WHAT TO DO WHEN COMPLICATIONS ARISE:
TREATING DEPRESSION AND ANXIETY IN THE PRIMARY CARE SETTING

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DISCLOSURES

• I was on the following Speaker Bureaus:
  2003 - 2010  Shire Pharmaceuticals, Inc.
  2004 - 2012  Forest Pharmaceuticals, Inc.
  2006 - 2010  Novartis Pharmaceuticals Corporation
  2008 - 2010  AstraZeneca Pharmaceuticals

• I presented a poster funded by Shire Development LLC at the American Academy of Nurse Practitioners National Conference (June 2012)
Objectives

At the end of this presentation you will be able to:

• Determine an effective way to manage common complications including, but not limited to, when to change or augment antidepressants

• Determine if pharmacogenetic testing is warranted
In any given year, in those age 18 and older in the US:

<table>
<thead>
<tr>
<th>Mental Health Disorder</th>
<th>Occurs in:</th>
<th>Rated “severe” in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depression</td>
<td>9.5%</td>
<td>45%</td>
</tr>
<tr>
<td>Bipolar</td>
<td>2.6%</td>
<td>---</td>
</tr>
<tr>
<td>Anxiety (all)</td>
<td>18.1%</td>
<td>---</td>
</tr>
</tbody>
</table>

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Patient must have a depressed mood or anhedonia for at least two weeks and four of the following:

**S**leep (insomnia or hypersomnia)

**I**nterests (diminished interest in or pleasure from activities)

**G**uilt (excessive or inappropriate guilt; feelings of worthlessness)

**E**nergy (loss of energy or fatigue)

**C**oncentration (diminished concentration or indecisiveness)

**A**ppetite (decrease or increase in appetite; weight loss or gain)

**P**sychomotor (retardation or agitation)

**S**uicide (recurrent thoughts of death, suicidal ideation or suicide attempt)
Antidepressants

• Tricyclics
  • Not first line because they are lethal in small amounts
  • Several require blood monitoring and have a narrow window
  • Several cause EKGs changes and require monitoring in children, as well as adults with cardiac issues

• SSRIs
  • First line for depression because they are not lethal in small amounts
  • Do not require blood or EKG monitoring*
  • Three approved to be used in children/adolescents
  • Several have anxiety indications as well
Antidepressants continued

• SNRIs
  • Not lethal in small amounts
  • One has an anxiety indication as well
  • Can cause an increase in BP (dose-dependent effect)

• DNRI
  • Not lethal in small amounts
  • Can cause an increase in BP (dose-dependent effect)
The Black Box Warning

- December 2006, the FDA issued the black box warning; May 2007, it was updated to include patients up to age 24
- The warning includes ALL antidepressants and mood stabilizers approved to treat the depressed phase of Bipolar Disorder

“Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Medication] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need.”
<table>
<thead>
<tr>
<th>Medication</th>
<th>Approved Ages</th>
<th>Indication(s)</th>
<th>Dosage Range</th>
<th>2D6</th>
<th>2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td>bupropirion</td>
<td>adults</td>
<td>MDD</td>
<td>100mg-300mg SR 150mg-450mg XL</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>citalopram</td>
<td>adults</td>
<td>MDD</td>
<td>10mg-60mg*</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>desvenlafaxine</td>
<td>adults</td>
<td>MDD</td>
<td>50mg</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>duloxetine</td>
<td>adults</td>
<td>MDD, GAD</td>
<td>30mg-60mg</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>escitalopram</td>
<td>12-adults adults</td>
<td>MDD, GAD</td>
<td>10mg-20mg</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>7-adults</td>
<td>OCD</td>
<td>10mg-60mg</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>8-adults</td>
<td>MDD, Panic Bulimia, PMDD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>6-adults</td>
<td>OCD</td>
<td>100mg-200mg</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Medication</td>
<td>Approved Ages</td>
<td>Indication(s)</td>
<td>Dosage Range</td>
<td>2D6</td>
<td>2C19</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
<td>----------------------------------------</td>
<td>--------------</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>levomilnacipran</td>
<td>adults</td>
<td>MDD</td>
<td>40mg-120mg</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>paroxetine</td>
<td>adults</td>
<td>MDD, GAD, Panic, Social, PTSD, PMDD</td>
<td>10mg-60mg</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>sertraline</td>
<td>6-adults, adults</td>
<td>OCD, MDD, GAD, Panic, Social, PTSD, PMDD</td>
<td>50mg-200mg</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>venlafaxine XR</td>
<td>adults</td>
<td>MDD, GAD, Social, Panic</td>
<td>75mg-225mg</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>vilazodone</td>
<td>adults</td>
<td>MDD</td>
<td>20mg-40mg</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>vortioxetine</td>
<td>adults</td>
<td>MDD</td>
<td>5mg-20mg</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
STAR*D

