Identification and Treatment of Major Depressive Disorder (MDD) for Adults

Purpose

To improve the identification and treatment of adult patients with Major Depressive Disorder (MDD) in the primary care setting. Persistent Depressive Disorder, formerly known as Dysthymic Disorder, Seasonal Affective Disorder and Bipolar Disorder, are not considered to be the focus of this guideline.

Key Points

- Approximately one in eight patients in primary care settings meet current MDD criteria.
- Untreated depression may interfere with recovery from co-morbid conditions and increase the chance of death, for example post MI or CVA.
- MDD is treatable: expect one-third of patients to remit with first anti-depressant trial, but up to 75% can achieve remission with subsequent interventions and properly applied medication management.
- Mild to moderate depression may be treated by medication and/or psychotherapy, typically more severe depression requires medication or other somatic treatments.
- Adequate dosing of antidepressant medication, patient adherence with medication and/or psychotherapy are keys to favorable outcomes.
- Remission is the goal of treatment.
    - Patients not treated to remission of symptoms by 3 months are nearly 3 times more likely to have a relapse/recurrence at long-term follow-up.
    - Patients who achieve remission have the best outcomes including lower risk of relapse and occurrence of suicidal behaviors.
- Continuation phase antidepressant treatment for 9-12 months after remission prevents early recurrence.
- Decisions about the maintenance phase of antidepressant treatment depend upon whether this is a 1st, 2nd or 3rd or more episode and other factors including whether there are warning signs before an episode, the severity of the episode, presence of psychosis, level of functioning and the insight of the individual.
- Use of antidepressants in Bipolar Disorder is controversial and should generally be avoided when possible. Antidepressants appear to increase the risk of rapid cycling and induction of mania, particularly in the Bipolar I subtype. When used, a mood stabilizing agent should be in place to protect against mood destabilization. For more information see International Conference on Bipolar Disorder Task Force Guidelines of Antidepressant Use in Bipolar Disorder.

Quality Measures Commonly Used by National Organizations

Depression is recognized as a major public health challenge and an important driver of health care cost and disability. Various quality of care enhancements to improve screening, treatment and outcome have become reflected in quality accounting and payment systems. Useful starting points for resources to explore these quality measures are found at these sites:

- National Committee of Quality Assurance HEDIS measures: https://www.ncqa.org/hedis/the-future-of-hedis/hedis-depression-measures-specified-for-electronic-clinical-data/
- The 2020 core set of behavioral health measures for Medicaid and CHIP: https://www.medicaid.gov/medicaid/quality-of-care/downloads/performance-measurement/2020-bh-core-set.pdf

High Risk Populations/Disparities

- Depression affects about twice as many women as men, regardless of racial and ethnic background or income.
- Suicide among males with known mental illness is about three times higher than among females with known mental illness and represents 69% of all U.S. suicides(1).Depression is one of the most common conditions associated with suicide in older adults, but it is not always recognized and is often undertreated.
- As of the latest NCHS report in 2018, the prevalence of depression in descending order of prevalence by race and Hispanic origin was as follows: Non-Hispanic black, Hispanic, non-Hispanic white and non-Hispanic Asian. (2)
- Poverty and low socioeconomic status contribute to depression prevalence and burden of illness. (2)
- Medical conditions can contribute to depressive symptoms. For example, CAD, diabetes, chronic pain, dementia, cancer, HIV/AIDS, trauma, obesity, pregnancy/ postpartum, chronic medical/psychiatric conditions.
- Research has demonstrated that certain factors increase the risk of depression. These include age, gender, family history, stress (i.e., marital problems, divorce, death of loved one, unemployment) and emotional trauma.

