CLINICAL PRACTICE GUIDELINES

Depression

Ministry
of Health

Chapter of Psychiatrists
Academy of Medicine
Singapore

SINGAPORE PSYCHIATRIC
ASSOCIATION

NMRC
National Medical
Research Council

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MOH Clinical Practice Guidelines 3/2004

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial, as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

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Depression

MOH Clinical Practice Guidelines 3/2004

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Statement of Intent

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

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Foreword

It is normal to feel low now and then, as we react to the things that happen around us. However when a low mood persists and is of greater severity than a normal emotional experience, it becomes a source of distressing morbidity.

Depression is a major mental health problem with physical, mental and social consequences. In Singapore, it has been estimated that almost 9% of the adult population may suffer from it. The disorder is not easy to manage and treatment is often required long-term. Fortunately, many treatments that have been shown to be effective are available.

These guidelines were developed by an expert workgroup and are intended for all doctors who are likely to encounter patients with depression in their practice. Various modalities of treatment and the evidence supporting their use are discussed. Management of specific groups like children, adolescents and the elderly is also considered. I hope you find these guidelines useful in your own practice.

PROFESSOR TAN CHORH CHUAN
DIRECTOR OF MEDICAL SERVICES

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Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

C The basic assessment of depression includes the history, the mental state examination and physical examination. (pg 9)

- Take a detailed history of the presenting symptoms and determine the severity and duration of the depressive episode. Establish history of prior episodes, prior manic or hypomanic episodes, substance abuse and other psychiatric illnesses. Look out for co-existing medical conditions. Check for family history of mental illness, depression and suicide. Establish the personal history and the available supports and resources. Evaluate functional impairment and determine life events and stressors.

- Do a mental state examination. This includes an evaluation of the severity of symptoms and assessment for psychotic symptoms. All assessments of depression will include an assessment of the risk of suicide, self-harm and risk of harm to others. (See Annex II on page 32).

- Do a physical examination to exclude a medical or surgical condition.

- Laboratory testing may be indicated if there is a need to rule out medical conditions that may cause similar symptoms.

Grade C, Level IV

C Referrals to a psychiatrist are warranted when

- there are co-morbid medical conditions for which expertise is required regarding drug-drug interactions.
- there is diagnostic difficulty,
- one or two trials of medication have failed,
- if augmentation or combination therapy is needed
- for those with co-morbid substance abuse or severe psychosocial problems
- the patient is pregnant or plans to become pregnant

- for post-natal depression
- if specialized treatment like electroconvulsive therapy is indicated but unavailable in the primary care setting

(pg 10) **Grade C, Level IV**

C Once an antidepressant has been selected, start with a low dose and titrate to the full therapeutic dose gradually, while assessing patients mental state and watching for the development of side-effects. The frequency of monitoring will depend on the severity of the depression, suicide risk, the patient's cooperation and the availability of social supports. (pg 13)

Grade C, Level IV

B All antidepressants, once started should be continued for at least 4 to 6 weeks. (pg 14)

Grade B, Level IIb

C If there is little or no improvement after switching, it is recommended that a psychiatric referral is sought for the following:

(1) Augment the first antidepressant with a second medication (Augmentation)

(2) Add a second antidepressant to the first (Combination)

(pg 15) **Grade C, Level IV**

GPP At the end of the Continuation phase the antidepressant medication should be gradually tapered to avoid discontinuation symptoms. Patients should be followed up during the next few months to ensure that a new depressive episode does not occur. If recurrence occurs, the patient is likely to respond to the same antidepressant at the same dosage that was effective previously, which should then be continued for 6 months. (pg 16)

GPP

A Psychotherapy alone is as efficacious as antidepressant medication in patients with mild to moderate major depression and can be used as first-line treatment. (pg 18)

Grade A, Level Ia

A Cognitive Behaviour Therapy is also an effective maintenance treatment and is recommended for patients with recurrent depression who are no longer on medication. (pg 19)

Grade A, Level 1a

A Concurrent combined psychotherapy and pharmacotherapy is recommended in severe depression and chronic depression as it is more effective than either alone in these conditions. (pg 21)

Grade A, Level Ib

B Electroconvulsive therapy may be considered as the first-line treatment for patients with severe depression, depression with psychotic features, marked functional impairment, catatonic stupor, high suicide risk or food refusal leading to nutritional compromise. It is also considered in any other situation when a particularly rapid antidepressant response is required, such as in pregnancy and in those with co-morbid medical conditions that preclude the use of antidepressant medications. (pg 22)

Grade B, Level IIb

1 Introduction

Depression is a major mental health problem. It impairs psychosocial and occupational functioning and is associated with significant morbidity and mortality. In the 1990 Global Burden of Disease list, depression was the fourth leading cause of disability in terms of physical, social and mental impact of disease. It is predicted to become the second most important cause of disability worldwide by the year 2020.[1,2]

Epidemiological studies have revealed the high prevalence of depression. Between 9-20% of the population may be affected during their lifetime.[3,4] In Singapore, the prevalence of depression was found to be 8.6% in adults and 5.7% in the elderly.[5,6]

Depression is a recurrent disorder; each additional depressive episode increases the probability of a more rapid onset of subsequent episodes.[7] The risk of recurrence is estimated at 50% after the first episode, 80-90% after two episodes and greater than 90% after three episodes.[8]

In addition, co-morbidity is an important clinical finding in depression and is associated with increased disease severity and a poorer prognosis.[9] Depression can co-exist with many medical conditions such as cancers (25-38%), diabetes (24%) or coronary artery disease (16-19%), other psychiatric disorders and may even be associated with medication use (See Annex I on page 30).

The most serious complication of depression is of course suicide. The lifetime risk of suicide in mood disorders is 10-15% and the risk of attempted suicide was increased 41-fold in depressed patients compared with those with other diagnoses.[10,11]

Unfortunately, under-recognition and under-treatment of depression are serious clinical issues requiring our attention. It is estimated that 30-50% of cases of depression in primary care and medical settings are not detected.[12] This is because a depressed mood may not necessarily be the presenting symptom. Instead multiple somatic complaints, co-existing medical or psychiatric illness, stressors and life-events may obscure the depression. A high index of suspicion and alertness is therefore crucial for recognition and diagnosis.

1.1 Aim

These guidelines are developed to raise awareness and assist in the detection of depression and to ensure that treatment is adequate and effective.

1.2 Scope

The guidelines will cover the treatment of mild to moderate depression in children, adults and the elderly. Treatment of major depression in bipolar disorder, psychotic depression and cases with high suicide risk are not included in these guidelines.

