ICSI Institute for Clinical Systems Improvement

Health Care Guideline

Depression in Primary Care

How to cite this document:

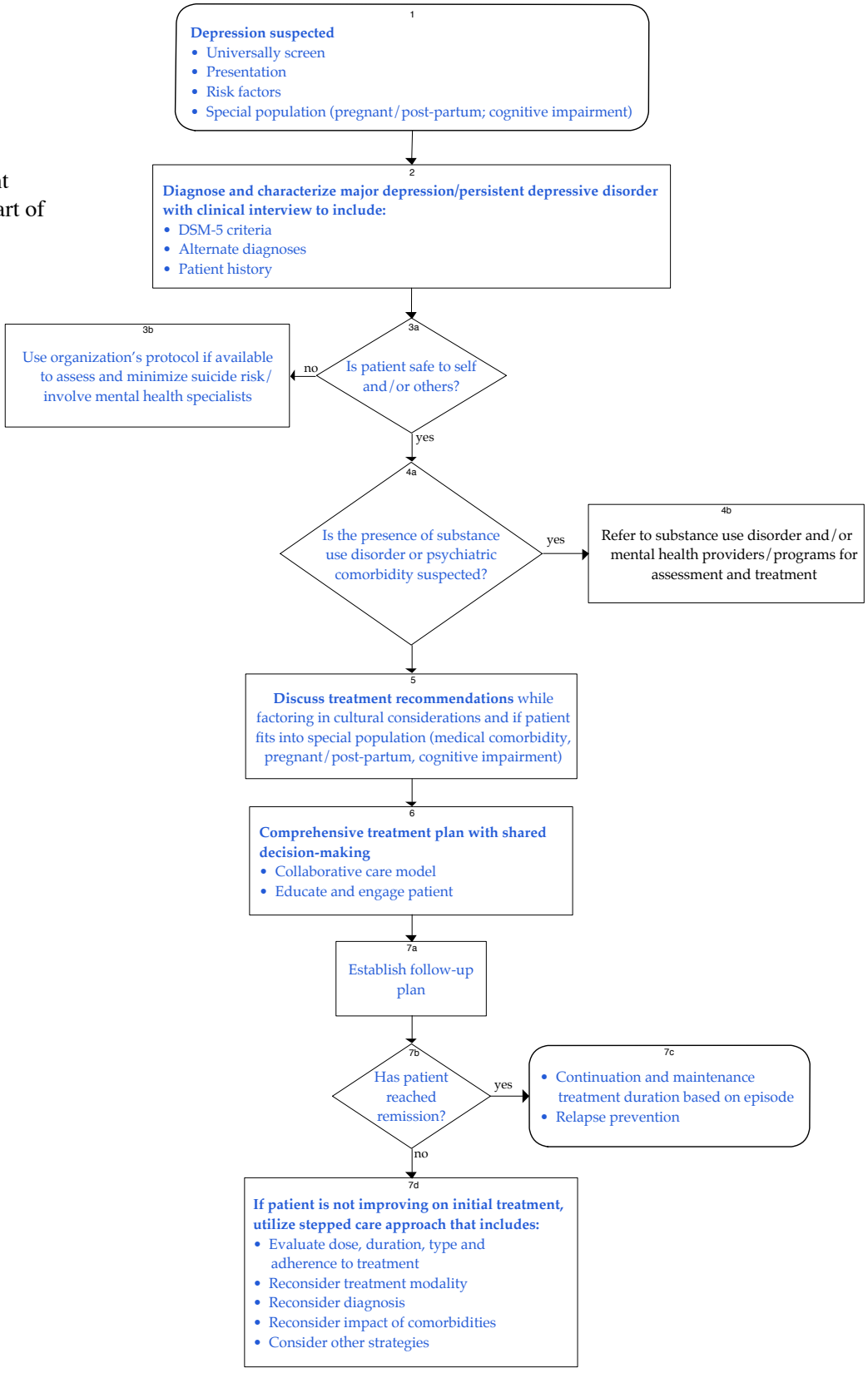
Trangle M, Gursky J, Haight R, Hardwig J, Hinnenkamp T, Kessler D, Mack N, Myszkowski M. Institute for Clinical Systems Improvement. Adult Depression in Primary Care. Updated March 2016.

ICSI
Institute for Clinical Systems Improvement

Health Care Guideline:
Adult Depression in Primary Care

Seventeenth Edition
March 2016

Text in blue in this document indicates a link to another part of the document or website.



Return to Table of Contents

Table of Contents

Work Group Leader
Michael Trangle, MD
Psychiatry, HealthPartners Medical Group and Regions Hospital

Work Group Members
Allina Medical Clinic
Daniel Kessler, LP
Psychology

Essentia Health
Jeffrey Hardwig, MD
Psychiatry
Todd Hinnenkamp, RN
Internal Medicine

Fairview Health Services
Robert Haight, PharmD, BCPP
Pharmacy

Mayo Clinic
Mioki Myszkowski, MD
Family Medicine

North Memorial Health Care
Nicky Mack, RN
Family Medicine

Olmsted Medical Center
Jeffrey Gursky, MD
Psychiatry

ICSI
Jodie Dvorkin
Project Manager/Health Care Consultant
Senka Hadzic
Clinical Systems Improvement Facilitator

Evidence Grading

Literature Search

A consistent and defined literature search process is used in the development and revision of ICSI guidelines. Two literature searches were conducted for this guideline. The searches were conducted in PubMed, Ovid and PsychInfo.

The first search included systematic reviews, meta-analyses, randomized controlled trials and observational studies from January 2013 – February 2015. The search was limited to adults over 18 years of age. The search excluded animal studies and non-English language studies. The terms included screening; patient health questionnaire-9 (PHQ-9); insomnia; therapeutic alliance in depressed patients; psychotherapies; antidepressants; implementation and best practices; special populations and disparities; telepsychiatry and outcomes; complementary medicine; integrated care, coordinated care, collaborative care; continuity of patient care, follow-up, office visits and frequency; effective treatments for adults with major depression who also have diabetes; prevalence and treatment of depression in patients who had stroke; after care; follow-up; remission; remission induction; functional impairment; cognitive impairment; genomics, genetics and pharmacogenetics; shared decision-making; and TMS (transcranial magnetic stimulation).

The second literature search was specific to treatment recommendations for major depressive disorder and persistent depressive disorder and included systematic reviews, meta-analyses and randomized controlled trials. It covered the period between January 2005 and September 2015 and was limited to adults over 18 years of age. The search excluded animal studies and non-English language studies. The terms included treatment, treatment outcomes and multiple treatment comparison; psychological treatment and supportive therapy, cognitive behavioral therapy; antidepressant agents, pharmacotherapy and drug therapy; combined treatment; duration of treatment, acute phase, continuation phase, maintenance phase; depression and major depression; dysthymia disorder and persistent depressive disorder, chronic depression and chronic major depression.

In addition to the literature searches, articles were obtained by work group members and ICSI staff. Those vetted by the work group were included in the guideline when appropriate.

Return to Table of Contents

GRADE Methodology

ICSI utilizes the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology system.

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

- development 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.

GRADE involves systematically evaluating the quality of evidence (high, moderate, low, very low) and developing a strength of recommendation (strong, weak). For more detailed information on GRADE, please go to: http://www.gradeworkinggroup.org/.

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.

Return to Table of Contents

Foreword

Introduction

In 2016, the U.S. Preventive Services Task Force (USPSTF) updated its recommendations to include routine screening for depression of the general adult population, pregnant and postpartum women *(Siu, 2016)*. There was moderate evidence that screening pregnant and postpartum women reduced depression prevalence and increased remission and treatment response even in the absence of additional treatment supports. Outcomes were better with such supports. There was low to moderate evidence showing the same for the general adult primary care population but insufficient evidence to show benefit in older adults. They concluded that generalizing from evidence in all adults to older adults may be reasonable *(O'Connor, 2016)*. 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)*. Given that the outcomes are better when reliable systems and supports are put in place to diagnose, follow-up and modify treatment as needed, this guideline will be highlighting evidence-based, effective ways to implement such supports *(O'Connor, 2016)*.

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 and Education:** The patient and his/her family are actively educated, 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 is in place to ensure ongoing contacts with the patient during the first 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 and improve outcomes for 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; Schonfeld, 1997)*. Additionally, more than 80% of patients with depression have a medical comorbidity *(Klinkman, 2003)*. Usual care for depression in the primary care setting has resulted in only about half of depressed adults getting treated *(Kessler, 2005)* and only 20-40% showing substantial improvement over 12 months *(Unützer, 2002; Katon, 1999)*. 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)*.

At any given time, 9% of the population has a depressive disorder, and 3.4% has major depression *(Strine, 2008)*. 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)*.

Return to Table of Contents

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)*.

In a 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)*.

A 2011 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)*.

Cultural Considerations

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

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 optimally 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)*.

Assessment and treatment tools

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

Cultural beliefs and common presentations

- When dealing with patients from diverse cultures, the impact of patient's cultural beliefs around depression, cultural stigma and manifestation of depression in physical symptoms vs. psychological can play a role in how patients perceive depression and subsequently seek treatment *(Kleinman, 2004)*.
- 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; Miranda, 2004)*.
- 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)*.
- 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)*.

Return to Table of Contents

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 years 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 with significant overlap of symptoms outside the scope of this guideline include anxiety disorder, adjustment disorder and bipolar disorder.

Return to Table of Contents

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 where there is overlap. The work group has elected to use PHQ-9 in the measures, since it is broadly utilized by various organizations. There are other evidence-based tools that may be used. If other tools are chosen for measurement, they should be sensitive, specific, reliable and valid for measuring intensity levels and response and remission rates.

1. Increase the percentage of patients accurately diagnosed with major depression or persistent depressive disorder. *(Annotation #2)*
2. Decrease the number of completed suicides in patients with major depression or persistent depressive disorder managed in primary care. *(Annotation #3a)*
3. Increase the percentage of patients with major depression or persistent depressive disorder who are screened for substance use disorders. *(Annotation #4a)*
4. Increase the screening 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. *(Appendix D)*
5. Improve communication between the primary care physician and the mental health care clinician (if patient is co-managed). *(Annotation #7a)*
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 #5, 6)*
7. Increase the percentage of patients with major depression or persistent depressive disorder who have follow-up to assess for outcomes from treatment. *(Annotations #5, 6, 7a)*

Return to Table of Contents

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 routinely screen all adults for depression using a standardized instrument.	Strong	1	*O'Connor, 2016; Kroenke, 2010; Duffy, 2008; Gilbody, 2006; Rush, 2003*
Diagnose and characterize major depression	Good Practice Statement	Clinicians should use the DSM-5 criteria to determine diagnosis of major depression, persistent depressive disorder, other specified depressive disorder, and unspecified depressive disorder.	Strong	2	*American Psychiatric Association, 2013; Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*
Treatment for major depression 1	Moderate	Consider combining pharmacotherapy and psychotherapy treatments for patients with major depressive disorder when practical, feasible, available and affordable.	Weak	5	*Cuijpers, 2014b; Hollon, 2014; Peeters, 2013; Spijker, 2013; van Hees, 2013; Cuijpers, 2012; Jakobsen, 2012b; Guidi, 2011; Oestergaard, 2011; Cuijpers, 2009a; Cuijpers, 2009c; de Maat, 2008*
Treatment for major depression 2	Moderate	When unable to do combined therapy due to patient preferences, availability and affordability of the treatments: 1. Consider starting with psychotherapy for mild to moderate major depression; 2. Consider starting with pharmacotherapy for severe major depression.	Weak	5	*Cuijpers, 2015; Kuyken, 2015; Biesheuvel-Leliefeld, 2015; Menchetti, 2014; Steinert, 2014 Cuijpers, 2013; Piet, 2011; Segal, 2010; Dobson, 2008*

Return to Table of Contents

Topic	Quality Of Evidence	Recommendations	Strength of Recommendation	Annotation Number	Relevant References
Treatment for persistent depressive disorder 1	High	Consider starting with medication in pure dysthymia patients. The work group feels that it is reasonable to consider stepped care, which includes augmenting medications and adding psychotherapy for patients who don't improve.	Strong	5	*Kriston, 2014; von Wolff, 2013; Cuijpers, 2012; Levkovitz, 2011; Cuijpers, 2010b; Cuijpers, 2009b; Imel, 2008; Markowitz, 2005; Browne, 2002;*
Treatment for persistent depressive disorder 2	High	For patients with chronic major depression, start with combined antidepressant medication and psychotherapy.	Strong	5	*Kriston, 2014; Weirsma, 2014; Spijker, 2013; Cuijpers, 2012; Cuijpers, 2010b; Kocsis, 2009a; Imel, 2008; Browne, 2002*
Collaborative Care Model	High	Collaborative care approach is recommended for patients with depression in primary care.	Strong	6	*Fortney, 2013; Archer, 2012; Gjerdingen, 2007; Katon, 2008; Gilbody, 2006; Hunkeler, 2006; Belnap, 2006; Simon, 2001a; Katon, 1999*
Patient engagement and shared decision-making	Low	Before initiating treatment, it is important to establish a therapeutic alliance with the patient regarding diagnosis and treatment options (in which there is overlap in the patient's and clinician's definition of the problem and agreement on which steps are to be taken by each).	Strong	6	*Kocsis, 2009b; Loh, 2007; Krupnick, 1996*

Topic	Quality Of Evidence	Recommendations	Strength of Recommendation	Annotation Number	Relevant References
Establish follow-up plan. Use of PHQ-9 as monitor and management tool	Low	Clinicians should establish and maintain follow-up with patients.	Strong	7a	*Trivedi, 2006b; Unützer, 2002; Hunkeler, 2000; Simon, 2000*
Pregnant and post-partum women	Low	Clinicians should screen and monitor depression in pregnant and post-partum women.	Strong	Appendix D	*O'Connor, 2016; Yonkers, 2009; Vesga-López, 2008; Gjerdingen, 2007; Gaynes, 2005*

Return to Table of Contents

Summary Table of Recommendations for Major Depressive Disorder and Persistent Depressive Disorder

At every level of severity, add education, physical activity and behavioral activation to standard treatment recommendations.

Severity	PHQ-9 Scores	Possible Diagnoses	Treatment Recommendations
Undefined	Initial Score: 5-9	Does not meet criteria for major depressive disorder Consider for persistent depressive disorder	Stay in touch: a) If no improvement after one or more months, consider treating or referral to behavioral health. b) If symptoms deteriorate, start treatment or make a referral.
	Follow-up Score: 5-9	Partial remission	Continue stepped therapies approach.
Per DSM-5: 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.	10-14	Mild major depression	Combined psychotherapy and pharmacotherapy treatment. When unable to do combined therapy due to patient preferences, availability and affordability of the treatments, start with psychotherapy. Initially consider weekly contacts to ensure adequate engagement, then at least monthly.
Per DSM-5: The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for "mild" and "severe."	15-19	Moderate major depression	Combined psychotherapy and pharmacotherapy treatment. When unable to do combined therapy due to patient preferences, availability and affordability of the treatments, start with psychotherapy. Initially consider weekly contacts to ensure adequate engagement, then at least every 2-4 weeks.
Per DSM-5: The number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning.	≥20	Severe major depression	Combined psychotherapy and pharmacotherapy treatment. When unable to do combined therapy due to patient preferences, availability and affordability of the treatments, start with pharmacotherapy. Weekly contacts until less severe.
Meets DSM-5 criteria for persistent depressive disorder		Pure dysthymia	Consider starting with medication. Consider stepped care, which includes augmenting medications and adding psychotherapy for patients who don't improve.
Meets DSM-5 criteria for persistent depressive disorder		Chronic major depression	Combined psychotherapy and pharmacotherapy treatment.

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)."

(Cuijpers, 2015; Kuyken, 2015; Biesheuvel-Leliefeld, 2015; Cuijpers, 2014b; Hollon, 2014; Kriston, 2014; Menchetti, 2014; Steinert, 2014; Wiersma, 2014; American Psychiatric Association, 2013: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; Cuijpers, 2013; Peeters, 2013; Spijker, 2013; van Hees, 2013; von Wolff, 2013; Cuijpers, 2012; Jakobsen, 2012b; Guidi, 2011; Levkovitz, 2011; Oestergaard, 2011; Piet, 2011; Cuijpers, 2010b; Fournier, 2010; Kroenke, 2010; Segal, 2010; Cuijpers, 2009a; Cuijpers, 2009c; Kocsis, 2009a; Dobson, 2008; de Maat, 2008; Imel, 2008; Cuijpers, 2007; Markowitz, 2005; Browne, 2002)

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. 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)*.

Return to Table of Contents

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. The following points have not been updated during this revision.

See Annotation #6, "Comprehensive Treatment Plan with Shared Decision-Making," for definitions of the collaborative care model.

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

Return to Table of Contents

- Structured, frequent monitoring and follow-up with patient
- Nurse/care manager phone care and use of other modalities for patient follow-up

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; Simon, 2001a; Simon, 2001b)*. 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. The two-year studies show mixed results possibly indicating a turning point *(Dickinson, 2005)*, 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)*.

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.

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; Schoenbaum, 2001)*. 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)*.

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; Rost, 2004)*.

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

Return to Table of Contents

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

Return to Table of Contents

Algorithm Annotations

Screening

1. Depression Suspected

Recommendation	Quality of Evidence and Strength of Recommendation
Clinicians should routinely screen all adults for depression using a standardized instrument.	Quality of Evidence: Low Strength of Recommendation: Strong
Benefit: There is evidence that screening adults whom one suspects as being depressed improves outcomes. There is low to moderate evidence that screening all adults, pregnant and postpartum women improves outcomes even in the absence of treatment protocols, care managers and specialty trained providers. There is less evidence supporting this recommendation with geriatric patients. The benefit is that one would be finding and treating many more depressed patients and improving their outcomes/functioning not only for depression but for the other medical diseases with depression as a co-morbidity. There is also some evidence that this might save overall medical costs for depressed patients. The optimum interval at which to screen for depression is unknown; more evidence for all populations is needed to identify ideal screening intervals. **Harm:** The only harm identified is the cost of screening patients who are not depressed. **Benefit-Harms Assessment:** Although direct evidence of the isolated health benefit of depression screening in primary care is weak, the totality of the evidence supports the benefits of screening in pregnant and postpartum and general adult populations, particularly in the presence of additional treatment supports such as treatment protocols, care management and availability of specially trained depression care providers. Evidence is least supportive of screening in older adults, where direct evidence is most limited.	
Relevant Resources: *O'Connor, 2016; Kroenke, 2010; Duffy, 2008; Gilbody, 2006; Rush, 2003*	

Overview. Major depressive disorder is characterized by discrete episodes of at least two weeks' duration (although most episodes last considerably longer) involving clear-cut changes in affect, cognition and neurovegetative functions and inter-episode remissions. A diagnosis based on a single episode is possible, although the disorder is a recurrent one in the majority of cases. Careful consideration is given to the delineation of normal sadness and grief from a major depressive episode. Bereavement may induce great suffering, but it does not typically induce an episode of major depressive disorder. When they do occur together, the depressive symptoms and functional impairment tend to be more severe, and the prognosis is worse compared with bereavement that is not accompanied by major depressive disorder. Bereavement-related depression tends to occur in persons with other vulnerabilities to depressive disorders, and recovery may be facilitated by antidepressant treatment *(American Psychiatric Association, 2013)*.

A more chronic form of depression, persistent depressive disorder (dysthymia), can be diagnosed when the mood disturbance continues for at least two years in adults or one year in children. This diagnosis, new in DSM-5, includes both the DSM-IV diagnostic categories of chronic major depression and dysthymia *(American Psychiatric Association, 2013)*.

Suspect Depression

Many patients with major depression do not initially complain of depressed mood or anehdonia *(American Psychiatric Association, 2013)*. Clinicians need to suspect this diagnosis based on a profile of common presentations and risk factors, taking into account cultural considerations *(American Psychiatric Association, 2013)*.

Return to Algorithm *Return to Table of Contents*

Common Presentations

Common presentations for patients not complaining of major depression or anhedonia include *(American Psychiatric Association, 2013)*:

- 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

The close relationship of mind and body results in the presentation of medical illness with major depression in various forms: *(American Psychiatric Association, 2013)*

- Medical illness may be a biological cause (e.g., thyroid disorder, stroke).
- Medical illness or the patient's perception of his/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)*.

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)*.

Major depression may also be associated with medical disorders or the patient's perception of his/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; Briggs, 1993)*.

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

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

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

Return to Algorithm *Return to Table of Contents*

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

Note: Genomics: There have been a number of genome-wide association studies for major depression. So far there have been no robust, replicable, single nucleotide polymorphisms identified for depression *(Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013)*.

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)*.

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

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)*.

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 guideline.

Whenever 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)*.

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)*.

The PHQ-9 has been validated for measuring depression severity *(Kroenke, 2001; Spitzer, 1999)* and is validated as a tool for both detecting and monitoring depression in primary care settings *(Kroenke, 2010; Wittkampf, 2007)*. It has a sensitivity (false negative) of 0.77 and specificity (false positive) of 0.85 when using the screened item scoring method. Two other tools with good utility in case finding, aiding diagnosis and severity grading are the Structural Clinical Interview DSM-IV Axis-I Disorders (SCID-I) with a sensitivity of 85% and specificity 82% and the Mini International Neuropsychiatric Interview (MINI) with a sensitivity of 78% and specificity of 85% *(Pettersson, 2015)*.

It can be administered telephonically *(Pinto-Meza, 2005)* and read to the patient. Elderly patients with mild cognitive impairment can reliably fill out the PHQ-9 *(Löwe, 2004)*. A recent study found the PHQ-9 is useful in psychiatric practices, as well. PHQ-9 scores influenced clinical decision-making for 93% of more than 6,000 patient contacts *(Duffy, 2008)*. The PHQ-9 tool can be found on www.phqscreeners.com or Appendix A of this guideline.

Other recognized and validated tools include the Beck Depression Inventory (http://www.beckinstitute.org/beck-inventory-and-scales/), Hamilton Rating Scale for Depression (HAM-D) (http://www.ids-qids.org/) and the Quick Inventory of Depressive Symptomatology Self-Report (QID-SR) (http://www.ids-qids.org/) *(Rush, 2003)*.

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)*. Language versions that are validated for use in primary care are Spanish *(Wulsin, 2002)* and Chinese *(Yeung, 2008)*. 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)*. 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; Donnelly, 2007)*.

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.

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

Special Populations

See Appendix D, "Special Populations," for more information regarding screening for the following conditions/populations, as applicable: 1) cardiovascular and cerebrovascular disease, 2) diabetes, 3) chronic pain, 4) geriatrics [includes dementia/cognitive impairment], and 5) pregnant and postpartum women.

Return to Algorithm *Return to Table of Contents*

Diagnosis

2. Diagnose and Characterize Major Depression/Persistent Depressive Disorder with Clinical Interview

Recommendation	Quality of Evidence and Strength of Recommendation
Clinicians should use the DSM-5 criteria to determine diagnosis of major depression, persistent depressive disorder, other specified depressive disorder, and unspecified depressive disorder.	Quality of Evidence: Good Practice Statement Strength of Recommendation: Strong
Benefit: Proper use of diagnostic criteria assists in accurately diagnosing and directing the treatment plan toward appropriate evidence-based interventions. **Harm:** There is a risk of exclusively utilizing the criteria in a checklist manner, which could lead to inappropriate diagnosis and treatment. **Benefit-Harms Assessment:** With proper training and education, the proper use of the diagnostic criteria from the DSM-5 aids in driving the correct diagnosis and proper evidence-based interventions, which outweighs any potential harm.	
Relevant Resources: *American Psychiatric Association, 2013; Diagnostic and Statistical Manual of Mental Disorders, 5th edition*	

The content in this entire annotation comes from the American Psychiatric Association, 2013: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.

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.

