Medication Algorithm for the Treatment of Major Depressive Disorder

Discuss psychotherapy options initially and at any point during treatment

SSRI, SNRI, bupropion or mirtazapine

No response or an intolerance to medication

- Assess psycho-social circumstances.
- Re-assess the diagnosis.
- Assess patient adherence.

Switch to another first-line agent

No response

- Assess psycho-social circumstances.
- Assess patient adherence.
- Refer to guidelines for treatment-resistant depression.
- Consider referral to a specialist.

Any first-line agent that was not tried above.

Consider second and third-line options (tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOIs). Also, consider transcranial magnetic stimulation (TMS), deep brain stimulation (DBS) or electroconvulsive therapy (ECT).

Partial response

Maximize dose if the patient can tolerate side effects.

(It may take 4–8 weeks at an effective dose to work.)

Response or remission

Partial response

Next-step options:

- Switch to another first-line agent
- Augment first-line agent with another medication. See Drug Augmentation for Treatment-resistant Depression
- Consider referral to a specialist.

Response or remission

Response or remission

***Continuation therapy* for 4–9 months**

Assess the need for *maintenance therapy* in patients at risk for recurrence.

***Maintenance therapy* for 12–36 months**

Table 1. Considerations for selecting the initial agent:

- Patient preference
- Nature of prior response to medication
- The relative efficacy and effectiveness
- Safety, tolerability and anticipated side effects
- Co-occurring psychiatric or general medical conditions
- Potential drug interactions
- Half-life
- Cost

Table 2. Considerations for choosing next-step options:

- Keep in mind shared decision-making principles throughout this process.
- The use of multiple medications has the highest potential for side-effects.
- Patients may be reluctant to try switching agents in fear of losing even a partial response.
- Evidence for combination strategy is not as strong as switching or augmentation.
- Refer to guidelines for treatment-resistant depression.

See supplemental information for more details and justifications of the algorithm.

Supplemental information

- **The algorithm is intended for the treatment of mild to moderately severe major depression (PHQ-9 <20) with the absence of psychotic features.**
- Psychotherapy (cognitive behavior therapy (CBT), interpersonal therapy (IPT) has been shown to have similar efficacy to pharmacotherapy. It is reasonable to recommend psychotherapy at any stage in treatment.
- Psychotherapy in combination with pharmacotherapy is more effective than either monotherapy with psychotherapy or pharmacotherapy.
- Recommended first-Line agents: Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine (see table of first-line agents for individual characteristics)
- SSRIs are generally prescribed first due to their safety and tolerability. However, guidelines do not make a strong recommendation for any first-line agent over another.
- Guidelines do not make a recommendation for any single agent within a class of medication. Agent selection is based on criteria shown in Table 1.
- Non-response to one SSRI does not predict non-response to an alternate SSRI.
- Second-generation antipsychotics with FDA approval as adjuncts: Aripiprazole, Brexiprazole, Quetiapine, Olanzapine in combination with fluoxetine. (risperidone with evidence to support off-label use)
- Four to eight weeks are needed before the patient and provider can conclude that a patient is partially responsive or unresponsive to a specific intervention.
- Duration of the acute phase treatment is 6-12 weeks
- Maintenance therapy is recommended for patients who have had three or more prior episodes of major depressive disorder (MDD). Consider maintenance therapy in patients that have high-risk factors for recurrence.

High risk factors for recurrence:

- A persistence of subthreshold depressive symptoms.
- Prior history of multiple episodes of major depressive disorder.
- The severity of initial and any subsequent episodes.
- Earlier age at onset.
- The presence of an additional nonaffective psychiatric diagnosis, psychiatric illness, particularly mood disorder.
- The presence of a chronic general medical disorder.
- A family history of psychiatric illness, particularly mood disorder.
- Ongoing psychosocial stressors or impairment.
- Negative cognitive style.
- Persistent sleep disturbances.

End notes:

1. American Psychiatric Association. Practice Guidelines for the Treatment of Patients With Major Depressive Disorder, Third. Published October 2010. Accessed Aug. 21, 2020. http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx.
2. National Institute for Health and Care Excellence. Depression in adults: recognition and management. 28 October 2009. Accessed Aug. 21, 2020. Available at: https://www.nice.org.uk/guidance/cg90
3. Bauer. M, Pfennig. A, Severus. E. WFSBP, "Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the Acute and Continuation Treatment of Unipolar Depressive Disorders. The World Journal of Biological Psychiatry, 2013 [cited Aug. 21, 2020]; 14:334–385. https://www.wfsbp.org/fileadmin/user_upload/Treatment_Guidelines/WFSBP_TG_Unipolar_depressive_disorders_Bauer_et_al_2013.pdf
4. U.S Department of Veteran Affairs. VA/DoD Clinical Practice Guidelines: Management of Major Depressive Disorder (MDD) (2016). Published April 2016. [Cited Aug. 21, 2020] https://www.healthquality.va.gov/guidelines/MH/mdd/
5. Nutt. D, Blier. P, Cleare. A. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology. May 12, 2015 [cited Aug. 22, 2020] available with subscription at: https://journals.sagepub.com/doi/abs/10.1177/0269881115581093
6. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. Can J Psych. 2016;61(9):540–560 [cited Aug. 24, 2020] available at: https://journals.sagepub.com/doi/pdf/10.1177/0706743716659417
7. Rush. J, Trivedi. M, Wisniewski. S. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. The American Journal of Psychiatry. Nov 2006. 163:11, 1905-1917 (cited Aug. 21, 2020) available at: https://ajp.psychiatryonline.org/doi/pdf/10.1176/ajp.2006.163.11.1905
8. Thase. M, Connolly. R. Unipolar depression in adults: Choosing treatment for resistant depression. UpToDate. WoltersKluwer. Nov. 13, 2019 [cited Aug. 24, 2020). Available with subscription at: https://www.uptodate.com/contents/unipolar-depression-in-adults-choosing-treatment-for-resistant-depression?search=depression%20treatment&topicRef=1725&source=see_link#H6076917

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