1.3 Target Group

The content of the guidelines will be useful for all doctors treating patients with depression and will be a resource for allied health and nursing staff who assist in the care of depressed people. The doctor treating the patient is ultimately responsible for the treatment decisions which should be made after reviewing the patient's history, clinical presentation and treatment options available.

1.4 Development of Guidelines

These guidelines have been produced by a committee of psychiatrists and family practitioners appointed by the Ministry of Health. They were developed by the adaptation of existing guidelines, by the review of relevant literature and by expert clinical consensus with consideration of local practice.

1.5 Review of Guidelines

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

2 Clinical Evaluation

2.1 Diagnosis

The term 'depression' is used to describe a normal emotional experience as well as a disorder. Normal sadness or unhappiness is however, different from the nature, experience and severity of depressive symptoms in a disorder. In addition, a depressive disorder may involve other emotional changes such as anxiety, irritability or apathy. There are also cognitive, behavioral and somatic symptoms. In cases where agitation or slowing is present, it is observable by others around the individual and are not just subjective feelings or reports of restlessness or being slowed down. The symptoms associated with depression cause clinically significant distress and/or impairment in social, occupational and other areas of functioning.

The following symptoms are pathognomonic of depression:

Sleep increase/decrease
Interest in formerly compelling or pleasurable activities diminished
Guilt, low self esteem
Energy poor
Concentration poor
Appetite increase/decrease
Psychomotor agitation or retardation
Suicidal ideation

A convenient way to remember this is the SIGECAPS mnemonic.

When depressed mood or loss of interest is present with 4 (or more) of the above symptoms for 2 or more weeks, a diagnosis of **major depressive disorder** is made.*

When depressed mood or loss of interest is present with 2 (or more) of the above symptoms most days for 2 or more years, then a diagnosis of **dysthymia** is made.*

* Terminology taken from the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) published by the American Psychiatric Association.

A **major depressive disorder** (also called unipolar depression) is characterized by absence of episodes of pathologically elevated mood (hypomania, mania). Depressive symptoms caused by substance abuse, medical conditions and medications do not qualify for a diagnosis of major depressive disorder. The depressive symptoms in these cases are considered as a secondary mood disorder. A major depressive disorder may co-exist with other psychiatric or medical disorders.

In **dysthymia**, the depressive symptoms are chronic and longer-term but symptoms are less severe than in major depressive disorder.

Sometimes there are distinct stressors that cause distress and give rise to mild symptoms. When the symptoms of depression develop within 3 months of an identifiable stressor(s) a diagnosis of **adjustment disorder** (with depressed mood) is made.*

Some depressive disorders are unique to women. These include **depression with postpartum onset** and **premenstrual dysphoric disorder**. In the latter, depressive and anxiety symptoms together with affective lability and decreased interest in activities usually occur in the last week of the luteal phase and remit within a few days of the onset of menses.

In some depressed patients the presenting features may be quite the opposite and the term **atypical depression** is used. The features are grouped into two, the vegetative features (overeating, oversleeping, weight gain, a mood that still responds to events, extreme sensitivity to interpersonal rejection, a feeling of heaviness in the limbs) and the anxious features (marked anxiety, difficulty falling asleep, phobic symptoms, symptoms of sympathetic arousal).

A history of manic or hypomanic episodes would indicate that the patient has an affective disorder or a bipolar disorder and the treatment would then be different.

* Terminology taken from the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) published by the American Psychiatric Association.

There are some patients who may not admit to a depressed mood or may be reluctant to talk about it. In addition there are patients who present with multiple unexplained somatic symptoms, irritability, anxiety and frequent consultations. They should be carefully assessed for depression.

2.2 Terminology

Acute treatment aims to remove all signs and symptoms of the current episode of depression and to restore psychosocial and occupational functioning (a remission). A **remission** (absence of symptoms) may occur either spontaneously or with treatment. If the patient improves significantly, but does not fully remit with treatment, a **response** is declared. If the symptoms return and are severe enough to meet syndromal criteria within 6 months following remission, then a **relapse** (return of symptoms of the current episode) has occurred.

Continuation treatment is intended to prevent this relapse. Once the patient has been asymptomatic for at least 6 months following the acute phase (12 weeks) of an episode, **recovery** from the episode is declared. At recovery, continuation treatment may be stopped. For those with recurrent depressions, however, a new episode (**recurrence**) may occur months or years later.

Maintenance treatment is aimed at preventing a new episode of depression and may be prescribed for 1 year to a lifetime, depending on the likelihood of recurrences.

The initial treatment should be applied for a sufficient length of time to permit a reasonable assessment of the patient's response (or lack of response). If the treatment is going to be effective, a 4- to 6-week trial of medication or a 6- to 8-week trial of psychotherapy usually results in at least a partial symptomatic response; a 10- to 12-week trial of antidepressants usually results in a symptomatic remission, though full recovery of psychosocial function appears to take longer.

If the patient shows a **partial response** to treatment by 4-6 weeks, the same treatment should be continued for 4 or 6 more weeks. If the patient **does not respond at all** by 6 weeks or responds only partially by 10-12 weeks, other treatment options should be considered.

2.3 Assessment

C The basic assessment of depression includes the history, the mental state examination and physical examination.[13]

- Take a detailed history of the presenting symptoms and determine the severity and duration of the depressive episode. Establish history of prior episodes, prior manic or hypomanic episodes, substance abuse and other psychiatric illnesses. Look out for co-existing medical conditions. Check for family history of mental illness, depression and suicide. Establish the personal history and the available supports and resources. Evaluate functional impairment and determine life events and stressors.

- Do a mental state examination. This includes an evaluation of the severity of symptoms and assessment for psychotic symptoms. All assessments of depression will include an assessment of the risk of suicide, self-harm and risk of harm to others. (See Annex II on page 32).

- Do a physical examination to exclude a medical or surgical condition.

- Laboratory testing may be indicated if there is a need to rule out medical conditions that may cause similar symptoms.