- Sequenced Treatment Alternatives to Relieve Depression (STAR*D) was a collaborative study on the treatment of depression, funded by the National Institute of Mental Health.

- It’s the largest and longest study ever done to evaluate depression treatment. Over a seven-year period, the study enrolled more than 4,000 outpatients, aged 18-75 years.

- Its main focus was on the treatment of depression in patients where the first prescribed antidepressant proved inadequate.
• 2/3 of patients had one or more concurrent general medical conditions

• 2/3 of patients had one or more concurrent psychiatric condition

• Almost 40% had their first depressive episode prior to age 18

• More than half of the patients met criteria for an anxiety disorder
STAR*D (continued)

• 1/3 of patients DID NOT RESPOND until ≥ 6 weeks of treatment

• Used standardized symptom and side effect measures at each visit
  • This detects smaller changes than asking patients for their global impression

• If ≥ 20% reduction in symptoms, increase the dose at week 6 and wait up to 10 weeks
**STAR*D (continued)**

<table>
<thead>
<tr>
<th>Step</th>
<th>Treatment</th>
<th>Note</th>
<th>Likelihood of remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SSRI (citalopram)</td>
<td></td>
<td>37%</td>
</tr>
<tr>
<td>2</td>
<td>Another SSRI or SNRI or DRI or CBT</td>
<td>Despite substantial pharmacological differences between agents, there was no substantial change in clinical efficacy</td>
<td>31%</td>
</tr>
<tr>
<td>3</td>
<td>Augment with lithium or augment with $T_3$</td>
<td>$T_3$ did better than lithium with fewer side effects</td>
<td>14%</td>
</tr>
<tr>
<td>4</td>
<td>venlafaxine XR + mirtazapine or tranylcypromine</td>
<td></td>
<td>13%</td>
</tr>
</tbody>
</table>
Lessons Learned From STAR*D

- Patients and providers less likely to aim for remission in those with treatment resistance
- Higher relapse rates occur in those with more trials
- Use standardized rating scales at each visit
  - PHQ-9
- Reinforces the need for remission versus response!
PHQ-9: Depression Screening Tool

- 9 item scale designed to be used in primary care to screen for depression and measure treatment response
- It is completed by the patient
- It’s use is reimbursed by most health insurances
- The adult and adolescent scales can be viewed at:
  - and
Complication: Minimal Response at an Average Dose at Week 6

- Increase dose to FDA maximum
- Wait until week 10 before changing medications or augmenting
Complication: Side Effects at Low Doses

• Start an agent that can be up-titrated in incrementally small doses
Consider Pharmacogenetic Testing (PGT)

- Non-invasive genetic test using an oral swab or saliva specimen

- When a patient has:
  - minimal response at average dose
  - side effects at a low dose
  - failed multiple antidepressants
Common PGT for Depression: CYP2D6

• Major pathway for:
  • fluoxetine, fluvoxamine, paroxetine, vortioxetine, duloxetine, venlafaxine, mirtazapine, TCAs
  • aripiprazole

• Minor pathway for:
  • citalopram, escitalopram, sertraline, levomilnacipran, bupropion, vilazodone
  • quetiapine, olanzapine
Common PGT for Depression: CYP219

