CLINICAL PRACTICE GUIDELINES

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Management of Major Depressive Disorder

MINISTRY OF HEALTH MALAYSIA

MALAYSIAN PSYCHIATRIC ASSOCIATION

ACADEMY OF MEDICINE OF MALAYSIA

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

This guideline was issued in 2007 and will be reviewed in 2010 or sooner if new evidence becomes available.

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http://www.moh.gov.my
http://www.acadmed.org.my
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GUIDELINE DEVELOPMENT AND OBJECTIVE

GUIDELINE DEVELOPMENT

The development group for this guideline consisted of psychiatrists, a family medicine specialist and a clinical psychologist, from the Ministry of Health and the Ministry of Education, Malaysia. During the process of development of this guideline, there was active involvement of a review committee.

Literature search was carried out at the following electronic databases: International Health Technology Assessment websites, PUBMED, Cochrane Database of Systematic Reviews (CDSR), Journal full text via OVID search engine, PsycINFO, Biomedical Reference Collection, Comprehensive; Database of Abstracts of Reviews of Effectiveness; Psychology and Behavioural Sciences Collection, Cochrane Controlled Trials Registered, CINAHL via EBSCO search engine. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. The following free text terms or MeSH terms were used either singly or in combination: *suicide; suicide attempted; depressive disorder; depressive disorder major; major depressive disorder; refer; referral; hospital admission; psychiatrist; drug therapy; psychotic; treatment resistant depression; refractory depression; difficult to treat depression; chronic depression; treatment; diagnosis; switching; substitution; combination; potentiation; optimisation; augmentation; ECT electroconvulsive therapy; psychotherapy; counselling; computer assisted; computerised cognitive behaviour therapy; CBT; depress*; gestalt therapy; light therapy; exercise; acupuncture; St John's Wort; Hypericum Extracts; elderly depression; diagnosis; assessment*.

Reference was also made to other guidelines on the management of major depression, which include the National Institute for Clinical Excellence (NICE) (2004) Depression: Management of depression in primary and secondary care; the American Psychiatric Association Practice guideline for the treatment of patients with major depressive disorder (2002); the World Federation of Societies of Biological Psychiatry (WFSBP) Guideline for Biological Treatment of Unipolar Depressive Disorders, Parts 1 and 2; the Australian and New Zealand clinical practice guidelines for the treatment of depression (2004). This guideline is based largely on the findings of systematic reviews and meta-analyses in the literature, taking into consideration local practices.

The articles were graded using the modified version of the criteria used by the Catalonia Agency for Health Technology Assessment and Research (CAHTAR) Spain, while the grading of recommendation in this guideline was modified from the Scottish Intercollegiate Guidelines Network (SIGN).

Assessment of evidence was done independently by individual members and discussed by the members of both the development group and review committee before the recommendations were formulated. Where the evidence was insufficient the recommendations were derived by consensus of both the development group and review committee.

The draft guideline was posted on both the Ministry of Health Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. This guideline has also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVE

To provide evidence-based guidance in the management of major depressive disorder (mild/moderate/severe) as classified in the DSM-IV/ICD-10 in adults and the elderly. Less common therapies such as Gestalt therapy, sleep deprivation, deep brain stimulation and vagus nerve stimulation are excluded from this review.

CLINICAL QUESTIONS

How can Major Depressive Disorder be assessed and diagnosed?
How do we manage Major Depressive Disorder?

TARGET POPULATION

This guideline is developed for the management of major depressive disorder in adults and the elderly. It does not cover the management of depression in children or pre- and post-natal women, or the management of dysthymic disorder, depressive episodes in patients with bipolar disorder or adjustment disorder with depressed mood.

TARGET GROUP/USER

This guideline is applicable to all health care professionals involved in treating patients with major depressive disorder.

POSSIBLE CLINICAL INDICATORS FOR QUALITY MANAGEMENT

Treatment setting : Primary care/secondary care

Name of indicator : Rate of Selective Serotonin Reuptake Inhibitor (SSRI) prescription for newly diagnosed cases of Major Depressive Disorder

Numerator : Number of newly diagnosed cases of Major Depressive Disorder prescribed SSRIs at initiation of treatment per month

Denominator : Total number of newly diagnosed cases of Major Depressive Disorder given pharmacotherapy per month

Rate of SSRI prescription = (Numerator/Denominator) x 100%

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SUMMARY OF RECOMMENDATIONS

SCREENING
Routine use of screening instruments to identify depression is not recommended. C

TREATMENT OF MAJOR DEPRESSIVE DISORDER (MDD)
Mild Major Depressive Disorder
Pharmacotherapy
Acute Phase Treatment
The treating doctor may choose to start antidepressant medication. B
When antidepressants are prescribed, SSRI should be considered as first line. A
Patients who are managed without medication may be offered other means of managing their depression. C
Patients should be closely monitored and given a follow-up appointment within 2 weeks. C
If the depression persists or worsens, antidepressants can be considered. C
In patients who have a past history of moderate to severe depression, who now present with mild depression, consider prescribing antidepressants as an initial measure. C
Continuation Phase Treatment
Antidepressants should be continued for at least 6-9 months after remission of the depressive episode. A
The antidepressant dose used for the acute treatment should be maintained for continuation treatment. C
Maintenance Phase Treatment
After antidepressants have been continued for 6-9 months following remission, the need for continuing antidepressant medication should be reviewed. C
Factors to consider include the number and severity of previous episodes, the presence of residual depressive symptoms, and ongoing psychosocial stressors. C
The antidepressant dose used for the acute treatment should be used for maintenance treatment. C
Patients who have had at least 2 recent depressive episodes that had caused significant functional impairment should continue antidepressant medication for at least 2 years. C
For patients who are regarded as being at greater risk for relapse, consider giving maintenance antidepressants for up to 5 years or more. C
Psychotherapy
Patients who are managed without medication may be offered other means of managing their depression. C
Consider giving supportive therapy, problem-solving therapy, counselling or cognitive behaviour therapy (CBT). A
Computerised Cognitive Behaviour Therapy (CCBT)
CCBT may be used for mild to moderate depression. A
Exercise therapy
Patients of all ages with mild to moderate depressive disorder can be recommended for exercise therapy. A

Moderate To Severe Major Depressive Disorder
Pharmacotherapy
Acute Phase Treatment
Antidepressant medication should be offered. A
SSRI should be considered as first line antidepressants. A
Patients should preferably be seen again within 2 weeks, unless the clinical situation (e.g. suicide risk) makes an earlier appointment necessary. The frequency of subsequent appointments will be determined by various clinical factors. C
If there is insufficient response, and there are no significant side effects, consider titrating the dose upwards. C
Consider switching antidepressants if there is no response after 1 month of an adequate dose of antidepressant. C
If there is partial response, consider continuing on the same medication for another 2 weeks before deciding to switch antidepressants. C
If a decision to switch antidepressant is made, a single second antidepressant should be chosen (i.e. monotherapy rather than combination therapy). C
The second antidepressant may be another SSRI, or a drug from another antidepressant class. B
Continuation Phase Treatment
Antidepressants should be continued for at least 6-9 months after remission of the depressive episode. A
The antidepressant dose used for the acute treatment should be maintained for continuation treatment. C
Maintenance Phase Treatment
After antidepressants have been continued for 6-9 months following remission, the need for continuing antidepressant medication should be reviewed. C
Factors to consider include the number and severity of previous episodes, the presence of residual depressive symptoms, and ongoing psychosocial stressors. C
The antidepressant dose used for the acute treatment should be used for maintenance treatment. C
Patients who have had at least 2 recent depressive episodes that had caused significant functional impairment should continue antidepressant medication for at least 2 years. C
For patients who are regarded as being at greater risk for relapse, consider giving maintenance antidepressants for up to 5 years or more. C
Psychotherapy
When considering psychological therapies, the intervention of choice is cognitive behaviour therapy (CBT). A
CBT should be offered to patients who do not take or who refuse antidepressant treatment. B
When patients present with severe depression, a combination of antidepressants and CBT should be considered. C
Where patients have responded to a course of individual CBT, consideration should be given to follow-up sessions. B
Exercise therapy
Exercise therapy can be prescribed as an adjunct to pharmacotherapy. B