Introduction

Sadness is a part of human existence that the majority of the time does not necessitate treatment. These periods should not be diagnosed as a depressive episode if they do not met criteria for severity and duration, and include clinically significant distress or impairment *(American Psychiatric Association, 2013)*.

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

Return to Algorithm *Return to Table of Contents*

Criteria Required for Diagnosis

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.

Return to Algorithm *Return to Table of Contents*

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.

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

- Mild, single episode ICD-10 F32.0, recurrent episode ICD-10 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 ICD-10 F32.1, recurrent episode ICD-10 F33.1: The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for "mild" and "severe."
- Severe, single episode ICD-10 F32.2, recurrent episode ICD-10 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 ICD-10 F32.4, recurrent episode ICD-10 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, recurrent episode ICD-10 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, ICD-10 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.

Return to Algorithm *Return to Table of Contents*

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.

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)

Other specified depressive disorder ICD-10 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

Return to Algorithm *Return to Table of Contents*

Unspecified Depressive Disorder ICD-10 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 somatic symptom and related disorders

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, factitious 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. Ask patients about personal history of mania or hypomania. If any, ask about family history and, if any consider using MDQ, if any, to assess further. The diagnostic criteria for an episode of major depression in bipolar disorder are the same as the criteria for unipolar major depressive disorder. Use 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).

Return to Algorithm *Return to Table of Contents*

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)
- 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)*. 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; Goodwin, 2007)*. 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)* for bipolar disorder. Treatment for bipolar disorder falls out of the scope of this guideline.

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)*. 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.

Post-traumatic stress disorder (PTSD)

PTSD may include symptoms shared by a depressive episode and may also be comorbid with a depressive episode. PTSD is associated with exposure to actual or threatened death, serious injury, and/or sexual violence. It includes intrusive flashbacks, nightmares, psychological and/or physical reactivity to cues of

the event, avoidance of cues of the event (both internal and external), negative alterations in mood, and hyperarousal and reactivity *(American Psychiatric Association, 2013)*.

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.
- **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)*. Ongoing utility of behavioral activation, skill building and self-management practices is recommended *(Mazzucchelli, 2009; Vittengl, 2009; Cuijpers, 2007)*.

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

Return to Algorithm *Return to Table of Contents*

- 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.

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)*.
- 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.

Return to Algorithm *Return to Table of Contents*

3a. Is Patient Safe to Self and/or Others?

Ensure Patient Safety First: Assess, Develop and Use Suicide Protocol to Minimize Suicide Risk/Involve Mental Health Specialists

The estimated 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)*.

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?

Return to Algorithm *Return to Table of Contents*

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?

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).

Return to Algorithm *Return to Table of Contents*

3b. Use Organization's Protocol if Available to Assess and Minimize Suicide Risk/Involve Mental Health Specialists

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
- When and how to use local or national hotlines
- When to use on-site security, if available
- When and how to access 911, and what to with the patient while waiting

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.

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)*.

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)*.

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)*. 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.

Return to Algorithm *Return to Table of Contents*

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)*.

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)*.

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)*.

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)*.

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)*.

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
- Referral to the emergency department

(Dieserud, 2001; Whooley, 2000)

Return to Algorithm *Return to Table of Contents*

4a. Is the Presence of Substance Use Disorder or Psychiatric Comorbidity Suspected?

The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians screen adults ages 18 years or older for alcohol misuse and provide persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce alcohol misuse (Grade B recommendations) *(U.S. Preventive Services Task Force, 2014)*.

Return to Algorithm *Return to Table of Contents*

Substance Use Disorders Prevalence

According to DSM-5, 12-month prevalence of specific substance use disorder among adults is following: *(American Psychiatric Association, 2013)*

- Alcohol use disorder: 8.5%
- Cannabis use disorder: 1.5%
- Phencyclidines use disorder: 1.3 – 2.9%
- Opioid use disorder: 0.37%
- Sedative, hypnotic or anxiolytic use disorder: 0.2%
- Stimulants use disorder: 0.2%

Alcoholism and major depressive disorder are distinct clinical entities. They are 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, it is about 7.8% *(Davis, 2006)*. However, alcohol-use disorders are under reported in primary care (for example, higher risk drinking 1% males, 0.5% females) in comparison with Opinions survey (8% males, 7% females) *(Hawkins, 2007)*.

Screening for Alcohol and Other Drug Use (CAGE, CAGE-AID, AUDIT, AUDIT-C, DAST-10)

CAGE and CAGE-AID

The CAGE tool questions are sensitive and specific in screening for alcohol dependence. One positive response has a sensitivity of 85% and a specificity of 89%, and two positive responses have a specificity of 96% *(Bush, 1987)*. Additionally, a 2000 systematic review showed that the CAGE questions were superior in detecting alcohol abuse and dependence compared to the AUDIT tool (sensitivity, 43%-94%; specificity, 70-97%) *(Fiellin, 2000)*.

The CAGE-AID questionnaire broadens the CAGE to include other drugs. One or more Yes responses had sensitivity of 79% and specificity of 77% in detecting alcohol abuse and dependence *(Brown, 1995)*. Two or more Yes responses had sensitivity of 70% and specificity of 85% *(Brown, 1995)*. The CAGE tool shows promise in identifying pregnant, low-income women at risk for heavier drug use *(Midanik, 1998)*.

AUDIT and AUDIT-C

The Alcohol Use Disorder Identification Test (AUDIT) is a widely used screening tool that consists of 10 questions; it can be self-administered, or the questions can be read aloud *(Babor, 2001)*. The AUDIT tool questions are most effective in identifying patients with at risk, hazardous or harmful drinking (sensitivity, 51-97%; specificity, 78-96%) *(Fiellin, 2000)*. The AUDIT-C is a modified three-question version of the AUDIT tool.

DAST-10

The Drug Abuse Screening Test (DAST) is a 10-item, yes/no self-report instrument that has been condensed from the 28-item DAST questionnaire. See the following reference for details: Gavin DR, Ross HE, Skinner HA, "Diagnostic validity of the Drug Abuse Screening Test in the assessment of DSM-III drug disorders," *Brit J Addiction* 1989;84:301-07.

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

Return to Algorithm *Return to Table of Contents*

reviewed, success in treating dependency on alcohol, cocaine and other abused substances is more likely if accompanying depression is simultaneously treated.

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. The National Institute on Alcohol Abuse and Alcoholism and other agencies offer tools to guide primary care-based medical treatment of alcohol abuse. For more information, see also the ICSI Healthy Lifestyles guideline and the following online resources by Substance Abuse and Mental Health Services Administration (SAMHSA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

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)*. 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

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.

Return to Algorithm *Return to Table of Contents*

Treatment

5. Discuss Treatment Recommendations

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)*.

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)*.

Patient participation in shared treatment decision-making improves depression treatment adherence and clinical outcomes in depressed patients *(Loh, 2007)*. 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; Hamann, 2005; Garfield, 2004)*. For more information, see the ICSI Shared Decision-Making Model in Appendix B.

Major Depressive Disorder Treatment Recommendation 1

Recommendation	Quality of Evidence and Strength of Recommendation
Consider combining pharmacotherapy and psychotherapy treatments for patients with major depressive disorder when practical, feasible, available and affordable.	Quality of Evidence: Moderate Strength of Recommendation: Weak
Benefit: The preponderance of moderate quality literature shows that outcomes are better when pharmacotherapy and psychotherapy treatments are combined than either treatment alone. **Harm:** The potential negative cumulative impact of time away from work and family to do psychotherapy, office visits to do psychotherapy, and potential side effects of medications could affect the patients. **Benefit-Harms Assessment:** When balancing better outcomes of the combined treatment with negative impacts of treatment on patients, the group felt the benefits of combined treatment outweigh the potential harms.	
Relevant Resources: *Cuijpers, 2014b; Hollon, 2014; Peeters, 2013; Spijker, 2013; van Hees, 2013; Cuijpers, 2012; Jakobsen, 2012b; Guidi, 2011; Oestergaard, 2011; Cuijpers, 2009a; Cuijpers, 2009c; de Maat, 2008*	

The decision to combine both antidepressants with psychotherapy is often individually decided for each patient, and many factors including patient preference, treatment availability, psychosocial factors and cost-effectiveness are often considered by clinicians.

Many times the clinician is faced with consideration of adding psychotherapy to patients who are treated with antidepressants. We reviewed 12 studies in regard to this and found 11 to show superiority of combined treatment in comparison to antidepressant-only treatment of depression *(Cuijpers, 2014a; Hollon, 2014; Spijker, 2013; van Hees, 2013; Cuijpers, 2012; Jakobsen, 2012b; Guidi, 2011; Oestergaard, 2011; Cuijpers, 2009b; Cuijpers, 2009c; de Maat, 2008)*. However, this superiority of combined treatment was limited and unlikely to be of consistent clinical relevance.

Conversely, clinicians are also faced with the consideration of adding antidepressants to patients treated with psychotherapy. We reviewed six studies, which all showed superiority of combined treatment over psychotherapy alone *(Cuijpers, 2014; Peeters, 2013; Spijker, 2013; Cuijpers, 2009b; Cuijpers, 2009c; de Maat, 2008)*. Similarly, this superiority also was of limited clinical significance.

Return to Algorithm *Return to Table of Contents*

Although many of these studies suggest that combining antidepressants and psychotherapy regularly for the treatment of depression may have limited added benefit, each decision should be made individually for each patient. There may be patients that respond better to combined treatment in comparison to either antidepressants or psychotherapy alone. In addition to this, patients being treated for depression may have other areas in need of treatment that either antidepressants or psychotherapy may not treat alone, such as comorbid mental health disorders or psychosocial stressors or medical issues.

Major Depressive Disorder Treatment Recommendation 2

Recommendation	Quality of Evidence and Strength of Recommendation
When unable to do combined therapy due to patient preference or availability/affordability of the treatments: **1. Consider starting with psychotherapy for mild to moderate major depression; 2. Consider starting with pharmacotherapy for severe major depression.**	Quality of Evidence: Moderate Strength of Recommendation: Weak
Benefit: Generally, the evidence shows that both medication and therapy are reasonably effective. For mild to moderate major depression, psychotherapy alone may lengthen the time to relapse and patients may be more successfully withdrawn from the medications. For severe major depression, it appears that medications have a significantly higher effect size than psychotherapy. **Harm:** For mild to moderate major depression, disruptions include taking time for office visits to do psychotherapy, and time away from work and family. For severe major depression, these are the potential side effects of medications. **Benefit-Harms Assessment:** Even though the quality of the majority of individual articles are moderate to high, the overall literature is quite weak in documenting harms, availability and costs to the individual patient. There was no scientific or easy way to directly compare the benefits to costs. The seasoned clinicians in the group chose to go with the benefits in terms of somewhat better outcomes based upon the literature but qualify this by making the recommendations weak. This is an area where shared decision-making is likely to be especially valuable.	
Relevant Resources: *Cuijpers, 2015; Kuyken, 2015; Biesheuvel-Leliefeld, 2015; Menchetti, 2014; Steinert, 2014; Cuijpers, 2013; Piet, 2011; Segal, 2010; Dobson, 2008*	

Major depressive disorder is often a chronic disorder, and treatments need to reduce symptoms over long periods of time. There is evidence that an acute course of psychotherapy may lengthen the period of time before relapse or recurrence *(Biesheuvel-Leliefeld, 2015; Steinert, 2014)*. In addition to this, Cuijpers, 2013 and Dobson, 2008 found acute phase-only cognitive behavioral therapy (CBT) without maintaining patients on antidepressants to be equal in efficacy to maintaining patients on antidepressants for 6-18 months after remission *(Cuijpers, 2013; Dobson, 2008)*.

It appears that antidepressants may have a significantly higher effect size in patients with severe depression *(Fournier, 2010)*. In addition to this, there is some evidence that patients with mild depression may preferentially respond to psychotherapy, while patients with moderate to severe depression may preferentially respond to antidepressants *(Spielmans, 2011)*.

Segal, 2010 and Kuyken, 2015 found patients given psychotherapy and withdrawn off of antidepressants to have comparable rates of relapse to those remaining on maintenance antidepressant treatment for up to 24 months *(Kuyken, 2015; Segal, 2010)*.

Generally, antidepressants and psychotherapy appear to be equally effective in the acute treatment of depression *(Spielmans, 2011)* and the selection of the treatment modality may be affected by patient preference, treatment availability and relative cost.

Return to Algorithm *Return to Table of Contents*

Persistent Depressive Disorder

The majority of the literature on persistent depressive disorder is based on DSM-IV criteria and divides it into the following categories:

1) Pure dysthymia for the whole duration
2) Major depression that is chronic for at least two years
3) Eecurrent major depression without inter-episode recovery
4) Major depression that is superimposed on a pre-existing dysthymic disorder (persistence for at least two years defines this category)

DSM-5 consolidated DSM-IV and included dysthymic disorder and chronic major depressive disorder into one large category called persistent depressive disorder. DSM-5 details four subsets of persistent depressive disorder, which are a slight variation of the above.

However, for treatment purposes, the subsets of chronic depressive disorders/persistent depressive disorder can be placed into two main categories – pure dysthymia and chronic disorders involving major depression. Available literature indicates that pure dysthymia responds differently to treatment than the three other subsets of chronic depressive disorders involving major depression.

Pure Dysthymia Treatment Recommendation

Recommendation	Quality of Evidence and Strength of Recommendation
Consider starting with medication in pure dysthymia patients. The work group feels that it is reasonable to consider stepped care, which includes augmenting medications and adding psychotherapy for patients who don't improve.	Quality of Evidence: High Strength of Recommendation: Strong
Benefit: Antidepressant treatment of pure dysthymia outperforms both placebo and psychotherapy in acute trials and can begin to reverse the symptoms, suffering and impairment of a condition that can go on for decades left untreated. **Harm:** A significant percentage of patients will fail to respond and require additional treatment. For those who ultimately require a trial of psychotherapy and benefit from it, starting medication first will have represented a delay in receiving effective care. Antidepressants and augmenting agents have side effects and adverse interactions with other drugs. It is not clear how long to continue psychotherapy that has not yet started to work. **Benefit-Harms Assessment:** Evidence supports starting with antidepressant medication and one can choose later to add psychotherapy for those who fail to respond or recover. It is reasonable to start with antidepressant medication since it tends to work more quickly than psychotherapy. Access to high-quality psychotherapy is not available in many primary care settings.	
Relevant Resources: *Kriston, 2014; von Wolff, 2013; Cuijpers, 2012; Levkovitz, 2011; Cuijpers, 2010b; Cuijpers, 2009b; Imel, 2008; Markowitz, 2005; Browne, 2002*	

The impact of dysthymia with lifetime prevalence of 3-6% is often underestimated even though the cumulative burden after years of symptoms results in greater impairment in functioning than that seen in briefer major depressive episodes that remit. Consequences include loss of well-being; increased psychiatric comorbidity; more impairments in social, psychological and emotional functioning; increased health care utilization; and more suicide attempts and hospitalizations *(Kriston, 2014)*.

Meta-analyses by von Wolff, 2013 and Levkovitz, 2011 show that antidepressant treatment was significantly more effective than placebo in pure dysthymia. This was due in part to the lower placebo response rate in

Return to Algorithm *Return to Table of Contents*

dysthymia patients compared to patients with major depression (29.9 vs. 37.9%). The authors believe this may be because many dysthymic patients have been depressed so long they no longer expect to recover *(von Wolff, 2013; Levkovitz, 2011)*.

Further literature showed that medication alone was significantly more effective than psychotherapy alone in pure dysthymia in meta-analyses *(Kriston, 2014; Cuijpers, 2012; Cuijpers, 2010b; Imel, 2008)* and a randomized control study *(Browne, 2002)*.

Medication alone was equal to combined psychotherapy and medication in meta-analyses *(Cuijpers, 2012; von Wolff, 2013)* when the subjects were dysthymic patients. Similarly, in the study *(Browne, 2002)*, medication alone was superior to combined treatment in terms of symptom reduction, but the difference was not statistically significant. In that study, one-third of the patient sample suffered from pure dysthymia.

Chronic Major Depression Treatment Recommendation

Recommendation	**Quality of Evidence and Strength of Recommendation**
For patients with chronic major depression, start with combined antidepressant medication and psychotherapy.	Quality of Evidence: High Strength of Recommendation: Strong
Benefit: Antidepressant treatment with psychotherapy outperforms either treatment as monotherapy and more rapidly begins the process of reversing symptoms, suffering and functional impairment in a condition that can go on for decades untreated. Psychotherapy can produce quality-of-life improvements and lower health and human services costs. **Harm:** Combined medication and psychotherapy increase short-term costs. Access to high-quality psychotherapy is not available in many primary care settings. In the Keller, 2000 study of chronic major depression, which excluded pure dysthymic disorder, the overall drop-out rate was the same for the three treatment groups, but reasons for dropping out varied. More patients dropped out of the medication-alone arm because of adverse events, and more psychotherapy patients withdrew consent because therapy was too time consuming, they did not want psychotherapy, or they wanted medication. This highlights the need to consider patient preferences. The benefits of psychotherapy are delayed and may cause some patients to give up on it prematurely. **Benefit-Harms Assessment:** The chronic nature of persistent depressive disorder, which produces serious life consequences that are often underestimated, justifies the combination of medication and psychotherapy. In the Keller, 2000 study, those in the combined treatment group had fewer dropouts than the medication-alone group due to adverse events (14% vs. 7%). There is some evidence that although benefits of psychotherapy are delayed, they continue even after psychotherapy is stopped.	
Relevant Resources: *Kriston, 2014; Weirsma, 2014; Spijker, 2013; Cuijpers, 2012; Cuijpers, 2010b; Kocsis, 2009a; Imel, 2008; Browne, 2002*	

Persistent depressive disorders that include major depression can be summarized in the following categories: chronic major depression, recurrent major depression without inter-episode recovery, and major depression superimposed on preexisting dysthymic disorder.

The higher the ratio of chronic major depression to dysthymic disorder in the patient groups studied, the greater the likely advantage of combined treatment over medication alone *(Kriston, 2014)*.

Combined psychotherapy and medication was superior to medication alone in meta-analyses *(Kriston, 2014; Cuijpers, 2010b)* (both involving mixed samples of dysthymia and chronic depression), *(Spijker, 2013; Kocsis, 2009)* (both involving chronic major depression).

Combined treatment was superior to psychotherapy alone in a 2010 meta-analysis by Cuijpers.

Return to Algorithm *Return to Table of Contents*

The differential response to treatment in dysthymia compared to chronic depression also held true in a meta-analysis, where combined treatment was superior to psychotherapy alone for chronic depression but not superior in dysthymia, at least in the short term *(Cuijpers, 2012)*.

The evidence is promising for CBASP (Cognitive Behavioral Analysis System of Psychotherapy), which was superior in a head-to-head comparison with interpersonal psychotherapy (IPT) *(Schramm, 2011)*. It also was superior to a robust "care as usual" comparison of medication combined with other psychotherapy at 52 weeks (borderline significance) in patients with chronic major depression *(Wiersma, 2014)*. Here, too, the differential influence of depressive subtype may have come into play. Spijker, 2013 notes that the literature is mixed on the question of which psychotherapy is best and that most evidence-based psychotherapies in combination with medication can enhance results.

Shortcomings of the literature. Psychotherapy was of relatively short term in most studies, and there was not always long-term follow-up data.

In some studies and meta-analyses comparing psychotherapy with medication and combination treatment, psychotherapy was stopped and medication was continued. For example, Browne's 2002 study compared subjects on sertraline, sertraline plus interpersonal therapy, and interpersonal therapy alone. The 10 interpersonal psychotherapy sessions were complete at six months, but subjects were allowed to continue sertraline in the 18-month naturalistic follow-up. The authors suggest that further investigation into maintenance IPT would be useful. In spite of the short duration of therapy, the two groups receiving IPT had lower health and human service costs during the first six months, and total cost of treatment was less in the IPT alone group.

Imel, 2008 questions whether it is reasonable to expect a short-term treatment to reverse the signs and symptoms that in some cases have been present for decades. The author also adds that the length of follow-up after psychotherapy, at least in chronic depression, was predictive of a positive outcome, indicating that results take time. He noted that quality-of-life outcomes were significantly better with combined treatments *(Imel, 2008)*.

There was a dose-response effect with psychotherapy for chronic major depression and dysthymia, with 18 sessions estimated to realize optimal effect sizes. Cuijpers, 2010 and Imel, 2008 reported finding that an average of 31 sessions of psychotherapy were necessary to treat dysthymia to remission *(Cuijpers, 2010b; Imel, 2008)*.

Another shortcoming is that this literature does not address treatment resistance. Only one study in Cuijpers, 2012 meta-analysis focused on treatment-resistant patients, and combined treatment was superior to medication alone in that study. A study by Keller, 2000 of 681 randomized patients on the advantage of combined treatment (73% response rate) over monotherapy with CBASP or the antidepressant nefazodone in chronic major depression (both groups had a 48% response rate) excluded both pure dysthymic patients and treatment resistant patients, limiting its generalizability to those populations.

Spijker, 2013 wrote that there were likely more treatment-resistant patients among chronic depressives compared with pure dysthymics. Spijker, 2013 meta-analysis cites a randomized controlled study of 801 patients with chronic major depression seeking treatment in a mental health center in which only 33% had received an adequate trial of antidepressants. Dysthymic patients may be even less likely to have had a medication trial *(Spijker, 2013)*.

Clinicians should be aware of the high risk of treatment resistance in chronic depressive disorder. Even combined treatment can fail, and referral for specialty treatment may be necessary. Psychotherapy may take longer to be effective, and there is some indication that positive results are delayed relative to medication. There is also some evidence that long-term benefits occur that remain even after psychotherapy is stopped, which is not the case with stopping medication *(Wiersma, 2014; Imel, 2008; Keller, 2000)*.

Longer-term studies of psychotherapy are needed, and better treatments for treatment resistance must be found.

Return to Algorithm *Return to Table of Contents* **www.icsi.org**

More About Individual Treatments

- Behavioral activation
- Appropriate physical activity
- Psychotherapies
- Pharmacotherapy
- Integrative medicine

Behavioral Activation

Contact with others and engaging in activities are often seen by depressed patients as unpleasant or undesirable. Because of this discomfort, depressed patients often avoid pleasurable or even routine activities. This may have the impact of increasing depressive symptoms. Behavioral activation seeks to interrupt this process and bring about symptom relief through increasing positive interactions with others and their environment. Two meta-analyses of a combined 50 studies published over the past 40 years have demonstrated that behavioral activation produces improvement in depression comparable with 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; Cuijpers, 2007)*.

The efficacy of behavioral activation is fairly clear as compared with traditional psychotherapy. It may even be as effective as antidepressant medications *(Dimidjian, 2006)*. Given the problem of medication side effects, behavioral activation provides for an attractive intervention for the treatment of depression. It is also a relatively easy treatment to administer, furthering its appeal.

Activity scheduling is 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)*.

Given the benefits of this procedure, low risks and the relative ease of incorporating it into ongoing treatment, whether with traditional psychotherapy, antidepressant medications or both, it seems that this would be a prudent intervention to add almost across the board.

Based on the work group members' experience with using behavioral activation, consider following when doing behavioral activation with the patients:

- The role of the clinician is to help patients increase their exposure to the positive life experiences they had prior to onset of depression. Reinforce the positive to slowly replace the negative coping skills they have learned.
- Goals should be focused on external factors (resuming activities that patients have been avoiding) and not on internal factors (waiting for patients to be motivated to make a change).
- Help patients set priorities for long- and short-term goals and to understand the difference.
- Help patients decide what changes are necessary to reach their goal – the what, when, where. Goals should be SMART (specific, measurable, attainable, realistic, timely).
- Do not recommend new life or health goals (smoking cessation, weight loss, etc.) even though this may feel like a great time to encourage them to reinvent themselves.

