Disclosure

Relevant Financial Relationships
Research support: AHRQ, Mayo Foundation

Off-Label/Investigational Uses
None
Mental health and substance use disorders affect an estimated 450 million people worldwide.

World Health Organization. *Investing in Mental Health*, 2003
Burden of depression in the U.S. and worldwide

• Estimated lifetime prevalence: 16.9%
• Estimated 12-month prevalence:
  • 3.2% without comorbid chronic medical illness;
  • 9.3%-23.0% with comorbid chronic medical disease
• Major depression is fourth-highest cause of disability worldwide
• By 2020, major depression will be the second-highest cause of disability worldwide
Major depressive disorder (DSM-5)

**Criterion A. Five or more:**
- Depressed mood*
- Anhedonia*
- Appetite/weight change
- Changes in sleep duration
- Observable psychomotor change
- Fatigue/loss of energy
- Feeling worthless, excessive guilt
- Poor concentration, decision making
- Suicidality/thoughts of death

**Criteria B-E:**
- Impairment in ≥1 life domain
- Not caused by substance(s) or medical condition(s)
- Depression not better explained by psychotic illness(es)
- No evidence of manic or hypomanic episodes
DSM-5 Field Trials in the U.S. and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses

Intra-class kappa

- Schizophrenia
- Schizoaffective
- Bipolar I
- MDD
- GAD
- PTSD
- Alcohol use
- Binge eating
- Major neurocog.
- Borderline pers.
- Antisocial pers.

Clinical heterogeneity and treatment outcome

- 60% of patients do not fully recover following a single antidepressant trial
- Personalized treatment approach is therefore needed
- No single set of assessments predict antidepressant treatment outcome with sufficient validity for routine clinical use
- Serially conducted therapeutic trials (systematic trial-and-error) is the main approach

Clinical subtyping in patients with MDD

- Melancholic depression
- Psychotic depression
- Atypical depression
- Anxious depression (MDD with anxious distress)
- Seasonal affective disorder (MDD with seasonal pattern)
- Perinatal depression (MDD with peripartum onset)
- Single episode, recurrent, chronic
- Mild, moderate, severe
Criteria for clinically significance of MDD subtypes:

- Unique genetic or neurobiological characteristics
- Prognostic implications
- Treatment implications

Clinical importance of psychotic depression

• Risk factor for bipolar depression

• 5x the rate of suicide in hospitalized patients with MDE + delusions, vs. MDE without delusions

• Combination pharmacotherapy (AD + APD) is mainstay
  • Few specific combinations have been studied

• ECT is especially advocated
  • Very few direct comparisons with combination pharmacotherapy
Pharmacological treatment for psychotic depression

Systematic review of 12 RCTs (929 participants)

<table>
<thead>
<tr>
<th>Risk Ratio (Clinical Response)</th>
<th>Primary intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X^2=0.0, df=1, I^2=0.0%$</td>
<td>APD vs. PLC</td>
<td>RR 1.1 (0.7,1.7)</td>
</tr>
<tr>
<td>$X^2=0.2, df=1, I^2=0.0%$</td>
<td>AD + APD vs. PLC</td>
<td>RR 1.9 (1.2,2.8)</td>
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<tr>
<td>$X^2=2.1, df=3, I^2=0.0%$</td>
<td>AD + APD vs. PLC + APD</td>
<td>RR 1.8 (1.4,2.4)</td>
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<tr>
<td>$X^2=2.8, df=4, I^2=0.0%$</td>
<td>AD + APD vs. PLC + AD</td>
<td>RR 1.4 (1.1,1.8)</td>
</tr>
</tbody>
</table>

ECT Remission Rates: Psychotic vs Nonpsychotic Depression

- Multi-site randomized trial – 253 psychotic and non-psychotic MDD patients
- Bitemporal ECT at 50% above seizure threshold, up to 12 treatments


* Pooled t-test, p<0.0001

**Remission rates:**
- Psychotic: 95%
- Non-psychotic: 83%
Misdiagnosis of psychotic major depression

- **Population studies** -- prevalence estimates for MDD + hallucinations and/or delusions:
  - 14–19% of patients with MDD
  - Lifetime population prevalence >2%

- Samples of **hospitalized depressed patients** -- up to 25% meeting criteria for psychotic depression (PD)

- **63% misdiagnosis rate**, usually due to missing the psychosis, rather than the mood disorder

References:
Psychotic depression: clinical features and questions

- **Delusions** are more common than hallucinations or having both delusions and hallucinations (11% vs. 7% vs. 1% of patients with MDE)
  - Pathological guilt
  - Worthlessness
  - Hopelessness
  - Nihilistic thoughts
  - Persecutory themes
  - Fidelity
  - Somatic delusions

Psychotic depression: clinical probes

- Are you a good person? Do you feel guilty? Do you deserve to feel this way?
- Do you feel worthless? Why?
- Do you feel you are the cause of problems for others? What problems? Why?
- Have you done things that are unpardonable? Do you feel you (need to be) punished for something you have done?
- Are you being watched or monitored (spied upon/followed) by anyone? Are you being singled out for any reason? Are you feeling threatened by anyone? Are others trying to do you harm?
- Do you have something physically wrong with you? Can you explain your concerns to me? What evidence do you have?
Clinical importance of seasonal depression

