Treating Depression in the Primary Care Office

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Disclosures

- Harvard Pilgrim quality grant
- Blue Cross provider council
Objectives

• Preparing the Practice—update on effective care models to treat depression in Primary Care settings

• Preparing the Practitioner—update on specific expertise for the practitioner and on adaptive expertise (what do best providers do?). You will be wise as well informed.
Hope to Cover

• A helpful heuristic model for PCP and Patient
• Key Role of the provider-patient relationship
• The collaborative care model for treating depression in the primary care office
• The screening-in-primary-care debate
• Recent studies to guide antidepressant use
• Any questions on your mind.
What is depression—a better theoretical model

• Why models matter clinically
  – Patient beliefs influence outcome (less biological belief systems correlate with better outcomes)
  – Models may influence beliefs (a cornerstone for many therapies of depression)
  – A shared treatment rationale correlates with treatment alliance (strong positive predictor of response)
  – Feeling understood correlates with positive outcomes (how we explain depression matters)
Features of a good model

• Supports patient role in dealing with depression and preventing it
• Supports “therapeutic” interventions—belief and behavior changes
• Helps PCP in engaging a wide variety of patients with different beliefs—create a common understanding and basis for Tx
• Should offer an explanation of the key aspects of depression—persistence, vulnerability, low mood/anhedonia, thinking changes, behavior changes.
• Consistent with science, but readily understandable
Convergence of psychological theories and neuroscience

• Moving well beyond “chemical imbalance”
  – Promotes passive patient role
  – Poorly connected to many patients’ beliefs
  – Pharmaceutically centered
  – Feeble explanation and not c/w current science

• Alternative model— “negative feedback loop”
  – Explains equilibrium—”stuckness”, persistence
  – Explains how many vulnerabilities can lead to same clinical condition (integrative and inclusive)
  – Correlates with many psychological therapy models
  – Consistent with new neuroscience of depression
Depression as a stuck state
Cognitive model as example

• Cognitive models: Negative schema arise from life experiences and biological predisposition
• These dysfunctional attitudes generate cognitive vulnerability (biases in thinking, attention, perception, memory, and so on)
• Can get activated by stressful events
• Leads to getting stuck in pervasive and persistent state—depression.
Neural mechanisms of the cognitive model of depression

Nature Reviews Neuroscience 12, 467-477 (August 2011)
Vulnerability
- Genetic
- Personality

Environmental triggers

Schema activation
- Increased amygdala and ACC activity
- Reduced serotonin binding in ACC, putamen and thalamus
  - Increased MPFC activity
  - Deficient serotonin binding in PFC

Biased attention
- Increased and sustained amygdala activity
- Increased rostral ACC activity when inhibiting negative stimuli
- Decreased right VLPFC, DLPFC and right SPC activity

Biased processing
- Increased and sustained amygdala reactivity to negative stimuli
- Increased thalamic activity
- Blunted NA and caudate nucleus responses to positive stimuli (positive blockade)
  - DLPFC hypoactivity associated with decreased amygdala reactivity to negative stimuli
  - PFC hypoactivity correlated with truncated NA activity and decreased positive mood

Biased memory and rumination
- Increased amygdala, hippocampus and ACC activity
- Increased amygdala activity correlated with increased hippocampal, caudate and putamen activity, which in turn predicts recall of negative information
  - Increased MPFC activity
  - Decreased DLPFC activity

Depressive symptoms
Comparing depressed patients to controls in response to negative stimuli—Loss of capacity for reappraisal correlates with loss of “top-down” control