Return to Algorithm *Return to Table of Contents*

- If the patient recommends a new goal, discourage him/her from taking on a new life challenge. This sets patients up for high risk of failure and frustration, which will only worsen their depression. Use language: "That sounds like a very challenging goal. I think it would be better if we started with something a little less complex. How does that sound to you?"
- When you see patients for follow-up, ask them about the progress on their goals. It reinforces that you care and that you find all their effort important (positive experience).
- If they don't achieve the goal, congratulate them on their efforts and whatever parts they did accomplish. Ask them about what they struggled with. It provides insight into the hurdles they face on a daily basis, which is likely having an effect on the other aspects of their health care.

More about generating goal ideas:

- What was the patient doing when he/she was not depressed? One way to ask is this: "When you think back to when you were last happy, what did your life look like?" (Ask him/her to describe the environment – what was he/she doing, who is around him/her, etc.).
- What activities have they been avoiding – work, time with friends, hobbies, hygiene, housework, parenting, etc.?
- What activities have they found to be fun in the past? Choosing a fun goal can help them rebuild positive experiences. They may not initially find the activity as fun as it had been in the past, but it is the baby steps that will help get them back on track.

More about setting goals with the patients:

1. Help patients break down their goal idea into action steps.
2. Help them arrange the steps from simple to complex.
3. Set a goal with one simple step to accomplish the first week. It is important that you start this process with a goal that has a high likeliness of success, as early wins will encourage them to keep going and tackle more complex goals that were identified in step 2.
4. Week two goal is to accomplish the second action step identified in step 2 above, week three builds on week two goal, etc.
5. Encourage patients to set a reward at the end of the week for accomplishing goals. For some patients, they may struggle at this initially because they don't find themselves worthy of a reward.

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; Babyak, 2000)*. 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)*.

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:

- Aerobic exercise was not more effective than resistance (weight lifting) training *(Danielsson, 2013; Rethorst, 2013; Silveria, 2013)*. Other research found a larger effect size for mixed aerobic and resistance training than either alone *(Cooney, 2013)*.
- The largest effect size was observed for 13-36 sessions, but there was an observable benefit for less (0-12) *(Cooney, 2013)*.

Return to Algorithm *Return to Table of Contents*

- Total calories expended may be more important than frequency *(Rethorst, 2013)*.
- Like medication, it must be continued to have an antidepressant effect. In eight studies with long-term follow-up, only a small effect size remained, suggesting the benefits are lost if exercise is stopped *(Cooney, 2013)*.

Psychotherapies

A preponderance of randomized controlled trials (RCTs) and meta-analyses show that various psychotherapies – interpersonal (IP), psychodynamic (PD), cognitive behavioral (CBT), behavioral activation, problem-solving therapies and mindfulness-based cognitive therapies, brief psychotherapies – are effective at reducing depressive symptoms *(Cuijpers, 2014b; Churchill, 2013; van Hees, 2013; Jakobsen, 2012a; McCarney, 2012; Cuijpers, 2011b; Jakobsen, 2011a; Jakobsen, 2011b; Manicavasgar, 2011; Cuijpers, 2010a; Driessen, 2010; Hofmann, 2010; Cuijpers, 2009b; Bortolotti, 2008; Cuijpers, 2008; Ekers, 2008; Haby, 2006)*. (A separate section discusses comparisons with antidepressants.) A number of these articles highlight that results tend to be overestimated due to selection bias and potential random errors *(Cuijpers, 2014a; Jakobsen, 2011b, Jakobsen, 2011a; Jakobsen, 2011c; Cuijpers, 2010a)*. Individual RCTs and meta-analyses also looked at whether a specific psychotherapy was better than another or better for a subpopulation such as age, severity or comorbidities. When one looks at a large sample of such studies, it does not appear that there is sufficient evidence to definitely recommend one over another *(Cuijpers, 2014a; Flückiger, 2014; Okumura, 2014; Churchill, 2013; van Hees, 2013; Jakobsen, 2012a; McCarney, 2012; Cuijpers, 2011a; Cuijpers, 2011b; Jakobsen, 2011a; Jakobsen, 2011b; Jakobsen, 2011c; Manicavasgar, 2011; Cuijpers, 2010a; Driessen, 2010; Hofmann, 2010; Bortolotti, 2008; Cuijpers, 2008; Ekers, 2008; Haby, 2006)*. There were mixed results in claims about how effective psychotherapies are for severe depression *(Cuijpers, 2011a; Cuijpers, 2011b; Driessen, 2010)*.

Pharmacotherapy

Medications

The acute treatment phase is focused on treating the patient to remission. Acute therapy typically lasts 6-12 weeks but should last until remission is reached *(American Psychiatric Association, 2013; Diagnostic and Statistical Manual of Mental Disorders, 5th Edition)*.

Definition: Full remission is defined as a two-month period devoid of major depressive signs and symptoms *(American Psychiatric Association, 2013; Diagnostic and Statistical Manual of Mental Disorders, 5th Edition)*.

For antidepressant medications, treatment adherence and achieving clinical goals are more important than the specific medication selected. Successful treatment often involves dosage adjustments and/or trial of a different medication to maximize response and minimize side effects *(American Psychiatric Association, 2010)*.

Selection of an antidepressant medication

The overall effectiveness of antidepressant medications is generally equivalent between and within classes of medications *(American Psychiatric Association, 2010)*. However, there are distinct differences in individual patient response to and 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)
- Patient preferences
- Side effect profile (e.g., sedating, activating, weight gain, impact on sex life)

Return to Algorithm *Return to Table of Contents*

- Antidepressant medications with anticholinergic side effects contribute to dry mouth/xerostoma, caries, gingivitis and periodontal disease *(Tschoppe, 2010; Shinkai, 2006)*. 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 or anxiety). See Annotation #4a, "Is the Presence of Substance Use Disorder or Psychiatric Comorbidity Suspected?" for more information on psychiatric comorbidities.

Medications and Genomics. The genetic differences in the metabolism of certain medications including antidepressants can be determined by cytochrome P450 genetic testing. This testing may identify individual patients who may be more sensitive to serious adverse reactions or medications with narrow therapeutic windows of specific medications. However, the clinical significance and applicability to daily clinical practice has not yet been established *(Narasimhan, 2012; Porcelli, 2011)*.

Is medication needed? A meta-analysis of efficacy of acute (three-month) treatment with antidepressants *(Fournier, 2010)* for depression found the magnitude of benefit from antidepressant medications increased with the severity of a patient's depressive symptoms. If a patient's initial symptoms are minimal or qualified as mild or moderate depression, symptom benefits from antidepressants may not significantly differ from placebo. They suggested that for short-term and less-severe patients, behavioral activation plus lifestyle modifications may be enough. For patients with very severe depression, the authors found the benefit of medications over placebo is substantial *(Fournier, 2010)*.

Classes of Medications

Selective serotonin reuptake inhibitors (SSRIs) and other antidepressants

SSRIs and other second-generation antidepressants such as venlafaxine, duloxetine, desvenlafaxine, mirtazapine, bupropion, levomilnacipran, vilazolone and vortioxetine 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, 2010; Trivedi, 2001)*. They generally lack the common adverse reactions (anticholinergic, sedative effects) of the tricyclics antidepressants and cause fewer problems when taken in overdose. However, they may cause headache, nervousness, insomnia and sexual side effects *(von Wolff, 2013)*. Newer antidepressant agents such as vilazodone, vortioxetine and levomilnacipran are available, but data on their long-term use is limited. They may also be more expensive or not routinely covered by insurance plans for some patients.

The current evidence does not support the choice of one second-generation antidepressant over another due to differences in efficacy or effectiveness. The choice of medication may depend on onset of action and adverse events *(Gartlehner, 2008)*.

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.

Return to Algorithm *Return to Table of Contents* **www.icsi.org**

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

The atypical antipsychotics are recommended by the American Psychiatric Association as second-line augmentation options *(American Psychiatric Association, 2010)*. Three atypical antipsychotics have been approved for the adjunctive treatment of major depressive disorder: aripiprazole, quetiapine and the combination of olanzapine and fluoxetine. There is some evidence regarding the use of quetiapine as monotherapy for the treatment of major depression *(Zhornitsky, 2011)*. Unfortunately, the adverse effects of atypical antipsychotics may concern some patients *(Wright, 2013)*. In a review of three randomized, placebo-controlled studies of quetiapine extended-release monotherapy in adults with major depressive disorder, the authors found it effective in response and remission of symptoms of depression. However, quetiapine was associated with a higher rate of side effects compared to placebo *(Maneeton, 2012)*. When used as part of an augmentation strategy, doses should be individualized and safety (and efficacy) should be frequently reassessed *(Wright, 2013)*.

Adherence, Patient Interaction and Monitoring

Adherence is important. 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)*.

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 of treatment goals:

- Side effects from medication often precede therapeutic benefit and typically recede over time. It is important to expect side effects prior to symptom benefit.
- Most people should be on medication at least 6-12 months after adequate response to symptoms *(American Psychiatric Association, 2010)*.
- Patients may have symptom improvement after two weeks but will need a longer length of time for full 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)*. 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 one study *(Solomon, 2000)*. Each episode of recurrence increased the risk of subsequent episodes by 16% *(Solomon, 2000)*.
- 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

Return to Algorithm *Return to Table of Contents*

a previous course of treatment *(Vanelli, 2008)*. In addition to medication monitoring, clinical management of patients placed on antidepressants should include the clinician's support and reassurance.

Duration of Pharmacotherapy

Without long-term antidepressant treatment, major depressive relapses and recurrences occur in 50-80% of patients *(American Psychiatric Association, 2010)*. 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.

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; Flint, 2000; Frank, 1993)*.

Discuss 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.

There is no difference between brand versus generic medications based on adverse clinical outcomes.

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 with patients who require fewer medication changes to achieve remission *(Rush, 2006)*.

A recent review of maintenance trials for patients with major depression found continuing medication treatment after initial response to an antidepressant was successful in significantly reducing relapse rates compared with placebo. Mean relapse rates were 18% for antidepressants and 37% for placebo *(Borges, 2014)*.

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)*. These patients are candidates for long-term or lifetime prophylactic treatment. Analysis suggests that recurrence rates are reduced by 70% when patients are maintained on antidepressants for three years following their previous episode (average recurrence on placebo is 41% versus 18% on active treatment) *(Hirschfeld, 2001; Greden, 1993)*.

Depression Medication Treatment Duration Based on Episode

Episode	Treatment Duration
1st episode (major depression, single episode)	• Continue medication treatment for 4-9 months once remission is reached. • Total = approximately 6-12 months
2nd episode (major depression, recurrent)	Continue medication treatment for 2-3 years once remission is reached. Withdraw gradually.
Persistent depressive disorder or 3+ episodes or 2 episodes (major depression, recurrent) with complicating factors such as: • Rapid recurrent episodes • Patients with partial/inadequate response to initial treatment	Continue medication treatment indefinitely.

(Sources: National Institute for Health and Care Excellence, 2012; American Psychiatric Association, 2010; Hirschfield, 2001; Keller, 1998; Greden, 1993)

Return to Algorithm *Return to Table of Contents*

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; Schoenbaum, 2002)*.

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)

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)*.

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.

Risks

Clinicians should be alert for worsening of symptoms. Health care clinicians should carefully evaluate their patients in whom depression persistently worsen, or emergent suicidality is severe or 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 #3a, "Is Patient Safe to Self and/or Others?"

Risks Related to Special Populations

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.

Be alert for worsening of symptoms. Health care clinicians should carefully evaluate their patients in whom depression persistently worsen, or emergent suicidality is severe or 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 #3a, "Is Patient Safe to Self and/or Others?"

Return to Algorithm *Return to Table of Contents*

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 medications. For elderly patients with moderate to severe depression, TCAs such as nortriptyline continue to be regarded as the most effective treatment *(Alpert, 2003; Gastó, 2003)*. 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.

Risks of Medication Interactions

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.

Risks Associated with Specific Medications

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 "contra-indicated" 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 *(Zivin, 2013)*.

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; Gillman, 2006)*. 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)*.

Return to Algorithm *Return to Table of Contents*

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)*.

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. 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; Gillman, 2010; Wenzel, 2008)*.

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.

Acupuncture

There is considered to be high-level evidence to support the use of acupuncture during pregnancy for the treatment of depressive episodes *(Sniezek, 2013)*. An open, parallel-arm, randomized study showed acupuncture to result in equal efficacy in comparison to counseling with a significant reduction in depressive symptoms for both in comparison to usual care *(MacPherson, 2013)*. Existing meta-analyses and systematic reviews vary with respect to acupuncture protocol (manual, electroacupuncture or sham), methodological soundness and efficacy results *(Freeman, 2010)*. Both sham and active acupuncture participants generally report symptomatic depression improvement *(Freeman, 2010)*. 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).

Yoga

Yoga has been shown to be effective as an adjunctive treatment to decrease symptom severity *(Ravindran, 2009)*. It has yet to be determined what aspects of yoga are responsible for any potential depressive symptom improvements *(Louie, 2014)*.

Tai Chi

Limited evidence suggests that Tai Chi may be effective for psychological well-being measures that include depressive symptoms *(Wang, 2014)*. There is yet insufficient evidence, though, to recommend Tai Chi for the treatment of depressive episodes.

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)*, 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 St.

Return to Algorithm *Return to Table of Contents*

John's Wort in the treatment of major depression. Research is limited by lack of large scale RCTs and high risk of bias in the majority of trials meeting inclusion criteria for the meta-analysis *(Smith, 2010; Linde, 2008)*.

Saffron (Crocus sativus L.)

A recent meta-analysis show potential efficacy of saffron in comparison to placebo, with possible equal efficacy to fluoxetine and imipramine. The studies included were small and only studied the acute phase of treatment *(Hausenblas, 2013)*. It will require further study to adequately assess the acute efficacy, as well as establish the safety, tolerability and durability of efficacy in the continuous and maintenance phases of therapy.

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; Siwek, 2010; Colangelo, 2009)*.

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, 2012)*.

Vitamin D. At this time, there is insufficient evidence on the antidepressant effects of vitamin D *(Shaffer, 2014; Li, 2014; Thacher, 2011)*.

Medical cannabis

There is insufficient evidence to support use of cannabis in treatment of depression. A systematic review and meta-analysis of randomized, clinical trials of cannabinoids for the treatment of several indications, including depression, was published in June 2015. No studies of cannabinoids for the treatment of depression met the authors' inclusion criteria. The authors evaluated five studies of other primary indications (chronic pain and spasticity in multiple sclerosis) that reported depression as an outcome measure. Three of the studies found no difference between cannabinoids (dronabinol and nabiximols) in depression outcomes, compared with placebo. The majority of these studies were found to have a high risk of bias *(Whiting, 2015)*.

Special Populations

See Appendix D, "Special Populations," for more information regarding treatment for the following conditions/populations, as applicable: 1) cardiovascular and cerebrovascular disease; 2) diabetes; 3) chronic pain; 4) geriatrics [includes dementia/cognitive impairment]; and 5) pregnant and postpartum women.

Return to Algorithm *Return to Table of Contents*

6. Comprehensive Treatment Plan with Shared Decision-Making

Collaborative Care Model

Recommendation	Quality of Evidence and Strength of Recommendation
A collaborative care approach is recommended for patients with depression in primary care.	Quality of Evidence: High Strength of Recommendation: Strong
Benefit: Collaborative care model has demonstrated improvement in treatment adherence, patient quality of life and depression outcomes. It has demonstrated beneficial impact on direct and indirect economic benefits. Evidence suggests the collaborative care model is also effective for depression during pregnancy and postpartum period. **Harm:** There are challenges in providing the collaborative care model, such as identifying depressed patients, identifying care managers with the right experience and background, establishing the responsibilities and scope of practice of the care managers, whether to locate care managers in a clinic vs. centrally based, determining the level of psychiatric supervision, seeking adequate reimbursement for services provider to ensure program sustainability, and feasibility of small clinics to employ on-site mental health specialists or full-time care managers. **Benefit-Harms Assessment:** Collaborative care has shown to improve patient outcomes and provider satisfaction while decreasing cost outweighing the challenges of implementing a collaborative care program.	
Relevant Resources: *Fortney, 2013; Archer, 2012; Katon, 2008; Gjerdingen, 2007; Belnap, 2006; Gilbody, 2006; Hunkeler, 2006; Simon, 2001a; Katon, 1999*	

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 and others). The work group recommends three key references *(Gilbody, 2006; Hunkeler, 2006; Katon, 1999)*. This model has demonstrated improvement in treatment adherence, patient quality of life and depression outcomes *(Archer, 2012; Gilbody, 2006; Hunkeler, 2006; Katon, 1999)*.

Beneficial impact on direct medical costs can also be found. Further dissemination of this model has been recommended *(Simon, 2001a)*. Katon, 2008 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)*. Evidence suggests the collaborative care model is also effective for depression during pregnancy and postpartum *(Gjerdingen, 2007)*.

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)*. Care management facilitates continuous use of antidepressants by providing close follow-up and early intervention when side effects occur.

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)*.

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)*.

Return to Algorithm *Return to Table of Contents*

Improved Provider Satisfaction

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)*, 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 *(Levine, 2005)*.

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 *(Levine, 2005)*.

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)*.

Implementing a Collaborative Care Approach

Design. The design of a team-based collaborative care approach *(Unützer, 2002)* 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 and self-management support, and monitor for response in order to aid in facilitating treatment changes and in relapse prevention
- 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

A 2013 systematic review and meta-analysis of nurse-delivered collaborative care showed that there was no statistical difference between deciding on type of delivery approach of intervention (phone versus in person) *(Ekers, 2013)*.

Telemedicine technologies now make possible the virtual co-location of mental health specialists and primary care providers. This is achieved using telephones, video conferencing and electronic health records. Compared with usual practice-based care, telemedicine has shown to have significantly and substantially greater treatment response, remission rates, reductions in depression severity, and increases mental health status and quality of life. These outcomes were achieved without increasing the number of primary care visits *(Fortney, 2013)*.

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 *(Belnap, 2006)*:

- 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

Return to Algorithm *Return to Table of Contents*

- Locating the care managers (centrally versus clinic-based)
- Determining level of supervision by psychiatrists
- Seeking adequate reimbursement for services provided to ensure program sustainability
- Clinic size: typically not feasible for small clinics to employ on-site mental health specialists or full time care managers *(Fortney, 2013)*

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

Recommendation: Patient Engagement	**Quality of Evidence and Strength of Recommendation**
Before initiating treatment, it is important to establish a therapeutic alliance with the patient regarding diagnosis and treatment options (in which there is overlap in the patient's and clinician's definition of the problem and agreement on which steps are to be taken by each).	Quality of Evidence: Low Strength of Recommendation: Strong
Benefit: Therapeutic alliance is a potent predictor of treatment outcomes whether the treatment is psychotherapy or pharmacotherapy. Patient participation in shared decision-making improves adherence to treatment and clinical outcomes. When patients express a treatment preference, the use of that treatment, whether psychotherapy or pharmacotherapy, predicts a positive outcome. **Harm:** A therapeutic alliance can take time to develop, and time is difficult to find in a busy clinical practice. If treatment is delayed because of an uncertain alliance or initiated before an alliance is attained, it could adversely affect outcomes. Difficult experiences with the treatment of depression may cause clinicians to avoid treating depressed patients. **Benefit-Harms Assessment:** The benefits of a therapeutic alliance in terms of improved patient outcomes more than offsets the investment of time.	
Relevant Resources: *Kocsis, 2009b; Loh, 2007; Krupnick, 1996*	

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)*.

However, there are ways to improve engagement and adherence.

Therapeutic alliance: It is essential to know the patient and cultivate a therapeutic alliance-defined as a collaborative bond between patient and clinician *(Krupnick, 1996)*. This alliance can have a greater effect on outcomes than the actual treatment used (psychotherapy vs. pharmacotherapy) and can have a large effect even when the treatment is pharmacotherapy *(Krupnick, 1996)*.

It is essential that both the patient and the clinician feel invested in the outcome. Within the context of what the clinician is able to recommend, patient's preferences matter. In a study by Kocsis, 2009, patients who preferred psychotherapy but received medication had a 7.7% remission rate vs 50.0% if they received psychotherapy. Those who preferred medication but received psychotherapy had a 22.2% remission rate vs 45.5% if they received medication *(Kocsis, 2009b)*.

Past history's influence on adherence

Accurate history-taking remains the cornerstone of medical treatment. A patient's past experience with depression predicts adherence to the treatment plan, and past history is common given the lifetime prevalence

Return to Algorithm *Return to Table of Contents*

of major depression of 17% *(Johnston, 2013)*. Other findings from Johnston's review of patients' experience influence on adherence include:

- Patients who had endured a prior episode of depression were found to have higher adherence to treatment with antidepressant agents.
- People who know someone with a history of depression tended to view depression as a biomedical condition and were more accepting of medication.
- Interactions with providers, receiving information, feeling heard and understood, and gaining experience with medication all have a major influence on decisions to continue treatment.
- Patient-provider relationships and overall treatment experience were crucial, especially when many realized that long-term treatment was likely required.

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). See the "Establish Follow-Up Plan" section for information on frequency of follow-ups
- Early warning signs of relapse or recurrence
- Length of treatment
- Communication with the caregiver

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

While the clinician goal of utilizing 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)*.

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 his/her 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.
- 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)*. 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)*.

Patient Engagement

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; Anderson, 2005; Gregory, 2004)*.

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

Decision-making capacity

The ICSI shared decision-making model is a useful primer on the collaborative conversation with the main focus on things the clinician can do to assist the patient in making a shared decision regarding treatment. This means factoring in patient values and preferences in decisions regarding treatment. See Appendix B, "ICSI Shared Decision-Making Model," for full description of ICSI Shared-Decision Making model. It is important to keep in mind what is required of the patient in order to make informed decisions. Some patients, especially those with neurocognitive disorders, lack the required capacities to truly participate in the process. There are four abilities adults need in order to decide on treatments for depression *(Applebaum, 2007)*:

1. The ability to express a choice
2. The ability to understand information for treatment decision-making
3. The ability to appreciate the significance of that information for one's own situation, especially concerning one's illness and the probable consequences of one's treatment options
4. The ability to reason with the relevant information in order to engage in a logical process of weighing treatment options

Although competency is a legal termination, medical opinions regarding the patient's cognitive capacities are typically sought, and the ability to assess these capacities is a necessary skill set for physicians.

General vs. specific competency

When the clinician decides to consult psychiatry, referral questions should address a specific competency such as "Is this patient competent to refuse surgery?" rather than the general question "Is this patient competent?" A person can be competent to do some things (make a will) but incompetent to do others (live independently) *(Nichita, 2007)*.

In questions of competency, patients need to have had the information provided to them in order to make informed decisions. Since patients' abilities may fluctuate, it is important that the information is presented at least twice. A patient whose decisions vary each time lacks reliability *(Sorrentino, 2014)*.

Return to Algorithm *Return to Table of Contents*

Follow-Up

7a. Establish Follow-Up Plan

Recommendation	Quality of Evidence and Strength of Recommendation
Clinicians should establish and maintain follow-up with patients.	Quality of Evidence: Low Strength of Recommendation: Strong
Benefit: Appropriate, reliable follow-up is highly correlated with improved response and remission scores. It is also correlated with the improved safety and efficacy of medications and helps prevent relapse. **Harm:** Potential harms may include added expense and unnecessary visits. **Benefit-Harms Assessment:** Benefits appear to outweigh potential harms by a wide margin.	
Relevant Resources: *Trivedi, 2006b; Unützer, 2002; Hunkeler, 2000; Simon, 2000*	

Proactive follow-up contacts (in person, telephone) based on the collaborative care model have been shown to significantly lower depression severity *(Unützer, 2002)*. 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; Unützer, 2002)*. 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; Simon, 2000)*.

