Guidelines For the Management of Major Depressive Disorder
University of Louisville Depression Center

Statement of Purpose

The purpose of this document is to provide a general framework for the management of major depression. This framework takes into account the quality of evidence supporting different treatment approaches, focusing primarily on controlled clinical trials. The philosophy underlying this approach will involve incorporating a collaborative model that respects a patient's believe system and integrates the patient's support system and community partners in a multidisciplinary fashion. The original Institute of Medicine report on evidence based practice, however, defined "evidence" as the combined data from research studies, patient preference, and accumulated clinical wisdom. These guidelines are provided with full realization that there is no single approach that is appropriate for all patients with this illness. Additionally, it is recognized that physicians will utilize insights and experience that cannot be quantified nor categorized which can improve outcome. These guidelines are to be implemented as a resource for evidence-based approaches to treatment of major depression, but should not be used as a constraint to the psychiatrist's clinical decision making with any individual patient. This document is intended for use as a supplement to the American Psychiatric Association Practice Guidelines. It provides an updated and succinct guideline for treatment of major depression.

Utilization of Guidelines

The guidelines are divided into diagnosis- and state-based treatment approaches. Both the patient's diagnosis and current disease state need to be taken into account to provide optimal treatment. The data are presented in the approach of a "menu of reasonable choices"

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General Principles

The general approach for decision making in treatment of psychiatric patients is presented in Figure 1 (Sachs 2006).** In this scheme, an initial Critical Decision Point arises due to illness factors (e.g., onset of a mode episode, or resolution of a mood episode). The clinician integrates both evidence-based choices with individual patient factors that may modify those choices or help determine which is the most reasonable choice. The patient is then presented with the choice or possible choices, educated regarding the evidence, and a collaborative decision is reached. The choice is implemented and outcome

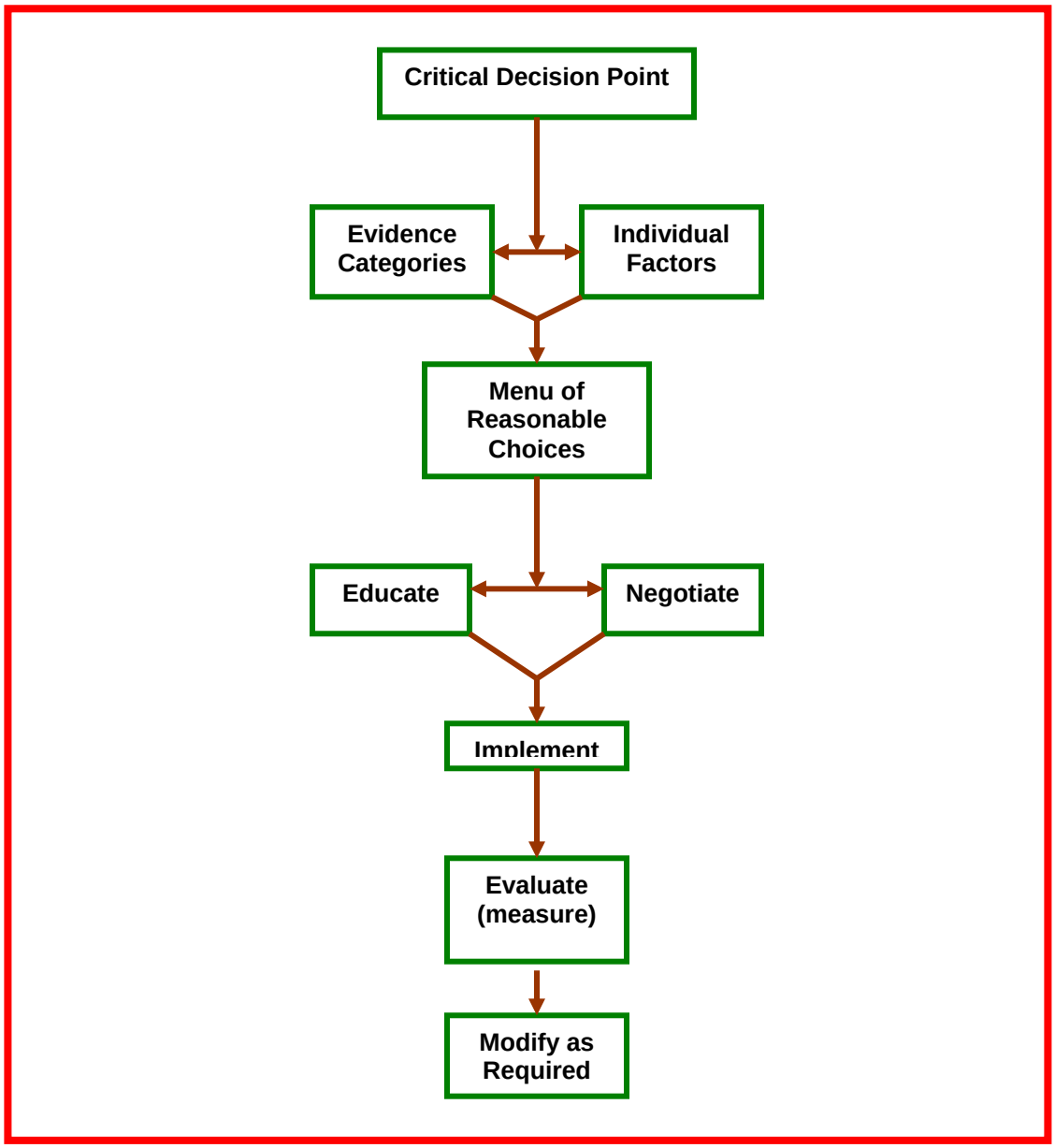
measured in a mutually agreed on predetermined method (e.g., target symptoms). Ongoing evaluation of how these goals are being met determines ongoing treatment decisions.