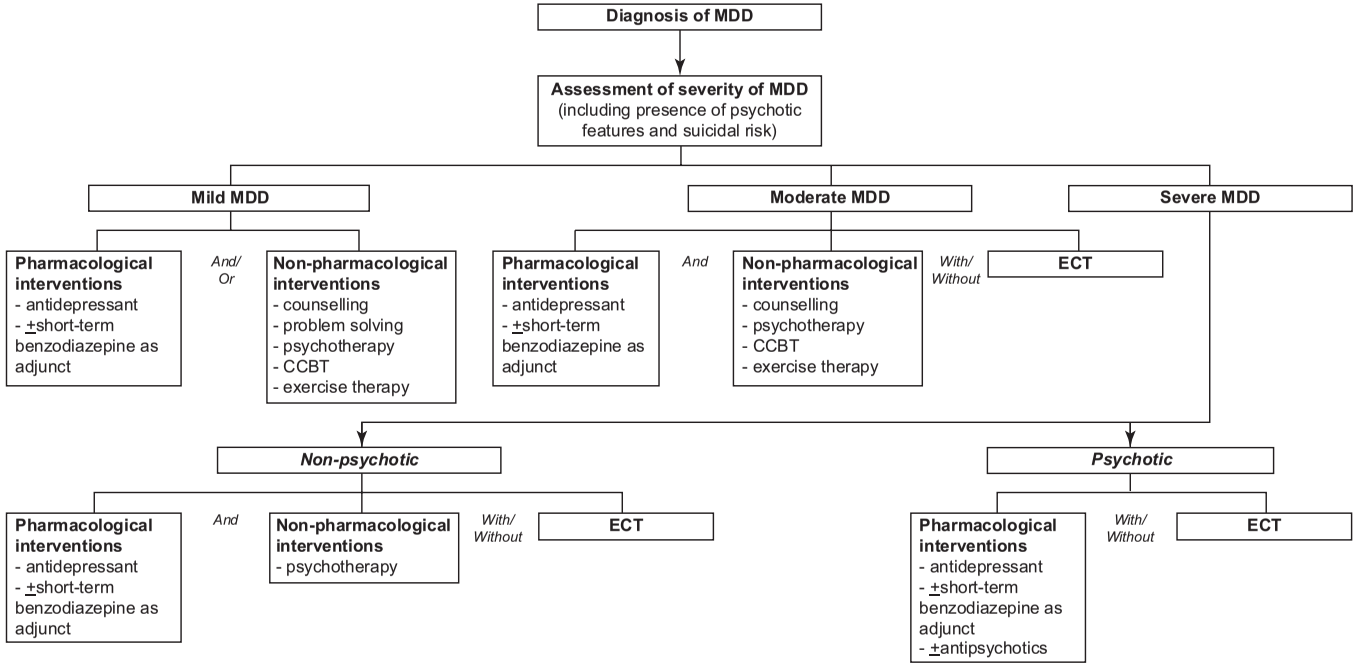
Electroconvulsive therapy (ECT)
ECT is recommended if there is a life-threatening condition such as refusal to eat or high suicidality due to the depressive illness. B
ECT may be considered for the acute treatment of moderate or severe depression for short-term therapeutic benefits. A
Major Depression With Psychotic Features
Pharmacotherapy
In psychotic depression, antipsychotics may be given in combination with antidepressants. C
Antipsychotic therapy should be maintained at least until full remission of the psychotic symptoms. C
Electroconvulsive (ECT)
ECT may be considered in psychotic depression. A
The Role Of Benzodiazepines
After weighing the potential risks and benefits, clinicians may consider prescribing benzodiazepines as an adjunct to antidepressants. A
If benzodiazepines are prescribed, avoid giving them for more than 2-4 weeks. A
Failed Response To Initial Treatment
Optimisation
If there has been an inadequate response to the initial antidepressant, and if there are no significant side effects, a gradual increase in dose should be considered. C
Switching
If there has been little response after an adequate trial of the initial antidepressant, consider switching to another antidepressant, either from the same class or from a different class. A
Treatment Resistant Depression
Switching
If there has been little response after an adequate trial of one antidepressant, consider switching to another antidepressant, either from the same class or from a different class. A
Augmentation
Lithium augmentation may be considered in treatment resistant depression. A
Lithium should be given for a minimum of 7 days achieving serum levels ≥ 0.5 mEq/L. A
Atypical antipsychotics may be considered in the augmentation of treatment resistant depression. A
Combination Therapy
Combination of an antidepressant with another antidepressant may be considered. Particular care should be taken to monitor for adverse events. B
Electroconvulsive therapy (ECT)
ECT may be considered in treatment resistant depression. B
Psychotherapy
For patients with treatment resistant depression, one may consider a combination of antidepressant medication with CBT. C

DEPRESSION IN THE ELDERLY
Pharmacotherapy
The elderly should also be offered antidepressants, with dosage adjustments for age where appropriate. A
SSRIs should be considered as first line antidepressants. A
Psychotherapy
Psychological therapy should also be offered to the elderly with depression. A
Electroconvulsive therapy (ECT)
ECT is recommended if there is a life-threatening condition such as refusal to eat or high suicidality due to the depressive illness. B
ECT may be considered for the acute treatment of moderate or severe depression for short-term therapeutic benefits. A
Exercise therapy
Elderly patients with mild to moderate depression can be recommended for exercise therapy. A
Exercise therapy can be prescribed as an adjunct to pharmacotherapy. B

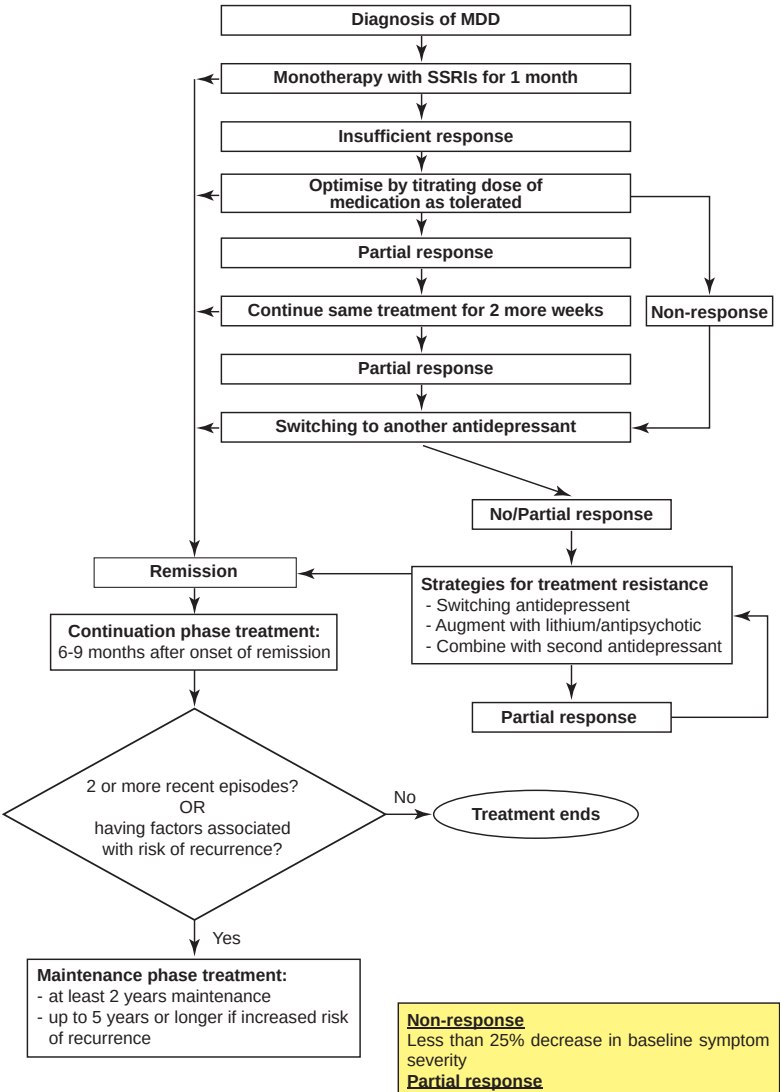
OTHER THERAPIES
St. John's Wort (SJW)
Although there is evidence for the effectiveness of SJW, its prescription is not recommended. A
Acupuncture
There is insufficient evidence with regards to the use of acupuncture in depression. A

* Please refer the grades (A B C) at the back cover.

Algorithm (1) for the Management of MDD



Algorithm (2) for the Pharmacotherapy of MDD



Non-response
Less than 25% decrease in baseline symptom severity

Partial response
26-49% decrease in baseline symptom severity

Response
A 50% or more reduction in depressive symptoms and at least a moderate degree of global improvement

Remission
Absence of signs and symptoms in current episode of depression and restoration of function

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1 INTRODUCTION

Major depressive disorder (MDD) is a significant mental health problem that disrupts a person's mood and adversely affects his psychosocial and occupational functioning. MDD is associated with significant morbidity and mortality.[1] MDD should not be mistaken for simple feelings of unhappiness or grief brought about by the death of a loved one. Sadness and grief are normal reactions to stressful life events and often resolve without medical intervention.

Untreated depression can last for six months or more. In a prospective psychiatric epidemiological survey, the mean time to recovery was 8.4 months and nearly 20% had not recovered at 24 months.[2] A majority of patients improve significantly with antidepressants treatment;[3] however, MDD often has a recurrent course, with multiple episodes of relapse.[4]

2 PREVALENCE

Lifetime prevalence levels from community-based surveys range from 4.9% to 17.1%.[5,6] In Malaysia, a cross sectional study done among adult primary care attendees reported the prevalence of MDD as 5.6%.[7] Longitudinal studies suggest that about 80% of individuals experiencing a major depressive episode will have at least one more episode during their lifetime and approximately 12% of patients who suffer from depression will have a chronic, unremitting course.[8]

3 DISEASE BURDEN

By the year 2020 major depression is projected to be the second largest contributor to the global burden of disease, after heart disease.[9] Depression incurs substantial public health and economic costs. It is estimated that the annual economic burden of depression in the US is about $43 billion with $17 billion of that resulting from lost work days.[10]

The most serious consequence of MDD is suicide. The risk for suicide associated with depressive disorders is elevated 12 to 20 fold compared to the general population. The lifetime risk of completed suicide is 10-15%.[12]

Depression is often under-recognised and under-treated.[13,14] It is estimated that about 30-50% of cases of depression in primary care and medical settings are not detected.[15] The overlap between symptoms of depression and symptoms of physical illnesses may lead to unnecessary utilisation of medical services in an attempt to treat complaints that are actually caused by depression rather than physical illness.[16]

4 ASSESSMENT AND DIAGNOSIS OF DEPRESSION

4.1 Diagnosis

The diagnosis of MDD is made using internationally accepted diagnostic

criteria i.e. either the 10th Revision of the International Classification of Diseases[17] (Appendix 1) or the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders IV[18] (Appendix 2).