PHQ-9 as monitor 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; Löwe, 2004)*. 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)*.

Every time that the PHQ-9 is assessed, suicidality is assessed, as well. If the suicidality was indeed of high risk, urgent referral to crisis specialty health care is advised. In case of low suicide risk, the patient can proceed with treatment in the primary care practice *(Huijbregts, 2013)*.

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 or history of mania)
- Suspicion or history of substance abuse
- Clinician discomfort with the case
- Medication advice (psychiatrist or other mental health prescriber)
- Patient request for more specialized treatment

Return to Algorithm *Return to Table of Contents*

7b. Has Patient Reached Remission?

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

Full remission is defined as a two-month period devoid of major depressive signs and symptoms *(American Psychiatric Association, 2013: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition)*. If using a PHQ-9 tool, remission translates to PHQ-9 score of less than 5 *(Kroenke, 2001)*. Results from the STAR*D study showed that remission rates lowered with more treatment steps, but the overall cumulative rate was 67% *(Rush, 2006)*.

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. This definition is based on how the depression literature defines response.

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 remission by Quick Inventory of Depressive Symptomatology (QIDS), 50% did so only at or after six weeks of treatment *(Trivedi, 2006b)*. 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)*.

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)*.

Return to Algorithm *Return to Table of Contents*

7c. Continuation and Maintenance Treatment Duration Based on Episode

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)*. Full remission is defined as a two-month period devoid of major depressive signs and symptoms *(American Psychiatric Association, 2013; Diagnostic and Statistical Manual of Mental Disorders, 5th Edition)*.

Continuation therapy is the four-to-nine 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)*. 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)*.

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)*. 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)*.

Return to Algorithm *Return to Table of Contents*

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)*.

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; Katon, 1999)*.

Relapse Prevention

The prevention of relapse is of primary importance in the treatment of major depression. From 50 to 80% of people who suffer an episode of major depression will have a recurrence, usually within two or three years *(American Psychiatric Association, 2010)*. 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)*.

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

Pharmacotherapy. A Katon, 1996 study 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)*. For information on duration of pharmacotherapy post-remission to prevent relapse, see the "Duration of Pharmacotherapy" section in Pharmacotherapy.

Return to Algorithm *Return to Table of Contents*

7d. If Patient is Not Improving on Initial Treatment, Utilize Stepped Care Approach

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

1. Whether adequate engagement of patient/family exists and whether recommendations are being followed (adherence).
2. Optimize antidepressant dose. A systematic review and meta-analysis found higher doses of SSRIs were associated with an increased likelihood of response. Higher doses were also associated with an increased risk of side effects. The overall rate of treatment dropouts was reduced, possibly due to improved efficacy. Balancing these results, the authors recommended titrating SSRI doses in patients who had not responded to lower doses *(Jakubovski, 2016)*. Additionally, it has been well established that raising the dose of tricyclics or MAOIs 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; Perry, 1994)*.
3. 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)*, 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; Thase, 1997; Brown, 1995)*.

Return to Algorithm *Return to Table of Contents*

4. Reconsider treatment modality:

    - 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)*. 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.

    - 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)*.

5. Reevaluating the diagnosis and the possibility of a bipolar diagnosis. Bipolar patients require a different treatment approach and may not consistently come forward with their hypomanic, mixed or manic histories *(Sharma, 2005)*. Consult with a behavioral health clinician if personality disorders are present.

6. Looking for comorbidities, such as substance abuse issues, and involving addiction specialists as needed.

7. Augmentation strategies (such as lithium or low-dose thyroid, making a referral to psychiatry for possible MAOI treatment). Many patients unresponsive to tricyclics are responsive to monoamine oxidase inhibitors (MAOIs). Rarely, the combination of tricyclics and MAOIs is used. This combination should be undertaken with extreme caution. Studies measuring response to MAOIs in SSRI non-responders have not been done *(McGrath, 1994; McGrath, 1993)*. See the "Augmentation Therapy" section in this annotation for more information.

8. Other strategies: light therapy, ECT and hospitalization. See the "Consider Other Strategies" section in this annotation for more information.

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 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.

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 differences were statistically insignificant, but bupropion SR was better tolerated *(Trivedi, 2006a)*.

    - 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; Bodkin, 1997; Marshall, 1996)*.

    - Five open studies supported potential utility of this treatment, and a response rate of approximately 60% was observed *(Dimitriou, 1998; Bouwer, 1997)*.

Return to Algorithm *Return to Table of Contents*

- **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; Dam, 1998; Cappiello, 1995)*.
- **T_3 augmentation of antidepressants.**
  - Antidepressant augmentation with T_3 had a remission rate of 24.7% in the STAR*D study *(Nierenberg, 2006)*. 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)*.
  - Placebo-controlled studies found mixed results. Usual dose of T_3 varied between 25 and 50 micrograms/day *(Nelson, 2000)*.
- **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; Ninan, 2004)*.
  - 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, 2008; Dunlop, 2007; Fava, 2005)*.
  - 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.
- **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; Preskorn, 1990)*.
  - 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)*.
  - 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; Baumann, 1996; Katona, 1995; Joffe, 1993)*.
- **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

Return to Algorithm *Return to Table of Contents*

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)*.

- A meta-analysis of 16 trials that included a total of 3,480 patients with treatment-resistant, non-psychotic, 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)*.
- 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; Berman, 2007)*.

Consider Other Strategies

- 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.
- Electroconvulsive treatment is effective and can sometimes be administered safely in an outpatient setting.
- Use of bright light therapy for treatment of major depression with a seasonal specifier is well established.

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; Keller, 2005; Geddes, 2003)*.

Hospitalization

Partial or full hospitalization may be indicated in patients with unrelenting depressive symptoms, particularly if safety issues are a concern *(American Psychiatric Association, 2010)*.

The most important consideration from a primary care standpoint is the hospital communicating the details of partial and full hospitalization back to primary care, and patients having follow-up visits for chronic or acute physical and psychiatric problems arranged with their clinician prior to hospital discharge. Patients without a primary care provider should be connected with shortly after hospital discharge for a physical assessment and preventive interventions to help decrease the rate of readmission. If no medication reconciliation was done in the hospital, there should be follow-up on it during the primary care visit.

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

Return to Algorithm *Return to Table of Contents* **www.icsi.org**

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; UK ECT Review Group, The, 2003)*. 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; Sackeim, 2001a)*.

One study showed that 64.2% of patients referred for ECT achieved major depression remittance *(Kellner, 2006)*. 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 with nortriptyline and lithium treatment and found no difference in relapse rates *(Kellner, 2006)*.

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)*. For more information regarding the treatment of depression in pregnant women, refer to Appendix D, "Special Populations."

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

- Geriatric depression *(Mitchell, 2005)*
- 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)*.
- If depression has psychotic features
- If melancholic symptoms are predominant
- Depression and Parkinsonism

(National Institute for Clinical Excellence, 2003)

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 and cerebrovascular accident. ECT is a relatively safe and effective treatment for patients with treatment-refractory and severe depressive illness, and death is very rare.

Light Therapy

Use of bright light therapy for treatment of major depression with a seasonal specifier is well established *(Leppämäki, 2002; Golden, 2005)*. 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; Prasko, 2002)*. For non-seasonal depression, light therapy's benefit as an adjunctive treatment is more robust than its benefit as monotherapy *(Freeman, 2010)*. Bright

Return to Algorithm *Return to Table of Contents*

light therapy may also quicken and enhance the effects of antidepressant medication *(Benedetti, 2003)*. In two small pilot studies, promising results were seen in pregnant and postpartum women with non-seasonal depression *(Epperson, 2004; Oren, 2002)*.

Dosage. The standard starting dose for depression with a seasonal specifier is 10,000 lux for 30 minutes each morning *(Freeman, 2010)*. 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)*.

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)*.

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) and deep brain stimulation (DBS). See Appendix C, "Specialized Therapies."

Return to Algorithm *Return to Table of Contents*

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

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 where there is overlap. The work group has elected to use PHQ-9 in the measures, since it is broadly utilized by various organizations. There are other evidence-based tools that may be used. If other tools are chosen for measurement, they should be sensitive, specific, reliable and valid for measuring intensity levels and response and remission rates.

1. Increase the percentage of patients accurately diagnosed with major depression or persistent depressive disorder. *(Annotation #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 #3a)*

   Measure for accomplishing this aim:

   a. Number 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 screened for substance use disorders. *(Annotation #4a)*

   Measure for accomplishing this aim:

   a. Percentage of patients who are screened for substance use disorders with an appropriate screening tool.

4. Increase the screening 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. *(Appendix D)*

   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 or PHQ-9.

   b. Percentage of patients with cardiovascular disease with documentation of screening for major depression or persistent depressive disorder using either PHQ-2 or PHQ-9.

   c. Percentage of patients who had a stroke with documentation of screening for major depression or persistent depressive disorder using either PHQ-2 or PHQ-9.

   d. Percentage of patients with chronic pain with documentation of screening for major depression or persistent depressive disorder using either PHQ-2 or PHQ-9.

   e. Percentage of perinatal patients with documentation of screening for major depression or persistent depressive disorder using either PHQ-2 or PHQ-9.

Return to Table of Contents

5. Improve communication between the primary care physician and the mental health care clinician (if patient is co-managed). *(Annotation #7a)*

   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 #5, 6)*

   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., 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., had 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 for outcomes from treatment. *(Annotations #5, 6, 7a)*

   Measures for accomplishing this aim:

   a. 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.

   b. 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.

Return to Table of Contents

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 10 codes include F32.x, F33.x and F34.1.

Data of Interest

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

---

# 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 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

Return to Table of Contents

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.

Return to Table of Contents

Measurement #2a

Number 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 10 codes include F32.x, F33.x and F34.1.

Data of Interest

Number of patients under depression management in primary care who commit suicide at any time while managed in primary care.

Numerator and Denominator Definitions

Number of patients with major depression or persistent depressive disorder who are in active panel in primary care who commit suicide at any time while managed 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

Quarterly.

Notes

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

Return to Table of Contents

Measurement #3a

Percentage of patients who are screened for substance use disorders with an appropriate screening tool.

Population Definition

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

Data of Interest

$$\frac{\text{\# of patients who are screened for substance use disorders with an appropriate screening tool}}{\text{\# of patients diagnosed with major depression or persistent depressive disorder}}$$

Numerator/Denominator Definitions

Numerator: Number of patients who are screened for substance use disorders with an appropriate screening tool.

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

Method/Source of Data Collection:

Query electronic medical records for patients diagnosed with major depression or persistent depressive disorder diagnosis in the last 12 months from the measurement date. Determine from medical records if a patient was screened for substance use disorders with an appropriate screening tool.

Time Frame Pertaining to Data Collection

Monthly.

Notes

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

Return to Table of Contents

Measurement #4a

Percentage of patients with type 2 diabetes with documentation of screening for major depression or persistent depressive disorder using either PHQ-2 or PHQ-9.

Population Definition

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

Data of Interest

$$\frac{\text{\# of patients who were screened for depression symptoms with PHQ-2 or PHQ-9}}{\text{\# of patients with type 2 diabetes}}$$

Numerator/Denominator Definitions

Numerator: Number of patients screened for depression symptoms with PHQ-2 or PHQ-9.

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 were screened for depression symptoms with PHQ-2 or PHQ-9 at any of the contacts. Count only one screen.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

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

Return to Table of Contents

Measurement #4b

Percentage of patients with cardiovascular disease with documentation of screening for major depression or persistent depressive disorder using either PHQ-2 or PHQ-9.

Population Definition

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

Data of Interest

$$\frac{\text{\# of patients who were screened for depression symptoms with PHQ-2 or PHQ-9}}{\text{\# of patients with cardiovascular disease}}$$

Numerator/Denominator Definitions

Numerator: Number of patients screened for depression symptoms with PHQ-2 or PHQ-9.

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 were screened with PHQ-2 or PHQ-9 for depression symptoms at any of the contacts. Count only one screen.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

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

Return to Table of Contents

Measurement #4c

Percentage of patients who had a stroke with documentation of screening for major depression or persistent depressive disorder using either PHQ-2 or PHQ-9.

Population Definition

Patients age 18 years and older who had a stroke.

Data of Interest

$$\frac{\text{\# of patients who were screened for depression symptoms with PHQ-2 or PHQ-9}}{\text{\# of patients who had a stroke}}$$

Numerator/Denominator Definitions

Numerator: Number of patients screened for depression symptoms with PHQ-2 or PHQ-9.

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 were screened for depression symptoms with PHQ-2 or PHQ-9 at any of the contacts. Count only one screen.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

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

Return to Table of Contents

Measurement #4d

Percentage of patients with chronic pain with documentation of screening for major depression or persistent depressive disorder using either PHQ-2 or PHQ-9.

Population Definition

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

Data of Interest

$$\frac{\text{\# of patients who were screened for depression symptoms with PHQ-2 or PHQ-9}}{\text{\# of patients with chronic pain}}$$

Numerator/Denominator Definitions

Numerator:	Number of patients screened for depression symptoms with PHQ-2 or PHQ-9.
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 were screened with PHQ-2 or PHQ-9 for depression symptoms at any of the contacts. Count only one screen.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

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

Return to Table of Contents

Measurement #4e

Percentage of perinatal patients with documentation of screening for major depression or persistent depressive disorder using either PHQ-2 or PHQ-9.

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 with PHQ-2 or PHQ-9.
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 were screened with PHQ-2 or PHQ-9 for depression symptoms at any of the contacts. Count only one screen.

Time Frame Pertaining to Data Collection

Quarterly.

Notes

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

Return to Table of Contents

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 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.

Return to Table of Contents

Measurement #6a

Percentage of patients who have had a response to treatment at six months (+/- 30 days) after diagnosis or initiating treatment, e.g., 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 diagnosis of major depression or persistent depressive disorder, ICD 10 codes include F32.x, F33.x and F34.1 and PHQ-9 > 9.

Data of Interest

$$\frac{\text{\# of patients whose PHQ-9 decreased by 50\% at six months after diagnosis or initiating treatment (+/- 30 days)}}{\text{\# of patients with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9, six months earlier}}$$

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 with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9, six months earlier.

Diagnosis can be new or existing.

Method/Source of Data Collection:

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

Return to Table of Contents

Measurement #6b

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

Population Definition

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

Data of Interest

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

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 with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9, six months from the measurement date.

Diagnosis can be new or existing.

Method/Source of Data Collection:

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

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.

Return to Table of Contents

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 diagnosis of major depression or persistent depressive disorder, ICD 10 codes include F32.x, F33.x and F34.1 and PHQ-9 > 9.

Data of Interest

$$\frac{\text{\# of patients whose PHQ-9 decreased by 50\% at 12 months after diagnosis or initiating treatment (+/- 30 days)}}{\text{\# of patients with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9 12 months earlier}}$$

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 diagnosis and PHQ-9 > 9, with major depression or persistent depressive disorder 12 months earlier.

Diagnosis can be new or existing.

Method/Source of Data Collection:

Query electronic medical records for patients with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9, 12 months from the measurement date. Determine if a patient had a follow-up contact at 12 months 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 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.

Return to Table of Contents

Measurement #6d

Percentage of patients who reached remission at 12 months (+/- 30 days) after diagnosis or 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 diagnosis of major depression or persistent depressive disorder, ICD 10 codes include F32.x, F33.x and F34.1 and PHQ-9 > 9.

Data of Interest

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

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 with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9, 12 months from the measurement date.

Diagnosis can be new or existing.

Method/Source of Data Collection:

Query electronic medical records for patients with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9, 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 +/- 30 days.

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.

Return to Table of Contents

Measurement #7a

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 diagnosis of major depression or persistent depressive disorder, ICD 10 codes include F32.x, F33.x and F34.1 and PHQ-9 > 9.

Data of Interest

$$\frac{\text{\# of patients whose symptoms are reassessed with PHQ-9 at six months of diagnosis or initiating treatment}}{\text{\# of patients with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9}}$$

Numerator/Denominator Definitions

Numerator: Number of patients whose symptoms are reassessed with 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 and PHQ-9 > 9.

Diagnosis can be new or existing.

Method/Source of Data Collection:

Query electronic medical records for patients with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9, 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.

Time Frame Pertaining to Data Collection

Monthly.

Notes

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

Return to Table of Contents

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 diagnosis of major depression or persistent depressive disorder, ICD 10 codes include F32.x, F33.x, and F34.1 and PHQ-9 > 9.

Data of Interest

$$\frac{\text{\# of patients whose symptoms are reassessed with PHQ-9 at 12 months after diagnosis or initiating treatment}}{\text{\# of patients with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9}}$$

Numerator/Denominator Definitions

Numerator: Number of patients whose symptoms are reassessed with PHQ-9 at 12 months, +/- 30 days after diagnosis or initiating treatment.

Denominator: Number of primary care patients age 18 years and older with major depression or persistent depressive disorder diagnosis and PHQ-9 > 9.

Diagnosis can be new or existing.

Method/Source of Data Collection:

Query electronic medical records for patients with major depression or persistent depressive disorder, diagnosis and PHQ-9 > 9, 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.

Time Frame Pertaining to Data Collection

Monthly.

Notes

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

Return to Table of Contents

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. The following points have not been updated during this revision.

See Annotation #6, "Comprehensive Treatment Plan with Shared Decision-Making," for definitions of the collaborative care model.

See below for health care cost analysis of a collaborative care model compared with 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 case load 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

Return to Table of Contents

- 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

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)*.

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; Simon, 2001a; Simon, 2001b)*. 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. The two-year studies show mixed results possibly indicating a turning point *(Dickinson, 2005)*, 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)*.

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.

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; Schoenbaum, 2001)*. 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)*.

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; Rost, 2004)*.

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

Return to Table of Contents

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.

Return to Table of Contents

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
Medication Assisted Treatment (MAT)	Medication-assisted treatment (MAT), including opioid treatment programs (OTPs), combines behavioral therapy and medications to treat substance use disorders.	Health Care Professionals	http://www.samhsa.gov/medication-assisted-treatment
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
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	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

Return to Table of Contents

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
Dennis Greenburger and Christine Padesky	Mind over Mood (215-page workbook)	Patients and Families	Bookstores
DVD Resource	Understanding Depression: Hope through Treatment **and** Understanding Depression: The Suicide Connection	Patients and Families	http://www.understandingdepression.org
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 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
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/

Return to Table of Contents

Author/Organization	Title/Description	Audience	Web Sites/Order Information
General (Continued)			
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
The National Suicide Lifeline		Patients and Families	1-800-273-TALK 1-800-273-8255
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/
Minnesota Department of Health	Clinical Guidelines for Implementing Universal Postpartum Depression Screening in Well Child Checks **and** Documenting and Charting for Postpartum Depression in Well Child Checks	Patients and Families	http://www.health.state.mn.us/divs/cfh/topic/pmad/

Return to Table of Contents

Author/Organization	Title/Description	Audience	Web Sites/Order Information
Perinatal (Continued)			
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://mothertobaby.org/
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

Return to Table of Contents

The subdivisions of this section are:

- References
- Appendices

References

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

Aan Het Rot M, Zarate Jr CA, Charney DS, Mathew SJ. Ketamine for depression: where do we go from here? *Biol Psychiatry* 2012;72:537-47.

Adams JR, Drake RE, Wolford GL. Shared decisioin-making preferences of people with severe mental illness. *Psych Serv* 2007;58:1219-21.

Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. *Biol Psychiatry* 1988;23:271-84.

Allan CL, Herrmann LL, Ebmeier KP. Transcranial magnetic stimulation in the management of mood disorders. *Neuropsychobiology* 2011;64:163-69.

Alpert M, Silva RR, Pouget ER. Prediction of treatment response in geriatric depression from baseline folate level: interaction with an SSRI or a tricyclic antidepressant. *J Clin Psychopharmacol* 2003;23:309-13.

American Psychiatric Association. *In* Diagnostic and Statistical Manual of Mental Disorders DSM-5. Fifth Edition. Washington, DC/London, England. 2013.

American Psychiatric Association. *In* Practice Guideline for the Treatment of Patients with Panic Disorder. 2nd Edition, 2010.

Anderson EL, Reti IM. ECT in pregnancy: a review of the literature from 1941 to 2007. *Psychosomatic Med* 2009;71:235-42.

Anderson L, Lewis G, Araya R, et al. Self-help books for depression: how can practitioners and patients make the right choice? *Br J Gen Pract* 2005;55:387-92.

Appelbaum PS. Assessment of patients' competence to consent to treatment. *N Engl J Med* 2007;357:1834-40.

Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. *Am J Clin Nutr* 2010;91:757-70.

Archer J, Bower P, Gilbody S, et al. Collaborative care for depression and anxiety problems. *Cochrane Database of Systematic Reviews* 2012(10):CD006525.

Areán PA, Ayalon L, Hunkeler E, et al. Improving depression care for older, minority patients in primary care. *Med Care* 2005;43:381-90.

Austin MP. To treat or not to treat: maternal depression, SSRI use in pregnancy and adverse neonatal effects. *Psychol Med* 2006;36:1663-70.

Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. Audit. *In* The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. Second Edition. World Health Organization. 2001.

Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med* 2000;62:633-38.

Baik S, Gonzales JJ, Bowers BJ, et al. Reinvention of depression instruments by primary care clinicians. *Ann Fam Med* 2010;8:224-30.

Bajbouj M, Merkl A, Schlaepfer TE, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. *J Clin Psychopharmacol* 2010;30:273-81.

Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement on depression, anxiety, and cardiovascular disease. *J Clin Psychiatry* 2001;62:24-27.

Return to Table of Contents

Barca ML, Engedal K, Selbaek. A reliability and validity study of the Cornell scale among elderly inpatients, using various clinical criteria. *Dement Geriatr Cogn Disord* 2010;29:438-47.

Baumann P, Nil R, Souche A, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *J Clin Psychopharmacol* 1996;16:307-14.

Beck A, Crain AL, Solberg LI, et al. Severity of depression and magnitude of productivity loss. *Ann Fam Med* 2011;9:305-11.

Belnap BH, Kuebler J, Upshur C, et al. Challenges in implementing depression care management in the primary care setting. *Adm Policy Ment Health* 2006;33:65-75.

Benedetti F, Colombo C, Pontiggia A, et al. Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. *J Clin Psychiatry* 2003;64:648-53.

Bérard A, Ramos É, Rey É, et al. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. *Birth Defects Res B Dev Reprod Toxicol* 2007;80:18-27.

Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol Med* 2014;44:225-39.

Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007;68:843-53.

Biesheuvel-Leliefeld KE, Kok GD, Bockting CL, et al. Effectiveness of psychological interventions in preventing recurrence of depressive disorder: meta-analysis and meta-regression. *J Affect Disord* 2015;174:400-10.

Birrer RB, Vemuri SP. Depression in later life: a diagnostic and therapeutic challenge. *Am Fam Physician* 2004;69:2375-82.

Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Mol Psychiatry* 2012;17:1272-82.

Blomstedt P, Sjöberg RL, Hansson M, et al. Deep brain stimulation in the treatment of depression. *Acta Psychiatr Scand* 2011;123:4-11.

Blumenthal JA, Lett HS, Babyak MA, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet* 2003;362:604-09.

Bodkin JA, Lasser RA, Wines JD Jr., et al. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. *J Clin Psychiatry* 1997;58:137-45.

Borges S, Chen YF, Laughren TP, et al. Review of maintenance trials for major depressive disorder: a 25-year perspective from the U.S. food and drug administration. *J Clin Psychiatry* 2014;75:205-14.

Bortolotti B, Menchetti M, Bellini F, et al. Psychological interventions for major depression in primary care: a meta-analytic review of randomized controlled trials. *Gen Hosp Psychiatry* 2008;30:293-302.

Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. *Am J Psychiatry* 2000;157:1925-32.

