

INITIAL TREATMENT FOR MAJOR DEPRESSIVE DISORDER

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SPEAKER DISCLOSURES

✓ No conflicts of interest



OBJECTIVES

- 1. Review the diagnosis of Major Depressive Episodes.
- 2. Identify initial treatments for Major Depressive Episodes.
- 3. Discuss when you would not prescribe antidepressants.
- 4. Highlight essential prescribing practices for antidepressants for people with MDD.



DSM-5 MAJOR DEPRESSIVE EPISODE

- A. 5 (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
 - Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful). (NOTE: In children and adolescents, can be irritable mood.)
 - 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).
 - Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.)
 - Insomnia or hypersomnia nearly every day.
 - Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
 - Fatigue or loss of energy nearly every day.
 - Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
 - Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others).
 - 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 cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition.



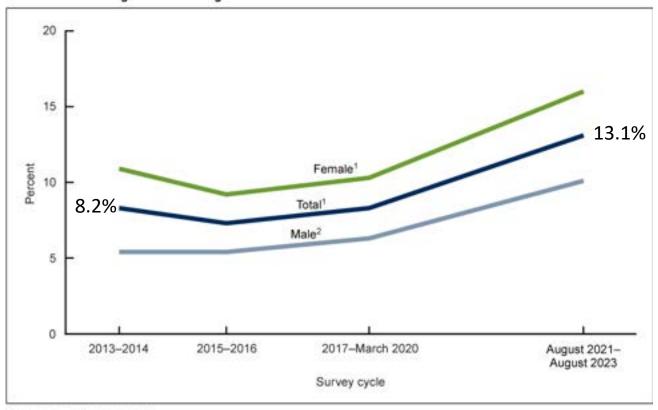
OTHER CAUSES OF DEPRESSIVE SYMPTOMS

- Persistent depressive disorder
- Premenstrual dysphoric disorder
- Substance induced depressive disorder
- PTSD
- Seasonal Affective Disorder
- Depressive disorder due to a medical condition (ex: sleep apnea, thyroid, anemia, hormonal changes, dementia)
- Adjustment disorder
- Bipolar Disorder
 - The majority of presentations of bipolar disorder to primary care are depressive phase!
 - Need to rule out bipolar disorder as most antidepressants do not work for BPD or make it worse, trigger hypo/mania



WHAT IS THE PREVALENCE OF MAJOR DEPRESSION EPISODE IN US?

Figure 3. Trends in depression prevalence in people age 12 and older, by sex: United States, 2013–2014 to August 2021–August 2023



^{*}Increasing quadratic trend (p < 0.05).

https://www.nimh.nih.gov/health/statistics/major-depression Products - Data Briefs - Number 527 - April 2025



^{*}Increasing linear trend (p < 0.05).

NOTE: Depression is defined as a score greater than or equal to 10 on the Patient Health Questionnaire.

SOURCE: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2013–2014 through August 2021–August 2023.

IMPACT OF DEPRESSION

- 8-fold increase in risk of suicide
- Only 18% of people with significant depressive symptoms experience a 50% reduction in symptoms after 6 months.

MoitraM, SantomauroD, DegenhardtL, et al. Estimating the risk of suicide associated with mental disorders: a systematic review and meta-regression analysis. J Psychiatr Res. 2021;137: 242-249. doi:10.1016/j.jpsychires.2021.02.053



DEPRESSION IN PRIMARY CARE?

- Epidemiology:
 - Primary care: 5% to 25% of patients with depressive sxs
 - 60% of people with depression don't get treatment
 - if they do, up to 50% get treatment in primary care!



SCREENING

- USPSTF, AAFP: universal, if adequate mgmt and follow up in place
- Screening tools:
 - Depression: PHQ-2 vs PHQ9
 - Substances: AUDIT C and Single Item Screener, CUDIT-r
 - Perinatal: Edinburgh Postnatal Depression Scale or PHQ-9 in pregnant/postpartum people
 - Bipolar Disorder: CIDI to rule out bipolar disorder (MDQ less specific)
 - Labwork: TSH, CBC, B12, Vit D, folate, BMP
 - Sleep apnea: STOP-BANG, sleep study
- **Suicide risk screening**: PHQ-9, VA Algorithm, Columbia (CSSRS), SAFE-T card (https://sprc.org/settings/primary-care/toolkit/)
 - All Patient's Safe: Basic, Advanced, Firearm risk: https://www.apsafe.uw.edu/



MAJOR DEPRESSION TREATMENTS 101



DO ANTIDEPRESSANTS WORK FOR: MAJOR DEPRESSIVE DISORDERS?