Quality of data supporting clinical decisions is based upon study design. The rating system for quality of studies is presented in Table 1 (based on Sachs 2006). Because available data are primarily from randomized, controlled trials (RCTs) of treatment with antidepressants, it is recognized that the value of a variety of psychotherapies, some of which have had limited or no testing the RCTs, may not be fully recognized in this system of rating the quality of evidence. Accumulated clinical wisdom indicates that a variety of psychotherapies may be helpful in treatment of depression. Combining psychotherapy with pharmacotherapy is a reasonable choice for treatment of depression, with an emerging view that combined treatment as an initial approach produces better outcomes in general.. Monotherapy with psychotherapy is supported best for therapies that have had demonstrated evidence of efficacy in RCTs, although a vast amount of clinical experience provides support for forms of psychotherapy, such as supportive or psychodynamic, with a less extensive base of RCT's.

Table 1. Rating of quality of evidence (A is highest, F is lowest) (Sachs 2006)

Rating	Definition
A	More than 1 placebo controlled study
B	Blinded active comparator study
C	Open comparator study
D	Uncontrolled observations (e.g., case series)
E	No published evidence or single case reports
F	Negative evidence

Figure 1. Scheme for decision making in the treatment of major depression.



General Background

Major depression is a common illness. In the National Comorbidity Survey –Replication study the lifetime prevalence of major depressive disorder (MDD) was 16.2% (95% confidence interval [CI], 15.1-17.3) (32.6-35.1 million US adults) and the 12-month prevalence was 6.6% (95% CI, 5.9-7.3) (13.1-14.2 million US adults) (Kessler et al. 2003, 2005). Of these cases, the severity was defined as mild in 10.4%, moderate in 38.6%, severe in 38.0%, and very severe in 12.9% (Kessler et al 2003, 2005). The average duration of a major depressive episode is 16 weeks (95% CI, 15.1-17.3) (Kessler et al 2003). However, dysfunction is substantial with 59.3% of patients experiencing severe or very severe role

impairment (Kessler et al 2003). Globally, MDD is the fourth leading cause of disability (World Health Organization 2001). Additionally, suicide is a major cause of morbidity in depressed patients with estimates that vary widely (Kessler et al 2005). There are over 30,000 suicides in the USA each year (Center for Disease Control and Prevention, 2006).