<table>
<thead>
<tr>
<th>Structure</th>
<th>Direction of Effect</th>
<th>Valence Specific Effect?</th>
<th>Talairach Coordinates</th>
<th>Cluster Size (mm$^3$)</th>
<th>Number</th>
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<tbody>
<tr>
<td>Amygdala</td>
<td>Depressed &gt; Comparison</td>
<td>Yes</td>
<td>24, –4, –13</td>
<td>318</td>
<td>1</td>
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<td>Dorsal anterior cingulate cortex</td>
<td>Depressed &gt; Comparison</td>
<td>Yes</td>
<td>–2, 30, 20</td>
<td>196</td>
<td>2</td>
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<td>Insula and superior temporal gyrus</td>
<td>Depressed &gt; Comparison</td>
<td>Yes</td>
<td>–38, –6, –8</td>
<td>834</td>
<td>3</td>
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<tr>
<td>Precentral gyrus</td>
<td>Depressed &gt; Comparison</td>
<td>Yes</td>
<td>–30, –15, 44</td>
<td>621</td>
<td>–</td>
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<tr>
<td>Middle temporal gyrus</td>
<td>Depressed &gt; Comparison</td>
<td>Yes</td>
<td>–39, –64, 17</td>
<td>440</td>
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<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>Comparison &gt; Depressed</td>
<td>Yes</td>
<td>30, 13, 47</td>
<td>1,380</td>
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<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>Comparison &gt; Depressed</td>
<td>No</td>
<td>–22, 27, 42</td>
<td>949</td>
<td>–</td>
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<tr>
<td>Caudate body</td>
<td>Comparison &gt; Depressed</td>
<td>No</td>
<td>10, 20, 6</td>
<td>382</td>
<td>5</td>
</tr>
</tbody>
</table>
How to interrupt negative feedback loops (Peter Senge—Fifth Discipline)

- Symptomatic solutions bring us further from fundamental solutions perpetuating the problem. *Lying in bed is a solution to anergia, but at the end of the day leaves you feeling more depressed!*
- Change requires supporting the fundamental solution—e.g. behavioral activation
Therapies intentionally interrupt negative feedback loop, prime the pump for a positive feedback loop and upward spiral

- **Cognitive Therapy**: negative attitudes reinforce negative biases in attention, memory, processing—change the thinking and the mood will lift
- **Problem Solving Therapy**: problems pile up increasing depressed mood, making problem solving more difficult—help solve problems and you’ll lift mood
- **CBSAP**: low mood creates passivity and magical thinking (I need to feel better to do better—most of us do things to feel better)—reverse this behavior and create a positive feedback loop
- **IPT**: depression can lead to social isolation, relational problems can lead to depression (bidirectionality). Improving relational situation
- **Mindfulness based Tx**: ruminative thinking perpetuates persistent depressed mood—support contemplative thinking and the mood may lift
- **Somatic therapy**: neural network correlates to negative feedback loop—interrupt the loop—meds, DBS, ECT, rTMS and restore functioning
Also a model for treatment difficulties and relapse prevention

• Predisposing vulnerabilities from many paths create a tougher rut
  – Genetic
  – Childhood trauma (learned helplessness)
  – Life experiences

• Current factors make it harder to escape rut
  – Ongoing external stressors (poverty, violence, etc)
  – Ongoing substance abuse
  – Pain, Co-morbid medical illness, other misery

• Relapse prevention as well as acute treatment can be improved through multiple paths
Other things besides treatment can break the loop—a good thing!

- Positive events and good fortune
- Fresh thinking, new philosophies
- Spiritual awakening and epiphany
- Affection, new relationships, repair

Supports an open mind in provider and patient

Inquire about patient and family efforts

Encourage a variety of approaches

Maintain hope—even if provider and patient are stumped, it’s an open system
Preparing the Practitioner: Why you matter

Start with an old 1989 study — compared CBT, IPT, meds-CM, Placebo-CM


National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments.

