Treatment of Patients With Major Depressive Disorder from the American Psychiatric Association (APA) that was amended by the following Guideline Watch from the APA, October 2010.

These guidelines were based in part on the following:
http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf

Practice Parameter for the Assessment and Treatment of Children and Adolescents With Depressive Disorders from the American Academy of Child and Adolescent Psychiatry, June 2007:
https://jaacap.org/article/S0890-8567(22)01852-4/abstract

The practice guidelines included in this document are not intended to be required treatment protocols. Physicians and other health professionals must rely on their own expertise in evaluating and treating patients. Practice guidelines are not a substitute for the best professional judgment of physicians and other health professionals. Behavioral health guidelines may include commentary developed by the Company's behavioral health committees. Further, while authoritative sources are consulted in the development of these guidelines, the practice guideline may differ in some respects from the sources cited. With respect to the issue of coverage, each individual should review his/her Policy or Certificate and Schedule of Benefits for details concerning benefits, procedures and exclusions prior to receiving treatment. The practice guidelines do not supersede the Policy or Certificate and Schedule of Benefits.

Summary

Wellpoint considers professional society guidance when implementing guidelines. The American Psychiatric Association Depression guideline was last updated in 2010. Any future revisions will receive timely consideration with the intent of capturing the most current approach to the diagnosis and management of depression.

Wellpoint has summarized some of the more recent findings until the guidelines are updated. Wellpoint also relies on guidance in the 2007 American Academy of Child and Adolescent Psychiatry Practice Parameter on Depression in Children and Adolescents.

Rationale

Depressive disorders are highly prevalent illnesses that affect about 10% of the US adult population annually.[1] According to the *National Co-morbidity Survey*, the lifetime prevalence of major depression is 17.1% in the general population.[2] Episodes of major depression are about twice as common among women as men and impact all age groups.[3, 4] The direct costs to society for untreated and undertreated depressive disorders are estimated to approach $44 billion.[5]

The degree of disability arising from depressive disorders is comparable to other chronic conditions such as hypertension, diabetes, and arthritis.[6] Research supports an association with morbidity and mortality for certain medical diagnoses and co-morbid depression. For example, depression has been identified as an independent major risk factor for the development of several serious medical conditions, including cardiovascular disease, myocardial infarction, diabetes, and immune response.[7] A large body of evidence exists that demonstrates that the treatment of depression in conjunction with medical disorders decreases both the degree of human suffering and improves the clinical outcome of the co-morbid medical illness.

Research in the last decade found that in primary care settings, approximately one-third of patients with major depressive disorder (MDD) are diagnosed, and of those identified, only half are treated by behavioral health care providers. For this reason, systematic screening for depression has been advocated and numerous initiatives have been developed for this purpose. With the changing conceptualization of depression as a primary care disorder, treatment guidelines that can be followed by both primary care providers and specialists have emerged.

Identification

Screening for MDD can take place as part of a complete history, or in the more restrictive setting of a brief office visit. Primary care physicians should have a high index of suspicion regarding MDD in those patients who present with the following:

- Somatic complaints where no organic basis can be found
- Failure to respond to several trials of appropriate medications for somatic complaints
- Complaints of insomnia, unexpected weight change, or fatigue in the absence of a clear medical cause
- Symptoms of sadness, irritability, apathy, or sexual complaints

Particular attention should also be paid to members of the following risk groups:

- Co-existing chronic illness (for example, diabetes, thyroid disorders, congestive heart failure, post-stroke, or post-MI)
- Women who have given birth within the last 12 months
- Those over the age of 65
- Active or remitted history of substance abuse/dependence
- Prior history of depressive episodes or family history of psychiatric disorders
- Prior history of suicidal ideation/attempt

Screening

The U.S. Preventative Services Task Force recently updated their prior recommendation for primary care physicians to remain alert for depressive disorders and now encourages formal screenings of all adult patients.[8] Early detection and treatment may reduce the psychological complications of untreated mental disorders. The panel found that the routine administration of the following two questions is as effective as using longer screening instruments:

1. Over the past two weeks, have you ever felt down, depressed, or hopeless?
2. Have you felt little interest or pleasure in doing things?

The use of supplemental screening instruments with a high degree of specificity should be considered for patients who screen positive on either question or patients in high-risk groups for MDD. The *Patient Health Questionnaire-9 (PHQ-9)* is a brief, easy-to-use screen. Other instruments include the *Beck Depression Inventory (BDI)*, the *Beck Depression Inventory – Fast Screen for Medical Patients (BDI-Fast Screen)*, the *Hamilton Depression Rating Scale (HAMD)*, the *Zung Depression Scale (Zung)*, and the *Hospital Anxiety and Depression Scale (HADS)*. As yet, no laboratory findings have been identified that are diagnostic of MDD. Information on where to obtain these instruments is available in the Reference section.