- Yes
 - SSRIs generally offer the best balance between effects and side effects
- Slightly more effective: escitalopram, mirtazapine, venlafaxine, vortioxetine

Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018 Apr 7;391(10128):1357-1366. doi: 10.1016/S0140-6736(17)32802-7. Epub 2018 Feb 21. PMID: 29477251; PMCID: PMC5889788.

DO ANTIDEPRESSANTS ONLY WORK FOR: SEVERE DEPRESSION?

- No
 - they work in mild to severe depression to the same degree
 - In mild symptoms therapy alone is reasonable

Thase ME, Greenhouse JB, Frank E, Reynolds CF 3rd, Pilkonis PA, Hurley K, Grochocinski V, Kupfer DJ. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. Arch Gen Psychiatry. 1997 Nov;54(11):1009-15. doi: 10.1001/archpsyc.1997.01830230043006. PMID: 9366657.



HOW FAST CAN ANTIDEPRESSANTS WORK?

- 1-4 weeks
- Change dose every 2-4 weeks

Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. Arch Gen Psychiatry. 2006 Nov;63(11):1217-23. doi: 10.1001/archpsyc.63.11.1217. PMID: 17088502; PMCID: PMC2211759.

Lam RW. Onset, time course and trajectories of improvement with antidepressants. Eur Neuropsychopharmacol. 2012;22 Suppl 3:S492-8. doi: 10.1016/j.euroneuro.2012.07.005. PMID: 22959114.

HOW LONG SHOULD I WAIT BEFORE CHANGING MEDS?

- 6-12 weeks
 - Potentially sooner if no response

Rush AJ. STAR*D: what have we learned? Am J Psychiatry. 2007 Feb;164(2):201-4. doi: 10.1176/ajp.2007.164.2.201. PMID: 17267779. Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. Arch Gen Psychiatry. 2006 Nov;63(11):1217-23. doi: 10.1001/archpsyc.63.11.1217. PMID: 17088502; PMCID: PMC2211759.



ARE THERE THINGS TO DO TO MAKE ANTIDEPRESSANTS WORK BETTER?

- See patients frequently at the beginning of treatment (1-4 weeks)
 - Monitor response: PHQ9
- Start low and titrate as needed
 - − 1/3 to ½ of usual dose
- Provide education about the illness and treatments
- Build therapeutic alliance
 - Be curious
 - Validate
 - Listen



MEASUREMENT BASED CARE

Why?

- Help Improve Patient Outcomes
 - Clinical judgement alone is not always enough
 - Enhanced precision and effectiveness
 - Help overcome clinical inertia
 - Provide providers monitor clinical effectiveness
 - Allow systems the ability to monitor effectiveness
 - Help streamline assessments
- Increase in remission
 - 53% remission with measure vs 43 % without



CHOOSING AN ANTIDEPRESSANT

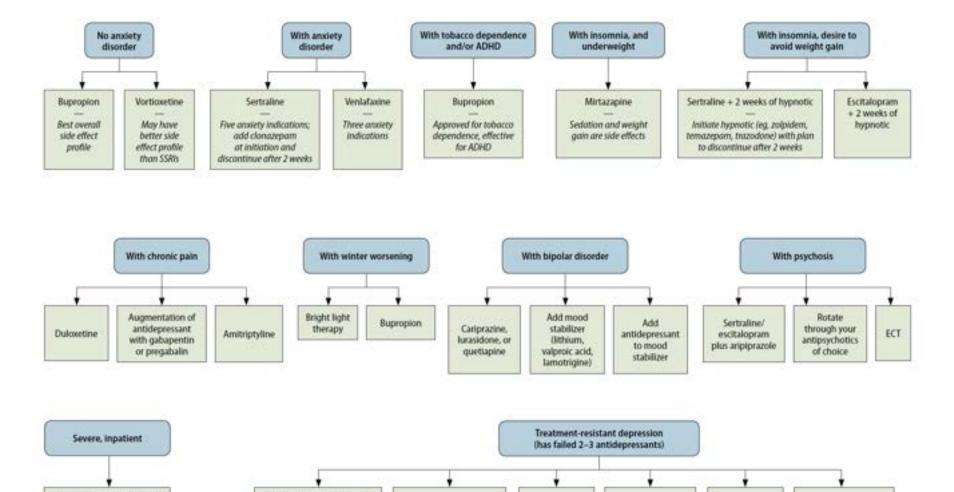
- Anticipated side effects
- Pharmacologic properties (half-life, med interactions)
- Past response to med
- Family history of response
- Depressive symptoms
- Comorbid illnesses

Use an antidepressant selection tool if needed!