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Common Presentation

- Unexplained pain complaints- Vague aches & headaches
- Low energy-fatigue & low motivation
- Apathy, irritability, stress & anxiety
- Sexual complaints-Low libido
- Disrupted sleep patterns-Sleep disturbances
- Vague GI symptoms
- Appetite changes- Abdominal & appetite complaints
- Social avoidance- Loneliness & social isolation
- Headaches

Assess Family History
(First degree relatives with MDD, Bipolar Disorder and/or Suicidal Behavior) **For any mental illness and treatment**

Assess Trauma History
For Adverse childhood experiences (ACEs); adult abuse, accidents, or losses

Suicide and Violence Assessment
Does your patient have the...

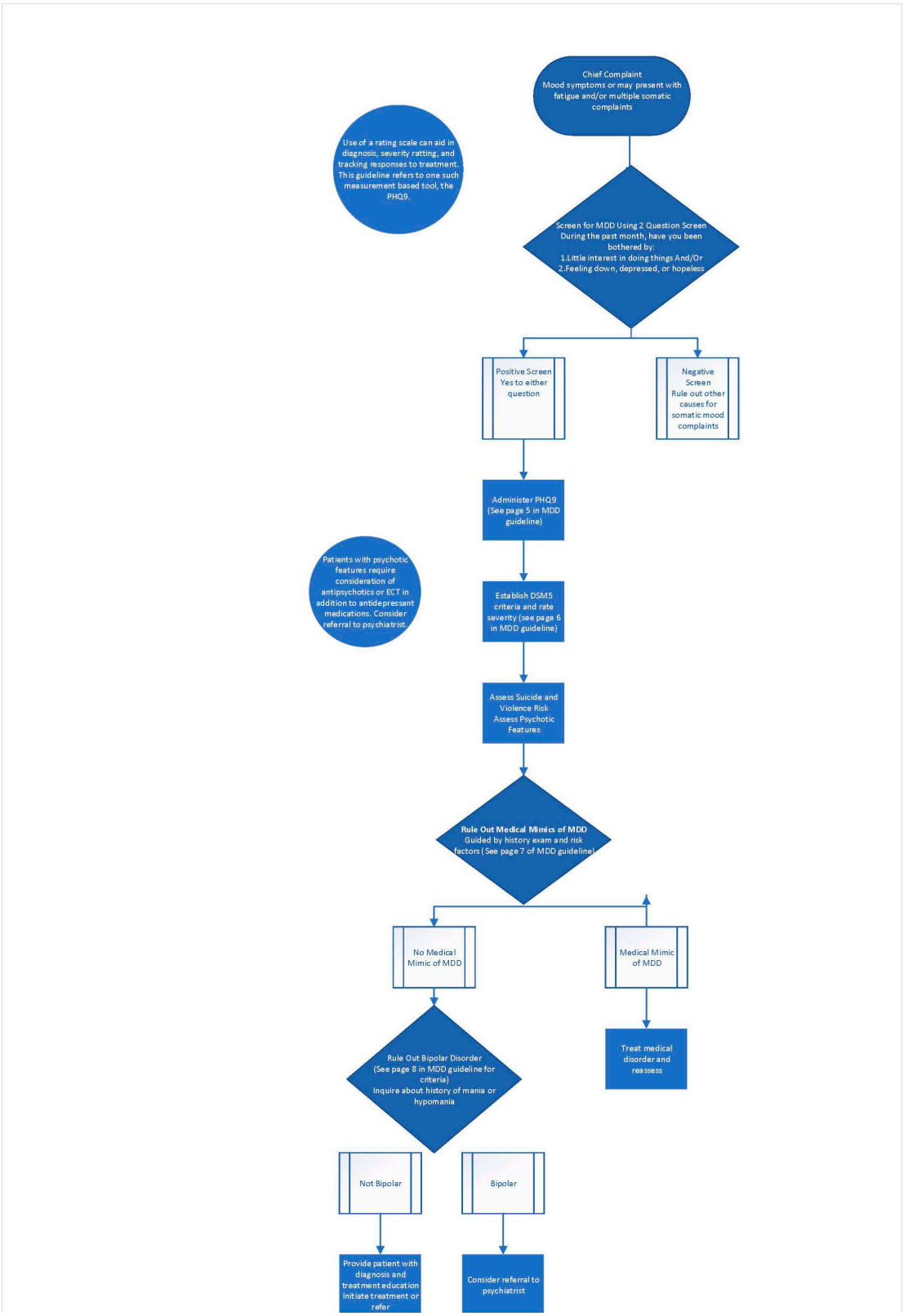
- Thoughts
- Intent
- Plan
- Means (including access to firearms)
- Behavior