Boukhris T, Sheehy O, Mottron L, Bérard A. Antidepressant use during pregnancy and the risk of autism spectrum disorder in children. *JAMA Pediatr* 2016;170:117-24.

Return to Table of Contents

Bouwer C, Stein DJ. Buspirone is an effective augmenting agent of serotonin selective re-uptake inhibitors in severe treatment-refractory depression. *S Afr Med J* 1997;87:534-37.

Bower P, Kontopantelis E, Sutton A, et al. Influence of initial severity of depression on effectiveness of low intensity interventions: meta-analysis of individual patient data. *BMJ* 2013;346: f540.

Briggs JH, Bauer MS, McBride L, et al. Screening for thyroid disease in ambulatory patients with depression. *American Psychiatric Association Abstracts* NR144, 1993.

Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. *Wis Med J* 1995;94:135-40.

Brown C, Schulberg HC, Prigerson HG. Factors associated with symptomatic improvement and recovery from major depression in primary care patients. *Gen Hosp Psychiatry* 2000;22:242-50.

Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *J Clin Psychiatry* 1995;56:30-34.

Browne G, Steiner M, Roberts J, et al. Sertraline and/or interpersonal psychotherapy for patients with dysthymic disorder in primary care: 6-month comparison with longitudinal 2-year follow-up of effectiveness and costs. *J Affect Disord* 2002;68:317-30.

Bruce MT, Ten Have TR, Reynolds III CF, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. *JAMA* 2004;291:1081-91.

Bull SA, Hu XH, Hunkeler EM, et al. Discontinuation of use and switching of antidepressants: influence of patient-physician communication. *JAMA* 2002;288:1403-09.

Bush B, Shaw S, Cleary P, et al. Screening for alcohol abuse using the CAGE questionnaire. *Am J Med* 1987;82:231-35.

Candy M, Jones L, Williams R, et al. Psychostimulants for depression (review). *Cochrane Database of Systematic Reviews* 2008(2):CD006722.

Cappiello A, McDougle CJ, Malison RT, et al. Yohimbine augmentation of fluvoxamine in refractory depression: a single-blind study. *Biol Psychiatry* 1995;38:765-67.

Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354:579-87.

Chen YM, Huang XM, Thompson R, Zhao YB. Clinical features and efficacy of escitalopram treatment for geriatric depression. *J Int Med Res* 2011;39:1946-53.

Churchill R, Moore THM, Furukawa TA, et al. 'Third wave' cognitive and behavioural therapies versus treatments as usual for depression. *Cochrane Database Syst Rev* 2013(10)CD008705.

Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med* 2000;160:3278-85.

Claassen CA, Trivedi MH, Rush AJ, et al. Clinical differences among depressed patients with and without a history of suicide attempts: findings from the STAR*D trial. *J Affect Disord* 2007;97:77-84.

Coelho HF, Murray L, Royal-Lawson M, Cooper PJ. Antenatal anxiety disorder as a predictor of postnatal depression: a longitudinal study. *J Affect Disord* 2011;129:348-53.

Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA* 2006;295:499-507.

Colangelo LA, He K, Whooley MA, et al. Higher dietary intake of long-chair w-3 polyunsaturated fatty acids is inversely associated with depressive symptoms in women. *Nutrition* 2009;25:1011-19.

Return to Table of Contents

Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. *Cochrane Database of Systematic Reviews* 2013(9)CD004366.

Cooper C, Katona C, Lyketsos K, et al. A systematic review of treatments for refractory depression in older people. *Am J Psychiatry* 2011;168:681-88.

Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh postnatal depression scale. *Br J Psychiatry* 1987;150:782-86.

Cristancho P, Christancho MA, Baltuch GH, et al. Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year. *J Clin Psychiatry* 2011;72:1376-82.

Cuijpers P, Andersson G, Donker T, van Straten A. Psychological treatment of depression: results of a series of meta-analyses. *Nord J Psychiatry* 2011a;65:354-64.

Cuijpers P, Dekker J, Hollon SD, Andersson G. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. *J Clin Psychiatry* 2009a;70:1219-29.

Cuijpers P, Geraedts AS, van Oppen P, et al. Interpersonal psychotherapy for depression: a meta-analysis. *Am J Psychiatry* 2011b;168:581-92.

Cuijpers P, Hollon SD, van Straten A, et al. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ Open* 2013;3:e002542.

Cuijpers P, Karyotaki E, Andersson G, et al. The effects of blinding on the outcomes of psychotherapy and pharmacotherapy for adult depression: a meta-analysis. *Eur Psychiatry* 2015;30:685-93.

Cuijpers P, Karyotaki E, Weitz E, et al. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. *J Affect Disord* 2014a;159:118-26.

Cuijpers P, Reynolds CF 3rd, Donker T, et al. Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. *Depress Anxiety* 2012;29:855-64.

Cuijpers P, Sijbrandij M, Koole SL, et al. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry* 2014b;13:56-67.

Cuijpers P, van Straten A, Andersson G, van Oppen P. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *J Consult Clin Psychol* 2008;76:909-22.

Cuijpers P, van Straten A, Bohlmeijer E, et al. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychol Med* 2010a;40:211-23.

Cuijpers P, van Straten A, Schuurmans J, et al. Psychotherapy for chronic major depression and dysthymia: a meta-analysis. *Clin Psychol Rev* 2010b;30:51-62.

Cuijpers P, van Straten A, Smit F, Andersson G. Is psychotherapy for depression equally effective in younger and older adults? A meta-regression analysis. *Int Psychogeriatr* 2009b;21:16-24.

Cuijpers P, van Straten A, Warmerdam L. Behavioral activation treatments of depression: a meta-analysis. *Clin Psychol Rev* 2007;27:318-26.

Cuijpers P, van Straten A, Warmerdam L, Andersson G. Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. *Depress Anxiety* 2009c;26:279-88.

Dam J, Ryde L, Svejso J, et al. Morning fluoxetine plus evening mianserin versus morning fluoxetine plus evening placebo in the acute treatment of major depression. *Pharmacopsychiatry* 1998;31:48-54.

Return to Table of Contents

Danielsson L, Noras AM, Waern M, Carlsson J. Exercise in the treatment of major depression: a systematic review grading the quality of evidence. *Physiother Theory Pract* 2013;29:573-85.

Davalos DB, Yadon CA, Tregellas HC. Untreated prenatal maternal depression and the potential risks to offspring: a review. *Arch Womens Ment Health* 2012;15:1-14.

Davanzo R, Copertino M, De Cunto A, et al. Antidepressant drugs and breastfeeding: a review of the literature. *Breastfeed Med* 2011;6:89-98.

Davis LL, Frazier E, Husain MM, et al. Substance use disorder comorbidity in major depressive disorder: a confirmatory analysis of the STAR*D cohort. *Am J Addict* 2006;15:278-85.

de Maat S, Dekker J, Schoevers R, et al. Short psychodynamic supportive psychotherapy, antidepressants, and their combination in the treatment of major depression: a mega-analysis based on three randomized clinical trials. *Depress Anxiety* 2008;25:565-74.

Delgado PL, Price LH, Charney DS, Heninger GR. Efficacy of fluvoxamine in treatment-refractory depression. *J Affect Disord* 1998;15:55-60.

Dickinson LM, Rost K, Nutting PA, et al. RCT of a care manager intervention for major depression in primary care: 2-year costs for patients with physical vs psychological complaints. *Ann Fam Med* 2005;3:15-22.

Dieserud G, Røysamb E, Ekeberg O, Kraft P. Toward an integrative model of suicide attempt: a cognitive psychological approach. *Suicide Life Threat Behav* 2001;31:153-68.

Dietz PM, Williams SB, Callaghan WM, et al. Clinically identified maternal depression before, during, and after pregnancies ending in live births. *Am J Psychiatry* 2007;164:1515-20.

Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *J Consult Clin Psychol* 2006;74:658-70.

Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. *J Clin Psychopharmacol* 1998;18:465-69.

Dobson KS, Hollon SD, Dimidjian S, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression. *J Consult Clin Psychol* 2008;76:468-77.

Donnelly PL. The use of the patient health questionnaire-9 Korean version (PHQ-9K) to screen for depressive disorders among Korean Americans. *J Transcult Nurs* 2007;18:324-30.

Dørheim SK, Bondevik GT, Eberhard-Gran M, Bjorvatn B. Sleep and depression in postpartum women: a population-based study. *Sleep* 2009;32:847-55.

Driessen E, Cuijpers P, Hollon SD, Dekker JJ. Does pretreatment severity moderate the efficacy of psychological treatment of adult outpatient depression? A meta-analysis. *J Consult Clin Psychol* 2010;78:668-80.

Duffy FF, Chung H, Trivedi M, et al. Systematic use of patient-rated depression severity monitoring: is it helpful and feasible in clinical psychiatry? *Psychiatric Serv* 2008;59:1148-54.

Dunlop BW, Crits-Christoph P, Evans DL, et al. Coadministration of modafinil and a selective serotonin reuptake inhibitor from the initiation of treatment of major depressive disorder with fatigue and sleepiness: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2007;27:614-19.

Dunn AL, Madhukar HT, Kampert JB, et al. Exercise treatment for depression: efficacy and dose response. *Am J Prev Med* 2005;28:1-8.

Return to Table of Contents

Egede LE. Effect of comorbid chronic diseases on prevalence and odds of depression in adults with diabetes. *Psychosomatic Med* 2005;67:46-51.

Ekers D, Murphy R, Archer J, et al. Nurse-delivered collaborative care for depression and long-term physical conditions: a systematic review and meta-analysis. *J Affect Disord* 2013;149:14-22.

Ekers D, Richards D, Gilbody S. A meta-analysis of randomized trials of behavioural treatment of depression. *Psychol Med* 2008;38:611-23.

Eng JJ, Reime B. Exercise for depressive symptoms in stroke patients: a systematic review and meta-analysis. *Clin Rehabil* 2014;28:731-39.

Epperson CN, Terman M, Terman JS, et al. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. *J Clin Psychiatry* 2004;65:421-25.

Evans RW, Tepper SJ, Shapiro RE, et al. The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American headache society position paper. *Headache* 2010;50:1089-99.

Fava M, Rosenbaum JF, McGrath PJ, et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. *Am J Psychiatry* 1994;151:1372-74.

Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. *J Clin Psychiatry* 2005;66:85-93.

Ferreira E, Carceller AM, Agogué C, et al. Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics* 2007;119:52-59.

Fiellin DA, Carrington Reid M, O'Connor PG. Screening for alcohol problems in primary care: a systematic review. *Arch Intern Med* 2000;160:1977-89.

Flint AJ, Rifat SL. Maintenance treatment for recurrent depression in late life. *Am J Geriatr Psychiatry* 2000;8:112-16.

Flückiger C, Del Re AC, Munder T, et al. Enduring effects of evidence-based psychotherapies in acute depression and anxiety disorders versus treatment as usual at follow-up: a longitudinal meta-analysis. *Clin Psychol Rev* 2014;34:367-75.

Flynn HA, Sexton M, Ratliff S, et al. Comparative performance of the Edinburgh postnatal depression scale and the patient health questionnaire-9 in pregnant and postpartum women seeking psychiatric services. *Psychiatry Res* 2011;187:130-34.

Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology* 2014;231:3663-76.

Fortney JC, Pyne JM, Mouden SB, et al. Practice-based versus telemedicine-based collaborative care for depression in rural federally qualified health centers: a pragmatic randomized comparative effectiveness trial. *Am J Psychiatry* 2013;170:414-25.

Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA* 2010;303:47-53.

Fraguas R Jr, Iosifescu DV, Alpert J, et al. Major depressive disorder and comborbid cardiac disease: is there a depressive subtype with greater cardiovascular morbidity? results from the STAR*D study. *Psychosomatics* 2007;48:418-25.

Frank E, Kupfer DJ, Perel JM, et al. Comparison of full-dose versus half-dose pharmacotherapy in the maintenance treatment of recurrent depression. *J Affect Disord* 1993;27:139-45.

Return to Table of Contents

Frasure-Smith N, Lespérance F, Talajic M. Depression in 18-month prognosis after myocardial infarction. *Circulation* 1995;91:999-1005.

Freeman MP, Davis M, Sinha P, et al. Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. *J Affect Disord* 2008;110:142-48.

Freeman MP, Fava M, Lake J, et al. Complementary and alternative medicine in major depressive disorder: the American psychiatric association task force report. *J Clin Psychiatry* 2010;71:669-81.

Frye MA. Bipolar disorder – a focus on depression. *N Engl J Med* 2011;364:51-59.

Ganzini L, Smith DM, Fenn DS, Lee MA. Depression and mortality in medically ill older patients. *J Am Geriatr Soc* 1997;45:307-12.

Garakani A, Win T, Virk S, et al. Comorbidity of irritable bowel syndrome in psychiatric patients: a review. *Am J of Therapeutics* 2003;10:61-67.

Garfield S, Francis SA, Smith FJ. Building concordant relationships with patients starting antidepressant medication. *Patient Educ Couns* 2004;55:241-46.

Garrard JM. Patient outcomes associated with antidepressant drugs. Agency for Healthcare Research and Quality (AHRQ). AHRQ 2001-64. April 2001.

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.

Gastó C, Navarro V, Marcos T, et al. Single-blind comparison of venlafaxine and nortriptyline in elderly major depression. *J Clin Psychopharmacol* 2003;23:21-26.

Gaynes BN, DeVeaugh-Geiss J, Weir S, et al. Feasibility and diagnostic validity of the M-3 checklist: a brief, self-rated screen for depressive, bipolar, anxiety, and post-traumatic stress disorders in primary care. *Ann Fam Med* 2010;8:160-69.

Gaynes BN, Gavin N, Meltzer-Brody S, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Summary, evidence report/technology assessment no. 119. (Prepared by the RTI-University of North Carolina evidence-based practice center under contract no. 290-02-0016.) AHRQ publication no. 05-E006-1. Rockville, MD: Agency for Healthcare Research and Quality. February 2005.

Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 2003;361:653-61.

George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010;67:507-16.

George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry* 2005;58:364-73.

Gilbody S, Bower P, Fletcher J, et al. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern Med* 2006;166:2314-21.

Gilchrist G, Hegarty K, Chondros P, et al. The association between intimate partner violence, alcohol and depression in family practice. *BMC Fam Pract* 2010;11:72.

Gillman PK. A review of serotonin toxicity data: implications for the mechanisms of antidepressant drug action. *Biol Psychiatry* 2006;59:1046-51.

Gillman PK. Triptans, serotonin agonists, and serotonin syndrome (serotonin toxicity): a review. *Headache* 2010;50:264-72.

Return to Table of Contents

Gjerdingen D, Crow S, McGovern P, et al. Postpartum depression screening at well-child visits: validity of a 2-question screen and the PHQ-9. *Ann Fam Med* 2009;7:63-70.

Gjerdingen DK, Yawn BP. Postpartum depression screening: importance, methods, barriers, and recommendations for practice. *J Am Board Fam Med* 2007;20:280-88.

Gold KJ, Singh V, Marcus SM, Palladino CL. Mental health, substance use and intimate partner problems among pregnant and postpartum suicide victims in the national violent death reporting system. *Gen Hosp Psychiatry* 2012;34:139-45.

Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 2005;162:656-62.

Goodwin FK, Jamison KR. Clinical depression and diagnosis. *In* Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. 2nd Edition. Chapter 1. New York: Oxford University Press. 2007.

Goyal D, Gay C, Lee K. Fragmented maternal sleep is more strongly correlated with depressive symptoms than infant temperament at three months postpartum. *Arch Womens Ment Health* 2009;12:229-37.

Greden JF. Antidepressant maintenance medications: when to discontinue and how to stop. *J Clin Psychiatry* 1993;54:39-47.

Green RC, Cupples A, Kurz A, et al. Depression as a risk factor for alzheimer disease: the MIRAGE study. *Arch Neurol* 2003;60:753-59.

Gregory RJ, Canning SS, Lee TW, Wise JC. Cognitive bibliotherapy for depression: a meta-analysis. *Prof Psychology Res and Prac* 2004;35:275-80.

Guidi J, Fava GA, Fava M, Papakostas GI. Efficacy of the sequential integration of psychotherapy and pharmacotherapy in major depressive disorder: a preliminary meta-analysis. *Psychol Med* 2011;41:321-31.

Haby MM, Donnelly M, Corry J, Vos T. Cognitive behavioural therapy for depression, panic disorder and generalized anxiety disorder: a meta-regression of factors that may predict outcome. *Aust NZ J Psychiatry* 2006;40:9-19.

Hamann J, Cohen R, Luecht S, et al. Do patients with schizophrenia wish to be involved in decisions about their medical treatment? *Am J Psychiatry* 2005;162:2382-84.

Han C, Jo SA, Kwak J, et al. Validation of the patient health questionnaire-9 Korean version in the elderly population: the Ansan geriatric study. *Compr Psychiatry* 2008;49:218-23.

Hausenblas HA, Saha D, Dubyak PJ, Anton SD. Saffron (*Crocus sativus L.)* and major depressive disorder: a meta-analysis of randomized clinical trials. *J Integr Med* 2013;11:377-83.

Hawkins EJ, Kivlahan DR, Williams EC, et al. Examining quality issues in alcohol misuse screening. *Subst Abus* 2007;28:53-65.

Hedayati SS, Minhajuddin AT, Afshar M, et al. Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. *JAMA* 2010;303:1946-53.

Hirschfeld RMA. Clinical importance of long-term antidepressant treatment. *Br J Psychiatry Suppl* 2001;179:S4-S8.

Hirschfeld RMA, Williams JBW, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the mood disorder questionnaire. *Am J Psychiatry* 2000;157:1873-75.

Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: a meta-analytic review. *J Consult Clin Psychol* 2010;78:169-83.

Return to Table of Contents

Hollon SD, DeRubeis RJ, Fawcett J, et al. Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 2014;71:1157-64.

Huang FY, Chung H, Kroenke K, et al. Using the patient health questionnaire-9 to measure depression among racially and ethnically diverse primary care patients. *J Gen Intern Med* 2006;21:547-52.

Huijbregts KML, de Jong FJ, van Marwijk HWJ, et al. A target-driven collaborative care model for major depressive disorder is effective in primary care in the Netherlands: a randomized clinical trial from the depression initiative. *J Affect Dis* 2013;146:328-37.

Hunkeler EM, Katon W, Tang L, et al. Long term outcomes from the IMPACT randomised trial for depressed elderly patients in primary care. *BMJ* 2006;332:259-63.

Hunkeler EM, Meresman JF, Hargreaves WA, et al. Efficacy of nurse telehealth care and peer support in augmenting treatment of depression in primary care. *Arch Fam Med* 2000;9:700-08.

Ialongo N, McCreary BK, Pearson JL, et al. Major depressive disorder in a population of urban, African-American young adults: prevalence, correlates, comorbidity and unmet mental health service need. *J Affect Disord* 2004;79:127-36.

Imel ZE, Malterer MB, McKay KM, Wampold BE. A meta-analysis of psychotherapy and medication in unipolar depression and dysthymia. *J Affect Disord* 2008;110:197-206.

Jakobsen JC, Hansen JL, Simonsen S, et al. Effects of cognitive therapy *versus* interpersonal psychotherapy in patients with major depressive disorder: a systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. *Psychol Med* 2012a;42:1343-57.

Jakobsen JC, Hansen JL, Simonsen E, Gluud C. The effect of adding psychodynamic therapy to antidepressants in patients with major depressive disorder. A systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. *J Affect Disord* 2012b;137:4-14.

Jakobsen JC, Hansen JL, Simonsen E, Gluud C. The effect of interpersonal psychotherapy and other psychodynamic therapies versus 'treatment as usual' in patients with major depressive disorder. *PLoS One* 2011a;6:e19044.

Jakobsen JC, Hansen JL, Storebø OJ, et al. The effects of cognitive therapy versus 'no intervention' for major depressive disorder. *PLoS One* 2011b;6:e28299.

Jakobsen JC, Lindschou Hansen J, Storebø OJ, et al. The effects of cognitive therapy versus 'treatment as usual' in patients with major depressive disorder. *PLoS One* 2011c;6:e22890.

Jakubovski E, Varigonda AL, Freemantle N, et al. Systematic review and meta-analysis: dose-response relationship of selective serotonin reuptake inhibitors in major depressive disorder. *Am J Psychiatry* 2016;173:174-83.

Janicak PG, Nahas Z, Lisanby SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimul* 2010;3:187-99.

Jeeva F, Dickens C, Coventry P. Is treatment of depression cost-effective in people with diabetes? A systematic review of the economic evidence. *Int J Technol Assess Health Care* 2013;29:384-91.

Jiang W, Davidson JRT. Antidepressant therapy in patients with ischemic heart disease. *Am Heart J* 2005;150:871-81.

Joffe RT, Singer W, Levitt AJ, et al. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. *Arch Gen Psychiatry* 1993;50:387-93.

Return to Table of Contents

Johnston BJ. The role of patient experience and its influence on adherence to antidepressant treatment. *J Psychosoc Nurs Ment Health Serv* 2013;51:29-37.

Jorm AF, Christensen H, Griffiths KM, Rodgers B. Effectiveness of complementary and self-help treatments for depression. *Med J Aust* 2002;176:S84-S96.

Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002;59:530-37.

Karasz A. Cultural differences in conceptual models of depression. *Social Science & Medicine* 2005;60:1625-35.

Katon W, Robinson P, Von Korff M, et al. A multifaceted intervention to improve treatment of depression in primary care. *Arch Gen Psychiatry* 1996;53:924-32.

Katon W, Von Korff M, Lin E, et al. Stepped collaborative care for primary care patients with persistent symptoms of depression: a randomized trial. *Arch Gen Psychiatry* 1999;56:1109-15.

Katon W, Von Korff M, Ciechanowski P, et al. Behavioral and clinical factors associated with depression among individuals with diabetes. *Diabetes Care* 2004a;27:914-20.

Katon WJ, Lin EHB, Russo J, et al. Cardiac risk factors in patients with diabetes mellitus and major depression. *J Gen Intern Med* 2004b;19:1192-99.

Katon WJ, Seelig M. Population-based care of depression: team care approaches to improving outcomes. *J Occup Environ Med* 2008;50:459-67.

Katon WJ, Schoenbaum M, Fan M, et al. Cost-effectiveness of improving primary care treatment of late-life depression. *Arch Gen Psychiatry* 2005;62:1313-20.

Katona C, Abou-Saleh MT, Harrison DA, et al. Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *Br J Psychiatry* 1995;166:80-86.

Keller MB. Issues in treatment-resistant depression. *J Clin Psychiatry* 2005;66:5-12.

Keller MB, Kocsis JH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA* 1998;280:1665-72.

Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;342:1462-70.

Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the consortium for research in electroconvulsive therapy (CORE). *Arch Gen Psychiatry* 2006;63:1337-44.

Kennedy SH, Giacobbe P, Rizvi SJ, et al. Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. *Am J Psychiatry* 2011;168:502-10.

Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* 2005;62:617-27.

Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. *BMJ* 2011;344:d8012.

Kim KH, Lee SM, Paik JW, Kim NS. The effects of continuous antidepressant treatment during the first 6 months on relapse or recurrence of depression. *J Affect Disord* 2011;132:121-29.

Return to Table of Contents

Kirmayer LJ. Cultural variations in the clinical presentation of depression and anxiety: implications for diagnosis and treatment. *J Clin Psychiatry* 2001;62:22-28.

Kleinman A. Culture and depression. *N Engl J Med* 2004;351:951-53.

Klinkman MS. The role of algorithms in the detection and treatment of depression in primary care. *J Clin Psychiatry* 2003;64:19-23.

Kocsis JH, Gelenberg AJ, Rothbaum BO, et al. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: the REVAMP trial. *Arch Gen Psychiatry* 2009a;66:1178-88.