The effect of psychopharmacological treatment on both dysfunction and suicide has been controversial (Simon 2006). Most recently, the Food and Drug Administration has found that antidepressant treatment doubles the rate of significant suicide ideation in young people compared to placebo. These findings have led to a "black box" warning regarding possible increases in suicidal ideation in children, adolescents, and young adults treated with antidepressants. However, other reports have suggested that the overall suicide attempt rate in this population went down during previous years in which antidepressants were used more heavily, and that the "black box" warning may have led to a decreased use of antidepressants and a concomitant rise in suicide attempts in younger persons. CBT has been shown to reduce the risk of subsequent suicide attempts by about 50%, and thus is an especially useful treatment for depressed patients with suicidal ideation (Brown et al, 2005). The finding of a positive effect of CBT on suicidality is a strong reason for including this form of treatment in a comprehensive approach to depression.

Acute Phase Treatment of Major Depressive Disorder (MDD)

There is general agreement that utilization of an antidepressant agent is a first line treatment. Evidence based psychotherapies, including cognitive-behavior therapy (CBT) and interpersonal therapy (IPT) have also been found to be effective in multiple RCTs and can be used as first line treatments, either alone or with pharmacotherapy (Blackburn et al, 1986; Simons et al, 1986; Hollon et al, 1992, 2005; DeRubeis et al, 199, 2005; Elkin et al, 1989). Further, psychodynamic and supportive psychotherapies, based on a substantial amount of accumulated clinical wisdom, and clinical trials (such as the 30 year Menninger Psychotherapy Research Project by Robert Wallerstein, et al., (1989), as well as a meta-analytic study of psychodynamic psychotherapy by Luborsky et al (1993), and meta-analyses by Leichsenring, et al (2005, 2006) are also reasonable treatments to consider. There are a multitude of antidepressant medications which can be used in the treatment of major depression (Table 2). Full remission (i.e., total resolution of depressive symptoms) is an important goal in the treatment of major depression (Fava et al 2007). Patients who do not reach full remission have a higher rate of relapse.

Table 2. Menu of reasonable choices for acute phase treatment of major depression

Intervention	Quality of Supportive Evidence	Comment
Any FDA approved antidepressant	A	Specific serotonin reuptake inhibiting (SSRI), buproprion, and newer serotonin and norepinephrine reuptake inhibiting agents (SNRI) are felt to be safer. Older agents (tricyclic antidepressants and monoamine oxidase inhibitors) are generally seen as 2nd or 3rd line agents.
Psychotherapy with forms of treatment that have been demonstrated to be efficacious in multiple trials (CBT, IPT)	A	Severe depression is generally believed to be an indication for pharmacotherapy, although a meta-analysis of available data found CBT to be no less effective than medication for severe depression.
Alprazolam	A	Despite a well-designed short-term study showing acute efficacy (Rickels et al. 1987), this treatment option is not recommended. Alprazolam and other benzodiazepines have been shown to impair learning and interfere with the effects of psychotherapy.
ECT	B	Generally not seen as first-line. May be considered for first line treatment for very severe depression with psychotic features and/or intense suicidality. ECT can be

		highly effective for these types of patients.
Psychodynamic and supportive psychotherapy	C	These therapies are typically used in combination with pharmacotherapy for acute phase treatment of MDD.

Inadequate Response to First Option

A multitude of strategies have been recommended after failure of the first option, but there is a dearth of data that support one option over another. The STAR*D trial (Rush et al., 2006) found no evidence that one approach was superior to others. Most experts recommend the following general steps for inadequate response to an initial antidepressant: (1) raise dose of first agent; (2) switch to another antidepressant (there is no evidence that switch to a different class is superior to switch within class). Also, evidence based psychotherapy can be added at any point if not used initially. A recent meta-analysis by Friedman et al. (2006) found added benefit for combined CBT and pharmacotherapy over either treatment individually. There is, in addition to a wealth of clinical experience, an emerging consensus that combined medication and any form of psychotherapy as an initial treatment, may, for many patients, produce a greater response to treatment, and a longer period of symptom relief once treatment has ended.