Grade C, Level IV

2.4 Questionaires

Both subjective and objective questionnaires are available for the evaluation of depression (see Annex III on page 33). Although they are sensitive instruments, they are not very specific and this limits their usefulness. They are most useful when a depressive disorder is suspected and to monitor symptom change.[13]

2.5 Psychiatric Referral

A psychiatric referral is indicated when the depression is associated with high suicide risk, in severe postnatal depression, when there are psychotic symptoms present and if the patient has a bipolar disorder. The treatment is more urgent and requires a different level of care.[14,15]

C Referrals to a psychiatrist are warranted when

- there are co-morbid medical conditions for which expertise is required regarding drug-drug interactions.
- there is diagnostic difficulty,
- one or two trials of medication have failed,
- if augmentation or combination therapy is needed
- for those with co-morbid substance abuse or severe psychosocial problems
- the patient is pregnant or plans to become pregnant
- for post-natal depression
- if specialized treatment like electroconvulsive therapy is indicated but unavailable in the primary care setting

Grade C, Level IV

2.6 Treatment

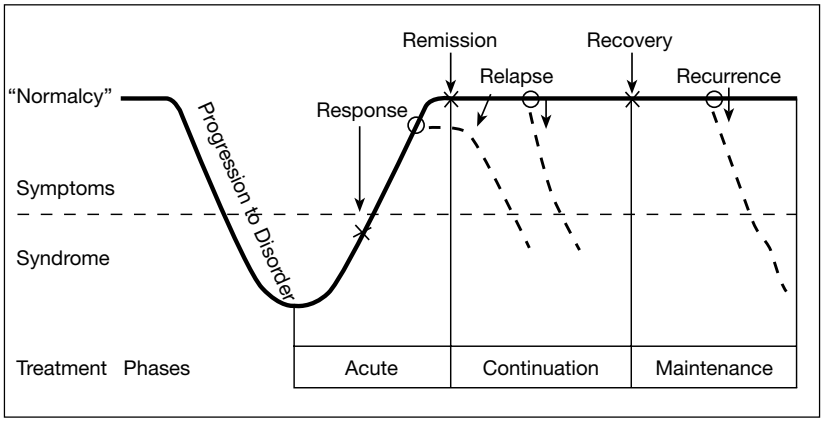
Treatments for depression can be grouped into the following broad categories: Psychoeducation, Pharmacotherapy, Psychotherapy, Combination of Pharmacotherapy and Psychotherapy and Electroconvulsive Therapy. Each treatment has its own benefits and risks. Options from one or more of these categories could be used. Treatment must be appropriate, effective, optimal, associated with minimal adverse effects and acceptable to the patient.

The key initial objectives of treatment are:

1) Symptomatic remission of all the signs and symptoms of depression
2) Restore occupational and psychosocial function and
3) Reduce the likelihood of relapse and recurrence

Treatment proceeds in three phases: acute treatment, continuation treatment and maintenance treatment. The following chart presents the phases of treatment for Major Depression as well as the progression and risks of relapse and recurrence[16] (Figure 1).

Figure 1 Phases of Treatment of Major Depression



Source: Kupfer DJ: Long-term treatment of depression. J Clin Psychiatry 1991: 52 (Suppl): 28-34. Copyright 1991. Physicians Postgraduate Press. Adapted and reprinted with permission.

3 Psychoeducation

Psychoeducation includes the illness concept of depression, the expectation for response (that is, instillation of hope) and the need to adhere to the treatment regime.[14]

Strategies such as providing information and advice are useful in relieving anxiety, enhancing compliance and assisting recovery.[17,18]

A The following should be done:

(a) Educating the patient about the illness helps clarify uncertainty and misconceptions. Depression should be explained as a medical illness that is associated with changes in neurochemicals and brain functioning.

(b) Adequate follow-up improves treatment adherence, allows closer monitoring and earlier detection of changes in condition.

(c) Discuss the type and duration of treatment. If antidepressants are used it is advisable to explain that they are not addictive. Provide information on the different types of antidepressants available and about the possible side-effects.

(d) Advise on lifestyle changes such as exercise and reducing stress.[19]

Grade A, Level Ia

Where indicated and with patients agreement, involve family members or friends in their care so that there is adequate support. This involvement is particularly important when there is a risk of suicide.

4 Pharmacotherapy

The effective pharmacotherapeutic agents are the antidepressants and they are effective in the treatment of all forms of depression.[20] The antidepressants that are available work by six distinct pharmacologic mechanisms[21] (See Annex IV on page 35). There is comparable efficacy between and within the classes[22,23] and all have been consistently shown to be effective in treating depression.

4.1 Choice of Antidepressant

The choice of antidepressant depends on the side-effect profile, their safety and tolerability, presence of co-morbid conditions, concurrent medications, cost, patients history of prior response and risk of lethality in overdose.[13,14,15]

C If patient has previously responded well to and has had minimal side-effects with a particular drug, that medication is preferred. Alternatively, if the patient, has previously failed to respond to an adequate trial of one antidepressant or found the side-effects of a particular antidepressant intolerable, that medication should generally be avoided.[13,14,15]

Grade C, Level IV

C Once an antidepressant has been selected, start with a low dose and titrate to the full therapeutic dose gradually, while assessing patients mental state and watching for the development of side-effects. The frequency of monitoring will depend on the severity of the depression, suicide risk, the patient's cooperation and the availability of social supports.[13,14]

Grade C, Level IV

GPP Either Tricyclic Antidepressants (TCAs) or Selective Serotonin Reuptake Inhibitors (SSRIs) may be used as first-line medication (see Annex V on page 36).

GPP

Tricyclic antidepressants may cause a wide-range of side-effects due to widespread receptor blockade. These side-effects could lead to poor compliance, use of suboptimal therapeutic doses, and can be lethal in overdose.[24] TCAs may be more effective in more severely depressed patients such as those who need hospitalization.[25]

Selective Serotonin Reuptake Inhibitors are better tolerated. They are less associated with anticholinergic adverse effects, cardiotoxicity, sedation or weight gain. They have been shown to be more effective than TCAs for patients with atypical depressive symptoms such as hypersomnia, hyperphagia, mood reactivity and hypersensitity to rejections.[26] Reversible inhibitors of monoamine oxidase A (RIMA) can also be used for atypical depressive symptoms.

4.2 Treatment Response

All antidepressants require 4 to 6 weeks to achieve their maximum therapeutic effects.[27] Some patients may begin to show improvement by the end of the first week and some by the second to third week.[28] Generally if treatment is going to be effective, at least a partial symptomatic response will be seen by 4 to 6 weeks of medication.[29]

B All antidepressants, once started should be continued for at least 4 to 6 weeks.[29,39]

Grade B, Level IIb

Several options are available for partial responders and non-responders:
(1) Continue the current antidepressant at an increased dose.
(2) Discontinue the first antidepressant and begin a second (Switching).