Kocsis JH, Leon AC, Markowitz JC, et al. Patient perference as a moderator of outcome for chronic forms of major depressive disorder treated with nefazodone, cognitive behavioral analysis system of psychotherapy, or their combination. *J Clin Psychiatry* 2009b;70:354-61.

Kok RM, Heeren TJ, Nolen WA. Continuing treatment of depression in the elderly: a systematic review and meta-analysis of double-blinded randomized controlled trials with antidepressants. *Am J Geriatr Psychiatry* 2011;19:249-55.

Kok RM, Nolen WA, Heeren TJ. Efficacy of treatment in older depressed patients: a systematic review and meta-analysis of double-blind randomized controlled trials with antidepressants. *J Affect Disord* 2012;141:103-15.

Kozhimannil KB, Pereira MA, Harlow BL. Association between diabetes and perinatal depression among low-income mothers. *JAMA* 2009;301:842-47.

Kraft JB, Slager SL, McGrath PJ, Hamilton SP. Sequence analysis of the serotonin transporter and associations with antidepressant response. *Biol Psychiatry* 2005;58:374-81.

Kriston L, von Wolff A, Westphal A, et al. Efficacy and acceptability of acute treatments for persistent depressive disorder: a network meta-analysis. *Depress Anxiety* 2014;31:621-30.

Kroenke K, Spitzer RL, Williams JBW, Löwe B. The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatry* 2010;32:345-59.

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606-13.

Kroenke K, Wood DR, Mangelsdorff AD, et al. Chronic fatigue in primary care: prevalence, patient characteristics, and outcome. *JAMA* 1988;260:929-34.

Krupnick JL, Sotsky SM, Simmens S, et al. The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: findings in the national institute of mental health treatment of depression collaborative research program. *J Consult Clin Psychol* 1996;64:532-39.

Kuyken W, Hayes R, Barrett B, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. *Lancet* 2015;386:63-73.

Lancaster CA, Gold KJ, Flynn HA, et al. Risk factors for depressive symptoms during pregnancy: a systematic review. *Am J Obstet Gynecol* 2010;202:5-14.

Lavretsky H, Reinlieb M, St. Cyr N, et al. Citalopram, methylphenidate, or their combination in geriatric depression: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 2015;172:561-69.

Leichsenring F, Rabung S, Leibing E. The efficacy of short-term psychodynamic psychotherapy in specific psychiatric disorders: a meta-analysis. *Arch Gen Psychiatry* 2004;61:1208-16.

Return to Table of Contents

Lépine JP, Briley M. The epidemiology of pain in depression. *Hum Psychopharmacol* 2004;19:S3-S7.

Leppämäki SJ, Partonen TT, Hurme J, et al. Randomized trial of the efficacy of bright-light exposure and aerobic exercise on depressive symptoms and serum lipids. *J Clin Psychiatry* 2002;63:316-21.

Levine S, Unützer J, Yip JY, et al. Physicians' satisfaction with a collaborative disease management program for late-life depression in primary care. *Gen Hosp Psychiatry* 2005;27:383-91.

Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of antidepressants for dysthymia: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry* 2011;72:509-14.

Li D, Liu L, Odouli R. Presence of depressive symptoms during early pregnancy and the risk of preterm delivery: a prospective cohort study. *Hum Reprod* 2009;24:146-53.

Li G, Mbuagbaw L, Samaan Z, et al. Efficacy of vitamin D supplementation in depression in adults: a systematic review. *J Clin Endocrinol Metab* 2014;99:757-67.

Lichtman JH, Bigger Jr JT, Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American heart association prevention committee of the council on cardiovascular nursing, council on clinical cardiology, council on epidemiology and prevention, and interdisciplinary council on quality of care and outcomes research: endorsed by the American psychiatric association. *Circulation* 2008;118:1768-75.

Linde K, Berner MM, Kriston L. St John's wort for major depression. *Cochrane Database Syst Rev* 2008:CD000448.

Lo Sasso AT, Rost K, Beck A. Modeling the impact of enhanced depression treatment on workplace functioning and costs: a cost-benefit approach. *Med Care* 2006;44:352-58. (Cost Effectiveness Analysis)

Loh A, Leonhart R, Wills CE, et al. The impact of patient participation on adherence and clinical outcome in primary care of depression. *Patient Educ Couns* 2007;65:69-78.

Lotrakul M, Sumrithe S, Saipanish R. Reliability and validity of the Thai version of the PHQ-9. *BMC Psychiatry* 2008; 8:46.

Louie L. The effectiveness of yoga for depression: a critical literature review. *Issues Ment Health Nurs* 2014;35:265-76.

Löwe B, Unützer J, Callahan CM, et al. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Med Care* 2004;42:1194-1201.

Lozano AM, Mayberg HS, Giacobbe P, et al. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry* 2008;64:461-67.

Ludman EJ, Katon W, Russo J, et al. Depression and diabetes symptom burden. *Gen Hosp Psychiatry* 2004;26:430-36.

MacPherson H, Richmond S, Bland M, et al. Acupuncture and counselling for depression in primary care: a randomised controlled trial. *PLoS Med* 2013;10:e1001518.

Maes M, Libbrecht I, van Hunsel F, et al. Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. *J Clinic Psychopharmacol* 1999;19:177-82.

Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, Ripke S, Wray NR, et al. A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry* 2013;18:497-511.

Malone Jr DA, Dougherty DD, Rezai AR, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 2009;65:267-75.

Return to Table of Contents

Maneeton N, Maneeton B, Srisurapanont M, Martin SD. Quetiapine monotherapy in acute phase for major depressive disorder: a meta-analysis of randomized, placebo-controlled trials. *BMC Psychiatry* 2012;12:160.

Manicavasgar V, Parker G, Perich T. Mindfulness-based cognitive therapy vs cognitive behaviour therapy as a treatment for non-melancholic depression. *J Affect Disord* 2011;130:138-44.

Manu P, Matthews DA, Lane TJ. The mental health of patients with a chief complaint of chronic fatigue: a prospective evaluation and follow-up. *Arch Intern Med* 1988;148:2213-17.

Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2008;28:156-65.

Markowitz JC, Kocsis JH, Bleiberg KL, et al. A comparative trial of psychotherapy and pharmacotherapy for "pure" dysthymic patients. *J Affect Disord* 2005;89:167-75.

Marshall RD, Liebowitz MR. Paroxetine/bupropion combination treatment for refractory depression. *J Clin Psychopharmacol* 1996;16:80-81.

Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005;45:651-60.

Mazzucchelli T, Kane R, Rees C. Behavioral activation treatments for depression in adults: a meta-analysis and review. *Cin Psychol Sci Prac* 2009;16:383-411.

McCarney RW, Schulz J, Grey AR. Effectiveness of mindfulness-based therapies in reducing symptoms of depression: a meta-analysis. *Eur J Psychotherapy Couns* 2012;14:279-99.

McGrath PJ, Stewart JW, Nunes EN, et al. Treatment response of depressed outpatients unresponsive to both a tricyclic and a monoamine oxidase inhibitor antidepressant. *J Clin Psychiatry* 1994;55:336-39.

McGrath PJ, Stewart JW, Nunes EV, et al. A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment-refractory depression. *Am J Psychiatry* 1993;150:118-23.

Meehan J, Kapur N, Hunt IM, et al. Suicide in mental health in-patients and within 3 months of discharge: national clinical survey. *Br J Psychiatry* 2006;188:129-34.

Melfi CA, Chawla AJ, Croghan TW, et al. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Arch Gen Psychiatry* 1998;55:1128-32.

Menchetti M, Rucci P, Bortolotti B, et al. Moderators of remission with interpersonal counselling or drug treatment in primary care patients with depression: randomised controlled trial. *Br J Psychiatry* 2014;204:144-50.

Merikangas KR, Ames M, Cui L, et al. The impact of comorbidity of mental and physical conditions on role disability in the US adult household population. *Arch Gen Psychiatry* 2007;64:1180-88.

Mian AI. Depression in pregnancy and the postpartum period: balancing adverse effects of untreated illness and treatment risks. *J Psychiatr Pract* 2005;11:389-96.

Midanik LT, Zahnd EG, Klein D. Alcohol and drug CAGE screeners for pregnant, low-income women: the California perinatal needs assessment. *Alcohol Clin Exp Res* 1998;22:121-25.

Milgrom J, Gemmill AW. Screening for perinatal depression. *Best Pract Res Clin Obstet Gynaecol* 2014;28:13-23.

Miranda J, Schoenbaum M, Sherbourne C, et al. Effects of primary care depression treatment on minority patients' clinical status and employment. *Arch Gen Psychiatry* 2004;61:827-34.

Return to Table of Contents

Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *Am J Psychiatry* 2005;162:1588-1601.

Mojtabai R, Olfson M. National patterns in antidepressant treatment by psychiatrists and general medical providers: results from the national comorbidity survey replication. *J Clin Psychiatry* 2008;69:1064-74.

Morgan AJ, Jorm AF. Self-help interventions for depressive disorders and depressive symptoms: a systematic review. *Ann Gen Psychiatry* 2008;7:13.

Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* 2007;370:851-58.

Muñoz RF, Mendelson T. Toward evidence-based interventions for diverse populations: the San Francisco general hospital prevention and treatment manuals. *J Consulting Clin Psychol* 2005;73:790-99.

Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry* 2013;170:1134-42.

Nahas Z, Marangell LB, Husian MM, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depression episodes. *J Clin Psychiatry* 2005;66:1097-1104.

Narasimhan S, Lohoff FW. Pharmacogenetics of antidepressant drugs: current clinical practice and future directions. *Pharmacogenomics* 2012;13:441-64.

National Institute for Clinical Excellence. Guidance on the use of electroconvulsive therapy. Technology Appraisal Guidance 59. London:England. April 2003.

National Institute for Health and Care Excellence. Depression in adults. Available at: nice.org.uk/guidance/qs8. 2011.

Nelson JC. Augmentation strategies in depression 2000. *J Clin Psychiatry* 2000;61:13-19.

Nelson JC, Mazure CM, Bowers MB Jr, Jatlow PI. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. *Arch Gen Psychiatry* 1991;48:303-07.

Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry* 2009;166:980-91.

Nichita EC, Buckley PF. Informed consent and competency: doctor's dilemma on the consultation liaison service. *Psychiatry (Edgmont)* 2007;4:53-55.

Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6,362 events among 146,538 participants in 54 observational studies. *Eur Heart J* 2006;27:2763-74.

Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T_3 augmentation following two failed medication treatments for depression: a STAR*D report. *Am J Psychiatry* 2006;163:1519-30.

Nierenberg AA, McColl RD. Management options for refractory depression. *Am J Med* 1996;101:45S-52S.

Nimalasuriya K, Compton MT, Guillory VJ. Screening adults for depression in primary care: a position statement of the American college of preventive medicine. *J Fam Pract* 2009;58:535-38.

NIMH/NIH Consensus Development Conference Statement. Mood disorders: pharmacologic prevention of recurrences. *Am J Psychiatry* 1985;142:469-76.

Ninan PT, Hassman HA, Glass SJ, McManus FC. Adjunctive modafinil at initiation of treatment with a selective serotonin reuptake inhibitor enhances the degree and onset of therapeutic effects in patients with major depressive disorder and fatigue. *J Clin Psychiatry* 2004;65:414-20.

Return to Table of Contents

Oberlander TF, Warburton W, Misri S, et al. Neonatal outcomes after prenatal exposure to selective serotonin reputake inhibitor antidepressants and maternal depression using population-based linked health data. *Arch Gen Psychiatry* 2006;63:898-906.

O'Connor AM, Bennett C, Stacey D, et al. Do patient decision aids meet effectiveness criteria of the international patient decision aid standards collaboration? A systematic review and meta-analysis. *Med Decis Making* 2007;27:554-74.

O'Connor EA, Rossom RC, Henninger M, et al. Screening for depression in adults: an updated systematic evidence review for the U.S. preventive services task force. AHRQ Publication No. 14-05208-EF-1. January 2016.

Oestergaard S, Møldrup C. Optimal duration of combined psychotherapy and pharmacotherapy for patients with moderate and severe depression: a meta-analysis. *J Affect Disord* 2011;131:24-36.

O'Hara MW. Postpartum depression: what we know. *J Clin Psychol* 2009;65:1258-69.

O'Hara MW, Stuart S, Gorman LL, Wenzel A. Efficacy of interpersonal psychotherapy for postpartum depression. *Arch Gen Psychiatry* 2000;57:1039-45.

O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. *Best Pract Res Clin Obstet Gynaecol* 2014;28:3-12.

Okumura Y, Ichikura K. Efficacy and acceptability of group cognitive behavioral therapy for depression: a systematic review and meta-analysis. *J Affect Disord* 2014;164:155-64.

Onyike CU, Crum RM, Lee HB, et al. Is obesity associated with major depression?: results from the third national health and nutrition examination survey. *Am J Epidemiol* 2003;158:1139-47.

Oquendo MA, Friend JM, Halberstam B, et al. Association of comorbid posttraumatic stress disorder and major depression with greater risk for suicidal behavior. *Am J Psychiatry* 2003;160:580-82.

O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007; 62:1208-16.

Oren DA, Wisner KL, Spinelli M, et al. An open trial of morning light therapy for treatment of antepartum depression. *Am J Psychiatry* 2002;159:666-69.

Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry* 2006;63:530-38.

Oxman TE, Dietrich AJ, Williams JW Jr, Kroenke K. A three-component model for reengineering systems for the treatment of depression in primary care. *Psychosomatics* 2002;43:441-50.

Pan A, Sun Q, Okereke OI, et al. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA* 2011;306:1241-49.

Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry* 2007;68:826-31.

Paulson JF, Bazemore SD. Prenatal and postpartum depression in fathers and its association with maternal depression: a meta-analysis. *JAMA* 2010;303:1961-69.

Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. *Psychological Medicine* 1995;25:1171-80.

Pearlstein T. Perinatal depression: treatment options and dilemmas. *J Psychiatry Neurosci* 2008;33:302-18.

Return to Table of Contents

Peeters F, Huibers M, Roelofs J, et al. The clinical effectiveness of evidence-based interventions for depression: a pragmatic trial in routine practice. *J Affect Disord* 2013;145:349-55.

Perry PJ, Zeilmann C, Arndt S. Tricyclic antidepressant concentrations in plasma: an estimate of their sensitivity and specificity as a predictor of response. *J Clin Psychopharmacol* 1994;14:230-40.

Petrak F, Herpertz S, Albus C, et al. Study protocol of the diabetes and depression study (DAD): a multi-center randomized controlled trial to compare the efficacy of a diabetes-specific cognitive behavioral group therapy versus sertraline in patients with major depression and poorly controlled diabetes mellitus. *BMC Psychiatry* 2013;13:206.

Pettersson A, Boström KB, Gustavsson P, Ekselius L. Which instruments to support diagnosis of depression have sufficient accuracy? A systematic review. *Nord J Psychiatry* 2015;69:497-508.

Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. *Clin Psychol Rev* 2011;31:1032-40.

Pinquart M, Duberstein PR, Lyness JM. Effects of psychotherapy and other behavioral interventions on clinically depressed older adults: a meta-analysis. *Aging Ment Health* 2007;11:645-57.

Pinto-Meza A, Serrano-Blanco A, Peñarrubia M, et al. Assessing depression in primary care with the PHQ-9: can it be carried out over the telephone? *J Gen Intern Med* 2005;20:738-42.

Pizzi C, Rutjes AW, Costa GM, et al. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. *Am J Cardiol* 2011;107:972-79.

Porcelli S, Fabbri C, Drago A, et al. Genetics and antidepressant: where we are. *Clin Neuropsychiatry* 2011;8:99-150.

Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry* 1992;149:999-1010.

Prasko J, Horacek J, Klaschka J, et al. Bright light therapy and/or imipramine for inpatients with recurrent non-seasonal depression. *Neuro Endocrinol Lett* 2002;23:109-13.

Preskorn SH. Ketamine: the hopes and the hurdles. *Biol Psychiatry* 2012;72:522-23.

Preskorn SH, Beber JH, Faul JC, Hirschfeld R. Serious adverse effects of combining fluoxetine and tricyclic antidepressants. *Am J Psychiatry* 1990;147:532.

Ravindran AV, Lam RW, Filteau MJ, et al. Canadian network for mood and anxiety treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. V. complementary and alternative medicine treatments. *J Affect Disord* 2009;117:S54-64.

Ray S, Nizamie SH, Akhtar S, et al. Efficacy of adjunctive high frequency repetitive transcranial magnetic stimulation of left prefrontal cortex in depression: a randomized sham controlled study. *J Affect Disord* 2011;128:153-39.

Ray S, Stowe ZN. The use of antidepressant medication in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2014;28:71-83.

Rethorst CD, Sunderajan P, Greer TL, et al. Does exercise improve self-reported sleep quality in non-remitted major depressive disorder? *Psychol Med* 2013;43:699-709.

Reynolds III CF. Treatment of depression in special populations. *J Clin Psychiatry* 1992;53:45-53.

Reynolds III CF, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med* 2006;354:1130-38.

Return to Table of Contents

Robinson M, Oakes TM, Raskin J, et al. Acute and long-term treatment of late-life major depressive disorder: duloxetine versus placebo. *Am J Geriatr Psychiatry* 2014;22:34-45.

Rost K, Nutting P, Smith JL, et al. Managing depression as a chronic disease: a randomised trial of ongoing treatment in primary care. *BMJ* 2002;325:934-37.

Rost K, Smith JL, Dickinson M, et al. The effect of improving primary care depression management on employee absenteeism and productivity: a randomized trial. *Med Care* 2004;42:1202-10.

Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med* 2002;23:51-61.

Rush AJ. Strategies and tactics in the management of maintenance treatment for depressed patients. *J Clin Psychiatry* 1999;60:21-26.

Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry* 2005;58:347-54.

Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003;54:573-83.

Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163:1905-17.

Rush AJ, Warden D, Wisniewski SR, et al. STAR*D: revising conventional wisdom. *CNS Drugs* 2009;23:627-47.

Sackeim HA. Magnetic stimulation therapy and ECT. *Convulsive Therapy* 1994;10:255-58.

Sackeim HA, Brannan SK, Rush AJ, et al. Durability of antidepressant response to vagus nerve stimulation (VNS™). *Int J Neuropsychopharmacol* 2007;10:817-26.

Sackheim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA* 2001a;285:1299-1307.

Sackeim HA, Keilp JG, Rush AJ, et al. The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression. *Neuropsychiatry Neuropsychol Behav Neurol* 2001b;14:53-62.

Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS™) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 2001c;25:713-28.

Schatzberg AF, Rush AJ, Arnow BA, et al. Chronic depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. *Arch Gen Psychiatry* 2005;62:513-20.

Schlaepfer TE, Frick C, Zobel A, et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med* 2008;38:651-61.

Schoenbaum M, Unützer J, McCaffrey D, et al. The effects of primary care depression treatment on patients' clinical status and employment. *Health Serv Res* 2002;37:1145-58.

Schoenbaum M, Unützer J, Sherbourne C, et al. Cost-effectiveness of practice-initiated quality improvement for depression: results of a randomized controlled trial. *JAMA* 2001;286:1325-30.

Schonfeld WH, Verboncoeur CJ, Fifer SK, et al. The functioning and well-being of patients with unrecognized anxiety disorders and major depressive disorder. *J Affect Disord* 1997;43:105-19.

Schramm E, Zobel I, Dykierek P, et al. Cognitive behavioral analysis system of psychotherapy versus interpersonal psychotherapy for early-onset chronic depression: a randomized pilot study. *J Affect Disord* 2011;129:109-16.

Return to Table of Contents

Schraufnagel TJ, Wagner AW, Miranda J, Roy-Byrne PP. Treating minority patients with depression and anxiety: what does the evidence tell us? *Gen Hosp Psychiatry* 2006;28:27-36.

Schuch FB, Vasconcelos-Moreno MP, Borowsky C, Fleck MP. Exercise and severe depression: preliminary results of an add-on study. *J Affect Disord* 2011;133:615-18.

Schulberg HC, Katon W, Simon GE, Rush AJ. Treating major depression in primary care practice: an update of the agency for health care policy and research practice guidelines. *Arch Gen Psychiatry* 1998;55:1121-27.

Schwartz TL, Azhar N, Cole K, et al. An open-label study of adjunctive modafinil in patients with sedation related to serotonergic antidepressant therapy. *J Clin Psychiatry* 2004;65:1223-27.

Segal ZV, Bieling P, Young T, et al. Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. *Arch Gen Psychiatry* 2010;67:1256-64.

Shaffer JA, Edmondson D, Wasson LT, et al. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. *Psychosom Med* 2014;76:190-96.

Sharma V, Khan M, Smith A. A closer look at treatment resistant depression: is it due to a bipolar diathesis? *J Affective Disorders* 2005;84:251-57.

Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. *CNS Drugs* 2010;24:131-61.

Shinkai RS, Hatch JP, Schmidt CB, Sartori EA. Exposure to the oral side effects of medication in a community-based sample. *Spec Care Dentist* 2006;26:116-20.

Silveira H, Moraes H, Oliveira N, et al. Physical exercise and clinically depressed patients: a systematic review and meta-analysis. *Neuropsychobiology* 2013;67:61-68.

Simon GE, Katon WJ, VonKorff M, et al. Cost-effectiveness of a collaborative care program for primary care patients with persistent depression. *Am J Psychiatry* 2001a;158:1638-44.

Simon GE, Manning WG, Katzelnick DJ, et al. Cost-effectiveness of systematic depression treatment for high utilizers of general medical care. *Arch Gen Psychiatry* 2001b;58:181-87.

Simon GE, Savarino J. Suicide attempts among patients starting depression treatment with medications or psychotherapy. *Am J Psychiatry* 2007;164:1029-34.

Simon GE, Van Korff M, Ludman EJ, et al. Cost-effectiveness of a program to prevent depression relapse in primary care. *Medical Care* 2002;40:941-50.

Simon GE, Van Korff M, Rutter C, Wagner E. Randomised trial of monitoring, feedback, and management of care by telephone to improve treatment of depression in primary care. *BMJ* 2000;320:550-54.

Siu AL, US Preventive Services Task Force (USPSTF), Bibbins-Domingo K, et al. Screening for depression in adults: U.S. preventive services task force recommendation statement. *JAMA* 2016;315:380-87.

Sivojelezova A, Shuhaiber S, Sarkissian L, et al. Citalopram use in pregnancy: prospective comparative evaluation of pregnancy and fetal outcome. *Am J Obstet Gynecol* 2005;193:2004-09.

Siwek M, Dudek D, Schlegel-Zawadzka M, et al. Serum zinc level in depressed patients during zinc supplementation of imipramine treatment. *J Affect Disord* 2010;126:447-52.

Smith CA, Hay PP, Macpherson H. Acupuncture for depression. *Cochrane Database Syst Rev* 2010;(1):CD004046.

Sniezek DP, Siddiqui IJ. Acupuncture for treating anxiety and depression in women: a clinical systematic review. *Med Acupunct* 2013;25:164-72.

Return to Table of Contents

Solomon DA, Keller MB, Leon AC, et al. Multiple recurrences of major depressive disorder. *Am J Psychiatry* 2000;157:229-33.

Sonawalla SB. Citalopram in the maintenance treatment of major depressive disorder. *J Clin Psychiatry* 2001;62:993.

Sorrentino R. Performing capacity evaluations: what's expected from your consult: core components of a capacity evaluation are understanding, free choice, and reliability. *Curr Psychiatry* 2014;1:41-44.

Spielmans GI, Berman MI, Usitalo AN. Psychotherapy versus second-generation antidepressants in the treatment of depression: a meta-analysis. *J Nerv Ment Dis* 2011;199:142-49.

Spier SP. Use of bupropion with SRIs and venlafaxine. *Depression and Anxiety* 1998;7:73-75.

Spijker J, van Straten A, Bockting CL, et al. Psychotherapy, antidepressants, and their combination for chronic major depressive disorder: a systematic review. *Can J Psychiatry* 2013;58:386-92.

