Update on Depression-2012

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Disclosures - None

Learning Objectives

- Understand the spectrum of depressive disorders and treatment implications
- Appreciate recent developments in the psychopharmacologic management of depression, including refractory depression
- Enhance skills in suicide risk assessment

Emerging Issues - 2012

- Suicide Risk and antidepressants – the role of occult bipolar depression
- Treatment Resistant Depression – Augment, Switch, Combine?
- Novel neuroleptic/antipsychotic medications as antidepressant boosters
- What role for TMS and brain stimulation techniques?

Prevalence of Mood Disorders

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<thead>
<tr>
<th></th>
<th>1 Year (%)</th>
<th>Lifetime (%)</th>
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<tbody>
<tr>
<td>Major Depressive Episode</td>
<td>10.3</td>
<td>17.1</td>
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<tr>
<td>Manic Episode</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>2.5</td>
<td>6.4</td>
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<tr>
<td>Any Mood Disorder</td>
<td>11.3</td>
<td>19.3</td>
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DSM-IV Classification of Mood Disorders
Screening for Mood Disorders

- Personal Health Questionnaire 2 (PHQ-2); longer version PHQ-9
- Quick Inventory of Depressive Symptoms
- Beck Depression Rating Scale
  - Self-report
- Hamilton Rating Scale for Depression
  - Clinician administered
- Young Mania Depression Rating Scale
- Columbia Classification Algorithm for Suicide Assessment (C-CASA)

Subtypes of Depressive Disorders

- Bipolar/Unipolar
  - Rapid Cycling as a sub-variant
- Melancholic/Non-Melancholic
- Psychotic/Non-Psychotic
- Agitated/Retarded
- Responsive/Non-responsive
- Atypical
  - Rejection Sensitive Dysphoria
- Seasonal Affective Disorder

DSM-IV Criteria for Melancholic Features

A. Either of the following, occurring during the most severe period of the current episode:
1. Loss of pleasure in all, or almost all, activities
2. Lack of reactivity to usually pleasurable stimuli

B. Three or more of the following:
1) Distinct quality of depressed mood (ie, different from feelings experienced after loved one’s death)
2) Depression regularly worse in the morning
3) Early morning awakening
4) Marked psychomotor retardation or agitation
5) Significant anorexia or weight loss
6) Excessive or inappropriate guilt

Endogenous Versus Atypical Depression

Endogenous
- Middle or terminal insomnia
- Appetite
- Weight loss
- Worse in AM
- Non-reactive mood
- Absence of interpersonal hypersensitivity as a trait

Atypical
- Initial insomnia or hypersomnia
- Appetite
- Weight gain
- Worse in evening
- Reactive mood
- Interpersonal hypersensitivity as a trait

Recurrence is Common

Rate of recurrence per episode

<table>
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<tr>
<th>Depressive Episode(s)</th>
<th>Rate (%)</th>
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<tr>
<td>After 1</td>
<td>50</td>
</tr>
<tr>
<td>After 2</td>
<td>70</td>
</tr>
<tr>
<td>After 3</td>
<td>90</td>
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Risk Factors for Depressive Recurrence

- Residual symptoms
- More than three prior depressive episodes
- Chronic depression (episode > 2 years)
- Family history of mood disorders
- Comorbidities (e.g., anxiety disorder, substance abuse)
Detecting Bipolar Disorder

- History of mood elevation
- Family history of bipolar disorder
- Sub-syndromal mood elevation
- Mixed states/racing thoughts
- Antidepressant associated mania
- Response to mood stabilizers
- No biological markers established

NIMH Collaborative Depression Study
- Depression as the Unmet-Need

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<thead>
<tr>
<th></th>
<th>Wks depressed</th>
<th>Wks manic</th>
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<tr>
<td>BP I</td>
<td>31%</td>
<td>10%</td>
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<tr>
<td>n=135</td>
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<tr>
<td>BP II</td>
<td>52%</td>
<td>1.4%</td>
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<tr>
<td>n=71</td>
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10 years follow-up; BP II - greater chronicity and comorbidity
Judd et al., Arch Gen Psych 2002; 59:530-537

Three Phases of Drug Therapy in Depression

- Acute Phase – attain response
- Continuation Phase – maintain control of symptoms; aim for remission
- Maintenance Phase – prevent recurrent episodes
Psychodynamic Perspectives on Depression
- Freud’s “Mourning and Melancholia”
- Ego psychology – the ego and ego ideal
- The affective state of the ego-helplessness
- Object relations theory – the power of unconscious identification, reenactment
- Self-psychology- Three Strands of Narcissism – self-love, self-esteem and omnipotence