Increased Dose

C Using higher antidepressant doses may be helpful for patients who have shown a partial response and when only low or modest doses have been tried. The patient should be closely monitored for side-effects with the increase in dose. [14,15]

Grade C, Level IV

Switching Strategy

C Switching is preferred to augmentation as an initial strategy in accordance with general principles that combinations should preferably not be used when monotherapy will suffice.[14,15]

Grade C, Level IV

C When a patient fails to respond to an adequate trial of an antidepressant from one group, it is appropriate to try an antidepressant from a different group (for example, switching from a TCA to a SSRI or Serotonin/Norepinephrine Reuptake Inhibitor [SNRI]). Alternatively another antidepressant from the same class may also be tried (for example, switching one SSRI for another SSRI). Switching within the SSRIs is useful only when the patient had shown at least partial response with the initial SSRI tried. Switching within the class for tricyclics however is considered a poor choice.[30]

Grade C, Level IV

C Caution is needed when switching from one antidepressant to another because of the possibility of drug interactions. The first antidepressant may either be stopped or tapered before starting the next antidepressant without any washout period; the exceptions are with fluoxetine which has a long half-life and with moclobemide for which a three-day washout is recommended.[30]

Grade C, Level IV

A The newer antidepressants venlafaxine, mirtazapine and bupropion can be used in the switching strategy.[31]

Grade A, Level Ia

All are as efficacious as tricyclic antidepressants and SSRIs. Venlafaxine has been shown to be effective across depression of different severities;[31] lower doses provide a good response in milder depressive disorders and higher doses are more efficacious in severe major depression.[32]

C If there is little or no improvement after switching, it is recommended that a psychiatric referral is sought for the following:

(1) Augment the first antidepressant with a second medication (Augmentation)
(2) Add a second antidepressant to the first (Combination)

Grade C, Level IV

Augmentation Strategy

In this strategy, a pharmacologic agent is used to enhance the effect of an antidepressant. It is preferred for those patients who have had previous antidepressant trials and have not responded to adequate trials of other individually prescribed antidepressants.

A Lithium augmentation and thyroid hormone augmentation (using levothyroxine or triodothyromine) are two traditional augmentation strategies that are recommended.[33,34]

Grade A, Level Ia

Combination Strategy

There is limited evidence to support the use of combination antidepressant medication. This strategy involves increased risk of side-effects, the potential for drug interactions and higher costs.

However a combination of desipramine or other TCA with an SSRI may produce a more rapid onset of action.[35] Caution is advised as both are substrates of the CYP2D6 isoenzyme, a common metabolic pathway for drug metabolism, and plasma concentrations of TCAs are likely to rise, increasing the risk of cardiotoxicity.

B Other combinations that may be tried include a SSRI and a RIMA, SSRI and bupropion, bupropion and venlafaxine, a TCA and venlafaxine and a TCA and mirtazapine.

Grade B, Level III

4.3 Continuation Treatment

The Continuation phase is from about 6 months after achieving remission. The aim is to prevent a relapse immediately following symptomatic recovery. Although there is limited data for this, the studies that are available indicate that those with a first episode of depression who have satisfactorily responded to treatment in the acute phase should continue to receive the full therapeutic dose for about 6 months after achieving and maintaining full remission.[36]

GPP At the end of the Continuation phase the antidepressant medication should be gradually tapered to avoid discontinuation symptoms.[37] Patients should be followed up during the next few months to ensure that a new depressive episode does not occur. If recurrence occurs, the patient is likely to respond to the same antidepressant at the same dosage that was effective previously, which should then be continued for 6 months.

GPP

4.4 Maintenance Treatment

There are several factors to consider in deciding whether maintenance treatment is indicated. These include the risk of recurrence (number of prior episodes, presence of co-morbid conditions, residual symptoms between episodes), severity of episodes (suicidality, psychotic features, severe functional impairments), side-effects experienced with continuous treatment and patient preferences.[38] The maintenance antidepressant given is generally the same type and dosage found effective in the acute phase of treatment.

Indications for Maintenance Treatment

The following features are indications for maintenance treatment:[38,39]

1. Three or more episodes of major depression

   Or

2. Two episodes of major depressive disorder and one or more of the following:

   a) family history of bipolar disorder

   b) history of recurrence within one year after previously effective medication was discontinued

   c) a family history of recurrent major depression

   d) early onset (before age 20) of the first depressive episode

   e) depressive episodes were severe, sudden or life-threatening within the past 3 years

GPP Maintenance antidepressant treatment should be carried on for as long as necessary.

GPP

In pregnancy and nursing mothers, the relative risks and benefits of using antidepressants must be carefully weighed. There is no evidence of increased risk of teratogenesis or spontaneous abortions following exposure to antidepressants such as TCAs and SSRIs in early pregnancy.[40] Antidepressants however are secreted in breast milk and levels of antidepressants have been detected in infant serum samples. Paroxetine has the lowest milk/plasma ratio amongst the SSRIs.[40,41]

5 Psychotherapy

Psychotherapy is the psychological treatment of psychiatric disorders through the establishment of a relationship between the therapist and patient for the purpose of alleviating psychological symptoms and preventing or correcting maladaptive patterns of behaviour.

A Psychotherapy alone is as efficacious as antidepressant medication in patients with mild to moderate major depression and can be used as first-line treatment.

Grade A, Level Ia

The decision to use psychotherapy depends on patient preference, patient suitability (able to be self-aware and able to communicate thoughts and feelings), therapist availability and severity of the illness.[14] Clinical features that may suggest the use of psychotherapeutic interventions include the presence of significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties, or a co-morbid personality disorder.[38] Marked vegetative symptoms such as psychomotor retardation, severe early morning awakening or weight loss would favour the use of pharmacotherapy as first-line treatment.

The frequency of psychotherapy sessions may range from once a week to several times per week in the acute phase.

Although a range of psychotherapeutic interventions are available they all have common therapeutic factors, such as:

1) A trained therapist
2) Establishment of a treatment alliance between therapist and patient
3) A theory that offers a plausible explanation for the patient's symptoms
4) Expectations of patient change and renewal of a sense of hope
5) A structured series of contacts between the therapist and patient designed to bring about change

There is only limited evidence that the various forms of psychotherapy have differential effects.[42,43]

Cognitive-Behaviour Therapy

Among the specific psychotherapeutic interventions, Cognitive Behaviour Therapy (CBT) has the best documented efficacy for the treatment of depression.[44] It focuses on identifying and modifying distorted, negatively biased thoughts.

A CBT is recommended when the patient has distorted negative thoughts.[44]

Grade A, Level 1a

A CBT is also an effective maintenance treatment and is recommended for patients with recurrent depression who are no longer on medication.[45]

Grade A, Level 1b

Interpersonal Therapy

This therapy focuses on clarification and resolution of difficulties in current interpersonal relationships and has good evidence of efficacy. The basic assumption is that dealing with these relationship issues whether they contributed to or were the consequences of depression, would lead to relief and resolution of the depressive symptoms.

A Interpersonal Therapy is recommended when there are interpersonal difficulties.[46]

Grade A, Level Ib

Psychodynamic Psychotherapy

Short-term Psychodynamic Psychotherapy especially Psychodynamic-Interpersonal Therapy is comparable to CBT. It focuses on the therapist-client relationship as a vehicle for revealing and resolving interpersonal difficulties.[47]

A Psychodynamic-Interpersonal Therapy is a viable alternative when there are interpersonal difficulties.