Spitzer RL, Kroenke K, Williams JBW. Validation and utility of a self-report version of prime-md: the PHQ primary care study. *JAMA* 1999;282:1737-44.

Steinert C, Hofmann M, Kruse J, Leichsenring F. Relapse rates after psychotherapy for depression – stable long-term effects? A meta-analysis. *J Affect Disord* 2014;168:107-18.

Stewart DE. Depression during pregnancy. *N Engl J Med* 2011;365:1605-11.

Stewart WF, Ricci JA, Chee E, et al. Cost of lost productive work time among US workers with depression. *JAMA* 2003;289:3135-44.

Strine TW, Mokdad AH, Balluz LS, et al. Depression and anxiety in the United States: findings from the 2006 behavioral risk factor surveillance system. *Psychiatr Serv* 2008;59:1383-90.

Szymkowicz SM, Finnegan N, Dale RM. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. *J Affect Disord* 2013;147:416-20.

Teasdale JD, Scott J, Moore RG, et al. How does cognitive therapy prevent relapse in residual depression: evidence from a controlled trial. *J Consult Clin Psychol* 2001;69:347-57.

Thacher TD, Clarke BL. Vitamin D insufficiency. *Mayo Clin Proc* 2011;86:50-60.

Thase ME, Blomgren SL, Birkett MA, et al. Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. *J Clin Psychiatry* 1997;58:16-21.

Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *Am J Psychiatry* 2007;164:739-52.

Thormahlen GM. Paroxetine using during pregnancy: is it safe? *Ann Pharmacother* 2006;40:1834-37.

Trivedi MH. Tools and strategies for ongoing assessment of depression: a measurement-based approach to remission. *J Clin Psychiatry* 2009;70:26-31.

Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006a;354:1243-52.

Trivedi MH, Kleiber BA. Algorithm for the treatment of chronic depression. *J Clin Psychiatry* 2001;62:22-29.

Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006b;163:28-40.

Return to Table of Contents

Tschoppe P, Wolgin M, Pischon N, Kielbassa AM. Etiologic factors of hyposalivation and consequences for oral health. *Quintessence Int* 2010;41:321-33.

UK ECT Review Group, The. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 2003;361:799-808.

U.S. Preventive Services Task Force. Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: recommendation statement. *Am Fam Phys* 2014;89.

Unützer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA* 2002;288:2836-45.

Unützer J, Katon WJ, Fan MY, et al. Long-term cost effects of collaborative care for late-life depression. *Am J Manag Care* 2008;14:95-100.

Unützer J, Tang L, Oishi S, et al. Reducing suicidal ideation in depressed older primary care patients. *J Am Geriatr Soc* 2006;54:1550-56.

van Dijk SE, Pols AD, Adriaanse MC, et al. Cost-effectiveness of a stepped-care intervention to prevent major depression in patients with type 2 diabetes mellitus and/or coronary heart disease and subthreshold depression: design of a cluster-randomized controlled trial. *BMC Psychiatry* 2013;13:128.

van Hees ML, Rotter T, Ellermann T, Evers SM. The effectiveness of individual interpersonal psychotherapy as a treatment for major depressive disorder in adult outpatients: a systematic review. *BMC Psychiatry* 2013;13:22.

Vanelli M, Coca-Perraillon M. Role of patient experience in antidepressant adherence: a retrospective data analysis. *Clin Ther* 2008;30:1737-45.

Vesga-López O, Blanco C, Keyes K, et al. Psychiatric disorders in pregnant and postpartum women in the United States. *Arch Gen Psychiatry* 2008;65:805-15.

Vittengl JR, Clark LA, Jarrett RB. Continuation-phase cognitive therapy's effects on remission and recovery from depression. *J Consult Clin Psychol* 2009;77:367-71.

von Wolff A, Hölzel LP, Westphal A, et al. Selective serotonin reuptake inhibitors and tricyclic antidepressants in the acute treatment of chronic depression and dysthymia: a systematic review and meta-analysis. *J Affect Disord* 2013;144:7-15.

Wang F, Lee EO, Wu T, et al. The effects of tai chi on depression, anxiety, and psychological well-being: a systematic review and meta-analysis. *Int J Behav Med* 2014;21:605-17.

Wang PS, Simon GE, Avorn J, et al. Telephone screening, outreach, and care management for depressed workers and impact on clinical and work productivity outcomes: a randomized controlled trial. *JAMA* 2007;298:1401-11.

Watkins S, Meltzer-Brody S, Zolnoun D, Stuebe A. Early breastfeeding experiences and postpartum depression. *Obstet Gynecol* 2011;118:214-21.

Watson LC, Zimmerman S, Cohen LW, Dominik R. Practical depression screening in residential care/assisted living: five methods compared with gold standard diagnoses. *Am J Geriatr Psychiatry* 2009;17:556-64.

Wenzel RG, Tepper S, Korab WE, Freitag F. Serotonin syndrome risks when combining SSRI/SNRI drugs and triptans: is the FDA's alert warranted? *Ann Pharmacother* 2008;42:1692-96.

Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neurophatic pain. *Neurology* 2006;67:1411-20.

Return to Table of Contents

Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015;313:2456-73.

Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA* 2008;300:2379-88.

Whooley MA, Simon GE. Managing depression in medical outpatients. *N Engl J Med* 2000;343:1942-50.

Wiersma JE, Van Schaik DJ, Hoogendorn AW, et al. The effectiveness of the cognitive behavioral analysis system of psychotherapy for chronic depression: a randomized controlled trial. *Psychother Psychosom* 2014;83:263-69.

Williams Jr JW, Noel PH, Cordes JA, et al. Is this patient clinically depressed? *JAMA* 2002;287:1160-70.

Wisner KL, Sit DKY, Hanusa BH, et al. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. *Am J Psychiatry* 2009;166:557-66.

Wittkampf KA, Naeije L, Schene AH, et al. Diagnostic accuracy of the mood module of the patient health questionnaire: a systematic review. *Gen Hosp Psychiatry* 2007;29:388-95.

Wright BM, Eiland III EH, Lorenz R. Augmentation with atypical antipsychotics for depression: a review of evidence-based support from the medical literature. *Pharmacotherapy* 2013;33:344-59.

Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantiative review. *Psychosom Med* 2003;65:201-10.

Wulsin L, Somoza E, Heck J. The feasibility of using the Spanish PHQ-9 to screen for depression in primary care in Honduras. *Prim Care Companion J Clin Psychiatry* 2002;4:191-95.

Yates WR, Mitchell J, Rush AJ, et al. Clinical features of depression in outpatients with and without co-occurring general medical conditions in STAR*D: confirmatory analysis. *Prim Care Companion J Clin Psychiatry* 2007;9:7-15.

Yeung A, Fung F, Yu SC, et al. Validation of the patient health questionnaire-9 for depression screening among Chinese Americans. *Compr Psychiatry* 2008;49:211-17.

Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American psychiatric association and the American college of obstetricians and gynecologists. *Gen Hosp Psychiatry* 2009;31:403-13.

Zhornitsky S, Potvin S, Moteshafi H, et al. Dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders: a systematic review of the placebo-controlled monotherapy and add-on trials. *Int Clin Psychopharmacol* 2011;26:183-92.

Zivin K, Pfeiffer PN, Bohnert AS, et al. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. *Am J Psychiatry* 2013;170:642-50.

Return to Table of Contents

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
☐	☐	☐	☐

Return to Table of Contents

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

Return to Table of Contents

Appendix B – ICSI Shared Decision-Making Model

ICSI Institute for Clinical Systems Improvement

The Collaborative Conversation™
Shared Decision-Making and the Translation of Evidence into Practice

A consistent finding from clinical and health services research is the failure to translate research into practice. The translation of evidence into practice can be advanced through the use of shared decision-making since shared decision-making results in evidence being incorporated into patient and clinician consultations.

Shared decision-making (SDM) is a process in which patient and clinicians collaborate to clarify all acceptable options, ensure that the patient is well-informed, and chose a course of care consistent with patient values and preferences and the best available medical evidence *(Minnesota Shared Decision-Making Collaborative [MSDMC], 2011)*.

Evidence based guidelines may recommend the use of shared decision-making for decisions in instances where the evidence is equivocal, when patient action or inaction (such as medication adherence or lifestyle changes) can impact the potential outcome, or when the evidence does not indicate a single best recommendation.

SDM is a patient-centered approach that involves a conversation between the patient and the clinician. It is ideal to involve caregivers and family members in these conversations as well. Family members and caregivers can participate in discussions, ask questions, hear content the patient may miss, and provide invaluable support in decision follow through. Although only patients and clinicians are specifically mentioned throughout this document for brevity purposes, this does not diminish the importance of caregivers and families in patient-centered care.

Both the patient and the clinician bring expertise to the shared decision-making conversation. Clinicians' expertise includes disease etiology, prognosis, options for treatment including the burden and benefit to the patient, and outcome probabilities. Patients' expertise lies in their knowledge of their risk tolerance, body, priorities, family and financial issues, as well as their daily experience with the condition (adapted from "Making Shared Decision-Making a Reality. No Decision About Me, Without Me." Coulter, A., Collins, A., The King's Fund 2011).

Treatment options vary in their burden on a patient. SDM offers an opportunity to help the patient select a treatment to which he/she can adhere. When conversations discussing options occurs, patients and clinicians are actively engaged while considering the attributes and issues of the available options. This empathic approach results in the clinician and patient co-creating a decision and a plan of care (adapted from Montori, V., the Mayo Clinic KER UNIT, April 2015). Decision aids can be supportive of this conversation when they communicate the best available evidence to inform the patient and clinician discussion.

Without a conversation, clinicians may make assumptions about what the patient prefers. This creates the potential for discrepancies between what clinicians assume and what patients want resulting in a "preference misdiagnosis" (adapted from Health Policy Publishing, LLC, May 2013).

Difficulty in initiating a conversation is cited by patients and clinicians as one of the barriers to shared decision-making. To address this impediment, ICSI worked with patients, practicing clinicians, and other stakeholders to develop the Collaborative Conversation™ model for use across the care continuum.

Return to Table of Contents

Collaborative Conversation™

A collaborative approach towards decision-making is a fundamental tenet of Shared Decision-Making (SDM). The Collaborative Conversation™ is an inter-professional approach that nurtures relationships, enhances patients' knowledge, skills and confidence as vital participants in their health, and encourages them to manage their health care. Within a Collaborative Conversation™ , the perspective is that the patient, rather than the clinician, knows which course of action is most consistent with the patient's values and preferences.

Use of Collaborative Conversation™ elements and tools is even more necessary to support patient, care clinician and team relationships when patients and families are dealing with high stakes or highly charged issues. A diagnosis of a life-limiting illness is one example of such a circumstance.

The overall objective for the Collaborative Conversation™ approach is to create an environment in which the patient, family, and care team work collaboratively to reach and carry out a decision that is consistent with the patient's values and preferences along with the best available evidence. A rote script, completed form or checklist does not constitute this approach. Rather it is a set of skills employed appropriately for the specific situation. These skills need to be used artfully to address all aspects of the person involved in making a decision: cognitive, affective, social and spiritual.

Key communication skills help build the collaborative conversation approach. These skills include: (adapted from O'Connor, Jacobsen, "Decisional Conflict: Supporting People Experiencing Uncertainty about Options Affecting their Health" [2007], and Bunn H, O'Connor AM, Jacobsen MJ, "Analyzing Decision Support and Related Communication" [1998, 2003]).

1. **Listening skills:**

   Encourage patient to talk by providing prompts to continue such as ***go on, and then?, uh huh,*** or by repeating the last thing a person said, ***It's confusing***.

   Paraphrase content of messages shared by patient to promote exploration, clarify content and to communicate that the person's unique perspective has been heard. The clinician should use their own words rather than just parroting what they heard.

   Reflection of feelings usually can be done effectively once trust has been established. Until the clinician feels that trust has been established, short reflections at the same level of intensity expressed by the patient without omitting any of the message's meaning is appropriate. Reflection in this manner communicates that the clinician understands the patient's feelings and may work as a catalyst for further problem solving. For example, the clinician identifies what the person is feeling and responds back in his/her own words like this: ***"So, you're unsure which choice is the best for you."***

   Summarize the person's key comments and reflect them back to the patient. The clinician should condense several key comments made by the patient and provide a summary of the situation. This assists the patient in gaining a broader understanding of the situation rather than getting mired down in the details. The most effective times to do this are midway through and at the end of the conversation. An example of this is, ***"You and your family have read the information together, discussed the pros and cons, but are having a hard time making a decision because of the risks."***

   Perception checks ensure that the clinician accurately understands a patient or family member perspective, and may be used as a summary or reflection. They are used to verify that the clinician is interpreting the message correctly. The clinician can say, ***"So you are saying that you're not ready to make a decision at this time. Am I understanding you correctly?"***

Return to Table of Contents

2. **Questioning Skills:**

   Open and Closed questions are both used with the emphasis on open questions. Open questions ask for clarification or elaboration and cannot have a yes or no answer. An example would be, ***"What else would influence you to choose this?"*** Closed questions are appropriate if specific information is required such as, ***"Does your daughter support your decision?"***

   Other skills such as summarizing, paraphrasing, and reflection of feeling can be used in the questioning process so that the patient doesn't feel pressured by questions.

   Verbal tracking, referring back to a topic the patient mentioned earlier, is an important foundational skill (Ivey & Bradford-Ivey). An example of this is the clinician saying, ***"You mentioned earlier…"***

3. **Information-Giving Skills:**

   Providing information and **providing feedback** are two methods of information giving. The distinction between providing information and giving advice is important. Information giving allows a clinician to supplement their knowledge and helps to keep the conversation patient centered. Giving advice, on the other hand, takes the attention away from the patient's unique goals and values, and places it on those of the clinician.

   Providing information can be sharing facts or responding to questions. An example is, ***"If we look at the evidence, the risk is…"*** **Providing feedback** gives the patient the clinician's view of the patient's reaction. For instance, the clinician can say, ***"You seem to understand the facts and value your daughter's advice."***

Return to Table of Contents

When to Initiate a Collaborative Conversation™

Certain seminal events occur along the care continuum creating especially opportune times for collaborative conversations. More than one of these opportunities may present at a time and they will occur in no specific order.

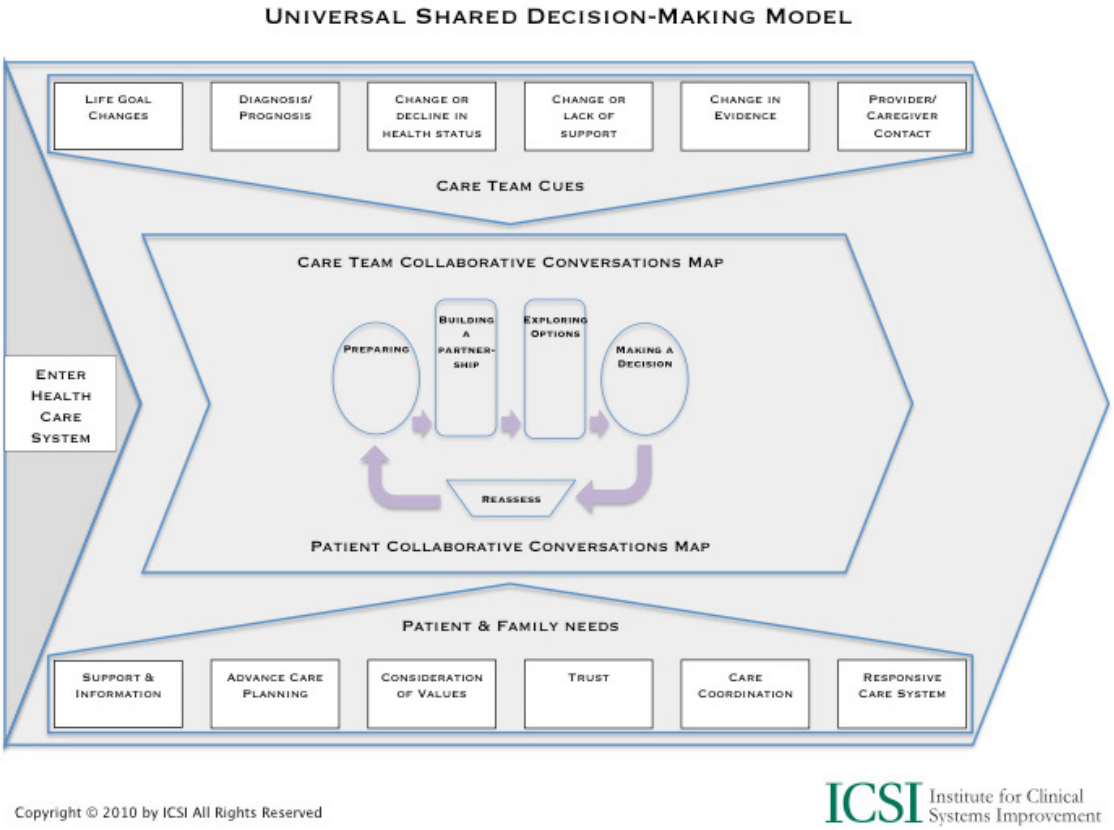


Table 1

Cues for the Care Team to Initiate a Collaborative Conversation™:

- Life goal changes: *Patient's priorities change related to things the patient values such as activities, relationships, possessions, goals and hopes, or things that contribute to the patient's emotional and spiritual well-being.*
- Diagnosis/prognosis changes: *Additional diagnoses, improved or worsening prognosis.*
- Change or decline in health status: *Improving or worsening symptoms, change in performance status or psychological distress.*
- Change or lack of support: *Increase or decrease in caregiver support, change in caregiver, change in caregiver status, change in financial standing, difference between patient and family wishes.*
- Disease progression: *Change in physical or psychological status as a result of the disease progression.*
- Clinician/caregiver contact: *Each contact between the clinician/ caregiver presents an opportunity to reaffirm with the patient that their care plan and the care they are receiving is consistent with their values.*

Return to Table of Contents

Patient and Family Needs within a Collaborative Conversation™

- Request for support and information: *Decisional conflict is indicated by, among other things, the patient verbalizing uncertainty or concern about undesired outcomes, expressing concern about choice consistency with personal values, exhibiting behavior such as wavering, delay, preoccupation, distress or tension. Support resources may include healthcare professionals, family, friends, support groups, clergy and social workers. When patient expresses need for information regarding options and their potential outcomes, the patient should understand the key facts about their options, risks and benefits, and have realistic expectations. The method and pace with which this information is provided to the patient should be appropriate for the patient's capacity at that moment.*
- Advance Care Planning: *With the diagnosis of a life-limiting illness, conversations around advance care planning open up. This is an opportune time to expand the scope of the conversation to other types of decisions that will need to be made as a consequence of the diagnosis of a life-limiting illness.*
- Consideration of Values: *The personal importance a patient assigns potential outcomes must be respected. If the patient is unclear how to prioritize his/her preferences, value clarification can be achieved through the use of decision aids. Detailing the benefits and harms of potential outcomes in terms of how they will directly affect the patient, and through collaborative conversations with the clinician.*
- Trust: *The patient must feel confident that his/her preferences will be communicated to and respected by all caregivers.*
- Care Coordination: *Should the patient require care coordination; this is an opportune time to discuss the other types of care related decisions that need to be made. These decisions will most likely need to be revisited often. Further, the care delivery system must be capable of delivering coordinated care throughout the continuum of care.*
- Responsive Care System: *The care system needs to support the components of patient and family centered care so the patient's values and preferences are incorporated into the care they receive throughout the care continuum.*

Return to Table of Contents

The Collaborative Conversation™ Map is the heart of this process. The Collaborative Conversation Map™ can be used as a stand-alone tool that is equally applicable to clinicians and patients as shown in Table 2. Clinicians use the map as a clinical workflow. It helps get the shared decision-making process initiated and provides navigation for the process. Care teams can use the Collaborative Conversation™ to document team best practices and to formalize a common lexicon. Organizations can build fields from the Collaborative Conversation™ Map in electronic medical records to encourage process normalization. Patients use the map to prepare for decision-making, to help guide them through the process and to share critical information with their loved ones.

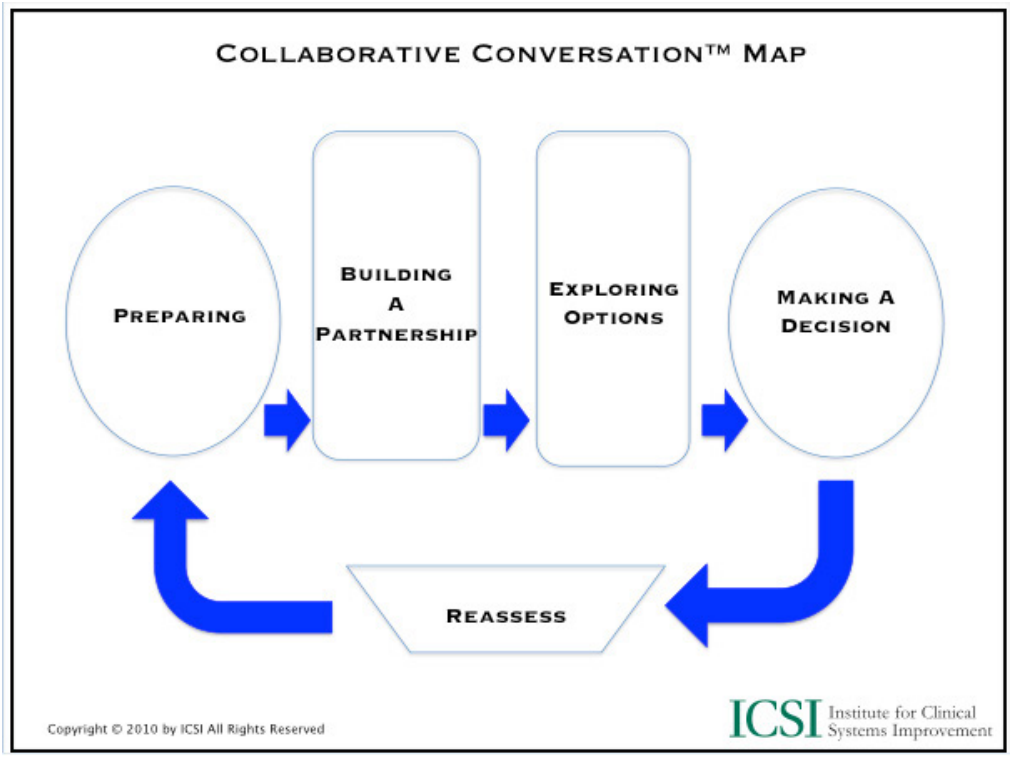


Table 2

Return to Table of Contents

Evaluating Shared Decision-Making

It has proven challenging to assess shared decision-making. Measuring shared decision-making remains important for continued adoption of shared Decision-Making as a mechanism for translating evidence into practice, promoting patient centered care, and to understand the impact of shared decision-making on patient experience, outcomes and revenues. Many assessments exist, but they are often proxy measures.

Two suggested methods for measuring shared Decision-Making are the CollaboRATE tool and the SURE Test. These two tools measure different aspects of shared Decision-Making, as described below.

The CollaboRATE tool measures the level of shared Decision-Making in the clinical encounter from the patient's perspective. It is a brief patient reported measure of shared decision-making. The tools and guidance on their use can be found at http://www.collaboratescore.org/.

The SURE Test is a brief screening questionnaire the patient uses to access their readiness and capacity to make a decision or to determine whether they are comfortable with the choice that was made. In other words, it provides information on how likely a patient may be experiencing decisional conflict. If the SURE screening test indicates decisional conflict may exist, the Decisional Conflict Scale should be completed in order to assess clinically significant decisional conflict.

