collaborative approach to maintenance care should be adopted. Furthermore, both pharmacological and psychological treatment strategies should be used to eliminate subsyndromal depressive symptoms, since disability is closely related to the depressive component of the illness. Psychosocial stressors should be addressed; address problem-solving skills and the development of social support networks (especially with chronic depressive symptoms); encourage a healthy lifestyle (good sleep hygiene, exercise, regular routine); treat comorbidities, particularly substance misuse; monitor clinical response to medications, adherence and side-effects; monitor social and occupational functioning; provide PE for the family; and address caregiver support.

4.4.1 Psychological interventions as an adjunct to medication
These appear to have the greatest benefit in reducing the risk of relapse and can improve functioning. By targeting euthymic patients in the maintenance phase of illness, therapeutic effects can be optimised, but are likely to be less effective in those with a high number of prior mood episodes (>12 episodes). There is strong evidence for interventions that focus on the recognition of early warning signs (level 1) and this includes:
- CBT (level 2)
- FFT (level 2)
- IPSRT (level 2)
- Group PE (level 2)

4.4.2 Maintenance pharmacotherapy
As a first step, any adjunctive agents that have been used to manage behavioural disturbance associated with an acute mood episode should be withdrawn. As little evidence currently exists for combining treatments, monotherapy is preferred. Medications shown to be effective maintenance agents include:
- Lithium (level 1), mainly for preventing manic episodes
- Lamotrigine (level 2), mainly for preventing depressive episodes
- Valproate (level 2)
- Atypical antipsychotics: olanzapine (level 2)
- Aripiprazole (level 2)
- Quetiapine adjunctive to lithium or valproate (level 2).

Other atypical antipsychotics that have a limited evidence base (restricted to small trials or retrospective data) include:
- Ziprasidone (level 3)
- Risperidone (level 3)
- Adjunctive depot risperidone (level 3)
- Adjunctive clozapine (level 3).

Selection of maintenance agents should be based on their efficacy and tolerability profiles. In addition, consideration needs to be given to individual patient factors (preference, past response, safety). In this regard and to maintain therapeutic blood levels, lithium needs to be monitored regularly (0.6 - 1.2 mmol/l). The evidence for carbamazepine as a maintenance treatment is mixed, while there is no evidence for the efficacy of conventional antidepressants (e.g. TCAs, SSRIs and SNRIs) in maintenance. That said, if depressive episodes are recurrent, an antidepressant may be considered as an adjunctive to a maintenance agent, after carefully weighing up the benefits of prevention versus the risk of precipitating mania or rapid cycling. The recommendations for maintenance pharmacotherapy of BD are summarised in Table 3.
4.4.3 How long to treat
Treatment of BD is often lifelong, and a minimum of 6-monthly reviews is recommended.

The strength of evidence for monotherapy treatments for acute bipolar II depression, and for maintenance of BD II are summarised in Tables 4 and 5, respectively.

4.5 Complex bipolar presentations
4.5.1 Rapid cycling
This presentation is associated with higher rates of morbidity, increased suicide risk, and poorer long-term treatment response.

It is important to screen for and, where possible, exclude factors that may precipitate or exacerbate rapid cycling:
- Antidepressants
- Substance misuse
- Medications
- Medical illness, e.g. hypothyroidism.

Treatment options for rapid cycling:\[2\]
- There is a limited evidence base of effective treatments for rapid cycling.
- Current treatments appear to be less effective in countering depressive symptoms than manic symptoms.

Pharmacological monotherapy:
- Consider valproate (level 2)
- Lithium (level 2)
- Olanzapine (level 2)
- Lamotrigine (level 2) (primarily for BD II patients)
- Quetiapine (level 3).

Combination therapies:
- Consider adjunctive psychological interventions (level 5) as outlined under maintenance treatments.
- There is limited evidence to support combination pharmacological treatments and this should be decided according to clinical need, e.g.:
  - Lithium + valproate (level 3)
Distinguish mixed states from both mania and agitated depression. Studies focusing on monotherapy and adjunctive treatment options for mixed states are scant, although patients with mixed states have been included in trials of acute mania and acute bipolar depression. As a start, it is important to taper and cease medications with mood-elevating properties, especially those that may induce inter-episode switching. Antidepressants can worsen or induce rapid cycling and are thus not recommended. Lithium may have reduced efficacy for treating mixed states. Treatment options include:

- Lithium + carbamazepine (level 3)
- Adjunctive lamotrigine (level 5).
- Physical treatments: ECT (level 3).

### 4.5.2 Mixed states

Therapeutic strategies for non-response in mania:

- Optimise antimanic agent:
  - Check levels
  - Adjust dose
  - And/or augment
  - And/or combine with another antimanic agent.

Consider combination therapy. This is often used in clinical settings where response to monotherapy has been inadequate. Head-to-head comparison studies of different combinations are scant. Combinations that have been assessed in clinical trials include:

- Lithium and valproate (level 2)
- Lithium and carbamazepine (level 2)
- Lithium or valproate and olanzapine (level 2)
- Adjunctive clozapine or risperidone (level 3).

Substitute antimanic agent with another and/or consider ECT (level 3) if episode is very severe or there is a high suicide risk. Bipolar depression: non-response:

- Optimise dose (check blood levels and/or adjust dose) of medication being used and/or
- Switch to alternative bipolar depression agent and/or
- Augment and/or combine agents
- Consider adjunctive psychological therapy that will target depressive symptoms (e.g. CBT, IPSRT, FFT).
- Consider using conventional antidepressants, but closely monitor for switch to mania.
- Consider ECT (level 3) if episode is very severe, or there is marked or significant risk for treatment resistance.

Treatment non-adherence is common in BD. Depot treatment of either an injectable atypical antipsychotics (level 3) (e.g. risperidone) or an injectable first-generation antipsychotic (level 3) should be considered in cases of ongoing persistent non-compliance, and after failure of other appropriate interventions. A first-generation depot antipsychotic is not recommended where the course of BD is characterised predominantly by depression.

### 4.7 Algorithm

Fig. 2 outlines the treatment algorithm. Please refer to Appendix A for other aspects of treatment and management.
5. Summary points
• For acute symptoms of mania, commence treatment with an antimanic agent. Antimanic agents with evidence for efficacy in acute mania include lithium, valproate, olanzapine, aripiprazole, quetiapine, risperidone, ziprasidone, paliperidone, haloperidol and to a lesser extent carbamazepine.
• Recent studies have shown superior efficacy of lithium or valproate in combination with the short-term administration of an atypical antipsychotic.
• Gabapentin, lamotrigine, topiramate, phenytoin and oxcarbamazepine are not recommended for the treatment of acute mania.
• If IM administration is required for acute agitation/behavioural control, it is advisable to use an injectable atypical or a combination of an injectable typical antipsychotic and a benzodiazepine. RCT data support the use of IM aripiprazole or IM olanzapine for acute agitation.
• First-line monotherapy treatment options for bipolar depression include quetiapine, lamotrigine, olanzapine, lithium, and valproate.
• For concurrent psychotic symptoms, both in bipolar mania and depression, atypical antipsychotics can be used as augmentation.
• In bipolar depression, an antidepressant should be administered concurrently with an anti-manic maintenance agent to reduce the possibility of switching. The antidepressant should then gradually be tapered after 2 - 3 months of sustained recovery.
• Antidepressants should not be prescribed in rapid-cycling BD.
• For rapid cycling, consider valproate, lithium, olanzapine (for BD II), or quetiapine.
• Psychotherapies are best used as adjuncts to medication in bipolar depression. CBT (cognitive-behaviour therapy) and family-focused therapy (FFT) are efficacious, with interpersonal social rhythm therapy (IPSRT) possibly efficacious, as adjuncts to medication, in the treatment of bipolar depression. Adjunctive psychotherapy can reduce the risk of relapse and improve functioning.
• Maintenance treatment must be considered if there has been a mood episode in the past 5 years, if there have been 2 previous mood episodes over any time period, if acute episodes are severe with psychotic features or if there is a suicide risk, or if there is ongoing functional disability.
• Medications shown to be effective maintenance agents include lithium (mainly for preventing manic episodes), lamotrigine (mainly for preventing depressive episodes), valproate, atypical antipsychotics (olanzapine, aripiprazole, and quetiapine adjunctive to lithium or valproate).
• For non-response in bipolar mania, consider combining 2 mood stabilisers (e.g. lithium + valproate, lithium + carbamazepine, lithium or valproate + olanzapine) or combining a mood stabiliser with an atypical antipsychotic; for non-response in bipolar depression consider switching to another bipolar depression agent or augmenting with another bipolar depression agent or with psychotherapy.
Appendix A: Other aspects of treatment and management

1. Definition of the bipolar disorder prescribed minimum benefit as defined in the Medical Schemes Act
The chronic disease list (CDL) specifies medication and treatment for the 25 chronic medical conditions that are covered in the section on prescribed minimum benefits. Bipolar disorder (BD) is one of the 25 conditions. The section on these conditions stipulates the following:

‘To manage risk and ensure appropriate standards of healthcare, so-called treatment algorithms were developed for the CDL conditions. The algorithms, which have been published in the Government Gazette, can be regarded as benchmarks, or minimum standards, for treatment. This means that the treatment your medical scheme must provide for may not be inferior to the algorithms. If you have one of the 25 listed chronic diseases, your medical scheme not only has to cover medication, but also doctors’ consultations and tests related to your condition. The scheme may make use of protocols, formularies (lists of specified medicines) and designated service providers (DSPs) to manage this benefit.’

2. Indications for hospital admission
Consider hospitalisation in patients who:
- Pose a serious threat of suicide or harm to others
- Are severely ill
- Are ill and lack social support outside of a hospital
- Demonstrate significantly impaired judgment
- Have complicating general medical or psychiatric conditions
- Have not responded adequately to outpatient psychiatric treatment
- Need urgent revisions of medication treatment requiring constant supervision in hospital.

3. Guidelines for intravenous treatment
Intravenous (IV) drug treatment is rarely appropriate in the treatment of BD and may only be indicated in the following cases:
- Where taking of oral medication is not possible, as in intensive care settings
- As part of treatment of secondary syndromes related to treatment side-effects, i.e. acute dystonia
- For IV sedation of acutely agitated/manic patients
- IV sodium valproate has been described for the initial treatment of acute mania but is not deemed a routine treatment. It may be considered when a manic presentation poses a life-threatening risk to patient or others.
Panic disorder

C P Szabo

1. Introduction
Panic disorder (PD) is a prevalent anxiety disorder with lifetime prevalence rates ranging from 1.1% to 3.7% in the general population and 3.0% to 8.3% in clinic settings.[1] The presence of agoraphobia in patients with PD is associated with substantial severity, comorbidity (e.g., major depression, other anxiety disorders, alcohol abuse) and functional impairment.[2] The disorder is more common in women than in men, with a 3:1 ratio in patients with agoraphobia and 2:1 in patients without agoraphobia. While panic attacks are a core feature of PD, panic attacks are also experienced by patients with post-traumatic stress disorder, social anxiety disorder and specific phobias. However, unlike in PD, these are typically cued by exposure to or anticipation of specific anxiety-provoking situations.[2]

2. Diagnosis and clinical characteristics
PD is an anxiety disorder characterised by recurrent panic attacks involving intense fear/discomfort and accompanied by at least 4 of 13 somatic or cognitive symptoms which develop abruptly and reach a peak within 10 minutes (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)).[2] Attacks should not be substance-induced, nor related to a medical condition or as a consequence of another psychiatric disorder, and should be spontaneous in nature. Panic attacks that occur with fewer than 4 of the 13 panic symptoms are termed limited symptom attacks.[2] To make the diagnosis of PD, at least one of the attacks must be followed by a month or more of persistent concern regarding the possibility of a subsequent attack, worry about the implications of the attacks and/or behavioural change, e.g., avoidant behaviours such as agoraphobia – anxiety about being in places from which escape might be difficult or where help may not be available in the event of a panic attack.[2] PD may occur with or without agoraphobia.[2] The disorder has been described as a ‘common, persistent and disabling’ condition.[3] Notwithstanding such a description, both pharmacological and psychotherapeutic interventions have established efficacy.

3. Assessment
Based on the clinical characteristics, and awareness of the potential diagnostic pitfalls, i.e., substance/medically/other related psychiatric disorders, the assessment requires not only a careful history but also the possibility of toxic screening and physical investigation to rule out medically or substance-related presentations.

4. Treatment
4.1 Treatment goals
The initial goal of any intervention is symptom relief together with maintenance of functioning, followed by ongoing alleviation of symptoms accompanied by optimal functioning. PD represents a specific challenge, given the experience of panic attacks as events characterised by fear and accompanied by a range of somatic symptoms.[2] Therefore the goal remains to reduce the severity and intensity of panic attacks, avoidance, fearful anticipation, and cognitive distortions. Of specific relevance is the unpredictability of episodes and the need for clinicians to meaningfully reassure patients of the planned intervention in terms of outcome, for both future episodes and functioning.