250 Patients with moderate to severe depression randomized to:
- Cognitive Behavioral Tx
- Interpersonal Tx
- Imipramine/Case mgt
- Placebo/Case mgt

16 to 20 week manualized treatments, trained therapists, ongoing supervision, multi-site

Assessed by symptom and functional scales
Findings—typical of comparison studies for the treatment of depression

- High response in placebo group (caution—this was a very active “placebo” with intense CM)
- All of the treatments had similar outcomes for moderate depression (the Dodo bird effect)
- For severe depression medication edged therapy
- A lot of variation in outcome among the providers in each group, some variation among sites

• Analysis of videotapes of TDCRP sessions
• Assessed for quality of treatment alliance
• How well provider and patient working together—quality of interaction, agreement on goals and roles, shared expectations
• Alliance highly predictive of outcome across treatment modalities including medication
Interesting findings in subsequent analyses of the TDCRP data and videotapes

• Quality of Treatment alliance could reliably be assessed in first meeting
• This predicted outcome more than treatment selection or fidelity to treatment!
• Patient variables more predictive than therapist variables (some people are good at collaboration and getting help)
• The psychiatrists with good alliances performed better with placebo than the psychiatrists with poor alliances armed with medications
Follow-up analyses over the next 20 years...

• Treatment works for depression
• Lots of treatments work for moderate depression; meds more critical for severe depression
• Treatment relationship matters as much as treatment selection when reasonable treatment provided
• Patient variables important for good treatment relationships—(risk factors—severity of illness, personality disorders, substance abuse, trauma history)
• Provider variables matter, but not as much as patient variables (empathic and validating style, provider interest and experience with depression)
• Findings extended to Primary Care Settings
Implications for primary care

• We can improve outcomes in primary care settings by
  – Picking only “good” patients for our practices—ethical? Is current benchmarking ethical?
  – Improving practitioners’ routine expertise (standards) and adaptive expertise (response to patient variation, particularly patients with poor collaboration histories in clinic and in life).
  – Preparing patients for their role

• Being a good practitioner can improve both the patient’s mood and the provider’s mood
Why treat in the Primary Care setting?

(Simon Gilbody in Depression in Primary Care, Cambridge Univ Press, 2011, )

• The burden is great (*leading disability 18-44 y/o*)
• The treatment gap is enormous (*1/4 adequate tx*)

**And some potential advantages over specialty care!:**

• Mental health and physical health problems are interwoven (*comorbid RR of 1.81 for overall mortality*)
• Primary care for mental health enhances access (*10% lifetime incidence for men/20% for women*)
• Respects human rights (less stigma)
• More affordable and cost effective
• Generates good health outcomes
Collaborative Care Models for treating Depression in Primary Care

• Many RCTs support adapting Chronic Disease Management models to the treatment of depression
• Similar key elements developed to treat depression:
  
  – Self-management support (helping the patient care better for themselves—websites, books, info, etc.)
  – Delivery system design (a proactive plan involving a team—screening, plan for contacts and follow-up, focus on adherence to the plan)
  – Decision support (helping the PCP—guidelines, consultation)
  – Clinical information systems (registries to allow system monitoring, supports for providers and patients to stay on track—how is the patient doing? How are the patients doing)
Collaborative Care Models Work—Cumulative Meta-analysis, Gilbody et. al Archives of Internal Medicine, November 2006
Recent Cochrane Review 2012
Archer et al. October 17, 2012

• 79 RCTS for collaborative care models for treatment in primary care involving 24,000 patients
• Significant improvement over TAU for short to long term care up to 2 years
• Significant improvement in primary outcome measures (depression symptoms) and secondary outcome measures (mental health QOL and satisfaction)
Typical elements of Collaborative Care Models for the treatment of depression

- Prepared practices—measurement based care, stepped care, a plan
- Care managers track outcomes, support follow-up, educate patients, may provide PST, help with referral for more difficult cases
- Specialist consultations and registry review
- Activated, involved patient
  - [http://www.depression-primarycare.org](http://www.depression-primarycare.org) MacArthur
  - [http://www.depressioninprimarycare.org/](http://www.depressioninprimarycare.org/) RWJ
  - [http://impact-uw.org/](http://impact-uw.org/) IMPACT study for older adults
RESPECT-D Response Rate (50% Drop in HSCL)

