ICSI
Institute for Clinical Systems Improvement

Health Care Guideline:

Adult Depression in Primary Care Guideline

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM) is a classification of mental disorders with associated criteria designed to facilitate more reliable diagnoses of these disorders. With successive editions over the past 60 years, it has become a standard reference for clinical practice in the mental health field. In May 2013, the most recent edition, DSM-5, was published. It is the product of more than 10 years of effort by hundreds of international experts in all aspects of mental health.

The sixteenth edition of the Adult Depression in Primary Care Guideline uses DSM-5 as a reference. Throughout the guideline, both ICD-9-CM codes and ICD-10-CM codes are identified (the latter scheduled for adoption in October 2014). This reflects how DSM-5 classifications of mental health disorders were harmonized with the World Health Organization's *International Classification of Diseases* (ICD).

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Health Care Guideline

Adult Depression in Primary Care

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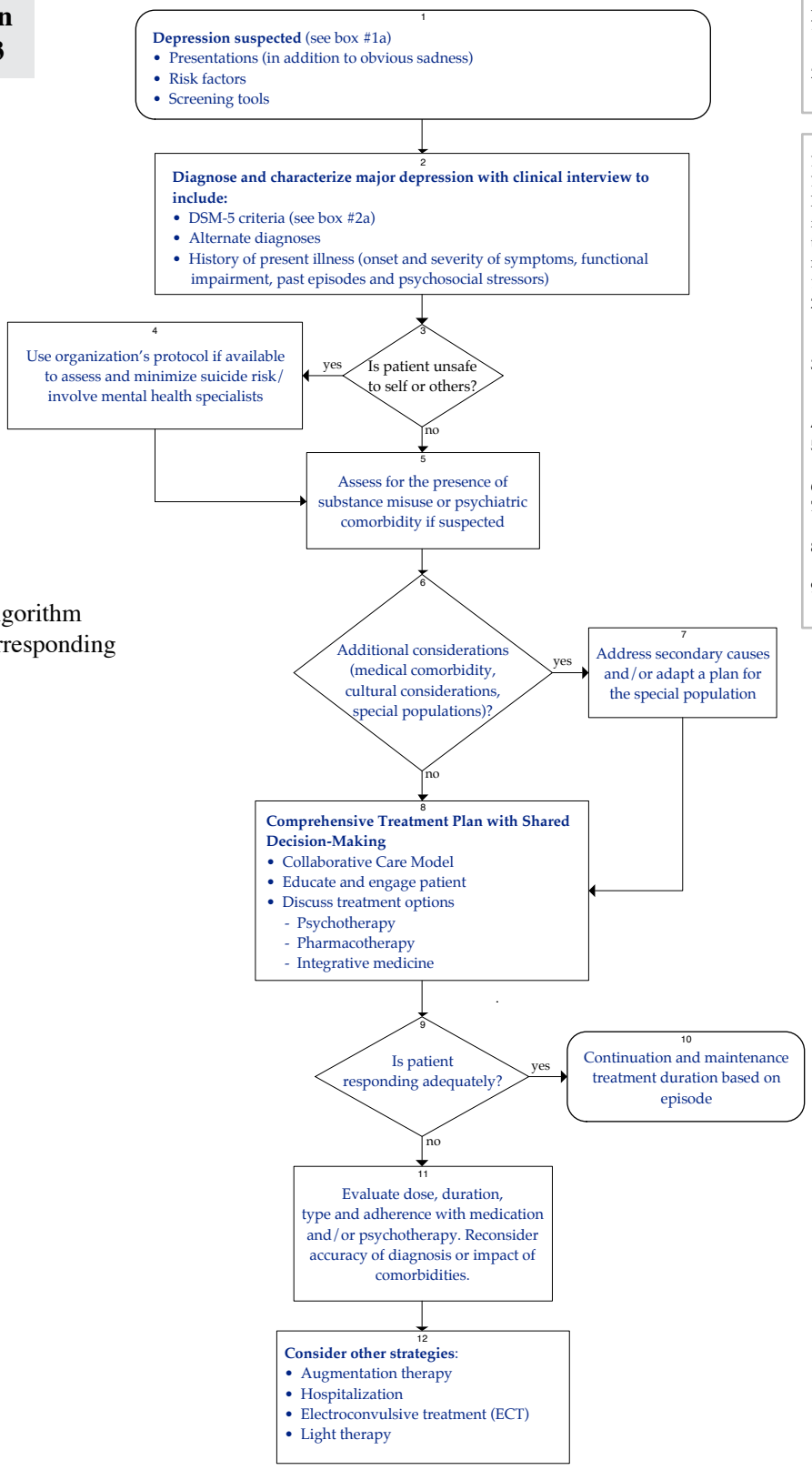
Health Care Guideline:
Adult Depression in Primary Care

Sixteenth Edition
September 2013

Text in blue in this algorithm indicates a linked corresponding annotation.



1a
The two-question screen:
Over the past two weeks have you been bothered by:
1. Little interest or pleasure in doing things?
2. Feeling down, depressed or hopeless?

2a
DSM-5 Criteria for Major Depressive Episode:
Must have a total of 5 symptoms for at least 2 weeks. One of the symptoms must be depressed mood or loss of interest.
1. Depressed mood
2. Markedly diminished interest or pleasure in all or almost all activities
3. Significant (> 5% body weight) weight loss or gain, or increase or decrease in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feeling of worthlessness or inappropriate guilt
8. Diminished concentration or indecisiveness
9. Recurrent thoughts of death or suicide

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Evidence Grading

Literature Search

A consistent and defined process is used for literature search and review for the development and revision of ICSI guidelines. The literature search was divided into two stages to identify systematic reviews, (stage I) and randomized controlled trials, meta-analysis and other literature (stage II). Literature search terms used for this revision are below and include literature acupuncture and yoga, persistent depressive disorder, anxiety, panic disorder, psychotherapy, pain, diabetes and heart failure in depressed patients January 2012 through December 2012.

GRADE Methodology

GRADE has advantages over other systems including the current system used by ICSI. Advantages include:

- developed by a widely representative group of international guideline developers;
- explicit and comprehensive criteria for downgrading and upgrading quality of evidence ratings;
- clear separation between quality of evidence and strength of recommendations that includes a transparent process of moving from evidence evaluation to recommendations;
- clear, pragmatic interpretations of strong versus weak recommendations for clinicians, patients and policy-makers;
- explicit acknowledgement of values and preferences; and
- explicit evaluation of the importance of outcomes of alternative management strategies.

Category	Quality Definitions	Strong Recommendation	Weak Recommendation
High Quality Evidence	Further research is very unlikely to change our confidence in the estimate of effect.	The work group is confident that the desirable effects of adhering to this recommendation outweigh the undesirable effects. This is a strong recommendation for or against. This applies to most patients.	The work group recognizes that the evidence, though of high quality, shows a balance between estimates of harms and benefits. The best action will depend on local circumstances, patient values or preferences.
Moderate Quality Evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	The work group is confident that the benefits outweigh the risks but recognizes that the evidence has limitations. Further evidence may impact this recommendation. This is a recommendation that likely applies to most patients.	The work group recognizes that there is a balance between harms and benefits, based on moderate quality evidence, or that there is uncertainty about the estimates of the harms and benefits of the proposed intervention that may be affected by new evidence. Alternative approaches will likely be better for some patients under some circumstances.
Low Quality Evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain.	The work group feels that the evidence consistently indicates the benefit of this action outweighs the harms. This recommendation might change when higher quality evidence becomes available.	The work group recognizes that there is significant uncertainty about the best estimates of benefits and harms.

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Recommendations Table

The following table is a list of evidence-based recommendations for the Adult Depression in Primary Care guideline.

Note: Other recommendation language may appear throughout the document as a result of work group consensus but is not included in this evidence-based recommendations table.

Topic	Quality Of Evidence	Recommendations	Strength of Recommendation	Annotation Number	Relevant References
Suspect and screen for major depression	Low	Clinicians should use a standardized instrument to screen for depression if it is suspected based on risk factors or presentation.	Strong	1	*Kroenke, 2010; Duffy, 2008; Gilbody, 2006; Rush, 2003*
Diagnose and characterize major depression	Guideline	Clinicians should use the DSM-5 criteria to determine a diagnosis of major depression, persistent depressive disorder, and unspecified depressive disorder.	Strong	2	*DSM-5 American Psychiatric Association, 2013*
Comorbidites, cultural and special populations	Low	Clinicians should assess and treat for depression in patients with some comorbidities.	Strong	6	*Kozhimmanil, 2009; Egede, 2008; Trivedi, 2006; Katon, 2004; Ciechanowski, 2000*
		Clinicians should acknowledge the impact of culture and cultural differences on physician and mental health.	Strong	6	*Karasz, 2005; Muñoz, 2005; Miranda, 2004*
		When using pharmacotherapy in elderly patients, the clinician should carefully consider how the metabolism of the drug may be affected by physiologic changes, their comorbid illnesses and the medications used for them.	Strong	6	*Cuijpers, 2008*
		Clinicians should screen and monitor depression in pregnant and post-partum women.	Strong	6	*Yonkers, 2009; Vesga-Lopez, 2008; Gjerdingen, 2007; Gaynes, 2005*

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Topic	Quality Of Evidence	Recommendations	Strength of Recommendation	Annotation Number	Relevant References
Comprehensive treatment plan	High	A collaborative care approach is recommended for patients with depression in primary care.	Strong	8	*Katon, 2008; Hunkeler, 2006; Unützer, 2006; Gilbody, 2006; Unützer, 2002; Katon, 1999;*
Active patient engagement and shared decision-making	Low	A written and mutually agreed-upon treatment plan engaging the patient and family is recommended.	Strong	8	*Bower, 2013; Baik, 2010; Adams, 2007; Loh, 2006; Hamann, 2005*
Medications, psychotherapy, physical activity	Low	Clinicians should provide antidepressant medications and/or referral for psychotherapy as treatment for major depression.	Strong	8	*American Psychiatric Association, 2013; Vollestad, 2011; Dimidjian, 2006; DeJonghe, 2004; Brown, 2000*
Establish follow-up plan. Use of PHQ-9 as monitor and management tool	Low	Clinicians should establish and maintain follow-up with patients.	Strong	8	*Trivedi, 2009; Trivedi, 2006; Löwe, 2004; Unützer, 2002; Duffy, 2000; Hunkeler, 2000; Simon, 2000*

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Foreword

Introduction

The U.S. Preventive Services Task Force (USPSTF) recommends routine depression screening for all adults and adolescents (age 12-18) but only in clinical practices that have systems in place with care management, staff assistance or mental health specialist involvement to assure accurate diagnosis, effective treatment and follow-up *(O'Connor, 2009 [Systematic Review])*. Furthermore, the American College of Preventive Medicine (ACPM) supports this recommendation and adds that all primary care practices should have such systems of care in place *(Nimalasuriya, 2009 [Low Quality Evidence])*. The purpose of this guideline is to assist ICSI members to develop systems that support effective diagnosis and treatment of major depression.

A reasonable way to evaluate whether a system is successfully functioning in its diagnosis, treatment and follow-up of major depression would be to consider the following:

1. **Diagnosis**: The clinic or medical group should have a reliable process for routine evaluation and documentation of DSM-5 criteria for major depression.
2. The clinic or medical group should have a systematic way to provide and document:
    a. **Engagement Education:** The patient and his/her family are actively engaged and participating in self-management, based on knowledge of the nature of the disease, risk/benefits of treatment options, and consideration of patient preferences.
    b. **Ongoing Contacts:** A documented system to assure ongoing contacts with the patient during the first 6 to 12 months of care (scheduled follow-up appointments, phone calls and some way to react and/or reach out if the patient drops out of treatment) based on use of a standardized, objective tool used at each contact to document and track treatment response.
3. **Outcomes:** The system should have a way to reliably and consistently monitor outcomes of individuals and to improve systemwide individual care and the effectiveness of the clinical practice overall.

Importance of Major Depression Focus in Primary Care

Major depression is a treatable cause of pain, suffering, disability and death, yet primary care clinicians detect major depression in only one-third to one-half of their patients with major depression *(Williams Jr, 2002 [Low Quality Evidence]; Schonfeld, 1997 [Low Quality Evidence])*. Additionally, more than 80% of patients with depression have a medical comorbidity *(Klinkman, 2003 [Low Quality Evidence])*. Usual care for depression in the primary care setting has resulted in only about half of depressed adults getting treated *(Kessler, 2005 [Low Quality Evidence])* and only 20-40% showing substantial improvement over 12 months *(Unützer, 2002 [High Quality Evidence]; Katon, 1999 [High Quality Evidence])*. Approximately 70-80% of antidepressants are prescribed in primary care, making it critical that clinicians know how to use them and have a system that supports best practices *(Mojtabai, 2008 [Low Quality Evidence])*.

At any given time, 9% of the population has a depressive disorder, and 3.4% has major depression *(Strine, 2008 [Low Quality Evidence])*. In a 12-month time period, 6.6% of the U.S. population will have experienced major depression, and 16.6 % of the population will experience depression in their lifetime *(Kessler, 2005 [Low Quality Evidence])*.

Additionally, major depression was second only to back and neck pain for having the greatest effect on disability days, at 386.6 million U.S. days per year *(Merikangas, 2007 [Low Quality Evidence])*.

In another WHO study of more than 240,000 people across 60 countries, depression was shown to produce the greatest decrease in quality of health compared to several other chronic diseases. Health scores worsened when depression was a comorbid condition, and the most disabling combination was depression and diabetes *(Moussavi, 2007 [Low Quality Evidence])*.

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A recent study showed a relationship between the severity of depression symptoms and work function. Data was analyzed from 771 depressed patients who were currently employed. The data showed that for every 1-point increase in PHQ-9 score, patients experienced an additional mean productivity loss of 1.65%. And, even minor levels of depression symptoms were associated with decrements in work function *(Beck, 2011 [Low Quality Evidence])*.

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Scope and Target Population

The purpose of this guideline is to assist primary care in developing systems that support effective assessment, diagnosis and ongoing management of initial and recurrent major depression and persistent depressive disorder in adults age 18 and over, and assist patients to achieve remission of symptoms, reduce relapse and return to previous level of functioning. This guideline does not address the pediatric population. Diagnoses outside the scope of this guideline include adjustment disorder and bipolar disorder.

This guideline is an evidence-based document based on best care; it has also evolved to include information on best-practice systems for implementation. A system that has embedded the elements of best practice and has capacity to effectively manage the volume should consider routine screening of all patients, based on the recommendations of the U.S. Preventive Services Task Force. Depending on resources and systems, a group or clinic might also consider an interim plan of screening high-risk patients such as those with diabetes, cancer, chronic pain, coronary artery disease and post-stroke, all perinatal patients, as well as those with a history of previous depression.

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Aims

The aims and measures in this guideline are based upon evidence supporting impact of system elements and process elements, and promoting actual symptom and functional patient improvement and outcomes, and are aligned with MN Community Measurement and the DIAMOND Initiative where there is overlap.

1. Increase the percentage of patients accurately diagnosed with major depression or persistent depressive disorder. *(Annotations #1, 2)*
2. Decrease the number of completed suicides in patients with major depression or persistent depressive disorder managed in primary care. *(Annotation #4)*
3. Increase the percentage of patients with major depression or persistent depressive disorder who are assessed for the presence and severity (mild to moderate, moderate to high) and dependent on substance misuse. *(Annotation #5)*
4. Increase the assessment for major depression or persistent depressive disorder of primary care patients presenting with additional high-risk conditions such as diabetes, cardiovascular disease, post-stroke, chronic pain and all perinatal women. *(Annotation #6, 11)*
5. Improve communication between the primary care physician and the mental health care clinician (if patient is co-managed). *(Annotations #4, 8, 12)*
6. Increase the percentage of patients with major depression or persistent depressive disorder who have improvement in outcomes from treatment for major depression or persistent depressive disorder. *(Annotations #8, 9)*
7. Increase the percentage of patients with major depression or persistent depressive disorder who have a follow-up to assess of response to treatment. *(Annotations #8, 10)*

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Clinical Highlights

- A reasonable way to evaluate whether a system is successfully functioning in its diagnosis, treatment plan and follow-up of major depression is to consider:
  - how well the diagnosis is documented,
  - how well the treatment team engages and educates patients/families,
  - how reliably the ongoing patient contacts occur and response/remission to treatment are documented, and
  - how well the outcomes are measured and documented.

  (Introduction; Annotations #1, 2, 8, 9, 10; Aims #1, 6, 7)
- Use a standardized instrument to document depressive symptoms. Document baseline symptoms and severity to assist in evaluating future progress, including response and remission rates. *(Annotations #1, 2; Aims #1, 3)*
- Additional considerations that should be taken into account:
  - Patients with a high risk of common comorbid depression conditions such as substance misuse, diabetes, cardiovascular disease and chronic pain should be screened for depression.
  - Perinatal depression treatment should involve a thorough risk-benefit assessment in order to minimize the risks of both depression and its treatment to the mother and child.
  - Older persons and the cultural experiences of patients should receive special considerations regarding risk, assessment and treatment of depression.

  (Annotation #6; Aim #3)
- Antidepressant medications and/or referral for psychotherapy are recommended as treatment for major depression. Factors to consider in making treatment recommendations are symptom severity, presence of psychosocial stressors, presence of comorbid conditions, and patient preferences. Physical activity and active patient engagement are also useful in easing symptoms of major depression. *(Annotation #8; Aim #6)*
- If the primary care clinician is seeing incremental improvement, continue working with the patient to increase medication dosage or augment with psychotherapy or medication to reach remission. This can take up to three months. Studies have shown that depression can be treated successfully in primary care. *(Annotations #8, 9, 10)*
  - For medication treatment, patients may show improvement at two weeks but need a longer length of time to really see response and remission. Most people treated for initial depression need to be on medication at least 6-12 months after adequate response to symptoms. Patients with recurrent depression need to be treated for three years or more. *(Annotation #11)*
  - For psychotherapy treatment, 8-10 weeks of regular and frequent therapy may be required to show improvement. *(Annotation #11)*
- The key objectives of treatment are to:
  - achieve remission of symptoms in the acute treatment phase for major depression,
  - reduce relapse and reduction of symptoms, and
  - return patient to previous level of occupational and psychosocial function.

  (Annotations # 10, 11; Aim #6)

Implementation Recommendation Highlights

The following system changes were identified by the guideline work group and represent a collaborative care model as key strategies for health care delivery systems to incorporate in support of the implementation of this guideline.

* See below for health care cost analysis of a collaborative care model compared to outpatient primary care depression care as usual and review of the cost analysis for enhanced collaborative care and the impact on the workplace, e.g., absenteeism.

- Detection and diagnosis
  - Systems in place to reliably determine if a patient is depressed
  - Use of DSM-5 criteria and structured questionnaires (such as PHQ-9)
- Patient-centered care, education and self-management programs
  - Structured attention to patient preferences
  - Patient and family education materials/protocols
  - Patient self-management skills such as journal writing or self-monitoring

    When appropriate, encourage family or loved ones to attend appointments for patient support and advocacy.
  - Involving families, as well, in care management programs
  - Care manager role to coordinate the disease management for patients with depression including such things as patient contacts, education, self-management tools and tips
- Mental health/behavioral medicine specialist involvement
  - Shared care – collaborative care between behavioral health specialists and primary care clinicians in the primary care setting. Care manager and /or primary care clinician consulting with psychiatry on a regular basis regarding the caseload of patients with depression managed in the depression care management program.
  - Appointment availability – access to behavioral health in timely manner
- Outcomes measurement
  - Build in plans for outcome measures, as well as ongoing process measures
  - Response rate to various treatments
  - Remission rates – improvement in response is stable over time
- Systems to coordinate care, ensure continuity and keep clinicians informed of status
  - Build automated processes for the first four core elements wherever possible
  - Reduce dependence on human behavior to ensure delivery of patient care processes
  - Use of components of the chronic care model for depression care, e.g., use of registries, community outreach
  - Structured, frequent monitoring and follow-up with patient
  - Nurse/care manager phone care and use of other modalities for patient follow-up

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Cost-Effectiveness Impact of Collaborative Care Models

In a collaborative care model, the primary treatment for depression is provided by a multidisciplinary team. Most studies have concluded that creating and implementing a collaborative care model will increase effectiveness – producing significant and sustained gains in "depression-free days" *(Katon, 2005 [High Quality Evidence]; Simon, 2001a [Cost-Effectiveness Analysis]; Simon, 2001b [Cost-Effectiveness Analysis]*). The six-month and one-year studies show increased cost to the outpatient care system. This is balanced by continuous accumulation of clinical and economic benefits over time. One of the factors is the decrease in the utilization of general medical services in patients with chronic medical comorbidities *(Simon, 2008 [Low Quality Evidence])*. The two-year studies show mixed results possibly indicating a turning point *(Dickinson, 2005 [High Quality Evidence]),* and the only longer-term study conducted was the IMPACT study. This was a well-done study analyzing the costs of performing collaborative care for one year over a four-year period. The study illustrated a cost savings of $3,363 per patient over the four-year period *(Unützer, 2008 [High Quality Evidence])*.

Almost all the studies done on this aspect have compared enhanced/collaborative care with care as usual. Typically enhanced care has involved creating a list of depressed patients under treatment, having a care manager provide education, calling or meeting with patient periodically to ensure compliance with medications and/or psychotherapy, and reliably ensuring follow-up visits and measurement of outcomes. Some have involved varying participation of physicians, behavioral health professionals and/or patients.

For more information, see Annotation #8, "Comprehensive Treatment Plan with Shared Decision-Making."

Workplace Impact of Collaborative Care Models

These randomized controlled trials looked at cost of doing enhanced care and specifically tallied decreases of "absenteeism" and improved work performance (which means that employees are present and effectively achieving good work results, sometimes referred to as decreasing "presenteeism") *(Schoenbaum, 2001 [High Quality Evidence]; Wang, 2007 [High Quality Evidence])*. Some studies monetized the results and compared them to usual care. The significance of these studies and this analysis is that in the U.S., depression costs employers $24 billion in lost productive work time *(Stewart, 2003 [Low Quality Evidence])*.

In two randomized controlled trials, employers received significant return on investment (ROI) from collaborative care treatment of depression by increasing productivity/decreasing absenteeism in the workplace. Increased productivity in one study ranged from 2.6 hours to 5.6 hours per week after one year. Studies going out to two years showed continued gains in year two *(Lo Sasso, 2006 [Cost-Effectiveness Analysis]; Rost, 2004 [High Quality Evidence])*.

Several of the articles recommend consideration of coverage of collaborative care to ensure better patient outcomes and the ROI illustrated.

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Related ICSI Scientific Documents

Guidelines

- Assessment and Management of Chronic Pain
- Healthy Lifestyles
- Heart Failure in Adults
- Management of Type 2 Diabetes Mellitus
- Palliative Care for Adults
- Preventive Services for Adults
- Stable Coronary Artery Disease

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Abbreviations

AUDIT	Alcohol Use Disorders Identification Test
CSDD	Cornell Scale for Depression in Dementia
DIAMOND	Depression Improvement Across Minnesota, Offering a New Direction
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DBS	Deep brain stimulation
ECT	Electroconvulsive treatment
FDA	Food and Drug Administration
GDS	Geriatric Depression Scale
HAM-D	Hamilton Rating Scale for Depression
ICD-9 & 10	International Statistical Classification of Diseases and Related Health Problems
IMPACT	Improving Mood Promoting Access to Collaborative Treatment
MAOI	Monoamine Oxidase Inhibitor
MDQ	Mood Disorders Questionnaire
MST	Magnetic seizure therapy
PHQ-9	Patient Health Questionnaire, 9-Item
PPHN	Persistent pulmonary hypertension
PTSD	Post-traumatic stress disorder
QIDS-SR	Quick Inventory of Depressive Symptomatology Self-Report
rTMS	Repetitive transcranial magnetic stimulation
ROI	Return on investment
SSRI	Selective Serotonin Reuptake Inhibitors
STAR*D	Sequenced Treatment Alternatives to Relieve Depression Study
USPSTF	U.S. Preventive Services Task Force
TCA	Tricyclic antidepressant
VNS	Vagus nerve stimulation

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Algorithm Annotations

1. Depression Suspected

Recommendation:

- Clinicians should use a standardized instrument to screen for depression if it is suspected based on risk factors or presentation *(Low Quality Evidence, Strong Recommendation)*.

Overview. The major depression syndrome is a disorder of mood involving disturbances in emotional, cognitive, behavioral and somatic regulation. The mood disorder is called secondary if it occurs in association with drug intoxication or withdrawal, as a biologic consequence of various general medical conditions, in association with other psychiatric conditions or as a consequence of selected prescription medications. The mood disorder is called primary if it does not occur in association with these conditions. Primary mood disorders are categorized into depressive (unipolar) and manic depressive (bipolar) conditions. Unipolar mood conditions are divided into major depressive disorder, persistent depressive disorder and depression not otherwise specified.

Suspect Depression

Many patients with major depression do not initially complain of depressed mood or anehdonia. Clinicians need to suspect this diagnosis based on a profile of common presentations and risk factors, taking into account cultural considerations. See Annotation #6, "Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations?)"

Common Presentations

Common presentations for patients not complaining of major depression or anhedonia include:

- Multiple (more than five per year) medical visits
- Multiple unexplained symptoms
- Work or relationship dysfunction
- Dampened affect
- Changes in interpersonal relationships
- Poor behavioral follow-through with activities of daily living or prior treatment recommendations
- Weight gain or loss
- Sleep disturbance
- Fatigue
- Memory/other cognitive complaints such as difficulty concentrating or making decisions
- Irritable bowel syndrome
- Volunteered complaints of stress or mood disturbance

Since medical illness does co-exist in patients with primary mood or anxiety disorders, it is necessary that physical complaints not be dismissed and/or merely accounted for as part of the depression. Medical issues should still be specifically addressed, especially when new symptoms are reported.

The close relationship of mind and body results in the presentation of medical illness with major depression in various forms:

- Medical illness may be a biological cause (e.g., thyroid disorder, stroke).
- Medical illness or the patient's perception of his or her clinical condition and health-related quality of life may trigger a psychological reaction to prognosis, pain or disability (e.g., in a patient with cancer).
- Medical illness may exist coincidentally in a patient with primary mood or anxiety disorder.

Non-Mood Presentations

Non-mood presentations of major depression include fatigue, pain or other somatic complaints, sleep disturbances, sexual dysfunction, multiple medical visits and work or relationship dysfunction. Fatigue is the seventh most common symptom in primary care, and up to 24% of all patients surveyed in primary care clinics indicate that fatigue is a major problem *(Kroenke, 1988 [Low Quality Evidence])*.

A mood disorder (major depression, persistent depressive disorder or bipolar) may be present in 39% of patients with a presenting complaint of **chronic fatigue** (fatigue present at least half the time for at least one month) *(Manu, 1988 [Low Quality Evidence])*.

Major depression may also be associated with medical disorders or the patient's perception of his or her clinical condition. Although **thyroid function** abnormalities may cause depressive symptoms, screening for thyroid disease in all patients with major depression is not necessary because the prevalence of unidentified thyroid disease in patients with major depression is the same as in the general population *(Garrard, 2001 [Low Quality Evidence]; Briggs, 1993 [Low Quality Evidence])*.