4.2 Assessment

Assessment of depression consists of detailed history taking, mental state examination, physical examination, and investigations where indicated.[19, *level 1*]

History taking includes:

- presenting symptoms
- mode of onset
- duration and severity of symptoms
- number and severity of past episodes
- response to treatment
- hospitalisations
- psychosocial stressors
- family history
- suicide attempts
- past history of manic or hypomanic episodes
- substance abuse or other psychiatric illnesses
- social history and social support
- social and occupational impairment

Mental state examination includes the evaluation of the severity of depressive symptoms, the presence of psychotic symptoms and the risk of harm to self and others.

A relevant medical history, including prescribed and over-the-counter medications, should be taken and physical examination done to rule out any medical or surgical conditions that may cause or mimic depressive symptoms.

Laboratory tests may be required, particularly if the presentation is atypical, if symptoms suggest a medical cause, in older patients, in a first major depressive episode after the age of 40, in the absence of precipitating factors and in depression not responding fully to standard treatment.[19, *level 1*]

MDD can be categorised into mild, moderate and severe (Appendix 1).

4.3 Screening

The routine use of screening instruments to identify depression is not recommended for several reasons. Each tool requires translation into local languages and validation, and the usefulness of such tools in terms of positive predictive values and benefits to patients is questionable.[20, *level 9*] In primary care, clinicians often find these tools cumbersome and too time-consuming for routine use.[21, *level 9*]

Recommendation

- The routine use of screening instruments to identify depression is not recommended. **(Grade C)**

However, the following two questions may be used to screen for depression

(1) "During the past month, have you often been bothered by feeling down, depressed or hopeless?"
(2) "During the past month, have you often been bothered by having little interest or pleasure in doing things?"

If the answer is "Yes" to one or both questions, assess the patient for depression. For this Two-Question Case-Finding Instrument, the reported sensitivity is 96% and specificity 57%.[22, *level 9*] Clinicians are encouraged to screen for at least these two core symptoms of depression, especially in high risk groups e.g. those with physical health problems causing disability, a past history of depression, a family history of depression and those with other mental health problems such as substance abuse or dementia.

4.4 Assessment of Suicide Risk

The possibility of a suicide attempt in MDD may persist until significant remission occurs. An often cited figure is that up to 15% of hospitalised patients with severe unipolar depression eventually commit suicide.[12, *level 1*] In a recent meta-analysis the lifetime risk of suicide was reported to be 8.6% for those depressed patients hospitalised for suicidality and 4% for those admitted without specification of suicidality.[23, *level 1*] In any case, close supervision of high-risk patients is recommended, especially during initial drug therapy.

The following are risk factors:

- Loss of relationship[24, *level 6;* 25, *level 7*]
- Financial or occupational difficulties[26, *level 8;* 25, *level 7;* 24, *level 6;* 27, *level 7*]
- Poor social support[26, *level 8;* 28, *level 8;* 29, *level 8;* 30, *level 8;* 31, *level 8*]
- Past suicide attempt[32, *level 6;* 25, *level 7;* 33, *level 8;* 28, *level 8;* 34, *level 6;* 24, *level 6;* 35, *level 6*]
- Family history of suicide[25, *level 7*]
- Alcohol abuse/dependence[26, *level 8;* 25, *level 7;* 36, *level 7;* 37, *level 8;* 30, *level 8*]
- Other co-morbidities
- Suicidal ideation[26, *level 8;* 38, *level 8;* 34, *level 6;* 39, *level 8;* 40, *level 8*]
- Severity of depression[35, *level 6;* 33, *level 8;* 24, *level 6;* 41, *level 7;* 42, *level 7;* 32, *level 6;* 26, *level 8*]
- Psychomotor agitation[39, *level 8;* 40, *level 8;* 43, *level 8*]
- Low self-esteem[43, *level 8;* 39, *level 8*]
- Hopelessness[26, *level 8;* 38, *level 8;* 34, *level 6;* 29, *level 8*]

5 SELECTIVE SEROTONIN REUPTAKE INHIBITOR AND SUICIDE

There is conflicting evidence regarding the effect of selective serotonin reuptake inhibitors (SSRI) on suicide risk. Randomised trials have been limited by small sample sizes, short durations of follow-up, and their tendency to exclude patients with high suicide risk from the trials.[44, *level 9*]

Two recent meta-analyses addressed this issue. Fergusson et al.[45, *level 1*]

found an increase in the odds for non-fatal suicide attempts in those given SSRIs compared with those on placebo or non-tricyclic antidepressants. Gunnell, Saperia & Ashby et al.[46, *level 1*] found no significant difference between SSRIs and placebo in terms of suicides, non-fatal self-harm and suicidal thoughts.

Several observational studies generally have not found a suicide risk specific to SSRIs.[47, *level 7;* 48, *level 7;* 49, *level 9*] The risk of suicide from SSRIs was not different from the risk due to tricyclic antidepressants.

Recommendation

- There is conflicting evidence regarding the risk of suicide with SSRI use, but it is prudent to monitor patients closely in the first few weeks after starting treatment. **(Grade B)**

6 CRITERIA FOR REFERRAL TO PSYCHIATRIC SERVICES

In the local setting, referral to the psychiatric services may be done through the Accident & Emergency Department or directly to the psychiatric clinic.

Indications for referral to Psychiatric Services include:

- Unsure of diagnosis[50, *level 9;* 51, *level 7*]
- Attempted suicide[52, *level 1*]
- Active suicidal ideas / plans[52, *level 1*]
- Failure to respond to treatment[50, *level 9;* 52, *level 1;* 51, *level 7*]
- Advice on further treatment[50, *level 9;* 51, *level 7*]
- Clinical deterioration[50, *level 9*]
- Recurrent episode within 1 year[52, *level 1*]
- Psychotic symptoms[52, *level 1*]
- Severe agitation[52, *level 1*]
- Self neglect[52, *level 1*]

7 CRITERIA FOR ADMISSION

There are circumstances where outpatient care may be insufficient and admission required. Locally, admission to the psychiatric unit can be voluntary or involuntary.

Indications for admission include:

- Risk of harm to self[53, *level 8;* 52, *level 1;* 54, *level 9*]
- Psychotic symptoms[53, *level 8*]
- Inability to care for self[53, *level 8*]
- Lack of impulse control[53, *level 8*]
- Danger to others[55, *level 9*]

8 PHASES OF TREATMENT

8.1 Acute Phase

Patients are given antidepressants until they achieve remission.[4, *level 9*]

8.2 Continuation Phase

The duration of continuation phase treatment is generally 6 to 9 months from the acute phase.[56, *level 9;* 57, *level 9;* 52, *level 9;* 58, *level 9;* 59, *level 9*] However, the American Psychiatric Association (APA) recommended 16 to 20 weeks.[55, *level 9*]

8.3 Maintenance Phase

The maintenance phase is a period to prevent recurrence[4, *level 9*] and the optimal duration is difficult to determine because some patients require a longer period and some an indefinite period.[57, *level 9*] Several factors should be considered in determining the need for maintenance phase treatment[55, *level 9*]

- Risk of recurrence
- Severity of the episodes (suicidality, psychotic features, severe functional impairment)
- Side effects experienced with continuous treatment
- Patient preferences

Acute Phase of Treatment
The acute phase is a period where remission is achieved.
Continuation Phase of Treatment
The continuation phase is a period after sustained and complete remission from the acute phase.
Maintenance Phase of Treatment
The maintenance phase is a period to prevent recurrence (a new episode of depression) and development of chronicity.