Diagnostic criteria

Five (or more) of the following diagnostic criteria[3] must be present during the same two-week period and represent a change from previous functioning; at least one of the criteria is either (1) depressed mood or (2) loss of interest or pleasure:

1. Depressed mood most of the day, nearly every day, as indicated by subjective report or observation. **Note:** In children and adolescents, it can be an irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities.
3. Significant weight loss when not dieting, weight gain (for example, a change of more than five percent of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
4. Insomnia or hypersomnia nearly every day (insomnia includes early morning awakening, as well as difficulty falling asleep)
5. Psychomotor agitation or retardation nearly every day (includes nervousness, increased anxiety, and in its dramatic forms, hand-wringing or sitting in a chair staring off into space for hours at a time).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or self-recrimination (which may reach delusional proportions).
8. Diminished ability to think or concentrate (patients will often subjectively experience this symptom as difficulty with their memory).

9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Exclusions to the diagnosis of major depressive disorder:

1. The symptoms are not due to the direct physiological effects of a substance (for example, a drug of abuse or a medication) or a general medical condition (for example, hypothyroidism).
2. The symptoms are not accounted for by the death of a loved one (normal bereavement) within the last two months.

Patients with bipolar disorder (manic depressive disorder) should be differentiated from patients with MDD by a history of a manic or hypomanic episode. Symptoms of mania include abnormally elevated or irritable mood, inflated self-esteem, decreased need for sleep, rapid speech and thoughts, distractibility and agitation, and excessive involvement in pleasurable activities with a high potential for negative consequences such as gambling, buying sprees, and sexual indiscretions. Identification must be based on historical information since their clinical presentation may look the same as MDD. It is important to note that these patients should not be treated with an antidepressant alone as this may lead to a manic episode. The complexity of these patients generally warrants a referral to a specialist.

Refer to *Clinical Practice Guidelines for the Evaluation and Treatment of Bipolar Disorder* for additional information.

Treatment

Treatment may be initiated on an outpatient basis by the primary care physician in the adult patient who is not suicidal. It is recommended that MDD patients with psychotic depression or a well-documented history of bipolar disorder should be referred to a specialist as their treatment is more complicated to manage. Patients with substance use disorders should have concurrent treatment for both disorders and should be referred to a dual diagnosis (substance use disorder and mental health disorder) treatment program or care provider. Adolescents with depression can be treated in a primary care setting, and a new Practice Guideline is available as a resource.

The results of the *Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study*, the largest and longest study ever conducted to evaluate depression treatment for adults in primary and specialty care settings, provide the basis for the most up-to-date rational approaches to treatment of MDD, but these findings have been incorporated into only one formal Practice Guideline so far (ICSI — see resources), and one set of medication algorithms (TMAP), so a brief summary of key findings is included below.[9-14] One of the references included is a more detailed summary of the implications of STAR*D for primary care.[14]

STAR*D follows a system called measurement-based care, which requires consistent use of easily administered measurement tools at each visit. The use of these tools has been found to be practical in both primary care and psychiatric settings. The authors of the primary care summary cited above[14] stated that the use of this approach likely accounts for the improved outcome over usual care. Systematic measuring of symptoms allows for a sharpened and

more refined evaluation of illness severity, treatment response, and timing of interventions. Several brief rating scales for depression have been published that are useful for this purpose and are referenced at the end of this document.

In the STAR*D trial, half of the patients with MDD became symptom-free after trying either one selective serotonin reuptake inhibitor (SSRI) antidepressant or if unsuccessful, trying a different one or a combination of an SSRI plus bupropion.

More specifically, a single SSRI antidepressant used for 12 to 14 weeks resulted in remission for one in three people, and half of this group reached remission after six weeks of treatment. For the two-thirds who did not reach remission, switching to a different antidepressant resulted in an additional one in four gaining remission, and adding bupropion to the SSRI resulted in an additional one in three gaining remission. The study found no difference between switching to a different SSRI, bupropion, or venlafaxine if the first SSRI did not work. The study found that adding bupropion as the combined drug worked better than adding buspirone, which was the other combination choice for the second level of treatment.

For those who did not reach remission at the first two levels, patients could either switch to try a different class of antidepressants, either mirtazapine or nortriptyline, or they could stay with what they were already on and combine with either triiodothyronine or lithium. The results showed that both approaches resulted in an additional 12% to 20% of patients reaching remission, with either switch medication having equal benefits, and either combination medication working, although T3 had fewer adverse effects than lithium.