Irritable bowel syndrome is strongly correlated with psychiatric illness. Treatment of the underlying psychiatric disease may provide more than adequate management of IBS *(Garakani, 2003 [Low Quality Evidence])*.

For women, severe obesity (body mass index greater than 40) has been strongly associated with depression *(Onyike, 2003 [Low Quality Evidence])*.

Major depression is also seen in **elderly patients with comorbid illnesses**, such as CVA, cancer, dementia or disabilities.

See also Annotation #6, "Additional Considerations (Medical Cormobidity, Cultural Considerations, Special Populations)?" in the "Medical Comorbidity" section.

Risk Factors

Risk factors for major depression include:

- Family or personal history of major depression and/or substance abuse
- Recent loss
- Chronic medical illness
- Stressful life events that include loss (death of a loved one, divorce)
- Traumatic events (example: car accident)
- Major life changes (examples: job change, financial difficulties)
- Domestic abuse or violence

Patients with chronic illnesses such as diabetes, cardiovascular disease and chronic pain are at higher risk for depression.

One **previous episode** of major depression is associated with a 50% chance of a subsequent episode, two episodes with a 70% chance, and three or more episodes with a 90% chance *(NIMH/NIH Consensus Development Conference Statement, 1985 [Low Quality Evidence])*.

Most studies indicate that in 40 to 60% of patients, a **major life event** precedes the first episode of major depression *(Post, 1992 [Low Quality Evidence])*.

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Domestic abuse and violence. In a recent survey, a stronger association was found between depressed symptoms and ever being afraid of a partner compared with depressed symptoms and hazardous drinking in both men and women, even after adjusting for age group, income, employment status, marital status, living alone and education level *(Gilchrist, 2010 [Low Quality Evidence])*.

No single tool has been identified as the gold standard for screening of domestic violence or abuse. These two questions are commonly used in assessments:

1. Does your partner put you down or try to control what you can do?
2. In the past year have you ever been hit, pushed, restrained or choked during an argument?

For more information on domestic violence screening, see the ICSI Preventive Services for Adults guidleine.

If You Suspect Depression, Screen for it

Validated and reliable tools can help clinicians identify and systematically monitor patients with major depression. Use screening and tracking tools to enhance but not replace the clinical interview.

Either the PHQ-2 or the PHQ-9 can be used to screen for depression. There is stronger evidence supporting the use of the PHQ-9 in patients with chronic disease.

Use the Patient Health Questionnaire **(PHQ) two-question tool** in routine screening settings *(Gilbody, 2006 [Meta-analysis])*.

Over the past two weeks, have you been bothered by:

- Little interest or pleasure in doing things?
- Feeling down, depressed or hopeless?

If the patient answers "yes" to either of the above questions, administer the full PHQ-9 depression instrument *(Kroenke, 2010 [Systematic Review])*.

The **PHQ-9** has been validated for measuring depression severity *(Kroenke, 2001 [Low Quality Evidence]; Spitzer, 1999 [Low Quality Evidence])* and is validated as a tool for both detecting and monitoring depression in primary care settings *(Kroenke, 2010 [Systematic Review]; Wittkampf, 2007 [Systematic Review])*.

It can be administered telephonically *(Pinto-Meza, 2005 [Low Quality Evidence])* and read to the patient. Elderly patients with mild cognitive impairment can reliably fill out the PHQ-9 *(Löwe, 2004 [Low Quality Evidence])*. A recent study found the PHQ-9 useful in psychiatric practices, as well. PHQ-9 scores influenced clinical decision-making for 93% of more than 6,000 patient contacts *(Duffy, 2008 [Low Quality Evidence])*.

Other recognized and validated tools include the Beck Depression Inventory, Hamilton Rating Scale for Depression (HAM-D) and the Quick Inventory of Depressive Symptomatology Self-Report (QID-SR) *(Rush, 2003 [Low Quality Evidence])*. See Appendices for example questionnaires.

Regardless of the screening tool chosen, it is crucial to document that the patient meets the criteria of at least five symptoms for at least two weeks as defined by the DSM-5 criteria for major depression. One of the symptoms must be depressed mood or loss of interest or pleasure.

The primary objective is to use a standardized instrument that will quantify baseline intensity and document future progress, including response and remission rates.

Use of tools with diverse populations. The factor structure of the nine items in the PHQ-9 is comparable when tested with African Americans, Chinese Americans, Latino and non-Hispanic white patient groups *(Huang, 2006 [Low Quality Evidence])*. Other language versions that are validated for use in primary care are Spanish *(Wulsin, 2002 [Low Quality Evidence])* and Chinese *(Yeung, 2008 [Low Quality Evidence])*.

A Thai-language version has also been validated; however, the sensitivity is low (53%). This version could therefore be a useful and reasonable tool to help confirm a suspected depression but less so to screen general populations *(Lotrakul, 2008 [Low Quality Evidence])*. The PHQ-9 has also been validated in Korean-American patients, although a cutoff point of 5 is suggested for elderly Korean-Americans *(Han, 2008 [Low Quality Evidence]; Donnelly, 2007 [Low Quality Evidence])*.

The tool and many other language versions can be found at http://www.phqscreeners.com. When administering the PHQ-9, be aware of cultural factors and involve an interpreter if needed. As research develops on risk adjustment and stratification using this tool, the work group will report and refine recommendations.

See also Annotation #6, "Additional Considerations (Medical Cormobidity, Cultural Considerations, Special Populations)?" for more information on cultural beliefs and common presentations.

Clinicians should choose the screening method that best fits their personal preference, the patient population served and the practice setting.

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2. Diagnose and Characterize Major Depression with Clinical Interview

Recommendation:

- Clinicians should use the DSM-5 criteria to determine a diagnosis of major depression, persistent depressive disorder, other specified depressive disorder and unspecified depressive disorder *(Low Quality Evidence, Strong Recommendation)*.

This section begins with the lists of specific criteria required for diagnosing major depression, persistent depressive disorder, other specified depressive disorder and unspecified depressive disorder. Next, it offers guidance on considering alternative diagnoses. Finally, this section provides guidance on obtaining an appropriate patient history, including history of present illness, medical history, and medication history, including any substance abuse/dependence.

Criteria Required for Diagnosis

Depressed mood or anhedonia (diminished interest or pleasure in activities) is necessary to diagnose major depression.

The use of a mnemonic may be helpful for remembering the symptoms of major depression and persistent depressive disorder. SIGECAPS or SIG + Energy + CAPS is easily remembered and can be used in the clinical interview. Developed by Dr. Carey Gross of Massachusetts General Hospital, it stands for:

Sleep disorder (increased or decreased)
Interest deficit (anhedonia)
Guilt (worthlessness, hopelessness, regret)
Energy deficit
Concentration deficit
Appetite disorder (increased or decreased)
Psychomotor retardation or agitation
Suicidality

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DSM-5 Criteria: Major Depressive Episode

To qualify for a diagnosis of major depressive episode, the patient must meet criteria A through E:

A. Five or more of the following symptoms have been present and documented during the same two-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 attributable to another medical condition.

   1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) 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 by either subjective account or observation)
   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 a specific plan for committing suicide

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

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

   Note: Criteria A-C represent a major depressive episode.

   Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history of and the cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

   Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

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Severity is based on the number of criterion, the severity of those symptoms and the degree of functional disability.

- Mild, single episode 296.21 (F32.0), recurrent episode 29.31 (F33.0): Few, if any symptoms in excess of those required to make the diagnosis are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning.
- Moderate, single episode 296.22 (F32.1), recurrent episode 296.32 (F33.1): The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for "mild" and "severe."
- Severe, single episode 296.23 (F32.2), recurrent episode 296.33 (F33.2): The number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning.

Further specifications include:

- In partial remission, single episode 296.25 (F32.4), recurrent episode 296.35 (F33.41): Symptoms of the immediately previously major depressive episode are present, but full criteria are not met, or there is a period lasting less than two months without any significant symptoms of a major depressive episode following the end of such an episode.
- In full remission, single episode 296.26 (F32.5), recurrent episode 296.36 (F33.42): During the past two months, no significant signs or symptoms of the disturbance were present.

DSM-5 Criteria: Persistent Depressive Disorder

This disorder represents a consolidation of the DSM-IV-defined chronic major depressive disorder and dysthymic disorder, 300.4 (F34.1). To qualify for a diagnosis of persistent depressive disorder, the patient must meet criteria A through H:

A. Depressed mood for most of the day, for more days than not, as indicated by either subjective account of observation by others, for at least two years.

B. Presence while depressed of two or more of the following:

   1. Poor appetite or overeating
   2. Insomnia or hypersomnia
   3. Low energy or fatigue
   4. Low self-esteem
   5. Poor concentration or difficulty making decisions
   6. Feelings of hopelessness

C. During the two-year period of the disturbance, the individual has never been without the symptoms in criteria A and B for more than two months at a time.

D. Criteria for major depressive disorder may be continuously present for two years.

E. There has never been a manic episode or hypomanic episode, and criteria have never been met for cyclothymic disorder.

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F. The disturbance is not better explained by persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum or other psychotic disorder.

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).

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

Note: Because the criteria for a major depressive episode include four symptoms that are absent from the symptom list for persistent depressive disorder, a very limited number of individuals will have depressive symptoms that have persisted longer than two years but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder is warranted.

Severity is based on the number of criterion, the severity of those symptoms and the degree of functional disability.

- Mild: Few, if any symptoms in excess of those required to make the diagnosis are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning.
- Moderate: The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for "mild" and "severe."
- Severe: The number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning.

(American Psychiatric Association, 2013 [Guideline])

Other Specified Depressive Disorder 311 (F32.8)

This category applies to presentations in which symptoms characteristic of a depressive disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the depressive disorders diagnostic class. The other specified depressive disorder category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for any specific depressive disorder. This is done by recording "other specified depressive disorder" followed by the specific reason (e.g., "short-duration depressive episode").

Examples of presentations that can be specified using the "other specified" designation include the following:

1. Recurrent brief depression – Depressed mood and at least four other symptoms of depression for 2-13 days at least once/month (not associated with menstrual cycle for at least 12 months)
2. Short-duration depressive episode – Depressed mood plus greater than or equal to four other symptoms of depression for 4-13 days
3. Depressive episode with insufficient symptoms – Depression with greater than or equal to one other symptom with clinically significant distress/impairment for more than two weeks

Unspecified Depressive Disorder 311 (F32.9)

This category applies to presentations in which symptoms characteristic of a depressive disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

predominate but do not meet the full criteria for any of the disorders in the depressive disorders diagnostic class. The unspecified depressive disorder category is used in situations in which the clinician chooses not to specify the reason that the criteria are not met for a specific depressive disorder, and includes presentations for which there is insufficient information to make a more specific diagnosis (e.g., in emergency room settings). It should also be noted that premenstrual dysphoric disorder is now a separate diagnosis.

Consider Alternate Diagnoses

Anxiety or somatoform disorder

Presentations particularly suggestive of an anxiety or somatoform disorder include medically unexplained symptoms such as:

- Cardiac (chest pain, atypical chest pain, palpitations, shortness of breath, hyperventilation)
- Gastrointestinal (epigastric distress chronic nausea, bloating vomiting)
- Neurologic (headache, dizziness, paresthesias) pseudoseizures, paralysis, aphonia, blindness
- Sexual or reproductive symptoms (other than pain)
- Panic attacks

The text of the fifth edition of DSM-5 includes **seven specific somatic symptom and related disorders**: somatic symptom disorder, illness anxiety disorder, conversion disorder, psychological factors affecting other medical conditions, facticious disorder, other specified somatic symptom and related disorder, and unspecified somatic symptom and related disorder. Refer to the DSM-5 for a full description of each somatic symptom and related disorder. Treatment of these disorders falls out of the scope of this guideline.

Adjustment disorder

Adjustment disorder is the development of emotional or behavioral symptoms in response to an identifiable stressor. The symptoms occur within three months of the onset of the stressor and last less than six months after the termination of the stressor. These symptoms or behaviors are in excess of what would be expected from exposure to the stressor, and they cause significant impairment in social and occupational functioning. In adjustment disorder with depressed mood, predominant symptoms such as low mood, feelings of hopelessness and tearfulness are exhibited. Treatment of adjustment disorder falls out of the scope of this guideline.

Bipolar disorder

Many patients with bipolar disorder experience hypomania or mania before their first major depressive episode. The diagnostic criteria for an episode of major depression in bipolar disorder are the same as the criteria for unipolar major depressive disorder. Because treatment for bipolar depression is different than treatment for unipolar depression, screen for previous episodes of hypomania and mania using DSM-5 criteria when considering a diagnosis of unipolar major depressive disorder:

A) A distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B) During the period of mood disturbances and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

- Inflated self-esteem or grandiosity
- Decreased need for sleep (e.g., feels rested after only three hours of sleep)

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- More talkative than usual or pressure to keep talking
- Flight of ideas or subjective experience that thoughts are racing
- Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
- Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity)
- Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C) The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D) The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode, and therefore, a bipolar I diagnosis.

Note: Criteria A-D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

In addition to screening for hypomania and mania, consider the following historical elements that are more likely to occur in bipolar depression than unipolar depression: a family history of bipolar disorder, onset of depressive symptoms before 25 years of age, and more frequent depressive episodes of shorter duration *(Goodwin, 2007 [Low Quality Evidence])*. Hypersomnia and hyperphagia may also be more common features of bipolar depression than early morning awakening and reduced appetite, which are more typical of unipolar depression *(Frye, 2011 [Low Quality Evidence]; Goodwin, 2007 [Low Quality Evidence])*. For more guidance on diagnosing and treating bipolar depression, consider psychiatric consultation.

One screening tool for further assessment is the Mood Disorder Questionnaire (MDQ) *(Hirschfeld, 2000 [Low Quality Evidence])* for bipolar disorder. Treatment for bipolar disorder falls out of the scope of this guideline.

A new tool, the M-3 (My Mood Monitor) Checklist, has been created to assess for the presence of depression, anxiety, bipolar disorder and post-traumatic stress disorder *(Gaynes, 2010 [Low Quality Evidence])*. It has similar specificity and sensitivity to the single-disorder screens currently in use, with the advantage of being a single page that the patient can complete. More than 80% of clinicians were able to review it in 30 seconds or less. It needs further validation but is a promising tool for primary care in screening for mental health disorders. Details can be found at http://www.whatsmym3.com.

Obtain Patient History

An appropriate patient history includes information about the present illness, the medical history and medication history, including any substance abuse or dependence.

History of present illness

Determine history of present illness:

- **Onset** may be gradual over months or years or may be abrupt.

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- **Severity** of symptoms and degree of functional impairment:

  People diagnosed with major depression have a heterogeneous course from self-limiting to life-threatening. Predictors of poor outcome include higher severity at initial assessment, lack of reduction of social difficulties at follow-up and low educational level.

  Categorize severity of symptoms and degree of functional impairment as follows:

  Mild: few, if any, symptoms in excess of those required to make the diagnosis and only minor impairment in occupational and/or social functioning

  Moderate: symptoms or functional impairment between mild and severe

  Severe: several symptoms in excess of those necessary to make the diagnosis and marked interference with occupational and/or social functioning

- Determine **prior history:** Number and severity of previous episodes, treatment responses and suicide attempts.
- Ask about **concurrent psychiatric conditions**. Obtaining a past psychiatric history is important in terms of understanding prognosis and risk factors. For example, knowing past episodes of major depression, past co-occuring mental/behavioral health conditions, and past self-harm attempts helps establish risk and need to involve other mental health professionals.
- Assess **psychosocial stressors** (significant loss, conflict, financial difficulties, life change, abuse). Consider duration and severity of stressor(s) and likelihood for spontaneous improvement

For short-term subclinical and mild cases, close follow-up and monitoring are still needed *(Fournier, 2010 [Meta-analysis])*. Ongoing utility of behavioral activation, skill building and self-management practices is recommended *(Mazzucchelli, 2009 [Meta-analysis]; Vittengl, 2009 [High Quality Evidence]; Cuijpers, 2007 [Meta-analysis])*.

For more information, see Annotation #8, "Comprehensive Treatment Plan with Shared Decision-Making," sections titled "Behavioral activation – scheduled pleasant activities" and "Discuss Treatment Options."

Medical history

It is important to consider medical conditions that may mimic or directly cause symptoms of depression. A past medical history and brief review of systems is generally sufficient to rule out medical disorders causing major depression.

Examples of such disorders include:

- Dementia
- Delirium
- Hypothyroidism
- Parkinson's disease
- Stroke
- Connective tissue diseases

A review of the patient's medication and substance use may also provide an explanation for depressive symptoms. Sedatives, withdrawal from stimulants and other specific medications (e.g., interferon alpha, varenicline) may be contributing.

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Review of the patient's medical history may find conditions that can impact pharmacological treatments: for example, prostatism, cardiac conduction abnormalities and impaired hepatic function.

Perform a focused physical examination and diagnostic testing as indicated by the review of systems. The benefit of screening laboratory tests, including thyroid tests, to evaluate major depression has not been established.

Consideration of laboratory tests should be greater if:

- the medical review of systems detects symptoms that are rarely encountered in mood or anxiety disorders,
- the patient is older,
- the first major depressive episode occurs after the age of 40, or
- the depression does not respond fully to routine treatment.

Medication history and substance abuse/dependence

Determine medication history and substance abuse/dependence:

- Medications such as steroids, interferon, alpha-methyldopa, isotretinoin, varenicline and hormonal therapy may be associated with major depression.
- Use of alcohol and hypnotics might mimic and/or induce depression, and comorbidity is common *(Davis, 2006 [High Quality Evidence])*.
- Withdrawal from cocaine, anxiolytics and amphetamines may mimic depression.
- Idiosyncratic reactions to other medications can occur. If possible, a medication should be stopped or changed if depression develops after beginning its use. If symptoms persist after stopping or changing medication, reevaluate for a primary mood or anxiety disorder.

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4. Use Organization's Protocol If Available to Assess and Minimize Suicide Risk/Involve Mental Health Specialists

The estimate of the lifetime prevalence of suicide in those ever hospitalized for suicidality is 8.6%. The lifetime risk is 4% for affective disorder patients hospitalized without specification of suicidality *(Bostwick, 2000 [Systematic Review])*.

This section provides guidance and references on assessing suicidal tendencies, developing a clinic suicide protocol, risk factors for suicide and interventions to reduce suicide ideation.

Assess Suicidal Tendencies

Assessing suicidal tendencies is a critical but often difficult process with a depressed patient. Consider asking and documenting the following progression of questions.

1. Do you feel that life is worth living?
2. Do you wish you were dead?
3. Have you thought about ending your life?
4. If yes, have you gone so far as to think about how you would do so? Be specific, what method would you use?
5. Do you have access to a way to carry out your plan?
6. What keeps you from harming yourself?

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Many patients will not answer #4 directly or will add, "But I'd never do it." Give them positive feedback (e.g., "I'm glad to hear that") but do not drop the subject until she/he has told you the specific methods considered (e.g., gun, medication overdose, motor vehicle accident).

Develop a Suicide Protocol

It is important for a health care clinic to develop its own suicide protocol, taking into account the organization's workflow and resources. Each individual clinic should determine:

- a clear process for risk assessment,
- when to involve the on-call mental health clinician,
- use of local or national hotlines, and
- next steps.

A recommended resource for establishing a clinic-based protocol to assess and minimize suicide risk is Bonner, L., et al., Suicide Risk Response: Enhancing Patient Safety Through Development of Effective Institutional Policies. Advances in Patient Safety: From Research to Implementation. Vol 3, February 2005 http://www.ahrq.gov/qual/advances/.

See also Appendix C, "Example Suicidality Screening Flow."

More About Risk Factors for Suicide

Literature suggests that a history of self-harm attempts, in combination with a history of well-developed suicide plans, place the patient at a greater eventual risk of completing a suicide attempt *(Bostwick, 2000 [Systematic Review])*.

In a national clinical survey, suicides were found to be most frequent in the first two weeks following hospital discharge. The highest suicide completion rate occurred on the first day post-discharge. Additional suicide risk factors included patients being less likely to continue community care, more likely to have missed the last follow-up appointment, and more often out of contact with services at the time of suicide (*Meehan, 2006 [Low Quality Evidence]).*

Circumstances such as clear past examples of a sense of competence to execute an attempt, a sense of courage to make the attempt, behaviors that ensure the availability of means and opportunity to complete, concrete preparations to enact the suicide plan, and a current episode of severe depression combine to pose a greater danger of eventual completed suicide. The clinician should consider previous history of suicide attempts; chemical dependency; personality disorder and/or physical illness; family history of suicide; single status; recent loss by death, divorce or separation; insomnia; panic attacks and/or severe psychic anxiety; diminished concentration; anhedonia; hopelessness post-traumatic stress disorder (PTSD); or suicidal ideation *(Claassen, 2007 [Low Quality Evidence])*.

Patients with comorbid major depressive episode and PTSD are more likely to have attempted suicide. Women with both disorders were more likely than men with both disorders to attempt suicide *(Oquendo, 2003 [Low Quality Evidence])*.

In addition to the risk factors listed above, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that previous suicide attempters had more concurrent general medical and psychiatric comorbidities, an earlier age of onset of the first depressive episode, as well as more depressive episodes. The study found no racial or ethnic distinctions between previous attempters and non-attempters, when controlled for age, gender and severity of depressive symptoms *(Claassen, 2007 [Low Quality Evidence])*.

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More About Interventions to Prevent Suicide

In the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) study, suicidal ideation rates declined in patients who receive care based on treatment guidelines and who used a care manager *(Bruce, 2004 [High Quality Evidence])*.

In the Improving Mood Providing Access to Collaborative Treatment (IMPACT) Study, 1,801 primary care patients were randomly assigned to collaborative care or usual care. Intervention subjects had less suicidal ideation at 6 and 12 months, and there were no completed suicides for either group in 18 months *(Unützer, 2006 [High Quality Evidence])*.

Another study found suicide attempt incidences highest in patients who received medication from psychiatry (1,124 per 100,000 patients) versus from primary care (301 per 100,000 patients) *(Simon, 2007 [Low Quality Evidence])*.

Involve Mental Health Specialists

Involve **same-day mental-health** for any of these situations:

- Suicidal thoughts and/or plans that make the clinician uncertain of the patient's safety
- Assaultive or homicidal thoughts and/or plans that make the clinician uncertain about the safety of the patient or others
- Recent loss of touch with reality (psychosis)
- Inability to care for self/family

Involvement could include:

- appointment with psychiatrist and/or psychotherapist,
- phone consultation with psychiatrist and/or psychotherapist, or
- referral to the emergency department.

(Dieserud, 2001 [Low Quality Evidence]; Whooley, 2000 [Low Quality Evidence])

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5. Assess for the Presence of Substance Misuse or Psychiatric Comorbidity If Suspected

Substance Abuse Prevalence

Alcoholism and major depressive disorder are distinct clinical entities. They not different expressions of the same underlying condition. Within the general population, substance abuse prevalence ranges from 8% to 21% in people with major depression *(Davis, 2006 [High Quality Evidence])*.

Screening (CAGE, CAGE-AID, AUDIT, AUDIT-C)

Current alcohol or other drug problems can be screened by asking a few questions that can be easily integrated into a clinical interview. The work group reviewed the literature on instruments designed to screen for substance use disorders.

CAGE and CAGE-AID. The CAGE questions are sensitive and specific for diagnosing alcoholism. One positive response has a sensitivity of 85% and a specificity of 89%, and two positive responses have a specificity of 96% *(Bush, 1987 [Low Quality Evidence])*. The CAGE-AID questionnaire broadens the CAGE to include other drug use.

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AUDIT and AUDIT-C. The AUDIT screening tool accurately detects alcohol dependency in depressed/anxious men and women; however, the overall performance of the AUDIT in detecting alcohol abuse is limited *(Boschloo, 2010 [Low Quality Evidence])*. The AUDIT-C, a modified version of the 10-question AUDIT instrument, can help identify persons who are hazardous drinkers or have active alcohol use disorders.

Other instruments that were reviewed included MAST SMAST, SMAST-AID.

See Appendix G, "Alcohol Use Disorders Identification Test (AUDIT) Structured Interview."

Examples of Other Substance Abuse Screening Tools

Tool	Description	*Sensitivity/Specificity %
AUDIT	10-item questionnaire – self-administered or clinical interview to assess for harmful use; cross-cultural validity	Score of 12: 97/28
DAST	28-item questionnaire – self-administered or clinical interview to detect drug problems; adapted from MAST	Score of 6 or more: 96/79
MAST	25-item questionnaire – self-administered or clinical interview to detect alcoholism	Score of 5 or more: 95/98
TWEAK	5-item questionnaire – clinical interview to detect high-risk use; adapted from CAGE	Score of 2: 73/64

*Note: Sensitivity/specificity can differ with regard to efficacy for specific subpopulations.
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Treatment

The medical literature does not support definitive statements about the best way(s) to treat patients who are diagnosed with both major depression and substance abuse/dependence. Based on the majority of studies reviewed, success in treating dependency on alcohol, cocaine and other abused substances is more likely if accompanying depression is addressed.

Fewer investigators have looked at whether treating substance abuse is helpful in reducing depression. There is some evidence that patients with major depression that is secondary to their substance abuse may have remission of their depressed mood once the substance abuse is treated. However, it is difficult to separate secondary depression from primary depression that predates or is separate from the substance use.

Additional Resources. A complete discussion of evaluation and treatment for chemical dependency is beyond the scope of this guideline. However, **SBIRT (Screening, Brief Intervention, Referral and Treatment)** is a process wherein a care coordinator uses motivational interviewing to assist patients who have high-risk drinking behavior. Additionally, the National Institute on Alcohol Abuse and Alcoholism and other agencies offer tools to guide primary care-based medical treatment of alcohol abuse. See Web site links below. A referral may be appropriate. For more information, see also the ICSI Healthy Lifestyles guideline.

http://www.cdc.gov/injuryresponse/alcohol-screening/index.html,

http://www.samhsa.gov/samhsanewsletter/Volume_17_Number_6/SBIRT.aspx

http://pubs.niaaa.nih.gov/publications/arh28-2/78-79.htm

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Psychiatric Comorbidity

Bipolar Disorder

Be aware of ongoing mental illness diagnosis or other mental health illnesses and comorbidities. Patients with a history of manic (bipolar) symptoms now presenting with major depression may be destabilized if treated only with antidepressant drugs. If a manic or hypomanic episode occurs while treating a patient for depression, change the diagnosis to bipolar affective disorder and treat accordingly *(Judd, 2002 [Low Quality Evidence])*. Behavioral health involvement is advised with these patients unless a patient has a prior history of successful primary care management.

Generalized Anxiety Disorder and Panic Disorder

Depressed patients may present with comorbid panic symptoms and generalized worries. Primary care clinicians should screen for symptoms of these disorders and potential causes. Assess for the following:

- Excessive use of stimulant containing products such as energy drinks or shots and caffeinated beverages
- Presence of medical causes of symptoms:
  - Thyroid disease
  - Cardiac disease
  - Irritable bowel syndrome
  - Migraines
  - Vestibular disorders
  - Respiratory and pulmonary disorders
- Use of medications like psychostimulants
- Use of or withdrawal of substances like cocaine, methamphetamine, THC, or alcohol

Psychotherapy is an effective treatment for anxiety and panic, and a referral to a therapist who provides a short-term, evidence-based focused treatment protocol for anxiety is likely to be helpful. A comprehensive discussion of the treatment of anxiety disorders in primary care is beyond the scope of this guideline. However, the AHRQ's clinical practice guideline for the treatment of patients with anxiety disorders in primary care is a good reference point *(Agency for Healthcare Research and Quality, 2008 [Guideline])*.