9 TREATMENT OF MAJOR DEPRESSIVE DISORDER

9.1 Pharmacological Treatment

9.1.1 Acute Phase Treatment

Mild Major Depressive Disorder

A substantial proportion of primary care patients have mild major depressive disorder.[60, *level 8*] There is a greater placebo response in mild depression compared to moderate and severe depression[61, *level 1*] and there is more evidence for the effectiveness of antidepressants in moderate to severe depression than in mild depression.[62, *level 3;* 63, *level 1*] The American Psychiatric Association (APA) gives antidepressant medication as an option rather than as a mandatory measure in the initial primary treatment of mild major depressive disorder.[55, *level 9*]

Recommendation

- For patients with MDD of mild severity, the treating doctor may choose to start antidepressant medication. **(Grade B)**
- Patients who are managed without medication may be offered other means of managing their depression. **(Grade C)**
- Patients should be closely monitored, and given a follow-up appointment within 2 weeks. **(Grade C)**
- If the depression persists or worsens, antidepressants can be considered. **(Grade C)**
- In patients who have a past history of moderate to severe depression, who now present with mild depression, consider prescribing antidepressants as an initial measure. **(Grade C)**

Moderate to Severe Major Depressive Disorder

NICE[52, *level 1*] found that antidepressants are efficacious for reducing depressive symptoms and that SSRIs do not differ in efficacy from tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) in both in-patients and psychiatric outpatients or primary care patients. However, SSRIs are better tolerated compared to other antidepressants,[52, *level 1*] and therefore, make appropriate drugs of first choice. The newer antidepressants i.e. mirtazapine, venlafaxine, escitalopram have also been found to be efficacious.[52, *level 1*] In a systematic review, Hansen et al.[64, *level 1*] found that overall, the various newer antidepressants did not differ substantially from each other.

Antidepressants are as effective as psychological interventions,[52, *level 1*] and more easily available in this country. Therefore, it is appropriate to offer them as a first-line measure.

If a patient does not show any response after 4 weeks of antidepressant treatment at adequate dosage, the likelihood of a later response on the same medication is low. If there is partial response by 4-6 weeks, there is a likelihood of further response after several more weeks of treatment.[57, *level 9*]

Antidepressants may be started at the doses suggested in Appendix 3. The dose may be titrated to therapeutic levels over the first few weeks of treatment, taking into consideration side effects, the patient's age, and co-morbid medical illnesses.[55, *level 9*]

Recommendation

- For patients with moderate to severe depression, antidepressant medication should be offered. **(Grade A)**
- SSRIs should be considered as first line antidepressants. **(Grade A)**
- Patients should preferably be seen again within 2 weeks, unless the clinical situation (e.g. suicide risk) makes an earlier appointment necessary. The frequency of subsequent appointments will be determined by various clinical factors. **(Grade C)**
- If there is insufficient response, and there are no significant side effects, consider titrating the dose upwards. **(Grade C)**
- Consider switching antidepressants if there is no response after 1 month of an adequate dose of antidepressant. **(Grade C)**
- If there is partial response, consider continuing on the same medication for another 2 weeks before deciding to switch antidepressants. **(Grade C)**
- If a decision to switch antidepressant is made, a single second antidepressant should be chosen (i.e. monotherapy rather than combination therapy). **(Grade C)**
- The second antidepressant may be another SSRI, or a drug from another antidepressant class. **(Grade B)**

9.1.2 Continuation Phase Treatment

Reimherr et al.[65, *level 1*] showed significantly lower relapse rates for at least 26 weeks for fluoxetine-treated patients compared with placebo-treated patients following 12 weeks of successful acute treatment. Geddes et al[66, *level 1*] found that continuing antidepressant therapy consistently reduced the risk of relapse in patients who had responded to acute phase treatment. NICE[52, *level 1*] also found strong evidence to suggest that continuing antidepressant treatment reduces the risk of relapse. Bauer et al.[57, *level 9*; 67, *level 9*] recommend that the same dose of medication given during the acute phase be given for the continuation and maintenance phases.

Recommendation

- Antidepressants should be continued for at least 6-9 months after remission of the depressive episode. **(Grade A)**
- The antidepressant dose used for the acute treatment should be maintained for continuation treatment. **(Grade C)**

Discontinuation of pharmacotherapy

Except in emergencies or in case of intolerable side effects, drug therapy should not be terminated abruptly. Drugs should be tapered down gradually over weeks or in some cases months.

9.1.3 Maintenance Phase Treatment

After acute treatment for depression, continuing antidepressant therapy consistently reduced the risk of recurrence for up to 2 years.[52, *level 1*] In trials

of 2-3 years' duration, the proportional risk reduction in the subsequent 12-36 months was similar to that in the first 12 months.[66, *level 1*]

There is some variation in the literature regarding the duration of maintenance medication. Factors to be considered include the patient's absolute risk for recurrence (Appendix 4) and patient preferences. NICE[52, *level 1*] considers that for patients who have had multiple recurrences, it is worthwhile to continue antidepressant medication for up to 2 years, but others have recommended maintenance treatment for up to 5 years, with a possibility of life-long treatment.[58, *level 9*]

Recommendation

- After antidepressants have been continued for 6-9 months following remission, the need for maintenance phase antidepressant medication should be considered. **(Grade A)**
- Factors to consider include the number and severity of previous episodes, the presence of residual depressive symptoms, and ongoing psychosocial stressors. **(Grade C)**
- The antidepressant dose used for the acute treatment should be used for maintenance treatment. **(Grade C)**
- Patients who have had at least 2 recent depressive episodes that had caused significant functional impairment should continue antidepressant medication for at least 2 years. **(Grade C)**
- For patients who are regarded as being at greater risk for recurrence, consider giving maintenance antidepressants for up to 5 years or more. **(Grade C)**

Discontinuation of pharmacotherapy

Except in emergencies or in case of intolerable side effects, drug therapy should not be terminated abruptly. Drugs should be tapered down gradually over weeks or in some cases months.

Major Depression with Psychotic Features

Although many clinicians routinely prescribe antipsychotics to patients with psychotic depression, the evidence supporting this is unclear. NICE[52, *level 1*] found insufficient evidence to determine if there was a clinically significant difference between a TCA plus an antipsychotic and either amoxapine or a TCA. A small meta-analysis (2 RCTs) by Wijkstra et al.[68, *level 1*] found no conclusive evidence that an antidepressant-antipsychotic combination was more effective than antidepressant alone. However, the general lack of available data limited confidence in the conclusions drawn, hence necessitating a cautious approach.

Recommendation

- In psychotic depression, antipsychotics may be given in combination with antidepressants. **(Grade C)**
- Antipsychotic therapy should be maintained at least until full remission of the psychotic symptoms. **(Grade C)**

The Role of Benzodiazepines

Benzodiazepines have been used to treat depressive symptoms, especially outside the psychiatric setting. However, benzodiazepines are not thought to have a specific antidepressant effect,[52, *level 1*] and many experts believe that the depressive state is not improved by benzodiazepines alone.[57, *level 9*] Beyond the fact that the antidepressant properties of benzodiazepines are in doubt, their use has also led to problems with dependence.

However, the adjunctive use of benzodiazepines may confer some benefit. Furukawa et al.[69, *level 1*] conducted a systematic review of RCTs that compared combined antidepressant-benzodiazepine treatment with antidepressants alone for adults with major depression. The antidepressant-benzodiazepine combination group was more likely to show a response at 1-4 weeks than the antidepressant alone group, but not beyond this period.

Recommendation

- After weighing the potential risks and benefits, clinicians may consider prescribing benzodiazepines as an adjunct to antidepressants. **(Grade A)**
- If benzodiazepines are prescribed, avoid giving them for more than 2-4 weeks. **(Grade A)**

Failed Response to Initial Treatment

Approximately 20-30% of people with depressive illness do not respond satisfactorily to the usual recommended dose of antidepressants and approximately 15% may develop chronic depression.[70, *level 9*] Patients who have not responded after 4 weeks of antidepressant therapy at an adequate dose are regarded as acute phase non-responders. The clinician should evaluate the patient for factors that may contribute to non-response.

Reasons for treatment failure include[67, *level 9;* 71, *level 9*]

- incorrect diagnosis (e.g. failure to diagnose bipolar disorder)
- psychotic depression
- organic conditions such as anaemia or hypothyroidism
- co-morbid psychiatric disorder such as substance abuse or dependence, panic disorder, obsessive-compulsive disorder, and personality disorder
- adverse psychosocial factors
- non/poor compliance

Strategies used to treat patients who fail to respond to initial treatment include:

- Optimisation
- Switching

- **Optimisation**

Clinicians should first consider optimising the dosage of the initial antidepressant as there is wide inter-individual variation in dosage, and a clear dose-response relationship has not been well established for most antidepressants.[71, *level 9*]

Recommendation
- If there has been an inadequate response to the initial antidepressant, and if there are no significant side effects, a gradual increase in dose should be considered. **(Grade C)**

- **Switching**

This refers to a change from one antidepressant to another.[71, *level 9*]

Some evidence exists to support the strategy of switching. Rush et al.[72, *level 1*] randomly assigned 727 adult outpatients who did not respond to or tolerate citalopram to receive one of the following drugs for up to 14 weeks: sustained-release bupropion, sertraline, or extended-release venlafaxine. They found that about a quarter of patients had a remission of symptoms after switching to another antidepressant, and concluded that any one of the three medications provided a reasonable second-step choice for patients with depression.