Shared decision-making is a useful mechanism for translating evidence into practice. While research on the impacts of shared decision-making continues to grow, there is mounting evidence that both patients and clinicians benefit from SDM. Shared decision-making offers the opportunity to bring evidence and the patient's values into the patient/clinician discussion of health choices.

Return to Table of Contents

Appendix C – 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 IV ketamine for patients suffering from treatment resistant depression (TRD). Ketamine is an antagonist at the N-methyl-D-aspartate (NMDA) receptor, which modulates the excitatory neurotransmitter, glutamate *(Preskorn, 2012)*. Ketamine has generally been studied via IV administration, because the oral and IM formulations also do not provide the rapid response seen with IV administration *(Aan Het Rot, 2012)*.

In some reports, significant patient response has been observed within 2 to 24 hours of ketamine administration *(Murrough, 2013)*. Two systemic reviews of published literature on the antidepressant effects of ketamine found it to have a rapid antidepressant effect in data on 163 patients in one study and 310 in another, which included treatment-resistant patients, as well as 118 patients undergoing concurrent ECT *(Fond, 2014; Aan Het Rot, 2012)*.

Despite the promise of a robust and rapid response, few studies have followed patients longer than 72 hours after their IV infusion of ketamine. One study followed 73 patients who were randomized to IV ketamine or IV midazolam and found a higher response rate at 24 hours for the IV ketamine vs. the IV midazolam group (64% vs. 28%). They also found that over seven days, the IV ketamine group had a lower and longer time to relapse *(Murrough, 2013)*. 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)*. One study found two of three subjects did not demonstrate significant responses to ketamine until after they received multiple infusions *(Szymkowicz, 2013)*.

Future studies of ketamine for the treatment of depression are needed prior to recommendations of its use in typical clinical practice settings. These future studies should also evaluate a way to sustain symptom remission following IV ketamine and evaluate larger groups of patients *(Szymkowicz, 2013)*.

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; Kraft, 2005; Nahas, 2005; Sackeim, 2001b; Sackeim, 2001c; Rush, 2005)*.

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; Sackeim, 2001c)*.

Sackeim, 2007 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)*. More recent studies *(Cristancho, 2011; Bajbouj, 2010)* 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%.

Return to Table of Contents

Repetitive transcranial magnetic stimulation (rTMS)

Repetitive TMS is a 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; Janicak, 2010)*. 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; George, 2010)*.

Several studies have shown efficacy of an acute course of rTMS. In an intention-to-treat sample of 190 patients treated with left prefrontal cortex rTMS versus active sham treatment, active rTMS patients had 4.2 times greater odds of remission than sham patients, which was statistically significant *(George, 2010)*.

O'Reardon, 2007 reported on a large 301-patient multicentered, acute, randomized controlled trial of rTMS showing remission rates 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%) at six weeks *(O'Reardon, 2007)*.

Ray, 2011 showed a 75% remission rate for rTMS vs. 10% in the control group in a small 41-patient prospective randomized hospital-based study. This study included patients with psychotic depression *(Ray, 2011)*.

In a recent meta-analysis including 29 randomized, controlled trials, rTMS was found to have response and remission rates comparable to antidepressants with numbers needed to treat for response of 6 and for remission of 8 *(Berlim, 2014)*.

TMS has also shown some evidence in sustaining the durability of efficacy. In a multisite, naturalistic, observational study, it was shown that of the 120 patients with a history of pharmaco-resistant major depressive disorder who met criteria for response or remission after an acute course of treatment, 62.5% continued to meet response criteria through one year. Of note, these patients had access to TMS during the study, and 36.2% of the study patients received reintroduction of TMS.

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)* showed less amnesia and faster reorientation than ECT and some improvement in depression scores.

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 *(Blomstedt, 2011)*. So far, evidence involves small non-blinded trials.

One open label trial *(Mayberg, 2005)* 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)* 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)*. Malone, 2009 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 *(Malone, 2009)*.

Return to Table of Contents

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.

Return to Table of Contents

Appendix D – Special Populations

Overview

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

- Cardiovascular disease and cerebrovascular disease
- Diabetes
- Chronic pain
- Geriatric and cognitively impaired patients
- Pregnant and 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)*.

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)*.

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 *(Kozhimnanil, 2009; Egede, 2005; Katon, 2004b)*.

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

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)*. 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.

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

Cardiovascular and Cerebrovascular Disease

Interplay of risks

Some studies have shown that major depression is associated with an increased risk of developing coronary artery disease (*Wulsin, 2003; Rugulies, 2002)*.

Studies have shown an increased risk of mortality in patients after myocardial infarction by as much as fourfold *(Lichtman, 2008; Frasure-Smith, 1995)*, while other analyses have disputed this *(Jiang, 2005; Nicholson, 2006)*.

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)*.

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)*.

Return to Table of Contents

A meta-analysis in regards to the relationship between stroke and depression found a pooled hazard ratio of 1.45, on par with the association smoking and obesity have with stroke *(Pan, 2011)*.

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)*, 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)*.

A 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)*.

It has been suggested that the potential causative mechanisms for the association between stroke and depression are similar to those discussed above for cardiovascular disease *(Pan, 2011)*.

Treating depression in this population

A recent meta-analysis suggested that SSRI treatment of depression may improve coronary heart disease prognosis *(Pizzi, 2011)*. In addition, consensus opinion is to treat depressed cardiac patients with a safe drug rather than watchful waiting since they would not only benefit from symptomatic relief of their depressive symptoms but also have a potential improvement in their cardiovascular risk profile *(Ballenger, 2001)*.

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)*. SSRI treatment also has been shown to significantly decrease depressive symptoms in coronary heart disease patients *(Pizzi, 2011)*.

The American Heart Association science advisory *(Lichtman, 2008)* suggests **sertraline and citalopram** as first-line drugs for patients with coronary heart disease. See "SSRIs and Other Antidepressants" and "Citalopram Warning" in the Pharmacotherapy section.

A recent meta-analysis showed that treatment with SSRIs after stroke in non-depressed patients significantly reduced the risk of development of a depressive episode after stroke (odds ratio [OR] of 0.34). In addition to this, it has been shown that an ongoing exercise program after stroke also significantly reduces depressive symptoms post-stroke *(Eng, 2014)*.

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

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 *(Petrak, 2013; Katon, 2004b)*.

Return to Table of Contents

Individuals with diabetes have two to threefold higher odds of depression than those without diabetes *(Jeeva, 2013)*. Additionally, depression earlier in life increases the risk of developing diabetes *(Katon, 2004a)*. Depressive symptom severity is associated with poor self care and medication compliance in addition to higher health care-related costs *(van Dijik, 2013)*. Patient physical and mental quality of life is also decreased *(Petrak, 2013)*.

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)*.

Treatment goals should focus on improvement of glycemic control and improvement or remission of depression via pharmacologic therapy, psychological therapy or combination of both *(Petrak, 2013)*.

For more information, see 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)*. 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.

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

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

Out of 31 million elderly Americans (65 years and older), nearly 5 million have clinical depression and 1 million have major depression *(Birrer, 2004)*. The rate of depression in adults older than 65 years of age treated in primary care settings ranges from 17 to 37% *(Birrer, 2004)* and is between 14 to 42% in patients who live in long-term care facilities *(Robinson, 2014)*. 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%), Alzheimer's disease (20 to 40%) and dementia (17 to 31%) *(Birrer, 2004)*. The recurrence rate is also extremely high at 40% *(Birrer, 2004)*.

Similar to other groups, the elderly with depression are more likely than younger patients to underreport depressive symptoms. Major depression in the elderly can present with combined clinical symptoms including depressed mood, somatic complaints and sleep disorders *(Chen, 2011)*. This incudes symptoms such as insomnia, headache, dizziness, 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.

Return to Table of Contents

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)*.

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)*. 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)*.

Pharmacotherapy and psychotherapy. Pharmacotherapy and psychotherapy are appropriate modalities to treat depression in the elderly *(Birrer, 2004)*. 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 *(Ganzini, 1997; Reynolds, 1992)*. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) do not have significant differences in efficacy; however, in the elderly, the better option for treatment may be SSRIs due to potential side effects of TCAs *(Kok, 2012)*. In those individuals who do not respond to the different antidepressants alone, augmentation therapies may be appropriate *(Nierenberg, 1996)*. This would include psychostimulants, such as cytomel or methylphenidate, or the addition of lithium *(Lavretsky, 2015; Cooper, 2011)*. Psychotherapy is also appropriate, limited only by cognitive impairments *(Cuijpers, 2008)*. Cognitive and/or behavioral therapy in particular can have a significant impact on major depression compared with other forms of non-pharmacological interventions such as interpersonal psychotherapy, psychodynamic therapy and physical exercise *(Pinquart, 2007)*.

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, 2007)*.

Maintenance therapy. With a recurrence risk of 50, 70 and 90% after the first three episodes respectively, once a patient reaches remission, data supports that continuing with antidepressants is effective regardless of patient age *(Kok, 2011; Birrer, 2004)*. After the first episode of major depression, therapy should be continued for at least one year after remission. The second and third episodes should be treated for at least two and three years after remission *(Birrer, 2004)*. Another study showed that maintenance therapy with an SSRI (paroxetine) 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 *(Reynolds, 2006)*. See also Annotation #7d, "If Patient is Not Improving on Initial Treatment, Utilize Stepped Care Approach," "Consider Other Strategies," for electroconvulsive treatment.

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)*. 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; Watson, 2009)*.

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; Green, 2003)*.

Pregnant and Postpartum Women

Recommendation	Quality of Evidence and Strength of Recommendation
Clinicians should screen and monitor depression in pregnant and post-partum women.	Quality of Evidence: Low Strength of Recommendation: Strong
Benefit: Untreated prenatal depression has been associated with negative pregnancy outcomes such as poor maternal self-care, poor nutrition, preterm labor and low birth weight, as well as negative effects on children such as developmental delay and cognitive impairment. There is low to moderate evidence that screening pregnant and post-partum women improves outcomes even in the absence of treatment protocols, care managers and specialty trained providers. The benefit is that by screening patients, one would be finding and treating many more patients with depression. **Harm:** The only harm identified is the cost of screening patients who are not depressed. **Benefit-Harms Assessment:** Although direct evidence of the isolated health benefit of depression screening in primary care is weak, the totality of the evidence supports the benefits of screening in pregnant and post-partum women, particularly in the presence of additional treatment supports such as treatment protocols, care management, and availability of specially trained depression care providers.	
Relevant Resources: *O'Connor, 2016; Yonkers, 2009; Vesga-López, 2008; Gjerdingen, 2007; Gaynes, 2005*	

Prevalence of depression during pregnancy can vary depending on how depression in pregnancy is defined. DSM-5 acknowledges depression during pregnancy (peripartum onset), which is consistent with recent publications that identify perinatal depression beginning at pregnancy onset or the first 12 months after birth. These periods previously referred to as antenatal depression and postpartum depression. A systematic review by Gaynes, 2005 suggests that between 14 and 23% of pregnant women and 10-15% of postpartum women will experience a depressive disorder *(Gaynes, 2005)*. A review by Milgrom, 2014 cites a point prevalence of 13% at three months after delivery and an average of 9% during each trimester of pregnancy *(Milgrom, 2014)*. According to a large-scale epidemiological study by Vesga-López, 2008, depression during the postpartum period may be more common than at other times in a woman's life *(Vesga-López, 2008)*.

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)*.

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 *(Milgrom, 2014; Davalos, 2012; Li, 2009)*. A 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)*. Studies are demonstrating that untreated paternal depression has an impact on infant and child development similar to untreated maternal depression *(Paulson, 2010)*.

Screening

Two key strategies facilitate early intervention: routine screening and monitoring of known risk factors *(O'Hara, 2014)*. Increased acceptability is found when patients are educated regarding routine screening *(Milgrom, 2014)*. A large scale study by Kaiser Permanente *(Dietz, 2007)* 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

Return to Table of Contents

- Stressful life events
- Fragmented or poor sleep
- Substance use
- Past or current abuse
- Premorbid or gestational diabetes
- Difficulty breastfeeding in the first two months postpartum

(Watkins, 2011; Coelho, 2011; Lancaster, 2010; Dørheim, 2009; Goyal, 2009; Pearlstein, 2008)

The United States Preventive Services Task Force 2016 recommendations for depression screening recommend that pregnant and postpartum women be screened for depression even in the absence of treatment protocols, care managers and specialty trained providers *(Siu, 2016)*.

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

Validated tools for screening pregnant and postpartum women. "Edinburgh Postnatal Depression Scale (EPDS)" and Patient Health Questionnaire (PHQ-2 or PHQ-9).

A 1987 validation study by Cox et al. that included 84 mothers showed that EPDS had satisfactory sensitivity and specificity, and was also sensitive to change in the severity of depression over time. The scale can be completed in about 5 minutes and has a simple method of scoring *(Cox, 1987)*.

PHQ-2 or PHQ-9 questionnaire can also be used to screen pregnant and postpartum women for depression. An observational study by Gjerdingen, 2009 that included 506 women to determine the validity of PHQ-2 and PHQ-9 for identifying postpartum depression during well child visits found that the two-question screen was highly sensitive and the PHQ-9 was highly specific for identifying postpartum depression. Both screens can be easily administered in primary care clinics *(Gjerdingen, 2009)*.

A study of 81 pregnant and 104 postpartum patients by Flynn et al. 2010 on comparative performance of EPDS and PHQ-9 in pregnant and postpartum women seeking psychiatric services for depression found few significant differences in the performance of the PHQ-9 and EPDS in detecting clinician-diagnosed MDD in a psychiatry outpatient sample of pregnant and postpartum women *(Flynn, 2011)*.

Treatment

Psychotherapies

Psychotherapeutic treatment recommendations for mild to moderate perinatal depression are interpersonal therapy (IPT) and cognitive behavioral therapy (CBT) *(Cuijpers, 2011a; Cuijpers, 2011b; O'Hara, 2000)*. 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, 2011a; Cuijpers, 2011b; O'Hara, 2009)*.

Pharmacotherapy

The recommendation for moderate to severe perinatal depression is antidepressant medication in combination with supportive interventions or psychotherapy *(Stewart, 2011)*. Since partial SSRI treatment during pregnancy does not successfully treat the depression, it is not a recommended option *(Wisner, 2009)*. Clinicians

Return to Table of Contents

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)*.

Light therapy and integrative medicine

There is promising preliminary evidence for bright light therapy, acupuncture, progressive relaxation, music therapy, reduced sleep deprivation, and exercise *(Pearlstein, 2008)*. Evidence for omega-3 fatty acids is still insufficient; however, they pose little to no risk *(Freeman, 2008)*.

Other

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)*.

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

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 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)*.

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; Mian, 2005; Sivojelezova, 2005)*.

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; Thormahlen, 2006)*.

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.

Factors to consider when choosing an antidepressant *(Ray, 2014)*.

- If there is a history of positive response to medication prior to pregnancy it is recommended to continue with the same medication. This includes effective antidepressants with unplanned pregnancies.

Return to Table of Contents

- Data is limited regarding new or improved medications in the peripartum period. Consider starting older medications if there is not a history of prior antidepressant use as more data is available for safety assessment and education.

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)*. 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; Austin, 2006; Oberlander, 2006; Sivojelezova, 2005)*.

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 undertreatment or no treatment of depression during pregnancy." (http://www.fda.gov/Drugs/DrugSafety/ucm283375.htm) *(Kieler, 2011; Austin, 2006; Bérard, 2007; Chambers, 2006)*.

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)*. If choosing to use antidepressant during breastfeeding, the same antidepressant during pregnancy should be maintained because evidence regarding risk with breastfeeding, excludes use of a different antidepressant during pregnancy *(Ray, 2014)*.

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.

SSRIs and Autism

A recently published observational study of 145,456 infants suggested the maternal use of SSRIs during the second and third trimester may increase the risk of autism spectrum disorders of their infants. The women using antidepressants were older and were more likely to have had a previous child with autism spectrum disorder. Women who used SSRIs during the first trimester or during the year prior to their pregnancy did not have an increased risk of ASD *(Boukhris, 2016)*. Additional research and evaluation of this risk is needed before definitive correlations can be made.

Return to Table of Contents

ICSI has long had a policy of transparency in declaring potential conflicting and competing interests of all individuals who participate in the development, revision and approval of ICSI guidelines and protocols.

In 2010, the ICSI Conflict of Interest Review Committee was established by the Board of Directors to review all disclosures and make recommendations to the board when steps should be taken to mitigate potential conflicts of interest, including recommendations regarding removal of work group members. This committee has adopted the Institute of Medicine Conflict of Interest standards as outlined in the report, Clinical Practice Guidelines We Can Trust (2011).

Where there are work group members with identified potential conflicts, these are disclosed and discussed at the initial work group meeting. These members are expected to recuse themselves from related discussions or authorship of related recommendations, as directed by the Conflict of Interest committee or requested by the work group.

The complete ICSI Policy regarding Conflicts of Interest is available at http://bit.ly/ICSICOI.

Funding Source

The Institute for Clinical Systems Improvement provided the funding for this guideline revision. ICSI is a not for profit, quality improvement organization based in Bloomington, Minnesota. ICSI's work is funded by the annual dues of the member medical groups and three sponsoring health plans in Minnesota. Individuals on the work group are not paid by ICSI, but are supported by their medical group for this work.

ICSI facilitates and coordinates the guideline development and revision process. ICSI, member medical groups and sponsoring health plans review and provide feedback, but do not have editorial control over the work group. All recommendations are based on the work group's independent evaluation of the evidence.

Return to Table of Contents

Disclosure of Potential Conflicts of Interest

Jeffrey Gursky, MD (Work Group Member)
Department Chair of Psychiatry and Psychology, Olmsted Medical Center
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Robert Haight, Pharm D, BCPP (Work Group Member)
Clinical Pharmacy Specialist, Psychiatry, Fairview Health Services
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: Paid expert testimony for the State of Minnesota. On request case, consulting for specific patient cases involving psychiatric medications to be reviewed by various departments.

Jeffrey Hardwig, MD (Work Group Member)
Psychiatrist, Essentia Health
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Todd Hinnenkamp, RN, NC (Work Group Member)
Nurse Clinician, Internal Medicine, Essentia Health
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Daniel Kessler, LP (Work Group Member)
Lead Psychologist, Allina Medical Clinic – Part of Allina Health
National, Regional, Local Committee Affiliations: Minnesota Psychological Association
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Nicki Mack, RN (Work Group Member)
Care Navigator, North Memorial Health Care
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Return to Table of Contents

Mioki Myszkowski, MD (Work Group Member)
Mayo Clinic
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Michael Trangle, MD (Work Group Leader)
Senior Medical Director for Behavioral Health Services, Psychiatry, HealthPartners Medical Group and Regions Hospital
National, Regional, Local Committee Affiliations: None
Guideline Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Return to Table of Contents

ICSI seeks review from members and the public during the revision process.

Member Review

All ICSI documents are available for member review at two points in the ICSI revision process. The ICSI Response Report is sent to members at the beginning of a document revision. The goal of this report is to solicit feedback about the guideline, including but not limited to the algorithm, content, recommendations and implementation. Members are also welcome to participate in the public comment period (see below).

The work group would like to thank the following organizations for participating in the Adult Depression in Primary Care pre-revision review:

- *Fairview Health Services*
- *HealthPartners Health Plan*
- *Mayo Clinic*

Public Comment

ICSI makes a draft of the guideline available to the public on the ICSI website. The public is invited to comment in an effort to get feedback prior to its finalization. All comments will be reviewed by the ICSI facilitator and work group members when needed. ICSI work group may or may not make changes to the guideline based on public comment responses.

The work group would like to thank all those who took time to thoughtfully and thoroughly review our draft and submitted comments for the Adult Depression in Primary Care guideline.

Invited Reviews

For some guidelines, ICSI will invite experts in the community to comment on a guideline draft prior to finalization. This is done during the public comment period.

No invited review was done for the depression guideline.

ICSI Patient Advisory Council (PAC)

The ICSI Patient Advisory Council responds to any guideline review requests put forth by ICSI facilitators and work groups. The PAC members may be involved at the beginning, middle, and/or end of the revision process. Patient advisors who serve on the council consistently share their experiences and perspectives in either a comprehensive or partial review of a document.

The ICSI Patient Advisory Council did not review the Adult Depression in Primary Care guideline.

Return to Table of Contents

ICSI
Institute for Clinical Systems Improvement

Document History and Development:
Adult Depression in Primary Care

Document Drafted
May – Jul 1995

First Edition
Jan 1996

Second Edition
Feb 1997

Third Edition
Apr 1998

Fourth Edition
Apr 1999

Fifth Edition
June 2001

Sixth Edition
June 2002

Seventh Edition
Oct 2003

Eighth Edition
June 2004

Ninth Edition
Jun 2006

Tenth Edition
Jun 2007

Eleventh Edition
Jun 2008

Twelfth Edition
Jun 2009

Thirteenth Edition
Jun 2010

Fourteenth Edition
Jun 2011

Fifteenth Edition
Jun 2012

Sixteenth Edition
Oct 2013

Seventeenth Edition
Begins March 2016

Original Work Group Members

David J. Abelson, MD
Work Group Leader
Park Nicollet Clinic

Richard Anderson, MD
Mental Health
HealthPartners

Larry Berger, MD
Mental Health
Park Nicollet Clinic

Nancy Bologna, PhD, MS, LP
Mental Health
Park Nicollet Clinic

Nancy R. Cohen, MD
Mental Health
Group Health, Inc.

Barry Cosens, MD
Mental Health
Park Nicollet Clinic

Susan Czapiewski, MD
Mental Health
Park Nicollet Clinic

Sandy Dahl
Business Health Care Action Group
Honeywell, Inc.

Laura Ellis, RN
Health Education
HealthPartners

Susan E. Erikson, LPN
Internal Medicine
Park Nicollet Clinic

Gary Goldetsky, PsyD
Health Psychology
HealthPartners

Ed Gould, MD
Family Practice
Maple Grove Medical Center

Mary Pat Hanauska, RN
Internal Medicine
Park Nicollet Clinic

Kate Harri
Business Health Care Action Group
Norwest

Lakhbir Kang, MD
Family Practice
HealthPartners

Jeanette Kiefert, MD
Family Practice
North Suburban Family Physicians

Dave Knutson
Measurement Advisor
Park Nicollet Medical Foundation

Eric W. Larson, MD
Mental Health
Mayo Clinic/Park Nicollet Clinic

Steve Lucas, MD
Family Practice
HealthPartners

Mark Mellstrom, MD
Family Practice
Family Physicians of Northfield

Robert Nesse, MD
Family Practice
Mayo Clinic

Teresa Rummans, MD
Mental Health
Mayo Clinic

Catherine Spurr, RN
Facilitator
Park Nicollet Clinic

Kathy Van Guilder
Health Education
Park Nicollet Medical Foundation

David von Weiss, MD
Family Practice
Park Nicollet Clinic

Steve Wetzell
Business Health Care Action Group
BHCAG

Thomas E. Will, PsyD, MPH, LP
Health Psychology
Group Health, Inc.

Document History

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.

The next revision will be no later than March 2021.

This document is celebrating its 20th anniversary of the first edition.

Return to Table of Contents

Contact ICSI at:
8009 34th Avenue South, Suite 1200; Bloomington, MN 55425; (952) 814-7060; (952) 858-9675 (fax)
Online at http://www.ICSI.org

ICSI Document Development and Revision Process

Overview

Since 1993, the Institute for Clinical Systems Improvement (ICSI) has developed more than 60 evidence-based health care documents that support best practices for the prevention, diagnosis, treatment or management of a given symptom, disease or condition for patients.

Audience and Intended Use

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 and implementation strategies. 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 that have been formally evaluated and tested. Measures are included that 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 as indicated by changes in clinical practice and literature. ICSI staff monitors major peer-reviewed journals for any pertinent evidence that would affect a particular guideline and recommendation.

Return to Table of Contents