• Classical description
  • Recurrent (by definition)
  • Onset usually in Fall, resolution by late Spring
  • Full inter-episode recovery

• Missed diagnoses
  • Geography – prevalence <2% in Florida, 10% in New England
  • Subsyndromal worsening 2-3 times more common
  • Residual subsyndromal depression also common
The efficacy of light therapy (luminotherapy) in the treatment of mood disorders

- Seasonal depression (bright light) Cohen’s d=0.84
- Non-seasonal depression (bright light) Cohen’s d=0.53
- Non-seasonal depression (adjunctive bright light) Cohen’s d=-0.01

Seasonal depression: missed diagnosis

- Outcomes of Depression International Network (ODIN) project
  - Diagnostic surveys to assess prevalence and RF’s for depression in Europe (n=1,250 respondents)
  - Screen (+) for seasonal depression: n=66 (5.3%)
  - Confirmed (+) for seasonal depression: n=25 (2.4%)
    - Previous diagnosis: n=1 (4%)
    - Previous antidepressant treatment: n=15 (60%)
    - Previous luminotherapy: n=0 (0%)

Forms of depression possibly related to sensitivity to fluctuating gonadal steroid levels

- **Premenstrual dysphoric disorder (PMDD)**
  - 5 of 11 symptoms – last week of luteal phase, remission within a few days of onset of menstrual flow

- **Post-partum depression (MDD with peripartum onset)**
  - Onset of mood symptoms during pregnancy or in the first 4 weeks following delivery

Both are risk factors for depression in menopause transition.
Depression in women during midlife: risk of CV mortality

Severe depressive symptoms and/or AD use and their relationship to cardiac events in the Nurses' Health Study, 1991-2000
Risk of CV death: HR 1.49, 95% CI 1.11-2.00
Depression Subtypes in Predicting Antidepressant Response: A Report From the iSPOT-D Trial

Features of depression that (may) predict poorer response to antidepressants

• Chronic (rather than episodic) depression (15-25%)
  • Dysthymic disorder
  • Major depression + dysthymic disorder
  • Chronic major depression
• Mild depression
• Clinically significant anxiety
  • Clinically significant (subsyndromal) symptoms
  • Comorbid syndromal anxiety (especially if chronic, e.g., GAD)
Difference in Treatment Outcome in Outpatients With Anxious Versus Non-anxious Depression in STAR*D

A. Time to response

<table>
<thead>
<tr>
<th></th>
<th>Anxious depression</th>
<th>Non-anxious depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1,490</td>
<td>1,324</td>
</tr>
<tr>
<td>4 weeks</td>
<td>1,397</td>
<td>1,243</td>
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<tr>
<td>6 weeks</td>
<td>1,065</td>
<td>939</td>
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<tr>
<td>9 weeks</td>
<td>769</td>
<td>647</td>
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<tr>
<td>12 weeks</td>
<td>485</td>
<td>399</td>
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<tr>
<td>14 weeks</td>
<td>255</td>
<td>182</td>
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<tr>
<td>16 weeks</td>
<td>95</td>
<td>62</td>
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</table>

Log-rank statistic=22.7, p<0.0001.

B. Time to remission

<table>
<thead>
<tr>
<th></th>
<th>Anxious depression</th>
<th>Non-anxious depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1,524</td>
<td>1,345</td>
</tr>
<tr>
<td>4 weeks</td>
<td>1,428</td>
<td>1,269</td>
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<tr>
<td>6 weeks</td>
<td>1,210</td>
<td>1,055</td>
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<tr>
<td>9 weeks</td>
<td>968</td>
<td>829</td>
</tr>
<tr>
<td>12 weeks</td>
<td>667</td>
<td>562</td>
</tr>
<tr>
<td>14 weeks</td>
<td>410</td>
<td>312</td>
</tr>
<tr>
<td>16 weeks</td>
<td>161</td>
<td>115</td>
</tr>
</tbody>
</table>

Log-rank statistic=41.7, p<0.0001.
Antidepressant Drug Effects and Depression Severity: A Patient-Level Meta-analysis

Meta-analysis of 6 randomized trials of FDA-approved AD’s for MDD
Persisting depression/anxiety and high stress-reactivity with super-imposed major depressive episodes

Mild but chronic (and disabling) depression and anxiety/worry

Formulation on the fly: rumination and disengagement

- **Rumination**
  - Very common residual symptom
  - Contributes to chronicity and therapy resistance
  - Contents can be anxious, depressive, or both

- **Passive coping**
  - Disengagement, isolation, inactivity, excessive distraction, substance use, other “escape” behavior
  - Leads to feelings of guilt, further reduction in self esteem, increased sense of helplessness

Applications in the clinic

• Need to actively screen for:
  • Psychosis (especially delusions)
  • Seasonal pattern of onset/resolution and relative exacerbation/alleviation of persisting symptoms
  • Comorbid anxiety disorders and symptoms

• Chronic, mild depressive disorders can respond to antidepressants, but hard to achieve remission with medication alone

• Formulation on the fly – behaviorally targetable factors that sustain misery but are amenable to change