Also see Annotation #8, "Comprehensive Treatment Plan with Shared Decision-Making," for medication and psychotherapy and integrative medicine treatments.

Other Disorders

Major depression may also be associated with other psychiatric problems including personality disorders, psychosis, eating disorders and substance abuse. Patients with these conditions may need specialty care services, and details of treatment are beyond the scope of this guideline.

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6. Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations)?

Recommendations:

- Clinicians should assess and treat for depression in patients with some comorbidities *(Low Quality Evidence, Strong Recommendation)*.
- Clinicians should acknowledge the impact of culture and cultural differences on physician and mental health *(Low Quality Evidence, Strong Recommendation)*.
- When using pharmacotherapy in elderly patients, the clinician should carefully consider how the metabolism of the drug may be affected by physiologic changes, their comorbid illnesses and the medications used for them *(Low Quality Evidence, Strong Recommendation)*.
- Clinicians should screen and monitor depression in pregnant and postpartum women *(Low Quality Evidence, Strong Recommendation)*.

Overview

This section summarizes evidence related to the prevalence, assessment and treatment of depression in patients with:

- Medical comorbidities (cardiovascular disease, cerebrovascular disease, diabetes)
- Chronic pain
- Diverse cultures (ethnic minority women, African American, Latino/Hispanic, Asian)
- Special populations (geriatric, cognitively impaired, and perinatal-through-postpartum women)

Medical Comorbidity

The importance of the interplay between depression and many medical comorbidities cannot be overstated. **Depressed patients often have comorbid conditions.**

In the STAR*D trial, study entry subjects had an average of 3.3 general medical conditions *(Trivedi, 2006b [High Quality Evidence])*.

A study utilizing the second cohort of STAR*D patients reported a prevalence of significant general medical conditions of 50% in the study population *(Yates, 2007 [Low Quality Evidence])*.

A long list of medical conditions has been associated with increased risk for depression; these include chronic pain, diabetes, cancer, HIV, Parkinson's disease, cardiovascular and cerebrovascular disease, and multiple sclerosis, to name a few *(Kozhimmanil, 2009 [Low Quality Evidence]; Egede, 2005 [Low Quality Evidence]; Katon, 2004b [Low Quality Evidence])*.

Undiagnosed or undertreated depression has been associated with worsened outcomes in cancer, cardiovascular disease and other conditions *(Hedeyati, 2010 [Low Quality Evidence]; Lichtman, 2008 [Guideline])*.

Conversely, one would expect that effective identification and treatment of comorbid depression would be associated with improved medical outcomes. Studies have demonstrated an association between effective treatment of depression and improved adherence to medical treatment for conditions such as cardiovascular disease *(Ciechanowski, 2000 [Low Quality Evidence])*. However, other suspected benefits of antidepressant therapy, such as decreased mortality after MI or CABG, have been more difficult to prove. See the "Implementation Tools and Resources Table" for more information.

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The following conditions are particularly important for screening, given the findings.

Cardiovascular disease

Interplay of risks

Some studies have shown that major depression is associated with an increased risk of developing coronary artery disease (*Wulsin, 2003 [Systematic Review]; Rugulies, 2002 [Systematic Review]),* and with an increased risk of mortality in patients after myocardial infarction by as much as fourfold *(Lichtman, 2008 [Guideline]; Frasure-Smith, 1995 [Low Quality Evidence])*, while other analyses have disputed this *(Jiang, 2005 [Low Quality Evidence]; Nicholson, 2006 [Systematic Review])*.

Moderate to severe depression before CABG surgery and/or persistent depression after surgery increases the risk of death after CABG more than twofold higher than non-depressed patients *(Blumenthal, 2003 [Low Quality Evidence])*.

Depression is three times more common in patients after acute myocardial infarction than in the general population and, notably, young women are at particularly high risk for depression after myocardial infarction *(Lichtman, 2008 [Guideline])*.

Potential explanations

Several possible mechanisms are proposed to explain why depression increases the risk of developing cardiovascular disease. These include behavioral issues such as increased smoking, obesity, sedentary lifestyle, and lack of adherence to medication.

A prospective study found that the association between depression and cardiovascular events disappeared after controlling for physical activity and other health behaviors *(Whooley, 2008 [Low Quality Evidence]),* suggesting depression's negative impact on activity and behavior may account for its contribution to cardiac risk.

Biologic phenomena associated with depression such as increased inflammatory processes (elevated C-reactive protein or cytokine levels), increased platelet dysfunction (heightened platelet aggregation or adhesiveness), and abnormalities in endothelial function may also explain possible mechanisms for an increased risk *(Katon, 2004b [Low Quality Evidence])*.

A recent cross-sectional study of depressed patients also found that, of their depressive symptomatology, specifically increased sympathetic arousal and insomnia were significantly associated with cardiac disease *(Fraguas, 2007 [Low Quality Evidence])*.

Treating depression in this population

As yet there are no data to support the hypothesis that antidepressant treatment decreases cardiac morbidity and mortality *(Jiang, 2005 [Low Quality Evidence])*. **Nevertheless, consensus opinion is to treat depressed cardiac patients with a safe drug rather than watchful waiting since they would benefit from symptomatic relief of their depressive symptoms and there is a potential improvement in their cardiovascular risk profile** *(Ballenger, 2001 [Low Quality Evidence])*.

Although **tricyclic antidepressants** are effective against depression, they are associated with cardiovascular side effects including orthostatic hypotension, slowed cardiac conduction, proarrhythmic activity, and increased heart rate. **SSRIs**, by contrast, are well tolerated and have a more benign cardiovascular profile; they would be preferred initial agents for treatment of depression in individuals with cardiovascular disease *(Jiang, 2005 [Low Quality Evidence])*.

The American Heart Association science advisory *(Lichtman, 2008 [Guideline])* suggests **sertraline and citalopram** as first-line drugs for patients with coronary heart disease. See Annotation #8, "Comprehensive Treatment Plan, with Shared Decision-Making" section: SSRI's and other anti-depressants.

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For more information, see also the ICSI Heart Failure in Adults guideline and Stable Coronary Artery Disease guideline.

Cerebrovascular disease

A recent meta-analysis *(Pan, 2011 [Systematic Review])* affirms earlier *(O'Donnell, 2010 [Low Quality Evidence]; Van der Kooy, 2007 [Systematic Review])* findings of an association between depression and stroke.

The pooled hazard ratio from the Pan study was 1.45, on par with the association between smoking and stroke, and obesity and stroke. The authors suggest potential causative mechanisms similar to those discussed above for cardiovascular disease. They also suggest the need for further studies to assess the "role of depression treatment in modulating subsequent risk of stroke."

Diabetes

Major depression is associated with an increased number of known cardiac risk factors in patients with diabetes and a higher incidence of coronary heart disease; therefore, screening and treatment of depression in this patient group should be emphasized *(Katon, 2004b [Low Quality Evidence])*.

Individuals with diabetes have twofold higher odds of depression than those without diabetes. High levels of symptoms associated with diabetes that do not correlate with physical or laboratory assessments should prompt the physician to assess for depression *(Ludman, 2004 [Low Quality Evidence])*.

Depression earlier in life increases the risk of developing diabetes by twofold *(Katon, 2004a [Low Quality Evidence])*.

Depressive symptom severity is associated with poorer diet, medication compliance, and self-care plus functional impairment and higher health care costs *(Ciechanowski, 2000 [Low Quality Evidence])*.

For more information, see also the ICSI Diagnosis and Management of Type 2 Diabetes Mellitus in Adults guideline.

Chronic Pain

Depression and pain symptoms commonly coexist, exacerbate or attenuate one another, and appear to share biological pathways and neurotransmitters.

Patients with chronic pain are more likely to have coexisting depression. In 2004, data were examined from primary care centers worldwide by the World Health Organization. They found that 22% of all primary care patients suffer from chronic debilitating pain. Further, chronic pain patients were four times more likely to have comorbid depressive disorder than pain-free primary care patients *(Lépine, 2004 [Low Quality Evidence])*. The findings also showed that the more diffuse the pain complaints, the greater the risk of depression and the bigger impact on the quality of life.

Important diagnostic and treatment findings:

- Increasing pain severity, diffuse (multiple site) pain, pain that interferes with functional performance, and pain refractory to treatment are all associated with increased risk of depression, more depressive symptoms, and greater depression severity. However, a recent study found no difference in chronicity of depressive symptoms for those patients with or without pain *(Husain, 2007 [Low Quality Evidence])*.
- The reciprocal nature of the depression-pain relationship is well established, i.e., the presence of depression in pain patients or the presence of pain in depressed patients is associated with poorer functional status and resulting disability, decreased quality of life, impaired social functioning, and decreased patient satisfaction.

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- Some antidepressant treatments may produce simultaneous improvement in both pain and depression symptoms *(Bair, 2003 [Low Quality Evidence])*.
- Another report from the STAR*D study found that depressed patients with anxious features, comorbid generalized anxiety disorder, or worsening premenstrual depressive symptoms were more likely to express pain *(Husain, 2007 [Low Quality Evidence])*.

Key clinical practice actions:

- In those patients presenting with either pain or depressive symptoms, assess both domains. Depression may be more than a facet of chronic pain when significant depression symptoms are present. If comorbidity is found between chronic pain and mild to moderate major depression, treat both conditions for optimal outcomes *(Bair, 2003 [Low Quality Evidence])*. If comorbid severe major depressive disorder is diagnosed concurrently with chronic pain, depressive symptoms should be the primary focus of treatment.
- Depression and pain symptoms appear to follow the same descending pathways of the central nervous system involving a functional deficiency of the neurotransmitters serotonin, norepinephrine and dopamine. Therefore, antidepressant medication is warranted, especially the dual-action tricyclic antidepressants such as amitriptyline or dual-action atypical antidepressant re-uptake inhibitors such as venlafaxine or duloxetine. Duloxetine is indicated for the management of neuropathic pain associated with **diabetic peripheral neuropathy** *(Wernicke, 2006 [High Quality Evidence])*.
- Combining pharmacologic treatment and cognitive-behavioral therapy appears to produce the most favorable treatment outcomes *(Bair, 2003 [Low Quality Evidence])*.

For more information, see also the ICSI Assessment and Management of Chronic Pain guideline.

Cultural Considerations

Clinicians should acknowledge the impact of culture and cultural differences on physical and mental health.

Successful care is most likely to occur when the clinician:

- uses **appreciative inquiry** asking questions that produce positive potential and strengths,
- regards the patient's cultural norms and beliefs,
- uses interpreters whenever possible, and
- seeks to incorporate the patient's beliefs into the treatment plan.

A person's cultural and personal experiences influence his/her beliefs and therefore attitudes and preferences. If these experiences are taken into consideration, openness to and readiness to change (including readiness to seek and adhere to treatment) will be enhanced. People of differing racial/ethnic groups are successfully treated using currently available evidence-based interventions when differential personal elements, from biological to environmental to cultural, are considered during the treatment planning process *(Schraufnagel, 2006 [Low Quality Evidence])*.

Online resources including http://www.culturecareconnection.org and http://minorityhealth.hhs.gov have readily available information and facts. See the "Implementation Tools and Resources Table" for more information.

Cultural beliefs and common presentations

- Clinicians can create a more comfortable environment for a patient of another culture by acknowledging the impact of culture and cultural differences on physical and mental health *(Muñoz, 2005 [Low Quality Evidence]; Miranda, 2004 [Low Quality Evidence])*.

- Bodily idioms of distress are very common in many cultures. In place of psychosomatic theories that emphasize individuals' inner conflict, many traditions of medicine have sociosomatic theories that link bodily and emotional distress to problems in the social world *(Kirmayer, 2001 [Low Quality Evidence])*.
- The most common somatic symptoms of depression and anxiety are musculoskeletal pain and fatigue. A clinician might consider starting the conversation with the patient on physical symptoms since this is a common presentation of depression in some cultures.
- The concept of depression varies across cultures. For example, in many cultures, for depression to become a problem for which a person seeks medical treatment, symptoms may include psychosis, conversion disorders or significant physical ailments *(Karasz, 2005 [Low Quality Evidence])*.
- There is evidence that non-majority racial and cultural groups in the U.S. are less likely to be treated for depression than European Americans. In an epidemiological study that compared rates of diagnosing and treating depression in the early 1990s to patterns 10 years later, only 4.9% of minorities were treated with antidepressants compared with 12.4% of non-Hispanic Caucasians *(Mojtabai, 2008 [Low Quality Evidence])*.

See also the "Implementation Tools and Resources Table," the "Stratis Health Culture Care Connection" entry.

Ethnic minority women

- Those women with somatization were more likely to indicate interest in medication and their faith as sources for mental health care *(Nadeem, 2008 [Low Quality Evidence])*.
- Ethnic differences tend to be most pronounced regarding medication preferences, with ethnic minority women showing less interest in medication than U.S.-born white women *(Nadeem, 2008 [Low Quality Evidence])*.
- Faith is frequently cited as more important to coping with depression for ethnic minorities as compared with Caucasian women *(Nadeem, 2008 [Low Quality Evidence])*.

African American

- African Americans are more likely than Caucasians to believe that mental health professionals can be helpful, but they are also more likely to believe mental illness will improve on its own. They may tend to seek service late, and therefore face poorer outcomes *(Anglin, 2008 [Low Quality Evidence])*.
- In a secondary analysis of STAR*D data, African Americans were more likely to seek treatment in primary care settings. They also reported higher major depression recurrence in comparison with Hispanics *(Lesser, 2007 [High Quality Evidence])*.
- When they perceive they have an emotional problem for which they need help, African American women show a preference for individual or group therapy rather than for use of medication *(Nadeem, 2008 [Low Quality Evidence])*.
- Three studies have found that coexisting diabetes increases the rate of death *(Richardson, 2008 [Low Quality Evidence]; Egede, 2005 [Low Quality Evidence]; Zhang, 2005 [Low Quality Evidence])*. The most recent study shows, for the first time, racial/ethnic differences in the mortality rate for male individuals with diabetes and depression. The finding suggests that older Caucasian men with depression and diabetes have an increased risk of dying compared with non-Hispanic African American males *(Richardson, 2008 [Low Quality Evidence])*.

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Latino/Hispanic

- In comparison with the general U.S. population, Latinos show no difference in the prevalence of major depression, but they often express psychological distress differently. Assessment for depressive symptoms alone may not adequately capture the contextual factors of psychological distress the Latino experiences *(Mendelson, 2008 [Meta-analysis])*.
- In a secondary analysis of STAR*D data, Hispanics were more likely to seek treatment in primary care settings. Also, African Americans and Caucasians reported higher major depression reoccurrence in comparison with Hispanics *(Lesser, 2007 [High Quality Evidence])*.
- Among Mexican American women, while treatment of depression is found to be helpful, cultural values may be inconsistent with accepting treatment *(Schmaling, 2008 [Low Quality Evidence])*.
- Traditional Latino values increase the likelihood that Latina women will express distress via depressive symptoms, while Latino men are more likely to externalize distress *(Mendelson, 2008 [Meta-analysis])*.
- When they perceive they have an emotional problem for which they need help, Latina women show a preference for individual or group therapy rather than for the use of medication *(Nadeem, 2008 [Low Quality Evidence])*.
- Although not clearly defined, the strongest predictor of clinical depressive symptoms in type II diabetes was the patient's (Mexican origin) perception of the burden of diabetes symptoms. Female gender, low levels of education and frequent emergency room visits were also associated with higher levels of depressive symptoms in U.S. Latino respondents *(Mier, 2008 [Low Quality Evidence])*.

Asian

- In a study of 12 providences in Canada, Caucasians were more likely to have used mental health services than immigrants from Asia, including Chinese, South Asians and Southeast Asians. Among the Asian participants, the Chinese were less likely to have used mental health services than other Asian groups *(Tiwari, 2008 [Low Quality Evidence])*.

Psychosocial and socioeconomic issues

- Be aware that psychosocial stressors may be more prevalent with certain populations. The health care team may want to take these issues into consideration as a treatment plan is made. Examples of possible stressors include housing, food, day care, transportation, employment, immigration status and financial stability.
- Cost implications for patients often affect adherence, including insurance coverage or generic versus brand name medications. Adherence factors are important for clinicians to discuss with the patient.
- Recent research on depression in low-income minority women in the United States documents significant improvement of symptoms and social functioning regardless of whether treatment was medication or psychotherapy when treatment was sufficiently accessible (availability of child care and transportation).
- Ten to 75% of patients are non-compliant with medication use, and non-compliance rates are higher in intercultural settings because of cultural expectations and communication problems *(Kirmayer, 2001 [Low Quality Evidence])*.
- A discrepancy between aspiration and achievement may be a better predictor of psychiatric illness than socioeconomic status. The larger the discrepancy between aspiration and achievement, the greater risk of emotional disturbance *(Ialongo, 2004 [Low Quality Evidence])*.

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Assessment and treatment tools

- Many **assessment tools** may not be useful for certain populations. Screening instruments are validated in certain groups. Use caution when using because a tool may not be applicable to all groups.
- Most empirically supported **therapies** have been evaluated with Caucasian, middle-class, English-speaking populations.

Another resource for more information is the DSM-5, "Cultural Formulation."

Special Populations

Geriatrics

Depression in the elderly is widespread, often undiagnosed and usually untreated. It is a common misperception that depression is a part of normal aging. Losses, social isolation and chronic medical problems that older patients experience can all contribute to depression.

Rates and presentation

The rate of depression in adults older than 65 years of age ranges from 7 to 36% in medical outpatient clinics and increases to 40% in the hospitalized elderly. Comorbidities are more common in the elderly. The highest rates of depression are found in those with strokes (30 to 60%), coronary artery disease (up to 44%), cancer (up to 40%), Parkinson's disease (40%), and Alzheimer's disease (20 to 40%). The recurrence rate is also extremely high at 40% *(Birrer, 2004 [Low Quality Evidence])*.

Similar to other groups, the elderly with depression are more likely than younger patients to underreport depressive symptoms. They often present with non-specific somatic complaints, such as insomnia, appetite disturbances, lack of energy, fatigue, chronic pain, constipation and musculoskeletal disorders.

Treatments and outcomes

The outlook for recovery for the elderly is similar to that for the young when appropriately treated. However, treatment usually has to be continued for longer periods than for the young, since it may take longer to reach remission.

Collaborative care. The IMPACT (Improving Mood: Promoting Access to Collaborative Treatment) study showed improvement in treating the depressed elderly over several measures. Patients were randomized to usual care or collaborative care. The latter involved a team composed of a depression care manager, primary care physician and psychiatrist, the team offered education, behavioral activation, antidepressants, brief behavior-based psychotherapy (problem-solving treatment), and relapse prevention geared to each patient's needs and preferences *(Unützer, 2002 [High Quality Evidence])*.

Outcomes from IMPACT included demonstration that collaborative care was more effective than usual care for the elderly, regardless of the elderly patients' ethnicity *(Areán, 2005 [High Quality Evidence])*. The intervention group also showed improved physical functioning, less suicidal ideation, improved continuation of antidepressant treatment, fewer depressive symptoms, remission of depression, plus increased quality of life, self-efficacy and satisfaction with care. The intervention lasted for one year. One year later the outcomes for the intervention group were still significantly better than for those who received usual care *(Hunkeler, 2006 [High Quality Evidence])*.

Pharmacotherapy and psychotherapy. Pharmacotherapy and psychotherapy are appropriate modalities to treat depression in the elderly. When using pharmacotherapy, the physician must carefully consider how the metabolism of the drug may be affected by physiologic changes in the elderly, their comorbid illnesses and the medications used for them. In those individuals who don't respond to the different antidepressants alone, **augmentation therapies** may be appropriate. This would include psychostimulants, such as cytomel

or methylphenidate, or the addition of lithium. **Psychotherapy** is also appropriate, limited only by cognitive impairments *(Cuijpers, 2008 [Meta-analysis])*.

Behavioral strategies. Behavioral activation strategies such as increasing daily involvement in pleasant activities are safe, simple and beneficial in treating depression in this population *(Cuijpers, 2008 [Meta-analysis])*.

Maintenance therapy. Recurrent depression is common in the elderly. Maintenance therapy with an SSRI (paroxetine in this study) for two years was shown to be effective in preventing recurrent depression after a first-time major depression in the elderly over 70 years of age. Interpersonal psychotherapy alone was ineffective *(Reynolds, 2006 [High Quality Evidence])*.

See also the Annotation #12, Consider Other Strategies," in the section "Electroconvulsive treatment (ECT)."

Dementia/Cognitive Impairment

Assessment. Patients with more severe cognitive impairments cannot reliably answer the PHQ-9 questions. The 19-item Cornell Scale for Depression in Dementia (CSDD) has the best sensitivity (93%) and specificity (97%). A cutoff of greater than or equal to six identifies depression in a demented population *(Alexopolous, 1988 [Low Quality Evidence])*. This is a clinician-administered tool to help diagnose depression in patients with dementia. It has been used in a variety of settings ranging from outpatient to assisted living to nursing homes. Its accuracy decreased when it was modified to be used by less-trained staff. Its usefulness for ongoing tracking purposes has not been studied *(Barca, 2010 [Low Quality Evidence]; Watson, 2009 [Low Quality Evidence])*.

See Appendix D, "Cornell Scale for Depression in Dementia (CSDD)," and Appendix E, "Geriatric Depression Scale (GDS)."

Interplay of risks. There is reasonably good evidence that having a major depressive episode increases the risk of developing Alzheimer's dementia (odds ratio of 2.03 with 95% confidence, with a range of odds ratio of 4.55 with 95% confidence ratio when depression occurred less than one year before diagnosis of Alzheimer's dementia to odds ratio of 1.71 when depression occurred more than 25 years earlier) *(Ownby, 2006 [Systematic Review]; Green, 2003 [Low Quality Evidence])*.

Pregnant and Postpartum Women

The section contains information on assessing and treatment depression in women in the perinatal and lactation periods (the period from conception through the first year postpartum).

Incidence

Between 14 and 23% of pregnant women and 10-15% of postpartum women will experience a depressive disorder *(Gaynes, 2005 [Systematic Review])*. According to a large-scale epidemiological study *(Vesga-Lopez, 2008 [Low Quality Evidence])*, depression during the postpartum period may be more common than at other times in a woman's life.

With growing understanding of the systemic impact of perinatal stressors, there is a new body of research examining **paternal depression**. A recent meta-analysis shows a 10-14% incidence of paternal depression during the perinatal period, with a moderate positive correlation with maternal depression *(Paulson, 2010 [Meta-analysis])*.

Safety assessment of psychotropic medication during pregnancy and lactation

Treatment of a psychiatric illness during pregnancy involves weighing potential risk of fetal exposure to psychotropic medication against potential adverse effects of an untreated disorder on mother and fetus. In

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conclusion, there is no zero-risk option. Clinicians must help patients assess these negative effects of depression on mothers and families against the risks and benefits of psychotropic medication and other treatment options *(Mian, 2005 [Low Quality Evidence])*.

The process of making decisions about the use of any medicine, particularly psychotropics, during pregnancy should be made on a case-by-case basis, weighing the varying amounts of information about the medicine and the patient's underlying disease state.

The available evidence about psychotropic medication in pregnancy is substantial but limited by ethical considerations that preclude prospective controlled trials of pregnant women. Most studies retrospective or reliant on databases that do not allow for accuracy in the determination of fetal exposure or other confounders. We will provide a more global risk assessment across pregnancy, including the perinatal period and lactation.

Medications taken during pregnancy are considered teratogenic if they increase the risk of congenital malformations above the baseline risk of 3 to 4%. The most reproductive safety information is available for the tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) *(Ferreira, 2007 [Low Quality Evidence]; Mian, 2005 [Low Quality Evidence]; Sivojelezova, 2005 [Low Quality Evidence])*.

Among the available pregnancy data, TCAs and SSRIs have not shown any evidence of increased risk of major congenital malformations, with the possible exception of paroxetine. In 2006 the FDA issued a warning that first-trimester paroxetine was associated with an increased risk of major malformations (4% vs. 3%), particularly cardiac malformations (2% versus 1%). The FDA changed the pregnancy labeling from category C to D, indicating that controlled or observational studies in pregnant women have demonstrated a risk to the fetus. Studies have suggested that first-trimester exposure to paroxetine at doses greater than 25 mg a day are associated with a greater risk of cardiac malformations *(Bérard, 2007 [Low Quality Evidence]; Thormahlen, 2006 [Low Quality Evidence])*

Based on these findings, paroxetine should not be considered a first-line choice for initiating an antidepressant in pregnancy. For women who are already on paroxetine and planning pregnancy, the risks of paroxetine should be weighed against the risks of discontinuing it. For some high-risk women, severe depression or anxiety could also adversely affect the pregnancy.

Impacts of untreated depression

Untreated prenatal depression has been associated with negative pregnancy outcomes such as low birth weight and preterm labor, as well as negative effects on children such as developmental delay and cognitive impairment *(Davalos, 2012 [Systematic Review]; Li, 2009 [Low Quality Review])*. Research has highlighted negative impact on fetal and infant development of both untreated maternal depression and antidepressant exposure. A recent study of pregnancy-associated suicide in women demonstrates pregnant women with mental health problems are at an increased risk of substance abuse and intimate partner problems *(Gold, 2012 [Low Quality Evidence])*. Recent studies are demonstrating that untreated paternal depression has an impact on infant and child development similar to untreated maternal depression *(Paulson, 2010 [Meta-analysis])*.

Risk factors and screening

Two key strategies facilitate early intervention: routine screening and monitoring of known risk factors. A large scale study by Kaiser Permanente *(Dietz, 2007 [Low Quality Evidence])* found that of those women identified and treated for depression, more than half had recurring indicators for depression. **Key risk factors** include:

- previous history of a mood disorder,
- depression or anxiety during pregnancy,
- poor social support,

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- stressful life events,
- fragmented or poor sleep,
- substance use,
- past or current abuse,
- premorbid or gestational diabetes, and
- difficulty breastfeeding in the first two months postpartum.

(Watkins, 2011 [Low Quality Evidence]; Coelho, 2010 [Low Quality Evidence]; Lancaster, 2010 [Systematic Review]; Dørheim, 2009 [Low Quality Evidence]; Goyal, 2009 [High Quality Evidence]; Pearlstein, 2008 [Low Quality Evidence])

Routine use of a self-report screening instrument that has been validated among pregnant women does not supplant clinical diagnosis *(Yonkers, 2009 [Low Quality Evidence])*. However, it significantly increases the incidence of systematic case finding over spontaneous detection during routine clinical evaluation *(Gjerdingen, 2007 [Low Quality Evidence])*. Routine maternal screening is highly recommended, followed by a clinical interview of those scoring above threshold *(Yonkers, 2009 [Low Quality Evidence])*.

See Appendix F, "Edinburgh Postnatal Depression Scale (EPDS)," for screening instruments and scoring instructions.

Perinatal depression treatment recommendations

The following recommendations come from the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG) work group *(Yonkers, 2009 [Low Quality Evidence])*.