...indicating risk to himself/herself and/or others

National Suicide Prevention Lifeline
Statewide 24/7
800-273-TALK (8255)
TTY line: 800-799-4889

Rochester Community Mobile Crisis Team
585- 275-5151 or (800) 310-1160
TTY line: 585-275-2700
On-call response available after-hours

Assessment and Identification



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Mon-Fri, 8:30am-10:00pm Weekends and Holidays, 10:00am-6:30pm Referrals can be made 24 hours a day, 365 days of the year. **In an emergency, contact one of the psychiatric ERs for guidance:** • **RGH Crisis Intervention Unit: 585-922-3728** • **SMH: 585-275-4501**	

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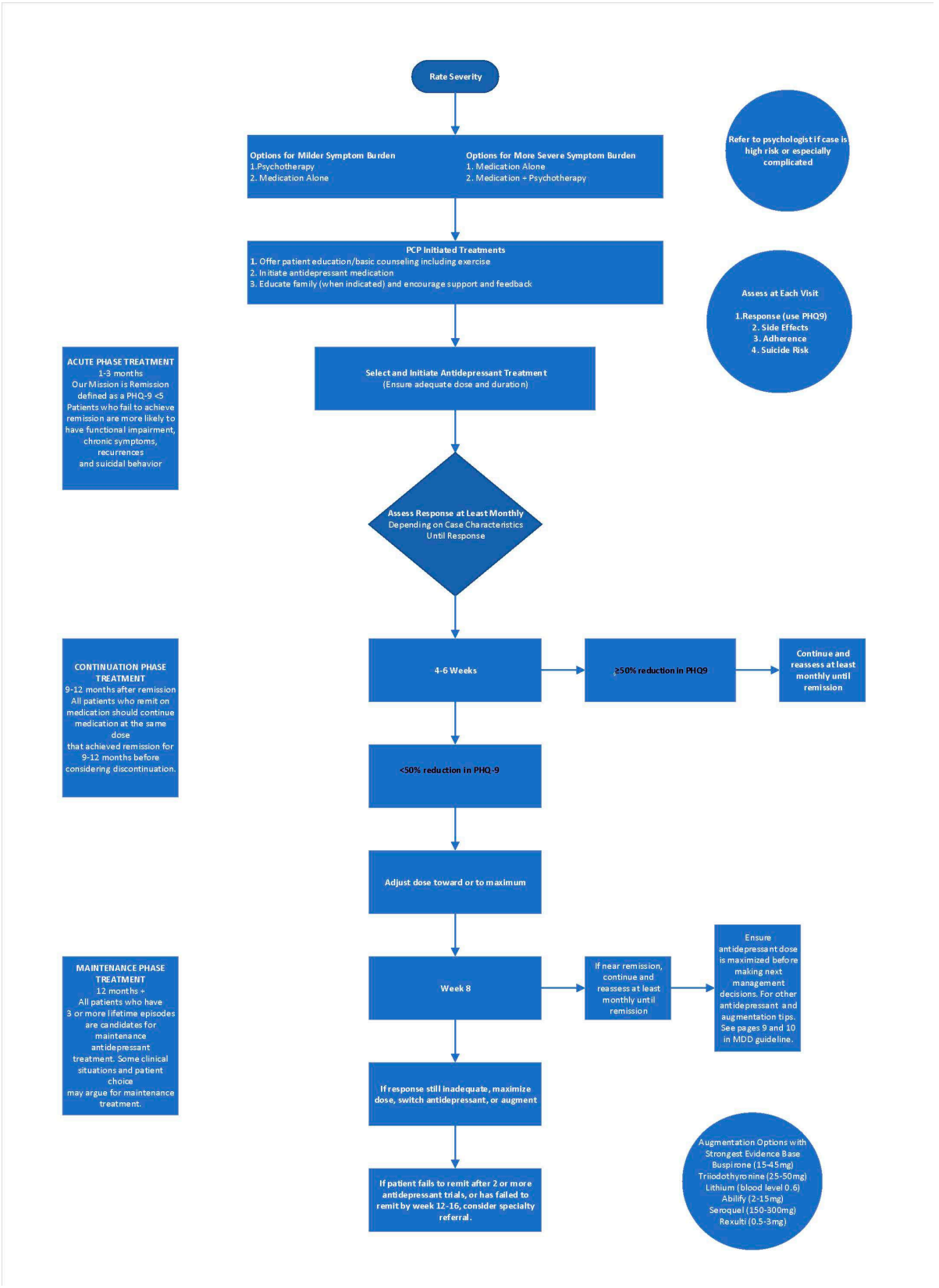
When to Consider Referring to a Mental Health Specialist

