Treatment of Adult Major Depressive Disorder - Nonpsychotic

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-7).

Most importantly assess for bipolarity, comorbidities (e.g. substance abuse, anxiety disorders), and clinical features (psychosis, suicidality).

Level 1 – Initial treatment

- Discuss treatment options, including evidence-based psychotherapy [Cognitive behavior therapy (CBT)/Interpersonal psychotherapy (IPT)]
- Monotherapy 4-8 week trial at adequate dose and evaluate:
  - SSRI (sertraline, escitalopram) or venlafaxine
  - Bupropion (if tolerability concerns) or mirtazapine (if insomnia)
- If no response at 4 weeks go to Level 2
- If partial response at 4 weeks may continue for another 4 weeks or go to Level 2

Level 2

- Switch to different monotherapy
  - Agent from different or same class (SSRI, SNRI, mirtazapine, bupropion)
- Dose increase
- Augment prior monotherapy with:
  - Evidence-based psychotherapy (CBT, IPT)
  - Combining antidepressants, but not SSRI + SNRI augmentation
  - Agent from different class (SSRI, SNRI, mirtazapine, bupropion, BUT NOT SSRI + SNRI

Treatment of Adult Major Depressive Disorder - Nonpsychotic
(continued)

Level 3

- Seek psychiatric consultation
- Electroconvulsive therapy (ECT)
- TCA, MAOI
- SSRI or SNRI + L-methylfolate, T3, lithium
- SSRI or SNRI + aripiprazole or quetiapine
- Fluoxetine + olanzapine (tolerability concerns)
- Augmentation after partial response with agent from different class (SSRI, SNRI, mirtazapine, bupropion, TCA)
- Transcranial magnetic stimulation

Level 4

- Re-evaluate diagnosis if patient has failed to respond to two or more treatments
- Augment antidepressant with Vagal Nerve Stimulation (VNS)
- MAOI augmentation (AVOID CONTRAINDICATED COMBINATIONS)
- Triple drug combination (little evidence exists supporting or refuting this strategy):
  - SSRI or SNRI + mirtazapine + bupropion
  - SSRI or SNRI + mirtazapine + lithium
  - SSRI or SNRI + bupropion + second generation antipsychotic (SGA)

If no response, try a different two or three drug combination.

SSRI = Selective serotonin reuptake inhibitor
SNRI = Serotonin-norepinephrine reuptake inhibitor
TCA = Tricyclic antidepressant
MAOI = Monoamine oxidase inhibitor

Treatment of Adult Major Depressive Disorder - Psychotic

Conduct comprehensive assessment and use measurement-based care as found in the Principles of Practice (review pages 4-7).

Most importantly assess for bipolarity, comorbidities (e.g. substance abuse, anxiety disorders), and clinical features (psychosis, suicidality).

Level 1 - Initial treatment

- Discuss treatment options, including evidence-based psychotherapy [Cognitive behavior therapy (CBT)/Interpersonal psychotherapy (IPT)]
- Antidepressant + antipsychotic

Level 2 - If level 1 is ineffective or not well tolerated

- Antipsychotic + SSRI or SNRI
- Electroconvulsive therapy (ECT) with patient consent (if severe)

Level 3 - If levels 1 and 2 are ineffective or not well tolerated

- Other drug combinations
- Electroconvulsive therapy (ECT) with patient consent if not attempted earlier
- Antidepressant (any including tricyclic) + antipsychotic (including perphenazine)
- Re-evaluate diagnosis if the patient has failed to respond to two or more treatments.

SSRI = Selective serotonin reuptake inhibitor
SNRI = Serotonin-norepinephrine reuptake inhibitor

Approaches to Treatment Resistant Depression (TRD): An Update Focusing on Studies Published in 2011-2013

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This is a summary of a review of approaches to treatment resistant depression (TRD), which refers to when a patient has received an adequate dose of a medication for an adequate duration and yet has not experienced an acceptable level of symptomatic response

In treating patients with TRD, it is recommended that the clinician should first assess the accuracy of the diagnosis of depression, whether it is unipolar or bipolar, and whether there are psychiatric and medical comorbidities involved. The clinician should also assess if the treatment offered was adequate in dose and duration, whether treatment was well tolerated, and whether patient has been adherent to treatment. After the clinician has done that, pharmacological approaches to TRD include: Dose increase, switching, combination of more than one antidepressant, and the use of an augmentation psychotropic agent to enhance the effect of the antidepressant. Neuromodulation approaches have also shown promise for treatment of TRD.

