Major Depressive Disorder

By

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Classification of Mood Disorders:

- Major Depressive Disorder
- Bipolar I Disorder
- Bipolar II Disorder
- Dysthymia
- Cyclothymia
- Mood Disorder due to a GMC
- Substance-induced Mood Disorder
- Bereavement
Medical reasons for Depression:

- Malignancies (especially Pancreatic cancer)
- Endocrinopathies: Hypothyroidism, Addison`s disease
- Viral Infections: Hepatitis, HIV
- Stroke
- Drugs: alcohol, benzos, antihypertensive, oral contraceptives, interferon, cocaine
Prevalence of MDD in specific medically ill populations:

- Terminal solid tumors: 25% to 38%
- Stroke: 27% to 35%
- Renal disease: 5% to 22%
- Chronic pain: 35% to > 50%
- Epilepsy: 20% to 30%
- Parkinson`s disease: 30% to 50%
- Coronary Artery Disease: 15% to 25%
- Diabetes mellitus: 10%

Etiology of Depression:

- Partly Genetic: 50% of patients with MDD have a first degree relative with a Mood d/o
- Adoption studies have supported a genetic etiology
- Neurochemical factors: NE, 5HT, and DA
- Neuroendocrine regulation: cortisol, thyroid
- Psychological & Social factors: stress, loss, and negative cognition
Brain atrophy in depression?

Atrophy of the Hippocampus in Depression


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Treatment Options for Depression:

- Pharmacotherapy alone
- Psychotherapy alone
- Combination of Pharmacotherapy and Psychotherapy
- Electroconvulsive Therapy (ECT)
- Light Therapy
- Vagal Nerve Stimulation (VNS)
- Herbal drugs e.g., St. John’s Wort
Current Treatment Practices in MDD

In MDD, “Adequate” Treatment Is Difficult to Achieve\textsuperscript{1-3}

Factors contributing to inadequate treatment include:

- Adequate Dosage
- Adequate Duration
- Lack of Efficacy
- Poor Tolerability
- Nonadherence
- Safety Issues
- Comorbidities

A Significant Percentage of Patients With MDD Remain Poorly Served

- 14 Million US Adults
- 7.2 Million Treated
  - 3.2 Million Adequately Treated
  - 4 Million Poorly Served
  - Inadequate response
  - Intolerant to side effects
- 6.8 Million Untreated

Rates of recovery diminish with duration of major depressive episode

Recovery=8 weeks of Psychiatric Status Rating (PSR) 1 or 2.
Recovery=sustained remission.

Sequenced Treatment Alternatives

STAR ★ D

to Relieve Depression

National Institute of Mental Health

http://www.edc.gsph.pitt.edu/stard
STAR*D: Patient Participants

- N = 4,000
- MDD, nonpsychotic
- Specialty and primary care
- Almost all co-morbidities
First Step of Treatment Protocol:

- Everyone gets CITALOPRAM
- Expect 50% response rate
STAR☆D: Levels

Level 1: CIT

Level 2:
  Switch: BUP, CT, SER, VEN
  Augment: BUP, BUS, CT

Level 3:
  Switch: NOR, MIR
  Augment: Li, THY

Level 4:
  Switch: TCP, VEN + MIR
Augmentation & Switching:

- **Augmentation:**
  To use another pharmacologic agent to enhance the effect of an Antidepressant response in treatment refractory patients, or to achieve remission in partial responders.

- **Switching:**
  It involves the substitution of the failed Antidepressant with another agent often with a different mechanism of action.
Treatment Duration:

- 12 weeks at each level
- 1 year follow up after a satisfactory therapeutic response
<table>
<thead>
<tr>
<th>Level</th>
<th>RR Range</th>
<th>% Average RR</th>
<th>% Original Population Still Symptomatic**</th>
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<td>28</td>
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<td>7-14</td>
<td>11</td>
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</tbody>
</table>

* Remission = a score of $\leq 7$ on a 17-item Hamilton Depression Rating Scale.