Grade A, Level Ib

When longer forms of Psychodynamic Psychotherapy are employed, they are frequently associated with broader long-term goals such as personality change.[48]

A Long-term Psychodynamic Psychotherapy is recommended when there is co-morbid personality disorder.

Grade A, Level Ia

Problem-Solving Therapy

Problem-Solving Therapy is as effective as antidepressants for primary care patients with mild depression.[49] Therapist and patient work together to identify and prioritise key problem areas, break problems down into specific manageable tasks, problem solve, and develop appropriate coping behaviours for problems.

A Problem-solving therapy is recommended for primary care patients with mild depression.

Grade A, Level Ib

Group Therapy

There is less evidence for the efficacy of group therapy, compared to individual forms of psychotherapy especially for severe depression.[49]

Couple/Marital Therapy

A Marital or couple therapy is effective and should be considered for patients with significant marital distress.[50]

Grade A, Level Ib

Duration of Treatment

There is little data on optimal duration of psychotherapy. CBT has been given in 12 weekly sessions and Interpersonal Therapy in 16-20 weekly sessions.

A It is recommended that CBT or Psychodynamic Interpersonal Therapy be delivered for a longer period of 16 weeks when the depression is severe.

Grade A, Level Ib

C If after 4-8 weeks of treatment at least a moderate improvement is not observed, it is recommended that a thorough review of the diagnosis, complicating conditions and issues, and treatment plan should be conducted. If there is no response, consider adding or changing to

medication. If there is partial response, consider changing the intensity of psychotherapy, changing the type of psychotherapy, or adding or changing to medication.[38]

Grade C, Level IV

Combined Psychotherapy and Pharmacotherapy

A Concurrent combined psychotherapy and pharmacotherapy is recommended in severe depression[51] and chronic depression[52] as it is more effective than either alone in these conditions.

Grade A, Level Ib

A Adding Cognitive-Behaviour Therapy for patients with residual depressive symptoms after acute treatment with pharmacotherapy is recommended as it has been shown to improve remission rates and reduce relapse rates.[53]

Grade A, Level Ib

A Combination therapy of Interpersonal Therapy and pharmacotherapy is beneficial in patients with severe depression.[46]

Grade A, Level Ib

6 Electroconvulsive Therapy

Electroconvulsive therapy (ECT) has been in use for more than 50 years in the treatment of psychiatric disorders. It is an exceptionally effective treatment for depression. It has been shown in controlled clinical trials to have efficacy that is superior to placebo, simulated ECT and antidepressant medication therapy.[54] 80-90% of patients with major depressive disorder showed improvement ECT.[55]

Indications

A The usual indications for ECT are when the moderate or severe depression is not responsive to pharmacological treatment[56] and when depression with psychotic symptoms have not responded to combination treatment of an antidepressant and anti-psychotic medication.[57,58]

Grade A, Level Ia

B ECT may be considered as the first-line treatment for patients with severe depression, depression with psychotic features, marked functional impairment, catatonic stupor, high suicide risk or food refusal leading to nutritional compromise. It is also considered in any other situation when a particularly rapid antidepressant response is required, such as in pregnancy and in those with co-morbid medical conditions that preclude the use of antidepressant medications.

Grade B, Level IIb

Prior histories of positive response to ECT and patient preference are important considerations that may influence the decision to select ECT as a treatment modality.[59]

Contraindications

Although there is no absolute contraindication to ECT, certain conditions are associated with greater risk of adverse events. These include recent myocardial infarction, congestive heart failure, cardiac arrhythmia, recent stroke, bleeding or unstable cerebral vascular aneurysm or malformation, phaeochromocytoma, retinal detachment, space occupying lesions in the brain and other conditions leading to raise intracranial pressure. In such situations, the relative risks and benefits of ECT treatment should be carefully weighed in collaboration with a

physician, cardiologist, anesthesiologist, neurologist or neurosurgeon, as the case requires.[59]

Procedure

ECT is performed only after informed written consent is given by the patient. The procedure of ECT involves the induction of a grand mal seizure by means of an electrical pulse through the brain. ECT is done under general anaesthesia and each induction of a seizure is considered one treatment. A course of ECT consists of several such treatments and should be such that maximal remission of symptoms is achieved. This typically involves six to 12 treatments. ECT may be administered via bilateral or unilateral placement of scalp electrodes. In the event that the patient does not respond satisfactorily to the initial treatments of unilateral ECT, bilateral placement is to be considered. Stimulus parameters vary from patient to patient but should be titrated to induce an adequate seizure that is typically at least 15-25 seconds in duration. ECT is typically administered every other day.[59,60,61,62]

Adverse Events

ECT is generally a very safe treatment. The common side effects of ECT are transient headaches, muscle soreness, nausea and memory impairment. Following each ECT treatment is a transient postictal confusional state and a longer period of anterograde and retrograde amnesia. The anterograde memory impairment typically resolves in a few weeks after cessation of ECT. Some degree of retrograde amnesia, particularly for recent memories, may continue for patients receiving bilateral ECT. This retrograde amnesia manifest as difficulty remembering information learned prior to the course of ECT. Unilateral placement induces less cognitive impairment but in some cases it is also less effective.[59,63,64,65]

The risk of death with ECT is very low, around 1 per 10,000 patients.[66] This rate is comparable to that which would be expected from a series of brief anaesthetic procedures alone. Most deaths occur in high-risk cases, and usually due to cardiac causes.

Maintenance Treatment

B It is recommended that patients be maintained on antidepressant (if indicated, including lithium) medication therapy following acute response to ECT.[67]

Grade B, Level IIb

B Patients who had ECT and do not respond to such maintenance medication therapies may require maintenance ECT treatment.[68]

Grade B, Level III

7 Depression in Children and Adolescents

Depression in children and adolescents is not well recognized but common with a propensity for persisting into adulthood if not well treated. It affects about 2.5% of Asian adolescents[69] although Western studies suggest a higher prevalence between 2-8%.[70] Both psychotherapy and medications have been shown to be useful although psychotherapy is recommended first-line treatment based on literature and local clinical experience. Antidepressants are most useful in severe depression.