Mild to moderate depression. Psychotherapeutic treatment recommendations for mild to moderate perinatal depression are interpersonal therapy (IPT) and cognitive behavioral therapy (CBT) *(Cuijpers, 2011[Meta-analysis]; O'Hara, 2000 [Systematic Review])*. Successful IPT treatment of antenatal depression has also improved functioning for six months postpartum. Existing literature clearly suggests that IPT and CBT are more efficacious than routine care for postpartum depression *(Cuijpers, 2011 [Meta-analysis]; O'Hara, 2009 [Low Quality Evidence])*.

There is promising preliminary evidence for bright light therapy, acupuncture, progressive relaxation, music therapy, reduced sleep deprivation, and exercise *(Pearlstein, 2008 [Low Quality Evidence])*. Evidence for omega-3 fatty acids is still insufficient; however, they pose little to no risk *(Freeman, 2008 [High Quality Evidence])*. Hormonal treatments such as estrogen or progesterone have not shown clear evidence for efficacy for postpartum depression, and in some cases may worsen symptoms *(Pearlstein, 2008 [Low Quality Evidence])*.

Moderate to severe depression. The recommendation for moderate to severe perinatal depression is antidepressant medication in combination with supportive interventions or psychotherapy *(Stewart, 2011 [Low Quality Evidence])*. Since partial SSRI treatment during pregnancy does not successfully treat the depression, it is not a recommended option *(Wisner, 2009 [Low Quality Evidence])*. Clinicians should be cautious in disrupting maintenance antidepressants during pregnancy. In a study of antidepressant discontinuation for pregnant women with a history of recurrent major depression, 68% relapsed, compared with 26% who maintained antidepressant treatment *(Cohen, 2006 [Low Quality Evidence])*.

Electroconvulsive therapy (ECT) may be considered. See Annotation #12, "Consider Other Strategies."

See the "Implementation Tools and Resources Table" for perinatal decision-making tools and clinical algorithms.

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Impact of antidepressants on neonates. Prenatal exposure to antidepressants has been associated with transient symptoms of possible medication withdrawal or toxicity in neonates *(Austin, 2006 [Low Quality Evidence])*. These neonatal syndromes have been described with most TCAs, SSRIs and non-SSRIs and can include jitteriness, irritability, breathing difficulties, bowel obstruction and urinary retention. These symptoms are transient and possibly confounded by physiologic effects from maternal depression and anxiety or other medications administered during delivery *(Ferreira, 2007 [Low Quality Evidence]; Austin, 2006 [Low Quality Evidence]; Oberlander, 2006 [Low Quality Evidence]; Sivojelezova, 2005 [Low Quality Evidence])*.

Pros and cons of tapering in late pregnancy. To minimize the risk of these neonatal syndromes, the FDA in 2004 encouraged antidepressant manufacturers to modify their drug labeling to include a recommendation to consider tapering antidepressants in the last part of pregnancy. For pregnant women at low risk for worsening depression or anxiety, this may be a reasonable strategy. However, for other women with moderate to severe depression or at high risk for postpartum depression, minimizing medication may undermine their emotional stability just as they enter the stressful period around delivery and the postpartum. After consultation with their physicians, pregnant patients who decide to discontinue or taper their doses of antidepressants should do so as gradually as possible over several weeks. Clinicians should monitor depression symptoms and overall well-being closely during this period, and should consider reinstating patients' higher maintenance dose of antidepressant after delivery.

Researchers who had published several of the original articles on the subject of these neonatal symptoms have not found any benefit in terms of reduction of neonatal effects with a late third-trimester "washout period" *(Warburton, 2010 [Low Quality Evidence])*.

Potential persistent pulmonary hypertension of the newborn (PPHN). While studies have evaluated a possible association between SSRI exposure after 20 weeks' gestation and persistent pulmonary hypertension of the newborn (PPHN), in 2011, the U.S. Food and Drug Administration issued a notification that "given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN." The FDA advisory committee suggested that health care professionals should "weigh the small potential risk of PPHN that may be associated with SSRI use in pregnancy against the substantial risks associated with under-treatment or no treatment of depression during pregnancy." (http://www.fda.gov/Drugs/DrugSafety/ucm283375.htm) *(Kieler, 2011 [Low Quality Evidence]; Austin, 2006 [Low Quality Evidence]; Bérard, 2006 [Low Quality Evidence]; Chambers, 2006 [Low Quality Evidence])*.

Postpartum depression

Postpartum women: Breastfeeding while taking antidepressants

For women with depression who require antidepressants, breastfeeding and remaining on medication can be highly compatible ways of caring for themselves and their infants. Clinicians can support nursing mothers with depression by helping them weigh the risks and benefits of different treatment options including supportive interventions and medication if indicated *(Davanzo, 2011 [Low Quality Evidence]*.

Clinicians should advise nursing women on psychotropic medications to monitor infants for behavioral changes such as excessive sedation, jitteriness or inconsolable crying. Infants who develop these symptoms should be evaluated by their clinician for possible drug toxicity.

For infants who are premature or have any medical problems, mothers on psychotropic medication who choose to breastfeed could consider pumping and storing/discarding breast milk until the infant is healthy and can metabolize medication more efficiently.

Consultation with a pediatrician or neonatologist may be warranted.

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7. Address Secondary Causes and/or Adapt a Plan for the Special Population

People with secondary causes for major depression may also have an underlying primary mood or anxiety disorder. Understanding and addressing nuances of special populations may enhance treatment outcomes. See Annotation #5, "Assess for the Presence of Substance Abuse or Psychiatric Comorbidity If Suspected," and Annotation #6, "Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations)?"

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8. Comprehensive Treatment Plan with Shared Decision-Making

Recommendations:

- A collaborative care approach is recommended for patients with depression in primary care *(High Quality Evidence, Strong Recommendation)*.
- A written and mutually agreed-upon treatment plan engaging the patient and family is recommended *(Low Quality Evidence, Strong Recommendation)*.
- Clinicians should discuss the spectrum of treatment options. These options include antidepressant medications and/or psychotherapy treatments and integrative medicine treatments *(Low Quality Evidence, Strong Recommendation)*.
- Clinicians should establish and maintain follow-up with patients *(Low Quality Evidence, Strong Recommendation)*.

Collaborative Care Model

Strong evidence

More than 37 randomized controlled trials have demonstrated the effectiveness of the collaborative care model, in which primary care treatment of depression is provided by a team (depression care manager, primary physician, consulting psychiatrist, others). The work group recommends three key references *(Gilbody, 2006 [Meta-analysis]; Hunkeler, 2006 [High Quality Evidence]; Katon, 1999 [High Quality Evidence])* . This model has demonstrated improvement in treatment adherence, patient quality of life and depression outcomes.

Beneficial impact on direct medical costs can also be found. Further dissemination of this model has been recommended *(Simon, 2001a [Low Quality Evidence])*. Katon summarizes and solidifies the argument for collaborative care in the treatment of depression, the direct and indirect economic benefits of collaborative care, as well as improved outcomes *(Katon, 2008 [Low Quality Evidence])*. Preliminary evidence suggests the collaborative care model is also effective for depression during pregnancy and postpartum *(Gjerdingen, 2008 [Low Quality Evidence])*.

Improved Patient Outcomes

Better medication compliance and reduced risk of relapse. The use of a collaborative care model can help with medication compliance, by providing closer follow-up than is possible without a care manager. Three or more follow-up visits in the first three months reduced the risk of relapse/recurrence of depression, as did continuous use of antidepressants *(Kim, 2011 [Low Quality Evidence])*. Care management facilitates continuous use of antidepressants, by providing close follow-up and early intervention when side effects occur.

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Reduced suicidal ideation. In the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) study, suicidal ideation rates declined in patients receiving care based on treatment guidelines and use of a care manager *(Bruce, 2004 [High Quality Evidence])*.

In the Improving Mood Providing Access to Collaborative Treatment (IMPACT) study, 1,801 primary care patients were randomly assigned to collaborative care or usual care. Intervention subjects had less suicidal ideation at 6 and 12 months, and there were no completed suicides for either group in 18 months *(Unützer, 2006 [High Quality Evidence])*.

The rewards for health care organizations that implement collaborative care models for their depressed patients are substantial, not only for the patients, but also for physician satisfaction. Of physicians participating in the IMPACT trial *(Levine, 2005 [Low Quality Evidence])*, only 54% were satisfied with the resources they had to treat depressed patients before the trial. This satisfaction was independent of practice setting (fee-for-service versus capitated). Sixty-four percent of physicians self-rated their ability to provide at least "very good" depression care before IMPACT. Eighty-five percent of clinicians before IMPACT felt that a collaborative care model would be helpful in treating patients with depression, diabetes or heart failure.

Afterwards, 90% of physicians described the collaborative care program as helpful in treating patients with depression. Ninety-three percent of physicians were at least somewhat satisfied with the resources available for treating depressed patients assigned to the IMPACT model, whereas only 61% were somewhat satisfied if their patients were assigned to usual care.

Ninety-four percent of clinicians rated the care managers as somewhat or very helpful in treating depression, and 82% indicated that IMPACT program improved their patients' clinical outcomes. Clinicians identified the two most helpful features of the program as "proactive patient follow-up" and "patient education" *(Levine, 2005 [Low Quality Evidence])*.

Implementing a Collaborative Care Approach

Design. The design of a team-based collaborative care approach *(Unützer, 2002 [High Quality Evidence])* involves:

- primary care clinicians using evidence-based approaches to depression care and a standard tool for measuring severity, response to treatment plan and remission;
- a systematic way of tracking and reminding patients at appropriate intervals of visits with their primary care physician and monitoring of treatment adherence and effectiveness;
- a team member (care manager role) to utilize the tracking system and make frequent contacts with the patients to provide further education, self-management support, and monitor for response in order to aid in facilitating treatment changes and in relapse prevention; and
- communication between primary care team and psychiatry to consult frequently and regularly regarding patient under clinical supervision, as well as direct patient visits as needed.

Challenges. There are challenges in providing the collaborative care model that need to be acknowledged and addressed by the health care organization. Some of these challenges include:

- Identifying depressed patients in the practice
- Identifying the desired background experience for care managers
- Establishing the responsibilities and scope of practice of the care managers
- Locating the care managers (centrally versus clinic-based)
- Deciding on type of care manager interaction with patients (telephonic versus face-to-face)

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- Determining level of supervision by psychiatrists
- Seeking adequate reimbursement for services provided to ensure program sustainability

(Belnap, 2005 [Low Quality Evidence])

See the "Implementation Recommendations" and " Implementation Tools and Resources Table" sections of this guideline for suggestions and information on implementing the collaborative care model.

Educate and Engage Patient

Successful care of major depression as an illness requires active engagement of each patient and his/her family, plus ongoing patient education, beginning at the time of diagnosis.

Often, the depressed patient's pessimism, low motivation, low energy, and sense of social isolation and guilt may lead to non-adherence with treatment *(American Psychiatric Association, 2010 [Guideline])*.

Patient Education

Topics to cover: Education topics should include:

- the cause, symptoms and natural history of major depression;
- treatment options and the process of finding the best fit for a given individual;
- information on what to expect during the course of treatment;
- how to monitor symptoms and side effects;
- follow-up protocol (office visits and/or telephone contacts);
- early warning signs of relapse or recurrence;
- length of treatment; and
- communication with the caregiver.

A patient should plan to make appointments for six months to one year. Frequency of visits will depend on depression severity. See "Establish Follow-Up Plan" further in this annotation.

Patient education should include diagnosis, prognosis and treatment options including costs, duration, side effects and expected benefits.

While the clinician goal of the PHQ-2 and PHQ-9 is detecting and diagnosing depression, these tools are, in real-world use, often used primarily in shared decision-making with patients to "suggest, tell, or convince patients to accept the diagnosis of depression" *(Baik, 2010 [Low Quality Evidence])*.

Support and education in the primary care setting are critical and contribute to the likelihood of good follow-through on treatment. It may help patients understand their options and resources if the primary care clinic explains that the support-plus-education component of treatment is not the same as a course of psychotherapy. Clinic staff may also want to identify a family member or support person of the patient's choosing and establish their role within the patient's treatment plan.

Key messages for patients and families: Emphasize the following points:

- Depression is a medical illness, not a character defect.
- Treatment is effective for most patients.
- The aim of treatment is remission – being predominately free of symptoms.

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- Relapse prevention is a key aspect of management – not just getting better, but also staying well. The risk of recurrence is significant: 50% after one episode, 70% after two episodes, 90% after three episodes *(NIMH/NIH Consensus Development Conference Statement, 1985 [Low Quality Evidence])*. Patient and family should be alert to early signs and symptoms of recurrence and seek treatment early if depression returns.

People of differing racial/ethnic groups can be successfully treated using currently available evidence-based interventions as long as distinctive personal elements, from biological to environmental to cultural, are considered during the treatment planning process *(Schraufnagel, 2006 [Low Quality Evidence])*.

Patient Engagement

Three broad types of patient engagement strategies have high-quality evidence supporting their use and documenting positive impacts: 1) patient self-management, 2) behavioral activation and 3) appropriate physical activity. This section provides a brief overview of each strategy and relevant literature.

Patient self-management

It is important for the patient to consider and adopt some self-care responsibilities. These responsibilities may range from simply demonstrating reliable behavior in taking medications and notifying the clinician about side effects to agreeing to participate in sessions, or journaling and completing homework, which is necessary for some cognitive behavioral therapies. Written materials are helpful to reinforce information shared during the discussion. Bibliotherapy, a therapy approach wherein the patient is encouraged to read self-help books and other relevant materials, has modest empirical support for benefitting patients who are motivated to augment their professional care with self-help literature *(Bower, 2013 [Meta-analysis]; Anderson, 2005 [Meta-analysis]; Gregory, 2004 [Meta-analysis])*.

See the "Implementation Tools and Resources Table" for examples of book titles.

Behavioral activation – scheduled pleasant activities

Activity scheduling is a straightforward behavioral intervention in which patients are taught to increase their daily involvement in pleasant activities and to increase their positive interactions with the environment *(Lewinsohn, 1973 [Low Quality Evidence])*. This is an attractive intervention for the treatment of depression because it is simple in concept, easily taught, and efficient. In addition, behavioral activation does not require complex skills on the part of either patient or clinician.

A meta-analysis of 16 studies conducted over the past 30 years and another including 34 studies over the past 40 years demonstrated that activity scheduling produces improvement in depression comparable to other manualized treatments for depression (such as cognitive behavioral therapy). Moreover, follow-up assessments showed that the improvements in depression persisted after the active treatment had been discontinued *(Mazzucchelli, 2009 [Meta-analysis]; Cuijpers, 2007 [Meta-analysis])*.

The relative simplicity of encouraging patients to increase their daily participation in pleasant activities makes activity scheduling an attractive treatment approach for individuals who may be difficult to treat, such as depressed dementia patients or depressed elderly patients. Regular outings and get-togethers, participation in a senior day care program, participation in available nursing home activities, etc., are all likely to reduce depression in the elderly *(Cuijpers, 2007 [Meta-analysis])*.

Appropriate physical activity

Evidence suggests that physical activity at a dose consistent with public health recommendations is a useful tool for easing major depression symptoms (*Dunn, 2005 [High Quality Evidence]; Babyak, 2000 [High Quality Evidence])*. Exercise has been shown to work well as monotherapy or adjuvant to medication in moderate depression. Exercise has shown promise as adjuvant therapy in treatment-resistant major depression in women, and there is a small but growing body of evidence of some long-term as well as preventive attributes *(Schuch, 2011 [High Quality Evidence]*.

When prescribing exercise either alone or as an adjunct to medication and psychotherapy, the complexity and the individual circumstances of each patient must be considered. When creating an exercise prescription, several caveats apply:

- Anticipate barriers. Hopelessness and fatigue can make physical exertion difficult.
- Keep expectations realistic. Some patients are vulnerable to guilt and self-blame if they fail to carry out the regime.
- Introduce a feasible plan. Walking, alone or in a group, is often a good option.
- Accentuate pleasurable aspects. The specific choice of exercise should be guided by the patient's preferences; the exercise must be pleasurable.
- Encourage adherence. Greater antidepressant effects are seen when training continues beyond 16 weeks.
- A goal of 30 minutes of moderate-intensity aerobic exercise, three to five days a week is recommended for otherwise healthy adults (17.5 kcal/kg/week of total energy expenditure). For more information, see the ICSI Prevention and Management of Obesity guideline.

Discuss Treatment Options

Primary goal. When considering treatment options, the primary goal is to achieve remission or to get the patient to be predominately symptom-free (i.e., a PHQ-9 score of less than five *(Kroenke, 2001 [Low Quality Evidence])* or a HAMD-17 score of less than or equal to 7) *(Zimmerman, 2004 [Low Quality Evidence])*.

Shared decision-making. Shared decision-making is a practice that guides patients, families and physicians through a reliable process that incorporates patient values, priorities and goals into discussions of risks and benefits of treatment options *(O'Connor, 2007 [Systematic Review])*.

Central aspects of the patient-physician partnership include exploring antidepressant concerns, working with treatment preferences, and providing continued supportive management.

There is at present a lack of good quality research evidence about the long-term effects of shared decision-making interventions in mental health conditions *(Duncan, 2010 [Systematic Review])*. A mismatch between patients' preferred and prescribed treatment acts as a significant barrier to sustained adherence *(Hunot, 2007 [Low Quality Evidence])*. Patient participation in shared treatment decision-making improves depression treatment adherence and clinical outcomes in depressed patients *(Loh, 2006 [Low Quality Evidence])*.

There is also evidence that mental health patients want to participate in health care decisions and to have more information about their illness and potential treatments *(Adams, 2007 [Low Quality Evidence]; Hamann, 2005 [Low Quality Evidence]; Garfield, 2004 [Low Quality Evidence])*. Clinical guidelines and health policies are already advocating the use of shared decision-making for other conditions, in advance of evidence of positive effect, but further research is urgently needed in this area *(National Institute for Health and Clinical Excellence, 2011 [Guideline])*.

Psychotherapy and pharmacotherapy

Presentation influences choice. If the initial presentation is mild to moderate, either an antidepressant or psychotherapy (or both) is indicated. If the presenting symptoms of depression are severe or chronic, the initial recommendation is to treat with antidepressants and psychotherapy. See the table "Translating PHQ-9 Depression Scores into Practice Based on DMS-5 Criteria" in this annotation.

In mild to moderate levels of depression, psychotherapy can be equally as effective as medication *(Williams, 2000 [High Quality Evidence])*. With severe depression, antidepressant medication may be necessary

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(Manber, 2003 [High Quality Evidence]). In the STAR*D study, CBT had equal efficacy to the addition of another antidepressant medication, or to the switching of antidepressant medication, when the patient had not responded to the initial medication *(Shelton, 2010 [Low Quality Evidence])*. If the patient presents with comorbid anxiety and initial pharmacological treatment does not work, refer patient for anxiety-based CBT for anxious depression and behavioral activation *(Farabaugh, 2012 [Low Quality Evidence])*.

Evidence supporting psychotherapy, alone or with pharmacotherapy. According to a meta-analysis focusing on response, remission and relapse *(Oestergaard, 2011 [Systematic Review])*, pharmacotherapy enhanced with psychotherapy was associated with a higher probability of remission and a lower risk of relapse, as compared with antidepressants alone for depression treatment. In addition, receiving psychotherapy in both the acute and continuation phases was the most effective option. There is documentation to support lower relapse rates and outcomes among patients receiving psychotherapy *(Leichsenring, 2007 [Meta-analysis]; Teasdale, 2001 [High Quality Evidence])*.

Factors to consider in making treatment recommendations. Consider symptom severity and chronicity, presence of psychosocial stressors, presence of comorbid conditions, cultural/health beliefs, resource accessibility and sufficiency, and patient preferences. Patients who perceive more self-control of their health experience greater reduction in depressive symptoms, whether treated with psychotherapy or an antidepressant *(Brown, 2000 [Low Quality Evidence])*. Results from a systematic review found clinical benefits when racial and ethnic minority female patients were allowed to choose their treatment (medication, psychotherapy or both) and were provided support and outreach services *(Ward, 2007 [Systematic Review])*. Because both antidepressants and psychotherapy are effective, careful consideration of patient preference for mode of treatment is appropriate *(Dimidjian, 2006 [High Quality Evidence]; De Jonghe, 2004 [High Quality Evidence]; King, 2000 [High Quality Evidence])*. (See the table "Translating PHQ-9 Depression Scores into Practice Based on DMS-5 Criteria" in this annotation, and Annotation #6, "Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations)?"

Psychotherapy

As with all depression treatment, the goal of psychotherapy is to reach remission and prevent or minimize relapse. Offer a referral for psychotherapy whenever psychological or psychosocial issues are prominent, or if the patient requests it.

Documented effectiveness. Cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), short-term psychodynamic psychotherapy (STPP) and problem-solving treatment (PST) have documented efficacy *(Nieuwsma, 2012 [Systematic Review]; Cuijpers, 2011 [Meta-analysis]; Cahill, 2003 [Low Quality Evidence]; Merrill, 2003 [Low Quality Evidence]; Ward, 2000 [High Quality Evidence])*. Early research on Internet-delivered psychotherapy for depression in adults is also promising *(Titov, 2011 [Low Quality Evidence])*.

Mindfulness-based therapies have been demonstrated as effective in reducing symptoms of anxiety and depression, and in reducing the incidence of relapse in depression *(Beshai, 2011 [Low Quality Evidence]; Klanin-Yobas, 2011 [Meta- analysis]; Vollestad, 2011 [Systematic Review])*.

Early research on protocolized computer-based CBT for depression in adults is also promising *(Titov, 2011 [Low Quality Evidence])*.

There is now significant evidence that psychotherapy plus medication is better than medication alone for moderate to severe unipolar depression *(Cuijpers, 2011 [Meta-analysis])*. In primary care settings, brief CBT and PST (defined as eight or fewer sessions) were effective treatments for the acute phase of depression and demonstrated modest effect sizes comparable to antidepressant medication and standard duration psychotherapy treatments *(Nieuwsma, 2012 [Systematic Review])*. Psychotherapy, especially focused psychotherapy, can significantly reduce symptoms, restore psychosocial and occupational functioning, and prevent relapse in patients with major depression *(Leichsenring, 2004 [Meta-analysis])*. Maintenance psychotherapy is useful in managing chronic forms of major depressive disorder *(Klein, 2004 [High Quality*

Evidence]). Evidence-based psychotherapy for depression does not specifically address treatment where there is comorbid anxiety.

Following up is essential. If the patient is newly involved in psychotherapy, the following are important:

- Contact with patient in 4 to 6 weeks
- Communicate with therapist in 4 to 6 weeks
- Return visit in 8 to 10 weeks to evaluate progress
- Communicate to the patient that it can take 8 to 10 weeks of regular and frequent therapy to show improvement

Integrative Medicine

While there are many integrative treatments available, our discussion highlights some of the types of treatments. They include acupuncture, yoga, herbs and dietary supplements. They were selected because they are evidence based and/or more commonly utilized.

Mindfulness-based stress reduction

Mindfulness-based stress reduction (MBSR) is a structured group program based on use of mindfulness meditation to reduce suffering associated with physical, psychosomatic and psychiatric disorders. It has received much attention since 2000 and has been found to be effective in reducing symptoms of depressive and risk of relapse *(Grossman, 2004 [Meta-analysis])*.

Acupuncture and yoga

Existing meta-analyses and systematic reviews vary with respect to acupuncture protocol (manual, electroacupuncture or sham), methodological soundness and efficacy results *(Freeman, 2010 [Systematic Review])*. Both sham and active acupuncture participants generally report symptomatic depression improvement *(Freeman, 2010 [Systematic Review])*. Serious adverse events from acupuncture are very uncommon, which may appeal to those who seek to avoid side effects associated with traditional treatments (e.g., medication side effects). Rigorous positive studies are needed before acupuncture can be recommended for the treatment of major depressive disorder.

Acupuncture and yoga are both effective as adjunctive treatment to decrease severity of symptoms *(Ravindran, 2009 [Guideline])*.

Herbals and dietary supplements

Caution: Many drugs interact with St. John's Wort, including other antidepressants, warfarin, oral contraceptives, antiretroviral, anti-cancer and anti-rejection drugs. Care should be taken to ask all patients what medications they are taking, including over-the-counter and supplements, to avoid these interactions.

Herbal products and nutritional supplements are not evaluated or regulated by the U.S. Food and Drug Administration for safety, efficacy or bioavailability.

St. John's Wort and Sam-E. In a meta-analysis *(Morgan, 2008 [Systematic Review])*, S-adenosylethione (Sam-E) and hypericum perforatum (St. John's Wort) were found to have indications for mild to moderate depression but not major depression. Sam-E and St. John's Wort should not be taken in combination with other antidepressant medications.

A Cochrane meta-analysis concluded that there is insufficient evidence to recommend the use of acupuncture or St. John's Wort in the treatment of major depression. Research is limited by lack of large scale RCTs

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and high risk of bias in the majority of trials meeting inclusion criteria for the meta-analysis *(Smith, 2010 [Systematic Review]; Linde, 2008 [Systematic Review])*.

Possible link between deficiency and depression. A number of researchers have published studies and review articles regarding an increased risk of depression in patients with low levels of zinc, omega-3 fatty acid or magnesium. Unfortunately, studies on appropriate supplementation of these dietary aides are often inconsistent in their design and results. While the replacement of zinc, omega-3 fatty acid and magnesium in patients with known deficiencies and who have major depression is often recommended, the exact dosages and durations of supplementation are not known *(Appleton, 2010 [Systematic Review]; Siwek, 2010 [High Quality Evidence]; Colangelo, 2009 [Low Quality Evidence])*.

Omega-3 fatty acid not helpful as treatment. A recent meta-analysis of randomized, placebo-controlled trials of omega-3 fatty acid (FA) in the treatment of major depressive disorder was designed to analyze the efficacy of omega-3 FAs in the treatment of MDD and to examine possible sources of heterogeneity between trials. The meta-analysis demonstrated no significant benefit of omega-3 FA treatment compared with placebo and significant heterogeneity in study design, as well as publication bias *(Bloch, 2011 [Systematic Review])*.

Vitamin D. At this time, there is insufficient evidence on the antidepressant effects of vitamin D *(Thacher, 2011 [Low Quality Evidence])*.

Medications

The first part of the "Medications" section discusses patient messages and monitoring, regardless of the medication selected. The second section reviews the process of selecting an antidepressant medication and then provides overviews of the major categories. The third section reviews two special situations: Medication interactions, and elderly patients.

The acute treatment phase is focused on treating the patient to remission. Acute therapy typically lasts 6-12 weeks but technically lasts until remission is reached *(American Psychiatric Association, 2010 [Guideline])*.

Definition: Full remission is defined as a two-month period devoid of major depressive signs and symptoms.

Adherence, Patient Interaction and Monitoring

Adherence is paramount. For antidepressant medications, adherence to a therapeutic dose and meeting clinical goals are more important than the specific drug selected. Successful treatment often involves dosage adjustments and/or trial of a different medication at some point, to maximize response and minimize side effects *(American Psychiatric Association, 2010 [Guideline])*.