Psychotherapy for Depression
- Cognitive Behavioral Therapy
- Interpersonal Psychotherapy for Depression
- Behavioral Therapy
- Psychodynamic Psychotherapy
- Problem Solving Psychotherapy
- Marital and Family Therapy

Pharmacotherapy of Depression
- Tricyclic antidepressants
- MAO – I antidepressants
- SSRI antidepressants
- SNRI antidepressants
- Atypical antidepressants
- Augmenting medications

Factors Effecting the Choice of Antidepressant
- Side effect profile
- History of previous response
- Family history of response
- Safety in overdose
- Differential effects in subtypes of depression

Selecting Among Antidepressants
- Initial choices – SSRI/SNRI
  - Half-life considerations
  - Activation – sedation
- Secondary options
  - Tricyclic antidepressants
  - Mirtazapine
  - Bupropion
- MAO-inhibitors
  - Phenelzine, Tranylcypromine
Treatment Recommendations

• In first episode patients
  – Use maximum tolerated dosage, Continue treatment for 6 months following remission. Discontinue medications gradually over 2-4 weeks.

• In patients with recurrent depression
  – Maintenance treatment for patients with three or more episodes of depression, or two severely disabling episodes.

Differences between the SSRIs

• Half-life of fluoxetine much greater than paroxetine

• Inhibition of P450 2D6 enzymes much greater with paroxetine and fluoxetine as compared to sertraline or citalopram

• Inhibition of P450 34A
  – Fluvoxamine delays clearance of alprazolam

• Inhibition of P450 1A2, 3A4, 2C9
  – Fluvoxamine delays clearance of warfarin, theophylline, propranolol, clozapine

SSRI Side Effects

• Jitters, fatigue, insomnia, headache
• Sexual dysfunction, erectile dysfunction, anorgasmia
• Weight gain may occur
• Rare risk of GI bleeding possibly due to inhibition of platelet function
• Inappropriate SIADH in the elderly
• Switch to mania, agitation
• Osteoporosis, risk of non-vertebral fracture in elderly (Diem et al, Arch Intern Med, 2007)

Serotonin Syndrome

• GI – cramping, diarrhea, bloating
• Neurological – Tremor, dysarthria
• Cardiovascular – tachycardia, hypertension
• Psychiatric – confusion, mania, restless

• Medications that may contribute:
  – Isoniazid, Linezolid
  – Tramadol, Dextromorphan, St. John’s Wort

SSRI Withdrawal

• CNS Symptoms
  – Sleep disturbance, vivid dreams
  – Anxiety, restlessness
  – Headache

• Parasympathetic Symptoms
  – Sweating, sialorrhea
  – Nausea, vomiting, cramps, diarrhea

Citalopram

• Highly selective SSRI; Minimal NE/Dopamine activity
• Dosage range 10 – 40 mg; QT prolongation FDA warning
• Metabolized by liver; No active metabolites
• SSRI side effects generally well tolerated
• Rare side-effects – hyponatremia, SIADH
• No in-patient depression studies conducted
Venlafaxine
• SNRI – serotonin effects at lower dosages;
• Norepinephrine effects at higher dosages
• Dosage range – 75 mg – 300 mg
• Monitor BP at higher dosage range
• FDA approved for generalized anxiety and major depression.
• Probable greater antidepressant efficacy at higher dosage
• Extended release formulation available

Wellbutrin (Bupropion)
• Dopaminergic/Noradrenergic agonist
• Stimulating antidepressant -75 -375 mg qd
– Sustained and Extended Release options
• No sexual dysfunction
• Contraindicated in patients with seizures
• Effective in ADHD
• Avoid concurrent use of stimulants
• Insomnia may be a side-effect
• Limited anti-anxiety properties; may cause anxiety

Standard MAOIs are Particularly Effective for:
• Atypical Depression
• Resistant Depression
• Elderly Depressives (maintenance effects)
• Social Phobia
• Neuroticism
• Interpersonal Hypersensitivity
• Phobic Avoidance

Mirtazapine
• Alternative to SSRI/SNRI
• Less sexual dysfunction
• Sedation and weight gain side-effects
• Anti-anxiety properties
• Dosage range 15-60 mg qd
• Excellent for sleepless, underweight patients, including elderly
• NE and 5HT1 agonist