4.2 General aspects of treatment
Two broad categories of intervention have demonstrable efficacy, i.e., pharmacological and psychotherapeutic. Both interventions may serve as first-line treatments, as meta-analytic reviews and large-scale comparative trials have shown comparable efficacy, with high remission rates (60 - 80%) and maintenance of gains over time for both modalities.[4] Systematic reviews have also confirmed that a combination of the two is most effective in the acute phase with ongoing superior effectiveness following the acute-phase treatment. This is compared to pharmacotherapy alone; however, combination therapy may offer only limited benefits beyond that derived from psychotherapy alone (viz. cognitive-behavioural therapy (CBT)). Pharmacotherapy includes the use of both antidepressant agents and benzodiazepines. Psychotherapeutic approaches include both cognitive and behavioural components either individually or in combination.[5]

4.3 Pharmacological treatment: Acute
The first-line pharmacotherapy of choice in this anxiety disorder is the selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine/paroxetine/fluvoxamine/sertraline/citalopram/escitalopram), or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (including the extended-release formulation), with multiple randomised controlled trials (RCTs) showing their efficacy and safety.[6,7] PD also responds to certain other antidepressants, such as the tricyclic antidepressants (TCAs) (while of equivalent efficacy to SSRIs, their use is limited by side-effects). Very-low-dose treatment should be initiated in PD (e.g., fluoxetine 5 mg/venlafaxine ER 75 mg) with gradual upward titration as required. At least 6 - 8 weeks of adequate doses of medication are required to assess whether an acute intervention is effective or not. While such an approach appears reasonable, the use of antidepressants as stand-alone, first-line intervention has, on the basis of systematic review, been cautioned against.[6] Although there is less evidence available for children/adolescents, SSRIs may again be useful.[6,7]

Given concerns about their side-effect profile (as well as tolerance and dependency), the use of high-potency benzodiazepines should generally be limited to short-term augmentation of antidepressant medication to rapidly stabilise PD symptoms.[8] Certainly the use of combination treatment (clonazepam/sertraline) has been found to provide rapid – and safe – stabilisation of panic symptoms.[9] Benzodiazepines (alprazolam, clonazepam and lorazepam) are effective...
and use patterns have demonstrated that this class of drug is the most commonly used, notwithstanding guidelines recommending SSRIs as the preferred treatment.\textsuperscript{10} Data regarding the use of benzodiazepine treatment combined with psychotherapy versus benzodiazepine treatment alone suggest superiority of combined treatment; however, there is a paucity of good-quality evidence, either supportive or non-supportive.\textsuperscript{11} Of note is a systematic review that failed to identify quality studies comparing benzodiazepines to newer antidepressants (now regarded as the first line of pharmacological intervention), with the suggestion that the promoted move away from first-line and maintenance treatment with benzodiazepines has occurred without appropriate evidence to support this approach.\textsuperscript{12} Most typically the benzodiazepines are seen to have value as ‘rescue’ agents, specifically alprazolam (including the extended-release formulation),\textsuperscript{13} in spite of a lack of evidence-based data supporting such use, notwithstanding clinician and patient support and preference for such use.\textsuperscript{14}

4.4 Pharmacological treatment: Maintenance
Maintenance treatment at the same dose on which improvement occurred should be continued for at least 1 year. Relapse rates following discontinuation have shown varying outcomes, with rates ranging from 25% to 50%.\textsuperscript{15} Of particular interest is that ongoing psychotherapy (CBT) is as effective as combination treatment (pharmacotherapy/psychotherapy), which suggests that this may be the preferred option in the longer term.

4.5 Non-pharmacological treatment
CBT has been shown to be effective for the treatment of anxiety disorders in multiple RCTs.\textsuperscript{16} CBT for PD consists of components of psycho-education, cognitive restructuring, and behavioural interventions, with the combination of exposure therapy, relaxation exercises and breathing retraining providing the most consistent evidence for efficacy.\textsuperscript{20} The typical duration of treatment is 12 - 15 sessions, but even briefer treatments have shown efficacy.\textsuperscript{16} The combination of pharmacotherapy and psychotherapy may have particular advantages (e.g. preventing relapse after medication discontinuation) and has been suggested as a first line of treatment (together with psychotherapy alone).\textsuperscript{16} In addition to these more traditional non-pharmacological interventions, the role of education, self-management and internet-based interventions have shown benefit and appear worthy of further study for select patients and situations.\textsuperscript{16} Also, the use of virtual-reality exposure therapy represents an interesting development, although it has not been clearly demonstrated to be superior to CBT.\textsuperscript{16}

4.6 Special populations
Comorbidity is common among psychiatric populations. Within the context of PD, the impact of panic symptoms in relation to outcomes of mood disorders is of relevance, because persistent panic symptoms appear to negatively influence treatment outcomes of major depression.\textsuperscript{21} Further, PD comorbid with bipolar disorder confers an increased risk for suicide.\textsuperscript{21} This underscores data demonstrating that PD is independently associated with risk for suicide attempts.\textsuperscript{21} The treatment of PD among patients with comorbid bipolar disorder represents a challenge in so far as the use of antidepressant agents may induce mania.\textsuperscript{21} Further, the presence of mood instability in PD patients may worsen the condition, as well as lead to resistance to antidepressants.\textsuperscript{21} A recently published trial of sodium valproate, at doses of 600 - 700 mg daily (commencing at 300 mg daily), co-administered with an antidepressant or as monotherapy in PD patients with comorbid bipolar disorder, produced symptom remission.\textsuperscript{18} There are limited controlled data in this regard; hence Perugi et al.\textsuperscript{19} provide limited but objective evidence to support the use of mood stabilisers as treatment for PD, in both ‘antidepressant-resistant’ sufferers as well as those with comorbid bipolar disorder. Another population of interest are those suffering from migraine where PD is strongly associated, with either condition impacting on the other bidirectionally.\textsuperscript{20} It is clear that clinical assessment regarding comorbidity covers a range of conditions and is critical for outcome and optimal treatment of PD. Of specific interest are those patients with anxiety disorders, including PD, who have comorbid substance-related conditions, specifically in relation to benzodiazepine use. It appears that the evidence does not preclude the use of such agents in these patients.\textsuperscript{20}

4.7 Partial and non-responders
Reviewing the studies for pharmacological management strategies, the majority of patients treated with a range of antidepressant agents achieve panic-free status during a trial of medication (with no clear cut dose-response relationship) with generally high rates of response and somewhat lower rates of remission.\textsuperscript{21} It should be noted that placebo response rates of up to 50% also occur,\textsuperscript{16} and when existing data have been subjected to systematic review, combination treatment (pharmacotherapy plus psychotherapy) response rates of just over 50% have been found.\textsuperscript{21} Most patients do respond, to varying degrees, to active treatment with a range of interventions that include both pharmacotherapy and psychotherapy, either alone or in combination. Obviously when either partial or non-response is encountered, accurate diagnosis is paramount; careful reassessment should occur. Multiple agents, at optimal doses for adequate duration as well as combination treatment, are all considerations when confronted with partial or non-response – specifically combinations of antidepressant medication and benzodiazepines. It has been suggested that benzodiazepine use be reserved for treatment-resistant patients,\textsuperscript{15,21} but it appears that actual clinical practice sees the use of benzodiazepines far more routinely and in various ways.\textsuperscript{22} While there are limited data related to treatment resistance, the role of mood instability has been postulated as a factor contributing to ‘resistance to antidepressants’ with a study of sodium valproate demonstrating improved outcomes where used as an adjunct or as monotherapy (doses ranging from 300 to 700 mg daily).\textsuperscript{18} Various other agents, i.e. gabapentin, olanzapine and quetiapine, have demonstrated efficacy in the treatment of PD and could potentially be considered under circumstances of partial or non-response.\textsuperscript{23} Within this context there has been increasing interest in the use of natural remedies for the treatment of anxiety disorders, of which inositol has been studied with regard to PD.\textsuperscript{18} In the most recent of such studies inositol (18 g/day) was compared to fluvoxamine (150 mg/day) using a double-blind crossover approach which demonstrated equivalent overall efficacy in the treatment of PD with inositol demonstrating superiority with...
6. Summary points

- Both pharmacological therapies and CBT are considered first-line treatments for PD.
- Antidepressant agents have proven efficacy in the treatment of PD.
- Agents from within the SSRIs and SNRIs are the preferred options, namely the SSRIs citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline and the SNRI venlafaxine.
- Adjunctive benzodiazepines have a role in treatment.
- For acute treatment, a combination of pharmacological treatment and CBT is likely to be more effective than either therapy alone.
- CBT and pharmacotherapy are not necessarily added concurrently – there is some evidence that adding CBT to patients previously treated with pharmacotherapy provides good benefits.
- Treatment with psychotherapy alone may be the preferred longer-term option.

**Acute treatment:** Combination treatment (pharmacotherapy + psychotherapy or pharmacotherapy + pharmacotherapy (e.g. antidepressant plus benzodiazepine/sodium valproate).

**Maintenance treatment:** Combination treatment or psychotherapy alone.

- In children and adolescents with PD, there are only non-randomised, controlled studies to support the utility of the SSRIs.
- CBT is a good alternative for women with PD who plan to become pregnant, and for pregnant women who need to discontinue medication.

5. Conclusion

Based on the existing data, it would appear that combination treatment (pharmacotherapy plus psychotherapy) is the intervention of choice, and that the judicious use of benzodiazepines together with an antidepressant will provide the most rapid initial response. Further combination treatment may ultimately be adequate in the longer term for maintenance of clinical improvement. However, maintenance should include the consideration that psychotherapy alone may be an option following longer term treatment and stabilisation on combination treatment. The data for partial or non-responders are limited, but there is a suggestion that sodium valproate may be a consideration either as an adjunctive agent or as monotherapy, specifically if there is mood instability or comorbid bipolar disorder.

6. References

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Generalised anxiety disorder

D J Stein

1. Introduction

Generalised anxiety disorder (GAD) is a common disorder with a lifetime prevalence of 6.1% and a 1-year prevalence of 2.9% in one large study.[1] It occurs most commonly in the 45 - 55-year age group with women twice as likely as men to have GAD.[1]

Although symptoms typically wax and wane in intensity over time, the disorder is characterised by chronicity and is associated with high levels of psychiatric comorbidity (e.g. major depression and other anxiety disorders), physical comorbidity (e.g. gastrointestinal, respiratory, and thyroid disorders) and reduced quality of life.[2]

There have been important advances in the nosology and treatment of this disorder. In particular, there is increasing evidence that patients with GAD and mixed anxiety-depression frequently present in primary care settings,[3] and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[4] provides fairly user-friendly criteria for the diagnosis of GAD. Table 1 lists the diagnostic criteria.[3]

A few simple points can perhaps be made to help conceptualise GAD. GAD can perhaps be viewed as a ‘tension disorder’. This is a useful term in so far as it crosses the boundary between psychic symptoms (worries, feeling ‘keyed up’, irritability) and somatic complaints (muscle tension, restlessness, insomnia). While GAD patients may not present with ‘worries’, they often describe themselves as ‘worriers’ – worry may represent an avoidance behaviour that is used to diminish tension (analogous to the way that agoraphobia may develop after panic attacks).

The algorithm presented here (Fig. 1)[4] provides a step-by-step approach to the pharmacotherapy of GAD, based on our reading of the research literature. It is important to mention at the outset, however, that psychotherapy approaches may be a first-line intervention in some GAD patients and should be considered in all patients with this disorder. In addition, psycho-education is of the utmost importance, particularly in the initial stages of treatment, and should address the direct effects of anxiety on the life of the patient, as well as possible effects on family members.

2. Diagnosis and clinical characteristics

GAD is characterised by chronic, excessive, difficult-to-control worry and a range of somatic symptoms. Making the correct diagnosis is essential. Given that GAD often presents with somatic symptoms and comorbid psychiatric disorders, the diagnosis is frequently overlooked. It is therefore important to establish (i) that persistent and excessive anxiety and worry about commonly occurring events and activities – on more days than not for at least 6 months – is present; (ii) that difficulty in controlling the worries is concomitant with physical and psychic symptoms; (iii) that the focus of anxiety and worry is not part of another Axis I disorder or due to the direct physiological effects of a substance or a general medical condition; and (iv) that clinically significant distress or functional impairment is evident.[4]

3. Assessment

Particular attention should be paid to the evaluation of symptoms that are chosen as targets for pharmacotherapy and to symptoms that may point to the presence of other psychiatric disorders. It is also useful to determine the severity of GAD symptoms using a scale such as the Hamilton Anxiety Scale. There are a number of other screening and assessment scales that can be used, including the 7-item GAD scale[7] for screening for GAD and assessing severity, the Generalized Anxiety Disorder Severity Scale (DGSS) which consists of 8 DSM-IV-TR GAD symptoms for the assessment of symptom frequency and intensity[8] and the Daily Assessment of Symptom-Anxiety (DAS-A) to assess for symptom improvement.[9] It is possible that the situation in GAD mirrors that in depression, where less severe forms of the disorder respond equally well to pharmacotherapy and to psychotherapy.

