Impact of Depression on Chronic Diseases:

*Optimizing Clinical Outcomes in the Treatment of Major Depressive Disorder (MDD)*

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YOU NEVER HEAR, "SNAP OUT OF IT, IT'S JUST DIABETES."

So why do some say that about depression?

Just like other life-threatening diseases, depression is a biological illness that can be treated. Which means there’s hope for everyone who has it.

Learn more at DepressionIsReal.org

American Psychiatric Foundation | Depression and Bipolar Support Alliance | Mental Health America | National Alliance on Mental Illness | National Medical Association
Presentation Objectives

- Discuss the relationships between depression and chronic medical conditions
- Discuss initiation, appropriate titration and duration of antidepressant therapy to achieve optimal clinical outcomes.
- Identify and manage treatment issues involving antidepressants such as discontinuation syndrome, adverse drug events and pregnancy/breast-feeding restrictions.
- Evaluate role of new antidepressant products and formulations
PCMH 2011 Goal
Integrate behaviors affecting health, mental health and substance abuse

Integration into Standards

- **PCMH 1: Enhance Access and Continuity**
  - Comprehensive assessment includes depression screening for adolescents and adults

- **PCMH 3: Plan and Manage Care**
  - One of three clinically important conditions identified by the practice must be a condition related to unhealthy behaviors (e.g., obesity) or a mental health or substance abuse condition.

- **PCMH 5: Track and Coordinate Care**
  - Track referrals and coordinate care with mental health and substance abuse services
Epidemiology and Background

- Prevalence of current depression in US is 9% (3.4% meet criteria for major depression) - CDC BRFSS data 2006 and 2008
  - Rates in South Carolina 9.6% (3.6% MDD)
    - Lowest reported rates in North Dakota (4.8%), highest in Mississippi (14.8%)
  - Higher prevalence of major depression reported: increased age, women, no health insurance coverage, persons previously married or never married, persons unable to work or unemployed

MMWR 2010;59(38):1229-1235
Epidemiology and Background

- Depressive disorder more common among persons with chronic conditions
  - Obesity, cardiovascular disease, diabetes, asthma, arthritis and cancer
- Depression more common among persons with unhealthy behaviors
  - Smoking, physical inactivity, binge drinking
Epidemiology and Background

- Costs more than $44 billion in absenteeism from work, lost productivity (‘presenteeism’) and direct treatment costs
  - Main cause of disability in ages 15-44
- Effects on quality of life greater than with hypertension, CAD, lung problems and back pain
### Table 2. Prevalence of Past-Year Depression Care Use Among Respondents Meeting 12-Month Major Depressive Episode Criteria in the United States

<table>
<thead>
<tr>
<th></th>
<th>% (SE)</th>
<th>Guideline-Concordant Use</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Use</td>
<td>Guideline-Concordant Use</td>
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<tr>
<td>Pharmacotherapy</td>
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<td>19.25 (4.34)</td>
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<td>African American</td>
<td>18.28 (2.97)</td>
<td>4.89 (1.13)</td>
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<tr>
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<td>37.28 (2.11)</td>
<td>12.29 (1.47)</td>
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<td>Total sample</td>
<td>33.86 (1.87)</td>
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<td>11.23 (3.78)</td>
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<tr>
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<td>42.87 (8.05)</td>
<td>18.75 (5.76)</td>
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<td>23.95 (10.82)</td>
<td>13.25 (10.90)</td>
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<tr>
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<td>34.44 (2.91)</td>
<td>13.59 (2.10)</td>
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<td>47.29 (2.86)</td>
<td>20.62 (1.78)</td>
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<td>Total sample</td>
<td>44.44 (2.49)</td>
<td>19.13 (1.51)</td>
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<td>Any depression therapy</td>
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<tr>
<td>Mexican American</td>
<td>33.61 (4.93)</td>
<td>12.07 (3.83)</td>
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<tr>
<td>Puerto Rican</td>
<td>49.19 (7.19)</td>
<td>24.41 (8.01)</td>
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<td>Caribbean black</td>
<td>29.21 (11.95)</td>
<td>13.50 (10.90)</td>
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<tr>
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<td>39.66 (3.08)</td>
<td>13.97 (2.08)</td>
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<tr>
<td>Non-Latino white</td>
<td>53.96 (3.17)</td>
<td>23.05 (1.88)</td>
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<td>Total sample</td>
<td>50.76 (2.76)</td>
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<td>Combined depression therapy</td>
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<td>15.18 (4.39)</td>
<td>4.73 (2.57)</td>
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<td>Puerto Rican</td>
<td>25.32 (8.05)</td>
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<td>Caribbean black</td>
<td>13.12 (10.93)</td>
<td>0.23 (0.24)</td>
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<td>African American</td>
<td>13.06 (2.44)</td>
<td>4.50 (1.16)</td>
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<tr>
<td>Non-Latino white</td>
<td>30.61 (1.66)</td>
<td>9.85 (1.25)</td>
</tr>
<tr>
<td>Total sample</td>
<td>27.55 (1.51)</td>
<td>8.83 (1.05)</td>
</tr>
</tbody>
</table>