The menu of reasonable choices in presented in Table 3.

Table 3. Menu of reasonable choices of the treatment of depression following an inadequate response to the initial intervention.

-Intervention	Quality of Supportive Evidence	Comment
Replace agent with another antidepressant with a different mechanism	B	
Add evidenced based psychotherapy (CBT, IPT)	B	
Replace agent with another antidepressant with the same mechanism	B	2D6 polymorphisms may explain why some patients are unresponsive to one SSRI and respond to another.

Treatment Resistant Depression

Treatment resistant depression has several definitions. For the purpose of these guidelines, if a person has failed at least two adequate trials of

antidepressant treatment (adequate dose for adequate duration of at least 4 weeks), they are defined as treatment resistant. Table 4 lists options for such patients. It should be remembered that there are many approaches to treatment resistant depression, and no specific approach has been documented as superior. The largest and most influential study of treatment resistant depression, the STAR*D trial (Rush et al., 2006) found no significant differences between options such as lithium, thyroid, or buspirone augmentation. All had some efficacy, but a declining percentage of patients (i.e., 36.8%, 30.6%, 13.7%, and 13.0% for steps 1-4) remitted at each subsequent step of the study.

G Fava and others (Fava et al., 1998, 2004, 2007; Keller et al., 2000) have demonstrated efficacy for CBT in treatment resistant depression. Also, a very large trial of CBT (a form of CBT termed the "Cognitive-behavioral Analysis System of Psychotherapy") for chronic depression found that CBT and nefazadone had the same response rates (about 55%) but combined treatment led to a much higher response (85%) (Keller et al., 2000). The STAR*D trial found no difference between CBT and pharmacotherapy for patients who failed to respond to initial treatment with citalopram (Thase et al., 2008).

Table 4. Menu of reasonable choices for treatment resistant depression

Intervention	Quality of Supportive Evidence	Comment
Add another antidepressant	A	
Add lithium, to antidepressant(s)	A	
Add aripiprazole or olanzapine to antidepressant(s)	A	
Add thyroid hormone to antidepressant(s)	A	
Add buspirone to antidepressant(s)	A	
Add CBT or IPT	B	
Add or switch to TCA	B	
Switch to MAOI	B	
ECT	B	Generally reserved for severe depression or several antidepressant failures
VNS	C	The initial study failed to show a difference, but comparative studies show that VNS may be effective
Add divalproex or other anticonvulsant to	C	

antidepressant(s)		
Add or replace antidepressants with stimulant	D	
Add pindolol, add antipsychotic other than olanzapine or aripiprazole	D	
Add psychotherapy other than CBT or IPT (e.g., psychodynamic therapy)	D	

Maintenance Treatments

There is significant evidence that continuation of antidepressants that have been effective acutely will be effective in prevention of relapse. For a single episode of major depression, ongoing treatment with an antidepressant is recommended for at least 6-9 months. If there is a history of multiple episodes, longer maintenance therapy or indefinite maintenance therapy is advised.

CBT has been shown to have efficacy in relapse prevention which is superior to pharmacotherapy when both treatments are discontinued (Simons et al., 1986, Blackburn et al.; Hollon et al., 2005). Also, continuation CBT (with booster sessions) has been shown to be superior to standard CBT (5-20 sessions) in relapse prevention (Jarrett et al., 2001). Thus, CBT offers an effective option for patients who do not want long-term maintenance therapy with antidepressants or may want to learn specific skills that help forestall relapse.

Table 5. Menu of reasonable choices for the maintenance treatment of depression.