- **Major pathway for:**
  - citalopram, escitalopram, imipramine

- **Minor pathway for:**
  - Fluoxetine, sertraline, vortioxetine, levomilnacipran,
    venlafaxine, vilazodone, amitriptyline, nortriptyline
Common PGT for Depression: MTHFR

FOLIC ACID ➔ dihydrofolatereductase

Dihydrofolate ➔ dihydrofolatereductase

Tetrafolate ➔ serine hydromethyltransferase

5, 10 Methylene THF ➔ methylenetetrahydrofolatereductase (MTHFR)

L-METHYLFOLATE
Common PGT for Depression: MTHFR
(continued)

- MTHFR (methylenetetrahydrofolatereductase)
- There is over 50 years of evidence linking folate deficiency and depression
- Patients who are MTHFR+ may be at increased risk for depression due to a reduced ability to convert dietary folate into its active form of L-methylfolate
Common PGT for Depression: MTHFR  
(continued)

• There is evidence that adding L-methylfolate to an SSRI or SNRI, improved treatment outcomes as compared to placebo or monotherapy alone

• There is evidence that L-methylfolate support the production of neurotransmitters that naturally help improve mood and boost antidepressant response, especially in depressed patients with a BMI ≥30
When to Test for MTHFR

- Mood disorders
- Schizophrenia
- Infertility and/or multiple miscarriages
- Migraines
- IBS
- Child or sibling with autism, spina bifida, cleft lip/cleft palate
Why Consider PGT?

• To determine if:

  • If a given mediation is appropriate for your patient
  • If the dose is appropriate
    • If an ultrarapid metabolizer, dosage may need to be increased
    • If a slow metabolizer, dosage may need to be decreased
  • If l-methylfolate should be added to the regimen
Treatment of MTHFR +

- L-methylfolate 15mg po daily
Complication: Ending Treatment

- Treatment:
  - Education about relapse rates
  - Change medication or consider resuming brand-name medication
  - Change to a different type of therapy/therapist
  - Prescribe a medication to treat side effects
Complication: End of Drug Response

• Treatment:
  • Change dosage or class of medicine
  • Add or increase therapy
Complication: Anxious Depression

- 53% of STAR*D participants were identified as having anxious depression
- They were more likely to be unemployed, have less education, more severe depression, and more coexisting medical and psychiatric conditions
- They were harder to treat...
## Complication: Anxious Depression (continued)

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Anxious Depressed</th>
<th>Nonanxious Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>42% response</td>
<td>53% response</td>
</tr>
<tr>
<td></td>
<td>22% remission</td>
<td>33.4% remission</td>
</tr>
</tbody>
</table>
Complication: Increased Anxiety/Panic Attacks

• Given that about half of the patients presenting with depression in primary care have a co-morbid Anxiety Disorder, the potential to induce some anxiety exists.

• Therefore, at the onset of treatment, let patients know they may experience increased anxiety symptoms.
Managing Increased Anxiety < 1 month

- Consider using a benzodiazepine in the first month of treatment.

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Length of Action</th>
<th>Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprazolam</td>
<td>2-4 hours</td>
<td>0.25mg-1mg up to QID</td>
</tr>
<tr>
<td>lorazepam</td>
<td>4-6 hours</td>
<td>0.5mg-2mg up to TID</td>
</tr>
<tr>
<td>clonazepam</td>
<td>6-8 hours</td>
<td>0.5mg-2mg up to TID</td>
</tr>
</tbody>
</table>
# Managing Increased Anxiety >1 month