Switching: Inoue et al. (2012) examined the long-term effectiveness and safety of switching to sertraline from other selective serotonin reuptake inhibitors (SSRIs) in the treatment of TRD. They concluded that switching from paroxetine or fluvoxamine to sertraline might be effective and well-tolerated in patients with non-remitted or treatment-intolerant major depressive disorder.
Comments: Switching from one SSRI which has inadequate response to another SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) has been reported to be an effective approach for TRD, not limited to switching to sertraline.

Combination: Holt et al. (2011) analyzed anonymous data to compare outcomes of patients who received augmentation therapy with either mirtazapine or atypical antipsychotics. They concluded that patient with mirtazapine combination, compared to those who received atypical antipsychotics augmentation, resulted in better discharge rates and reduction in suicidality.
Comments: Mirtazapine and bupropion are frequently used to combine with SSRIs/SNRIs for treatment of TRD with evidence supporting their efficacy.

Augmentation Strategies:

1. **Pramipexole:** Cusin et al. (2013) investigated the antidepressant efficacy of a flexible dose of the dopamine agonist pramipexole as an adjunct to standard antidepressant treatment in an 8-week, randomized, double-blind, placebo-controlled trial. They found a modest but statistically significant benefit for pramipexole (P = .038), and augmentation with pramipexole was well-tolerated, with no serious adverse effects identified.
   Comments: There is limited data on pramipexole augmentation of major depressive disorder (MDD) treatment. Pramipexole is associated with 3 rare but serious side effects: sleep attacks, compulsive behaviors and pathological gambling, and psychosis.
2. **Stimulants:** Trivedi et al. (2013) evaluated the efficacy and safety of lisdexamfetamine dimesylate augmentation for MDD in escitalopram nonremitters. They conclude that lisdexamfetamine dimesylate augmentation reduced depressive symptoms in participants with inadequate escitalopram response.
   Comments: Studies using stimulants to augment antidepressants have mostly shown negative outcomes.

3. **Atypical antipsychotics:** Spielmans et al. (2013) performed a meta-analysis to compare the outcomes of adjunctive antipsychotic medication to placebo for TRD in adults. They concluded that atypical antipsychotic medications for the adjunctive treatment of depression are efficacious in reducing observer-rated depressive symptoms, but effect sizes of the benefits were small-to-moderate, and quality of life or functional impairment did not improve. The authors warned about the abundant evidence of potential treatment-related harm.
   Comments: Strong evidence suggesting that newer antipsychotics, particularly quetiapine and aripiprazole augmentation improves depression symptoms, but they may cause serious adverse events.

4. **Use of glutamateric agents:** Ketamine. Murrough et al. (2013) studied the use of ketamine, a glutamate N-methyl-d-aspartate (NMDA) receptor antagonist, for treating patients with TRD. They reported that the ketamine group had greater improvement as soon as 24 hours after treatment.
   Comments: Ketamine demonstrated rapid antidepressant effects in this study. More studies are needed to replicate the findings, and more information on response durability and safety is required before implementation in clinical practice.

5. **Anticholinergic, antimuscarinic drugs:** Scopolamine. Khajavi et al. (2012) conducted a randomized clinical trial to evaluate the antidepressant effect of oral scopolamine as an adjunct to citalopram and showed that augmentation with scopolamine was safe and significantly more effective than placebo.
   Comments: As side effect potential for this agent includes confusion and delirium, safety remains a serious concern if scopolamine in any form is used in clinical practice.

6. **Mood Stabilizers:**

   a. **Lamotrigine:** Barbee et al. (2011) performed a large randomized clinical trial to examine the use of lamotrigine as an antidepressant augmentation agent in patients with TRD. They reported that patients with TRD failed to detect a statistically significant difference between lamotrigine and placebo given for 10 weeks.
   Comments: Existing data do not support the efficacy of lamotrigine to augment treatment of TRD.

   b. **Topiramate:** Mowla and Kardeh (2013) designed an 8-week randomized, placebo-controlled, double-blind study on 53 TRD patients. Patients were randomized to receive a flexible dose of topiramate (100-200 mg/day) or placebo beside their current antidepressant medication for a period of eight weeks. They showed that topiramate augmentation potentiate the efficacy of SSRIs in treatment of resistant MDD.
   Comments: This is a preliminary study with a small sample size. Data on topiramate is limited.

