

Treatment of Resistant Depression

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Initial Antidepressant Selection

- Selection of antidepressant is based on:
 - Anticipated side effects and safety/tolerability for the patient.
 - Pharmacological properties of the medication (T1/2, P450 enzymes, other drug interactions).
 - Additional factors: medication response in prior episodes, cost, & patient preference
- For most patients, start with a selective serotonin reuptake inhibitor (SSRI), mirtazapine, bupropion or serotonin norepinephrine reuptake inhibitor (SNRI).

Remission of Major Depressive Episode (MDE)*

- 4–8 weeks of treatment at a therapeutic dose are needed before concluding that a patient is partially responsive or unresponsive to a specific medication.
- Remission: ≥ 3 weeks of the absence of both sad mood & reduced interest and no more than 3 remaining sx of MDE.
- Patients often have substantial but incomplete sx reduction or improvement in functioning during acute phase treatment.

Treatment Resistant vs Treatment Refractory

- Treatment Resistant Depression: Major Depressive Episode (MDE) that does not respond to at least two trials of antidepressant monotherapy.
- Treatment Refractory: MDE that does not respond satisfactorily to numerous sequential treatment regimens.

Residual Depression

- Even mild residual symptoms at the end of a MDE are associated with:
 - Significant psychosocial disability, compared with asymptomatic remission.
 - More than 3 X faster relapse to a subsequent MDE.
 - More chronic future course.
- The presence of mild residual symptoms have been shown to be an even stronger predictor of a subsequent return to a MDE than a prior history of multiple episodes of major depression.

Strategies to Address Nonresponse

- If at least mild-moderate improvement in symptoms is not observed within 4–8 weeks of treatment initiation:
 - Reappraise diagnosis (rule out medical causes, personality disorder, substance-induced, psychotic depression or bipolar diagnoses).
 - Assess side effects.
 - Review complicating co-occurring conditions and psychosocial factors.
 - Adjust treatment plan.
- Assess the quality of the therapeutic alliance and treatment adherence.

Nonspecific Care Management

- Educate pts/families about depression, suicide, treatment options, sleep hygiene
- Regularly review & quantify w/ serial PHQ-9
 - >20: severe depression
 - <5: in remission
- Review adherence
- Manage side effects
- Assess suicidality and review crisis plan

Inadequate Response to Antidepressant

- Optimize the dose if the side effects are tolerable and the upper limit of a medication dose has not been reached.
- Augment the antidepressant with psychotherapy
- Change to another antidepressant
- Augment with other agents
- Electroconvulsive Therapy (ECT) or Repetitive Transcranial Magnetic Stimulation (RTMS)

Switching to Another Antidepressant

- SSRIs and SNRIs should be gradually tapered over a few weeks if changing to mirtazapine or bupropion. Exception: fluoxetine (Prozac®).
- Next antidepressant trial or augmentation w/ 2nd antidep should be chosen depending on residual depressive sx or adverse side effects experience w/ 1st antidepressant.
 - i.e. sexual dysfunction, insomnia, mood swings, anxiety, energy or appetite problems

Augmenting Strategies

- Add second antidepressant with different action (ie add bupropion or mirtazapine to SSRI)
- Add buspirone (serotonin agonist)
- Add mood stabilizer (lithium, lamotrigine, divalproex sodium)
- Add atypical antipsychotic
- Add triiodothyronine (T3) (Cytomel®)

Phases of Treatment

Continuation Phase

To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for 4–9 months.

Phases of Treatment

Maintenance Phase

- Patients w/ ≥ 3 prior MDEs or w/ chronic MDD should continue to the maintenance phase of treatment after completing the continuation phase.
- Maintenance therapy should also be considered for patients w/ risk factors for recurrence: presence of residual symptoms, ongoing psychosocial stressors, early age at onset, & family history of mood disorders.

Discontinuing Antidepressants

- Augmenting agents should be tapered first (T3, second antidepressant), at the same time (lithium, anticonvulsant, atypical antipsychotic) or after the antidepressant is stopped (lithium, anticonvulsant, antipsychotic).
- Best to taper the medication over the course of at least several weeks
- To minimize the likelihood of Serotonin Discontinuation Syndrome, patients should be advised not to stop abruptly.
- A slow taper or temporary change to a longer half-life antidepressant (fluoxetine) should reduce the risk of SSRI/SNRI discontinuation syndrome.

Discontinuation Syndromes

- Serotonin Discontinuation Syndrome
 - Worst: short acting SSRIs (ie paroxetine, sertraline, citalopram) and SNRIs (venlafaxine, duloxetine)
 - Least: fluoxetine, mirtazapine and bupropion, buspirone
- Tricyclic abrupt discontinuation: cholinergic rebound
- Anticonvulsant abrupt discontinuation: seizure, mania
- Antipsychotic abrupt discontinuation:
 - Neuroleptic (1st generation): withdrawal dyskinesia, manic or psychotic relapse
 - Atypical (2nd gen): weight loss, insomnia, manic or psychotic relapse

New Antidepressants

- **Agomelatine** – melatonin receptor agonist (only in Europe)
- **Vilazodone** (Viibryd®) – serotonin modulator (like nefazodone)
- **Vortioxetine** (Trintellix®) – serotonin modulator and stimulator
- **Levomilnacipran** (Fetzima®) – SNRI-much more adrenergic than serotonergic
 - [serotonin:norepinephrine ratios of SNRIs are as follows:
[venlafaxine](#) = 30:1, [duloxetine](#) = 10:1, [desvenlafaxine](#) = 10:1, milnacipran = 1:3, and levomilnacipran = 1:2]*

* Sansone RA, Sansone LA (March 2014). "[Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison](#)". *Innov Clin Neurosci*. 11 (3-4): 37–42.