Recommendation
- If there has been little response after an adequate trial of the initial antidepressant, consider switching to another antidepressant, either from the same class or from a different class. **(Grade A)**

Treatment Resistant Depression

This guideline adopts the NICE criteria which define treatment resistant depression (TRD) as depression that has **failed to respond to two or more antidepressant treatments** at an adequate dose for an adequate duration, given sequentially.[52, *level 1*] Adequate duration refers to at least 4 weeks, and adequate dose to at least 150mg/day of imipramine equivalent.[73, *level 9*]
Strategies used to treat treatment resistant depression include:

- Switching
- Augmentation
- Combination therapy

- **Switching**

Stimpson, Agrawal & Lewis[74, *level 1*] in a systematic review of RCTs assessing the efficacy of interventions for treatment resistant depression concluded that there was very little evidence to guide the management of those who have not responded to a standard dose of antidepressants for 4 weeks. Similarly, NICE[52, *level 1*] concluded that there was little evidence on which to make an evidence-

based recommendation of switching strategies in the treatment of treatment-resistant depression.

Nevertheless, there is some evidence to support the strategy of switching. Nelson[75, *level 9*] cited four open-labelled, uncontrolled studies which showed that switching from one SSRI to another resulted in further response. Thase et al.[76, *level 1*] studied outpatients who failed to respond to 12 weeks of double-blind treatment with either sertraline or imipramine, and were crossed over to 12 weeks of treatment with the alternate medication. They found that overall, more than 50% of the patients benefited from a switch from imipramine to sertraline, or vice versa. This provided some evidence for the usefulness of switching between antidepressant classes. Nelson[75, *level 9*] cited studies that provided some evidence for switching to venlafaxine and mirtazapine.

Poirier & Boyer[77, *level 2*] conducted a double-blind randomised comparison of venlafaxine and paroxetine in the treatment of 122 patients with TRD, and concluded that there is some evidence suggesting a clinical advantage for high dose venlafaxine (mean 269 mg) over paroxetine in terms of achieving remission.

A small retrospective chart review involving 24 patients with partial or non-response to treatment with other antidepressants found symptomatic improvement in 38% of the patients during an average of 14 months treatment with mirtazapine in open label fashion.[78, *level 9*] However, a STAR*D report comparing treatment with mirtazapine and nortriptyline in 235 patients who had failed 2 consecutive antidepressant trials found no significant difference in either response or remission rates between the two treatment groups.[79, *level 2*]

There are no studies addressing the relative efficacy of escitalopram in TRD. A meta-analysis of 10 studies comparing the efficacy of escitalopram with other antidepressants (SSRIs and venlafaxine) in patients with (non-treatment resistant) major depressive disorder found escitalopram to be superior to the SSRIs and comparable to venlafaxine in terms of remission and response.[80, *level 1*] However, the primary studies were all industry sponsored, and there was no indication that other studies were looked for or that publication bias was assessed.

There is a lack of studies looking at the efficacy of duloxetine in treatment resistant depression.

Recommendation

- If there has been little response after an adequate trial of one antidepressant, consider switching to another antidepressant, either from the same class or from a different class. **(Grade A)**

• Augmentation

Augmentation refers to the addition of a non-antidepressant drug to an ongoing antidepressant.[67, *level 9*]

Augmentation with Lithium

A meta-analysis of 9 placebo-controlled, double-blind studies involving data from 110 patients that used a minimum lithium dose of 800mg/day or a dose sufficient to reach lithium serum levels of ≥ 0.5mEq/L for a minimum duration of 2 weeks showed that the addition of lithium had a statistically significant effect on the response rate. The authors concluded that, with respect to efficacy, lithium augmentation is the treatment of first choice for depressed patients who fail to respond to antidepressant monotherapy.[81, *level 1*]

A meta-analysis of 2 small trials demonstrated that lithium had a statistically significant benefit.[74, *level 1*]

Studies comparing lithium plus an antidepressant with lithium plus placebo have shown a clinically significant difference favouring antidepressants augmented with lithium in terms of the likelihood of achieving a 50% reduction in depressive symptoms.[52, *level 1*]

Evidence for the efficacy of lithium augmentation comes from at least 10 double-blind placebo-controlled studies, 4 randomised comparator studies and 13 open-labelled studies. Overall about 50% of patients respond.[82, *level 9*]

Recommendation

- Lithium augmentation may be considered in treatment resistant depression. **(Grade A)**
- It should be given for a minimum of 7 days achieving serum levels ≥ 0.5 mEq/L. **(Grade A)**

Augmentation with Atypical Antipsychotics

Antipsychotic agents may exhibit antidepressant activity. Ostroff & Nelson[83, *level 8*] reported on eight patients with non-psychotic depression who failed to respond to an SSRI, but responded when risperidone was added.

Augmentation of fluoxetine with olanzapine demonstrated superior efficacy for treating resistant depression compared to fluoxetine monotherapy.[84, *level 3*] A later 8-week double blind study by Shelton et al.[85, *level 3*] involving 28 patients with TRD without psychotic features showed that olanzapine plus fluoxetine did not differ significantly from olanzapine and fluoxetine monotherapy at the endpoint, although it demonstrated a more rapid response that was sustained until the end of treatment. A retrospective study[86, *level 8*] demonstrated that aripriprazole may be effective as an augmentation agent in TRD. Patkar et al.[87, *level 8*] in his open-label, rater-blinded study on augmentation with aripiprazole showed a significant reduction in HAM-D score. An open label study showed that quetiapine as an augmenting agent in TRD resulted in lower scores on the HAM-D[44, *level 8*].

Recommendation

- Atypical antipsychotics may be considered as augmenting agents in treatment resistant depression. **(Grade A)**

Augmentation with Anticonvulsants

a) Augmentation with lamotrigine
NICE[52, *level 1*] did not find sufficient evidence to support the use of lamotrigine as an augmenting agent.

However, a retrospective chart review[88, *level 8*] of lamotrigine for TRD showed that 76% of the patients improved on the Clinical Global Impression (CGI) scale. Barbee & Jamhour[89, *level 8*] in their study on lamotrigine as an augmentation agent showed that 48% of the patients improved on the CGI scale and Global Assessment of Function. This positive effect is also reflected in another case series by Gutierrez et al.[90, *level 8*] where early and sustained response was observed.

b) Augmentation with valproate
There is insufficient evidence for the use of valproate as an augmenting agent in TRD.[52, *level 1*]

c) Augmentation with carbamazepine
There is insufficient evidence to support the use of carbamazepine as an augmenting agent in TRD.[52, *level 1*]

A small trial of 59 patients using antidepressant plus lithium compared with antidepressant plus carbamazapine did not show any significant difference in efficacy.[91, *level 3*]

d) Augmentation with benzodiazepines
There is insufficient evidence to support the use of benzodiazepines as augmenting agents in TRD.[52, *level 1*]

Recommendation
- There is insufficient evidence to recommend the use of anticonvulsants as augmenting agents in treatment resistant depression. **(Grade B)**
- There is insufficient evidence to recommend the use of benzodiazepines as augmenting agents in treatment resistant depression. **(Grade A)**

- **Combination Therapy**

Combination therapy refers to the addition of another antidepressant to the ongoing antidepressant treatment.[57, *level 9*]

Nelson et al.[92, *level 8*] found that a combination of fluoxetine plus desipramine was superior to monotherapy with either fluoxetine or desipramine in terms of response rate. However, the lack of statistical significance could be due to the small sample size.

Ferreri et al.[93, *level 2*] found that a combination of mianserin and fluoxetine was superior to either agent alone.

Carpenter et al.[94, *level 3*] randomised TRD patients to a combination of an antidepressant with placebo or with mirtazapine, and found a superior response rate for the mirtazapine-antidepressant group.

NICE found some evidence suggesting a clinically significant difference favouring two antidepressants over a single antidepressant on increasing the likelihood of achieving response or symptom reduction in TRD.[52, *level 1*]

Similarly, Dodd et al.[95, *level 1*] concluded that there is increasing evidence to suggest that combination therapy with different mechanism of action have an important role in the TRD. However, combination therapies may have an increased risk for adverse affects. Caution should be exercised in TCA and SSRI combinations in view of increased TCA blood levels and consequent cardiotoxicity.

Recommendation

- Combination of an antidepressant with another antidepressant may be considered in patients with TRD. Particular care should be taken to monitor for adverse events. **(Grade B)**

9.2 Electroconvulsive Therapy (ECT)

ECT is an effective form of somatic treatment for major depressive disorder. There is evidence which shows that real ECT is significantly more effective than sham or simulated ECT or placebo.[96, *level 1;* 97, *level 1;* 98, *level 1;* 99, *level 1*]

ECT is found to be superior to certain antidepressants in the short term,[96, *level 1;* 97, *level 1;* 98, *level 1;* 99, *level 1*] but its effects are short-lived.[98, *level 1*] ECT can bring about a rapid response in reducing symptoms as early by 3 ECTs, and early remission as early as by 6 ECTs.[100, *level 2*]

ECT is effective in psychotic depression.[101, *level 1;* 102, *level 5*]

ECT may be efficacious in TRD.[103, *level 3;* 104, *level 5*]

Although a retrospective review has shown that maintenance ECT helps to sustain symptom reduction and reduce hospitalisation rates in chronic TRD,[105, *level 8*] there is little evidence to show that it is more beneficial than pharmacotherapy.[52, *level 1*]

A systematic review has shown that there is no difference in efficacy between giving ECT twice a week or thrice a week.[98, *level 1*] Bilateral is more effective than unilateral ECT.[97, *level 1;* 98, *level 1*]

- There should not be a routine prescription of a fixed number of ECT sessions.
- The clinical status of the patient should be assessed following each ECT session to observe for side-effects and therapeutic response in order to determine subsequent ECT administration.
- A valid informed consent should be obtained before giving ECT.