Key messages for patients using antidepressant therapy. When antidepressant therapy is prescribed, the following key messages should be highlighted to support medication adherence and completion:

- Side effects from medication often precede therapeutic benefit and typically recede over time. It is important to expect some discomfort prior to the benefit.
- Successful treatment often involves dosage adjustments and/or trial of a different medication at some point to maximize response and minimize side effects.
- Most people need to be on medication at least 6-12 months after adequate response to symptoms.
- Patients may show improvement at two weeks but need a longer length of time to really see response and remission.
- Take the medication as prescribed, even after you feel better. Premature discontinuation of antidepressant treatment has been associated with a 77% increase in the risk of relapse/recurrence of symptoms *(Melfi, 1998 [Low Quality Evidence])*. The probability of recurrence of depressive symptoms was found to be 25% after one year, 42% after two years, and 60% after five years in

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one study *(Solomon, 2000 [Low Quality Evidence])*. Each episode of recurrence increased the risk of subsequent episodes by 16% *(Solomon, 2000 [Low Quality Evidence])*.

- Do not stop taking the medication without calling your clinician. Side effects often can be managed by changes in the dosage or dosage schedule.

Adherence strategies. Consider increasing education, engagement and follow-up for patients who are at higher risk for not adhering to treatment. For antidepressant treatment this includes patients who are newly diagnosed with depression, in the midst of their first depression, or who have lapsed in the middle of a previous course of treatment *(Vanelli, 2008 [Low Quality Evidence])*. In addition to medication monitoring, clinical management of patients placed on antidepressants should include the clinician's support and reassurance.

Risks for children, adolescents and young adults. The U.S. Food and Drug Administration has requested manufacturers of antidepressants include a warning statement regarding antidepressants increasing the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults. The full warning statement can be found at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273. FDA-approved medication guides are required to be distributed to patients who receive antidepressants. A complete list of specific medication guides can be found at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273.

Be alert for worsening of symptoms. Health care clinicians should carefully evaluate their patients in whom depression persistently worsen, or emergent suicidality is severe, abrupt in onset, or was not part of the presenting symptoms. Reassessment is required to determine what intervention, including discontinuing or modifying the current drug therapy, is indicated.

The clinician should instruct the patient and the patient's caregiver to be alert for the emergence of agitation, irritability and other symptoms. The emergence of suicidality and worsening depression should be closely monitored and reported immediately to the clinician.

See also Annotation #4, "Is Patient Unsafe to Self or Others?"

Selection of an antidepressant medication

The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications *(American Psychiatric Association, 2010 [Guideline])*. However, there are distinct differences in side effects caused by the classes of medications and individual agents.

Antidepressant drug selection should be based on:

- The patient's and family history of response to previous antidepressant medications (if any)
- Clinician experience with specific antidepressants
- Patient preferences
- Side effect profile (e.g., sedating, activating, weight gain, impact on sex life). Antidepressant medications with anticholinergic side effects contribute to dry mouth/xerostoma, caries, gingivitis and periodontal disease *(Tscoppe, 2010 [Low Quality Evidence]; Shinkai, 2006 [Low Quality Evidence])*. This risk should be discussed with patients prior to initiation of these medications.
- Safety in overdose (e.g., 10 days of a TCA can be a lethal overdose)
- Availability and costs
- Drug-drug interactions
- Positive or negative impacts on the patient's comorbid psychiatric or medical conditions (for example, smoking cessation, ADHD)

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- **Anxiety**

  The good news for the primary care clinician is that there is a great deal of overlap between effective pharmacotherapy for major depression, panic disorder, and generalized anxiety disorder. Selective serotonin reuptake inhibitors, (SSRIs) seratonin norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressant (TCAs) demonstrate efficacy in numerous controlled trials *(American Psychiatric Association, 2013 [Guideline])*. The favorable safety and side effect profiles of SSRIs and SNRIs make them natural first considerations for treating comorbid anxiety disorders. While similarly efficacious, TCAs introduce greater risk in overdose and potential side effects. With all antidepressant medications used to treat anxiety, consider a lower initial starting dose due to potential increased sensitivity to side effects in patients with panic and generalized anxiety disorders. Once the patient tolerates the lower starting dose, advance the dose gradually to a therapeutic and tolerable dose to minimize partial response and non-response *(American Psychiatric Association, 2013 [Guideline])*. Reference to psychotherapy section. For further discussion of assessment and treatment for anxiety, see Annotation #5, "Assess for the Presence of Substance Abuse or Psychiatric Comorbidity If Suspected."

- **Panic Disorder**

  Evidence supports benzodiazepine use in panic disorder treatment *(American Psychiatric Association, 2013 [Guideline])*. We encourage cautious and limited use due to risk for dependence and abuse. Benzodiazepines can be an effective means to manage more severe panic symptoms early in the initiation of other therapy (e.g., antidepressant or psychotherapy) or with acute exacerbation of anxious symptoms. If used, a scheduled course of a longer-acting benzodiazepine, such a clonazepam, is recommended over a shorter-acting benzodiazepine, such as alprazolam.

  Just as in the management of major depression, close initial follow-up is advised to gauge response to therapy. Additional medication options include use of or augmentation with mirtazapine, gabapentin or pindolol. The evidence for the use of these is less robust than for the medications above *(Freire, 2011 [Low Quality Evidence]; American Psychiatric Association, 2013 [Guideline])*.

- **Insomnia**

  When selecting an antidepressent in a patient whose symptoms include insomnia, consider prescribing a sedating antidepressant (e.g., trazodone, mirtazapine). If acute relief is needed, consider a benzodiazepine for short-term usage, but it is not recommended for long-term use. Also consider selective GABA agonist hypnotic (e.g., zolpidem, eszopiclone). The most common side effect of mirtazapine is sedation. It may be prescribed for depressed patients with initial insomnia and given at bedtime.

The Texas Medication Algorithm Project (TMAP) provides good overall parameters for care. See the "Implementation Tools and Resources Table" for more information. The STAR*D study has updated data on treatment response timelines and follow-ups.

There is no evidence regarding choice of brand versus generic based on adverse clinical outcomes.

While genetic differences in the metabolism of certain medications including antidepressants can be determined by genetic testing, the clinical significance and applicability to practice has not yet been established.

For up-to-date prescribing information, the work group recommends the following references:

- The Physician's Desk Reference: http://www.pdr.net
- The American Hospital Formulary Service (AHFS): http://ashp.org/ahfs

- Micromedex: http://www.micromedex.com
- Epocrates: http://epocrates.com

Consider discussing with the patient the specific side effect profiles, costs and benefits of different antidepressants, including generics. Cost implications for patients need to be discussed between clinician and patient.

Is medication needed? A meta-analysis of efficacy of acute (three-month) treatment with antidepressants *(Fournier, 2010 [Meta-analysis])* for depression suggested that for sub-clinical, mild or moderately depressed patients, antidepressants may not be better than placebo. They suggested that for short-term and less-severe patients, behavioral activation plus lifestyle modifications may be enough. But there is not enough evidence to change the recommendations.

Selective Serotonin Reuptake Inhibitors (SSRIs) and other antidepressants

For information about comparative benefits and harms of second-generation antidepressants, view Table 1 in the following article:

> Gartlehner G, Gaynes BN, Hansen RA, et al. Comparative benefits and harms of second-generation antidepressants: background paper for the American college of physicians. *Ann Intern Med* 2008;148:734-50.

SSRIs – as well as venlafaxine, duloxetine, desvenlafaxine, mirtazapine and bupropion – are frequently recommended as first-line antidepressant treatment options due to the quality and quantity of published data, relative tolerability of side effects compared to TCAs and MAOIs, and their overall relative safety *(American Psychiatric Association, 2013 [Guideline]; Trivedi, 2001 [Low Quality Evidence])*. They generally lack the common adverse reactions (anticholinergic, sedative effects) of the tricyclics and cause fewer problems when taken in overdose. However, they may cause headache, nervousness, insomnia and sexual side effects. They may also be more expensive because some may not yet be available as generics.

Citalopram Warning

In 2011, the Food and Drug Administration (FDA) published a "Medwatch" drug safety alert regarding the potential risk of abnormal heart rhythms associated with citalopram doses greater than 40 mg a day due to concerns about prolonged QT interval prolongation and the risk for torsades de pointes. Prescribers were initially told to avoid using citalopram doses higher than 40 mg and discouraged from using it at all in patients with congenital long QT syndrome, bradyarrhythmias, congestive heart failure, or at risk for developing hypokalemia or hypomagnesemia. In March 2012 this was revised by downgrading the warning from "contraindicated" to "not recommended" for patients with congenital long QT syndrome because patients with this condition have few viable alternative treatments. Ongoing monitoring was suggested, a maximum dose of 20 mg/day was recommended for age > 60, and discontinuation was recommended when QTc > 500ms.

A recent review of Veterans Health Administration patients who were prescribed citalopram between 2004 and 2009 (N=618,450) found daily doses of citalopram greater than 40 mg a day were associated with lower risks of ventricular arrhythmias, all-cause mortality, and non-cardiac mortality, compared with lower doses of citalopram. Overall, no increased risks of cardiac mortality were observed. These results were similar when compared with a cohort of patients prescribed sertraline (N=365,898) during the same time period.

Secondary amine tricyclics (TCAs)

The literature clearly supports the effectiveness of tricyclics. Because of associated side effects, TCAs are used less frequently as first-line agents.

Secondary (nortriptyline) amine tricyclics cause less orthostatic hypotension and sedation than do tertiary (amitriptyline) amine tricyclics.

These medications should be monitored cautiously in patients with heart problems, or in patients with potential for drug interactions. Monitoring blood levels and EKG may be advised.

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Monoamine oxidase inhibitors (MAOIs)

MAOIs, in general, should be restricted for patients who do not respond to other treatments, because of the potential for serious side effects and the necessity of dietary restrictions. Patients who have major depressive disorders with atypical features are one group for whom several studies suggest MAOIs may be particularly effective. However, in clinical practice, many psychiatrists start with SSRIs in such patients because of the more favorable adverse effect profile. Consider a dietary and/or psychiatry consultation if prescribing MAOIs.

Atypical antipsychotics

There is some evidence regarding the use of quetiapine as monotherapy for the treatment of major depression *(Zhornitsky, 2011 [Systematic Review])*.

Serotonin syndrome

Serotonin syndrome is a potentially life-threatening, pharmacodynamic drug interaction resulting in excessive nervous system levels of serotonin. Patients experiencing this reaction may present with mental status changes such as anxiety, confusion, delirium or coma. Autonomic symptoms may include tachycardia, labile blood pressure and hyperthermia. Muscle rigidity, ataxia, tremor, myoclonus and other neurologic symptoms are also common.

Serotonin syndrome has often been inaccurately reported and erroneously attributed to various serotonergic medications. Specific diagnostic criteria have been developed to assist prescribers in the diagnosis of the "toxidrome" *(Evans, 2010 [Low Quality Evidence]; Gillman, 2006 [Low Quality Evidence])*. Rather than an idiosyncratic reaction, serotonin syndrome, or serotonin toxicity, is the result of drug-induced elevations of intrasynaptic serotonin. Not all serotonergic agents are capable of producing the intrasynaptic elevation of serotonin associated with true serotonin toxicity *(Gillman, 2006 [Low Quality Evidence])*.

The primary criterion for an accurate diagnosis and risk assessment is recent exposure to a serotonergic agent or combination of agents able to produce significant elevations of synaptic serotonin. According to the Hunter Area Toxicology Service (HATS) data, the higher levels of intrasynaptic serotonin caused by combinations of MAOIs with an SSRI are likely to cause hyperpyrexia and death. The combinations of clomipramine, imipramine or venlafaxine with an MAOI have also been associated with fatalities *(Gillman, 2006 [Low Quality Evidence])*.

In 2006, the FDA issued a warning about the life-threatening risk of combining SSRIs with triptans (for the treatment of migraine headaches). The warning included 29 case reports. Subsequent reviews of these cases found all reports were Class IV level of evidence. Most of the case reports were incomplete and often did not meet established diagnostic criteria for serotonin syndrome. Current evidence does not support limiting the use of triptans with SSRIs or SNRIs *(Evans, 2010 [Low Quality Evidence]; Gillman, 2010 [Low Quality Evidence]; Wenzel, 2008 [Low Quality Evidence])*.

Medication interactions with antidepressant agents

Many antidepressant agents have clinically significant drug interactions, particularly those agents that undergo cytochrome P450 enzymatic metabolism in the liver. A complete discussion of this topic is beyond the scope of this guideline. Practitioners are advised to consult references such as the Physician's Desk Reference, American Hospital Formulary Service, Epocrates or Micromedex for more information about drug interactions with specific agents, and to assess the significance of the interaction prior to prescribing antidepressants.

Elderly patients

Because of the potential for decreased renal and hepatic function, and also for concomitant diseases and medications, the elderly are at higher risk of significant side effects or drug interactions with antidepressant

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medications. For elderly patients with moderate to severe depression, TCAs such as nortriptyline continue to be regarded as the most effective treatment *(Alpert, 2003 [Low Quality Evidence]; Gastó, 2003 [High Quality Evidence])*. Consider starting at the lowest possible dose and increasing slowly to effective dose or until side effects appear. Tertiary amine tricyclics should generally be avoided in elderly patients because of the high incidence of orthostatic hypotension, sedation, cognitive problems and cardiac effects with these agents.

Establish Follow-Up Plan

Proactive follow-up contacts (in person, telephone) based on the collaborative care model have been shown to significantly lower depression severity *(Unützer, 2002 [High Quality Evidence])*. In the available clinical effectiveness trials conducted in real clinical practice settings, even the addition of a care manager leads to modest remission rates *(Trivedi, 2006b [High Quality Evidence]; Unützer, 2002 [High Quality Evidence])*. Interventions are critical to educating the patient regarding the importance of preventing relapse, safety and efficacy of medications and management of potential side effects. Establish and maintain initial follow-up contact intervals (office, phone, other) *(Hunkeler, 2000 [High Quality Evidence]; Simon, 2000 [High Quality Evidence])*.

PHQ-9 as montitor and management tool. The PHQ-9 is an effective management tool, as well, and should be used routinely for subsequent visits to monitor treatment outcomes and severity. It can also help the clinician decide if/how to modify the treatment plan *(Duffy, 2008 [Low Quality Evidence]; Löwe, 2004 [Low Quality Evidence])*. Using a measurement-based approach to depression care, PHQ-9 results and side effect evaluation should be combined with treatment algorithms to drive patients toward remission. A five-point drop in PHQ-9 score is considered the minimal clinically significant difference *(Trivedi, 2009 [Low Quality Evidence])*.

Translating PHQ-9 Depression Scores into Practice Based on DSM-5 Criteria

PHQ-9 Symptoms and Impairment	PHQ-9 Scores	Intensity	Treatment Recommendations (for treatment durations, see also Annotation #10)
1-4 symptoms minimal functional impairment	5-9	Subclinical	• Education to call if deteriorates • Physical activity • Behavioral activation • If no improvement after one or more months, consider referral to behavioral health for evaluation • Consider for persistent depressive disorder*
2 symptoms, #1 or #2 > 0 score 2 +, functional impairment	10-14	Mild Major Depression	• Pharmacotherapy, psychotherapy, or both • Education • Physical activity • Behavioral activation • Initially consider weekly contacts to ensure adequate engagement, then at least monthly
≥ 3 symptoms, #1 or #2 > 0 score 2 +, functional impairment	15-19	Moderate Major Depression	• Pharmacotherapy psychotherapy, or both • Education • Physical activity • Behavioral activation • Initially consider weekly contacts to ensure adequate engagement, then minimum every 2-4 weeks
≥ 4 symptoms, question #1 or #2 > 0 score 2 +, marked functional impairment, motor agitation	≥ 20	Severe Major Depression	• Pharmacotherapy necessary and psychotherapy when patient is able to participate • Education • Physical activity • Behavioral activation • Weekly contacts until less severe

This table is designed to translate the PHQ-9 scores into DSM-5 categories and then integrate evidence-based best practice. It does not directly correspond to the PHQ-9 Scoring Guide in Appendix A, "Patient Health Questionnaire (PHQ-9)."

(Sources: Fournier, 2010 [Meta-analysis]; Trivedi, 2009 [Low Quality Evidence]; Cuijpers, 2007 [Meta-analysis]; Hunot, 2007 [Low Quality Evidence]; Kroenke, 2010 [Systematic Review])

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* Persistent depressive disorder is defined as low-level depression most of the day for more days than not for at least two years. Must include presence of at least two of the listed DSM-5 criteria affecting appetite, sleep, fatigue, self-esteem, concentration/ decision-making or hopelessness). Initiate pharmacotherapy or refer to mental health specialty clinician for evaluation, or both. See also Annotation #2, "Diagnose and Characterize Major Depression with Clinical Interview."

Referral or co-management with mental health specialty clinician if patient has:

- High suicide risk
- Inadequate treatment response
- Other psychiatric disorders such as bipolar, substance abuse, etc.
- Complex psychosocial needs

If the primary care clinician is seeing some improvement, continue working with that patient to increase medication dosage or augment with psychotherapy or medication to reach remission. This can take up to three months. Don't give up on the patient whether treating in primary care or referring. Stay connected through consultation or collaboration, and take the steps needed to get the patient to remission. This can take longer and can take several medication interventions or other steps. The STAR*D study has shown that primary care can be just as successful as specialty care *(Trivedi, 2006a [High Quality Evidence])*.

Relapse prevention

The prevention of relapse is of primary importance in the treatment of major depression. From 50 to 85% of people who suffer an episode of major depression will have a recurrence, usually within two or three years. Patients who have had three or more episodes of major depression are at 90% risk of having another episode. Relapse prevention interventions resulted in 13.9 additional depression-free days during a 12-month period *(Simon, 2002 [High Quality Evidence])*.

Focused psychotherapy through cognitive-behavioral therapy can reduce relapse by assisting patients with their depression-related beliefs *(Teasdale, 2001 [High Quality Evidence])*. In addition, focused psychotherapy can significantly reduce symptoms, and restore psychosocial and occupational functioning, in patients with major depression *(Leichsenring, 2004 [Meta-analysis])*.

Katon, et al., found that improving attitudes toward antidepressant medications, along with the patient's ability to handle medication side effects, are key factors in promoting greater adherence to maintenance treatment and thus greater likelihood of preventing relapse *(Katon, 1996 [High Quality Evidence])*. It is important to recognize that Katon and colleagues worked within a relatively small, closed system (Group Health Seattle) where tracking and registry information were readily available. They also had financing available to cover the training of depression prevention specialists, as well as the expense of visits, phone calls and follow-up letters. However, from a clinical standpoint, Katon's work demonstrates significant benefit for the patient *(Lin, 2003b [High Quality Evidence]; Crawford, 2002 [Systematic Review]; Katon, 2001 [High Quality Evidence])*.

Collaboration with mental health

Consider collaborating with a behavioral health care clinician for the following:

- Patient request for psychotherapy
- Presence of severe symptoms and impairment in patient, or high suicide risk
- Presence of other psychiatric condition (e.g., personality disorder, history of mania)
- Suspicion or history of substance abuse
- Clinician discomfort with the case

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- Medication advice (psychiatrist or other mental health prescriber)
- Patient request for more specialized treatment

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9. Is Patient Responding Adequately?

The **goals** of treatment should be to achieve remission, reduce relapse and recurrence, and return to previous level of occupational and psychosocial function.

Remission is defined as the absence of depressive symptoms, or the presence of minimal depressive symptoms such as HAM-D score of less than 7 or a PHQ-9 score of less than 5.

Response is defined as a 50% or greater reduction in symptoms (as measured on a standardized rating scale). Partial response is defined as a 25-50% reduction in symptoms.

Results from the STAR*D study showed that remission rates lowered with more treatment steps, but the overall cumulative rate was 67% *(Rush, 2006 [High Quality Evidence])*.

Response and remission take time. In the STAR*D study, longer times than expected were needed to reach response or remission. In fact, one-third of those who ultimately responded did so after six weeks. Of those who achieved QIDS remission, 50% did so only at or after six weeks of treatment *(Trivedi, 2006b [High Quality Evidence])*. If the primary care clinician is seeing some improvement, continue working with that patient to augment or increase dosage to reach remission. This can take up to three months.

A reasonable criterion for extending the initial treatment: assess whether the patient is experiencing a 25% or greater reduction in baseline symptom severity at six weeks of therapeutic dose. If the patient's symptoms are reduced by 25% or more, but the patient is not yet at remission, and if medication has been well tolerated, continue to prescribe. Raising the dose is recommended *(Trivedi, 2006b [High Quality Evidence])*.

Improvement with psychotherapy is often a bit slower than with pharmacotherapy. A decision regarding progress with psychotherapy and the need to change or augment this type of treatment may require 8 to 10 weeks before evaluation *(Schulberg, 1998 [Low Quality Evidence])*.

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10. Continuation and Maintenance Treatment Duration Based on Episode

Cognitive therapy and behavioral activation. Skill building and self-management practices learned through behavioral activation – plus other beneficial cognitive, behavioral, social and exercise activities – are recommended for continuation and maintenance of depression treatment *(Mazzucchelli, 2009 [Meta-analysis]; Vittengl, 2009 [High Quality Evidence]; Cuijpers, 2007 [Systematic Review])*. Recent studies demonstrate an enduring benefit of cognitive therapy and behavioral activation comparable to maintenance pharmacotherapy in reducing major depressive episode relapse and recurrence beyond one year of treatment *(Segal, 2010 [High Quality Evidence]; Dobson, 2008 [High Quality Evidence]; Hollon, 2005a [High Quality Evidence])*.

Patients withdrawn from cognitive therapy were significantly less likely to relapse compared to patients withdrawn from pharmacotherapy; furthermore, those withdrawn from cognitive therapy were no more likely to relapse than those who continued pharmacotherapy *(Hollon, 2005a [High Quality Evidence])*. For patients who reached remission but had periodic depressive symptoms (defined as unstable remission), mindfulness-based cognitive therapy or continuation pharmacotherapy significantly reduced depression relapse and recurrence rates *(Segal, 2010 [High Quality Evidence])*.

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Acute therapy is the treatment phase focused on treating the patient to remission. Acute therapy typically lasts 6-12 weeks but technically lasts until remission is reached *(American Psychiatric Association, 2010 [Guideline])*. Full remission is defined as a two-month period devoid of major depressive signs and symptoms *(American Psychiatric Association, 2000 [Guideline])*.

Continuation therapy is the 4-9 month period beyond the acute treatment phase during which the patient is treated with antidepressants, psychotherapy, ECT or other somatic therapies to prevent relapse *(American Psychiatric Association, 2010 [Guideline])*. Relapse is common within the first six months following remission from an acute depressive episode; as many as 20-85% of patients may relapse *(American Psychiatric Association, 2010 [Guideline])*.

Maintenance therapy is the treatment phase that follows continuation therapy. The goal of maintenance therapy is to prevent recurrence of new or future episodes of major depression *(Rush, 1999 [Low Quality Evidence])*. The best candidates for maintenance therapy are patients who meet any of these criteria:

- three or more previous episodes of major depression,
- two episodes of major depression and rapid recurrence of episodes,
- older in age at the onset of major depression (more than 60 years of age),
- severe episodes of major depression, family history of a mood disorder, or
- residual symptoms *(American Psychiatric Association, 2010 [Guideline])*.

Other risk factors for recurrence include the presence of a general medical condition, ongoing psychosocial stressors, negative cognitive styles, and persistent sleep disturbance *(American Psychiatric Association, 2010 [Guideline])*.

Maintenance therapy should also be considered for at-risk patients with double depression and patients with a comorbid anxiety disorder or substance abuse. Patients whose major depression has a seasonal pattern are also at risk for recurrence and may benefit from seasonal reinstatement of light therapy or antidepressant therapy. For patients on maintenance medication, contacts can occur every 3 to 12 months if everything else is stable *(Oxman, 2002 [Low Quality Evidence]; Katon, 1999 [High Quality Evidence])*.

Pharmacotherapy

The dose of antidepressant medication that leads to satisfactory acute therapeutic response should be maintained during long-term treatment to reduce the risk for relapse and recurrence of depression *(Sonawalla, 2001 [Low Quality Evidence]; Flint, 2000 [Low Quality Evidence]; Frank, 1993 [High Quality Evidence])*.

When considering how long to continue medication after the remission of acute symptoms, two issues need to be considered: maintenance and prophylactic treatment. Patients who require several medication changes to achieve remission of an acute major depressive episode have a higher rate of relapse and a shorter period of time until relapse in comparison to patients who require fewer medication changes to achieve remission *(Rush, 2006 [High Quality Evidence])*.

Significant data support the efficacy of antidepressants in preventing the recurrence of a major depressive episode. Although more research needs to be conducted, findings indicate that patients who are at highest risk of future episodes have had multiple prior episodes or were older at the time of the initial episode *(Keller, 1998 [High Quality Evidence])*. These patients are candidates for long-term or lifetime prophylactic treatment.

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For use of antidepressant medication, the following is recommended:

Depression Medication Treatment Duration Based on Episode

Episode	Treatment Duration*
1st episode (major depression, single episode 296.2x [F32.x])	• Acute phase typically lasts 6-12 weeks. • Continue psychotherapy/medication treatment for 4-9 months once remission is reached. • Total = approximately 6-12 months
2nd episode (major depression, recurrent 296.3x [F33.x])	Continue medication treatment for 3 years once remission is reached. Withdraw gradually.
Persistent depressive disorder (300.4 [F34.1]) or 3+ episodes or 2 episodes (major depression, recurrent 296.3x [F33.x]) with complicating factors such as: • Rapid recurrent episodes • More than 60 years of age at onset of major depression • Severe episodes or family history	Continue medication treatment indefinitely.

Sources: (American Psychiatric Association, 2013 [Guideline]; Segal, 2010 [High Quality Evidence]; Dobson, 2008 [High Quality Evidence]; Hollon, 2005b [High Quality Evidence])

* Treat to remission. Full remission is defined as a two-month absence of symptoms.

Analysis suggests that recurrence rates are reduced by 70% when patients are maintained on antidepressants for three years following their previous episode (average reurrence on placebo is 41% versus 18% on active treatment) *(Hirschfeld, 2001 [Low Quality Evidence]; Greden, 1993 [Low Quality Evidence])*.

Discontinuation of Pharmacotherapy

Premature treatment discontinuation can be triggered by a number of factors, including lack of adequate education about the disease, failure on the part of either physician or the patient to establish goals for follow-up, psychosocial factors and adverse side effects. **Appropriate ongoing collaborative care for depression can increase remission rates to as much as 76% by 24 months** *(Rost, 2002 [High Quality Evidence]; Schoenbaum, 2002 [High Quality Evidence])*.

Complicating factors are those situations where evidence either shows or suggests higher rates of recurrence after stopping antidepressants. Such factors include:

- pre-existing persistent depressive disorder,
- inability to achieve remission, and
- recurrence of symptoms in response to previously attempted lowering dose or discontinuation of pharmacotherapy.

(Paykel, 1995 [Low Quality Evidence])

If discontinuation of treatment is thought to be appropriate or necessary despite the known risks, a plan of action should be in place for prompt intervention if relapse occurs *(Greden, 1993 [Low Quality Evidence])*.

In general, it is recommended that the dose be tapered over a period of weeks to several months when discontinuing an antidepressant. (Note that this approach is only feasible when the starting dose is lower than the therapeutic dose.)

The various existing antidepressants exhibit a wide array of half-lives and therapeutic dose ranges. Therefore, a discussion of detailed discontinuation strategies is beyond the scope of this guideline.