- UpToDate
- Mayo



TREATMENT ALGORITHM: Depression



Augment antidepressant

with bupropion/lithium

Esketamine nasal or

ketamine infusion

MAOI (usually

tranylcypromine)

ECT

Switch to SNRI

Tricyclic-amitriptyline/

nortriptyline

Augment antidepressant

with aripiprazole

Most double-blind evidence of all augmenters

PHARMACOGENETIC TESTING?

JAMA

QUESTION Does provision of pharmacogenomic testing for drug-gene interactions affect selection of antidepressant medication and response of depressive symptoms in patients with major depressive disorder (MDD)?

CONCLUSION This clinical trial found that in patients with MDD, pharmacogenomic testing for drug-gene interactions vs usual care reduced prescription of medications with predicted drug-gene interactions and had small and nonpersistent effects on remission of depressive symptoms.

POPULATION

1453 Men 491 Women



Adults with MDD who were initiating or switching treatment with a single antidepressant

Mean age: 48 years

LOCATIONS

Veterans Affairs medical centers in the US

INTERVENTION



Pharmacogenomic guided

Results from a commercial pharmacogenomic test were given to clinicians

Usual care

Usual care and access to pharmacogenomic results after 24 weeks

OUTCOMES

Proportion of prescriptions with a predicted drug-gene interaction written in the 30 days after randomization and remission of depressive symptoms measured by the Patient Health Questionnaire-9

FINDINGS

Estimated risks of drug-gene interactions

Pharmacogenomic guided

None, 59.3% | Moderate, 30.0% | Substantial, 10.7%

Usual care

None, 25.7% | Moderate, 54.6% | Substantial, 19.7%

Estimated difference:

For none, 33.6% (95% CI, 28.9% to 38.4%)

For moderate, -24.6% (95% CI, -29.5% to -19.7%)

For substantial, -9.0% (95% CI, -12.7% to -5.3%)

Higher symptom remission rates over 24 weeks for intervention vs usual care:

Odds ratio, 1.28 (95% CI, 1.05 to 1.57)

Risk difference, 2.8% (95% CI, 0.6% to 5.1%)

Oslin DW, et al; PRIME Care Research Group. Effect of pharmacogenomic testing for drug-gene interactions on medication adherence on medication selection and remission of symptoms in major depressive disorder: the PRIME Care randomized clinical trial. JAMA. Published July 12, 2022. doi:10.1001/jama.2022.9805



O AMA

DOES THERAPY WORK FOR: MAJOR DEPRESSIVE DISORDERS?

- Yes
- And results may persist after acute course of treatment ends

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 Oct;78(5):668-80. doi: 10.1037/a0020570. PMID: 20873902.

DOES THERAPY WORK ONLY FOR: SEVERE DEPRESSION?

No, it can work for the range of severity

Farah WH, Alsawas M, Mainou M, Alahdab F, Farah MH, Ahmed AT, Mohamed EA, Almasri J, Gionfriddo MR, Castaneda-Guarderas A, Mohammed K, Wang Z, Asi N, Sawchuk CN, Williams MD, Prokop LJ, Murad MH, LeBlanc A. Non-pharmacological treatment of depression: a systematic review and evidence map. Evid Based Med. 2016 Dec;21(6):214-221. doi: 10.1136/ebmed-2016-110522. Epub 2016 Nov 11. PMID: 27836921.

IS COMBINATION MEDS AND THERAPY THE BEST?

Yes (but the effect size is small)



THERAPY FOR MAJOR DEPRESSIVE EPISODES

 Also behavioral activation, problem solving therapy SIDEBAR 3

EMPIRICALLY SUPPORTED TREATMENT RECOMMENDATIONS

- Recommend behavioral therapy, cognitive therapy, cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), mindfulness-based cognitive therapy, psychodynamic therapy, or supportive therapy.
- Recommend second-generation antidepressant medications (ADMs).
- If considering combined treatment,
 recommend CBT or IPT plus a secondgeneration ADM.