- **3 Months:**
  - TCM: 60%
  - Usual Care: 50%
- **6 Months:**
  - TCM: 60%
  - Usual Care: 50%
RESPECT-D Remission (HSCL <0.5)

- TCM
- Usual Care

3 Months: TCM 30%, Usual Care 20%

6 Months: TCM 40%, Usual Care 30%
Screening—second thoughts about Routine screening in primary care

• The USPSTF recommends screening adults for depression when staff-assisted depression care supports are in place.

• And with less certainty: The USPTF recommends against routinely screening adults for depression when staff-assisted depression care supports are not in place. There may be considerations that support screening for depression in an individual patient.

• NICE guidelines do not recommend routine screening in primary care (but do identify at risk populations where screening is recommended—high prevalence, e.g., prior history of depression, significant physical illness, disability, alcoholism, post-partum, the elderly, unexplained symptoms, victims of abuse—or hard to detect—e.g., parkinson’s, dementia.)
Rethinking recommendations for screening for depression in primary care
Thombs et. al. CMAJ, October 2012

• Surprisingly very little data on the specific question—does routine screening in primary care settings lead to improved outcomes

• Does screening really identify new cases that end up being helped?—NNT estimated as high as 700!

• Possible problems
  – Cost
  – False positives
  – Over treatment of self-remitting mild cases
  – Overemphasis on medication
  – Negative impact of labeling

• Don’t throwaway those PHQ-9’s yet!—very helpful in assisting diagnosis and monitoring treatment
Integrating these concerns

• Your listening still probably most important
• Formal screening should be part of a plan for your practice—not an isolated step
• If you do screen, consider non medication interventions for milder cases—can include watchful waiting, self-help, educational material, therapy referral
• If you don’t routinely screen, consider adding simple inquiry or screening about depression for high risk patients
• Support evidence based choice
8 key questions beyond the detection of a depressive episode

• **Is this recurrent depression?**
  – >50% of patients with MDD have recurrence
  – 70% with second episode have third
  – 90% with third episode have fourth
  – Need to understand what has and has not worked previously
  – Recurrence is a strong indicator for maintenance treatment

• **Is there a pattern of substance abuse?**
  – Frequent co-morbid condition and impacts treatment
How severe is the episode?
PHQ-9 can be used to assist in assessing severity
Treatment recommendations from RESPECT trials.

<table>
<thead>
<tr>
<th>PHQ-9 SCORE</th>
<th>PROVISIONAL DIAGNOSIS</th>
<th>TREATMENT RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9</td>
<td>Minimal symptoms (unless dysthymia)</td>
<td>Support, educate to call if worse; return in one month</td>
</tr>
<tr>
<td>10-14</td>
<td>Minor depression</td>
<td>Support, watchful waiting</td>
</tr>
<tr>
<td></td>
<td>Dysthymia</td>
<td>Antidepressant or psychotherapy</td>
</tr>
<tr>
<td></td>
<td>Major Depression, <em>mild</em></td>
<td>Antidepressant or psychotherapy</td>
</tr>
<tr>
<td>15-19</td>
<td>Major Depression <em>moderately severe</em></td>
<td>Antidepressant or psychotherapy</td>
</tr>
<tr>
<td>&gt;20</td>
<td>Major Depression <em>severe</em></td>
<td>Antidepressant and psychotherapy</td>
</tr>
</tbody>
</table>
• **Is there a history of bipolar illness?**
  – History of prior manic episodes can be difficult to elicit, family histories usually not helpful and no great screening tools
  – Bipolar type 1 and type 2

• **Is psychosis present?**
  – Poor response to antidepressants alone. Indication for antipsychotic medication. Consider referral.
• **Is there a history of trauma?**
  – Current abuse and violence should be addressed
  – Past history may impact treatment decisions
  – If positive history, screen for PTSD