*Based on World Mental Health Composite International Diagnostic Interview. Results are from the Collaborative Psychiatric Epidemiology Surveys.*
Epidemiology and Background

- Accurate diagnosis and treatment occurs in fewer than one in three patients.

- Patients with major depression often have co-morbid psychiatric diagnoses: panic attacks (31%) and obsessive-compulsive behaviors (11%).

- Greater than 10-15% of major depressive disorders caused by other medical conditions or drugs.
Drugs Associated with Depression

- **Psychoactive agents**
  - Amphetamines
  - Cocaine
  - Benzodiazepines
  - Barbiturates
  - Antipsychotics
  - Alcohol

- **Antihypertensives**
  - Beta-blockers
  - Reserpine
  - Clonidine
  - Methyldopa
  - Hydralazine

- **Analgesics**
  - Salicylates
  - Propoxyphene
  - Opioid analgesics

- **Hormonal agents**
  - Corticosteroids
  - Oral contraceptives

- **Anticonvulsants**
  - Phenytoin
  - Phenobarbital

- **Miscellaneous**
  - Histamine-2 antagonists
  - Metoclopramide
  - Levodopa
  - NSAIDs
## Likelihood of Developing Depression with Chronic Medical Conditions

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Frequency of Depression (%)</th>
<th>Frequency of Depression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine/Metabolic</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hyperthyroidism</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>50</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>40</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>6-57</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis of Depression

- Presence of 5 or more of following symptoms during same 2 week period and represent change from previous functioning *(at least one is either depressed mood or loss interest or pleasure)*
  - Depressed mood
  - Loss of interest in pleasurable activities
  - Significant appetite or weight change
  - Sleep disturbance
  - Psychomotor agitation or retardation
  - Fatigue or loss of energy
  - Feelings of worthlessness or excessive or inappropriate guilt
  - Loss of concentration
  - Recurrent suicidal thoughts or ideation
Screening Tools for Depression

- **Patient Health Questionnaire (PHQ-2)**

During the past month-
Have you often been bothered by feeling down, depressed or hopeless?
Have you often been bothered by little interest or pleasure in doing things?

**affirmative answer to either question is a positive test**
**sensitivity 96% and specificity 57%**
**indicates need for further assessment of depressive disorders**

- **Patient Health Questionnaire (PHQ-9)**

*can also be used to both screen and monitor treatment response*
### PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
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<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
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<tr>
<td>4. Feeling tired or having little energy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5. Poor appetite or overeating</td>
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<tr>
<td>6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down</td>
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<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
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<tr>
<td>8. Moving or speaking so slowly that other people could have noticed, or the opposite—being so fidgety or restless that you have been moving around a lot more than usual</td>
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<td></td>
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<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself in some way</td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| Add columns: |  |  |  |

Total: 

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10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

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PHQ-9 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Spitzer at rls@nyulangone.edu. Use of the PHQ-9 may only be made in accordance with the Terms of Use available at http://www.pfizer.com. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.
PHQ-9 QUICK DEPRESSION ASSESSMENT

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment on accompanying tear-off pad.
2. If there are at least 4 √’s in the blue highlighted section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.
3. Consider Major Depressive Disorder.
   —If there are at least 5 √’s in the blue highlighted section (one of which corresponds to Question #1 or #2)
   Consider Other Depressive Disorder.
   —If there are 2 to 4 √’s in the blue highlighted section (one of which corresponds to Question #1 or #2)