Indications for ECT in patients with MDD include[55, *level 9*]:

- A high degree of symptom severity and functional impairment
- Psychotic symptoms
- Catatonic features
- Urgent need for response or a life-threatening condition such as refusal to eat or highly suicidal due to the depressive illness

Side-effects of ECT

There is no absolute contraindication to ECT. Relative contraindications are recent myocardial infarction, congestive heart failure, recent stroke, cerebral vascular aneurysm, retinal detachment and space occupying lesions leading to raised intracranial pressure.[59, *level 9*]

The main risks of ECT are those associated with anaesthesia and medical co-morbidities, and the associated mortality is not in excess of that associated with minor surgery involving general anaesthesia.[97, *level 1*]

Those who are at increased risk include those with cardiovascular problems, pregnant women and elderly patients.[97, *level 1*]

The side-effects of ECT are mainly cognitive impairments that include short-term retrograde amnesia and anterograde amnesia,[97, *level 1;* 98, *level 1*] and a transient post-ictal confusional state following each ECT.[59, *level 9*]

A systematic review of RCTs suggested that objective cognitive impairments may not last beyond 6 months but subjectively patients did complain of prolonged cognitive impairment.[97, *level 1*] Imaging studies using CT scans and MRI did not show evidence that ECT caused structural brain damage.[98, *level 1*]

Less cognitive impairment is caused by unilateral ECT versus bilateral ECT, lower dose compared to higher dose ECT, and twice a week versus thrice a week ECT.[97, *level 1;* 98, *level 1*]

Other side-effects include headache, muscle soreness and nausea. Serious complications like status epilepticus and laryngospasm can occur.[97, *level 1*]

Good quality randomised studies on long-term adverse effects of ECT are still lacking and therefore, these adverse effects have not been clearly established.[97, *level 1;* 98, *level 1*]

ECT causes short term cognitive impairment but there is no evidence to show that it causes structural brain damage.

Recommendation

- ECT is recommended if there is a life-threatening condition such as refusal to eat or high suicide risk due to the depressive illness. **(Grade B)**
- ECT may be considered:
  - For the acute treatment of moderate or severe depression for short-term therapeutic benefits. **(Grade A)**
  - To achieve rapid improvement of severe symptoms in major depression with or without psychotic features. **(Grade A)**
  - In treatment resistant depression. **(Grade B)**

9.3 Psychological Interventions

9.3.1 Psychotherapy

Mild Major Depressive Disorder

NICE,[52, *level 1*] in a meta-analysis of 3 studies of problem-solving therapy over a period of 3 months, found some evidence favouring **problem-solving therapy** over placebo on reducing symptoms and inducing remission. It commented, however, that its value in secondary care is uncertain as all the above studies were carried out in primary care. Similarly, a Cochrane review concluded that there is good evidence that problem-solving therapy by GPs is no less effective than antidepressant treatment on depression, psychological symptoms and social functioning.[106, *level 1*]

In its meta-analysis of 3 trials, NICE[52, *level 1*] showed that there was evidence for the efficacy of **counselling** for depression in primary care for patients with mild to moderate depression of recent onset when it was compared with antidepressants, GP care and other psychological interventions. In a randomised trial of primary care patients King et al.[107, *level 1*] found counselling and CBT to be equally effective and superior to usual GP treatment, but the groups were comparable by one year. A meta-analysis of 7 studies found that counselling reduced symptoms of depression and anxiety over usual GP care in the short term, but the difference did not hold in the long term.[108, *level 1*]

A meta-analysis of 30 trials found strong evidence favouring **cognitive behavioural therapy (CBT)** over wait list control on reducing depression symptoms, and some evidence favouring CBT in achieving remission.[52, *level 1*] A systematic review found evidence in favour of CBT and other variants of psychotherapy over treatment as usual and wait list control in the treatment of depression.[109, *level 1*]

NICE[52, *level 1*] found insufficient evidence to suggest a difference between short-term **psychodynamic psychotherapy** and CBT on symptom reduction, for up to one year of therapy. Churchill et al.[109, *level 1*] found that the odds of recovery for those receiving variants of CBT were more than two times greater than for those receiving psychodynamic therapy, but in other respects the two therapies did not differ.

Churchill et al.[109, *level 1*] demonstrated evidence in favour of **supportive therapy** over treatment as usual and wait list controls in terms of recovery and symptom reduction. They also found the pooled odds ratio for recovery to favour CBT variants over supportive therapy, but this did not apply in the most severely depressed patients.

In a systematic review of brief psychological treatments for depression, Churchill et al.[109, *level 1*] found evidence in favour of **interpersonal therapy (IPT)** over treatment as usual and wait list control. They also found no significant differences between IPT and variants of CBT in terms of recovery and mean symptom difference. Similarly, a more recent systematic review by Mello et al.[110, *level 9*] showed IPT to be an efficacious psychotherapy for depressive spectrum disorders. However, IPT is not widely available in Malaysia.

Recommendation

- For major depression of mild severity, consider giving supportive therapy, problem-solving therapy, counselling or CBT. **(Grade A)**

Moderate to Severe Major Depressive Disorder

NICE[52, *level 1*] found evidence for the efficacy of **counselling** for depression in primary care for patients with mild to moderate depressive disorder of recent onset.

A meta-analysis of 30 trials found evidence suggesting no difference between **CBT** and antidepressants on reducing symptoms in moderate or moderate/severe depressive disorder.[52, *level 1*] A randomised controlled trial of 240 outpatients showed that cognitive therapy can be as effective as medications for the initial treatment of moderate to severe major depressive disorder, but this may depend on a high degree of therapist expertise.[111, *level 1*]

NICE[52, *level 1*] found some evidence favouring a **combination of CBT plus antidepressants** over antidepressants alone but there was insufficient evidence to say if this benefit persisted beyond the first few months. The effectiveness of CBT plus antidepressants was particularly marked for those with moderate and moderate/severe depressive disorder or severe/very severe depressive disorder.

The experience and expertise of the therapist are important considerations when offering psychological interventions.

Recommendation

- When considering psychological interventions in moderate and severe major depressive disorder, the intervention of choice is CBT. **(Grade A)**
- CBT should be offered to patients with moderate or severe depressive disorder who do not take or who refuse antidepressant treatment. **(Grade B)**
- For moderate and severe depressive disorder, the duration of psychological interventions should be in the range of 16 to 20 sessions over 6 to 9 months. **(Grade C)**
- When patients present with severe depressive disorder, a combination of antidepressants and CBT should be considered. **(Grade C)**
- For depressed patients with complex co-morbidities, consider giving brief psychodynamic psychotherapy. **(Grade C)**
- Where patients have responded to a course of individual CBT, consideration should be given to follow-up sessions. **(Grade B)**

Treatment Resistant Depression

A non-quantitative systematic review of 12 studies examined the effectiveness of psychological treatment interventions using a less restrictive definition of treatment resistance (not responding to a minimum of 4 weeks of antidepressant treatment at recommended dose). Of the 4 controlled studies, 2 showed a significant difference, while 2 did not. Of the 8 uncontrolled studies, 3 reported a significant reduction in depression scores.[112, *level 1*] The lack of pooled data and the small sample sizes of the primary studies limit the reliability of the evidence.

However, in an open trial of 19 patients treated by cognitive-behavioural methods, the completers showed a significant decrease in depression scores and 75% of them were in remission.[113, *level 8*]

Recommendation

- For patients with treatment resistant depression, one may consider a combination of antidepressant medication with CBT. **(Grade B)**

9.4 Computerised Cognitive Behaviour Therapy

Computerised cognitive behaviour therapy (CCBT) is a generic term that is used to refer to a number of methods of delivering CBT via an interactive computer interface. It can be delivered on a personal computer, over the internet or via the telephone using interactive voice response systems. There are three programmes for depression, Beating the Blues (BtB), COPE and Overcoming Depression.[114, *level 1*]

A randomised controlled trial found that CCBT is as effective as standard CBT for outpatients with non-psychotic MDD.[115, *level 3*]

A systematic review of 2 RCTs and 4 non-comparator trials looking at all three CCBT programmes showed that Beating the Blues statistically

significantly improved scores for Beck Depression Inventory (BDI) and work and social adjustment (WSA), compared with treatment as usual for patient with mild to moderate depressive disorder.[114, *level 1*]

An audit of public registrants to a cognitive behaviour therapy website (MoodGYM) showed significant change in anxiety and depression symptoms.[116, *level 9*]

Recommendation
- CCBT may be used for mild to moderate depression. **(Grade A)**

9.5 Other Therapies

9.5.1 Exercise therapy

Exercise therapy generally consists of structured and supervised exercise activity of 45-60 minutes per session, up to 3 times per week and prescribed for 10-12 weeks.