• **Is there a history of chronic mood problems?**
  – Dysthymia—persistent subsyndromal symptoms
  – Mood and behavioral lability, dysphoria, interpersonal conflicts, self-destructive behaviors c/w borderline PD
  – Co-morbid anxiety disorders that place patient at risk for recurrence and may impact tx decision
Is the patient suicidal?
Assessing Suicidality

THE BEST PRACTICES
• Routinely screens for suicidal ideation and previous history in depressed patients
• Assess risks and protective factors
• Provides information about warm lines and local emergency numbers
• 1-800-273-TALK
• Suicidepreventionlifeline.org
• On facebook, twitter, myspace
• Materials for spanish speakers

THE BEST PRACTITIONERS
• Comfortable with asking about suicidal thinking
• Attuned to making the patient comfortable with the discussion—tips:
  • The segue from eliciting mood
  • May explain the common nature of SI in depression
  • May explain the reasons for asking and monitoring—safety plan and a barometer
  • Elicits collaboration in dealing with risk
Prescribing antidepressants: A closer look at STAR-D
Sequential Treatment Alternatives to Relieve Depression

Figure 1
STAR*D treatment levels

Level 1
- Citalopram

Level 2
- Switch to:
  - bupropion (sustained release), or
  - venlafaxine (extended release), or
  - sertraline, or
  - cognitive therapy
- or Augment with:
  - bupropion (sustained release), or
  - buspirone, or
  - cognitive therapy

Level 2a (only for those receiving cognitive therapy in level 2)
- Switch to:
  - bupropion (sustained release) or
  - venlafaxine (extended release)

Level 3
- Switch to:
  - mirtazapine or
  - nortriptyline
- or Augment with:
  - lithium or
  - T3 thyroid hormone

Level 4
- Switch to:
  - tranylcypromine or
  - mirtazapine + venlafaxine (extended release)
STAR-D

- Largest clinical trial in “real life” settings
- 4041 patients
- Few exclusions
- Well represented primary care and MH settings
- Equipoise-stratified randomization
- 12 weeks at each level, up to 4 levels
- One year follow-up
A real life sample

• Recruited from 23 MH practices 18 Primary care with similar profiles
• 61% with co-morbid psychiatric disorder
• 75% with recurrent depression
• Mean of 7 lifetime episodes
• Average duration of illness>16 years
### Primary Results for 4041 patients

<table>
<thead>
<tr>
<th>Level</th>
<th># Entering Treatment</th>
<th>Remission Rate (%)</th>
<th>Relapse Rate (%)</th>
<th>Intolerance Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>3671</td>
<td>36.8</td>
<td>33.5</td>
<td>16.3</td>
</tr>
<tr>
<td>Level 2</td>
<td>1439</td>
<td>30.6</td>
<td>47.4</td>
<td>19.5</td>
</tr>
<tr>
<td>Level 3</td>
<td>390</td>
<td>13.7</td>
<td>42.9</td>
<td>25.6</td>
</tr>
<tr>
<td>Level 4</td>
<td>123</td>
<td>13.0</td>
<td>50.0</td>
<td>30.1</td>
</tr>
</tbody>
</table>
Results

**Figure 2**
Cumulative remission rate by STAR*D treatment level
Lessons from STAR-D

• In “Real life” settings remission rates were lower than expected from research trials (35% to 40%) for 1st Tx.
• No winner (not fully powered to detect)
• Switching, augmentation, cognitive therapy all reasonable next steps in this trial
• Tolerability differs, but not much support for selection based on subtyping depression
• After two trials, response rates dropped substantially
• Primary care equivalent for step 1 and 2 Tx
• Supports treatment to remission to reduce relapse risk
Second generation antidepressant selection—Picking which drug