Note since the questionnaire relies on patient self-report, all responses should be verified by the clinician and a definitive diagnosis made on clinical grounds, taking into account how well the patient understood the questionnaires, as well as other relevant information from the patient. Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #16) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (e.g., every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up √’s by column. For every √: Several days = 1; More than half the days = 2; Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying PHQ-9 Scoring Card to interpret the TOTAL score.
5. Results may be included in patients’ files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

**PHQ-9 SCORING CARD FOR SEVERITY DETERMINATION**

for healthcare professional use only

**Scoring—add up all checked boxes on PHQ-9**

For every √: Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day = 3

**Interpretation of Total Score**

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Depression Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>None</td>
</tr>
<tr>
<td>5-9</td>
<td>Mild depression</td>
</tr>
<tr>
<td>10-14</td>
<td>Moderate depression</td>
</tr>
<tr>
<td>15-19</td>
<td>Moderately severe depression</td>
</tr>
<tr>
<td>20-27</td>
<td>Severe depression</td>
</tr>
</tbody>
</table>
Treatment Options for Depression

- **Nonpharmacologic**
  - Cognitive behavioral therapy (CBT)
  - Physical activity
  - Nutritional therapy
  - Electroconvulsive Therapy (ECT)
  - Vagus nerve stimulation (VNS)
  - Transcranial magnetic resonance stimulation

- **Pharmacologic**
  - TCAs
  - SSRIs
  - SNRIs
  - Bupropion
  - Mirtazapine
  - Atypical antipsychotics
  - MAO inhibitors
Management Issues

- Initial selection of antidepressant
  - Selection criteria (effectiveness vs tolerability)

- Adequate trial (acute)
  - Time to response
  - Dose and duration
  - Treatment goals (response vs remission)

- Length of treatment (maintenance)

- Special populations
Pharmacologic options

Selection criteria

- All antidepressants are effective for treating the acute phase of major depression in adults
- 50-60% of patients will respond to the first medication prescribed
  - There is no evidence to guide selection of best initial drug for an individual
    - Selection should be individualized based on dosing, tolerability, safety profile, prior Hx and cost.
  - 1 out of 4 people will respond after switching to second drug
- Only 30% of patients will experience remission of symptoms with initial choice of antidepressant
Response versus Remission

- Clinical trials define positive response as 50% decrease from a baseline score on depression rating scales

- Remission = resolution of symptoms
  - PHQ-9 score < 5

- Implications
  - Relapse rate 76% when residual symptoms are present: only 25% with no residual symptoms
  - Suicide risk also increased if remission not achieved
Objective

- Assess effectiveness of depression treatments in patients diagnosed with major depressive disorder, in both primary and specialty care settings
  - Longest and largest study of antidepressants ever conducted
  - N=3671 patients
- Sponsored by National Institute of Mental Health (NIMH)
STAR*D Study
Sequenced Treatment Alternatives to Relieve Depression

Treatment options

- **Level 1** - citalopram
- **Level 2**
  - Switch group: sertraline, bupropion, venlafaxine
  - ‘add-on’ group: bupropion SR or buspirone
- **Level 3**
  - Switch group: Mirtazapine or nortriptyline
  - ‘add-on’ group: Lithium or triiodothyronine (T3)
- **Level 4**
  - All meds stopped and switched to MAOI tranylcypromine or combo of venlafaxine/mirtazapine
STAR*D Study
Sequenced Treatment Alternatives to Relieve Depression

- Level 1
  - 36.8% remission rate; response rate additional 10-15%

- Level 2
  - 50% of participants became symptom-free after two treatment levels
  - No significant difference between tx options
  - Almost 70% of participants who did not withdraw became symptom free if consider all 4 treatment levels
Meta-analysis of Antidepressant Efficacy and Acceptability

Analyzed 117 studies with newer antidepressants

- network meta analysis format allowed for integration of data from direct and indirect comparisons
- common definition of efficacy and tolerability

**Best efficacy** (≥50% decrease in standard rating scores)
- Sertraline, escitalopram, mirtazapine, venlafaxine

**Best tolerability** (discontinuation rates for any reason during first 8 weeks)
- Sertraline, escitalopram, citalopram, bupropion