- Higher suicide potential
- Psychotic symptoms
- Lack of response to treatment
- Need for psychotherapy/counseling
- Higher level of severity
- Active co-occurring substance abuse
- Poor adherence/compliance
- Diagnostic uncertainty
- Management uncertainty Electroconvulsive therapy (ECT) Consideration of TransCranial Magnetic Stimulation or Esketamine Nasal Spray
-
- Highly recurrent or chronic depression
- Patient or family request
- Complex cultural considerations
- Presence of significant psychosocial stressors or interpersonal difficulties

Treatment – Remission is the Goal of Treatment



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Patient Health Questionnaire (PHQ-9)*

NAME:_____ **DATE:** _____

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use a "✓" to indicate your answer)	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
Add Columns:		+	+	
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).	TOTAL:			

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____

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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
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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 (e.g., 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 the 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.

6. If a positive response on Question #9, conduct additional suicide risk assessment. It should be determined/distinguished whether the patient is conveying passive thoughts that he/she would be better off dead or active thoughts of self-harm.

7. Questions 1+2 must equal or exceed a score of 3.

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A Selection of Medical Conditions that May Mimic MDD

Workup for medical mimics is based on clinical history, exam and known risk factors to rule out medical causes for patients presenting with depression. Laboratory tests to consider complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, and urinalysis.

More Common	Less Common
Alcohol Use Disorder	Acute Intermittent Porphyria
Cushing's Syndrome	Adrenal Insufficiency
Dementia	Brain Tumor
Medication Side Effects	B12 Deficiency
Parkinson Disease	Folate Deficiency
Thyroid Disorders	Giant Cell Arteritis
Substance Use Disorder	Huntington's Disease
	Lupus
	Multiple Sclerosis
	Neuro-syphilis
	Pancreatic Carcinoma
	Paraneoplastic Syndromes
	Vitamin D Deficiency*
	Wilson's Disease

*The role of vitamin D deficiency and depressive disorder remains uncertain.