Exercise may be used as a form of therapy in the management of depression. Several mechanisms of action have been postulated.[52, *level 1*]

There is evidence that favours exercise over no exercise in reducing depressive symptoms[117, *level 1;* 52, *level 1;* 118, *level 1* and some evidence favouring exercise in achieving response or remission.[52, *level 1*]

There is evidence to support the effectiveness of exercise in the clinical population of depressed patients.[119, *level 3;* 120, *level 9*]

There is some evidence that exercise therapy may be as effective as antidepressant medication in achieving remission in depression.[119, *level 3*]

Recommendation
- Patients of all ages with mild to moderate depressive disorder can be recommended for exercise therapy. **(Grade A)**
- Exercise therapy can be prescribed as an adjunct to pharmacotherapy in the treatment of depression if agreeable to the patient. **(Grade B)**

9.5.2 Acupuncture

A Cochrane review showed there is insufficient evidence to determine the efficacy of acupuncture as compared to medication or wait list control or sham acupuncture in the management of depression.[121, *level 1*]

9.5.3 St John's Wort (SJW) (Hypericum Extracts)

Earlier meta-analyses found H. perforatum to be more effective than placebo,[122, *level 1;* 123, *level 1;* 124, *level 1* but more recent meta-analyses suggest that its effectiveness was less then previously thought, especially for major depression as opposed to non-major depression.[125, *level 1;* 126, *level 1*]

Adverse effects occurred less frequently with SJW than with standard antidepressants,[124, *level 1;* 122, *level 1;* 127, *level 3*] and NICE concluded that SJW appears more acceptable than antidepressants (particularly TCAs), with a lower rate of treatment dropouts.[52, *level 1*]

The main side effects of SJW are headache, dryness of mouth, nausea, gastrointestinal symptoms and sleepiness.[128, *level 3*]

Although there is evidence that SJW is more effective than placebo and better tolerated than standard antidepressant for the treatment of mild to moderately severe depressive disorder, there are problems associated with its use, in particular, uncertainty about appropriate doses, variation in the nature of preparations and potentially serious drug interactions.[52, *level 1*]

Recommendation

- Although there is evidence for the effectiveness of SJW, its prescription is not recommended. **(Grade A)**

10 FOLLOW-UP

NICE[52, *level 1*] recommends that patients should be seen again within 2 weeks of the first visit, and subsequently on an appropriate and regular basis, e.g. every 2-4 weeks in the first 3 months and at longer intervals after that, if the patient is responding well to treatment. However, the frequency of patient follow-up and monitoring will also have to take into consideration the severity of illness, the patient's compliance, social support and co-morbid conditions.[55, *level 9*]

11 DEPRESSION IN THE ELDERLY

INTRODUCTION

The prevalence rates of depression in the elderly vary enormously (0.4-35%) with an average of 13.5% for clinically relevant depressive syndromes.[129, *level 1*] A 15-year follow up study observed that the incidence of depression increases with age, and women are at greater risk to develop depression compared to men.[130, *level 4*]

Aging is associated with risk factors for depression, including brain changes, vascular risk factors, cognitive impairment, physical illness and its disability causing functional limitations, poor self-rated health, long-term pain, vision problems, medication use, major life events, stressors, financial strain, and having poor social support.[131, *level 9;* 132, *level 4;* 133, *level 4*]

CLINICAL PRESENTATION

The clinical presentation of depression in the elderly may vary from that of younger adults and this can often be misleading. The depressed elderly less often complain of sadness compared to the younger depressed.

Depressive disorder can be overlooked in the elderly if the diagnosis of major depressive disorder is made exclusively based on ICD or DSM-IV criteria. Symptoms suggestive of major depressive disorder in the elderly include:[134, *level 5;* 131, *level 5*]

- Psychomotor retardation
- Poor concentration
- Constipation
- Poor perceived health
- Prominent anxiety symptoms
- Cognitive deficits
- Prominent somatic symptoms

ASSESSMENT

Assessment is similar to the assessment of depression as mentioned earlier. Organic causes of depression need to be considered and appropriate laboratory investigations done when necessary (Appendix 5).

TREATMENT

Pharmacotherapy

Approximately 60-80% of the elderly with depression show good response to standard treatment.[135, *level 1*]

The data from 15 studies that included the elderly (providing data from more

than 1000 patients) shows that there is no difference in the efficacy or acceptability of the various antidepressants.[52, *level 1*] A systematic review by Wilson et al.[136, *level 1*] that included 17 trials showed that TCAs, SSRIs, and MAOIs were all effective in treating depression in the elderly. A systematic review by Mottram, Wilson & Strobl[137, *level 1*] that included 29 studies examined various antidepressants used for treating depression in the elderly. They found no difference in efficacy between SSRIs and TCAs.

With regards to continuing treatment, the evidence strongly suggests that it reduces the risk of relapse in the elderly.[52, *level 1*]

Caution is required when treating the elderly depressed patients with TCAs because of the side-effects profile. The main serious side-effects are the cardiac side-effects and pharmacodynamic interactions with other drugs.[138, *level 9*]

When prescribing antidepressants, take into consideration other factors associated with the elderly population, including the risk of drug-drug interactions with concomitant medications, and the increased risk of side effects.

Recommendation

- The elderly should be treated with antidepressants when necessary, with dosage adjustments for age where appropriate. **(Grade A)**
- SSRIs should be the first line antidepressants. **(Grade A)**

TREATMENT RESISTANT DEPRESSION

There are few studies on treatment resistant depression (TRD) among the elderly. Isolated studies show that venlafaxine (150-375mg/day) in combination with ECT,[139, *level 6*] addition of nortriptyline to SSRI,[140, *level 6*] and augmentation of lithium on nortriptyline[141, *level 6*] resulted in improvement of depressive symptoms.

PSYCHOLOGICAL INTERVENTIONS

In an overview of empirically validated treatments, Bartels et al.[142, *level 9*] concluded in the section on psychosocial treatments for geriatric depression that "In general, cognitive therapy, behavioral therapy, and cognitive-behavioral therapy have the greatest empirical support for effectiveness in the treatment of geriatric depression. A variety of other psychosocial interventions are likely to be efficacious including problem-solving therapy, interpersonal therapy, brief psychodynamic therapy, and reminiscence therapy."

NICE[52, *level 1*] concluded that there was insufficient evidence to determine if there was a clinically significant difference between CBT and antidepressants in reducing depression symptoms.

In a systematic review of the literature until November 2004, Frazer et al.[143, *level 1*] found evidence for the effectiveness of the following psychosocial interventions (among others) for depression in the elderly: CBT, psychodynamic psychotherapy and problem-solving therapy.

Recently, Pinquart et al.[144, *level 1*] conducted a meta-analysis of controlled studies involving a total of 5,328 elderly receiving pharmacotherapy or psychotherapy. In studies on major depression, pharmacotherapy and psychotherapy were similarly effective in decreasing observer-rated depression. The odds ratios for remission and response were also not significantly different for the two groups of interventions.

Recommendation

- Psychological interventions should also be offered to the elderly with depression. **(Grade A)**

ELECTROCONVULSIVE THERAPY

A Cochrane systematic review found that in elderly depression, real ECT is superior to simulated ECT.[145, *level 1*] Those who were given ECT had major improvement over those who were not given ECT.[97, *level 1*]

The elderly have an increased likelihood of having dementia and physical illness which may increase the risk of adverse effects due to ECT. Therefore, pre-ECT assessment is especially important. Anaesthetic consultation may be considered.[146, *level 9*]

Recommendation

- ECT is recommended if there is a life-threatening condition such as refusal to eat or high suicide risk due to the depressive illness. **(Grade B)**
- ECT may be considered:
  - For the acute treatment of moderate or severe depression for short-term therapeutic benefits. **(Grade A)**
  - To achieve rapid improvement of severe symptoms in major depression with or without psychotic features. **(Grade A)**
  - In treatment resistant depression. **(Grade B)**

EXERCISE THERAPY

There is evidence that exercise improves mood and reduces depression in elderly people.[143, *level 9*]

There is evidence that exercise reduces depressive symptoms in elderly patients who respond poorly to medication.[147, *level 3*]

Recommendation

- Elderly patients with mild to moderate depressive disorder can be recommended for exercise therapy. **(Grade A)**
- Exercise therapy can be prescribed as an adjunct to pharmacotherapy in the treatment of depression if agreeable to the patient. **(Grade B)**

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DSM-IV CRITERIA FOR MAJOR DEPRESSIVE EPISODE AND MAJOR DEPRESSIVE DISORDER

Major Depressive Episode

A. At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure.

Note : Do not include symptoms that are clearly due to general medical condition or mood-incongruent delusions or hallucinations

1. Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others)

3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day

4. Insomnia or hypersomnia nearly every day

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6. Fatigue or loss of energy nearly every day

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms are 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. hypothyroidism)

E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

Major Depressive Disorder - single episode

A. Presence of a single major depressive episode

B. The major depressive episode is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified

C. There has never been a manic episode, a mixed episode, or a hypomanic episode

Major Depressive Disorder - recurrent

A. Presence of two or more major depressive episodes (each separated by at least 2 months in which criteria are not met for a major depressive episode)

B. The major depressive episodes are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified

C. There has never been a manic episode, a mixed episode, or a hypomanic episode

Criteria or Severity/Psychotic/Remission Specifiers for Current (Or Most Recent) Major Depressive Episode

Mild : few, if any, symptoms in excess of those required to make the diagnosis and symptoms result in only minor impairment in occupational functioning or in usual social activities or relationships with others.