It is also necessary to rule out the presence of comorbid psychiatric and medical disorders. This includes a thorough physical examination, appropriate laboratory investigation (with attention to thyroid and glucose function), and assessment of current use of prescription or over-the-counter medications. Mood disorders, such as depression and dysthymia, other anxiety disorders, and alcohol and other substance use disorders are common in patients with GAD. In addition, attention

| Table 1. Criteria for generalised anxiety disorder[9] |
|------------------|------------------|
| A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least six months, about a number of events or activities (such as work or school performance) |
| B. The person finds it difficult to control the worry |
| C. The anxiety and worry are associated with three (or more) of the following 6 symptoms (with at least some symptoms present for more days than not for the past 6 months): |
| 1. Restlessness or feeling keyed up or on edge |
| 2. Being easily fatigued |
| 3. Difficulty concentrating or mind going blank |
| 4. Irritability |
| 5. Muscle tension |
| 6. Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep) |
| D. The focus of the anxiety and worry is not confined to features of an Axis I disorder |
| E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning |
| F. The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder |

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† In the DSM-V[9] this criterion has been changed to: "The disturbance is not better explained by another mental disorder."
4. Treatment

4.1 Treatment goals
The goal of treatment of GAD is reduction and ideally elimination of symptoms or worry and anxiety, and restoration of normal functioning.\textsuperscript{10}

4.2 General aspects of treatment

4.2.1 Geriatric patients
Research indicates that GAD in the elderly is not uncommon and is often accompanied by depression.\textsuperscript{11} Given the possibility of accumulation of the drug and consequent adverse effects such as motor vehicle accidents, falls and fractures, benzodiazepines (particularly in high doses or those with long half-lives) should be prescribed only with great caution in this population. In addition, dosages of many other psychotropic medications require adjustment in the elderly.

4.2.2 Alcohol and/or substance use
When the diagnosis of GAD predates the onset of substance abuse, treatment may be initiated relatively soon after abstinence. However, when symptoms of anxiety have their onset during substance abuse or withdrawal, it is likely that a longer period of abstinence is indicated prior to re-evaluation of the need for treatment. In addition, given the risk of dependence, benzodiazepines should be used with caution in patients with a history of substance abuse.\textsuperscript{12}

4.2.3 Other comorbid disorders
As noted earlier, there is a high rate of comorbidity among GAD, other anxiety disorders and mood disorders. GAD will often respond to the antidepressants that are used as first-line medication in these disorders, and these agents should therefore be considered initially. Similarly, in patients with chronic anxiety and comorbid personality disorder (e.g. borderline personality disorder), antidepressants may be a consideration.

4.2.4 Pregnancy, lactation, menopause
Pharmacotherapy should ideally be avoided during pregnancy and lactation. Nevertheless, where clinical considerations outweigh the risk of medication, such intervention should be considered after consultation with a specialist. In particular, there is a growing literature pointing toward relative safety of fluoxetine in pregnancy.\textsuperscript{13} Certain benzodiazepines (e.g. chlordiazepoxide) may be safer, while others (e.g. alprazolam) should be avoided during pregnancy and lactation; the lowest effective dose should be prescribed for the shortest possible duration, and high peak concentrations should be avoided by dividing the daily dosage into two or three doses.\textsuperscript{14} Anxiety symptoms may be exacerbated in susceptible patients during menopause, and hormone replacement therapy may be considered as an adjunct to standard pharmacotherapy.

4.2.5 Comorbid medical disorders and medications
Clinicians need to be aware of the multiple interactions between medications used in the treatment of GAD and the treatment of other disorders, as well as of the impact of the medication’s adverse effects on medical disorders.

4.3 Pharmacological treatment
The first-line treatment of uncomplicated GAD is a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) drug. Given the substantial comorbidity of GAD with depression and other disorders for which antidepressants are effective, expert consensus favours the use of one of these agents.\textsuperscript{15,16} However, there is evidence for

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\textbf{Fig. 1. Algorithm for pharmacotherapy of generalised anxiety disorder.}\textsuperscript{5}

should be paid to the possibility of comorbid somatisation disorder. Children with pervasive anxiety probably deserve specialist evaluation before a diagnosis of GAD is made.

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a range of other agents, including pregabalin, agomelatine, older antidepressants such as tricyclics (TCAs), benzodiazepines, the azapirone buspirone, the antihistamine agent hydroxyzine, the first-generation antipsychotic trifluoperazine and the second-generation antipsychotic quetiapine.[17] A recent meta-analysis and systematic review of the efficacy of nine drug treatments for GAD notes advantages and disadvantages of several of these agents.[18] For example, the TCAs (namely imipramine) have been shown effective in GAD in several controlled trials, but are currently considered a second-line option owing to their adverse event burden and toxicity in overdose.[19] Similarly, given concerns about their tolerability and side-effect profile, caution should be exercised in using atypical and typical antipsychotic medications as monotherapy in GAD.

The benzodiazepines are best reserved for short-term use (2 - 4 weeks) in the early phase of treatment of GAD with an SSRI or SNRI to provide some symptomatic relief until the antidepressant has begun to work, to treat insomnia if it is a predominant symptom, and to protect against occasional early worsening of anxiety seen with the initiation of therapy.[19] The high comorbidity of symptoms of depression in GAD, and the significant difficulties experienced by many patients during benzodiazepine withdrawal, constitute a strong argument against their long-term use. Benzodiazepines with longer half-lives or slow-release preparations may, however, be associated with fewer withdrawal problems.

Buspirone, a 5-HT1A agonist, takes 2 - 4 weeks or longer to begin working, and appears to be experienced as less helpful in patients recently treated with benzodiazepines.[19] Its advantage lies in its benign side-effect profile, the lack of dependence, and its proven efficacy in GAD. Disadvantages include a lack of efficacy against the depressive symptoms often found in GAD, and a lack of efficacy in some trials. Whereas some SSRIs have been shown useful in children and adolescents with GAD, a controlled study of buspirone in this population was negative.

Although beta-blockers (e.g. propranolol) are often prescribed by general practitioners for anxiety symptoms, they have unproven efficacy in GAD. Kava extract is a herbal that showed some promise for the treatment of anxiety,[20] but it has not been studied rigorously enough in GAD, and there are safety concerns, viz. hepatotoxicity.

4.4 Non-pharmacological treatment
Cognitive-behavioural treatment (CBT) has demonstrated efficacy in GAD, where the benefits are maintained at 6 months to 2 years of follow-up.[22] Treatment of GAD using CBT involves techniques of cognitive restructuring, worry exposure, and behaviour modification. There is currently little evidence that routinely initiating CBT together with medication improves outcome in GAD.

The first step after drug initiation is to determine response to the medication. This is achieved by careful evaluation of change in symptoms initially targeted for treatment. These are typically excessive worry, various somatic symptoms, and consequent functional impairment. Determining the side-effects of the medication is also important, as these may influence compliance. Patients who are intolerant of a particular medication can of course be switched to another agent or to another class of agents. For example, within the SSRIs, adverse effects may not be seen when an alternative SSRI is used.

When there is a poor response to medication, the first course of action is to optimise dose and duration of the treatment. For many of the antidepressants, there is a relationship between dose and response and also between dose and side-effects. Thus, optimal dosage is as close to maximum recommended doses that the patient can tolerate. Elderly patients generally require lower doses than younger adults. Particularly in the case of the TCAs, clinicians often prescribe suboptimal doses, rather than using doses of 150 mg or more of medications such as imipramine. Even in the case of the SSRIs, some patients may fail to respond to the standard initial starting dose, but do better at higher doses.

Furthermore, there is increasing awareness that some patients may be rapid metabolisers of antidepressant medication and, therefore, require significantly higher doses than usual. When patients on TCAs have little response and few anticholinergic side-effects on average doses of medication (e.g. imipramine 150 mg), it may be useful to further increase dosage with electrocardiogram and perhaps drug level monitoring. Although benzodiazepines are not recommended as first-line treatments, when used, they should be prescribed in an optimal fashion. In particular, it may be useful to replace short-acting agents with slow-release compounds or long-acting agents. All too frequently, patients on short-acting compounds have intermittent increases of anxiety before the next dose of medication is to be taken.

Buspirone treatment usually begins at 5 mg three times daily. This dose may be increased by 5 mg every 2 - 3 days. Therapeutic doses of buspirone range from 30 mg to 60 mg daily, typically given in divided doses. Buspirone has at least a 2 - 4-week time lag from initiation to clinical onset; optimum duration of a trial of treatment should thus be no less.

At the end of a clinical trial of optimal dose and duration, patients should be thoroughly reassessed. There is growing recognition of the importance of residual anxiety symptoms in causing disability and predicting relapse, and of the consequent necessity of aiming for remission of symptoms as the endpoint of treatment.[24]

4.6 Maintenance treatment
When the patient has a good response to medication, it is important to reinforce the necessity for continuing the medication at the therapeutic dose despite this improvement.[25] It is recommended that therapy be continued for at least 1 year where there is a good response, given that the disorder is chronic and randomised controlled trials have demonstrated relapse with shorter-term maintenance. It is also important to regularly monitor efficacy and tolerability during long-term treatment. Indeed, guidelines for maintenance therapy of GAD emphasise the safety of modern agents, the likelihood of additional episodes of illness in
patients with repeated past episodes, and the theoretical possibility that appropriate treatment may prevent the onset of secondary disorders. \cite{16} Such guidelines have become increasingly conservative, favouring longer courses of medication. When a decision is made to discontinue medication, a gradual taper is recommended (arguably with an even slower taper in the elderly and in medically ill patients).

### 4.7 Managing partial and non-responders

When GAD does not respond to a clinical trial of adequate dose and duration, it may be useful to reassess a number of important factors that may influence choice of further interventions.

#### 4.7.1 Comorbidity

It is important to establish whether comorbid mood or other anxiety disorders are present. For example, comorbid dysthymia may not respond to buspirone alone, comorbid social anxiety disorder is unlikely to respond to a TCA (other than clomipramine), and comorbid hypochondriasis may require high doses of SSRIs. Excluding important comorbid psychiatric disorders is perhaps the most important step in the evaluation and management of refractory GAD.

#### 4.7.2 Compliance

Many patients with GAD suffer from extreme anxiety and are in fact compliant with their medication. Nevertheless, there is perhaps a tendency for clinicians to overestimate patient compliance. Patients are particularly likely to be concerned about physical or psychological dependence on medication. It is well worth checking not only with the patient, but perhaps also with the family, whether medication is in fact taken as prescribed.

#### 4.7.3 Comorbid substance use

In the presence of active alcohol or substance use, it may be necessary to shift the emphasis of treatment towards a substance use disorder as the primary diagnosis, with the anxiety as a secondary problem. Detoxification is typically a first step in the management of these patients.\cite{20-21}

#### 4.7.4 Comorbid personality disorders

Although antidepressants may be useful, additional interventions such as psychotherapy may be helpful in patients with chronic anxiety and comorbid personality disorder. While improvement in anxiety symptoms may reduce maladaptive behaviour in patients with comorbid personality disorder, there are other patients (e.g. those with borderline personality disorder) in whom the personality disorder itself may need to be a major target of treatment.

#### 4.7.5 Underlying medical disorder

Patients with GAD who fail to show any noticeable response to treatment should be thoroughly reassessed for the possibility of an underlying medical condition. A range of different medical disorders may lead to chronic anxiety, including endocrine disorders (e.g. hyperthyroidism), respiratory disorders (e.g. chronic obstructive pulmonary disorders), cardiac disorders (e.g. congestive heart failure), and others. If present, such disorders naturally require specific intervention. Note that when using a benzodiazepine in patients with liver dysfunction, consider using those metabolised only by conjugation (e.g. lorazepam, oxazepam).

### 4.7.6 Pharmacokinetic issues

Drug-drug interactions may result in a subtherapeutic dose of the prescribed antidepressant.

### 4.7.7 Psychosocial issues

In some cases, a diagnosis of an adjustment disorder with anxious features may be more accurate than that of GAD, and a psychotherapeutic approach therefore indicated. This factor may partially explain high rates of placebo response in some clinical trials in GAD. In other cases of chronic anxiety, psychosocial factors may be enduring and therefore continuously complicate treatment of GAD until given independent attention.

Where there is only a partial response to an initial 12-week trial, it is prudent to re-evaluate the patient and to consider switching to another antidepressant within the same class or to a different class (e.g. SSRI to SNRI or agomelatine, SNRI to SSRI or agomelatine), or augmentation.\cite{24} Neither augmentation nor switching strategies in GAD have been well researched. Augmentation offers the advantage of retaining any possible gains from the first agent, but the potential disadvantages of polypharmacy (more side-effects, drug interactions).\cite{28} When insomnia is present, the use of an appropriate agent (e.g. non-benzodiazepine gamma-amino-butyric acid (GABA)-ergic hypnotics such as zolpidem, agomelatine, or mirtazapine) may be considered.\cite{24} If comorbid depression is present, augmentation with bupropion, buspirone, or an atypical antipsychotic may be considered. Similarly, if there is a comorbid bipolar disorder, a mood stabiliser, anticonvulsant or an atypical antipsychotic may be considered. Augmentation with psychotherapy is another important consideration.