Medical Mimics*	Examples
Drugs and poisons	Alcohol, β-blockers, steroids, opiates, barbiturates, withdrawal from cocaine and amphetamines, heavy-metal poisoning, cholinesterase inhibitors, cimetidine, chemotherapy agents
Metabolic and endocrine disorders	Hyper- and hypothyroidism, severe anemia, hyperparathyroidism, hypokalemia, hyponatremia, Cushing's disease, Addison's disease, uremia, hypopituitarism, porphyria, Wilson's disease, Wernicke-Korsakoff syndrome
Infectious diseases	Tuberculosis, Epstein-Barr infection, human immunodeficiency virus (HIV) infection, pneumonia, postinfluenza, tertiary syphilis, encephalitis, postencephalitic states
Neurodegenerative and demyelinating diseases	Alzheimer's disease, multiple sclerosis, Parkinson's disease, Huntington's disease
Other neurologic disorders	Subdural hematoma, normal-pressure hydrocephalus, strokes, other traumatic brain injury, cerebral tumors
Neoplasia	Carcinomatosis, cancers of the pancreas, lung, breast, others
Other disorders	Systemic lupus erythematosus, other collagen vascular disorders, other chronic inflammatory or autoimmune disorders, congestive heart failure

*Privitera MR, Lyness JM. Depression. Practice of Geriatrics. Fourth Edition Edmund H. Duthrie, Paul R Katz and Michael L. Malone. Saunders Elsevier Philadelphia PA 2007.pp345-358

Manic and Hypomanic Episodes

The focus is to treat major depressive disorder, which requires ruling out bipolar manic or hypomanic episodes.

Manic Episode

- 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 **1 week** and present most of the day, nearly every day (or any duration if hospitalization is necessary).
- During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree and represent a noticeable change from usual behavior:
    1. inflated self-esteem or grandiosity
    2. decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
    3. more talkative than usual or pressure to keep talking
    4. flight of ideas or subjective experience that thoughts are racing
    5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
    6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity)
    7. 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)
- The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Hypomanic episode

- Minimum of **four day** period of elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy with three or more (four if mood is only irritable) manic symptoms lasting at least 4 consecutive days and present most of the day, nearly every day.
- Not severe enough to cause marked impairment socially or occupationally, without psychosis, but sufficient to be uncharacteristic of the person when not symptomatic and are observable by others.

*American Psychiatric Association. Highlights of Changes from DSM-IV-TR to DSM-5. 2013. Available at: http://www.dsm5.org/Documents/changes%20from%20dsm-iv-tr%20to%20dsm-5.pdf

Antidepressant Medications

Classes by Mechanism of Action or Structure

Selective Serotonin Reuptake Inhibitors (SSRI)	• Celexa (citalopram) • Lexapro (escitalopram) • Luvox (fluvoxamine) • Paxil (paroxetine) • Prozac (fluoxetine) • Zoloft (sertraline)
Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)	• Cymbalta (duloxetine) • Effexor IR/XR (venlafaxine) • Fetzima (levomilnacipran) • Pristiq (desvenlafaxine)
Dopamine-Norepinephrine Reuptake Inhibitor (DNRI)	• Wellbutrin IR/SR/XL (bupropion)
Noradrenergic and Specific Serotonergic Antidepressants (NaSSA)	• Remeron (mirtazapine)
SSRI/5HT1A Partial Agonist/Other	• Viibryd (vilazodone) • Brintellix (vortioxetine)
SSRI/5HT2 Antagonist	• Desyrel (trazodone) • no brand available (nefazodone)
Tricyclic/Tetracyclic Antidepressants (TCA*)	• Adapin/Sinequan (doxepin) • Anafranil (clomipramine) • Asendin (amoxapine) • Elavil (amitriptyline) • Ludiomil (maprotiline) • Norpramine (desipramine) • Pamelor/Aventyl (nortriptyline) • Surmontil (trimipramine) • Tofranil (imipramine) • *Vivactil (protriptyline)*
Monoamine Oxidase Inhibitors (MAOI)	• Emsam (skin patch) (no generic available) • Marplan (isocarboxazid) • Nardil (phenelzine) • Parnate (tranylcypromine)

*TCAs are Type 1A antiarrhythmic agents which can: increase mortality post MI with PVCs; prolong atrial and ventricular depolarization; lengthen PR, QRS and QT intervals.