Star D – Key Findings
• 1/3 of responders and ½ of remitters did so after 6 weeks of treatment
• Within class switch or out-of-class switch equally effective
• Limited number of patients chose cognitive therapy
• T3 did as well as lithium as an augmenter
• Level 4 results were somewhat disappointing with only 13% additional remitters.
• Remission predicts lower rate of subsequent relapse
  • Rush Am J Psychiatry 164:2 Feb 2007

Medical Conditions and Antidepressants
• Post –MI Depression: SSRI, SNRI and Bupropion are safe options.
• Post-Stroke Depression: Monitor hematologic indices to avoid SSRI induced bleeding
• Interferon treatment for Hepatitis – Depression a common side effect of Interferon. Antidepressant responsive

Post –MI Depression: SSRI, SNRI and Bupropion are safe options.
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Medical Conditions and Antidepressants

- **Hypertension** – SNRI (venlafaxine) may induce dose related increase in BP
- **Obesity, Diabetes** – Novel neuroleptics increase BS, lipids, may induce weight gain. Aripiprazole and ziprasidone less so than olanzapine.
- **Parkinson’s Disease** – Monitor for agitation, increased tremor with SSRI. Selegeline interactions.

Medical Conditions and Antidepressants

- **Pregnancy** – Avoid mood stabilizers including divalproate, carbamazepine. Avoid Paroxetine, particularly in first trimester. In severe depression, consideration of antidepressants is warranted. Fluoxetine and sertraline most extensively studied.
- **HIV** – Check specific drug-drug interactions. Citalopram has least 2D6 enzyme interactions.

Treatment Resistant Depression

- Depression treated with antidepressant medication at maximal dose for 4-6 weeks with at least one but usually two different agents sequentially
- Chronic Depression comprises 30-35% of all cases of depression – includes dysthymic disorder, major depression, dysthymia + MDD, and partially remitted MDD
- 50% of depressives will experience a chronic or recurrent course
- Single trial of single medication – response rates of 50-60%, remission rates of 35-45 %.
- 5-10 % of depressed patients will be refractory to multiple medication interventions

Heterogeneity of Treatment Resistant Depression

- Bipolar Depression and Latent Bipolar
- Axis II Co-morbidity
- Substance Abuse
- Anxiety Disorders
- Trauma, Abuse and Psychosocial Crisis
- Occult Medical Disorders
- Undiagnosed Sleep Apnea
- Schizoaffective, Schizophrenia Spectrum

Augmentation Medication Strategies for TRD

- Lithium – best established (7/9 controlled studies) Lower blood levels -0.4-0.6 meq/l effective
- T3 – 25-50 mcg. Efficacy established with TCAs
- Novel neuroleptics – Aripiprazole (Abilify). 5-10 mg (FDA approved)
- Olanzapine-Fluoxetine combination in bipolar depression

Adapted from Fagiolini and Kupfer, Biol Psychiatry 2003;53:640-648
Switch Strategies for TRD

- Changes within class – uncontrolled studies show variable response rates
- SSRI to TCA – 40% response in open study (SSRI to nortriptylene)
- SSRI to Venlafaxine (43% remission)
- SSRI to Mirtazapine – open study after 8 weeks, 48% respond

Combination Strategies for TRD

- TCA + SSRI – supported by several open studies; monitor TCA blood levels
- Controlled data on paroxetine and mirtazapine; 50% of non-responders to either responded to the combination
- Small case reports support methylphenidate and SSRI; Modafinil and antidepressants

Atypical Antipsychotics in TRD

- Aripiprazole Augmentation
- SSRI augmentation with risperidone or ziprasidone - may facilitate response
- Tranylcypromine and risperidone (0.5-2.0 mg qd); positive report in 5 non-psychotic TRD patients
- Olanzapine – fluoxetine combination – large meta analysis demonstrates efficacy in TRD
  - Medical Letter vol 53 Sept. 19, 2011, p 74-75

Electroconvulsive Therapy

- Key indications – Psychotic Depression, Suicidal Press, Food Refusal, Treatment Refractory Depression, Parkinson’s Disease, Refractory Manic Excitement.
- Medical Concerns – 4 deaths/100,000 treatments. Cardiac risks- recent myocardial infarction, unstable angina, hypertension, atrial fibrillation, post-cerebrovascular accident, intracranial aneurysm or space-occupying lesions or other causes of increased intracranial pressure.
- Post ECT maintenance – High rate of relapse particularly with psychotic depression; Post ECT medications - nortriptylene and lithium, MAO-I, Maintenance ECT.