To view the full set of recommendations, including conditional recommendations and recommendations against treatments, please refer to <u>Table 3</u> of the full guideline document.



WHEN WOULD YOU RECOMMEND AN ANTIDEPRESSANT FOR FIRST TIME DEPRESSIVE SYMPTOMS?

- A. For a PHQ9>20, irrespective of cause
- B. For a mild major depressive episode (per DSM5)
- C. For a **moderate or severe** major depressive episode (per DSM5)
- **D.** Any level of severity of a major depressive episode
- E. I would always refer to therapy first



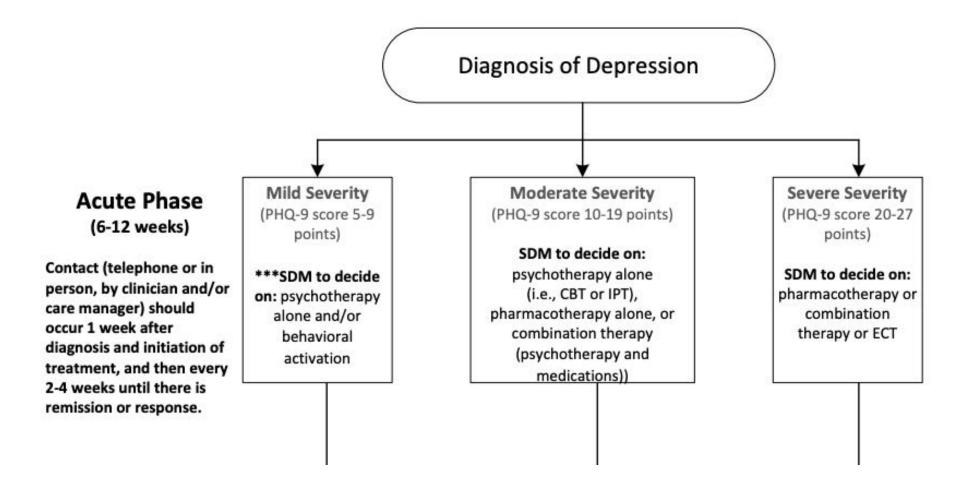
TREATMENT GUIDELINES REVIEW

- Veterans Affairs
- Dartmouth
- UK NICE

Common Theme: Shared Decision Making



APPENDIX 2: Depression Treatment in Adults Algorithm



Dartmouth: https://www.dartmouth-hitchcock.org/sites/default/files/2021-02/depression-clinical-practice-guideline.pdf

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2022 UK NICE TREATMENT GUIDELINES

Less Severe Depression

VS

More Severe Depression

- Less Severe Depression
 - -PHQ < 16

- More Severe Depression
 - -PHQ > 16

https://www.nice.org.uk/guidance/ng222/chapter/recommendations #less-severe-depression



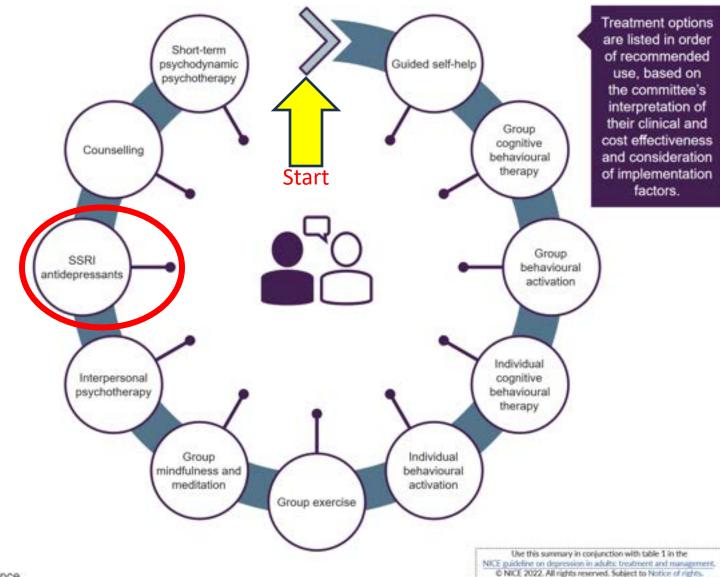
Depression in adults: discussing first-line treatments for less severe depression

Discuss treatment options and match the choice of treatment to clinical needs and preferences, taking into account that any option can be used as first line, but consider the least intrusive and least resource intensive treatment first (guided self-help).