Finally, a fourth level for those who failed at the first three offered either a combination of venlafaxine and mirtazapine or a trial of tranylcypromine, a monoamine oxidase (MAO) inhibitor, and an additional 7% to 10% of patients reached remission.

Cognitive therapy for 16 weeks was also offered both as an augmentation to the SSRI and as a switch alternative at the second level of the STAR*D trial, and the results showed that the remission rates were equivalent to both of the medication alternatives, except that a longer time was required for cognitive therapy. The withdrawal rate was also high and only 25% completed the full 16 weeks. Discussions among experts that followed the publication of the results suggested that better results may have been obtained if the trial of therapy had been longer as is customary, and also that therapy done at select study sites where there was more expertise with this method of therapy had better results.

A similar clinical effectiveness study was recently published for adolescents in 2004, the *Treatment for Adolescents With Depression Study (TADS)*, which provided the basis for current recommendations, including the *AACAP Practice Parameter for Depression in Children and Adolescents* released in 2007.[15] In general, either an SSRI antidepressant or cognitive-behavioral therapy (CBT) or the combination resulted in remission in about one-third of cases, and improvement in approximately 70%. A more recent clinical effectiveness study of the treatment of depression in adolescents who did not respond to an SSRI was published after this Guideline, in February 2008, and the findings of this study will be summarized below as they are likely to inform future revisions of the practice guideline.[16]

After a two-month trial of an SSRI, adolescents with depression who did not achieve response (improvement) were treated with one of four options for 12 weeks: a different SSRI antidepressant, a different SSRI plus CBT, venlafaxine, or venlafaxine plus CBT. The results showed that the addition of CBT resulted in a significantly higher response rate with either medication and that the venlafaxine was not more effective than any of the SSRIs compared, but did have more adverse effects.

The author concluded that for adolescents who have been treated with an SSRI alone and have not had a response to treatment, a switch to another SSRI should be augmented with CBT rather than medication alone.

Practice guidelines recommend treating severe depression with either medication and psychotherapy or medication followed by psychotherapy, and treating moderate depression with either medication, psychotherapy, or both.

The following medication algorithms released in 2008 include the results of STAR*D and other recent findings regarding treatment effectiveness for depression:
https://jpshealthnet.org/sites/default/files/inline-files/tmap_depression_2010.pdf

The following practice guidelines from 2008 are specifically written for primary care and include STAR*D results:
https://icsi.org/guidelines_and_more/depression__major__in_adults_in_primary_care_4/

SSRIs are the most widely prescribed class of medications for the treatment of MDD. SSRIs, which became available in the late 1980s, are as efficacious as the tricyclic antidepressants (TCAs)[17,18] and tend to have more benign side effect profiles. They may be particularly preferred for patients with pre-existing cardiovascular problems[19] and carry a reduced risk of overdose as compared to TCAs. The most prominent side effects of SSRIs are headaches, GI distress, agitation, and weight gain. A significant incidence of sexual dysfunction occurs with SSRIs and occurs in at least 25% of patients. Also, see the notice of the FDA warning regarding antidepressants listed below.

Bupropion and the serotonin-norepinephrine reuptake inhibitor (SNRI) are other novel antidepressants that are efficacious in treating MDD.[20,21] MAOIs are also effective for the treatment of depression but require special attention to potential adverse drug and food interactions.

TCAs, which have been around since the late 1950s, are still efficacious.[22,23] Potential adverse effects include significant changes in cardiac conduction, orthostatic hypotension, dry mouth, and urinary retention. Second-generation tricyclic and heterocyclic drugs have been developed which are generally less toxic and have modified side effect profiles. All tricyclics need to be titrated slowly to an effective dose to minimize side effects. They are more lethal in overdose.

Regardless of the anti-depressant chosen, there are some general principles that apply to all prescribing situations:

- Primary care physicians should foster a therapeutic alliance between themselves and the MDD patient.
- Patients who are newly started on antidepressant medication should be seen frequently at the beginning of treatment to encourage compliance and to assess for response and side effects. It is recommended that a patient receive at least three follow-up visits within the first 12 weeks after starting an antidepressant. The first month of treatment with antidepressant medications is the time of the highest risk of dropout by the patient. Support during this time is crucial.
- **An FDA Black Box Warning states that antidepressants may increase the risk of suicidal thinking and behavior (suicidality) in adults and pediatric patients with MDD and other psychiatric disorders. Anyone considering the use of antidepressants must balance this risk with the clinical need. Healthcare providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases. Although the FDA has not concluded that these drugs cause worsening depression or suicidality, healthcare providers should be aware that the worsening of symptoms could be due to the underlying disease or might be a result of drug therapy.**
- Patients should be reassured that their depression often has a biological component that is generally quite responsive to medication and/or psychotherapy. Anti-depressants need time (two to six weeks) to work.
- Patients should be educated about the mechanism of action of medications, including expectations of side effects and expected time for response.
- A therapeutic trial should not be considered a treatment failure until the patient has either been on the maximum tolerable dose, or therapeutic blood level when indicated for the drug, for six weeks with no benefit, or 12 weeks with only partial benefit. Severe or intolerable side effects should also be considered a treatment failure, and patients should be switched to different medications.
- Patients who respond positively should be maintained on that anti-depressant for approximately 12 months.
- Consideration should be given to maintenance anti-depressant treatment in those MDD patients who have had multiple (three or more) episodes within 10 years.
- Psychotherapy can be useful, either alone or as an adjunct, to anti-depressant treatment. Patients receiving psychotherapy in combination with medications have been found to have the highest degree of treatment success.

Referral to a psychiatrist for electroconvulsive therapy (ECT) should be considered with patients whose depression is severe or life-threatening, those who cannot take anti-depressant medications 24, and those who do not obtain symptom relief after a thorough trial of medications. Even though ECT is undoubtedly the most misunderstood and stigmatized of all treatment approaches, 80% to 90% of patients with severe depression improve dramatically following a course of ECT treatments.[25] Advances in recent years with ECT techniques have helped to make this treatment a safe approach with fewer side effects and improved outcomes.

Specialist referral criteria

Although many patients with depressive symptoms can be successfully treated within a primary care setting, the physician must consider the type, complexity, and severity of the symptomology as well as their own comfort level when determining if a referral to a specialist is required. Clinical consultation or referral to a specialist should be considered in the following situations:

- Psychiatrists:
  - Patients who have completed one or two trials of antidepressant treatments at an appropriate dose and duration without significant improvement in symptoms
  - Patients with current or prior history of psychosis or risk of harm to self or others
  - Patients with bipolar disorder often require complex medical management, especially depressed bipolar patients or those experiencing a decompensation
  - Patients with co-morbid substance use disorder, severe personality disorders, or anxiety disorders who require complex therapeutic management of all issues
- Therapist:
  - Psychotherapy has comparable efficacy as medications for patients with mild to moderate depression. Therapy in combination with medications is the optimal treatment for patients with severe depression.

Primary care physicians are encouraged to recommend and directly refer to any contracted behavioral healthcare provider with whom they are already familiar. A list of participating psychiatrists and psychotherapists is available on the plan's internet site or by contacting Provider Services at 833-476-1457.

Behavioral health treatment coordination

Wellpoint strongly supports efforts directed at the coordination of care between all professionals involved in providing treatment to a member. Communication between the various disciplines is essential to avoid conflicting treatment plans, eliminate duplicated efforts, and decrease the risk of medication errors. This type of dialogue is especially important between the primary care physician, psychiatrist, and/or therapist when treatment is being provided for a behavioral health issue.

Toward that end, we ask that all practitioners take an active role in coordinating behavioral health treatment by requesting authorization, ensuring that communication occurs, and then documenting the results. Primary care physicians are encouraged to communicate the rationale and any relevant medical information when a member is referred to a psychiatrist or therapist. Likewise, psychiatrists and other behavioral health specialists are encouraged to establish an ongoing dialogue with primary care physicians.

References:

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Where to obtain depression screening instruments

PHQ-9: The MacArthur Initiative on Depression and Primary Care:

- https://macfound.org/programs/pastwork/research-networks/initiative-on-depression-primary-care

PHQ-9 screening in English and Spanish:

- https://med.stanford.edu/content/dam/sm/ppc/documents/DBP/PHQ-9_bilingual.pdf

Montgomery and Asberg Depression Rating Scale:

- https://psychology-tools.com/test/montgomery-asberg-depression-rating-scale

Zung: Mental Health Source:

- 800-456-3003
- https://integrationacademy.ahrq.gov/sites/default/files/2020-07/Zung_Self_Rating_Depression_Scale.pdf

HAMD: Mental Health Source:

- 800-456-3003
- https://apa.org/depression-guideline/hamilton-rating-scale.pdf

Quick Inventory of Depressive Symptoms (QIDS):

- http://ids-qids.org/

Men and Mental Health:

- https://nimh.nih.gov/health/topics/men-and-mental-health

Male Depression Risk Scale (MDRS-22):

- https://solidaritycoach.com/wp-content/uploads/2021/11/MDRS-22-Handout.pdf

ICSI Guideline for Major Depression in Adults in Primary Care:

- https://icsi.org/guidelines_and_more/depression__major__in_adults_in_primary_care_4/