Cipriani et al. Lancet 2009;373:746-748
Length of Treatment

- Symptomatic improvement may occur within one week
  - Onset of improvement may vary by agent but not clinically significant (mirtazapine reported to have rapid onset)
- Takes about 6-12 weeks to get full therapeutic effect of antidepressants (acute phase)
- Total duration of treatment should last 9-12 months
  - Continue antidepressant at same dose after remission achieved for an additional 6-9 months (maintenance phase)
- Patients experiencing >2 MDD episodes or with other risk factors may benefit from lifelong therapy
Depression and Chronic Medical Conditions

Heart Disease

- Up to 20% of post-MI patients meet diagnostic criteria for MDD
- Depression adversely affects CV morbidity and mortality
- Behaviors associated with depression can promote heart disease
  - Inactivity, smoking, poor diet, medication nonadherence
Depression and Chronic Medical Conditions

Heart Disease

- One analysis suggests that SSRIs reduce mortality and recurrent MI
- Several studies indicate that SSRIs are safe and effective for MDD in patients with CV disease
  - SADHART trial
    - Sertraline s/p AMI or unstable angina
  - CREATE trial
    - Citalopram +/- psychotherapy in patients with CAD
Depression and Chronic Medical Conditions
Heart Disease

Recommendations

- Screen all patients with heart disease
  - AHA/APA guidelines  [Circulation 2008;118:1768-75]
- Consider nonpharmacological therapy options
- Pharmacotherapy options
  - SSRIs (sertraline, citalopram) first line choices
    - Mirtazipine, bupropion, trazodone also appear safe
  - Avoid TCAs
  - Avoid SNRIs – increase BP/HR, exacerbate HF
Depression and Chronic Medical Conditions

Stroke

- Fluoxetine for 12 weeks during first 6 months s/p stroke reduced mortality of both depressed and nondepressed patients
  - 59.2% vs 36.4% survival at 9 year f/u
  - NNT= 4

- Escitalopram given to prevent depression for 1rst 3 months s/p stroke
  - 22.4% placebo vs 8.5% escitalopram
  - NNT= 7

?Recommendations
Depression and Chronic Medical Conditions

Diabetes

- Rates of depressive symptoms range from 21-27% in type 1 and type 2 diabetes
  - 11.4% using structured interviews
- Lifetime history of depression increases risk of developing type 2 diabetes later in life
- Associated with worsened blood glucose levels and complications such as coronary heart disease
Depression and Chronic Medical Conditions

**Diabetes**

- Documented decreased adherence to diet, physical activity and medication regimens
- Patients with diabetes and depression have 4.5x higher medical expenditures than patients with diabetes alone
- 7x more likely to experience functional disability (impaired work or social activities)
- 2.3x increased risk of early mortality
Depression and Chronic Medical Conditions

Diabetes

Recommendations

- Treatment responsiveness associated with severity of depression and A1C at baseline
- Nonpharmacologic options: CBT and problem solving therapy
- Pharmacotherapy
  - Paroxetine, fluoxetine, sertraline and bupropion have been shown to be effective
  - Hypoglycemia noted with fluoxetine and bupropion
Depression and Chronic Medical Conditions

Tobacco Use (NHANES data 2005-2008)

Figure 1. Percentage of adults aged 20 and over who were current smokers, by age, sex, and depression status: United States, 2005–2008

All comparisons between depression and no depression are significant (p < 0.05).

NCHS Data Brief no. 34 April 2010
www.cdc.gov
Depression and Chronic Medical Conditions

Tobacco Use (NHANES data 2005-2008)

- Adults aged 20 and over with depression were more likely to be cigarette smokers than those without depression.
- Women with depression had smoking rates similar to men with depression, while women without depression smoked less than men.
- Percentage of adults who were smokers increased as depression severity increased.
- Among adult smokers, those with depression smoked more heavily than those without depression.
- Adults with depression were less likely to quit smoking than those without depression.