7. **Supplements:**

   a. **L-Methylfolate:** Papakostas et al. (2012) conducted two multicenter sequential parallel comparison design trials to investigate the effect of L-methylfolate augmentation in the treatment of patients with TRD. They concluded that adjunctive L-methylfolate at 15 mg/day may constitute an effective, safe, and relatively well tolerated treatment strategy for patients with MDD who have a partial response or no response to SSRIs.
   Comments: The positive evidence accumulated for using L-methylfolate to augment depression treatment and its great safety profiles make it a favorable candidate for augmentation treatment of TRD.

   b. **Omega 3:** Gertsik et al., (2012) studied 42 subjects in the efficacy of treatment with citalopram plus omega-3 fatty acids versus citalopram plus placebo in the treatment of individuals with MDD. They demonstrated that patients who received combination therapy had significantly greater improvement in depression symptoms.
   Lespérance et al. (2011) performed a randomized, controlled, 8-week study to investigate the effects of taking 8-weeks of 1,050 mg/d of eicosapentaenoic acid (EPA) and 150 mg/d of docosahexaenoic acid (DHA) or placebo. The intervention group showed a non-significant trend in the improvement of depression outcomes. For patients without comorbid anxiety disorders (n = 204), omega-3 supplementation was superior to placebo.
   Comments: Existing studies show different outcomes. Stronger evidence is needed to support the use of omega 3 as an augmentation agent for the treatment of depression.

   c. **Creatine:** Lyoo et al. (2012) randomized 52 women with MDD who were enrolled in an 8-week clinical trial to receive escitalopram in addition to either creatine (5 g/day, N=25) or placebo (N=27). They reported that patients receiving creatine augmentation showed significantly greater improvements in depression as early as week 2 of treatment.
   Nemets and Levine et al. (2013) performed a pilot study on 14 TRD women and treated them with a 4-week, double-blind, parallel augmentation study where creatine monohydrate 5 or 10 g was given daily or a placebo was added to ongoing antidepressant treatment. They found that, overall; there was no difference between creatine administered at 5 or 10 g daily and its corresponding placebos.
   Comments: Data on efficacy of creatine for TRD augmentation is limited.

8. **Tumor Necrosis Factor (TNF) Antagonist Infliximab:** Raison et al. (2013) administered three infusions of the TNF antagonist infliximab (5 mg/kg) (n = 30) or placebo (n = 30) to outpatients with MDD who were on either a consistent antidepressant or medication free. They reported no overall difference in change of depression outcomes between treatment groups was found.
   Comments: TNF antagonism may not have generalized efficacy in TRD, but may improve depressive symptoms in patients with high baseline inflammatory biomarkers.

9. **Neuromodulation:** High-Frequency Repetitive Transcranial Magnetic Stimulation (HF-rTMS). Berlim et al. (2013) performed a meta-analysis study and selected all randomized, double-blind, and sham-controlled trials on the use of HF-rTMS as an accelerating (add-on) strategy to antidepressants for MDD, and concluded HF-rTMS is a promising strategy for accelerating clinical response to antidepressants in MDD, providing clinically meaningful benefits.
   Comments: The technology of neuromodulation is promising for SSRI augmentation. More evidence from well-designed clinical trials is needed.
10. **Psychosocial Treatments:** Cognitive Behavioral Therapy (CBT). Wiles et al. (2013) randomized 469 patients with TRD in primary care settings to receive either CBT augmentation or usual care. The intervention group performed significantly better than the control group.
    Comments: This study has provided robust evidence that CBT is an effective adjunctive treatment for TRD.
11. **Exercise:** Trivedi et al. (2011) randomized 126 patients with TRD to augmentation treatment with either 16 kcal per kg per week (KKW) or 4 KKW of exercise for 12 weeks while SSRI treatment held constant. They reported a trend for higher remission rates in the higher-dose exercise group ($p < .06$), suggesting high exercise dose is an effective adjunctive treatment.
    Comments: Existing evidence supports that exercise is an effective adjunctive treatment of TRD.

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