### 5. Summary points

- Both pharmacotherapy and psychotherapy are efficacious first-line approaches for GAD.
- First-line pharmacotherapy of uncomplicated GAD comprises use of an SSRI or SNRI drug.
- A range of other psychotropics are useful for the treatment of GAD.
- Response time to a first-line selective SSRI (e.g. fluoxetine, citalopram, escitalopram, paroxetine, sertraline) or SNRI (e.g. venlafaxine, duloxetine) is usually between 4 and 12 weeks in GAD.
- Benzodiazepines (e.g. lorazepam, alprazolam, diazepam) are best reserved for short-term use (2 - 4 weeks) in the early phase of treatment of GAD with an SSRI or SNRI to provide symptomatic relief.
- Given concerns about their tolerability and side-effect profile, caution should be exercised in using atypical and typical antipsychotic medications as monotherapy in GAD.
- CBT for GAD involves techniques of cognitive restructuring, worry exposure, and behaviour modification.
- Neither augmentation nor switching strategies have been well researched in GAD. Where there is only a partial response to an optimal 12-week trial, consider switching to another antidepressant within the same class or to a different class (e.g. SSRI to SNRI or agomelatine, SNRI to SSRI or agomelatine).
References


13. Nudman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. New Engl J Med 1997;336:258-262.


Obsessive compulsive disorder

D J Stein

1. Introduction
This guideline focuses on the pharmacotherapy of obsessive-compulsive disorder (OCD). OCD is characterised by obsessions and compulsions. A number of other disorders are also characterised by repetitive thoughts and rituals and may also respond to modifications of standard OCD treatment. These so-called OCD spectrum disorders include body dysmorphic disorder (characterised by recurrent concerns with imagined ugliness), hypochondriasis (characterised by recurrent concerns with imagined illness), trichotillomania (characterised by recurrent hair-pulling), and obsessive-compulsive personality disorder. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition has a new chapter on obsessive-compulsive and related disorders, which includes several of these conditions.

2. Diagnosis and clinical characteristics
Evidence indicates that OCD is commonly underdiagnosed and undertreated. There is also the converse possibility that various disorders with intrusive symptoms, such as post-traumatic stress disorder or generalised anxiety disorder, can be misdiagnosed as OCD. Diagnostic criteria for OCD are provided in Table 1.4

3. Assessment
Most patients with OCD have both obsessions (which increase anxiety) and compulsions (which aim to decrease anxiety), particularly given that the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition definition of compulsion includes mental rituals. The most common obsessions centre around concerns of contamination, harm, hoarding, and sexual, somatic and religious preoccupations, while the most common compulsions include washing, checking, repeating, ordering, counting, and hoarding. The disorder is highly comorbid with obsessive-compulsive and related disorders, major depressive disorder, anxiety disorders, alcohol dependence, eating disorders and tic disorders. Evaluation should include assessment of symptom pattern, severity, and functional impairment. Comorbid Axis I and II disorders, including tic disorders, as well as medical conditions (including pregnancy) and disorders need to be accurately identified. There is growing evidence that OCD and/or tics in some patients, particularly children, are precipitated or exacerbated by streptococcal or other infections.

Evaluation of the OCD patient also requires attention to psychosocial factors that may have precipitated or exacerbated OCD symptoms. For example, are family members involved in the patient’s rituals? What is the patient’s explanatory model of OCD – does he or she regard it as a sign of weakness or as evidence of brain dysfunction?

4. Treatment
4.1 Treatment goals
The goals of treatment of OCD are to reduce symptom frequency and severity and to improve functioning and quality of life. Treatment goals also encompass minimising medication adverse effects, helping the patient develop coping strategies for their OCD and related stressors, and educating the patient and family regarding the disorder and its treatment.

4.2 General aspects of treatment
In this discussion, we assume that the patient is an adult. Nevertheless, there are increasing data on the pharmacotherapy of OCD in children. Indeed, the algorithm (see Fig. 1 below) can readily be adapted for children, bearing in mind considerations such as differences in dosing and differences in risk-benefit determination (e.g. clinicians are less likely to use untested augmentation strategies in children). Consultation with a child psychiatrist may well be indicated in such cases.

Table 1. Criteria for obsessive-compulsive disorder

<table>
<thead>
<tr>
<th>A. Either obsessions or compulsions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessions as defined by (1), (2), (3), and (4):</td>
</tr>
<tr>
<td>1. Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress</td>
</tr>
<tr>
<td>2. ‘The thoughts, impulses, or images are not simply excessive worries about real-life problems’</td>
</tr>
<tr>
<td>3. The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralise them with some other thought or action</td>
</tr>
<tr>
<td>4. ‘The person recognises that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)’</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compulsions as defined by (1) and (2):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Repetitive behaviours (e.g. hand washing, ordering, checking) or mental acts (e.g. praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly</td>
</tr>
<tr>
<td>2. The behaviours or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviours or mental acts either are not connected in a realistic way with what they are designed to neutralise or prevent or are clearly excessive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. At some point during the course of the disorder, the person has recognised that the obsessions or compulsions are excessive or unreasonable</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person’s normal routine, occupational or academic functioning, or usual social activities or relationships</td>
</tr>
<tr>
<td>D. ‘If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it’</td>
</tr>
<tr>
<td>E. The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.</td>
</tr>
</tbody>
</table>

* Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSM-IV-TR. For educational purposes only.
† Omitted from the DSM-V.
‡ This has been changed in the DSM-V. The disturbance is not better explained by the symptoms of another mental disorder.

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The initial treatment of OCD can arguably be either medication or psychotherapy as both approaches are efficacious. Several factors may complicate OCD, thus impacting on decisions about the choice of pharmacotherapy and other interventions. The most important factors, along with their treatment implications, are listed below. In addition, prior response to treatment and patient preference are important considerations.

4.2.1 Severity
Patients with severe symptoms may require brief hospitalisation to help contain symptoms. In general, however, the principles of behaviour therapy suggest that patients should attempt to continue with their ordinary daily routines where possible.

4.2.2 Melancholia
There is some evidence that tricyclic antidepressants (TCAs) may be more effective than selective serotonin reuptake inhibitors (SSRIs) in patients with depression accompanied by melancholic features[12] and in possibly related subgroups such as in-patients with depression,[11-13] although not all evidence is consistent.[14] Melancholic features of depression include loss of pleasure in activities, lack of reactivity to pleasurable stimuli, and various neurovegetative symptoms such as exacerbation of depression in the morning, early-morning awakening, and significant weight loss. The only TCA that is effective in OCD is clomipramine.

4.2.3 Tourette's disorder
This disorder is characterised by both motor and vocal tics. Many patients with Tourette's disorder have comorbid OCD. Although this OCD may respond to standard OCD treatments, additional medication that targets the tics (e.g. dopamine blockers such as haloperidol, pimozide, or risperidone) may be necessary for resolution of the range of symptoms that characterise the disorder.[15]

4.2.4 Pregnancy, lactation, menopause
Pharmacotherapy should ideally be avoided during pregnancy and lactation. Nevertheless, where clinical considerations outweigh the risk of medication, such intervention should be considered after consultation with a specialist. In particular, there is growing literature pointing toward the relative safety of fluoxetine in pregnancy.[16]

4.2.5 Comorbid medical disorders and medications
Clinicians need to be aware of the multiple interactions between medications used in the treatment of OCD and other medications, as well as the impact of a medication's adverse effects on medical disorders. Fortunately, certain SSRIs have relatively few interactions with other medications, and the SSRIs as a class are well tolerated in most medical disorders.

4.3 Pharmacological treatment
Refer to 4.5 and 4.6 below.

4.4 Non-pharmacological treatment
Psycho-education as part of the management of OCD is crucial. Similarly, cognitive-behavioural therapy (CBT) is an important aspect of OCD treatment, whether used alone or in combination with medication.[17] CBT for OCD has been delivered in individual, group, and family therapy formats. The number and length of treatment sessions vary across different studies, but some guidelines recommend 13 - 20 weekly sessions for most patients.[17]

4.5 Acute treatment
Patient motivation and ability to comply with pharmacotherapy and/or psychotherapy are important considerations in choosing a first-line treatment approach. CBT and serotonin reuptake inhibitors (SRIs) are both considered safe and effective first-line treatments for OCD.[17] The decision of whether to commence CBT or an SRI will depend on a number of factors including the nature and severity of symptoms, presence of co-occurring psychiatric and medical comorbidity and their treatments, patients’ access to CBT, past treatment history, and patient preference.[17] CBT alone, consisting of exposure and response prevention, is recommended as initial treatment for a patient who is not too depressed, anxious, or severely ill to co-operate with this treatment modality, or who prefers not to take medications and is willing to engage with CBT. Initiating treatment with an SRI is recommended for a patient who has previously responded well to an SRI or other drug, prefers medication treatment or is not suited for CBT.[17]

The first line of medication in the treatment of OCD should comprise an SRI. Consistent with growing evidence for the importance of serotonin in OCD, both clomipramine and the SSRIs appear to be more effective than the noradrenergic reuptake inhibitor, desipramine, in the treatment of OCD.[18,19] The efficacy and safety of clomipramine and the SSRIs in the treatment of OCD have been well researched, with studies indicating that at least half of patients will respond to one of these agents. The SSRIs are also useful for body dysmorphic disorder, hypochondriasis, obsessive-compulsive symptoms in Tourette's disorder, and possibly (albeit with relatively less robust responses) in hair-pulling disorder (trichotillomania), excoriation (skin-picking) disorder, so-called compulsive sexual behaviour, and pathological gambling.[20,21] Note, however, that other agents may be preferable as first-line options in some of these conditions, e.g. given recent data that N-acetyl-cysteine is useful in hair-pulling disorder, this is an important consideration.

An immediate question, however, is which SRI to use first. Given the apparent lack of differences in efficacy between the SSRIs, the side-effect profile of these agents may be an important issue in considering which agent to use first. Certainly, there are invariably fewer side-effects during treatment with the SSRIs than during treatment with clomipramine. Therefore, it seems reasonable to suggest that treatment of OCD be initiated with an SRI.

While all SSRIs appear to have similar efficacy, individual patients may respond well to one medication and not to another. In choosing among the SSRIs, it is important to consider the safety and acceptability of particular side-effects for the patient, potential drug interactions, past treatment response, and the presence of co-occurring general medical conditions.[17] Low doses should initially be used in patients with comorbid panic disorder.

Most patients will not experience substantial improvement until 4 - 6 weeks after initiating medication, and some patients who will ultimately respond will experience little improvement by 8 - 10 weeks.[17] To determine response to medication, it is important to ask about change in those symptoms initially targeted for treatment. Side-effects of the medication should also be determined, with particular
attention to those that patients may be reluctant to disclose (e.g. sexual dysfunction). It may be useful to complete a symptom rating scale (Table 2) to help quantify response to medication.

Patients who are intolerant of a particular medication can of course be switched to another agent. Within the SRIs, adverse effects may not be seen when an alternative SSRI or clomipramine is used.

When there is a poor response to medication, it is important to optimise dosage and duration of the medication. Although some patients with OCD respond to standard doses of SRIs, others require doses that are much higher than in depression. In adults, clomipramine should be increased to approximately 250 mg, and the SSRIs should be increased to maximal dosages (e.g. 60 - 80 mg of fluoxetine) bearing in mind recent black box warnings (e.g. citalopram should not be increased higher than 40 mg). Unfortunately, the likelihood of side-effects also increases at these doses. Electrocardiogram (ECG) monitoring may be necessary when children and adolescents, or patients with pre-existing heart disease, are treated with clomipramine.

Response to SRIs in OCD may take rather longer than in many other disorders - up to 12 weeks. It is obviously important to give each patient a trial of medication that is of adequate duration. Patients therefore need to be educated that response may take a significant length of time and that they need to remain optimistic even when no change is seen at first.

At the end of a clinical trial of optimal dose and duration, patients should be thoroughly reassessed. There is growing recognition of the importance of residual anxiety symptoms in causing disability and predicting relapse, and of the consequent necessity of aiming for remission of symptoms as the endpoint of treatment. Nevertheless, many OCD patients who are judged ‘responders’ to medication therapy may continue to experience obsessions and compulsions, albeit with less intensity. In clinical trials, a decrease of 25 - 35% on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) may correspond to a categorical treatment response.

4.6 Maintenance treatment
In patients where an SRI is effective, maintenance pharmacotherapy should be instituted. Rapid discontinuation of these agents risks the return of symptoms. Nevertheless, a maintenance dose of SRIs in OCD may be lower than the dose initially required during acute treatment. At least a year of maintenance pharmacotherapy is reasonable. When a decision is made to attempt discontinuation of medication, it is advisable to taper medication off slowly (e.g. by 25% every 2 months). Concomitant behavioural treatment (exposure therapy and response prevention) during pharmacotherapy may well increase chances of being able to discontinue medication without relapse.

4.7 Managing partial and non-responders
Comparison of augmentation with switching strategies in OCD has not been well researched. Augmentation offers the advantage of retaining any possible gains from the first agent, but the potential disadvantages of polypharmacy (more side-effects, drug interactions). Of all the augmentation strategies in the treatment of OCD, perhaps the most important is augmentation of pharmacotherapy with additional psychotherapy.

Combined SRI and CBT treatment can be considered when the patient has a co-occurring disorder that is SRI-responsive or has a partial response to monotherapy. Combination of an SRI and CBT may also reduce the chance of relapse when medication is discontinued. In patients who have had a partial response to CBT monotherapy, it may be useful to increase the intensity of treatments.

However, when there is a partial response despite an optimum trial of medication, or when there are comorbid tics, it may be useful to consider augmentation. Certainly, in patients with comorbid tics, there is good evidence that augmentation of an SRI with a dopamine blocker can be effective. About one-third to one-half of treatment-refractory OCD patients will have a meaningful treatment response to antipsychotic augmentation. The introduction of the new-generation antipsychotics has led to increased use of these agents in the augmentation therapy of OCD, and they appear useful in treatment-refractory patients even in the absence of comorbid tics. Another possible strategy is to supplement an SRI with a low dose of clomipramine, although careful monitoring of adverse effects and ECGs may be warranted with such a combination. Other augmentation strategies have been suggested, but there are few positive controlled trials. There is also relatively little work on augmentation strategies in OCD-related disorders, although addition of a dopamine blocker may also be useful in some of these patients.

When OCD does not respond to a clinical trial of optimal dose and duration, it is useful to reassess a number of factors. The presence of certain features may impact on the choice of the subsequent intervention.

4.7.1 Compliance
Clinicians often overestimate the compliance of their patients and it is often useful to check with patients and their families whether medication is being taken as prescribed. Many patients worry that medication is addictive or is a ‘crutch’.

4.7.2 Comorbid substance use
In patients who fail to respond to pharmacotherapy, the possibility of comorbid substance use should again be considered. There may be a need for withdrawal before tackling the OCD per se.

4.7.3 Comorbid personality disorders
Although SRIs may be useful, additional interventions such as psychotherapy may be crucial in patients with OCD and comorbid personality disorder. While improvement in OCD symptoms may reduce maladaptive behaviour in comorbid personality disorder, the personality disorder itself may need to be a major target of treatment.

4.7.4 Underlying medical disorder
Patients with obsessive-compulsive and related disorders who fail to respond to medication should be thoroughly reassessed for an underlying medical disorder. In OCD in children, the role of streptococcal throat infection may be particularly important.

4.7.5 Pharmacokinetic issues
Drug-drug interactions may result in a subtherapeutic dose of the prescribed antidepressant.

4.7.6 Psychosocial issues
Psychosocial circumstances that continue to complicate the course of OCD need to be assessed, as these may necessitate appropriate
Table 2. Yale-Brown Obsessive-Compulsive Scale

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am now going to ask several questions about your obsessive thoughts.</td>
<td>(Make specific reference to the patient’s target obsessions)</td>
</tr>
<tr>
<td>1. Time occupied by obsessive thoughts</td>
<td>Q: How much of your time is occupied by obsessive thoughts? How frequently do the obsessive thoughts occur?</td>
</tr>
<tr>
<td></td>
<td>0 = None.</td>
</tr>
<tr>
<td></td>
<td>1 = Mild, less than 1 hour/day or occasional intrusion.</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate, 1 to 3 hours/day or frequent intrusion.</td>
</tr>
<tr>
<td></td>
<td>3 = Severe, greater than 3 and up to 8 hours/day or very frequent intrusion.</td>
</tr>
<tr>
<td></td>
<td>4 = Extreme, greater than 8 hours/day or near constant intrusion.</td>
</tr>
<tr>
<td>2. Interference due to obsessive thoughts</td>
<td>Q: How much do your obsessive thoughts interfere with your social or work (or role) functioning? Is there anything that you don’t do because of them?</td>
</tr>
<tr>
<td></td>
<td>1 = Mild, slight interference with social or occupational activities, but overall performance not impaired.</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate, definite interference with social or occupational performance, but still manageable.</td>
</tr>
<tr>
<td></td>
<td>3 = Severe, causes substantial impairment in social or occupational performance.</td>
</tr>
<tr>
<td></td>
<td>4 = Extreme, incapacitating.</td>
</tr>
<tr>
<td>3. Distress associated with obsessive thoughts</td>
<td>Q: How much distress do your obsessive thoughts cause you?</td>
</tr>
<tr>
<td></td>
<td>0 = None.</td>
</tr>
<tr>
<td></td>
<td>1 = Mild, not too disturbing.</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate, disturbing, but still manageable.</td>
</tr>
<tr>
<td></td>
<td>3 = Severe, very disturbing.</td>
</tr>
<tr>
<td></td>
<td>4 = Extreme, near constant and disabling distress.</td>
</tr>
<tr>
<td>4. Resistance against obsessions</td>
<td>Q: How much of an effort do you make to resist the obsessive thoughts? How often do you try to disregard or turn your attention away from these thoughts as they enter your mind?</td>
</tr>
<tr>
<td></td>
<td>0 = Makes an effort to always resist, or symptoms so minimal doesn’t need to actively resist.</td>
</tr>
<tr>
<td></td>
<td>1 = Tries to resist most of the time.</td>
</tr>
<tr>
<td></td>
<td>2 = Makes some effort to resist.</td>
</tr>
<tr>
<td></td>
<td>3 = Yields to all obsessions without attempting to control them, but does so with some reluctance.</td>
</tr>
<tr>
<td></td>
<td>4 = Completely and willingly yields to all obsessions.</td>
</tr>
<tr>
<td>5. Degree of control over obsessive thoughts</td>
<td>Q: How much control do you have over your obsessive thoughts? How successful are you in stopping or diverting your obsessive thinking? Can you dismiss them?</td>
</tr>
<tr>
<td></td>
<td>0 = Complete control.</td>
</tr>
<tr>
<td></td>
<td>1 = Much control, usually able to stop or divert obsessions with some effort and concentration.</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate control, sometimes able to stop or divert obsessions.</td>
</tr>
<tr>
<td></td>
<td>3 = Little control, rarely successful in stopping or dismissing obsessions, can only divert attention with difficulty.</td>
</tr>
<tr>
<td></td>
<td>4 = No control, experienced as completely involuntary, rarely able to even momentarily alter obsessive thinking.</td>
</tr>
</tbody>
</table>

The next several questions are about your compulsive behaviours. (Make specific reference to the patient’s target compulsions)

| 6. Time spent performing compulsive behaviours                           | Q: How much time do you spend performing compulsive behaviours? How much longer than most people does it take to complete routine activities because of your rituals? How frequently do you perform compulsions? |
|                                                                          | 0 = None.                                                                                                                                 |
|                                                                          | 1 = Mild (spends less than 1 hour/day performing compulsions), or occasional performance of compulsive behaviours.                     |
|                                                                          | 2 = Moderate (spends from 1 to 3 hours/day performing compulsions), or frequent performance of compulsive behaviours.              |
|                                                                          | 3 = Severe (spends more than 3 and up to 8 hours/day performing compulsions), or very frequent performance of compulsive behaviours. |
|                                                                          | 4 = Extreme (spends more than 8 hours/day performing compulsions), or near constant performance of compulsive behaviours (too numerous to count). |

continued...
After the failure of an adequate clinical trial of medication in a patient where reassessment sheds no light on any further unresolved factors, a different agent should be used. Although an SRI has less chance of being effective in patients who have already failed a number of trials of other SRIs, some of these patients (approximately one-third of non-responders to initial SRI monotherapy) will in fact ultimately respond to a new SRI. Given the possible superiority of clomipramine in certain cases of OCD and depression, it may be argued that all OCD patients who have failed to respond to one or more of the SSRIs deserve a trial of clomipramine. While results of studies correlating plasma drug levels and therapeutic response in OCD have been mixed, in the case of clomipramine obtaining drug levels at high doses may be useful. Anecdotal experience suggests that certain non-SRI agents, such as the classic monoamine oxidase inhibitors and venlafaxine, may on occasion be effective in treatment-resistant OCD. Recent trials of intravenous clomipramine also show efficacy in treatment-resistant OCD.

For patients who have failed multiple medication and behavioural treatments (including intensive partial or full hospitalisation programmes), and where severity of the disorder is marked, neurosurgery should also be considered. Several studies have suggested that specific lesions to or deep-brain stimulation of components of corticostriatal and related pathways may lead to significant reduction in OCD symptoms in treatment-refractory cases.

### Table 2 (continued). Yale-Brown Obsessive-Compulsive Scale[22]

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Interference due to compulsive behaviours</td>
<td></td>
</tr>
<tr>
<td>Q: How much do your compulsive behaviours interfere with your social or work (or role) functioning? Is there anything that you don't do because of the compulsions?</td>
<td>0 = None. 1 = Mild, slight interference with social or occupational activities, but overall performance not impaired. 2 = Moderate, definite interference with social or occupational performance, but still manageable. 3 = Severe, causes substantial impairment in social or occupational performance. 4 = Extreme, incapacitating.</td>
</tr>
<tr>
<td>8. Distress associated with compulsive behaviour</td>
<td></td>
</tr>
<tr>
<td>Q: How would you feel if prevented from performing your compulsion(s)? How anxious would you become? How anxious do you get while performing compulsions until you are satisfied they are completed?</td>
<td>0 = None. 1 = Mild, only slightly anxious if compulsions prevented, or only slight anxiety during performance of compulsions. 2 = Moderate, reports that anxiety would mount but remain manageable if compulsions prevented, or that anxiety increases but remains manageable during performance of compulsions. 3 = Severe, prominent and very disturbing increase in anxiety if compulsions interrupted, or prominent and very disturbing increase in anxiety during performance of compulsions. 4 = Extreme, incapacitating anxiety from any intervention aimed at modifying activity, or incapacitating anxiety develops during performance of compulsions.</td>
</tr>
<tr>
<td>9. Resistance against compulsions</td>
<td></td>
</tr>
<tr>
<td>Q: How much of an effort do you make to resist the compulsions?</td>
<td>0 = Makes an effort to always resist, or symptoms so minimal doesn't need to actively resist. 1 = Tries to resist most of the time. 2 = Makes some effort to resist. 3 = Yields to almost all compulsions without attempting to control them, but does so with some reluctance. 4 = Completely and willingly yields to all compulsions.</td>
</tr>
<tr>
<td>10. Degree of control over compulsive behaviour</td>
<td></td>
</tr>
<tr>
<td>Q: How strong is the drive to perform the compulsive behaviour? How much control do you have over the compulsions?</td>
<td>0 = Complete control. 1 = Much control, experiences pressure to perform the behaviour but usually able to exercise voluntary control over it. 2 = Moderate control, strong pressure to perform behaviour, can control it only with difficulty. 3 = Little control, very strong drive to perform behaviour, must be carried to completion, can only delay with difficulty. 4 = No control, drive to perform behaviour experienced as completely involuntary and overpowering, rarely able to even momentarily delay activity.</td>
</tr>
</tbody>
</table>
patients. Patients can be referred to specialised centres for such treatments.

5. Algorithm
Fig. 1 outlines the treatment.

6. Summary points
- CBT and the serotonin reuptake inhibitors (SRIs), clomipramine and the SSRIs, are efficacious and safe first-line treatments for OCD.
- Whether to commence CBT or an SRI will depend on the nature and severity of symptoms, presence of co-occurring psychiatric and medical comorbidities and their treatments, a patient’s access to CBT, past treatment history, and patient preference.
- CBT alone, consisting of exposure and response prevention, is recommended as first-line for a patient who is not too depressed, anxious, or severely ill to co-operate with this treatment modality, or who prefers not to take medications and is willing to engage with CBT.
- SRI first-line treatment is recommended for a patient who has previously responded well to an SSRI or other drug, prefers medication treatment, or is not suited for CBT.
- Most patients will not experience substantial improvement until 4 - 6 weeks after initiating medication, and some patients who ultimately respond will experience little improvement by 8 - 10 weeks.
- Although some patients with OCD respond to standard doses of SRIs, others require doses that are much higher than those used for depression. In adults, clomipramine should be increased to approximately 250 mg, and the SSRIs should be increased to maximal safe dosages (e.g. 60 - 80 mg of fluoxetine).
- At least a year of maintenance pharmacotherapy is reasonable in patients who respond to medication.
- CBT (exposure and response prevention) can be used alone or in combination with medication. Psycho-education is also crucial.
- When there is a partial response to an optimal trial of medication, or when there are comorbid tics, it may be useful to consider augmentation. Many OCD patients will have a meaningful treatment response to antipsychotic augmentation.

Fig. 1. Algorithm for pharmacotherapy of obsessive-compulsive disorder [44]

Additional reading

References
Post-traumatic stress disorder

S Seedat

1. Introduction
Post-traumatic stress disorder (PTSD) is among the most prevalent anxiety disorders, both in terms of lifetime and 12-month prevalence rates documented in epidemiological studies worldwide. The National Comorbidity Survey Replication (NCS-R) study conducted in the USA, for example, found the lifetime prevalence of PTSD to be 6.8% while the 12-month prevalence was 3.5%. The South African Stress and Health Study (SASH) documented lower lifetime (2.3%) and 12-month (0.6%) rates, although PTSD was among the anxiety disorders with the highest proportion of severe cases (36% of all individuals diagnosed with PTSD were severely ill). High rates of PTSD (19.9%) have also been documented among South African patients attending primary healthcare clinics.

2. Diagnosis and clinical characteristics
The disorder represents a pathological response to a traumatic event, characterised by symptoms of recurrent and intrusive distressing recollections of the event (e.g. 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 (e.g. inability to recall important aspects of the trauma, loss of interest, estrangement from others); and increased arousal (sleep disturbances, irritability, difficulty concentrating, hypervigilance, and exaggerated startle response). These symptoms cut across three recognised symptom clusters (re-experiencing, avoidance or numbing and hyperarousal), produce distress and impairment for individuals, and form the essential targets for treatment. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) includes an additional cluster of symptoms characterised by negative alterations in cognition and mood. The full symptom picture must be present for more than 1 month for the diagnosis to be made. PTSD is classified in the category of trauma- and stressor-related disorders, and separate from the anxiety disorders, in the DSM-V. Risk factors that increase the likelihood of PTSD include severity of the traumatic exposure, history of past trauma or previous psychiatric disorder, female gender, experience of further stressful events and lack of social support.

3. Assessment
As a general rule, a comprehensive review of the differential diagnosis of the anxiety symptoms should be done, ruling out or treating other psychiatric diagnoses and medical causes. Thus, as part of the initial diagnostic assessment, and after each subsequent treatment trial, should response to treatment be unsatisfactory, it is important to evaluate symptoms associated with PTSD (e.g. insomnia, aggression, nightmares, suicidality, psychotic symptoms). Other considerations include comorbid diagnoses (including depression, other anxiety disorders, substance abuse, bipolar disorder), other issues such as concurrent medical illness especially that which may be undiagnosed (e.g. thyroid disease), ongoing trauma, and legal/compensation issues, ongoing use of anxiety-producing substances (e.g. caffeine, other stimulants), pregnancy, and poor adherence to treatment. Those with PTSD, with and without depression, are at increased risk for suicidality, and it is important to assess suicide risk both at the initial evaluation and subsequent follow-up visits.

Longitudinal studies indicate that PTSD is a disorder of chronicity in that symptoms appear shortly after the traumatic event, subside in many individuals, but can persist in as many as 40% in the form of chronic PTSD. Given that a significant number of cases of PTSD are undiagnosed and undertreated, it is important to inquire about exposure to trauma, and to maintain a high index of suspicion and a high level of awareness of the disorder. Patients with PTSD are frequent users of general medical and psychiatric services, have high rates of coexisting psychiatric (e.g. major depressive disorder, alcohol and drug use disorders, other anxiety disorders) and medical conditions (e.g. asthma, gastrointestinal disorders), and, as already mentioned, are at a high risk for suicide attempts. These comorbid diagnoses may complicate proper diagnosis and alter the course of treatment. The disorder is also highly reactive to environmental reminders of the traumatic event and to subsequent stressful life events and can therefore have a fluctuating course.

4. Treatment
4.1 Treatment goals in PTSD
There are several specific goals of treatment that should all be borne in mind: reducing symptom severity; preventing the occurrence of, and/or treating, comorbid disorders; decreasing functional impairment; modifying pathogenic fear schemas; building resilience; preventing relapse; and improving quality of life of patients. The most common definitions of treatment response in PTSD patients are a decrease of 30% or more in the Clinician Administered PTSD Scale (CAPS) score or a score of 1 (‘very much’) or 2 (‘much improved’) in the Clinical Global Impressions Scale-Improvement item (CGI-I).

4.2 General aspects of treatment
The treatment of PTSD has been the subject of several recent meta-analyses and systematic reviews. Several treatment guidelines are available and these together have informed the treatment guideline that is recommended here. They include guidelines from the World Federation of Societies of Biological Psychiatry; the US Institute of Medicine (IOM); the American Psychiatric Association; the UK National Institute of Clinical Excellence (NICE); the Australian National Centre for PTSD; the British Association for Psychopharmacology; and the International Psychopharmacology Algorithm Project (IPAP). All of these guidelines acknowledge that there are two distinct approaches that are of proven benefit in PTSD: pharmacological and psychotherapeutic. Therefore, the first choice...
to be made is whether to offer medication, psychotherapy, or both. Psychotherapeutic treatments, if not used initially, can be added to, or replace pharmacotherapy.

Chronic PTSD is defined as PTSD of more than 3 months’ duration. Most treatment guidelines recommend the use of either selective serotonin reuptake inhibitors (SSRIs) or exposure-based, trauma-focused cognitive-behaviour therapy (TF-CBT) as first-line therapy. However, it should be mentioned that both the US IOM guidelines[16] and the UK NICE guidelines[18] on the sum of data suggest that evidence for the efficacy of pharmacological therapies, namely SSRIs, is at best tentative. The NICE guidelines,[18] for example, do not recommend drug treatments as a routine first line for adults with PTSD (for prescription either by a general practitioner or psychiatrist), but rather advocate for the use of TF-CBT.

4.3 Acute treatment
An adequate trial requires 6 - 12 weeks, but the clinician should expect some response after 4 - 6 weeks with adequate dosage. A minimum course of exposure-based, TF-CBT is 8 - 12 weekly or biweekly sessions for exposure to a single-incident trauma. More sessions may be required in instances of multiple traumatic exposures or the presence of comorbidity.

4.4 Maintenance treatment
PTSD is a disorder that is characterised by symptom persistence and long-term treatment for at least 12 - 24 months is recommended. The SSRIs and the serotonin-norepinephrine reuptake inhibitor (SNRI), venlafaxine, have demonstrated long-term efficacy.

4.5 Pharmacological treatment
The SSRIs and SNRIs are the two groups of antidepressants that have, to date, been the most rigorously studied in placebo-controlled randomised controlled trials (RCTs) and are considered as first-line agents for PTSD. Long-term efficacy (treatment for at least 12 - 24 months) has also been demonstrated with both classes of agents.[12]

Of the SSRIs, paroxetine, sertraline and fluoxetine currently have the best evidence for efficacy.[13-15] Paroxetine and sertraline are the only two that are US Food and Drug Administration (FDA) indicated for PTSD. In a meta-analysis of 35 RCTs (of 14 weeks or less in duration) involving a total of 4 597 participants, evidence for efficacy was most convincing for the SSRIs, across all symptom clusters and for co-occurring depression and disability.[13] However, the SSRIs as a class seem to be less effective in combat-related PTSD than in non-combat-related PTSD.[17] Even when treated with this class of agents, response rates in PTSD rarely exceed 60% after a first trial of medication and less than 20 - 30% of patients achieve full remission.[13,15-17] This suggests that currently available, efficacious agents still fall short of the ideal because of limited response and remission rates, and tolerability issues.

4.6 Non-pharmacological treatment
There are now more than 50 published RCTs examining the efficacy of CBT for PTSD.[20] TF-CBT has the best established research base of well-designed RCTs. Prolonged exposure has been found to be highly effective in the treatment of women with PTSD following sexual or physical assault. A minimum course of 8 - 12 weekly or biweekly sessions is recommended.

The components of CBT associated with the largest treatment effects are cognitive therapy (CT) and prolonged exposure; they have been shown to be superior to waitlist, supportive counselling, non-specific therapies; and treatment as usual.[21] Eye movement desensitisation and reprocessing (EMDR) which combines imaginal exposure with lateral eye movements, like exposure and CT, also has established efficacy, but critics of this procedure cite poor methodological quality and evidence that the procedural component, which is purported to differentiate it from exposure, is in fact ‘inactive’. A recent Cochrane review[22] concluded that EMDR was more effective than traditional therapies or no therapy but not different from CBT and stress management. The IOM found the quality of the body of evidence for EMDR to be too low to inform conclusions regarding treatment efficacy.[24]

4.7 Special populations
4.7.1 Pregnancy and lactation
The risks of drug treatment during pregnancy need to be weighed against the risks of withholding treatment for PTSD. During the first trimester, SSRIs do not increase the risk of birth defects; the exception to this is paroxetine, which is associated with a 1.5-fold increased risk of congenital heart defects.[23] Clinical guidelines recommend that paroxetine be discontinued during pregnancy. SSRIs taken after 20 weeks’ gestation may be associated with an increased risk of persistent pulmonary hypertension in the neonate, and all antidepressants administered in the third trimester may cause discontinuation effects (e.g. increased muscle tone, irritability, disrupted sleep, jitteriness) although these tend to be mild and self-limiting. Newer antidepressants, such as venlafaxine, have been associated with poor neonatal adaptation syndrome (tremors, irritability, shivering, feeding disturbances, increased muscle tone, respiratory difficulties) although it is unclear whether this is the result of medication withdrawal or toxicity. Treatment is supportive and symptoms usually resolve within 2 weeks. Tricyclic antidepressants (TCAs) are regarded as relatively safe in pregnancy although there is an increased risk of preterm delivery compared with SSRIs or no antidepressants. Desipramine is the preferred TCA during pregnancy owing to its relatively weak anticholinergic effects.[24] Lithium (Erbstein’s anomaly) and antiepileptic medications such as carbamazepine (neural tube defects, craniofacial defects, cardiac malformations) and valproate (neural tube defects, spina bifida, pulmonary atresia) carry an increased risk of birth defects. To date, lamotrigine has not been associated with intrauterine growth defects or neurobehavioural toxicity. No significant risk of teratogenicity with the older atypical antipsychotics (olanzapine, risperidone, quetiapine) has been documented. However, the aforementioned antipsychotics are associated with maternal hyperglycaemia, impaired glucose tolerance and weight gain which could contribute to maternal complications during pregnancy.[24] Newer atypical antipsychotics (e.g. aripiprazole, ziprasidone) have been associated with delays in skeletal ossifications, increased fetal weight and fetal mortality.

Long-term safety data on the use of antidepressants in pregnancy are lacking. Important factors to consider include the time between medication administration and feeding, and infant size and infant
metabolism. Most SSRIs do not attain detectable levels in breast milk and are not associated with disturbed infant development or neuropathology. Sertraline and paroxetine may be good choices for lactating women as these SSRIs have specifically been associated with undetectable levels in infants. TCAs have been associated with few adverse effects in breastfed infants, while newer antidepressants such as venlafaxine and mirtazapine are considered to be moderately safe.

4.7.2 Children and adolescents
Young children with PTSD, rather than reliving the trauma through repeated intrusive memories, may re-experience the trauma through repetitive play. Avoidance phenomena may also be more difficult to elicit in very young children who may struggle to verbalise their experiences. In addition to PTSD and acute stress disorder (ASD), traumatised children and adolescents may have a broad range of other psychopathological outcomes, in particular mood and anxiety disorders, behavioural disorders (e.g. attention-deficit hyperactivity disorder, conduct disorder), and substance use disorders. As with adults, interventions comprising psychotherapy (e.g. TF-CBT, family therapy) and pharmacotherapy (e.g. SSRIs, alpha-adrenergic agonists) are used. Practice parameters developed by the American Academy of Child and Adolescent Psychiatry\[21] recommend that the treatment of mild PTSD begin with TF-CBT. Treatment studies suggest 12 sessions of TF-CBT where PTSD is uncomplicated, but a number of children and adolescents may require longer-term treatment. Currently little is known about the effectiveness of pharmacotherapeutic agents in paediatric PTSD as there have been few controlled studies of SSRIs. Children and adolescents with more severe PTSD and with comorbid mood and anxiety disorders are likely to benefit from an SSRI.\[21]

4.7.3 The elderly
The assessment and treatment of PTSD may pose challenges for psychiatrists involved in treating PTSD in older adults. Specific symptom profiles may differ in the older adult, particularly in those individuals with chronic PTSD. Distress when exposed to trauma-related cues appears to be potentially salient and it is possible that this symptom motivates other features of PTSD in older adults, such as avoidance and emotional numbing.\[20] This constellation of symptoms may lead to misdiagnosis, for example, major depression or dysthymic disorder. Several factors should be considered when selecting a medication for an older patient with PTSD. These include prior treatment response, target symptoms, concurrent physical illness and medications, and drug tolerability. In order to reach the optimal dose for an older patient without causing intolerable side-effects, it is well worth remembering the adage ‘start low and go slow’. Important considerations in pharmacological treatment also include the heightened sensitivity for anticholinergic drug effects, increased sensitivity for extrapyramidal symptoms, an increased risk for orthostatic hypotension and electrocardiograph changes, and the possibility of paradoxical reactions (e.g. aggression) to benzodiazepines. SSRIs have been shown to be relatively safe in the elderly and are generally better tolerated than TCAs. Recommended doses of SSRIs for PTSD are the same as for younger adults. However, the potential for SSRIs to cause gastrointestinal and other bleeds, hyponatraemia, postural hypotension, and falls needs to be borne in mind in this age group.

4.8 Managing partial and non-responders
See steps 3 and 4 of algorithm below.

4.9 Algorithm
Step 1. Initiating treatment
The starting dose can be low (fluoxetine 10 - 20 mg; sertraline 25 - 50 mg; paroxetine, 10 - 20 mg; venlafaxine 37.5 - 75 mg). Other SSRIs include citalopram (10 - 20 mg), fluvoxamine (25 - 50 mg) and escitalopram (5 - 10 mg), for which there is less evidence. Based on currently available data for the SSRIs and SNRIs, statistically and clinically significant improvement is often seen by weeks 2 to 4. An adequate trial typically requires 6 - 12 weeks at an adequate dosage (e.g. fluoxetine 20 - 40 mg; sertraline 50 - 100 mg; paroxetine 20 - 40 mg), but some response should be expected after 4 - 6 weeks.\[7]

Other antidepressant options for which there is less robust evidence include mirtazapine, bupropion, and nefazodone. The older antidepressants, such as TCAs, e.g. amitriptyline, imipramine and the monoamine oxidase inhibitors (MAOIs, e.g. phenelzine) have demonstrated efficacy in placebo-controlled studies that have primarily included individuals with combat-related PTSD. In light of the safety profiles and concerns of toxicity with these agents (cardiotoxicity, seizure risk, and anticholinergic effects with the TCAs, and dietary restrictions and risk of hypertensive crisis with the MAOIs), they should preferably not be used as a first or second choice.\[7,15-17] Table 1 lists recommended drug doses.\[15]

Step 2. Maintaining a response
It is important to note that while many patients will experience symptom improvement within 12 weeks with at least a 50% reduction in PTSD symptoms, further improvement in core symptoms, disability, and overall functioning often occurs with continued treatment. If a patient is adequately responsive (at least a 50% improvement) after 12 weeks of treatment and demonstrates no intolerance, medication should be continued for at least 1 - 2 years.

Step 3. Managing partial response
If the patient is only partially responsive to the first trial of medication (25 - 50% or more reduction in symptoms), it is prudent firstly to optimise the dose of medication (i.e. titrate up to the maximum allowed or tolerated dose). Before doing this, it is important to reassess for persisting core PTSD symptoms (intrusion, avoidance, numbing, and hyperarousal), sleep disturbances, other PTSD symptoms (e.g. irritability, hostility, aggression, panic, psychotic symptoms), bipolar spectrum disorder, and substance abuse.\[7]

These ongoing symptoms can be saliently targeted through augmentation strategies although it must be noted that the evidence-base for augmentation strategies is limited. For example, olanzapine and risperidone (for which there is double-blind, placebo-controlled evidence for efficacy) can be used to target associated psychotic symptoms (e.g. paranoid ideation), and aggression. It is important to mention that since augmentation studies of antipsychotics were essentially short-term trials, the possibility of occurrence of severe adverse effects (viz. metabolic effects, cardiac effects, tardive dyskinesia) remain a concern. Anticonvulsants (e.g. valproate, lamotrigine, carbamazepine, topiramate), given their well-known anti-kindling properties, may also be effective as augmentation.
Step 4. Managing non-response
If there is no response (i.e. less than 25% improvement) to an SSRI and core PTSD symptoms persist after 4 - 6 weeks of an adequate medication dose (e.g. fluoxetine 40 mg/day, sertraline 150 mg/day), then it is advisable to switch to another SSRI, SNRI, or noradrenaline and specific serotonergic antidepressant (NaSSA) such as mirtazapine, bupropion; or alternatively to augment the same medication with another agent. The choice of an augmentation agent will depend on the presence of comorbid disorders; for example, the presence of a comorbid anxiety or mood disorder would probably necessitate the utilisation of an agent (e.g. antidepressant) that is effective for both PTSD and that disorder. [23] It is not known whether a sequential trial of a second SSRI is as effective as switching to an SNRI or NaSSA after the first unsuccessful SSRI trial. [23] If there is still no response after 6 - 12 weeks, then it is recommended that one add an atypical antipsychotic, anticonvulsant, a TCA, or CBT. If the patient fails on all of the above, it is essential at this point to re-evaluate the diagnosis and to consider switching (e.g. to a TCA or MAOI if these have not been tried already) or to add a third medication.

4.10 Early interventions for PTSD
TF-CBT is the only early intervention (i.e. given 1 - 3 months after trauma) that at the present time has convincing evidence of efficacy in ASD and acute PTSD. [29] There is no good evidence that psychological interventions (i.e. psychological debriefing), either single or multiple sessions, given routinely to everyone following a traumatic exposure, irrespective of symptoms, work. At present there is no conclusive evidence for the use of drug treatments to prevent PTSD in the early aftermath of trauma. Benzodiazepines are frequently prescribed in the aftermath of a traumatic event to control associated nonspecific behavioural disturbances (e.g. marked anxiety or agitation, insomnia) and/or to reduce active post-traumatic symptoms (e.g. hypervigilance). However, there is no compelling scientific evidence of the effectiveness of benzodiazepines either in the prevention of PTSD or in the treatment of core PTSD symptoms once they have developed. [23] In fact, there is evidence to indicate that benzodiazepines may contribute to the development and/or chronicity of PTSD symptoms. [28, 29]

5. Summary points
- PTSD is a challenging disorder to treat.
- It should be recognised that the majority of individuals with PTSD in South Africa may not have guaranteed access to diagnostic, pharmacotherapeutic and evidence-based psychotherapeutic services as suggested in this guideline.
- Antidepressants (in particular SSRIs) and CBT (exposure-based, trauma-focused CBT) remain the mainstay of treatment for the disorder.
- Use an SSRI or SNRI as first-line therapy and treat the patient at the maximum tolerated dose for at least 4 - 6 weeks before assessing responsiveness.
- Once a patient has responded to drug treatment, it should be continued for at least 12 - 24 months before considering gradual withdrawal.
- Cost should be factored into the choice of medication; the most affordable medication should preferably be selected to allow for funding of the minimum of 1 year of suggested pharmacotherapy.
- The minimum course of exposure-based, trauma-focused CBT is 8 - 12 weekly or biweekly sessions for exposure to a single-incident trauma.
- In deciding on a treatment plan for the patient, it is important to consider the following at baseline and follow-up assessments: the presence of ongoing trauma, comorbid diagnoses (both psychiatric and medical), suicidality, substance abuse, psychosis, pregnancy, treatment compliance, pharmacokinetic (drug-drug interaction) issues, and legal or compensation issues.
- There is no evidence for the efficacy of systematic, brief, single-session interventions (i.e. debriefing) focusing on the traumatic incident. However, providing general practical and social support and guidance to anyone following a traumatic incident is recommended.

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The quest to investigate novel pharmacological agents (e.g. D-cycloserine, a partial agonist of N-methyl-D-aspartate (NMDA) receptor through its mechanism on fear extinction) and therapeutic strategies (e.g. virtual reality exposure therapy), for the management of PTSD remains an ongoing pursuit.

Several other novel agents (e.g. propranolol, hydrocortisone) have been investigated in the prevention of PTSD (i.e. as prophylaxis) with mixed results. Currently SSRIs are being investigated in placebo-controlled trials as an early intervention in ASD to prevent the later development of PTSD. However, there is insufficient evidence to recommend the use of any of these agents.

References


Social anxiety disorder (social phobia)

S Seedat

1. Introduction
According to epidemiological studies, rates of social anxiety disorder (SAD) or social phobia range from 3% to 16% in the general population.[1,2] Social phobia and specific phobias have an earlier age of onset than other anxiety disorders. The median age of onset for the disorder is 13 years with an onset after age 25 relatively uncommon. The disorder typically persists throughout adult life and is associated with significant functional impairment.[3,5] Individuals with SAD are more likely to be females; however in clinical samples SAD seems to be more equally distributed among men and women.[4]

2. Diagnosis and clinical characteristics
SAD is characterised by an exaggerated and persistent fear of being negatively evaluated in social and performance situations.[4] The disorder is associated with physical, cognitive and behavioural disturbances. The generalised subtype consists of fears of most interactional and performance situations, while the non-generalised (or circumscribed) subtype is restricted to a few specific situations, such as public speaking or dating.[6-8] The generalised subtype or generalised social anxiety disorder (GSAD) is associated with greater comorbidity, chronicity, and functional impairment.[7] The avoidance of feared situations impacts on daily routine, work, academic and social activities and relationships. More than 80% of patients with SAD have a lifetime history of at least one other psychiatric disorder, most commonly major depression, panic disorder, generalised anxiety disorder, agoraphobia and substance use disorders.[6-7] There is also considerable overlap between SAD and avoidant personality disorder.[5,6]

SAD generally runs a chronic course and precedes mood, anxiety and substance use disorders. Even in the absence of comorbidity, SAD is associated with significant distress, including financial problems, increased suicidal thoughts, reduced work and school performance, poor social support and greater use of psychotropic medications.[3,5] Despite significant suffering, only 50% of patients with SAD ever seek treatment and when they do, it is usually when a comorbid condition develops and necessitates treatment.[4]

3. Assessment
There are several aspects of the clinical presentation of patients with SAD that may impact on treatment decisions. First, it is important to assess the level of disability to help distinguish social phobia from shyness.[8]

Second, SAD may be complicated by comorbid major depression, which is usually responsive to first-line therapy options (e.g. selective serotonin reuptake inhibitors (SSRIs) and dual-acting serotonin-norepinephrine reuptake inhibitors (SNRIs)). Conversely, social anxiety symptoms should be excluded in patients presenting with depression, panic attacks restricted to social situations, or alcohol misuse.

Third, in patients with alcohol and substance use disorders it is generally advisable to detoxify first, prior to commencing pharmacotherapy for SAD.

Fourth, in women, pregnancy and lactation considerations may necessitate the use of a non-pharmacological intervention (e.g. cognitive-behavioural therapy) as first-line.

Fifth, the presence of comorbid medical disorders and the prescription of concurrent medications must be borne in mind when using an anti-anxiety agent, particularly in view of the potential for drug-drug interactions and the potential impact of pharmacotherapy for SAD on underlying medical conditions.

4. Treatment
4.1 Treatment goals
The need for treatment is determined by the severity and persistence of symptoms, the presence of comorbid psychiatric disorder or physical illness, the level of disability and impact on social functioning, concomitant medication, and a history of good response to, or poor tolerability of, previous treatment approaches. In line with this, the main goals of treatment in SAD are to treat core symptoms and comorbidities, reduce functional impairment and avoidance, and improve the quality of life.

4.2 General aspects of treatment
Several treatment guidelines are available including those from the World Federation of Societies of Biological Psychiatry,[10] World Council on Anxiety,[11] the British Association for Psychopharmacology[10] and the Canadian Psychiatric Association.[12] Broadly speaking, these guidelines advocate for both pharmacological and non-pharmacological approaches in the management of SAD.

4.3 Acute treatment
Current evidence clearly supports the use of SSRIs (escitalopram, fluvoxamine, fluvoxamine controlled release (CR), paroxetine, sertraline) and the SNRI venlafaxine extended release (ER) as first-line pharmacological agents in the treatment of GSAD. Improvement in symptoms should become manifest by week 4; however, up to 12 weeks of treatment are needed to more definitively assess efficacy. In terms of psychotherapy, cognitive-behavioural therapy (CBT) is the treatment of choice. There is no conclusive evidence that pharmacotherapy is more effective than CBT or vice versa and the evidence in favour of the combination of pharmacotherapy and CBT is also limited.

4.4 Maintenance treatment
Drug treatment should be continued for a minimum period of 6 months in patients who have responded at 12 weeks. Several long-term studies (double-blind and open-label) have been conducted to examine the issue of relapse prevention.[13] These studies have evaluated moclobemide, phenelzine and CBT, sertraline and exposure therapy, fluvoxamine, paroxetine and escitalopram and venlafaxine ER. Response rates in these studies range from 58% for venlafaxine ER to 88% for escitalopram.
4.5 Pharmacological treatment
Evidence from controlled trials indicates that SAD is responsive to a wide range of medication treatments.\[4\] Drugs recommended as first-line treatment include SSRIs (escitalopram, fluvoxamine, paroxetine and sertraline) and the SNRI, venlafaxine. In a meta-analysis of efficacy of the SSRIs, which examined outcomes from 15 separate controlled studies (including trials of escitalopram, sertraline, paroxetine, fluoxetine and fluvoxamine), all agents with the exception of a single trial of fluoxetine (which did not separate from placebo), showed efficacy in ameliorating symptoms of SAD.\[14\] Venlafaxine has also been widely studied and venlafaxine ER has regulatory approval for SAD in a number of countries.\[14\] In a head-to-head comparison of venlafaxine and paroxetine, venlafaxine ER was as effective as paroxetine, and both drugs were better than placebo.\[15\] The efficacy of venlafaxine ER in SAD does not appear to be dose-related, i.e. lower (75 mg/day) and higher (150 - 225 mg/day) doses have produced similar therapeutic effects in trials.\[16\] The other SNRI, duloxetine, has not been studied in controlled trials for SAD.

In addition to the SSRIs and venlafaxine, the monoamine oxidase inhibitor (MAOI) phenelzine and the reversible inhibitor of monoamine oxidase (RIMA) moclobemide have controlled evidence for efficacy. Phenelzine is not widely used because of its requirement of a low tyramine diet to prevent a hypertensive crisis. Moclobemide has demonstrated comparable effectiveness among patients with and without a comorbid anxiety disorder, as well as among patients with different SAD subtypes (generalised and non-generalised SAD).\[17\]

There is preliminary evidence from randomised controlled trials for the efficacy of pregabalin and gabapentin. Open trials of other anticonvulsants (e.g. levetiracetam, tiagabine, topiramate) and the antipsychotic olanzapine show some promise as acute treatments, but adequate randomised controlled trials (RCTs) are lacking.\[18,19\]

Evidence for the efficacy of benzodiazepines (bromazepam and clonazepam) in SAD is mixed. Treatments with unproven efficacy in generalised social phobia include the tricyclic antidepressant imipramine, buspirone, and the beta-blocker, atenolol.\[19\]

4.6 Non-pharmacological treatment
The non-pharmacological treatment of choice for SAD is CBT or exposure therapy alone. CBT for social phobia includes techniques of psycho-education, in-session and in vivo exposure to feared situations, and techniques intended to modify maladaptive or irrational thinking patterns. Other techniques in the CBT umbrella are applied relaxation and social skills training. The relative efficacy of CBT vs exposure therapy is unclear, with some studies indicating comparable efficacy while other studies show somewhat greater efficacy for CBT.\[18,20\] In a recent meta-analysis of 32 RCTs that examined a variety of non-pharmacological approaches, CBT was consistently shown to result in significantly greater improvements in SAD symptoms than other ‘placebo’ conditions, such as supportive group therapy, self-exposure, being wait-listed (i.e. waiting for an intervention) or pill placebo.\[20\]

4.7 Special populations
4.7.1 Pregnancy and lactation
The risks of drug treatment during pregnancy need to be weighed against the risks of withholding treatment for SAD. During the first trimester, SSRIs do not increase the risk of birth defects; the exception to this is paroxetine which is associated with a 1.5-fold increased risk of congenital heart defects.\[21\] Clinical guidelines recommend that paroxetine be discontinued during pregnancy. SSRIs taken after 20 weeks of gestation may be associated with an increased risk of persistent pulmonary hypertension in the neonate, and all antidepressants administered in the third trimester may cause discontinuation effects (e.g. increased muscle tone, irritability, disrupted sleep, jitteriness) although these tend to be mild and self-limiting. There are no data, other than a single case report, on the safety of moclobemide during pregnancy, while there are limited data on the safety of the MAOIs. As animal studies are suggestive of teratogenicity and use of MAOIs necessitates dietary modifications, MAOIs are not considered first-line treatments for SAD in pregnancy. Newer antidepressants, such as venlafaxine, have been associated with poor neonatal adaptation syndrome (tremors, irritability, shivering, feeding disturbances, increased muscle tone, respiratory difficulties) although it is unclear whether this is the result of medication withdrawal or toxicity. Treatment is supportive and symptoms usually resolve within 2 weeks. In general, venlafaxine is considered to be moderately safe in pregnancy. Benzodiazepine use during pregnancy has been associated with neonatal morbidity, some congenital malformations such as orofacial cleft, and may be associated with an increased risk for preterm birth, low birth weight, floppy infant syndrome, and neonatal withdrawal symptoms. Clonazepam monotherapy, specifically, has not been associated with an increased risk of major malformations. Gabapentin has been shown to be teratogenic in mice; its safety in pregnant women has not been established and is best avoided during pregnancy.\[22\]

Long-term safety data on the use of antidepressants in pregnancy are lacking. Factors that are important to consider include the time between medication administration and feeding, and infant size and infant metabolism. Most SSRIs do not attain detectable levels in breast milk and are not associated with disturbed infant development or neuropathology. Sertraline and paroxetine may be good choices for lactating women as these SSRIs have specifically been associated with undetectable levels in infants. Benzodiazepines, such as clonazepam, diazepam and lorazepam, are excreted in breast milk. However, published data indicate that the levels detected in breast milk are low; thus the nursing infant is unlikely to ingest significant amounts of the drug in this way. Breastfeeding is possible, but the infant should be carefully monitored for any adverse effects.

4.7.2 Children and adolescents
Shyness in young children may be a precursor to SAD in adulthood. In children, common fears include fears about performance situations such as speaking or performing in front of people, social interactional fears such as joining in or starting a conversation, and interacting with same-age peers.\[23\] Unlike adults, children with SAD are seen as generally anxious and may experience more somatic symptoms, such as headaches, stomach aches and nausea, as a result of their anxiety. Impairments range from low self-esteem, social skills deficits, few friendships to scholastic underachievement. Among adolescents, typical fears include formal and informal social interactions, public observation and performance, and situations requiring assertive behaviour. In addition, adolescents seem to have more pervasive patterns of fear and
avoidance, as well as higher levels of social distress than either children or adults. SAD in childhood and adolescence is highly comorbid with depression. Comorbidity with anxiety and substance use disorders is also common.[21]

Compared with adults, there is relatively less information available on the safety, efficacy and long-term outcomes (relapse rates) of SSRI or SNRI treatment. Open-label and double-blind placebo-controlled studies have shown response rates ranging from 36% to 100%.[9-12] Fluoxetine, fluvoxamine, paroxetine and venlafaxine ER have been evaluated in RCTs. These agents have been well tolerated in children and adolescents in doses comparable to the adult dose. Antidepressants, in particular SSRI use, have come under the spotlight in recent years owing to concerns about their potential to increase suicidal ideation and attempts.[21] While the safety profile of SSRIs and other antidepressants specifically in children and adolescents with SAD is not yet known, a review of 24 short-term (4 - 16 weeks) trials involving nine antidepressant medications (including SSRIs) in more than 4 000 youth with major depressive disorder, obsessive-compulsive disorder, and other psychiatric disorders, documented a 4% rate of suicidal ideation and suicidal behaviours in patients treated with antidepressants compared with a 2% rate in patients treated with a placebo.[22] It is important to note that there were no completed suicides in any of these studies.

CBT, as a 16-session treatment, has been shown to be an effective strategy in both children and adolescents with SAD, with continued improvement or maintenance of gains over a 1-year period.[21] The benefits of combining CBT and medication for childhood SAD have yet to be established.[23]

4.7.3 The elderly

The prevalence of SAD tends to decline in older adults (55 years of age and older). SAD is more common in elderly patients who have other psychiatric disorders, in particular major depression. Both pharmacological treatments (e.g. SSRIs, venlafaxine) and CBT are indicated for use in older adults with SAD; however, the standard of practice has been to infer from data in younger patients and assume their efficacy in older adults.[23]

Several factors should be considered when selecting a medication for an older patient with SAD. Prior treatment response, target symptoms, concurrent physical illness and medications, and drug tolerability should all be taken into account. In order to reach the optimal dose for an older patient without causing intolerable side-effects, it is well worth remembering the adage ‘start low and go slow’.[23] Important considerations in pharmacological treatment in the elderly include heightened sensitivity for anticholinergic drug effects, increased sensitivity for extrapyramidal symptoms, an increased risk for orthostatic hypotension and electrocardiograph changes, and the possibility of paradoxical reactions (e.g. aggression) to benzodiazepines. SSRIs have been shown to be relatively safe and recommended doses of SSRIs for SAD are the same as for younger adults. However, the potential for SSRIs to cause gastrointestinal and other bleeds, hyponatraemia, postural hypotension and falls needs to be borne in mind in this age group.

4.8 Managing partial and non-responders

See steps 3 and 4 of algorithm below.

4.9 Algorithm

Step 1. Initiating treatment with pharmacotherapy/psychotherapy

Choose an evidence-based pharmacological or psychological therapy for the acute treatment of SAD.[9] Take account of patient clinical features, needs and preference when choosing treatment. If the decision is to start pharmacological treatment with an SSRI or SNRI, the starting dose can be low (sertraline 25 - 50 mg; paroxetine 10 - 20 mg; venlafaxine 37.5 - 75 mg; fluvoxamine 25 - 50 mg; escitalopram 5 - 10 mg), with titration up to a maximally tolerated therapeutic dose (Table 1). Although routine prescription of higher doses of SSRls is not recommended,[9] individual patients may benefit from higher doses. For patients with comorbid mood (or anxiety) disorders, SSRls may be preferred because of their broad spectrum of action. There is some evidence to suggest that major depressive disorder symptoms tend to resolve before an improvement in SAD symptoms is seen.[24]

Evidence of symptom improvement should manifest by week 4. However, patients should be advised that treatment periods of up to 12 weeks are needed to assess efficacy, as there is some evidence from double-blind controlled trials to suggest that non-responders to treatment at 8 weeks become responders with 4 further weeks of double-blind treatment.[25]

Step 2. Maintaining a response and preventing relapse

Double-blind studies indicate that continuing SSRI or SNRI treatment from 12 weeks to 24 weeks (i.e. up to 6 months after initiation) is associated with an increase in overall treatment response rates.[9] Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment also reveal

Table 1. Recommended daily drug doses for social anxiety disorder[9]*

<table>
<thead>
<tr>
<th>Selective serotonin reuptake inhibitors (SSRIs)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram 10 - 20 mg</td>
<td></td>
</tr>
<tr>
<td>Paroxetine 20 - 50 mg</td>
<td></td>
</tr>
<tr>
<td>Sertraline 50 - 150 mg</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine 100 - 300 mg</td>
<td></td>
</tr>
<tr>
<td>Citalopram 20 - 40 mg</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine 20 - 40 mg</td>
<td></td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRI)</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine 75 - 225 mg</td>
<td></td>
</tr>
<tr>
<td>Monoamine oxidase inhibitor (MAOI)</td>
<td></td>
</tr>
<tr>
<td>Phenelzine 45 - 90 mg</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td>Clonazepam 1.5 - 8 mg</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td></td>
</tr>
<tr>
<td>Gabapentin 600 - 3 600 mg</td>
<td></td>
</tr>
<tr>
<td>Reversible inhibitor of monoamine oxidase (RIMA)</td>
<td></td>
</tr>
<tr>
<td>Moclobemide 300 - 600 mg</td>
<td></td>
</tr>
</tbody>
</table>

a significant advantage for staying on active medication (clonazepam, escitalopram, paroxetine, sertraline) for up to 6 months, compared with switching to placebo. Therefore, continue drug treatment for at least another 6 months in patients who are responding at 12 weeks (i.e. show at least a 50% improvement in symptoms). Several of the guidelines recommend continuing treatment for at least 12 months. In patients at a high risk of relapse, it may be prudent to consider cognitive therapy after an adequate response to drug treatment. It is also vital that efficacy and tolerability are regularly monitored during long-term treatment.

Step 3. Managing partial response
If after 12 weeks, there is only a 25 - 50% reduction in symptoms or a less than 25% reduction in symptoms, consider switching to venlafaxine after non-response to acute treatment with an SSRI. There is no clear evidence for the benefit of dose escalation after an initial non-response. Switching between treatments with proven efficacy is preferable. Alternative treatment strategies include a switch to non-SSRI antidepressants, anticonvulsants and benzodiazepines, as discussed above.

Open-label augmentation of SSRI treatment with buspirone has been reported as beneficial but placebo-controlled trials of pindolol augmentation and clonazepam augmentation, respectively, were not associated with greater treatment efficacy.

Step 4. Managing non-response
If there is still no response, re-evaluate the diagnosis and reassess for comorbid substance use disorders, undetected medical conditions, comorbid personality disorders, psychosocial stressors and poor compliance. Consider combining evidence-based pharmacological treatments only where there are no contraindications to doing so. An alternative strategy is to combine drug treatment with CBT. There is some preliminary evidence for the usefulness of this approach.

A recent randomised, double-blind placebo-controlled trial to determine whether combined medication and cognitive behavioural group treatment (CBGT) was superior to either monotherapy or pill placebo found that combined phenelzine and CBGT treatment was superior to either treatment alone and to placebo in terms of rates of response and remission. D-cycloserine, a partial N-methyl-D-aspartate (NMDA) receptor agonist that facilitates fear extinction, has been documented in several trials to be useful as an augmentation to CBT in patients with SAD.

5. Summary points
- SAD is highly responsive to evidence-based acute treatments.
- Pharmacological: most SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), venlafaxine, phenelzine, moclobemide, some benzodiazepines (clonazepam), anticonvulsants (gabapentin, pregabalin) and clonazapine.
- Psychological: cognitive-behavioural therapy (CBT).
- There is no conclusive evidence that pharmacotherapy is more effective than CBT for the treatment of social phobia.
- Treatment duration of up to 12 weeks is needed to assess efficacy.
- Drug treatment should be continued for at least a further 6 months in patients who have responded at 12 weeks.
- Cost should be factored into the choice of medication; the most affordable medication should preferably be selected to allow for funding of the minimum period of suggested pharmacotherapy.
- In the longer term, consider CBT as this may reduce relapse rates better than drug treatment.
- Monitor efficacy and tolerability regularly during long-term treatment.
- Combining a drug and psychological approach is recommended during the initial phase of treatment.
- Consider switching to venlafaxine after non-response to acute treatment with an SSRI.
- Consider combining evidence-based pharmacological treatments if there is non-response but only where there are no contraindications to do so.

References
4. Wustenberg HGM. Recent advances in understanding and treating social anxiety disorder. CNS Spectrums 2009;14:24-33.