NCHS Data Brief no. 34 April 2010

www.cdc.gov
Treatment of Depression during Pregnancy

- 14-23% of pregnant women meet criteria for depressive disorder during pregnancy

- Effects of untreated depression on fetal development and maternal health
  - Higher rates of nausea, vomiting, hyperemesis gravidarum and pre-eclampsia
  - No link with congenital anomalies
  - Premature birth, low birth weight, postnatal complications, etc
  - Confounding factors: poor prenatal care, drug, alcohol and nicotine use

APA/ACOG report – Obstetrics and Gynecology sept 2009
Treatment of Depression During Pregnancy

Effects of SSRIs on Neonates

- Poor Neonatal Adaption (Neonatal behavioral syndrome)
  - Class labeling change required in precaution section of SSRI Package inserts

- Teratogenic effects/ Congenital malformations
  - Paroxetine use in first trimester may increase risk for congenital cardiac malformations – Category D
  - Unclear whether this is class effect with SSRIs

- Persistent pulmonary hypertension
  - Use before 20 weeks not associated with increased risk
  - Use of non-SSRI antidepressants not associated with increased risk
Antidepressants and Breast Feeding/Lactation

- Risk of postpartum depression is >25% in women with history of depression
- Medication exposure significantly less than with tranplacental exposure
- No long-term neurobehavioral studies done in infants exposed to SSRIs through breast milk
Educational and Organizational Interventions to Improve Management of Depression in Primary Care

- Effective strategies
  - Collaborative care
  - Stepped collaborative care
  - Quality improvement
  - Case management
  - Pharmacist-provided prescribing information and patient education
  - Guideline implementation strategies embedded in complex interventions

JAMA 2003;289:3145-3151.
Classes of Antidepressants: Management Pearls

- TCAs
- SSRIs
- SNRIs
- Bupropion
- Mirtazapine
- Atypical antipsychotics (SGAs)
- MAO inhibitors
Selective Serotonin Reuptake Inhibitors (SSRIs)

- Most common adverse effects
  - Headache, diarrhea
- FDA approved indications
  - Major depressive disorder (MDD)
  - Generalized anxiety disorder (GAD), social anxiety, panic attacks and panic disorder, PTSD, OCD, PMDD
Selective Serotonin Reuptake Inhibitors (SSRIs)
Sexual Dysfunction

- Primarily decreased libido and anorgasmia
  - Noted in both men and women

- Management options
  - Reversible with discontinuation or dosage reduction
  - Switch to agent with less potential (bupropion*, velafaxine)
  - Consider drug holidays
  - PDE5 inhibitors: Viagra and others
  - Natural options: ginkgo, arginine, yohimbe
**SSRIs (Selective Serotonin Reuptake Inhibitors) and GI Bleeding**

- Patients taking SSRIs have a 2-4x greater risk of GI bleeds
  - Concurrent use of NSAIDs has 3-12x risk
    - 1 in 250 could experience GI bleed (without acid-suppression)
    - One in 500 people may develop upper GI bleed with SSRI + antiplatelet agent

- Mechanism:
  - no direct toxic effect
  - inhibits uptake of serotonin into platelets leading to decreased platelet activity

Arch Int Med 2003;163:59-64
SSRIs (Selective Serotonin Reuptake Inhibitors) and GI Bleeding

- Reports of increased bruising, nosebleeds, vaginal bleeding, post-surgical bleeding
  - Spontaneous bleeding unlikely; usually follows some injury
- No increased risk of ischemic or hemorrhagic stroke
- Use caution
  - NSAIDs, aspirin, antiplatelet agents, steroids, warfarin
  - Elderly
  - History of GI bleeds

Arch Int Med 2003;163:59-64
Selective Serotonin Reuptake Inhibitors (SSRIs)

Hyponatremia

- Seen with traditional antidepressants and antipsychotics but also noted with SSRIs and venlafaxine
  - Limited reports of SIADH syndrome
- Develops early in therapy usually within first month of treatment
- Elderly patients taking thiazides are at highest risk
Selective Serotonin Reuptake Inhibitors (SSRIs)
Fracture Risk

- Epidemiological studies on bone fracture risk following exposure to some antidepressants, including SSRIs, have reported an association between antidepressant treatment and fractures.

- There are multiple possible causes for this observation and it is unknown to what extent fracture risk is directly attributable to SSRI treatment.

- The possibility of a pathological fracture, that is, a fracture produced by minimal trauma in a patient with decreased bone mineral density, should be considered in patients treated with an SSRI who present with unexplained bone pain, point tenderness, swelling, or bruising.