If the person has a clear preference, or experience from previous treatment to use as a guide: support the person's choice, unless there are concerns about suitability for this episode of depression.

Do not routinely offer antidepressants as a first-line treatment, unless that is the person's preference.

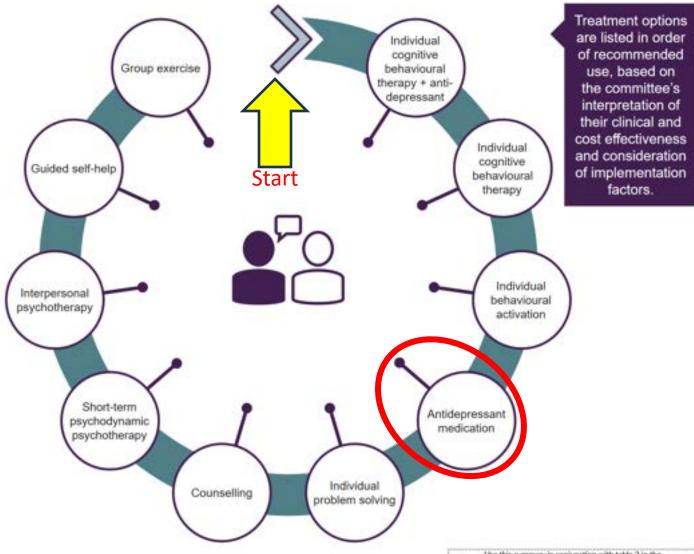
NICE National Institute for Health and Care Excellence



Depression in adults: discussing first-line treatments for more severe depression 2022

Discuss treatment options with people who have a new episode of more severe depression. Match their choice of treatment to their clinical needs and preferences.

If the person has a clear preference, or experience from previous treatment to use as a guide: support the person's choice, unless there are concerns about suitability for this episode of depression.





Use this summary in conjunction with table 2 in the NKE guideline on depression in adults: treatment and management. © NICE 2022. All rights reserved. Subject to Notice of rights.

VA TREATMENT GUIDELINES

Uncomplicated

or restart of past effective treatment

VS

Severe or partial or limited response to treatment

Complicated

- Treatment resistant (if applicable)
- More severe (PHQ9>???)
- Persistent
- Co-morbid disorders (substance use, other MH, medical)
- High suicide risk
- Psychosis
- Catatonic
- Low functional status
- https://www.healthquality.va.gov/guidelines/MH/mdd/

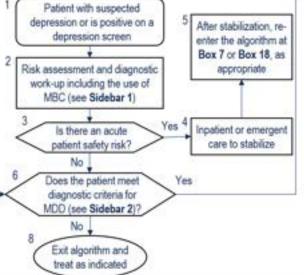


VA/DoD CLINICAL PRACTICE GUIDELINES

Management of Major Depressive Disorder (MDD)



Module A: Initial Assessment and Treatment



Sidebar 1: Risk Assessment and Work-up

Functional status, medical history, past treatment history, and relevant.

Evaluate for suicidal and homicidal ideation and history of suicide

attempts, and consult the VA/DoD Assessment and Management of

Rule out depression secondary to other causes (e.g., hypothyroidism,

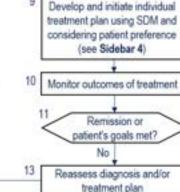
family history

Consider administration of PHQ-9

Patients at Risk for Suicide CPG, as appropriate

vitamin B-12 deficiency, syphilis, pain, chronic disease)

Incorporate MBC principles in the initial assessment



is this uncomplicated

MDD or a restart of

successful treatment

(see Sidebar 3)?