Suicidal Behavior and Depression

- 20-40% of patients with an affective disorder exhibit nonfatal suicidal behaviors, including thoughts of suicide
- Estimates associate 16,000 suicides in the US annually with depressive disorder
- 18% of those with a history of major depressive disorder (MDD) attempt suicide
- 15% of patients with severe primary MDD of at least 1 month’s duration eventually commit suicide

Risk Factors for Suicide

- Previous Attempts
- Psychosis
- Major Depression or Bipolar Diagnosis
- Alcohol or Drug Abuse
- Losses, deaths, shame, poverty
- Social isolation, unmarried, homosexual
- Lack of access to clinical care
- Access to firearms, toxins, medicines
- History of violence or impulsivity
- Prominent anxiety or agitation

**Suicide in the Elderly**

- 11.6% of the population accounts for 17% of all successful suicide attempts
- 39% saw primary care physician in last week of life
- White males’ suicide risk is six times that of general populations
- Pre-morbid clinical stability
- Peak prevalence 75+ years
- Attempt-success ratio high
- Associated with ill health, alcoholism, and bereavement.


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**Suicide Risk Assessment**

- Press
  - The sense of urgency to die
- Perturbation
  - The degree of stress imposed on the patient
- Pain
  - The subjective sense of anguish
- Risk-Rescue Assessment
  - Previous attempts-assessment of lethality
    - Guns, jumping, hanging, drowning are particularly malignant
  - Previous attempts-assessment of attempts to obtain help
- Psychosis
  - Command hallucinations
- Personality Disorder, Depression, Substance Abuse

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**Antidepressants and Suicide Risk**

- Increased risk of suicidal ideation and behavior in children, adolescents and adults age 24 and younger
- No effect on suicidal ideation or behavior in adults age 25-65
- Reduction in suicidal ideation and behavior in adults 65 and older.
- Risk appears secondary to emerging hypomania or agitation

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**FDA Clinical Guidelines for Antidepressant Therapy**

- Monitor depressed patients closely early in treatment
- Screen for occult bipolar disorder
- Intervene if depression worsens
- Beware of emerging “activation” (anger, insomnia, restlessness, mania)
- Discontinue antidepressants slowly
- Educate patient and family about risks

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**Transcranial Magnetic Stimulation for Major Depression**

- Left prefrontal rTMS, sham controlled 3 weeks of daily weekday treatment
- 195 antidepressant drug free patients with unipolar, non-psychotic depression
- Moderately treatment resistant
- Primary efficacy analysis, 14.1 % remitters with active rTMS and 5.1 % with sham
- “Statistically significant and clinically meaningful antidepressant effect”
  - George et al. Arch Gen Psych 2010;167:281-288
**TMS Treatment Considerations**

- TMS – 30-60 minute sessions daily for 4-6 weeks; High cost - 6-9 K per course of treatment
- Patient must be still during the session
- No cognitive deficits or significant side-effects; No driving restriction
- Efficacy – Remission rate of 15-20% in patients refractory to 1 or 2 medications; No clear efficacy in agitated, psychotic or severely refractory depression

**Summary – Key Points**

- Assess the Depressive Spectrum – Appreciate the longitudinal history and co-morbidity
- Watch for latent bipolarity
- Careful follow-up to assess early side-effect experience – particularly in young adults and adolescents
- Watch for latent psychosis in the elderly
- Follow-up phone calls after beginning antidepressants - Outreach

**Disclosures - None**

**Question 1**

Latent bipolar disorders is commonly associated with all except one of the following:

a. Childhood onset of depression
b. Hypersomnia as a depressive symptom
c. Family history of bipolarity
d. Therapeutic response to monotherapy with antidepressants
e. High frequency of depressive episodes

**Answers**

Question 1 (d)

Bipolar depressed patients generally respond poorly to treatment with antidepressants alone. Lamotrigine is a preferred option, or use of low dose antidepressant combined with a mood stabilizer such as lithium.

Question 2 (b)

MAO –I medications cannot be combined with other antidepressants as a hypertensive reaction may occur.

**Question 2**

Medication strategies for treatment resistant depression include all but one of the following:

a. Augmenting antidepressants with lithium
b. Combining MAO-I with bupropion
c. Electroconvulsive therapy
d. Changing from SSRI to SNRI
e. Adding aripiprazole to antidepressant
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<td>Gibbons et al: Benefits from antidepressants Arch Gen Psychiatry 2012;69 (6):572-579</td>
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