FDA 2010
Suicidality and Antidepressant Drugs

- Antidepressants may increase suicidal thoughts or behaviors in some children, adolescents and young adults especially within the first few months of treatment or when changing the dose.

- No increased risk has been shown for adults over age 24, and risk decreased for those over age 65.

- All patients starting therapy should be monitored appropriately and observed closely for new or worsening depression symptoms, suicidal thoughts or behavior, or unusual changes in behavior.
SNRIs

Warnings and Precautions

- Venlafaxine (and desvenlafaxine)
  - Tachycardia and elevated blood pressure
- Duloxetine (Cymbalta®)
  - Nausea, diarrhea – titrate dose to minimize
  - hepatotoxicity
    - Median time to changes in AST/ALT was 2 months
    - Elevations in AST/ALT appear to be dose-related
    - No specific recommendations provided for monitoring

http://www.fda.gov/medwatch/safety/2005/safety05.htm#Cymbalta
Bupropion

- Dopamine agonist
  - Can be used in combo with SSRI or SNRI
- Activating
  - Irritable, insomnia
- Least potential for sexual dysfunction
- Contraindicated in patients with seizure disorders
- Choice for tobacco cessation
Bupropion (Wellbutrin, Aplenzin)

- Contraindicated with abrupt discontinuation of alcohol or benzodiazepines
- May cause neuropsychiatric symptoms or reduced alcohol tolerance in patients who drink alcohol during treatment
Mirtazapine (Remeron)

- Most sedating
  - Lower doses most sedating
- Increases appetite
- May have slightly earlier onset of effect but not clinically relevant with sustained treatment
Atypical Antipsychotics
(adjunctive therapy for major depressive disorder)

- Quetiapine (Seroquel XR®)
  - Day 1 and 2: 50 mg  Day 3 and 4: 150 mg
  - Recommended dose 150-300 mg/day

- Aripiprazole (Abilify®)
  - Initial dose 2-5 mg/day (titrate q weekly)
  - Recommended dose 5-10mg/day (max 15 mg)

- Olanzapine/fluoxetine (Symbyax®)
  - 6/25mg daily (max 18mg olanzapine/75mg fluoxetine)
  - Acute tx of treatment resistant depression
Atypical Antipsychotics (approved as adjunctive therapy for major depressive disorder)

Benefits

- Effective in patients with psychotic symptoms or treatment resistant depression
- Also effective for treatment of bipolar depression (BPD)

All agents require monitoring for risk factors of metabolic syndrome:
Weight, blood pressure, glucose, lipids, family history of CVD
Atypical Antipsychotics (approved as adjunctive therapy for major depressive disorder)

- Limitations
  - Cost
    - $250 – 150 mg Seroquel XR®, $472 – 5mg Abilify®, $375 – 6/25mg Symbyax®
  - Adverse effects
    - All agents require monitoring for risk factors of metabolic syndrome:
      - Weight, blood pressure, glucose, lipids, family history
  - Short duration of clinical studies
Management Issues

- Discontinuation withdrawal syndrome
- Switching/ tapering
- Serotonin syndrome
Discontinuation syndrome

Symptoms (FInISH)

- Flu-like symptoms (nausea, headache, lethargy)
- Insomnia
- Imbalance (dizziness, ataxia, vertigo)
- Sensory disturbances (electric shock sensations, parethesias, numbness)
- Hyperarousal (anxiety, agitation, crying spells, irritability)

Related to dose and agent, but not to duration of therapy

- Paroxetine and venlafaxine >> sertraline and citalopram/escitalopram >> fluoxetine

Occurs 1-3 days after missed/decreased dose and resolves within 10 days- 3 weeks
Switching and Tapering

- Switching can be accomplished with a wash out period, cross-tapering, or direct switch.
- A wash out period may be necessary if there are clinically significant medication interactions.
- In cross tapering, the dose of original med is decreased over 3-7 days while initiating the new antidepressant.
- In general if the first antidepressant is being discontinued due to intolerance following a brief exposure (< 7 days), it can be stopped and the second medication started with no cross-tapering.
Switching and Tapering