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See also Annotation #11, "Evaluate Dose, Duration, Type and Adherence with Medication and/or Psychotherapy. Reconsider Accuracy of Diagnosis or Impact of Comorbidities."

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11. Evaluate Dose, Duration, Type and Adherence with Medication and/or Psychotherapy. Reconsider Accuracy of Diagnosis or Impact of Comorbidities

If remission has not been achieved when reevaluated up to six weeks later, consider:

- Reevaluating the diagnosis.
- The possibility of a bipolar diathesis. Bipolar patients require a different treatment approach and may not consistently come forward with their hypomanic, mixed or manic histories *(Sharma, 2005 [Low Quality Evidence])*.
- Looking for comorbidities, such as substance abuse issues, and involving addiction specialists as needed.
- Consulting with a behavioral health clinician if personality disorders present.
- Whether adequate engagement of patient/family exists and whether recommendations are being followed (adherence).
- Adding cognitive psychotherapy or adding another medication such as buspirone or bupropion. Both augmentation strategies showed similar improvement rates in the STAR*D study; however, the addition of medication resulted in a significantly more rapid response *(Thase, 2007 [High Quality Evidence])*.
- Switching to a different antidepressant medication. After a failed trial of citalopram, remission rates in the STAR*D study were 21.3% for bupropion SR, 17.6% for sertraline and 24.8% for venlafaxine XR *(Rush, 2006 [High Quality Evidence])*, although the differences were not statistically significant. Failure of a drug in one family does not rule out possible benefit from other drugs in that family. This is particularly true for SSRIs *(Bull, 2002 [Low Quality Evidence]; Thase, 1997 [Low Quality Evidence]; Brown, 1995 [Low Quality Evidence])*.
- Augmentation strategies (such as lithium or low-dose thyroid). See Annotation #12, "Consider Other Strategies."
- Making a referral to psychiatry for possible MAOI or ECT treatment. Many patients unresponsive to tricyclics are responsive to monoamine oxidase inhibitors. Rarely, the combination of tricyclics and MAOIs is used. This combination should be undertaken with extreme caution. Studies measuring response to MAO inhibitors in SSRI non-responders have not been done *(McGrath, 1994 [Low Quality Evidence]; McGrath, 1993 [High Quality Evidence])*. See Annotation #12, "Consider Other Strategies."
- Adding, switching or substituting treatment modality. A switch from an antidepressant to psychotherapy or vice versa appears useful for non-responders to initial treatment *(Schatzberg, 2005 [Low Quality Evidence])*. If there is less than 25% reduction of symptoms after six weeks at therapeutic dose (i.e., partial positive response to medication), add, switch or substitute another treatment modality. If there is a partial medication response and side effects are not prohibitive, increase the dose. As part of the evaluation, use a standardized assessment tool to gauge progress.

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Pharmacologic Therapy

Without long-term antidepressant treatment, major depressive relapses and recurrences occur in 50-80% of patients. Double-blind discontinuation studies reveal that antidepressants decrease the risk of relapse and recurrence; such studies have repeatedly shown antidepressants to be more efficacious than placebo substitution.

It has been well established that raising the dose of tricyclics or MAO inhibitors may improve response. Similarly, a controlled study showed that raising the dose of fluoxetine (from 20 mg to 40 or 60 mg) in partially responsive patients was more effective than adding desipramine (25-50 mg per day) or lithium (300-600 mg daily). In non-responders, raising the fluoxetine dose was as effective as adding lithium, and both were more effective than adding desipramine.

(Fava, 1994 [High Quality Evidence]; Perry, 1994 [Low Quality Evidence])

One study with a tricyclic antidepressant showed decreased risk of relapse after 18 months of treatment *(Mavissakalian, 1992 [Low Quality Evidence])*.

Surveys of patient populations have indicated that patients receiving prescriptions for one of the benzodiazepines or other minor tranquilizers or hypnotics tend to use less than prescribed and to reduce their use over time. Benzodiazepine abuse is usually seen as part of a pattern of abuse of multiple drugs often involving alcohol and sometimes opioids *(Woods, 1988 [Low Quality Evidence])*.

See also the "Discuss Treatment Options" section in Annotation #8, and Annotation #10, "Continuation and Maintenance Treatment Duration Based on Episode."

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12. Consider Other Strategies

- Augmentation strategies may be considered for partial responders, and combinations of antidepressants (when each has a different mechanism) have been shown to be options in those who fail to achieve remission.
- If patients do not respond to intensive outpatient treatment, partial or full hospitalization may be considered in patients who have not responded to outpatient management, particularly if safety issues are a concern.
- Use of bright light therapy for treatment of major depression with a seasonal specifier is well established.
- Electroconvulsive treatment is effective and can sometimes be administered safely in an outpatient setting.

Treatment-resistant depression has several definitions in the literature. It is important to distinguish treatment resistance from a lack of completion of a full course of treatment. The literature tends to focus on pharmacological treatments in the definition of treatment resistance without consistently incorporating psychotherapeutic modalities. True treatment resistance is seen as occurring on a continuum, from failure to reach remission after an adequate trial of a single antidepressant to failure to achieve remission despite several trials of antidepressants, augmentation strategies, ECT and psychotherapy. **For our purposes of making recommendations for primary care clinicians, we define true treatment resistance as failure to achieve remission with an adequate trial of therapy and three different classes of antidepressants at adequate duration and dosage** *(Nierenberg, 2006 [High Quality Evidence]; Keller, 2005 [Low Quality Evidence]; Geddes, 2003 [Systematic Review])*.

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Augmentation Therapy

Augmentation therapy is used for those situations in which the patient's depression is either treatment resistant or partially responsive to treatment. This is a good time to consult and/or refer to a mental health specialist.

Augmentation methods include:

- **Bupropion or buspirone-SSRI combination.**
  - Augmentation of citalopram with bupropion or buspirone after non-remission with a trial of citalopram alone yielded a remission rate of 29.7 and 30.1%, respectively, in the STAR*D study. These diferences were statistically insignificant, but bupropion SR was better tolerated *(Trivedi, 2006a [High Quality Evidence])*.
  - Three open series of cases and two other case reports have described beneficial results. The basis of this combination is the addition of a noradrenergic agent to a serotonergic agent to enhance effects; bupropion may also have dopaminergic actions *(Spier, 1998 [Low Quality Evidence]; Bodkin, 1997 [Low Quality Evidence]; Marshall, 1996 [Low Quality Evidence])*.
  - Five open studies supported potential utility of this treatment, and a response rate of approximately 60% was observed *(Dimitriou, 1998 [Low Quality Evidence]; Bouwer, 1997 [Low Quality Evidence])*.
- **Mirtazapine-SSRI combination.**
  - The addition of the alpha-2 antagonist mirtazapine is used to augment SSRI. Three controlled studies have found evidence of more rapid effects *(Maes, 1999 [High Quality Evidence]; Dam, 1998 [High Quality Evidence]; Cappiello, 1995 [Low Quality Evidence])*.
- **T_3 augmentation of antidepressants.**
  - Antidepressant augmentation with T_3 had a remission rate of 24.7% in the STAR*D study *(Nierenberg, 2006 [High Quality Evidence])*. There was no significant difference between T_3 augmentation or lithium augmentation (13.2%), but T_3 was better tolerated, despite being more vigorously dosed *(Rush, 2009 [High Quality Evidence])*.
  - Placebo-controlled studies found mixed results. Usual dose of T_3 varied between 25 and 50 micrograms/day *(Nelson, 2000 [Low Quality Evidence])*.
- **Stimulant augmentation of TCA-SSRI ("jump-start response").**
  - Some open label studies of modafinil augmentation of SSRI have reported benefit in sleepiness and fatigue, either disease-state-induced or secondary to the SSRI. The sample size and length of treatment are both small, and thus conclusions need to be taken with caution *(Schwartz, 2004 [Low Quality Evidence]; Ninan, 2004 [Low Quality Evidence])*.
  - Further research with larger higher-quality trials is needed to establish the benefit of stimulant augmentation and the clinical situations where this might be indicated *(Candy, 2009 [Systematic Review]; Dunlop, 2007 [High Quality Evidence]; Fava, 2005 [High Quality Evidence])*.
  - Cases of sudden death, stroke and myocardial infarction have been reported in adults taking stimulant medications at usual doses for ADHD. Adults with serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease or other serious cardiac problems should not be treated with stimulant medications.

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- **TCA-SSRI combination** (caution – elevated TCA level – to be monitored).
  - A 1991 study by Nelson reported this combination to be more rapidly effective and indicated that remission was more likely. The dose of TCA should be adjusted to achieve effective TCA levels because SSRIs may increase TCA levels. Fluoxetine and paroxetine raise TCA (desipramine) levels three- to fourfold, and citalopram and sertraline have modest effects *(Nelson, 1991 [Low Quality Evidence]; Preskorn, 1990 [Low Quality Evidence])*.
  - If a combination is used, monitor side effects and consider checking blood levels.
- **Lithium augmentation** with TCAs. Lithium augmentation with SSRI (caution – case reports of serotonin syndrome).
  - Augmentation with lithium at stage 3 of STAR*D yielded remission rate of 15.9% *(Nierenberg, 2006 [High Quality Evidence])*.
  - Seven placebo control studies have found positive evidence of efficacy of lithium augmentation. Combination of lithium and SSRIs have been relatively well studied. In early studies, the usual dose of lithium was 300 mg three times a day. At this dose, serum lithium levels were usually above 0.4 mEq/L *(Delgado, 1998 [Low Quality Evidence]; Baumann, 1996 [High Quality Evidence]; Katona, 1995 [High Quality Evidence]; Joffe, 1993 [High Quality Evidence])*.
- **Atypical antipsychotic-antidepressant combination.**
  - Several studies have been published supporting the use of atypical antipsychotics as augmentation agents with antidepressants for treatment-resistant depression. A meta-analysis study of 1,500 treatment-resistant patients indicated pooled remission and response rates for atypical antipsychotics and placebo were 47.4% vs. 22.3% and 57.2% vs. 35.4%, respectively. The atypical antipsychotics used were risperidone, olanzapine and quetiapine *(Papakostas, 2007 [Systematic Review])*.
  - A meta-analysis of 16 trials that included a total of 3,480 patients with treatment-resistant, nonpsychotic, unipolar major depressive disorder found augmentation with atypical antipsychotics was significantly more effective than placebo in measures of both response and remission. The agents reviewed included risperidone, olanzapine, quetiapine and aripiprazole. No significant differences in efficacy were noted among the reviewed medications. The rate of patient discontinuation due to adverse events was higher in patients receiving augmentation with atypical antipsychotics, compared with placebo *(Nelson, 2009 [Meta-analysis])*.
  - Aripiprazole, quetiapine and the olanzapine-fluoxetine combination are FDA-approved adjunctive agents for the acute treatment of major depressive disorder in adults. In two studies, patients diagnosed with major depressive disorder who had at least two documented trials of incomplete response to antidepressant medications were randomized to aripiprazole (2 mg to 20 mg a day) or placebo. Patients receiving aripiprazole experienced significant improvements in depression symptoms within one to two weeks of initiated aripiprazole. Average doses were approximately 10 mg a day by mouth. Patients receiving aripiprazole experienced higher rates of akathisia and fatigue, compared to those randomized to placebo *(Marcus, 2008 [High Quality Evidence]; Berman, 2007 [High Quality Evidence])*.

Hospitalization

Partial or full hospitalization may be indicated in patients with unrelenting depressive symptoms, particularly if safety issues are a concern. The RARE (Reducing Avoidable Readmissions Effectively) Campaign (http://www.RAREreadmissions.org) has demonstrated effectiveness at avoiding readmissions to the emergency room or hospital. Five key areas of improvement identified by the program include Patient/Family

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Engagement and Activation, Medication Management, Comprehensive Transition Planning, Care Transition Support and Transition Communication.

The most important consideration from a primary care standpoint is having follow-up visits for chronic or acute physical problems arranged with their clinician prior to hospital discharge. Patients without a primary care clinician should be connected with one within 60 days of hospital discharge for a physical assessment and preventive interventions to help decrease the rate of readmission.

The following are most commonly referred from a primary care setting. For other specialized therapies, see Appendix H, "Specialized Therapies."

Electroconvulsive Therapy (ECT)

Response and remission rates are higher with ECT than with any other form of antidepressant treatment, with 70-90% of patients showing improvement *(Kellner, 2006 [High Quality Evidence]; UK ECT Review Group, The, 2003 [Systematic Review])*. Patients may express a choice for ECT; shared decision-making should be engaged to determine if it is appropriate. Electroconvulsive treatment is usually performed on an inpatient basis, but for some individuals, it can be administered safely in an outpatient setting. A patient considering ECT would need to be able to tolerate anesthesia, and should consult with a psychiatrist about the risks and benefits *(UK ECT Review Group, The, 2003 [Systematic Review]; Sackeim, 2001a [High Quality Evidence])*.

One study showed that 64.2% of patients referred for ECT achieved major depression remittance *(Kellner, 2006 [High Quality Evidence])*. In addition to its use as a treatment in the acute phase, ECT is an effective maintenance therapy for major depression. The same study compared continuous ECT versus nortriptyline and lithium treatment, and found no difference in relapse rates *(Kellner, 2006 [High Quality Evidence])*.

ECT is also effective for treating major mental illness during pregnancy, and the risks of adverse events are low. It should be strongly considered in pregnant women with severe symptoms of mental illness, such as psychotic symptoms, catatonia or strong suicidal urges *(Anderson, 2009 [Systematic Review])*. For more information regarding the treatment of depression in pregnant women, please refer to Annotation #6, "Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations)?"

Factors that may suggest a given patient may be an ECT candidate include:

- Geriatric depression *(Mitchell, 2005 [Systematic Review])*
- If antidepressant medications have not been tolerated or pose a significant medical risk
- If antidepressant medication trials have not been successful
- If ECT has been successful in previous episodes
- If catatonia is present
- When a rapid response is needed because of severe suicide risk or because the patient's health has been significantly compromised by the depression (e.g., severe cachexia, inability to attend to the activities of everyday living). ECT has been shown to be effective in resolving expressed suicidal intent *(Kellner, 2006 [High Quality Evidence])*.
- If depression with psychotic features
- If melancholic symptoms are predominant
- Depression and Parkinsonism

(National Institute for Clinical Excellence, 2003 [Guideline])

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Common side effects associated with ECT include headaches, myalgias, nausea, drowsiness, confusion and amnesia. More serious and rare side effects include hypertension, tachycardia, myocardial infarction, cerebrovascular accident, or death.

Light Therapy

Use of bright light therapy for treatment of major depression with a seasonal specifier is well established *(Leppämäki, 2002 [High Quality Evidence]; Golden, 2005 [Meta-analysis])*. Additionally, there is evidence to support the use of bright light therapy for other types of depressive symptom patterns, including non-seasonal depression and milder variations of seasonal depressive patterns *(Jorm, 2002 [Systematic Review]; Prasko, 2002 [High Quality Evidence])*. For non-seasonal depression, light therapy's benefit as an adjunctive treatment is more robust than its benefit as monotherapy *(Freeman, 2010 [Systematic Review])*. Bright light therapy may also quicken and enhance the effects of antidepressant medication *(Benedetti, 2003 [High Quality Evidence])*. In two small pilot studies, promising results were seen in pregnant and postpartum women with non-seasonal depression *(Epperson, 2004 [High Quality Evidence]; Oren, 2002 [Low Quality Evidence])*.

Dosage. The standard starting dose for depression with a seasonal specifier is 10,000 lux for 30 minutes each morning *(Freeman, 2010 [Systematic Review])*. Research on bright light therapy for other types of depression has not necessarily utilized standard dosages and exposure times.

Side effects. The most common side effects are nausea, jitteriness and headache *(Freeman, 2010 [Systematic Review])*.

Equipment. It is important for light therapy treatment to utilize equipment that eliminates ultraviolet frequencies and produces bright light of known spectrum and intensity. For these reasons, use of client-constructed light therapy units is contraindicated.

Overall recommendation. The APA Task Force concluded that "light therapy is an evidence-based, effective, well-tolerated treatment for seasonal affective disorder, as well as an augmentation strategy for antidepressant treatment of nonseasonal depression" *(Freeman, 2010 [Systematic Review])*.

Additional Specialized Therapeutic Options

There are other more specialized therapies available, as well. Refer to psychiatry for consideration of vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy (MST), deep brain stimulation (DBS) and acupuncture. See Appendix H, "Specialized Therapies."

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The Aims and Measures section is intended to provide guideline users with a menu of measures for multiple purposes, which may include the following:

- Population health improvement measures
- Quality improvement measures for delivery systems
- Measures from regulatory organizations such as The Joint Commission
- Measures that are currently required for public reporting
- Measures that are part of Center for Medicare Services Physician Quality Reporting initiative
- Other measures from local and national organizations aimed at measuring population health and improvement of care delivery

This section provides resources, strategies and measurement for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Aims and Measures
- Implementation Recommendations
- Implementation Tools and Resources

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Aims and Measures

The aims and measures in this guideline are based upon evidence supporting impact of system elements and process elements, and promoting actual symptom and functional patient improvement and outcomes, and are aligned with MN Community Measurement and the DIAMOND Initiative where there is overlap.

1. Increase the percentage of patients accurately diagnosed with major depression or persistent depressive disorder. *(Annotations #1, 2)*

   Measure for accomplishing this aim:

   a. Percentage of patients with a diagnosis of major depression or persistent depressive disorder with documentation of DSM-5 criteria at the time of the diagnosis.

2. Decrease the number of completed suicides in patients with major depresssion or persistent depressive disorder managed in primary care. *(Annotation #4)*

   Measure for accomplishing this aim:

   a. Percentage of patients who commit suicide at any time while managed in primary care.

3. Increase the percentage of patients with major depression or persistent depressive disorder who are assessed for the presence and severity (mild to moderate, moderate to high) and dependent on substance misuse. *(Annotation #5)*

   Measure for accomplishing this aim:

   a. Percentage of patients who are assessed for presence and severity of mild to moderate, moderate to high, and dependent on substance use at the time of diagnosis or within six months of diagnosis for major depression or persistent depressive disorder using a tool.

4. Increase the assessment for major depression or persistent depressive disorder of primary care patients presenting with any additional high-risk conditions such as diabetes, cardiovascular disease, post-stroke, chronic pain and all perinatal women. *(Annotations #6, 11)*

   Measures for accomplishing this aim:

   a. Percentage of patients with type 2 diabetes with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

   b. Percentage of patients with cardiovascular disease with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

   c. Percentage of patients who had a stroke with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

   d. Percentage of patients with chronic pain with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

   e. Percentage of perinatal patients with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

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5. Improve communication between the primary care physician and the mental health care clinician (if patient is co-managed). *(Annotations #4, 8, 12)*

   Measure for accomplishing this aim:

   a. Percentage of patients with major depression or persistent depressive disorder whose primary care records show documentation of any communication between the primary care clinician and the mental health care clinician.

6. Increase the percentage of patients with major depression or persistent depressive disorder who have improvement in outcomes from treatment for major depression or persistent depressive disorder. *(Annotations #8, 9)*

   Measures for accomplishing this aim *(the following are patient-reported outcomes)*:

   a. Percentage of patients who have had a response to treatment at six months (+/- 30 days) after diagnosis or initiating treatment, e.g., have had a PHQ-9 score decreased by 50% from initial score at six months (+/- 30 days).

   b. Percentage of patients who have reached remission at six months (+/- 30 days) after diagnosis or initiating treatment, e.g., have any PHQ-9 score less than 5 at six months (+/- 30 days).

   c. Percentage of patients who have had a response to treatment at 12 months (+/- 30 days) after diagnosis or initiating treatment, e.g., had a PHQ-9 score decreased by 50% from initial score at 12 months (+/- 30 days).

   d. Percentage of patients who have reached remission at 12 months (+/- 30 days) after initiating treatment, e.g., had a PHQ-9 score less than 5 at 12 months (+/- 30 days).

7. Increase the percentage of patients with major depression or persistent depressive disorder who have follow-up to assess response to treatment. *(Annotations #8, 10)*

   Measures for accomplishing this aim:

   a. Percentage of patients who have a follow-up contact within three months of diagnosis or initiating treatment.

   b. Percentage of patients whose symptoms are reassessed by the use of a quantative symptom assessment tool (PHQ-9) within three months of diagnosis or initiating treatment.

   c. Percentage of patients whose symptoms are reassessed by the use of a quantitative symptom asessment tool (PHQ-9) at six months (+/- 30 days) after diagnosis or initiating treatment.

   d. Percentage of patients whose symptoms are reassessed by the use of a quantitative symptom assessment tool (such as PHQ-9) at 12 months (+/- 30 days) after diagnosis or initiating treatment.

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Measurement Specifications

Measurement #1a

Percentage of patients with a diagnosis of major depression or persistent depressive disorder with documentation of DSM-5 criteria at the time of the diagnosis.

Population Definition

Patients age 18 years and older with a new primary care diagnosis of major depression or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x or 300.4.

Data of Interest

of medical records containing documentation of DSM-5 criteria at the time of the initial diagnosis

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# of medical records reviewed for patients newly diagnosed with major depression or persistent depressive disorder

Numerator/Denominator Definitions

Numerator: Number of records containing documentation of DSM-5 criteria documentation at the time of the initial diagnosis.

Denominator: Number of primary care patients age 18 years and older with new diagnosis of major depression or persistent depressive disorder during the measurement period and patient has not been treated for depression.

Note: Major depression and persistent depressive disorder ICD-9 codes include 296.2x, 296.3x and 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

New diagnosis = patients diagnosed with major depression or persistent depressive disorder during the measurement period. Measurement period can be weekly, monthly, quarterly, annually or any other period that clinic determines needs to be for quality improvement.

Documentation of DSM-5 Criteria

Must have a **total of five** symptoms for at least two weeks. **One** of the symptoms **must** be depressed mood or loss of interest.

1. Depressed mood
2. Markedly diminished interest or pleasure in all or almost all activities
3. Significant (more than 5% body weight) weight loss or gain, or decrease or increase in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feeling of worthlessness or inappropriate guilt
8. Diminished concentration, or indecisiveness
9. Recurrent thoughts of death or suicide

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Method/Source of Data Collection

Query the electronic medical records for patients newly diagnosed with major depression diagnosis or persistent depressive disorder during the measurement period. Determine if DSM-5 criteria were used to diagnose major depression or persistent depressive disorder. The presence of narrative comments reflecting application of DSM-5 criteria in making the diagnosis is acceptable evidence for this measure.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #2a

Percentage of patients who commit suicide at any time while managed in primary care.

Population Definition

Patients age 18 years and older with major depression or persistent depressive disorder ICD-9 diagnosis codes of 296.2x, 296.3x or 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

Data of Interest

$$\frac{\text{\# of patients who commit suicide}}{\text{\# of patients under depression management in primary care}}$$

Numerator and Denominator Definitions

Numerator: Number of patients who commit suicide at any time in primary care.

Denominator: Number of patients with major depression or persistent depressive disorder who are in active panel in primary care.

Method of Data Collection

Query electronic medical records or registry for patients diagnosed with depression or persistent depressive disorder and in active panel. Determine if any of those patients committed suicide while managed in primary care.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is an outcome measure, and the goal is zero.

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Measurement #3a

Percentage of patients who are assessed for the presence and severity of mild to moderate, moderate to high, and dependent on substance use at the time of diagnosis or within six months of diagnosis for major depression or persistent depressive disorder using a tool.

Population Definition

Patients age 18 years and older with a new diagnosis of major depression or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x or 300.4 (ICD 10 codes include F32.x, F33.x, F34.1).

Data of Interest

$$\frac{\text{\# of patients who are assessed for presence and severity of mild to moderate, moderate to high, and dependent substance use}}{\text{\# of patients diagnosed with major depression or persistent depressive disorder}}$$

Numerator/Denominator Definitions

Numerator: Number of patients who were assessed for presence and severity of mild to moderate, moderate to high and dependent substance use, using a tool at the time of depression diagnosis or within six months of diagnosis.

Denominator: Number of patients age 18 years and older who were newly diagnosed with major depression or persistent depressive disorder.

New diagnosis = patients diagnosed with major depression or persistent depressive disorder six months from the measurement date.

Method/Source of Data Collection:

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder diagnosis six months from the measurement date. Determine from medical records if a patient was assessed for presence or severity of mild to moderate, moderate to dependent substance use either at the time of diagnosis or within six months of diagnosis to the measurement date. Patient completing any screen for presence and severity of mild to moderate, moderate to high and dependent substance use should count toward the numerator.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #4a

Percentage of patients with type 2 diabetes with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

Population Definition

Patients age 18 years and older with a diagnosis of type 2 diabetes.

Data of Interest

$$\frac{\text{\# of patients who were screened for depression symptoms}}{\text{\# of patients with type 2 diabetes}}$$

Numerator/Denominator Definitions

Numerator: Number of patients screened for depression symptoms.

Use PHQ-2, the two-question screen, to screen for depression symptoms:

Over the past month, have you been bothered by:

- Little interest or pleasure in doing things?
- Feeling down, depressed or hopeless?

Denominator: Number of patients age 18 years and older with type 2 diabetes who had at least one contact with a clinician in primary care in the last 12 months from the measurement date. Diagnosis may be either new or existing.

Method/Source of Data Collection

Query electronic medical records to determine the number of patients with type 2 diabetes with at least one contact with a primary care clinician in the last 12 months from the measurement date. Determine if those patients had a PHQ-2 two-question screen for depression symptoms done at any of the contacts.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #4b

Percentage of patients with cardiovascular disease with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

Population Definition

Patients age 18 years and older with a diagnosis of cardiovascular disease.

Data of Interest

$$\frac{\text{\# of patients who were screened for depression symptoms}}{\text{\# of patients with cardiovascular disease}}$$

Numerator/Denominator Definitions

Numerator: Number of patients screened for depression symptoms.

Use PHQ-2, the two-question screen, to screen for depression:

Over the past month, have you been bothered by:

- Little interest or pleasure in doing things?
- Feeling down, depressed or hopeless?

Denominator: Number of patients age 18 years and older with cardiovascular disease who had at least one contact with a clinician in primary care in the last 12 months from the measurement date. Diagnosis may be either new or existing.

Method/Source of Data Collection:

Query electronic medical records to determine the number of patients with cardiovascular disease with at least one contact with a primary care clinician in the last 12 months from the measurement date. Determine if those patients had a PHQ-2 two-question screen for depression done at any of the contacts.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #4c

Percentage of patients who had a stroke with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

Population Definition

Patients age 18 years and older who had a stroke.

Data of Interest

$$\frac{\text{\# of patients who were screened for depression symptoms}}{\text{\# of patients who had a stroke}}$$

Numerator/Denominator Definitions

Numerator: Number of patients screened for depression symptoms.

Use PHQ-2, the two-question screen, to screen for depression:

Over the past month, have you been bothered by:

- Little interest or pleasure in doing things?
- Feeling down, depressed or hopeless?

Denominator: Number of patients age 18 years and older who had at least one contact with a clinician in primary care in the last 12 months from the measurement date. Diagnosis may be either new or existing.

Method/Source of Data Collection:

Query electronic medical records to determine the number of patients who had a stroke with at least one contact with a primary care clinician in the last 12 months from the measurement date. Determine if those patients had a PHQ-2 two-question screen for depression symptoms done at any of the contacts.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #4d

Percentage of patients with chronic pain with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

Population Definition

Patients age 18 years and older with a diagnosis of chronic pain.