Antidepressant Management Tips

- The characteristics of the depressive episode, associated comorbid diagnoses and patient specific factors that influence safety, tolerability, ease of use and cost all influence the choice of antidepressant. Serotonin Specific Reuptake Inhibitor (SSRI) class antidepressants have become the mainstay of initial treatment of MDD, especially in the primary care community, because of their relatively good tolerability and safety profile, and familiarity with the agents. It is important to recognize that other classes of antidepressants may be indicated for depressive episodes with certain features (for example, MAOI class for MDD with atypical features) or when comorbid conditions may also be a target (for example bupropion in MDD and tobacco use disorder), and in cases that do not respond to an adequate trial of an SSRI. Choosing an antidepressant is an exercise in balancing these factors: safety, tolerability, efficacy, price, and simplicity of use. *MCMS does not advise abruptly stopping these medications, but to taper doses
- It is important to prescribe an antidepressant at adequate dose and duration before considering it a failed trial and switching or augmentation is considered.
- Switching and augmenting have similar rates of efficacy in research trials. Switching may be a less complicated choice in a primary care setting (exceptions being generic triiodothyronine and buspirone, which have few side effects and no significant monitoring demands). Lithium has the strongest efficacy evidence base, but drug interactions and monitoring demands for toxicity, thyroid and renal side effects may be limiting. The atypical antipsychotics (Abilify, Rexulti, and Seroquel) have good efficacy data, but also risks for metabolic syndrome and tardive dyskinesia and incur higher cost.
- When switching, typically it is better to switch between rather than within antidepressant class, though some studies have shown that a single switch to another SSRI is an acceptable option.
- Treatment of depression in pregnancy and lactating women requires special considerations that are beyond the scope of this guideline. (See resource section on page12 in MDD Guideline for further information.)
- All antidepressants: inform and discuss common and potential high-risk side effects including risk of agitation, precipitation of manic episode and/or provocation of suicidal ideation. Most antidepressants should be tapered to avoid a discontinuation syndrome and to give better odds of avoiding a recurrence of depression.
- Patients 24 and younger: highlight risk of provocation of suicidal ideation. The risk of provocation of suicidal ideation (small signal in research studies) must be balanced against the risk of untreated depression (greater risk according to most authorities).

Drug-drug Interactions

It is important to consider potential drug-drug interaction to ensure safe and effective antidepressant prescribing. Both inhibition and induction as well as protein binding effects can result in unexpected and sometimes dramatic differences in expected blood levels resulting in toxicity (e.g., like elevating Warfarin levels or beta blocker levels) or otherwise affecting the effectiveness of the drug. When prescribing antidepressants, it is a best practice to run a drug-drug interaction check using a program such as Epocrates (www.Epocrates.com).

Selected High-risk Antidepressant Side Effects

1. Effexor, Cymbalta and Pristiq: warn about hypertension (check baseline and follow-up blood pressure)
2. Cymbalta: warn about heavy drinking and about pre-existing liver disease (check baseline LFTs prior to prescription if risk factors for liver disease)
3. nefazodone: hepatotoxicity (check baseline and follow-up LFTs)
4. Wellbutrin: seizure provocation (highlight safe dosing parameters)
5. TCA: warn about orthostatic hypotension and overdose risk
6. MAOI: highlight dietary and medication restrictions (For further information, refer to patient education on page 11 in MDD Guideline - MAOI Diet and Medication Restrictions

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MAOI Diet and Medication Restrictions

MAOI class antidepressants are likely underutilized because they are not simple to use, but have indications for MDD with atypical features and in refractory cases. Primary care clinicians typically defer to psychiatric clinicians to determine indications for and management of this class of medications.

When MAOI class antidepressants are used in the treatment of MDD it is important that both provider and patient are informed about dietary and medication restrictions to prevent hypertensive crisis and/or serotonin syndrome. The detail of these restrictions is beyond the scope of this guideline. Readers are advised to consult interaction checking databases when prescribing MAOI class antidepressants.