Yes

No

Go to Module B

Determine completion.

continuation.

maintenance or relapse

prevention strategies

Sidebar 3: Factors to be Considered in Treatment Choice

- Prior treatment response
- Severity (e.g., PHQ-9)
- + Chronicity
- · Comorbidity (e.g., substance use, medical conditions, other psychiatric conditions)
- Suicide risk.
- Psychosis
- Catatonic or melancholic features
- · Functional status

Sidebar 2: DSM-5 Criteria

Criterion A: Five or more of the following symptoms present during the same 2-week period; at least one of the symptoms is either (1) depressed mood or (2) loss of interest/pleasure:

- . Depressed mood most of the day, nearly every day
- · Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day
- · Significant weight loss when not dieting or weight gain
- · Insomnia or hypersomnia nearly every day
- · Psychomotor agitation or retardation nearly every day
- · Fatigue or loss of energy every day
- Feelings of worthlessness or excessive inappropriate guilt
- Diminished ability to think, concentrate, or indecisiveness, nearly every
- Recurrent thought of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Criterion B: The symptoms cause significant distress or functional impairment

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

Sidebar 4: Considerations in Treatment of Uncomplicated MDD

- · For initial treatment, select pharmacotherapy, psychotherapy, or both based on SDM
- If previous treatment was successful, consider restarting this approach
- Based on patient preferences, consider self help with exercise. (e.g., yoga, tai chi, gi gong, resistance, aerobics), light therapy, patient education, and bibliotherapy
- Include patient characteristics (e.g., treatment of co-occurring) conditions, pregnant patients, geniatric patients) in SDM
- Consider collaborative care in primary care for appropriate patients

Access to the full guideline and additional resources is available at: https://www.healthquality.va.gov/.





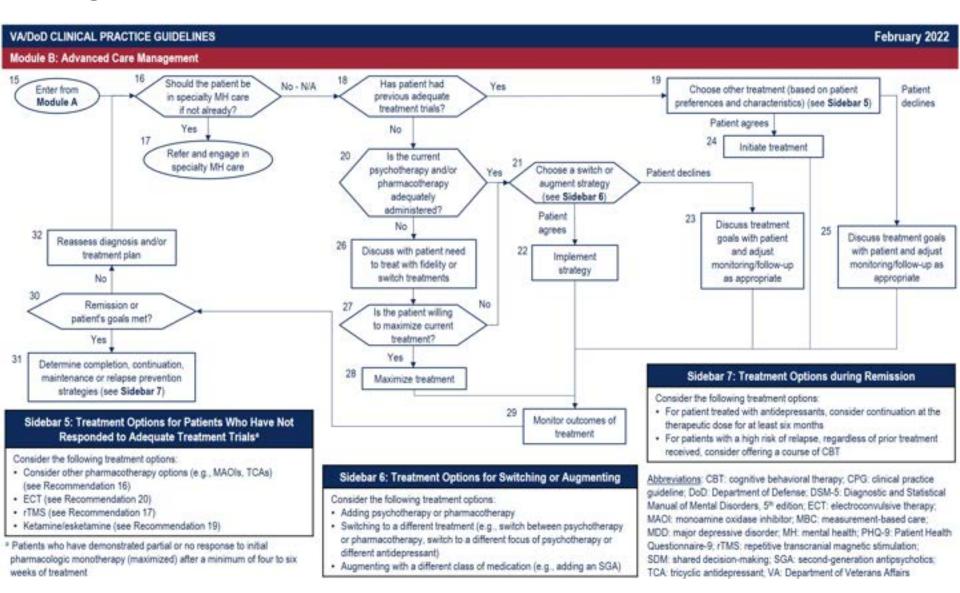
2022 VA MDD TREATMENT GUIDELINE

Sidebar 4: Considerations in Treatment of Uncomplicated MDD

- For initial treatment, select pharmacotherapy, psychotherapy, or both based on SDM
- If previous treatment was successful, consider restarting this approach
- Based on patient preferences, consider self help with exercise (e.g., yoga, tai chi, qi gong, resistance, aerobics), light therapy, patient education, and bibliotherapy
- Include patient characteristics (e.g., treatment of co-occurring conditions, pregnant patients, geriatric patients) in SDM
- Consider collaborative care in primary care for appropriate patients