- **Direct Switch**
  - SSRI → SSRI
  - SSRI → SNRI

- **Cross Taper**
  - SSRI → bupropion
  - SNRI → bupropion
  - bupropion → SNRI or SSRI
Serotonin Syndrome

- Syndrome: rigidity, restlessness, fever, autonomic instability, delirium, tachycardia, hypertension
- Precipitating agents: MAOIs, dextromethorphan, other antidepressants, atypical antipsychotics, triptans, tramadol, linezolid
- Treatment
  - Usually resolves within 24 hours after stopping precipitating agents
  - Supportive tx, maintain hydration, control hyperthermia
Antidepressant Pearls:

- New products
  - Desvenlafaxine (Pristiq®)
  - Milnacipran (Savella®)
  - Vilazodone (Viibryd)

- New formulations
  - Venlafaxine extended-release tablets
  - Bupropion ER (Aplenzin®)
  - Trazodone extended release (Oleptro®)
Antidepressant Pearls: New formulations

- Venlafaxine extended-release tablets
  - Bioequivalent but not interchangeable
  - Allows for max daily dose (225 mg) of venlafaxine with one tablet
  - Leaves ‘Ghost’ tablet in stool

- Bupropion hydrobromide (Aplenzin®)
  - can achieve max daily dose of bupropion with one tablet (522mg tablet = 450 mg buproprion HCl)
  - Leaves ‘Ghost’ tablet in stool

- Trazodone extended release (Oleptro®)
  - 150, 300mg scored tablets (max daily dose 375mg)
Dietary Supplements and Depression

- L-methylfolate (Deplin®)
  - ‘medical food’ for use with suboptimal folate levels
- Tryptophan, tyrosine, phenylalanine –
  - Biochemical imbalance and conversion of amino acids to neurotransmitters
- Gamma-linoleic acid –
  - Enhanced prostaglandin E1 production
- B vitamins, vitamin C and minerals
- Omega 3 fatty acids
- Low glycemic index foods

No evidence-based data to support claims
Optimizing Clinical Outcomes with MDD

- Screen patients with co-morbidities/risk factors for depression
- Initiate/titrate/switch medications to minimize adverse effects and achieve outcome
- Encourage adherence; educate about time to improvement
- Treat to remission not just response
Optimizing Clinical Outcomes with MDD

- Collaborative care – integrated behavioral health/team care in primary care

- SCORxE - South Carolina Offering Prescribing Excellence
  - Medication resource and academic detailing service providing ‘point of care’ best practices information on mental health topics to primary care providers
    - [http://www.sccp.sc.edu/centers/SCORxE](http://www.sccp.sc.edu/centers/SCORxE)
      - Click on Clinical Topics
Patient Centered Medical Home
PCMH 2011

- **Goal:** Integrate behaviors affecting health, mental health and substance abuse
- **Integration into Standards**
  - **PCMH 1: Enhance Access and Continuity**
    - Comprehensive assessment includes depression screening for adolescents and adults
  - **PCMH 3: Plan and Manage Care**
    - One of three clinically important conditions identified by the practice must be a condition related to unhealthy behaviors (e.g., obesity) or a mental health or substance abuse condition.
  - **PCMH 5: Track and Coordinate Care**
    - Track referrals and coordinate care with mental health and substance abuse services
Depression prevalence and treatment patterns among patients with Chronic Heart Failure

- The prevalence of depression within patients with heart failure is 36% which correlates with rates described in other studies.

- Less than 50% of patients on anti-depressants had a documented follow-up visit for management. An SSRI was prescribed to 86% of patients on anti-depressants.

- There is a low rate of documentation of depression screening (n= 1) and behavioral health referrals (n= 4) within the EMR.

- Male gender and black ethnicity were negative predictors of a co-morbid diagnosis of depression.

- The diagnosis of depression is associated with more frequent utilization of office visits (>10/yr) but not all-cause hospitalizations.

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Improving Depression Management Thorough the Use of the PHQ-9 Questionnaire

- 30% of patients previously treated with 2 or more medications never had screening tool to monitor treatment.
- 2 patients with documented PHQ-9 showed improvement in symptoms which lead to physician intervention and titration of medications.
- Lack of provider use of the screening tool failed to demonstrate improvement in depression management with the use of the PHQ9.

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