Recognition of symptoms

Symptoms may vary across different developmental stages and diverse ethnic groups.[71] Children may show more anxiety, somatic complaints and auditory hallucinations.[72] Children verbalise feelings less but develop behavioural problems, e.g. temper tantrums. Adolescents manifest more sleep, appetite disturbances, delusions, suicidal ideation and attempts compared to children but less than adults.[73] Children and adolescents are also more likely to have concomitant physical illness.[74]

Suicide

Suicide trends in the young in Singapore suggest a slowly rising trend especially in those aged 10-14 years.[75]

B When faced with a suicidal adolescent, doctors should maintain contact, ensure close supervision and engage support systems such as family and school, and consider a "no harm" contract if the adolescent is willing.[73, 76]

Grade B, Level III

B Hospitalization is indicated if suicide risk is high, support is unavailable and there are severe symptoms of depression.[76]

Grade B Level III

Screening

C Self-administered rating scales are useful for screening of symptoms, assessing severity and monitoring improvement in older children and adolescents. They should not be used for diagnosis.[77]

Grade C, Level IV

Treatment

A Cognitive behaviour therapy has been shown to be effective and maintained over time.[78]

Grade A, Level Ia

A Other psychotherapies used in youths include psychodynamic psychotherapy, interpersonal therapy, family therapy, supportive psychotherapy and group psychotherapy. Medication should not be the only treatment given but care must be given to increasing self esteem, coping skills to handle stress, adapting to the changes in life and improving relationships between family members and peers. Use of medications should be cautious and not necessarily first-line treatment for major depressive disorder.[79]

Grade A, Level Ib

Medications shown to be useful in adults with major depressive disorder may not be as useful in children (e.g. TCAs, monoamine oxidase inhibitors, venlafaxine).[80,81,82]

B Selective Serotonin Reuptake Inhibitors can be used in children and adolescents with caution.[73,83]

Grade B, Level III

There are reports of possible increased risk of suicidal thinking in using an SSRI such as paroxetine.[84,85]

C Medications are usually indicated for patients with severe depression, who have psychotic symptoms or who have failed psychotherapy.[73]

Grade C, Level IV

Use of electroconvulsive therapy is rarely indicated but has been shown to be safe in adolescents.[86]

8 Depression in Elderly

Several factors modify the presentation of depression in the elderly.[87] While there may be reduced complaints of sadness, hypochondriasis and somatic concerns may be more prominent. Marked anxiety, apathy and poor concentration are other frequent presenting symptoms. Sometimes the presentation is with subjective complaints of poor memory or a dementia-like picture.

C Referrals of elderly patients to specialists should be considered when the diagnosis is in doubt, when the depression is severe as evidenced by psychotic depression, severe risk to health because of failure to eat or drink, suicidal risk, when complex therapy is indicated as in cases with medical co-morbidity, and when the patient does not respond to an adequate antidepressant trial.[88]

Grade C, Level IV

Organic causes of depression occur more frequently in the elderly[89] so careful history, physical examination and laboratory tests as indicated are needed.

A Antidepressants are recommended in dysthymia as well as for mild to severe depression in the elderly. There is no difference in efficacy between the classes of antidepressants in the treatment of the elderly.[90]

Grade A, Level Ia

However the elderly are more sensitive to the unwanted actions of some antidepressants. Particularly troublesome are peripheral and central anticholinergic effects such as constipation, urinary retention, delirium and cognitive dysfunction, antihistaminergic effects such as sedation and anti-adrenergic effects such as postural hypotension.[91] Newer antidepressants may be better tolerated and safer especially in overdose.[92,93]

A SSRIs are recommended over TCAs as the first-line treatment choice for late-life depression.[94]

Grade A, Level Ia

B In frail elderly patients it is advisable to "start low, go slow".[89] In the acute phase at least six weeks of treatment may be needed to achieve optimal therapeutic effect. The elderly generally take longer to recover

from the depression.[87] A continuation period on the same dosage that improved them for 12 months is recommended for a first onset of major depression, longer for a recurrent episode. The duration of treatment is similar to the adult age group in the continuation and maintenance phases.[95,96,97]

Grade B, Level IIa

A Psychological interventions should be provided for the elderly with mild to moderate major depression.

Grade A, Level Ib

There is strong evidence that psychotherapy is efficacious particularly Cognitive Behaviour Therapy and Interpersonal Therapy.[92,94,95] There is some evidence of efficacy for brief dynamic psychotherapy, problem solving therapy and life review.[92,98]

A In severe major depression Combination antidepressant and psychotherapy treatment is recommended.[97,99]

Grade A, Level Ib

Even simple support to patient and caregiver is associated with fairly high rates of symptom resolution in mild depression.[100]

B Supportive care should be offered to elderly patients and where relevant, their caregivers.

Grade B, Level IIa

Electroconvulsive therapy is effective in treating the elderly depressed.[101] It is generally safe and does not cause serious long-term cognitive side-effects.[102]

A Electroconvulsive therapy is indicated in the elderly when the patient is actively suicidal, when there is a need to treat urgently to prevent deterioration in health (including food/fluid refusal), in psychotic depression, when there is inadequate response to two trials of medication, when there is intolerance to medication, or when there is good prior response.

Grade A, Level 1b

9 Clinical Audit Parameters

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

1. Percent of patients with depression, who have been assessed for the risk of suicide. (see page 9)

2. Percent of newly-diagnosed patients with depression on antidepressant medication, who receive at least 4 weeks of pharmacotherapy. (see page 14)

3. Percent of patients who receive electroconvulsive therapy for depression for the correct indication. (see page 22)

Annex I Factors Associated with Depression

Medical Conditions Associated with Depression

- Hypothyroidism
- Malignancy
- Parkinson's disease
- Myocardial Infarction
- Stroke
- Endocrinopathies (Cushing's syndrome, adrenal insufficiency, carcinoid, hyperparathyroidism)
- Infections (hepatitis, mononucleosis, influenza or other viral illnesses)
- Chronic disease (congestive heart failure, diabetes, systemic lupus erythematosus, rheumatoid arthritis)
- Alcoholism or other substance abuse/dependence
- Fibromyalgia/chronic fatigue syndrome
- B12 or folate deficiency
- Sleep disorders

Medications Associated with Depression

- Drugs of abuse (alcohol, amphetamines, cocaine, marijuana)
- Anti-hypertensives (reserpine, methyldopa, beta blockers)
- Psychoactive drugs (analgesics, sedative-hypnotics, anxiolytics)
- Steroid hormones (prednisone, oral contraceptives)
- Chemotherapy agents (vincristine, vinblastine, procarbazine, L-asparginase)
- Levodopa
- Cholesterol lowering agents

Psychiatric Disorders Associated with Depression

- Bipolar disorder
- Dysthymia
- Grief, bereavement
- Anxiety disorder
- Post-traumatic stress disorder
- Somatoform disorders
- Eating disorders

- Sleep disorders
- Substance abuse
- Anxiety Disorders

Life Situations Associated with Depression

- Coping with illness
- Marital discord
- Child rearing difficulties
- Work stress
- Abuse (domestic violence, physical or sexual abuse)

Adapted from the following sources:

- *Depression: A Guide to Diagnosis and Treatment, Brigham and Women's Hospital.*
- *University of Michigan Health System Depression Guidelines, June 1998.*

Annex II Assessment of Suicide Risk

Demographic factors
Social isolation (living alone, single) and lack family support
Older male
Recent loss

Check the History
History of prior suicide attempts especially if multiple/severe attempts
Family history of suicide
Substance abuse/dependency
Presence of Physical illness

Assess for
Severe depression
Anxiety
Hopelessness
Psychosis especially with command hallucinations

Ask about Suicidal Thinking
Presence of a specific plan
Means available to carry out the suicide plan
Absence of factors that would keep the patient from completing the plan
Rehearsal of the plan including preparations such as letters, will

Asking about suicidal thoughts and plans will not prompt a suicide attempt. It may be appropriate to ask a series of questions about how the individual views the future and whether there are feeling of hopelessness and helpless and thoughts about death before going on to directly asking about actual thoughts and plans.