2022





	Mild (PHQ-9 score <10)	Moderate (PHQ-9 score 10-14)	Moderately severe (PHQ-9 score 15-19)	Severe (PHQ-9 score ≥20)
American College of Physicians (2023) ⁵⁰	Cognitive behavioral therapy (conditional recommendation, low-certainty evidence)	Cognitive behavioral therapy OR second-generation antidepressant ^a (strong evidence, moderate-certainty evidence) Cognitive behavioral therapy AND second-generation antidepressant (conditional recommendation, low-certainty evidence)		
American Psychological Association (2019) ⁴⁸	Psychotherapy ^b (conditional recommendation for use)	Psychotherapy ^c OR second-generation antidepressant (recommendation for use)		
National Institute for Health and Care Excellence (2022) ⁴⁹	Guided self-help or group or individual psychotherapy ^d		Cognitive behavioral therapy and antidepressant medication Cognitive behavioral therapy alone Behavioral activation alone Antidepressant medication alone Problem-solving therapy alone Short-term psychodynamic psychotherapy alone Interpersonal psychotherapy alone	
Veterans Affairs and Department of Defense (2022) ⁴⁷	Clinician-guided internet-based cognitive behavioral therapy either alone or with antidepressant medication (weak recommendation)	Psychotherapy ^e OR antidepressant medication (strong recommendation)		Evidence-based psychotherapy AND antidepressant medication (weak recommendation)

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Simon GE, Moise N, Mohr DC. Management of Depression in Adults: A Review. JAMA. 2024;332(2):141–152. doi:10.1001/jama.2024.5756

33YO F WITH DEPRESSIVE SYMPTOMS

- Endorses low mood x 2 weeks. Broke up with partner about 1 month ago. Work is stressful. No past psych history. Poor sleep. Medicaid. Daily cannabis.
- PHQ9: 15. No SI.
- Patient would like some help and wonders if meds will help.

What would you offer?

- A. Start an antidepressant
- B. Refer to community mental health for therapy
- C. Recommend an online therapy option
- D. Recommend a supplement
- E. Recommend she reduce her cannabis and have her come back in 4 weeks because this is likely an adjustment disorder or substance induced



DSM-5 ADJUSTMENT DISORDER

The presence of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s)

- Distress that is out of proportion with expected reactions to the stressor
- Symptoms must be clinically significant—they cause marked distress and impairment in functioning
- Distress and impairment are related to the stressor and are not an escalation of existing mental health disorders
- The reaction isn't part of normal bereavement
- Once the stressor is removed or the person has begun to adjust and cope, the symptoms must subside within six months.



33YO F WITH HIGH DEPRESSIVE SYMPTOMS

What would you offer?

- A. Start an antidepressant?
- B. Refer to therapy?

Is there a role for antidepressants in adjustment disorders?

- Evidence is too weak to recommend.
- Maybe for severe symptoms?
 - Suicidal behaviors OR 1.8
 - Death by suicide OR 0.12



33YO F WITH HIGH DEPRESSIVE SYMPTOMS

What would you offer?

A. Recommend an online therapy option

Is online therapy the answer?

2022 VA Guidelines for Treatment of Uncomplicated MDD

- For patients with mild to moderate MDD, we suggest offering clinician-guided computer/internet-based cognitive behavioral therapy either as an adjunct to pharmacotherapy or as a first-line treatment, based on patient preference.
- Strength of Evidence: Weak



Home / Enforcement / FTC Refund Programs

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BetterHelp Refunds



The administrator is sending a second round of payments to eligible BetterHelp customers. The administrator first sent payments in June 2024, which resulted in nearly \$5.2 million in refunds. Because there is still money in the fund, the administrator is sending payments totaling over \$2.6 million to more than 534,000 people who accepted their first payment.

If you need help with your payment, please call the administrator at 1-833-637-4774 or send an email to info@BetterHelpRefundProgram.com.

What is the settlement about?

BetterHelp agreed to pay \$7.8 million to settle charges brought by the FTC.

The FTC says that, among other things, BetterHelp promised to keep users' information private but revealed data to Facebook, Snapchat, Pinterest, and Criteo for advertising purposes. This data included email addresses, IP addresses, and personal answers to health questions. BetterHelp offered online counseling through several websites, including:

Related Cases

BetterHelp, Inc., In the Matter of

33YO F WITH HIGH DEPRESSIVE SYMPTOMS

What would you offer antidepressants for possible substance induced depressive disorder?

- Setting: SUD treatment center
- Initial Evaluation
 - Substance-induced Depression: 51%
 - Co-occurring Major Depression: 49%
- 1 year follow-up
 - 32% of substance induced depression reclassified as having independent MDD



CHOOSING INITIAL TREATMENT SUMMARY

- Treatments for depression work best for Major Depressive Disorder.
- Therapy and medications are effective treatment for Major Depressive Disorder
- Choice of treatment should be driven by shared decision making
- Close follow-up at the start will help support your treatment recommendations

