MDD:  Primary Care Challenges

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A book about the potential of medications to modify personality traits....

.....that invigorated public discussion of depression
Hippocrates responds to claims of mental illness as inspiration...

...by designating melancholy as a *disease* of excess bile, leading to dejection, ulcers, rashes, lung diseases
Does heroic melancholy lend a nobleness....

....and make depression less than a disease?
“An utter depression of soul....

....the hideous dropping off of the veil.”
Is depression a heavy dose of artistic temperament?......

....and anti-depressants a means of remolding personality into a more acceptable form?
Are the depressed paying for their sins....
Depression as Disease

• The fourth leading cause of temporary and permanent disability in 1990
• Molecular and imaging technologies show abnormalities in:
  – Cell signaling
  – Neuronal and glial survival
  – Brain region connectivity
  – Genetic predisposition
  – Include ref

Rubinow DR. Treatment strategies after SSRI failure—the good and bad news. NEJM March 2006
Outline of Talk

- Diagnosis
  - Under-diagnosis or mis-diagnosis of depression in primary care?
  - Screening Tools
- Treatment: a focus on medications
  - Psychotherapy versus Medication
  - Monitoring and duration
  - Disease management programs
  - Comparison of classes of anti-depressants
  - Comparison of SSRI’s: efficacy, side effects, half-life
  - Suicide and SSRI’s
  - Bereavement and depression
  - Pregnancy and SSRI’s
  - Resistant depression
  - Somatization and depression treatment
# 3-Year Incidence and Probable Etiology of 14 Common Symptoms in 1000 Internal Medicine Outpatients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number with Symptoms</th>
<th>Organic Etiology (%)</th>
<th>Psychogenic Etiology (%)</th>
<th>Unknown (%)</th>
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</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>96</td>
<td>11</td>
<td>6</td>
<td>83</td>
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<tr>
<td>Fatigue</td>
<td>82</td>
<td>13</td>
<td>21</td>
<td>66</td>
</tr>
<tr>
<td>Dizziness</td>
<td>55</td>
<td>18</td>
<td>2</td>
<td>80</td>
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<tr>
<td>Headache</td>
<td>52</td>
<td>10</td>
<td>15</td>
<td>75</td>
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<tr>
<td>Edema</td>
<td>45</td>
<td>36</td>
<td>0</td>
<td>54</td>
</tr>
<tr>
<td>Back pain</td>
<td>41</td>
<td>10</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>37</td>
<td>24</td>
<td>3</td>
<td>73</td>
</tr>
</tbody>
</table>

### Prevalence of Major Depression in Patients with Medically Unexplained Symptoms versus Controls

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Lifetime Incidence of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Pain</td>
<td>CAD - 64%</td>
</tr>
<tr>
<td></td>
<td>CAD+ 16%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Irritable Bowel Syndrome 61%</td>
</tr>
<tr>
<td></td>
<td>Inflammatory Bowel Disease 17%</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>Fibromyalgia 86%</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid Arthritis 31%</td>
</tr>
</tbody>
</table>

Primary Care: Mis-diagnosis of Mental Disorders

- Only 33% of patients with a DSM-IV mental disorder receive treatment
- Medical treatment provided to patients who do not meet DSM-IV criteria (about ½ of treated patients)
- Treatment monitoring and duration not optimal

**DSM-IV Diagnosis**

- **Major Depressive Disorder**
  - At least 2 weeks of depressed mood and anhedonia and at least 5 associated sx: depressed mood, anhedonia, appetite, guilt, concentration, Suicidality, motor, sleep, ? libido

- **Dysthymia**
  - Depressed mood most days for at least 2 years. Does not meet criteria for MDD

- **Subsyndromal Depression (Or “Minor” or “Subthreshold”)**
  - Depressed mood at least 2 weeks, with fewer symptoms than MDD

- **Melancholia**
  - Severe MDD with anhedonia as major feature.
  - Includes early awakening, motor effects, and anorexia or weight loss
Screening Tools

• **Patient Centered Interviewing** techniques superior?
• **PHQ-9**: valid in primary care and reliable—does not require follow-up confirmation of diagnosis
  - Score > 10 likely MDD, > 20 Severe MDD
  - Can be used to follow response to treatment
• **PHQ-2** (anhedonia or depressed mood in past 2 weeks)
  - Sensitivity is 0.83 and specificity 0.92 for score >=3
• **Widespread Screening** of depression in primary care
  - Has not been shown to improve management or outcome of depression
• **Bipolar Screen** (family hx, mania, sleep, racing thoughts, Mood Disorder Questionnaire—MDQ or BSDS)
Therapy and public perception

From the extreme.....
Discussion with patient

• WHAT IS THE PATIENT’S PERCEPTION OF DEPRESSION AND ITS TREATMENT?
• Depression is common (15 to 20% life incidence)
• Associated with emotional and physical sx
• Due to chemical changes in the brain
• Medication and/or psychotherapy shortens the course and diminishes sx
Psychotherapy versus pharmacotherapy

• 69% of 203 pharmacotherapy trials sponsored by pharmaceuticals
  – “Real-World” study showed 28% remission in mean time of 6.7 weeks; 47% response rate (>= 50% reduction in symptom scores)

• Depression-specific psychotherapy with equivalent outcomes to well-monitored pharmacotherapy