** Assumes every nonremitter went through the next treatment level rather than dropping out.
Common Side Effects Of SSRIs:

- Gastrointestinal: nausea, vomiting, diarrhea
- Activation, restlessness, and insomnia
- Sexual dysfunction
- Neurological: can produce EPS, exacerbate both Migraine and Tension headaches
- Serotonin syndrome
- Drug-drug interactions
SSRIs Withdrawal Syndrome:

Serotonin Withdrawal Syndrome can be memorize by using the mnemonic FLUSH.

- Flu-like symptoms
- Lightheadedness/dizziness
- Uneasiness/restlessness
- Sleep & sensory disturbances
- Headache
Venlafaxine:

- **Safety:** wide therapeutic index. No to minimal effects on most CYP enzymes
- **Tolerability:** dose dependent hypertension
- **Efficacy:** equivalent to TCAs
- **Simplicity:** XR formulation is available
Duloxetine:

- More balanced of dual reuptake inhibitor from the start
- Immediate onset of therapeutic effects
- Linear pharmacokinetics
- Starting dose is 20 mg bid, then 30 mg bid, then 40 mg bid at weekly intervals
Duloxetine:

- Nausea is the most common s/e
- Small but statistically significant increase in both systolic & diastolic blood pressure consistent with NE potentiation
- Other s/e includes somnolence, dry mouth, dizziness, small decrease in body weight
- Moderate inhibitor of CYP2D6
Side Effects With Bupropion:

- Headaches, Tremors, and dose dependent risk of Seizures
- Development of Psychotic Symptoms
- Insomnia
- Gastrointestinal upset
Preferred use of Bupropion:

- SSRIs induced sexual dysfunction
- Depression secondary to Parkinson`s disease
- Retarded depression
- Non-responders to SSRIs
- Hypersomnia
- Non-tolerators of SSRIs
Preferred uses of Mirtazapine:

- Depression associated with,
  a) anxiety, agitation, and insomnia
  b) SSRI induced sexual dysfunction, nausea and GI disturbance
  c) weight loss
  d) panic
Common side effects with TCAs:

- Blurred vision
- Dry mouth
- Constipation
- Sedation
- Orthostatic hypotension
- Dizziness
- Weight gain
- Confusion
Adverse Effects of MAOIs:

- Insomnia
- Sexual dysfunction
- Hypertensive crisis
- Dietary restrictions
- Drug-drug interactions
Preferred uses of MAOIs:

- Third line agent
- Atypical depression with weight gain, hypersomnia, and mood reactivity
- Treatment resistant depression
- Depression associated with panic attacks
Duloxetine:

- Approval for both MDD and GAD
- Informal dosing range is 60-120 mg/day
- No published data on overdoses with duloxetine
- No published evidence of a faster onset of action with duloxetine vs other marketed antidepressants.
Indications for combined Pharmacotherapy and Psychotherapy:

- Patients with,
  1. Psychosocial issues
  2. Interpersonal problems
  3. Poor adherence with the treatment plan
  4. History of partial response from single treatment modality
  5. Co-morbid Axis-II disorders
Electro-convulsive Therapy:

Indications for Electro-convulsive Therapy:

1. Severe MDD associated with Psychosis, catatonic features, severe suicidality, or food refusal
2. Previous positive response to ECT
3. Severe MDD with pregnancy
4. Non-responders to antidepressants
St. John’s Wort:

- Whole plant product with antidepressant properties
- Not regulated by FDA, so preparations lack standardization regarding their ingredients, composition as well as potency
- Combined use of St. John`s Wort & MAOIs is contraindicated
Light Therapy:

- Bright light therapy is used as first line treatment for “winter blues” as well as adjunct in MDD with seasonal pattern
- 10,000 lux intensity for 30 minutes/day
- Usually improvement within one week
- Common side effects are, headache, eye strain, insomnia, irritability and occasionally hypomania