Moderate : symptoms or functional impairment between “mild” and “severe”.

Severe without psychotic symptoms : several symptoms in excess of those required to make the diagnosis, and symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

Severe with psychotic symptoms : delusions or hallucinations

In partial remission : symptoms of a major depressive episode are present but full criteria are not met, or there is a period without any significant symptoms of a major depressive episode lasting less than 2 months following the end of the major depressive episode.

In full remission : during the last 2 months, no significant signs or symptoms of the disturbance were present.

(Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition. Washington D.C.: American Psychiatric Association; 1994)

ICD-10 DIAGNOSTIC GUIDELINES FOR DEPRESSIVE EPISODE/DISORDER

Typical symptoms of depressive episodes

- Depressed mood
- Loss of interest and enjoyment
- Reduced energy

Common symptoms of depressive episodes

- Reduced concentration and attention
- Reduced self-esteem and self-confidence
- Ideas of guilt and unworthiness
- Bleak and pessimistic views of the future
- Ideas or acts of self-harm or suicide
- Disturbed sleep
- Diminished appetite

Mild depressive episode

- At least 2 typical symptoms plus 2 common symptoms
- No symptom should be present to an intense degree
- Minimum duration of whole episode is at least 2 weeks
- The person has some difficulty in continuing ordinary work and activities

Moderate depressive episode

- At least 2 typical symptoms plus 3 common symptoms
- Some symptoms may be present to a marked degree
- Minimum duration of whole episode is at least 2 weeks
- The person has considerable difficulty in continuing social, work or domestic activities

Severe depressive episode without psychotic symptoms

- All 3 typical symptoms plus at least 4 common symptoms
- Some of the symptoms are of severe intensity
- Minimum duration of whole episode is at least 2 weeks (may be <2 weeks if symptoms are very severe and of very rapid onset)
- The person is very unlikely to continue with social, work or domestic activities

Severe depressive episode with psychotic symptoms

- A severe depressive episode
- Delusions, hallucinations or depressive stupor are present

Recurrent depressive disorder

- Repeated depressive episodes (mild, moderate or severe)
- No history of independent manic episodes

Recurrent depressive disorder, current episode mild

- Fulfils criteria for recurrent depressive disorder
- Current episode fulfils criteria for mild depressive episode
- At least 2 episodes lasted a minimum of 2 weeks, and were separated by several months without significant mood disturbance

Recurrent depressive disorder, current episode moderate

- Fulfils criteria for recurrent depressive disorder
- Current episode fulfils criteria for moderate depressive episode
- At least 2 episodes lasted a minimum of 2 weeks, and were separated by several months without significant mood disturbance

Recurrent depressive disorder, current episode severe with/without psychotic symptoms

- Fulfils criteria for recurrent depressive disorder
- Current episode fulfils criteria for severe depressive episode with/without psychotic symptoms
- At least 2 episodes lasted a minimum of 2 weeks, and were separated by several months without significant mood disturbance

Recurrent depressive disorder, currently in remission

- Criteria for recurrent depressive disorder were fulfilled in the past
- Current state does not fulfill the criteria for a depressive episode of any severity, or of any other mood disorder
- At least 2 episodes lasted a minimum of 2 weeks, and were separated by several months without significant mood disturbance

(Adapted from the *ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization; 1992)

SUGGESTED ANTIDEPRESSANT DOSAGES AND ADVERSE EFFECTS [138, level 9; 148, level 9]

Name	Starting dose* (mg/day)	Usual dose range (mg/day)	Main adverse effects
Tricyclics and tetracyclics			
Amitriptyline	25-75	75-200	Sedation, often with hangover, postural hypotension, tachycardia/arrhythmia, dry mouth, blurred vision, constipation, urinary retention.
Clomipramine	10-75	75-150	
Dothiepin	50-75	75-225	
Imipramine	25-75	75–200 (up to 300 mg for in-patients)	As above but less sedative.
Mianserin	30	30–90	Sedation, rash, rarely blood dyscrasia, jaundice, arthralgia. No anticholinergic effects. Sexual dysfunction uncommon. Low cardiotoxicity.
Maprotiline	25-75	75–150 (up to 225 mg for in-patients)	Sedation, dry mouth, constipation, tiredness, sleep disturbance, rash.
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Citalopram	20	20–40 (60)	Nausea, vomiting, dyspepsia, abdominal pain, diarrhea, rash, sweating, agitation, anxiety, headache, insomnia, tremor, sexual dysfunction (male & female), hyponatraemia, cutaneous bleeding disorder. Discontinuation symptoms may occur.
Escitalopram	10	10–20	
Sertraline	50	50−200	
Paroxetine	20	20–40 (60)	As for citalopram but antimuscarinic effects and sedation more common. Extrapyramidal symptoms more common, but rare.
Fluoxetine	20	20	As for citalopram but insomnia, agitation and rash more common. May alter insulin requirements.
Fluvoxamine	50-100	100–200 (max 300)	As for citalopram but nausea more common.

Name	Starting dose* (mg/day)	Usual dose range (mg/day)	Main adverse effects
Reversible Inhibitor of MAO-A (RIMA)			
Moclobemide	150	150–600	Sleep disturbances, nausea, agitation, confusion. Hypertension reported – may be related to tyramine ingestion.
Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)			
Venlafaxine, extended release	37.5-75	75–225 (up to 375mg/ day in severe depression)	Nause, insomnia, dry mouth, somnolence, dizziness, sweating, nervousness, headache, sexual dysfunction. Elevation of blood pressure at higher doses.
Duloxetine	40–60	60 (max 120)	Nausea, insomnia, dizziness, dry mouth, somnolence, constipation, anorexia. Very small increase in heart rate and blood pressure, probably clinically insignificant.
Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)			
Mirtazapine	15	15–45	Increased appetite, weight gain, drowsiness, oedema, dizziness, headache, blood dyscrasia. Nausea/sexual dysfunction relatively uncommon.
Selective Serotonin Reuptake Enhancer (SSRE)			
Tianeptine	37.5	37.5	Dry mouth, constipation, dizziness/syncope, drowsiness, postural hypotension, insomnia, nightmares.

***** Lower starting doses are recommended for elderly patients and for patients with significant anxiety, hepatic disease, or medical co-morbidity.

FACTOR SUGGESTING THE NEED FOR MAINTENANCE MEDICATION [5, level 9; 57, level 9]

1. Three or more episodes of major depression.

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.

3. Residual symptoms.

4. Co-morbid dysthymic disorder, substance abuse or anxiety disorders.

ORGANIC CAUSES OF DEPRESSION IN THE ELDERLY

Causes of Organic (Symptomatic or Secondary) Depression[149, *level 6*]

Occult carcinoma
Lung, pancreas

Metabolic/endocrine
Hypothyroidism, hypercalcaemia, Cushing's disease

Drugs
Steroids, beta-blockers, methyldopa, clonidine, nifedipine, digoxin, L-dopa, tetrabenazine

Infection
Post-viral, myalgic encephalomyelitis, brucellosis, neurosyphilis

Organic brain disease
Space occupying lesion, dementia, Parkinson's disease

Laboratory Investigations
Particular emphasis is given to laboratory investigations for the elderly presenting with depressive symptoms. It is recommended that the following laboratory investigations are done in late life depression.[149, *level 6*]

Investigation	First episode	Recurrence
Full blood count	Yes	Yes
Urea & Electrolytes	Yes	Yes
Calcium	Yes	If Indicated
Thyroid Function	Yes	If indicated or more than 12 months
B_{12}	Yes	If indicated or more than 2 years
Folate	Yes	If Indicated by nutritional state
Liver Function	Yes	If Indicated (e.g. alcohol abuse)
Syphilitic serology	If clinically indicated	If indicated, if not done
CT Brain	If clinically indicated	Only if neurologically indicated
EEG	If clinically indicated	Only if neurologically indicated

LIST OF ABBREVIATIONS

BDI	-	Beck Depression Inventory
CBT	-	Cognitive behavioural therapy
CCBT	-	Computerised cognitive behavioural therapy
CGI	-	Clinical Global Impression scale
DSM-IV	-	Diagnostic and Statistical Manual of Mental Disorders – IV
ECT	-	Electroconvulsive therapy
ICD-10	-	International Classification Of Diseases, 10th revision
IPT	-	Interpersonal therapy
MAOI	-	Monoamine oxidase inhibitor
MDD	-	Major depressive disorder
RCT	-	Randomised controlled trial
SSRI	-	Selective serotonin reuptake inhibitor
SJW	-	St John's Wort
TCA	-	Tricyclic antidepressant
TRD	-	Treatment resistant depression
NICE	-	National Institute for Clinical Excellence
APA	-	American Psychiatric Association

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LEVELS OF EVIDENCE SCALE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4	Good to Fair	Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports anecdotes

SOURCE : ADAPTED FROM THE CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT & RESEARCH, (CAHTAR) SPAIN

GRADES OF RECOMMENDATIONS

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE : MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)