Annex III Questionnaires for Depressive Disorders

1. Hamilton Depression Rating Scale (HAM-D)

This is only used on patients already diagnosed with depression and is commonly used in research but is less practical in clinical settings because of its length. The commonly used version has 17 items and includes many somatic symptoms such as decreased appetite, weight loss, fatigue, anxiety symptoms and insomnia.

2. Hospital Anxiety and Depression Scale (HADS)

This scale covers depression and anxiety and was developed for use in general medical patients.

3. Montgomery-Asberg Depression Rating Scale (MADRS)

This is a 10-item clinician-rated scale that includes somatic symptoms.

4. Beck Depression Inventory

This is a subjective scale to be completed by the patient.

Scales relevant to children and adolescents:

1. Center for Epidemiologic Studies Depression Scale (CESD)

This is a 20-item self-report initially designed for an American epidemiological survey by the National Institute of Mental Health.

2. Child Depression Inventory (CDI)

This is a 27-item self-report scale for identifying depressive symptoms in children which has been well validated in large populations both in the West and in Asia.

3. Asian Children Depression Scale (ACDS)

This is a 20-item self-administered scale that was developed for Singapore children for the purpose of an epidemiological survey. It has been validated and shows good psychometric properties.

Annex IV Pharmacologic Mechanisms of Antidepressants

I. Classical Mechanism

Tricyclic Antidepressants (TCAs) act therapeutically through serotonin reuptake inhibition and norepinephrine reuptake inhibition. However there are differences amongst the tricyclics; clomipramine is a preferential inhibitor of the serotonin reuptake mechanism but imipramine and amitriptyline preferentially inhibit norepinephrine reuptake.

- Amitriptyline
- Imipramine
- Clomipramine

II Enzyme Inhibition

Monoamine Oxidase Inhibitors (MAOIs) and Reversible Inhibitors of Monoamine Oxidase Type A (RIMAs) act by inhibiting the monoamine oxidase enzyme.

III Selective Serotonin Reuptake Inhibitors (SSRIs)

- Fluoxetine
- Fluvoxamine
- Sertraline
- Paroxetine
- Citalopram

IV Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)

- Venlafaxine

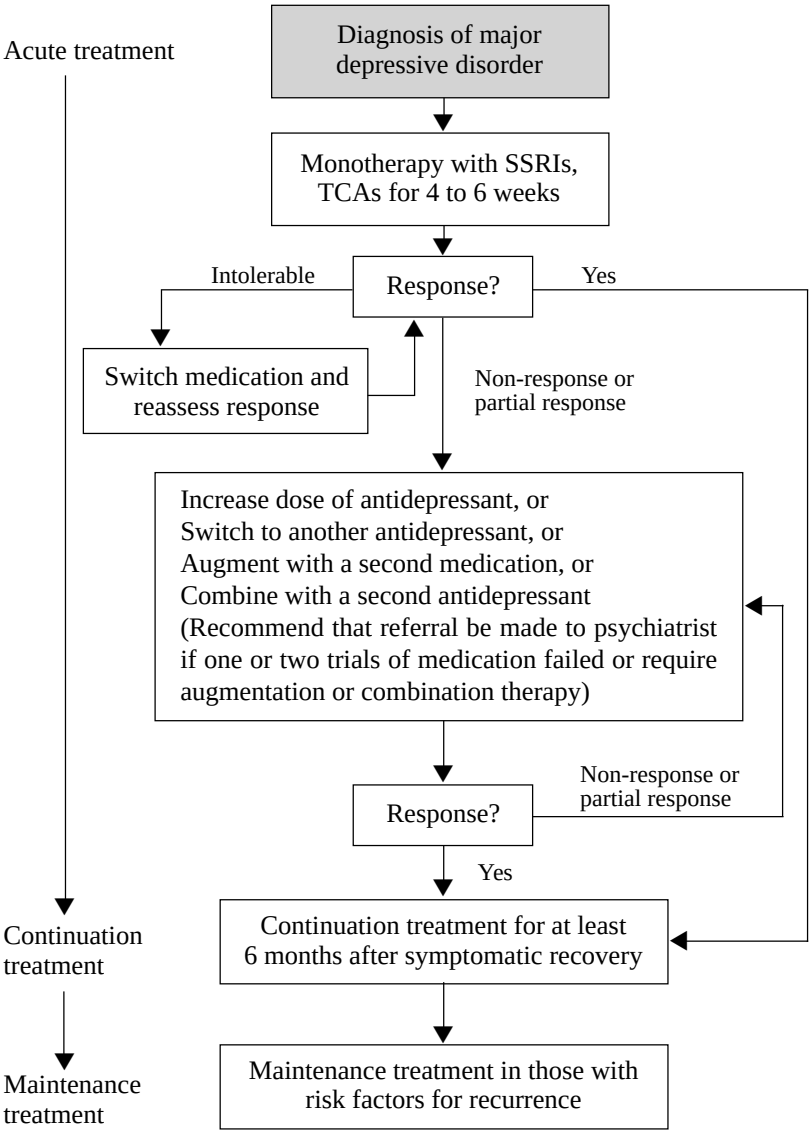
V Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs)

- Mirtazapine

VI Norepinephrine and Dopamine Reuptake Inhibitors (NDRI)

- Bupropion

Annex V Flow Chart for Pharmacotherapy of Major Depressive Disorder



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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this set of MCQs. This is an extension of the learning process and is not intended to "judge" your knowledge and is not compulsory. The answers can be found at the end of the questionnaire.

Instruction: Choose the best answer.