Data of Interest

$$\frac{\text{\# of patients who were screened for depression symptoms}}{\text{\# of patients with chronic pain}}$$

Numerator/Denominator Definitions

Numerator: Number of patients screened for depression symptoms.

Use PHQ-2, the two-question screen, to screen for depression:

Over the past month, have you been bothered by:

- Little interest or pleasure in doing things?
- Feeling down, depressed or hopeless?

Denominator: Number of patients age 18 years and older with chronic pain who had at least one contact with a clinician in primary care in the last 12 months from the measurement date. Diagnosis may be either new or existing.

Method/Source of Data Collection:

Query electronic medical records to determine the number of patients with chronic pain with at least one contact with a primary care clinician in the last 12 months from the measurement date. Determine if those patients had a PHQ-2 two-question screen for depression symptoms done at any of the contacts.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #4e

Percentage of perinatal patients with documentation of screening for major depression or persistent depressive disorder using PHQ-2.

Population Definition

Patients age 18 years and older who are perinatal.

Data of Interest

$$\frac{\text{\# of patients who were screened for depression symptoms}}{\text{\# of patients who are perinatal}}$$

Numerator/Denominator Definitions

Numerator: Number of patients screened for depression symptoms.

Use PHQ-2, the two-question screen, to screen for depression:

Over the past month, have you been bothered by:

- Little interest or pleasure in doing things?
- Feeling down, depressed or hopeless?

Denominator: Number of patients age 18 years and older who are perinatal who had at least one contact with a clinician in primary care in the last 12 months from the measurement date. Diagnosis may be either new or existing.

Method/Source of Data Collection:

Query electronic medical records to determine the number of patients who are perinatal with at least one contact with a primary care clinician in the last 12 months from the measurement date. Determine if those patients had a PHQ-2 two-question screen for depression symptoms done at any of the contacts.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #5a

Percentage of patients with major depression or persistent depressive disorder whose primary care records show documentation of any communication between the primary care clinician and the mental health care clinician.

Population Definition

Patients age 18 years and older with a new or existing major depression diagnosis or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x or 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

Data of Interest

$$\frac{\text{\# of patients with documentation of communication between clinicians}}{\text{\# of patients with major depression or persistent depressive disorder}}$$

Numerator/Denominator Definitions

Numerator:	Number of patients with documentation of communication between primary care clinician and mental health clinician during the measurement period.
Denominator:	Number of patients age 18 years with a new or existing diagnosis of major depression or persistent depressive disorder during the measurement period.

Method/Source of Data Collection:

Query electronic medical records to determine the number of patients with new or existing diagnoses of major depression or persistent depressive disorder during the measurement period. Determine if patients' records indicate any communication between primary care clinician and mental health clinician during the measurement period.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #6a

Percentage of patients who have had a response to treatment at six months (+/- 30 days) after diagnosis or initiating treatment, e.g., have had a PHQ-9 score decreased by 50% from initial score at six months (+/- 30 days).

Population Definition

Patients age 18 years and older with a new primary care diagnosis of major depression or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x or 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

Data of Interest

of patients whose results on a quantitative symptom assessment tool (such as PHQ-9) decrease by 50% at six months after diagnosis or initiating treatment (+/- 30 days)

# of patients newly diagnosed with major depression or persistent depressive disorder six months earlier

Numerator/Denominator Definitions

Numerator: Number of patients whose PHQ-9 administered at six months (+/- 30 days) after diagnosis or initiating treatment decreased by 50% or more from initial PHQ-9 score administered.

Denominator: Number of patients age 18 years and older who were newly diagnosed with major depression or persistent depressive disorder six months earlier and had an initial PHQ-9 done at the time of diagnosis or treatment initiation six months from the measurement date.

New diagnosis = patients diagnosed with major depression or persistent depressive disorder six months from the measurement date.

Method/Source of Data Collection:

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder diagnosis six months from the measurement date. Determine from medical records if a patient had an initial PHQ-9 done at the time of diagnosis. Then determine if a patient had a follow-up contact at six months from the diagnosis and PHQ-9 was done at six months, +/- 30 days. Determine if PHQ-9 done at six months decreased by 50% from the initial PHQ-9 done at the time of diagnosis six months from the measurement date.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a patient reported outcome measure, and improvement is noted as an increase in the rate. This measure is aligned with MN Community Measurement depression measure for public reporting.

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Measurement #6b

Percentage of patients who have reached remission at six months (+/- 30 days) after diagnosis or initiating treatment, e.g., have any PHQ-9 score less than 5 at six months (+/- 30 days).

Population Definition

Patients age 18 years and older with a new primary care diagnosis of major depression or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x, or 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

Data of Interest

$$\frac{\text{\# of patients with a PHQ-9 score < 5 at six months after diagnosis or initiating treatment (+/- 30 days)}}{\text{\# of patients newly diagnosed with major depression or persistent depressive disorder six months earlier}}$$

Numerator/Denominator Definitions

Numerator: Number of patients whose PHQ-9 score was less than 5 at six months (+/- 30 days) after diagnosis or initiating treatment.

Denominator: Number of patients age 18 years and older who were newly diagnosed with major depression or persistent depressive disorder six months from the measurement date.

New diagnosis = patients diagnosed with major depression or persistent depressive disorder six months from the measurement date.

Method/Source of Data Collection:

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder diagnosis six months from the measurement date. Determine if the patient had a follow-up contact at six months from the diagnosis and PHQ-9 was done at six months, +/- 30 days. Determine if PHQ-9 done < 5 at six months.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a patient-reported outcome measure, and improvement is noted as an increase in the rate. This measure is aligned with MN Community Measurement depression measure for public reporting.

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Measurement #6c

Percentage of patients who have had a response to treatment at 12 months (+/- 30 days) after diagnosis or initiating treatment, e.g., had a PHQ-9 score decreased by 50% from initial score at 12 months (+/- 30 days).

Population Definition

Patients age 18 years and older with a new primary care diagnosis of major depression or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x or 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

Data of Interest

of patients whose results on a quantitative symptom assessment tools (such as PHQ-9) decrease by 50% at 12 months after diagnosis or initiating treatment (+/- 30 days)

# of patients newly diagnosed with major depression or persistent depressive disorder 12 months earlier

Numerator/Denominator Definitions

Numerator: Number of patients whose PHQ-9 administered 12 months (+/- 30 days) after diagnosis or initiating treatment decreased by 50% or more from initial PHQ-9 score administered.

Denominator: Number of patients age 18 years and older who were newly diagnosed with major depression or persistent depressive disorder 12 months earlier and had initial PHQ-9 done at the time of diagnosis or treatment initiation six months from the measurement date.

New diagnosis = patients diagnosed with major depression or persistent depressive disorder 12 months from the measurement date.

Method/Source of Data Collection:

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder diagnosis 12 months from the measurement date. Determine from medical records if a patient had an PHQ-9 done at the time of diagnosis. Then determine if a patient had a follow-up contact at 12 months from the diagnosis and PHQ-9 was done at 12 months (+/- 30 days). Determine if PHQ-9 done at 12 months decreased by 50% from the initial PHQ-9 done at the time of diagnosis 12 months from the measurement date.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a patient-reported outcome measure, and improvement is noted as an increase in the rate. This measure is aligned with MN Community Measurement depression measure for public reporting.

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Measurement #6d

Percentage of patients who have reached remission at 12 months (+/- 30 days) after initiating treatment, e.g., had a PHQ-9 score less than 5 at 12 months (+/- 30 days).

Population Definition

Patients age 18 years and older with a new primary care diagnosis of major depression or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x, or 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

Data of Interest

$$\frac{\text{\# of patients with PHQ-9 < 5 at 12 months (+/- 30 days)}}{\text{\# of patients newly diagnosed with major depression or persistent depressive disorder 12 months earlier}}$$

Numerator/Denominator Definitions

Numerator: Number of patients whose PHQ-9 < 5 at 12 months (+/- 30 days) after diagnosis or initiating treatment.

Denominator: Number of patients age 18 years and older who were newly diagnosed with major depression or persistent depressive disorder 12 months from the measurement date.

New diagnosis = patients diagnosed with major depression or persistent depressive disorder 12 months from the measurement date.

Method/Source of Data Collection:

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder diagnosis 12 months from the measurement date. Determine if a patient had a follow-up contact at 12 months from the diagnosis and PHQ-9 was done at 12 months (+/- 30 days). Determine if PHQ-9 < 5 at 12 months.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a patient-reported outcome measure, and improvement is noted as an increase in the rate. This measure is aligned with MN Community Measurement depression measure for public reporting.

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Measurement #7a

Percentage of patients who have a follow-up contact within three months of diagnosis or initiating treatment.

Population Definition

Patients age 18 years and older with a new primary care diagnosis of major depression or persistent depressive disorder, ICD-9 codes 2.96.2x, 296.3x or 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

Data of Interest

$$\frac{\text{\# of patients who have a follow-up contact within three months of diagnosis or initiating treatment}}{\text{\# of patients newly diagnosed with major depression or persistent depressive disorder}}$$

Numerator/Denominator Definitions

Numerator: Number of patients who have a follow-up contact within three months of diagnosis or initiating treatment.

Denominator: Number of primary care patients age 18 years and older with new diagnosis of major depression or persistent depressive disorder who were diagnosed three months from the measurement date.

Contact = an office visit or phone contact with physician or other care clinician.

New diagnosis = patients diagnosed with major depression or persistent depressive disorder three months from the measurement date.

Method/Source of Data Collection:

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder diagnosis three months from the measurement date. Determine from medical records if a patient had a follow-up contact within three months of diagnosis to the measurement date.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #7b

Percentage of patients whose symptoms are reassessed by the use of a quantitative symptom assessment tool (such as PHQ-9) within three months of diagnosis or initiating treatment.

Population Definition

Patients age 18 years and older with a new primary care diagnosis of major depression or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x or 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

Data of Interest

$$\frac{\text{\# of patients whose symptoms are reassessed by the use of a quantitative symptom assessment tool (such as PHQ-9) within three months of diagnosis or initiating treatment}}{\text{\# of patients newly diagnosed with major depression or persistent depressive disorder}}$$

Numerator/Denominator Definitions

Numerator: Number of patients whose symptoms are reassessed by the use of a quantitative symptom severity scale instrument (such as PHQ-9) within three months of diagnosis or initiating treatment.

Denominator: Number of primary care patients age 18 years and older with new diagnosis of major depression or persistent depressive disorder who were diagnosed three months earlier from the measurement date.

New diagnosis = patients diagnosed with major depression or persistent depressive disorder three months from the measurement date.

Method/Source of Data Collection

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder diagnosis three months from the measurement date. Determine from medical records if a patient had a PHQ-9 follow-up contact within three months of diagnosis to the measurement date.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a process measure, and improvement is noted as an increase in the rate

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Measurement #7c

Percentage of patients whose symptoms are reassessed by the use of a quantitative symptom assessment tool (PHQ-9) at six months (+/- 30 days) after diagnosis or initiating treatment.

Population Definition

Patients age 18 years and older with a new primary care diagnosis of major depression or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x or 300.4 (ICD 10 codes include F32.x, F33.x and F34.1).

Data of Interest

$$\frac{\text{\# of patients whose symptoms are reassessed by the use of a quantitative symptom assessment tool (such as PHQ-9) at six months of diagnosis or initiating treatment}}{\text{\# of patients newly diagnosed with major depression or persistent depressive disorder}}$$

Numerator/Denominator Definitions

Numerator: Number of patients whose symptoms are reassessed by the use of a quantitative symptom severity scale instrument (such as PHQ-9) at six months (+/- 30 days) after diagnosis or initiating treatment.

Denominator: Number of primary care patients age 18 years and older with new diagnosis of major depression or persistent depressive disorder.

New diagnosis = patients diagnosed with major depression or persistent depressive disorder six months from the measurement date.

Method/Source of Data Collection:

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder diagnosis six months from the measurement date. Determine from medical records if a patient had a PHQ-9 done at follow-up contact at six months, +/- 30 days after initial diagnosis of the measurement date.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Measurement #7d

Percentage of patients whose symptoms are reassessed by the use of a quantitative symptom assessment tool (such as PHQ-9) at 12 months (+/- 30 days) after diagnosis or initiating treatment.

Population Definition

Patients age 18 years and older with a new primary care diagnosis of major depression or persistent depressive disorder, ICD-9 codes 296.2x, 296.3x or 300.4 (ICD 10 codes include F32.x, F33.x, and F34.1).

Data of Interest

of patients whose symptoms are reassessed by the use of a quantitative symptom assessment tool (such as PHQ-9) at 12 months after diagnosis or initiating treatment

---

# of patients newly diagnosed with major depression or persistent depressive disorder

Numerator/Denominator Definitions

Numerator: Number of patients whose symptoms are reassessed by the use of a quantitative symptom severity scale instrument (such as PHQ-9) at 12 months, +/- 30 days after diagnosis or initiating treatment.

Denominator: Number of primary care patients age 18 years and older with new diagnosis of major depression or persistent depressive disorder.

New diagnosis = patients diagnosed with major depression or persistent depressive disorder 12 months from the measurement date.

Method/Source of Data Collection:

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder, diagnosis 12 months from the measurement date. Determine from medical records if a patient had a PHQ-9 done at follow-up contact at 12 months, +/- 30 days after diagnosis of the measurement date.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a process measure, and improvement is noted as an increase in the rate.

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Implementation Recommendations

Prior to implementation, it is important to consider current organizational infrastructure that address the following:

- System and process design;
- Training and education; and
- Culture and the need to shift values, beliefs and behaviors of the organization.

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline:

* See below for health care cost analysis of a collaborative care model compared to outpatient primary care depression care as usual and review of the cost analysis for enhanced collaborative care and the impact on the workplace, e.g., absenteeism.

- Detection and diagnosis
  - Systems in place to reliably determine if a patient is depressed
  - Use of DSM-5 criteria and structured questionnaires (such as PHQ-9)
- Patient-centered care, education and self-management programs
  - Structured attention to patient preferences
  - Patient and family education materials/protocols
  - Patient self-management skills such as journal writing or self-monitoring

    When appropriate, encourage family or loved ones to attend appointments for patient support and advocacy.
  - Involving families, as well, in care management programs
  - Care manager role to coordinate the disease management for patients with depression including such things as patient contacts, education, self-management tools and tips
- Mental health/behavioral medicine specialist involvement
  - Shared care – collaborative care between behavioral health specialists and primary care clinicians in the primary care setting. Care manager and /or primary care clinician consulting with psychiatry on a regular basis regarding the caseload of patients with depression managed in the depression care management program.
  - Appointment availability – access to behavioral health in timely manner
- Outcomes measurement
  - Build in plans for outcome measures as well as ongoing process measures
  - Response rate to various treatments
  - Remission rates – improvement in response is stable over time
- Systems to coordinate care, ensure continuity and keep clinicians informed of status
  - Build automated processes for the first four core elements wherever possible
  - Reduce dependence on human behavior to ensure delivery of patient care processes

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- Use of components of the chronic care model for depression care, e.g., use of registries, community outreach
- Structured frequent monitoring and follow-up with patient
- Nurse/care manager phone care and use of other modalities for patient follow-up

A recent study showed a relationship between the severity of depression symptoms and work function. Data was analyzed from 771 depressed patients who were currently employed. The data showed that for every 1-point increase in PHQ-9 score, patients experienced an additional mean productivity loss of 1.65%. And, even minor levels of depression symptoms were associated with decrements in work function *(Beck, 2011 [Low Quality Evidence])*.

Cost-Effectiveness Impact of Collaborative Care Models

In a collaborative care model, the primary treatment for depression is provided by a multidisciplinary team. Most studies have concluded that creating and implementing a collaborative care model will increase effectiveness – producing significant and sustained gains in "depression-free days" *(Katon, 2005 [High Quality Evidence]; Simon, 2001a [Cost-Effectiveness Analysis]; Simon, 2001b [Cost-Effectiveness Analysis]*). The six-month and one-year studies show increased cost to the outpatient care system. This is balanced by continuous accumulation of clinical and economic benefits over time. One of the factors is the decrease in the utilization of general medical services in patients with chronic medical comorbidities *(Simon, 2008 [High Quality Evidence])*. The two-year studies show mixed results possibly indicating a turning point *(Dickinson, 2005 [High Quality Evidence]),* and the only longer-term study conducted was the IMPACT study. This was a well-done study analyzing the costs of performing collaborative care for one year over a four-year period. The study illustrated a cost savings of $3,363 per patient over the four-year period *(Unützer, 2008 [High Quality Evidence])*.

Almost all the studies done on this aspect have compared enhanced/collaborative care with care as usual. Typically enhanced care has involved creating a list of depressed patients under treatment, having a care manager provide education, call or meet with patient periodically to ensure compliance with medications and/or psychotherapy, and to reliably ensure follow-up visits and measurement of outcomes. Some have involved varying participation of physicians, behavioral health professionals and/or patients.

For more information, see Annotation #8, "Comprehensive Treatment Plan with Shared Decision-Making."

Workplace Impact of Collaborative Care Models

These randomized controlled trials looked at cost of doing enhanced care and specifically tallied decreases of "absenteeism" and improved work performance (which means that employees are present and effectively achieving good work results, sometimes referred to as decreasing "presenteeism") *(Wang, 2007 [High Quality Evidence]; Schoenbaum, 2001 [High Quality Evidence])*. Some studies monetized the results and compared them to usual care. The significance of these studies and this analysis is that in the U.S., depression costs employers $24 billion in lost productive work time *(Stewart, 2003 [Low Quality Evidence])*.

In two randomized controlled trials, employers received significant ROI (return on investment) from collaborative care treatment of depression by increasing productivity/decreasing absenteeism in the workplace. Increased productivity in one study ranged from 2.6 hours to 5.6 hours/week after one year. Studies going out to two years showed continued gains in year two *(Lo Sasso, 2006 [High Quality Evidence]; Rost, 2004 [High Quality Evidence])*.

Several of the articles recommend consideration of coverage of collaborative care to ensure better patient outcomes and the ROI illustrated.

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Implementation Tools and Resources

Criteria for Selecting Resources

The following tools and resources specific to the topic of the guideline were selected by the work group. Each item was reviewed thoroughly by at least one work group member. It is expected that users of these tools will establish the proper copyright prior to their use. The types of criteria the work group used are:

- The content supports the clinical and the implementation recommendations.
- Where possible, the content is supported by evidence-based research.
- The author, source and revision dates for the content is included where possible.
- The content is clear about potential biases and when appropriate conflicts of interests and/or disclaimers are noted where appropriate.

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Implementation Tools and Resources Table

Author/Organization	Title/Description	Audience	Web Sites/Order Information
Comorbidities			
American Cancer Society	Coping with physical and emotional changes.	Patients and Families	http://www.cancer.org/docroot/MBC/content/MBC_4_1X_Cancer_and_Depression.asp?sitearea=MBC
Screening, Brief Intervention and Referral to Treatment (SBIRT)	Provides an integrated, public health approach for early intervention and treatment services for persons with substance use disorders and those at risk.	Health Care Professionals	http://www.samhsa.gov/prevention/SBIRT/index.aspx
Substance Abuse and Mental Health Services Administration	Information on programs and publications for improving the quality and availability of substance abuse prevention, alcohol and drug addiction treatment, and mental health services.	Health Care Professionals	http://www.samhsa.gov/
Cultural Considerations			
National Institute of Mental Health	A colored, easy-to-read brochure called "Stories of Depression/Historias personales sobre la depresion," Spanish Version.	Patients and Families	http://www.nimh.nih.gov Publication No. 03-5122 del NIH English version NIH Publication No. 05-5084
National Institute of Mental Health	Spanish resources. "Depression," a 27-page booklet about depression, and treatment.	Patients and Families	http://www.nimh.nih.gov NIH Publication No. NIH-04-3561 (SP)
U.S. Dept of Health & Human Services, Office of Minority Health	Resources and information to improve and protect the health of racial and ethnic minority populations through the development of health policies and programs that will eliminate health disparities.	Patients and Families/ Health Care Professionals	http://www.minorityhealth.hhs.gov
Drug Interactions			
Epocrates Online Premium	Interactive tool for common drug interactions. Includes information on severity and dosing recommendations.	Health Care Professionals	https://online.epocrates.com
Medscape	Drug interaction checker	Health Care Professionals	http://www.medscape.com/druginfo/druginterchecker
University of Maryland Medical Center	Interactive drug checker	Health Care Professionals	http://www.umm.edu/adam/drug_checker.htm

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Author/Organization	Title/Description	Audience	Web Sites/Order Information
Electroconvulsive Therapy			
American Academy of Family Physicians	Depression: Electroconvulsive Therapy Handout	Patients and Families/ Health Care Professionals	http://familydoctor.org/familydoctor/en/diseases-conditions/depression/treatment/how-electroconvulsive-therapy-works.html
General			
American Psychiatric Association	Let's Talk about Depression (8-page booklet)	Patients and Families	American Psychiatric Publishers 1-800-368-5777 #2351; $49.00/50
American Psychiatric Association	Provides mental health news, online CME programs and legislation. Links to MEDEM for patient information.	Patients and Families/ Health Care Professionals	http://www.psych.org
American Psychiatric Association/American Academy of Child and Adolescent Psychiatry	Provides parents of children and adolescents information about pediatric depression, treatment alternatives and the latest science and research findings.	Patients and Families/ Health Care Professionals	http://www.parentsmedguide.org
Dennis Greenburger and Christine Padesky	Mind over Mood (215-page workbook)	Patients and Families	Bookstores
ICSI	Workplace Impact of Collaborative Care Models for Depression	Health Care Professionals	https://www.icsi.org/_asset/s9p6bx/White-Paper-on-Collaborative-Care-Model-ROI.pdf
National Alliance for the Mentally Ill	Advocacy, links to Minnesota chapter support groups	Patients and Families/ Health Care Professionals	http://www.nami.org
National Institute for Health and Clinical Excellence	NICE Depression guideline: management of depression in primary and secondary care	Health Care Professionals	http://guidance.nice.org.uk/CG90
National Institute of Mental Health	This government-sponsored site provides comprehensive information on the following topics: clinical trials, research and funding opportunities, and patient education materials for adults and children. Links to PubMed, MedlinePlus and other relevant sites are available.	Patients and Families/ Health Care Professionals	http://www.nimh.nih.gov

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Author/Organization	Title/Description	Audience	Web Sites/Order Information
General (Continued)			
National Library of Medicine MedlinePlus	This government-sponsored comprehensive site provides information on medications, diagnosis, treatments, clinical trials and links to other relevant sites. Spanish versions of some patient education materials are also provided.	Patients and Families/ Health Care Professionals	http://www.nlm.nih.gov/medlineplus Toxicology Data Network can be found at http://toxnet.nlm.nih.gov/
National Mental Health Association	Provides patient information, depression screening tool, community resources and discussion board.	Patients and Families/ Health Care Professionals	http://www.nmha.org
Stratis Health Culture Care Connection	One significant resource is fact sheets on numerous culturally diverse populations living in Minnesota. Includes information on such issues as social structure, diet, religion, health care beliefs and successful ways to communicate with people of the specific culture.	Patients and Families/ Health Care Professionals	http://www.culturecareconnection.org
Texas Department of State Health Services	The Texas Medication Algorithm Project (TMAP)	Health Care Professionals	http://www.dshs.state.tx.us/mhsa
Perinatal			
The Marcé Society for Perinatal Mental Health	An international society for the understanding, prevention and treatment of mental illness related to childbearing. Dedicated to supporting research and assistance surrounding prenatal and postpartum mental health for mothers, fathers and their babies.	Patients and Families/ Health Care Professionals	http://www.marcesociety.com
Massachusetts General Hospital Center for Women's Mental Health	Resources and information on reproductive psychiatry	Health Care Professionals	http://www.womensmentalhealth.org
Med Ed PPD	Online education about perinatal mental health and treatment options.	Patients and Families/ Health Care Professionals	http://mededppd.org/
Organization of Teratology Information Specialists	A non-profit organization made up of individual services throughout North America providing evidence-based, clinical information to patients and health care professionals about exposures during pregnancy and lactation. Ongoing research on antidepressant use during pregnancy, autoimmune disorders, vaccines and medication in pregnancy surveillance system.	Patients and Families/ Health Care Professionals	http://www.otispregnancy.org

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Author/Organization	Title/Description	Audience	Web Sites/Order Information
Perinatal (Continued)			
Postpartum Stress Center	Books, articles and information on PPD	Patients and Families/ Health Care Professionals	http://www.postpartumstress.com/
Postpartum Support International	Provides information on postpartum depression for clinicians as well as patients/consumers interested in learning more about postpartum depression. Expanded section for dads.	Patients and Families/ Health Care Professionals	http://www.postpartum.net
Pregnancy and Postpartum Support Minnesota (PPSM)	A group of mental health and perinatal practitioners, service organizations and mother volunteers offering emotional support and treatment to Minnesota families through the perinatal years.	Patients and Families	http://www.ppsupportmn.org
Wisconsin Association for Perinatal Care	Provide resources to improve the health of babies, mothers and families from preconception to early childhood. Site includes algorithms and medication charts for depression in perinatal women.	Patients and Families/ Health Care Professionals	http://www.perinatalweb.org

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References

Links are provided for those new references added to this edition (author name is highlighted in blue).

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Appendix A – Patient Health Questionnaire (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING

0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

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INSTRUCTIONS FOR USE

for doctor or healthcare professional use only

PHQ-9 QUICK DEPRESSION ASSESSMENT

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the two right columns (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.
3. ***Consider Major Depressive Disorder***
   • if there are at least 5 ✓s in the two right columns (one of which corresponds to Question #1 or #2).

   Consider Other Depressive Disorder
   • if there are 2 to 4 ✓s in the two right columns (one of which corresponds to Question #1 or #2).