- No difference in efficacy of various second generation medications
- Cost matters—generics are inexpensive and many are on the “$4” lists
- Indications for co-morbid conditions matter a lot
  - Ssris/snris: anxiety disorders, PTSD, premature ejaculation, OCD, eating disorders
  - Ssris/snris—fibromyalgia
  - Buproprion—nicotine dependence, ADHD
  - Mirtazapine—low weight, insomnia
- Less severe side effects differ and matter for adherence (N/V, diarrhea, somnolence, weight change, discontinuation syndrome, sexual)
- Risks vary but most are rare (cardiac, hyponatremia, seizure, hepatotoxicity, suicide?, serotonin syndrome)
- P450 inhibition varies and matters (elderly, multiple meds/prescribers—paroxetine, fluvoxamine, fluoxetine, buproprion)
- Black box warnings
  - Suicide risk—”may increase the risk of suicidal thoughts and behaviors in children and adolescents” (extended to young adults)
  - QTc interval prolongation for citalopram and escitalopram
Meta-analysis of drug comparison studies in treating MDD—adverse events


### Appendix Table 1. Main Differences in Specific Adverse Events

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparators</th>
<th>Differences in Adverse Events</th>
</tr>
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<tbody>
<tr>
<td>Bupropion</td>
<td>Escitalopram, fluoxetine, paroxetine, sertraline</td>
<td>Lower incidence of sexual dysfunction than comparator drugs (6% vs. 16%)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Fluoxetine, paroxetine, trazodone, venlafaxine</td>
<td>Greater weight gain than comparator drugs (mean, 0.8–3.0 kg after 6–8 wk)</td>
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<tr>
<td>Paroxetine</td>
<td>Escitalopram, duloxetine, fluoxetine, mirtazapine, nefazodone, and sertraline</td>
<td>Higher incidence of sexual dysfunction, particularly ejaculatory dysfunction, than comparator drugs</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine</td>
<td>Higher incidence of diarrhea than comparator drugs (mean, 16% [95% CI, 13%–20%] vs. 8% [CI, 4%–13%])</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Bupropion, fluoxetine, mirtazapine, paroxetine, venlafaxine</td>
<td>Higher incidence of somnolence than comparator drugs (mean, 42% [CI, 19%–64%] vs. 25% [CI, 3%–46%])</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>SSRIs as a class</td>
<td>Higher incidence of nausea and vomiting than SSRIs as a class (mean, 33% [CI, 23%–43%] vs. 22% [CI, 16%–29%])</td>
</tr>
</tbody>
</table>

SSRI = selective serotonin reuptake inhibitor.
Using antidepressants

• Side effects early and may subside, treatment effects later (2 weeks to >6 weeks and up to 12 weeks for a treatment trial). Give it time.

• In general, at four weeks reassess and titrate up as tolerated if minimal response. Repeat.

• Adherence is key--address concerns and ambivalence, anticipate side effects, (motivational interventions--roll with the resistance).

• Encourage non-pharm interventions
Beyond 2 levels in primary care—many patients will not respond to two tx trials

• Some interventions not too complicated:
  – 3rd choice—mirtazapine if not tried, TCA
  – T3 augmentation
  – Low dose atypical antipsychotic augmentation
  – EMSAM patch (easier to use MAOI, but…..)

• Reasonable role for a consultant to confirm diagnosis (esp. evaluate bipolar illness), assess contributing factors, help with algorithm and tx plan

• Therapy referral if not done earlier—it works!

• Psychiatric referral
Other old and new treatments your patients might be asking about

- **rTMS** (transcranial magnetic stimulation)
  - Probably similar efficacy to antidepressants
  - Not clearly helpful with treatment resistance
  - Limited information on long term course
  - Well tolerated, but limited coverage

- **New medications**
  - Vilazdone—marketed as ssri w/ less sexual side effects

- **Ketamine** (NMDA receptor agonist in the news)

- **Deep Brain Stimulation**

- **ECT**

- **VNS**
Summary