Intervention	Quality of Supportive Evidence	Comment
Any FDA approved antidepressant	A	SSRI better than placebo for 18-14 months (Lėpine et al. 2004; Reynolds et al. 2006; Franchini et al. 1999). The prophylactic effect of the SNRI agent, venlafaxine, has been shown to extend to at least 2 years (Keller et al. 2007).
CBT	A	Continuation CBT beyond acute phase treatment has been shown to reduce relapse rate
Maintenance ECT	C	

Treatment of Major Depression with Psychotic Features

Major depression with psychotic features (commonly referred to as psychotic depression) is a form of major depression in which delusions and/or hallucinations are present, in addition to other symptoms which meet diagnostic criteria for depression. Usually, the depressive symptoms are quite severe. Delusions are more common than hallucinations and usually (although not always) embody depressive themes. Paranoid delusions, delusions of guilt or punishment, or somatic delusions are common in psychotic depression. Some patients have fixed nihilistic or negative thoughts which can be appreciated as a subtle form of delusion. Psychosis can also occur is schizophrenia, schizoaffective disorder, delusional disorder, substance abuse disorders, delirium, dementia, or other conditions. Bipolar patients may experience psychotic symptoms in either the depressive or manic phase of illness. The risk of suicidal behavior, or destructive behavior related to impaired judgment, is elevated in patients suffering from psychotic depression.

Recommended treatment usually involves a combination of antidepressant and antipsychotic medications. Patients with fail to respond may be candidates for ECT, which is considered a particularly effective treatment for psychotic depression (especially when catatonic symptoms are present). ECT may also be considered as a first line therapy for patients who have responded to it in the past, or who are highly agitated, extremely suicidal, or have catatonic symptoms.

Other Considerations

Several new treatment options are emerging for major depression. These include transcranial magnetic stimulation (TMS, approved by FDA) and cranial electrical stimulation (also known as alpha-stimulation or alpha-stim) and Additionally, there are other options that may be reasonable early agents that have not been addressed here. For example, pramipexole is a dopamine agonist that has level C supportive evidence. Deep brain stimulation with implanted electrodes is being used on an experimental basis.

Treatment for Geriatric Depression

Depression is a common condition in old age. This is particularly true in medically ill or nursing home populations. Elders may emphasize anxiety or physical symptoms such as fatigue, insomnia, and aches and pains, contributing to under-diagnosis. Conversely, depression is more common among medically ill patients, including dementia, neurological diseases, stroke, cancer, and cardiovascular diseases. Depression in the elderly is more common among women, but suicide risk is especially high among elderly men. “Failure to thrive” syndromes with weight loss and loss of function often involve depression. Depression and dementia commonly co-exist. It is important to consider the possibility of a treatable depressive disorder when evaluating a case of cognitive impairment. While grief reactions are a normal aspect of loss, clinical depression

may be suspected when the grief reaction is unusually prolonged, severe, or disabling.

Major depression in old age is treatable, even when co-morbid with other disorders. Medication therapies center on the SSRI and SNRIs. TCA or MAOI are used only in very resistant cases. Elders are sensitive to side effects, and dosing is advised to cautious and gradual. Some antidepressants have cytochrome p450 or protein binding effects, contributing to potential drug-drug interactions. This may be an important consideration given the large number of drugs taken by elders. Geriatric specialists try to avoid polypharmacy whenever possible. ECT is considered a useful alternative in severe or persistent cases. A collaborative or team approach is usually best for very elderly, demented, or frail patients. Despite advanced age, many elderly patients can benefit from psychotherapies which range from supportive, psycho-educational approaches to CBT.

Management of Perinatal Depression

Methods of treating perinatal mood disorders are discussed in:

Burt VK: Major depression during pregnancy: Implications of illness and treatment considerations. Women's Health in Psychiatry, Nov-Dec 2006:7-14 Stowe ZN, Ragan K: ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologist April 2008;111(4):1001-1020

Wisner KL, Zarin DA, Holmboe ES, Appelbaum PS, Gelenberg AJ, Leonard HL, Frank E: Risk-benefit decision making for treatment of depression during pregnancy. Am J Psychiatry 2000;157:1933-1940

Treatment of Mood Disorders in Children and Adolescents

See separate guidelines for children and adolescents.

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