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age</th>
<th>Indication</th>
<th>Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>buspirone</td>
<td>adults *safety data 6-18</td>
<td>GAD</td>
<td>15mg-30mg BID</td>
</tr>
<tr>
<td>hydroxyzine</td>
<td>children - adults</td>
<td>Antihistamine</td>
<td>&lt; 6yo 50mg up to TID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Off label for anxiety</td>
<td>≥ 6yo 50mg-100mg up to TID</td>
</tr>
<tr>
<td>gabapentin</td>
<td></td>
<td>Anticonvulsant</td>
<td>Up to 3600mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Off label for anxiety</td>
<td>in divided doses</td>
</tr>
<tr>
<td>propranolol</td>
<td>adults</td>
<td>HTN (beta-blocker)</td>
<td>10-40mg single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Off label for Social Phobia</td>
<td>30 minutes prior to social event</td>
</tr>
</tbody>
</table>
Complication: Patient Becomes Pregnant

- Educate about the benefits and risks of continuing on antidepressant
  - Consider continuing medication if patient is currently depressed or has experienced more than two or more episodes of depression
Complication: Patient Becomes Pregnant (continued)

- Only Paxil is Pregnancy Category D, the rest are Category C
- Don’t change medications if it’s working; why expose the fetus to more agents?
- Maximize the dose of the current medication before augmenting with another agent
Resources Regarding Medication Use During Pregnancy

• www.womensmentalhealth.org
• www.emorywomensprogram.org
• www.motherisk.org
Complication: Sustained Depression

• Treatment:
  • Change dosage or class of medicine
  • Add or increase therapy
  • Augment with another antidepressant, mood stabilizer approved for augmentation
  • Augment with lithium or $T_3$
  • Add or increase therapy
Complication: Depression Turns to Hypomania…

- Bipolar patients present to us when depressed and unless specifically asked they *often do not report* hypomanic symptoms

- Keep in mind that bipolar patients are in a depressed phase three times more than they are in a hypomanic/manic phase so they may consider hypomania “normal”
What Does Hypomania Look Like?

- Distractibility
- Indiscretion or excessive risk taking
- Grandiosity
- Flight of ideas or racing thoughts
- Activity increase
- Sleep deficit *without fatigue*
- Talkativeness or pressured speech
MDQ: Screening Tool for Mania

• The Mood Disorder Questionnaire is a 15-item yes/no self-report

• It was designed for adults, but can be used with patients >12 years of age

• It can be repeated to measure improvement following treatment

• It can be viewed at:
  
  http://www.dbsalliance.org/site/PageServer?pagename=education_screeningcenter_mania
Mood Charting

- Encourage patients to use mood charting to get a sense of what happens over time

  - **Wellness Tracker** (www.dbsalliance.org/wellness_tracker)
    - Free iOS and Android
    - Tracks mood, sleep, medication, symptoms, exercise, medication, etc.
    - At-a-glance summary of trends
    - Download PDF reports

  - **T2 Mood Tracker** (t2health.dcoe.mil/apps/t-2mood-tracker)
    - Free iOS and Android
    - Tracks anxiety, stress, depression, general well-being
    - Download PDF reports

  - **Mood Tracker** (www.moodtracker.com)
    - Browser based tool
    - Tracks moods and medication
    - Has medication reminder
    - Provides audio relaxation and stress relief meditations
    - Can share profile with provider
STEP-BD
(Systematic Treatment Enhancement Program for Bipolar Disorder)

• NIMH funded study that revealed adding an antidepressant medication is no more effective than placebo in treating depressed phase of Bipolar Disorder but also didn’t show that an antidepressant triggered manic switching

• Bottom line: Use a mood stabilizer approved for antidepressant augmentation and/or to treat bipolar depression!
# Mood Stabilizers

<table>
<thead>
<tr>
<th>Medication</th>
<th>Approved For Antidepressant Augmentation</th>
<th>Approved for Bipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>N</td>
<td>Y (maintenance)</td>
</tr>
<tr>
<td>lurasidone</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>olanzapine</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>quietapine</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
Complication: Patient Becomes Suicidal

- Refer to the local ER to determine the level of care needed to maintain his safety
Additional Resources:

• National Alliance for the Mentally Ill
  http://www.nami.org/

• National Institute of Mental Health

• Depression and Bipolar Support Alliance
  http://www.dbsalliance.org/site/PageServer?pagename=home

• National Suicide Prevention Hotline
  1-800-273-TALK (8255)
References:


