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CP Freeman MBChB, FCPsych(SA), MMed(Psych) & JA Joska PhD, FCPsych(SA)

To cite this article: CP Freeman MBChB, FCPsych(SA), MMed(Psych) & JA Joska PhD, FCPsych(SA) (2013) Dealing with major depression in general practice, South African Family Practice, 55:4, 319-325, DOI: [10.1080/20786204.2013.10874369](https://doi.org/10.1080/20786204.2013.10874369)

To link to this article: <http://dx.doi.org/10.1080/20786204.2013.10874369>



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Published online: 15 Aug 2014.



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# Dealing with major depression in general practice

Freeman CP, MBChB, FCPsych(SA), MMed(Psych), Psychiatrist, Division of Neuropsychiatry

Joska JA, PhD, FCPsych(SA), Head of Division of Neuropsychiatry

Department of Psychiatry and Mental Health, University of Cape Town

Correspondence to: Carla Freeman, e-mail: carla.freeman@uct.ac.za

Keywords: major depression, general practice

## Abstract

One in ten South Africans will be diagnosed with major depressive disorder (MDD) at some point in their lives. MDD is a potentially disabling condition that affects many spheres of an individual's life and leads to marked social and occupational dysfunction. General practitioners are frequently required to diagnose and manage MDD, often in a time-pressured primary healthcare setting. This article aims to provide practitioners with an overview of MDD. It covers aspects of diagnosis, co-morbidity, pharmacology and special patient groups.

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## Introduction

According to the World Health Organization, unipolar major depression is set to become the leading cause of disease burden by 2030. Major depressive disorder, or MDD, is a syndrome hallmarked by a persistent low mood and/or lack of enjoyment in previously pleasurable activities. Typically, onset occurs from 20-30 years and is often episodic in nature, occurring throughout the patient's lifespan. MDD may also present in childhood or in older adulthood.

It is difficult for laypersons and general practitioners to differentiate between a "normal" depressed mood and MDD. If a patient has just been diagnosed with cancer, his or her depression is an understandable reaction. On the other hand, given the enormous distress and impairment associated with depression, and the availability of safe and effective treatments, perhaps clinicians should have a low threshold for diagnosis.

General practitioners are frequently required to diagnose and manage MDD in the primary care setting, often in the context of other medical conditions. This article aims to provide clinicians with an approach to MDD that covers important aspects of differential diagnosis, co-morbidity, pharmacological treatment and special groups.

## Epidemiology and burden of disease

According to the South African Stress and Health (SASH) study that was conducted between 2002-2004, South Africans have a 9.7% lifetime prevalence of MDD.<sup>1</sup> MDD is a disabling condition and when undiagnosed or untreated, can result in significant costs to patients, their families and society at large. The negative consequences of depression include suicide, increased medical morbidity and mortality,

workplace absenteeism and occupational and social dysfunction.<sup>2</sup>

## Making a diagnosis of major depression

Symptoms of depression include a sad or low mood that lasts for a minimum of two weeks and/or significant anhedonia (the absence of pleasure or the ability to experience it).<sup>3</sup> In addition, appetite or weight change, sleep disturbances, restlessness, fatigue, feelings of guilt or worthlessness, impaired concentration and suicidal ideation may form part of the clinical presentation. At least five of the above symptoms need to be present to confirm the syndrome.

The boundary between normal sadness and major depression is ultimately defined by a careful history, focusing on the severity of symptoms and their associated distress and impairment. Closely related syndromes include bereavement, post-partum depression, premenstrual dysphoric disorder and adjustment disorders. There is a range of well-validated depression scales that can quickly provide a very useful measure of symptom severity for clinicians who prefer objective indicators of severity. These scales are also important in monitoring the response to intervention.

It is essential to enquire about previous episodes of mania or hypomania (defined as a distinct period of elevated or irritable mood, coupled with a decreased need for sleep, talkativeness, grandiosity and increased goal-directed behaviour), in order to exclude a possible bipolar illness. As part of the diagnostic process, exclusion of an underlying substance use disorder or medical condition is essential and should be guided by both the history and examination.

## Co-morbidity and depression

MDD is frequently associated with a variety of medical and psychiatric co-morbidities.

Firstly, although the mechanism is not well understood, increased rates of MDD are associated with ischaemic heart disease (IHD), hypertension, stroke, dementia, obesity and metabolic syndrome. In addition, the presence of MDD in the context of the above illnesses significantly worsens their course and prognosis. Proposed contributory factors include detrimental lifestyle choices as a result of depression, e.g. smoking and drinking, as well as an altered physiological response to stress.<sup>4</sup>

Secondly, psychiatric co-morbidity is prominent in the context of MDD and occurs in up to three quarters of individuals.<sup>5</sup> It is notable that anxiety disorders often precede MDD. This emphasises the importance of treating anxiety disorders early. Substance use-disorders often begin after MDD, sometimes as a way of self-medicating a depressed mood.

## Neurobiology of depression

MDD is a notably heterogeneous condition, of which the neurobiology is still not well understood. Advances in genetics and neuroimaging continue to enhance understanding of this disease construct, which is likely to be the result of a complex interaction between multiple genes and environmental factors. Multiple neurocircuits and neurochemicals are thought to be involved in the pathogenesis of MDD and lead to a range of associated symptoms and disease subtypes.<sup>6</sup>

## Management of depression in general practice

For the purposes of this article, the approach to managing MDD has been divided into three sections, namely acute or short-term, intermediate and long-term management.

### Acute or short-term management

Once the diagnosis of MDD has been made and any contributory or underlying medical conditions have been actively managed, several steps should be taken to ensure both the safety and optimum management of the patient. A suicide-risk assessment is of paramount importance in the management of all depressed patients. Many individuals will not willingly volunteer suicidal thoughts or plans, due to feelings of shame and fears of stigma. The suicide-risk assessment involves identifying and weighing up high-risk patient factors vs. individual protective factors (Table I).

Suicide assessment cannot be reduced to an arithmetic exercise. Clinicians are cautioned against weighing up the factors against one another in order to "cancel out" risk. At any point, if there is uncertainty about the suicide risk involved, clinicians are advised to err on the side of caution and to seek a second opinion from a colleague or mental

Table I: Suicide risk and protective factors

Risk factors associated with suicide
<b>Demographic factors</b>
Age: 15-35 years, and the elderly
Gender: Male > female
Postpartum
Victim of domestic violence or intimate partner abuse
<b>Suicidality</b>
Previous suicide attempts
Frequent suicidal ideation
Suicidal intent
Existing suicide plan
Access to means, e.g. a firearm at home
<b>Psychiatric history or illness</b>
Psychosis, especially command-type hallucinations
Agitation and akathisia
Depression, anxiety and panic attacks
<b>Patient factors</b>
Co-morbid medical illness, e.g. HIV, chronic pain and malignancy
Lack of social support
Unemployment and loss of socio-economic status
Conflict at home
Poor coping skills
Family history of suicide
<b>Protective factors</b>
Absence of a psychiatric illness
Employment
Responsibility to family and children at home
Pregnancy
Strong social support
Good coping and problem-solving skills

health professional. Patients who are psychotic or actively suicidal and show intent to commit suicide constitute a high-risk to themselves and may require involuntary admission to a psychiatric hospital according to the Mental Health Care Act of 2002.

Once safety has been established, a comprehensive treatment plan, tailored according to individual needs, should be made in collaboration with the patient. Psychoeducation is a fundamental component of management and should be administered at each contact point. Target symptoms, previous response to treatment, choice of therapy, follow-up plan and duration of treatment should all be documented in the treatment plan. A variety of pharmacological and non-pharmacological strategies are available to clinicians. Patients with less severe symptoms of depression can be offered nonpharmacological treatment as first-line therapy, e.g. cognitive behavioural therapy for depression.<sup>7</sup> Moderate-to-severe cases of MDD require treatment with antidepressant medication.

Table II: Antidepressants, doses and side-effects

Class	Drug (trade name)	Recommended dose for adults	Common adverse effects	Additional notes
SSRIs	Citalopram (Celexa®, Cipramil®)	Start at 20 mg. Increase by 20 mg per day after one or more weeks, until desired efficacy is reached.	Gastrointestinal tract (nausea, diarrhoea and decreased appetite)	QT prolongation at doses ≥ 40 mg.
			Insomnia	
			Sedation and dizziness	
			Sexual dysfunction	
Bruising and bleeding (bleeding rare; caution with anticoagulants)				
Hyponatraemia				
SSRIs	Escitalopram (Lexapro®)	Start at 10 mg/day and increase to 20 mg/day, if necessary.	As above	No specific actions on hepatic CYP450 enzymes.
	Fluoxetine (Prozac®)	20-40 mg daily	As above May increase agitation initially	Inhibits CYP450 2D6 and 3A4.
SSRIs	Sertraline (Zoloft®)	Start at 50 mg/day, may increase to 100 mg/day after a week if well tolerated.	As above	Maximum dose 200 mg/day.
TCAs	Amitriptyline (Elavil®)	Initial dose of 25 mg at bedtime. Increase in 25 mg increments every 3-7 days to 150 mg/day.	Anticholinergic side-effects (sedation, dry mouth, constipation and blurred vision)	Substrate for CYP450 2D6 and 1A2.
			Weight gain	
			Dizziness	
			Hypotension	
SNRIs	Venlafaxine (Effexor®, Effexor XR®)	Initial dose of 37.5 mg daily for a week. If tolerated, increase to 75 mg daily for a week. Increase no more than 75 mg every four days. Maximum of 375 mg/day.	Headaches	Use with caution in cardiac disease. Older adults tolerate lower doses.
			Nervousness	
			Insomnia or sedation	
			Sexual dysfunction	
			Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)*	
			Hyponatraemia	
NaSSAs	Mirtazapine (Remeron®)	Initial dose of 15 mg/day at bedtime. Increase after a week or two to 30 mg/day. Maximum of 45 mg/day.	Anticholinergic side-effects (see TCAs)	Flu-like symptoms may indicate low white cell count. Useful for problematic insomnia, although caution required with other sedatives.
			Sedation	
			Dizziness	
			Hypotension	
			Lowers white cell count (rare)	
NDRIs	Bupropion (Wellbutrin®)	Start at 75 mg/day, increase to 75 mg twice daily after a week. Continue to increase in 75 mg increments if needed. Maximum of 300 mg/day in divided doses.	Anticholinergic side-effects (see TCAs)	Seizure threshold can be lowered. Drug is activating. Useful for psychomotor retardation. Sexual dysfunction is less likely.
			Insomnia	
			Dizziness	
			Headaches	
			Agitation	
			Sweating	
			Hypertension	
			Rash	
			Seizures (rare)	

The choice of antidepressant depends on the previous response to treatment and individual patient factors, e.g. IHD, tolerability of side-effects and affordability. Selective serotonin reuptake inhibitors (SSRIs) are considered to be first-line agents due to their tolerability and favourable

side-effect profile. Table II indicates recommended doses and common side-effects. Patients who demonstrate no response after approximately four weeks or partial response after approximately six weeks should be assessed for adherence to treatment. The dose of the existing drug may

either be increased or switched to an alternative agent, preferably in a different class, e.g. venlafaxine (a dual serotonin and norepinephrine reuptake inhibitor).<sup>8</sup> Patients who experience intolerable side-effects should be switched to an alternative agent earlier.

### Intermediate management

Ideally, patients with MDD should be followed-up within a week of commencing antidepressant treatment. It is important to enquire about and carefully document the side-effects of treatment, suicidal ideation and agitation. Treatment doses should be increased according to the recommended therapeutic range. In certain circumstances, e.g. treatment-resistant depression, referral to specialist psychiatric services is appropriate (Table III).

**Table III: When to refer to psychiatric services**

Treatment-resistant depression
Psychotic depression
Medically complicated patients with multiple co-morbidities
Actively suicidal patients
Depressed children and adolescents

Once treatment is stabilised, the therapeutic focus falls on optimising global levels of function. Extended periods off work should be discouraged and patients should actively re-engage with their previous social and occupational activities. Although there is a surprising lack of data on how best to sequence medication and psychotherapy, arguably psychotherapy that focuses on behavioural activation and restructuring cognition may offer particular benefit at this point in treatment.

### Long-term management

Most guidelines recommend that antidepressant therapy is continued for 6-9 months following the resolution of symptoms in first-episode MDD. Patients who are at high risk of relapse or who have experienced multiple episodes of depression may benefit from a longer period of maintenance treatment. The decision to discontinue treatment should be made in collaboration with the patient. The latter's mood should be carefully monitored. Treatment should be tapered slowly and patients should be informed of the risk of a discontinuation syndrome. Discontinuation symptoms usually occur when certain medications have been taken for six weeks or longer and include flu-like illness, insomnia, nausea, balance disturbance, odd sensations and hyperarousal.<sup>9</sup>

## Special groups

### Pregnancy

Approximately one in ten women will experience a depressive episode during their pregnancy or in the post-partum period. A previous history of major depression is the strongest indicator of increased risk of maternal depression.

Untreated maternal depression poses a high risk to both mother and infant. In some studies, it has been shown to result in preterm labour, lower birthweight and longer hospital stays.<sup>10</sup> Exposure to antidepressants in utero, e.g. SSRIs, is not without risk, and has been linked to conditions such as persistent pulmonary hypertension in the newborn and a modest increase in congenital abnormalities.<sup>11</sup> However, it is important to bear in mind that maternal depression has also been linked to foetal abnormalities in a small proportion of pregnant women.

An individual risk-benefit analysis should be undertaken in every depressed mother and a treatment plan should be derived in consultation with a psychiatrist or mental health practitioner. Treatment may include pharmacological and/or psychological therapy, depending on the nature and severity of the depression.

### Older adults

Depression remains grossly underdiagnosed and undertreated among older adults. It is frequently overlooked as a possible underlying cause of the behavioural and psychological symptoms associated with dementia. Between 10-15% of community dwelling, and up to 40% of nursing home residents over the age of 65 years, suffer from major depression.<sup>12</sup> Untreated depression in this group has far-reaching potential consequences, including premature placement in nursing homes, reduced quality of life, increased caregiver distress and increased morbidity and mortality.

Diagnosis of major depression in older adults includes a thorough medical evaluation in order to exclude a contributory or underlying general medical condition, e.g. hypothyroidism, as well as a suicide-risk assessment. Older adults with depression are at a significantly higher risk of completing suicide than any other age-group with depression. They frequently downplay symptoms and suicidal ideation.<sup>13</sup>

Clinical features of depression may differ qualitatively from those seen in younger people. There is greater emphasis on somatisation, irritability, agitation and psychomotor disturbance. Validated measurement tools, such as the Geriatric Depression Scale and the Cornell Scale for Depression in Dementia, may assist clinicians in assessing depression.<sup>14,15</sup> SSRIs are widely accepted as a first-line pharmacotherapy option in late-life depression, due to their tolerability and favourable side-effect profile. However, even SSRIs may be associated with safety issues. Citalopram, widely used in geriatric populations, has also been associated with QT prolongation in doses over 40 mg per day. As a rule, lower initiating doses should be used with a slow titration and longer treatment trial. Close monitoring of adverse effects is essential in the management of late-life depression.

## Children

Often, childhood depression is often a chronic, recurring condition that leads to significant impairments in psychological, scholastic and social functioning. Between 1-2% of children are depressed. This increases to eight per cent in adolescence. Several risk factors are associated with childhood depression, including parental psychopathology, rejecting or intrusive parenting, physical and sexual abuse, death or loss of a parent and family discord.<sup>16</sup>

Presenting features of depression in childhood include sadness, irritability, aggression or behavioural disturbance, a detached or disinterested demeanour, and occasionally, a pre-occupation with death or dying. Younger children may be unable to quantify their feelings and may present to primary care practitioners with non-specific medical symptoms, e.g. stomach aches, headaches, nausea, cramps, bed-wetting, failure to thrive and behavioural disturbance. Children may not verbally express their emotional distress. The detection of childhood depression relies on the vigilance of the caring clinician. A number of sound psychological and psychopharmacological therapeutic options are available for the treatment of childhood depression and should be guided by experts in the field of child and adolescent mental health.

## Conclusion

Depression is a common and debilitating illness, which may be associated with multiple medical and psychiatric co-morbidities. Timely detection and evidence-based management that is tailored according to individual patient needs may significantly improve global functioning, morbidity and mortality.

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