1) The prevalence of depression in the adult and elderly population in Singapore is:
   A. Between 6-9%
   B. Between 2-4%
   C. Between 10-20%
   D. Above 20%

2) The following is pathognomonic of depression:
   A. Loss of interest
   B. Somatic symptoms
   C. Anxiety
   D. Nightmares

3) Compared to tricyclic antidepressants, selective serotonin reuptake inhibitors are:
   A. Not associated with cardiotoxicity
   B. Not associated with anticholinergic adverse effects
   C. Are better tolerated
   D. All of the above

4) In partial responders to antidepressant treatment, one should:
   A. Continue with the current antidepressant at an increased dose
   B. Add an anxiolytic
   C. Add a mood stabilizer
   D. All of the above

5) When switching from one antidepressant to another, no washout period is required except for:
   A. Sertraline
   B. Paroxetine
   C. Imipramine
   D. Fluoxetine

6) After satisfactory response to treatment in the acute phase, the full therapeutic dose should continue for:
   A. 4-6 weeks
   B. 8-12 weeks
   C. 16-20 weeks
   D. 24-28 weeks

7) Indications for maintainence treatment include:
   A. 3 episodes of Depression
   B. Concomitant substance abuse
   C. Borderline personality disorder
   D. A drug overdose

8) The following antidepressant has the lowest milk/plasma ratio:
   A. Fluoxetine
   B. Sertraline
   C. Imipramine
   D. Paroxetine

9) In children and adolescents selective serotonin reuptake inhibitors could:
   A. Intensify attention deficit hyperactivity disorder symptoms
   B. Increase suicidal thinking
   C. Induce obsessional symptoms
   D. All of the above

10) The psychotherapy with the best documented efficacy is:
   A. Cognitive Behaviour Therapy
   B. Interpersonal Therapy
   C. Psychodynamic psychotherapy
   D. Problem Solving Therapy

Answers

1. A
2. A
3. D
4. A
5. D
6. D
7. A
8. D
9. B
10. A

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

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MOH CLINICAL PRACTICE GUIDELINES 3/2004
Depression

Ministry of Health

Chapter of Psychiatrists Academy of Medicine Singapore

SINGAPORE PSYCHIATRIC ASSOCIATION

NMRC National Medical Research Council

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

C The basic assessment of depression includes the history, the mental state examination and physical examination. (pg 9)

- Take a detailed history of the presenting symptoms and determine the severity and duration of the depressive episode. Establish history of prior episodes, prior manic or hypomanic episodes, substance abuse and other psychiatric illnesses. Look out for co-existing medical conditions. Check for family history of mental illness, depression and suicide. Establish the personal history and the available supports and resources. Evaluate functional impairment and determine life events and stressors.
- Do a mental state examination. This includes an evaluation of the severity of symptoms and assessment for psychotic symptoms. All assessments of depression will include an assessment of the risk of suicide, self-harm and risk of harm to others. (See Annex II on page 32 of the main text).
- Do a physical examination to exclude a medical or surgical condition.
- Laboratory testing may be indicated if there is a need to rule out medical conditions that may cause similar symptoms.

Grade C, Level IV

C Referrals to a psychiatrist are warranted when

- there are co-morbid medical conditions for which expertise is required regarding drug-drug interactions.
- there is diagnostic difficulty,
- one or two trials of medication have failed,

- if augmentation or combination therapy is needed
- for those with co-morbid substance abuse or severe psychosocial problems
- the patient is pregnant or plans to become pregnant
- for post-natal depression
- if specialized treatment like electroconvulsive therapy is indicated but unavailable in the primary care setting

(pg 10) **Grade C, Level IV**

C Once an antidepressant has been selected, start with a low dose and titrate to the full therapeutic dose gradually, while assessing patients mental state and watching for the development of side-effects. The frequency of monitoring will depend on the severity of the depression, suicide risk, the patient's cooperation and the availability of social supports. (pg 13)

Grade C, Level IV

B All antidepressants, once started should be continued for at least 4 to 6 weeks. (pg 14)

Grade B, Level IIb

C If there is little or no improvement after switching, it is recommended that a psychiatric referral is sought for the following:

(1) Augment the first antidepressant with a second medication (Augmentation)

(2) Add a second antidepressant to the first (Combination)

(pg 15) **Grade C, Level IV**

GPP At the end of the Continuation phase the antidepressant medication should be gradually tapered to avoid discontinuation symptoms. Patients should be followed up during the next few months to ensure that a new depressive episode does not occur. If recurrence occurs, the patient is likely to respond to the same antidepressant at the same dosage that was effective previously, which should then be continued for 6 months. (pg 16)

GPP

A Psychotherapy alone is as efficacious as antidepressant medication in patients with mild to moderate major depression and can be used as first-line treatment. (pg 18)

Grade A, Level Ia

A Cognitive Behaviour Therapy is also an effective maintenance treatment and is recommended for patients with recurrent depression who are no longer on medication.
(pg 19)

Grade A, Level 1a

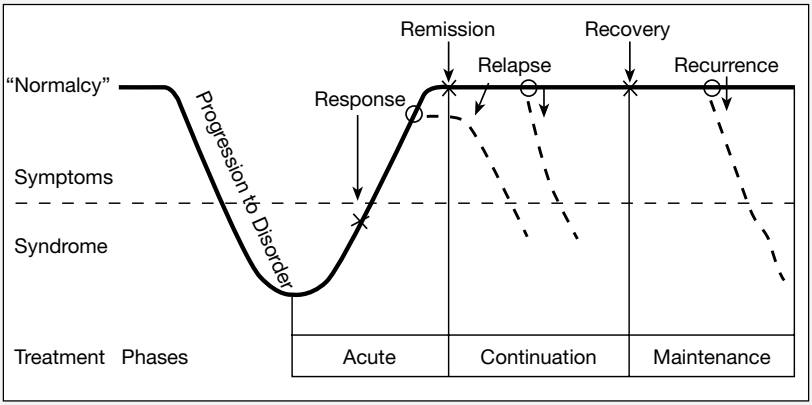
A Concurrent combined psychotherapy and pharmacotherapy is recommended in severe depression and chronic depression as it is more effective than either alone in these conditions. (pg 21)

Grade A, Level Ib

B Electroconvulsive therapy may be considered as the first-line treatment for patients with severe depression, depression with psychotic features, marked functional impairment, catatonic stupor, high suicide risk or food refusal leading to nutritional compromise. It is also considered in any other situation when a particularly rapid antidepressant response is required, such as in pregnancy and in those with co-morbid medical conditions that preclude the use of antidepressant medications. (pg 22)

Grade B, Level IIb

Phases of Treatment for Major Depression



Source: Kupfer DJ: Long-term treatment of depression. J Clin Psychiatry 1991: 52 (Suppl): 28-34. Copyright 1991. Physicians Postgraduate Press. Adapted and reprinted with permission.

Flow Chart for Pharmacotherapy of Major Depressive Disorder