• Combined psychotherapy and pharmacotherapy with better response than either alone
  – ? Cost effective; ? a viable option

Medication Choice

• Similar efficacy but less side effects for 2\textsuperscript{nd} generation versus 1\textsuperscript{st} generation anti-depressants
  – 1\textsuperscript{st} generation: tricyclics, MAO inhibitors
  – 2\textsuperscript{nd} generation: SSRI, SSNRI (duloxetine), SNRI (venlafaxine, mirtazapine), and other (bupropion)

Impact on Associated Symptoms

• No clear evidence of improved superiority of any 2nd generation agent impact on:
  – Anxiety
    • (10 head to head trials)
  – Sleep
    • (some mixed results over 8 head-to-head trials)
  – Pain
    • (Duloxetine versus paroxetine in 4 head-to-head trials)
Rates of Adverse Events

• GI side effects/Headaches/anxiety
  – similar side effect profiles
• Sexual Dysfunction
  – Rates are likely under-reported
  – Bupropion lower rate than fluoxetine
  – Paroxetine higher rate than multiple other SSRI’s
• Weight Gain
  – Paroxetine and Mirtazapine more weight gain than sertraline, trazodone, or venlafaxine
Therapy: Monitoring and Duration

• Assess for response and side effects 1-2 weeks after initiation of therapy
• Modify therapy at 6-8 weeks if insufficient response
• 4 to 9 months after a satisfactory response for first time episode
• Longer duration may be beneficial for patients with 2 or more episodes of depression

Disease Management Programs

• Studies of primary care nurses or telephone-based health coaches showed similar benefit

• 10% gain in depression recovery and appropriate treatment over 1 year

• Between 2 to 4 weeks of more work days in a year

• DH managed care: health coaches after SSRI initiation

Wells KB. Reducing the burden of depression. JAMA September 2007
Treatment of depression in selected populations

- No convincing difference in efficacy between agents for age, race, and sex
- Based on subgroup analyses in numerous studies: need RCT’s for these subgroups
Treatment-Resistant Depression

• Definition: failure to produce significant clinical improvement with trials of 2 different pharmacological classes of anti-depressant
  – Reassess dx, adherence, and barriers
• Augmentation with psychotherapy effectiveness is reasonable although evidence limited (1 high quality RCT)
• No good evidence for superior medication treatment strategy (Star*D Trial)—initial therapy citalopram
  – Level 2 (remission 25% response rate 25%)
    • Switch agents: sertraline, bupropion, or venlafaxine
    • augment with buspirone or bupropion or CBT
  – Level 3 (remission rate 8-20%; response rate (13-23%)
    • Switch agents mirtazapine or nortriptyline
    • Augmentation of citalopram with tri-iodothyronine, lithium, CBT
SSRI discontinuation and withdrawal
Discontinuation of SSRI’s

- Withdrawal sx: HA, GI, anxiety, insomnia
- ½ lives of SSRI’s after multiple doses: Fluoxetine > Citalopram > Sertraline > Fluvoxamine > Paroxetine
- Withdrawal sx observed with venlafaxine (not well studied), but infrequent with bupropion
- Small trial (N=28) comparing taper over 3 days versus 2 weeks showed no difference in withdrawal
- Common recommendation: taper over 2 to 4 weeks; dose reduction of 25% per week

Bereavement or depression?
Depression in Bereavement

• Part of the normal grieving process or a harbinger for prolonged, substantial morbidity?

• Expert opinion: treat for depression if meet criteria for MDD 6-8 weeks after a major loss
  – Studies (few and small) show decreased depressive symptoms but unchanged grief symptoms

• Risk factors for poor bereavement outcomes
  – Poor social support
  – h/o depression or psychiatric illness
  – Major concurrent stressors
  – h/o abuse or neglect
SSRI’s and Suicide
SSRI’s and Suicide in Adults
Two Contrasting Hypotheses

- **RCT’s**: No evidence of increased Risk
  - Small studies of short duration
  - Often exclude at-risk patients
- **Meta-analyses**: Increased SI
  - SI sometimes used as surrogate for suicide risk
- **Ecological Studies**: decreased suicides or no change in suicides with increased SSRI prescriptions
- **Observational Studies**: no difference in risk in SSRI’s and TCA’s
  - Confounding by indication
  - Small numbers of suicides
- **Conclusions**
  - If risk is increased, it is likely small
  - Benefits, at least in adults, outweigh risks
  - Prudent to monitor SI in first weeks of treatment (dz management programs)

Risk of teratogenicity from SSRI’s?
SSRI’s and teratogenicity

- Based on pharmaceutical safety data and 3 large studies
- Retrospective case-control methods
- Mixed results regarding risk of: cardiac malformations and CNS/neural tube defects
- Data suggests a small increased absolute risk of teratogenicity, unlikely to exceed absolute 1%
  - Risk may be higher with paroxetine

Greene MF. SSRI’s and teratogenicity NEJM June 2007
Somatization and Depression

- Kroenke: over 2/3 of somatic symptoms have no identifiable organic etiology
  - Hypothesis: psychosocial factors often precipitate symptoms
- Somatoform Disorder and concomitant MDD
  - Somatic Sx diminish with pharmacotherapy/CBT
- Somatization and failure to meet DSM criteria of MDD
  - Limited study of SSRI’s/psychotherapy

“On the plus side, you’ve cured my back pain.”