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓:
   "Several days" = 1 "More than half the days" = 2 "Nearly every day" = 3
3. Add together column scores to get a TOTAL score.
4. Refer to accompanying PHQ-9 Scoring Card to interpret the TOTAL score.
5. Results may be included in patients' files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

PHQ-9 SCORING CARD FOR SEVERITY DETERMINATION

for healthcare professional use only

Scoring—add up all checked boxes on PHQ-9

For every ✓: Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
0-4	None
5-9	Mild
10-14	Moderate
15-19	Moderately severe
20-27	Severe

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Appendix B – The Hamilton Rating Scale for Depression (HAM-D)

(to be administered by a health care professional)

Patient's Name: _____

Date of Assessment: _____

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless)

_____ **0 =** Absent
1 = These feeling states indicated only on questioning
2 = These feeling states spontaneously reported verbally
3 = Communicates feeling states non-verbally – i.e., through facial expression, posture, voice and tendency to weep
4 = Patient reports VIRTUALLY ONLY these feeling states in his/her spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT

_____ **0 =** Absent
1 = Self-reproach, feels he/she has let people down
2 = Ideas of guilt or rumination over past errors or sinful deeds
3 = Present illness is a punishment. Delusions of guilt
4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE

_____ **0 =** Absent
1 = Feels life is not worth living
2 = Wishes he/she were dead or any thoughts of possible death to self
3 = Suicidal ideas or gesture
4 = Attempts at suicide (any serious attempt rates 4)

4. INSOMNIA EARLY

_____ **0 =** No difficulty falling asleep
1 = Complains of occasional difficulty falling asleep – i.e., more than 1/2 hour
2 = Complains of nightly difficulty falling asleep

5. INSOMNIA MIDDLE

_____ **0 =** No difficulty
1 = Patient complains of being restless and disturbed during the night
2 = Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA LATE

_____ **0 =** No difficulty
1 = Waking in early hours of the morning but goes back to sleep
2 = Unable to fall asleep again if he/she gets out of bed

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7. WORK AND ACTIVITIES

_____ **0 =** No difficulty
1 = Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies
2 = Loss of interest in activity, hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities)
3 = Decrease in actual time spent in activities or decrease in productivity
4 = Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR (Slowness of thought and speech, impaired ability to concentrate, decreased motor activity)

_____ **0 =** Normal speech and thought
1 = Slight retardation at interview
2 = Obvious retardation at interview
3 = Interview difficult
4 = Complete stupor

9. AGITATION

_____ **0 =** None
1 = Fidgetiness
2 = Playing with hands, hair, etc.
3 = Moving about, can't sit still
4 = Hand wringing, nail biting, hair pulling, biting of lips

10. ANXIETY (PSYCHOLOGICAL)

_____ **0 =** No difficulty
1 = Subjective tension and irritability
2 = Worrying about minor matters
3 = Apprehensive attitude apparent in face or speech
4 = Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants of anxiety (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____ **0 =** Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____ **0 =** None
1 = Loss of appetite but eating without encouragement from others. Food intake about normal
2 = Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____ **0 =** None
1 = Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability
2 = Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as loss of libido, impaired sexual performance, menstrual disturbances)

_____ **0 =** Absent
1 = Mild
2 = Severe

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15. HYPOCHONDRIASIS

_____ **0 =** Not present
1 = Self-absorption (bodily)
2 = Preoccupation with health
3 = Frequent complaints, requests for help, etc.
4 = Hypochondriacal delusions

16. LOSS OF WEIGHT

_____ **A.** When rating by history:
0 = No weight loss
1 = Probably weight loss associated with present illness
2 = Definite (according to patient) weight loss
3 = Not assessed

17. INSIGHT

_____ **0 =** Acknowledges being depressed and ill
1 = Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 = Denies being ill at all

18. DIURNAL VARIATION

_____ **A.** Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0 = No variation
1 = Worse in A.M.
2 = Worse in P.M.
_____ **B.** When present, mark the severity of the variation. Mark "None" if NO variation.
0 = None
1 = Mild
2 = Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as feelings of unreality; nihilistic ideas)

_____ **0 =** Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

20. PARANOID SYMPTOMS

_____ **0 =** None
1 = Suspicious
2 = Ideas of reference
3 = Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

_____ **0 =** Absent
1 = Mild
2 = Severe

Total Score _____

Source: Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278-96.

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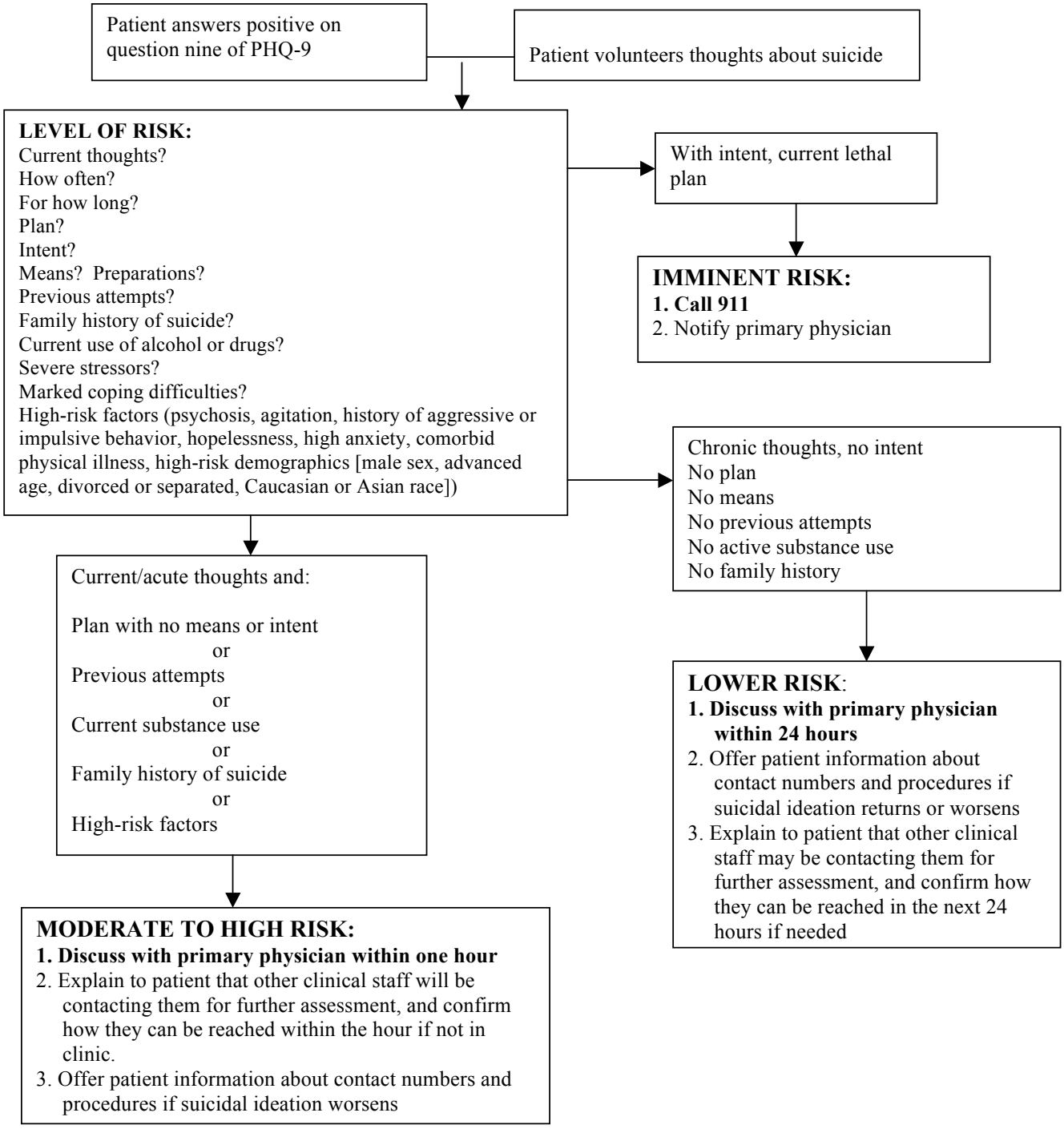
Appendix C – Example Suicidality Screening Flow*



Sources: Corson, 2004 [Low Quality Evidence]; Jacobs, 2004 [Guideline]; Schulberg, 2005 [Low Quality Evidence]; Stovall, 2003 [Low Quality Evidence]

***Note: A clear chain of responsibility within the clinic system needs to be established and distributed to all parties who may identify a suicidal patient. Well-defined follow-up procedures for contacting the patient for further evaluation need to be established. Events need to be well documented in the patient's medical record.**

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Appendix D – Cornell Scale for Depression in Dementia (CSDD)

Ratings should be based on symptoms and signs occurring during the week prior to interview. No score should be given if symptoms result from physical disability or illness.

Name: _____
Age: _____ Sex: _____ Date: _____

A. Mood-Related Signs	Unable to evaluate	Absent	Mild or Intermittent	Severe	Score
1. Anxiety (anxious expression, ruminations, worrying)	A	0	1	2	
2. Sadness (sad expression, sad voice, tearfulness)	A	0	1	2	
3. Lack of reactivity to pleasant events	A	0	1	2	
4. Irritability (easily annoyed, short tempered)	A	0	1	2	
B. Behavioral Disturbance					
5. Agitation (restlessness, handwringing, hairpulling)	A	0	1	2	
6. Retardation (slow movement, slow speech, slow reactions)	A	0	1	2	
7. Multiple physical complaints (score 0 of GI symptoms only)	A	0	1	2	
8. Loss of interest (less involved in usual activities; score only if change occurred acutely, i.e., in less than one month)	A	0	1	2	
C. Physical Signs					
9. Appetite loss (eating less than usual)	A	0	1	2	
10. Weight Loss (score 2 if greater than 5 lb in one month)	A	0	1	2	
11. Lack of energy (fatigues easily, unable to sustain activities; score only if change occurred acutely, i.e., in less than one month)	A	0	1	2	
D. Cyclic Functions					
12. Diurnal variation of mood symptoms worse in the morning	A	0	1	2	
13. Difficulty falling asleep later than usual for this individual	A	0	1	2	
14. Multiple awakenings during sleep	A	0	1	2	
15. Early morning awakening earlier than usual for this individual	A	0	1	2	
Ideational Disturbance					
16. Suicide (feels life is not work living, has suicidal wishes, or makes suicide attempt)	A	0	1	2	
17. Poor self-esteem (self-blame, self-depreciation, feelings of failure)	A	0	1	2	
18. Pessimism (anticipation of the worst)	A	0	1	2	
19. Mood-congruent delusions (delusions of poverty, illness, or loss)	A	0	1	2	
				Total Score =	

Interpretation of the Total Score:
A total score of 8 or more suggests significant depressive symptoms.
Assign the item a score of 0 if you cannot detect or evaluate the sign or symptom.

Reproduced with permission from Alexopoulos, G., et al. Cornell Scale for Depression in Dementia. Biological Psychiatry 1988;23(3):271-284.

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Appendix E – Geriatric Depression Scale (GDS)

Self-administered **Long form:** 30 questions; **Short form:** 15 questions

Time recall: Long form: "now or within the past week" **Short form:** "over the past week"

List of existing translations:

English, Chinese, Danish, Dutch, French, German, Greek, Hebrew, Hindi, Hungarian, Icelandic, Italian, Japanese, Korean, Lithuanian, Malay, Portuguese for Brazil, Romanian, Russian, Spanish, Swedish, Thai, Turkish, Vietnamese, Yiddish.

Geriatric Depression Scale - Short Form

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life? YES / **NO**
2. Have you dropped many of your activities and interests? **YES** / NO
3. Do you feel that your life is empty? **YES** / NO
4. Do you often get bored? **YES** / NO
5. Are you in good spirits most of the time? YES / **NO**
6. Are you afraid that something bad is going to happen to you? **YES** / NO
7. Do you feel happy most of the time? YES / **NO**
8. Do you often feel helpless? **YES** / NO
9. Do you prefer to stay at home, rather than going out and doing new things? **YES** / NO
10. Do you feel you have more problems with memory than most? **YES** / NO
11. Do you think it is wonderful to be alive now? YES / **NO**
12. Do you feel pretty worthless the way you are now? **YES** / NO
13. Do you feel full of energy? YES / **NO**
14. Do you feel that your situation is hopeless? **YES** / NO
15. Do you think that most people are better off than you are? **YES** / NO

Answers in **bold** indicate depression. Although differing sensitivities and specificities have been obtained across studies, for clinical purposes a score > 5 points is suggestive of depression and should warrant a follow-up interview. Scores > 10 are almost always depression.

Source: The Hartford Institute for Geriatric Nursing Division of Nursing, New York University.

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Appendix F – Edinburgh Postnatal Depression Screening (EPDS)

Edinburgh Postnatal Depression Scale[1] (EPDS)

Name: _____ Address: _____

Your Date of Birth: _____ _____

Baby's Date of Birth: _____ Phone: _____

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
□ Yes, all the time
☒ Yes, most of the time
□ No, not very often
□ No, not at all

This would mean: "I have felt happy most of the time" during the past week. Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - □ As much as I always could
   - □ Not quite so much now
   - □ Definitely not so much now
   - □ Not at all

2. I have looked forward with enjoyment to things
   - □ As much as I ever did
   - □ Rather less than I used to
   - □ Definitely less than I used to
   - □ Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   - □ Yes, most of the time
   - □ Yes, some of the time
   - □ Not very often
   - □ No, never

4. I have been anxious or worried for no good reason
   - □ No, not at all
   - □ Hardly ever
   - □ Yes, sometimes
   - □ Yes, very often

*5 I have felt scared or panicky for no very good reason
   - □ Yes, quite a lot
   - □ Yes, sometimes
   - □ No, not much
   - □ No, not at all

*6. Things have been getting on top of me
   - □ Yes, most of the time I haven't been able to cope at all
   - □ Yes, sometimes I haven't been coping as well as usual
   - □ No, most of the time I have coped quite well
   - □ No, I have been coping as well as ever

*7 I have been so unhappy that I have had difficulty sleeping
   - □ Yes, most of the time
   - □ Yes, sometimes
   - □ Not very often
   - □ No, not at all

*8 I have felt sad or miserable
   - □ Yes, most of the time
   - □ Yes, quite often
   - □ Not very often
   - □ No, not at all

*9 I have been so unhappy that I have been crying
   - □ Yes, most of the time
   - □ Yes, quite often
   - □ Only occasionally
   - □ No, never

*10 The thought of harming myself has occurred to me
   - □ Yes, quite often
   - □ Sometimes
   - □ Hardly ever
   - □ Never

Administered/Reviewed by _____ Date _____

[1]Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786 .

[2]Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

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Edinburgh Postnatal Depression Scale[1] (EPDS)

Postpartum depression is the most common complication of childbearing.[2] The 10-question Edinburgh Postnatal Depression Scale (EPDS) is a valuable and efficient way of identifying patients at risk for "perinatal" depression. The EPDS is easy to administer and has proven to be an effective screening tool.

Mothers who score above 13 are likely to be suffering from a depressive illness of varying severity. The EPDS score should not override clinical judgment. A careful clinical assessment should be carried out to confirm the diagnosis. The scale indicates how the mother has felt ***during the previous week***. In doubtful cases it may be useful to repeat the tool after 2 weeks. The scale will not detect mothers with anxiety neuroses, phobias or personality disorders.

Women with postpartum depression need not feel alone. They may find useful information on the web sites of the National Women's Health Information Center <www.4women.gov> and from groups such as Postpartum Support International <www.chss.iup.edu/postpartum> and Depression after Delivery <www.depressionafterdelivery.com>.

SCORING

QUESTIONS 1, 2, & 4 (without an *)
Are scored 0, 1, 2 or 3 with top box scored as 0 and the bottom box scored as 3.

QUESTIONS 3, 5-10 (marked with an *)
Are reverse scored, with the top box scored as a 3 and the bottom box scored as 0.

Maximum score: 30
Possible Depression: 10 or greater
Always look at item 10 (suicidal thoughts)

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Instructions for using the Edinburgh Postnatal Depression Scale:

1. The mother is asked to check the response that comes closest to how she has been feeling in the previous 7 days.

2. All the items must be completed.

3. Care should be taken to avoid the possibility of the mother discussing her answers with others. (Answers come from the mother or pregnant woman.)

4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.

[1]Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786.

[2]Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

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Appendix G – Alcohol Use Disorders Identification Test (AUDIT) Structured Interview

	Score				
Question	0	1	2	3	4
How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times / month	2-3 times / week	4 or more times / week
How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7-9	10 or more
How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week
How often during the last year have you found that you were unable to stop drinking once you had started?	Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week
How often during the last year have you failed to do what was normally expected from you because of drinking?	Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week
How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week
How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Two to three times per week	Four or more times a week
Have you or someone else been injured as a result of your drinking?	Never	Yes, but not in the last year (2 points)		Yes, during the last year (4 points)	
Has a relative or friend, doctor, or other health worker been concerned about your drinking or suggested you cut down?	Never	Yes, but not in the last year (2 points)		Yes, during the last year (4 points)	

*The minimum score (for non-drinkers) is 0 and the maximum score is 40. A score of 8 or more indicates a strong likelihood of a hazardous or harmful alcohol consumption.

Reprinted with permission from Saunders JB, Aasland OG, Babor TF, de la Fuente JR and Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption II. *Addiction* 1993; 88: 791-804.

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Appendix H – Specialized Therapies

The following are descriptions of emerging treatments for depression. Refer to psychiatry for further consideration.

Ketamine infusion therapy

There has been significant interest in using ketamine for patients suffering from treatment resistant depression (TRD) or acute suicidal thoughts. In some reports, significant patient response has been observed within 2 to 24 hours of ketamine administration. However, poor long-term response, concern about adverse effects, poor bioavailability of oral and intramuscular (IM) formulations, and small study sizes have limited ketamine's use in the maintenance of depression symptoms.

Ketamine is an antagonist at the N-methyl-D-aspartate (NMDA) receptor. By blocking NMDA receptors, ketamine targets the excitatory neurotransmitter, glutamate *(Preskorn, 2012 [Low Quality Evidence])*. A systemic review of published literature on the antidepressant effects of ketamine found its rapid antidepressant effects have been reported in data on 163 patients *(Aan Het Rot, 2012 [Low Quality Evidence])*.

Few studies have followed patients longer than 72 hours after their IV infusion of ketamine. It is also unclear why patients who have demonstrated treatment response at 24 hours post-ketamine infusion relapse less than 48 hours later *(Aan Het Rot, 2012 [Low Quality Evidence])*. One study found two of three subjects did not demonstrate significant responses to ketamine until after they received multiple infusions *(Szymkowicz, 2013 [Low Quality Evidence])*.

Future studies of ketamine for the treatment of depression are needed. Most sites collaborated with anesthesiologists and monitored patients in the hospital for a minimum of 24 hours after their ketamine infusion due to poor oral and IM bioavailability. The oral and IM formulations also do not provide the rapid response seen with IV administration *(Aan Het Rot, 2012 [Low Quality Evidence])*. These future studies should also evaluate a way to sustain symptom remission following IV ketamine and evaluate larger groups of patients *(Szymkowicz, 2013 [Low Quality Evidence])*.

Vagus nerve stimulation (VNS)

Vagus nerve stimulation is approved by the FDA for treatment-resistant depression on the basis of its potential benefit with long-term use. The evidence primarily stems from open labeled uncontrolled trials. It is not indicated for use in the acute treatment phase, and it has been studied only in treatment-resistant depression.

Vagus nerve stimulation involves the use of an implantable device, which provides intermittent stimulation to the left vagus nerve (80% afferent to the central nervous system). It is used as an adjunctive treatment along with other modalities such as psychotropic medications *(George, 2005 [Low Quality Evidence]; Kraft, 2005 [Low Quality Evidence]; Nahas, 2005 [Low Quality Evidence]; Sackeim, 2001b [Low Quality Evidence]; Sackeim, 2001c [Low Quality Evidence]; Rush, 2005 [High Quality Evidence])*.

Side effects include voice alterations (generally just while one is receiving the 30 seconds of stimulation each 5 minutes), increased rate of neck pain, cough, dyspnea and dysphagia *(Schlaepfer, 2008 [Low Quality Evidence]; Sackeim, 2001c [Low Quality Evidence])*.

Sackeim, et al. combined available efficacy studies to assess the durability of VNS benefit. Of those who responded by three months of VNS, 66.7% and 64.5% maintained benefit at one and two years, respectively. By comparison, for those who responded by 12 months of VNS, 68.5% maintained benefit at two years *(Sackeim, 2007 [Low Quality Evidence])*. More recent studies *(Cristancho, 2011 [Low Quality Evidence]; Bajbouj, 2010 [Low Quality Evidence])* have focused on long-term outcomes, which show six-month response rates at 21.4%, six-month remission rates at 14.3%, one-year response rates at 28.6-43%, one-year remission rates at 14.3-36.8%, two-year response rates at 53.1%, and two-year remission rates at 38.9%.

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Repetitive transcranial magnetic stimulation (rTMS)

Repetitive TMS is a second-line treatment for non-psychotic major depressive disorder approved in 2008 by the FDA for treatment-refractory major depressive disorder.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that utilizes briefly pulsed electromagnetic fields to induce electrical currents in the cerebral cortex *(Allan, 2011 [Meta-analysis]; Janicak, 2010 [Low Quality Evidence])*. Repetitive TMS is generally well tolerated. Transient scalp discomfort and headache are the most common side effects, seizures are very uncommon, and in contrast to ECT, cognitive impairment is not observed *(Allan, 2011 [Meta-analysis]; George, 2010 [High Quality Evidence])*.

While many rTMS studies have been conducted, results are heterogeneous, likely due to small sample sizes and significant variability of anatomical localizations and stimulation intensities and parameters. Compared with early rTMS studies, more recent studies improve upon methodological limitations including active sham treatment mimicking the somatosenory experience of rTMS, masking rTMS administrators and patients to acoustic signals produced by stimulation, and competency certification for outcome evaluators *(Broadbent, 2011 [Systematic Review]; George, 2010 [High Quality Evidence])*.

The left prefrontal cortex is the most commonly studied anatomical stimulus location; however, right prefrontal and bilateral cortical stimulation are also used *(Allan, 2011 [Meta-analysis])*. In an intention-to-treat sample of 190 patients treated with left prefrontal cortex rTMS versus active sham treatment with three weeks of daily weekday treatment, active rTMS patients remitted significantly more than sham patients (14.1% versus 5.1%; p=0.02). The odds of remitting with active rTMS were 4.2 times greater than with sham treatment (95% confidence interval 1.32-13.24). In the open-label follow-up study of active treatment with rTMS, nearly 30% of patients remitted *(George, 2010 [High Quality Evidence])*.

O'Reardon reported on a large (301 patients) multicentered randomized controlled trial of rTMS *(O'Reardon, 2007 [High Quality Evidence])* that showed that at six weeks, remission rates were almost double for active treatment versus sham (MADRS = 14.2% vs. 5.2%, HAMD-17 = 15.5% vs. 7.1%. HAMD-24 = 17.4% vs. 8.2%), whereas at four weeks, there was no statistically significant difference.

Recently Ray, et al. showed that 75% achieved remission as compared with 10% in the control group in a small (41 patients) prospective randomized hospital-based sham controlled study. This study included patients with psychotic depression *(Ray, 2011 [High Quality Evidence])*.

Like other somatic treatments for major depressive disorder (ECT and antidepressants as example), rTMS has been critiqued for its clinical benefit durability. Janicak, et al. studied relapse of major depression over the first 24 weeks following acute left dorsolateral rTMS response (defined as ≥ 25% reduction in baseline HAMD-17 score) *(Janicak, 2010 [Low Quality Evidence])*. Patients with a more robust response to acute treatment were less likely to relapse or require rTMS administration subsequent to the initial rTMS course. An exploratory analysis failed to identify predictive factors for outcome over the 24-week follow-up, which contrasts with prior studies that found less treatment resistance predicted more favorable acute rTMS benefit *(Janicak, 2010 [Low Quality Evidence]; Lisanby, 2009 [High Quality Evidence])*. At this time, a number of treatment and protocol variations for rTMS remain, and the optimum treatment protocol and patient characteristics may not yet be identified *(Allan, 2011 [Meta-analysis])*. Nonetheless, rTMS is a low-risk and appealing treatment for treatment-refractory depressed patients for whom it is practical and cost-effective.

Magnetic seizure therapy (MST)

Magnetic seizure therapy uses focused stimulation (generally of the right frontal area) to induce a focal seizure. This is designed to obtain efficacy of ECT without the cognitive side effects (which generally occur when seizures spread to the hippocampus). One open label trial *(Sackeim, 1994 [Low Quality Evidence])* showed less amnesia and faster reorientation than ECT and some improvement in depression scores.

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Deep brain stimulation (DBS)

Deep brain stimulation is the process of implanting electrodes to continuously stimulate various brain regions with high-frequency impulses to diminish major depressive symptoms among treatment refractory individuals. To date, five neuroanatomical targets have been studied with favorable effects and minor adverse effects: nucleus accumbens, subcallosal cingulate gyrus, inferior thalamic peduncle, ventral internal capsule/ventral striatum, and the lateral habenula *(Bloomstedt, 2011 [R])*. So far, evidence involves small non-blinded trials.

One open label trial *(Mayberg, 2005 [Low Quality Evidence])* showed four out of six patients achieved remission after surgery (and those with sham sessions did not). At two months, five out of six patients were in remission, and four out of six were in remission at six months. A follow-up study of these patients plus 14 additional patients *(Lozano, 2008 [Low Quality Evidence])* showed response/remission rates of 60% versus 35% at six months and 55% versus 35% (or were within one point of remission) at 12 months. At two years and three years, the response rates were 46.2% and 75%, respectively, and remission rates were 15-20% and 40-50%, respectively *(Kennedy, 2011 [Low Quality Evidence])*. Malone, et al. *(Malone, 2009 [Low Quality Evidence])* showed that 40% of treatment refractory depressed patients responded and 20% reached remission at six months of continuous DBS. The rates went up to 53.3% response and 40% remission at last follow-up, up to four years later.

Eye movement desensitization and reprocessing (EMDR)

The EMDR Institute's official position is that EMDR is only empirically validated for treatment of trauma-related disorders. At this time, there is no evidence to recommend EMDR as a treatment for depression.

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This guideline is a primary resource for Minnesota's statewide DIAMOND Depression Initiative. Depression Improvement Across Minnesota, Offering a New Direction (DIAMOND) is a primary care-based program modeled after and adapted from Project IMPACT. The DIAMOND model has demonstrated results for redesigning both health care and payment systems. For more information, go to DIAMOND for Depression on the ICSI Web site.

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ICSI Document Development and Revision Process

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The information contained in this ICSI Health Care Guideline is intended primarily for health professionals and other expert audiences.

This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients and families are urged to consult a health care professional regarding their own situation and any specific medical questions they may have. In addition, they should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in their individual case.

This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition.

Document Development and Revision Process

The development process is based on a number of long-proven approaches and is continually being revised based on changing community standards. The ICSI staff, in consultation with the work group and a medical librarian, conduct a literature search to identify systematic reviews, randomized clinical trials, meta-analysis, other guidelines, regulatory statements and other pertinent literature. This literature is evaluated based on the GRADE methodology by work group members. When needed, an outside methodologist is consulted.

The work group uses this information to develop or revise clinical flows and algorithms, write recommendations, and identify gaps in the literature. The work group gives consideration to the importance of many issues as they develop the guideline. These considerations include the systems of care in our community and how resources vary, the balance between benefits and harms of interventions, patient and community values, the autonomy of clinicians and patients and more. All decisions made by the work group are done using a consensus process.

ICSI's medical group members and sponsors review each guideline as part of the revision process. They provide comment on the scientific content, recommendations, implementation strategies and barriers to implementation. This feedback is used by and responded to by the work group as part of their revision work. Final review and approval of the guideline is done by ICSI's Committee on Evidence-Based Practice. This committee is made up of practicing clinicians and nurses, drawn from ICSI member medical groups.

Implementation Recommendations and Measures

These are provided to assist medical groups and others to implement the recommendations in the guidelines. Where possible, implementation strategies are included which have been formally evaluated and tested. Measures are included which may be used for quality improvement as well as for outcome reporting. When available, regulatory or publicly reported measures are included.

Document Revision Cycle

Scientific documents are revised every 12-24 months as indicated by changes in clinical practice and literature. Each ICSI staff monitors major peer-reviewed journals every month for the guidelines for which they are responsible. Work group members are also asked to provide any pertinent literature through check-ins with the work group mid-cycle and annually to determine if there have been changes in the evidence significant enough to warrant document revision earlier than scheduled. This process complements the exhaustive literature search that is done on the subject prior to development of the first version of a guideline.

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