Dietary restrictions must be observed for at least one day before initiation and two weeks after discontinuation of an MAOI. The duration of medication washout before MAOI initiation depends on the known pharmacokinetic properties of the restricted medication. For example, there should be a two-week washout period after most SSRIs before going to an MAOI, with the exception of Prozac for which there is a 5 week washout period. Medication restrictions must be observed for two weeks after the discontinuation of an MAOI.

Common drug interactions of concern include other antidepressant medications, dopamine agonists, carbamazepine, dextromethorphan, disulfuram, meperidine, stimulants and other sympathomimetic amines, and other synthetic narcotics. Over-the-counter medications may present risks, particularly those containing sympathomimetic amines or dextromethorphan. Herbal medications including ginseng, medicinal yeasts and St. John's Wort are also restricted. Drugs of abuse including cocaine, amphetamines and narcotics are hazardous in conjunction with an MAOI.

The following sources may be useful to readers interested in understanding dietary restrictions which have been refined over the years to be less onerous than they once were:

1. University of Wisconsin
   https://www.uwhealth.org/healthfacts/nutrition/154.pdf
2. Tyramine Menu Book by Kathrynne Holden, MS, RD
   https://www.scribd.com/document/35068841/Tyramine-Menu-Book-06227101

Resources for Physicians

American Psychiatric Association
(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf
The depression practice guideline is now in legacy status last updated in 2010. It provides evidence-based recommendations for the assessment and treatment of major depression as of that date. Many of the recommendations remain relevant but readers are advised that the guideline is aging. Additional guidelines for other mental disorders and special topics are available at the APA website, several in newer editions.

National Alliance on Mental Health
(http://www.nami.org/Learn-More/Mental-Health-Conditions/Depression)
An association of local affiliates, state organizations and volunteers who work in the community to raise awareness, provide support and education programs to help build better lives for those affected by mental illness.

National Institute of Mental Health
(http://www.nimh.nih.gov/health/topics/depression/index.shtml)
Provides educational information ranging from causes, signs and symptoms to treatment and clinical trials for depression.

New York Safe Act
Under the New York State Safe Act (Mental Hygiene Law § 9.46), physicians, licensed nurses and licensed social workers have additional responsibility to report individuals "likely to engage in conduct that would result in serious harm to self or others" to the Monroe County Director of Community Services, a county level Office of Mental Health administrator. The intent of the law is to limit individuals who are suicidal or potentially violent from owning firearms and/or removing firearms from their possession. To learn more about the NY Safe Act and medical/mental health provider responsibilities under it, consult the New York State OMH website (www.omh.ny.gov) and click on NY Safe Act on the left-hand navigation bar, or contact the Monroe County Office of Mental Health at 585 753-6047.

Project TEACH
https://projectteachny.org/

Resources for Patients

Depression and Bipolar Support Alliance
(http://www.dbsalliance.org/site/PageServer?pagename=home)
Provides help, support, and education to improve the lives of people who have mood disorders.

Helpful resources for treatment of depression in the pregnant or lactating woman

- **Massachusetts General Hospital Center for Women's Mental Health**
  (http://www.womensmentalhealth.org/)

Mental Health Association - Rochester
(http://www.mharochester.org/)

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Offers services (e.g., life skills workshops, peer navigation and support, education and training, employment support and self-help drop-in services) that help people recover from mental illness or maintain mental wellness.

References

Centers for Disease Control and Prevention.

Suicide information updated and available at:
https://www.cdc.gov/vitalsigns/suicide/index.html

NCHS Data Brief ■ No. 303 ■ February 2018
Prevalence of Depression Among Adults Aged 20 and Over: United States, 2013–2016
Debra J. Brody, M.P.H., Laura A. Pratt, Ph.D., and Jeffery P. Hughes, M.P.H.
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Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study results and Q&A at:
https://www.nimh.nih.gov/funding/clinical-research/practical/stard/index.shtml

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