B2: Depression - Are All Drugs Created Equal?
1:45pm - 2:45pm

ACPE UAN 107-000-13-017-L01-P 0.1 CEU/1.0 Hr
Activity Type: Knowledge-Based

**Learning Objectives for Pharmacists:** Upon completion of this CPE activity participants should be able to:
1. Review the symptoms of major depressive disorder
2. Compare and contrast the subtypes of depression in terms of symptoms and treatment
3. Identify which symptoms of depression may be related to noradrenergic dysfunction and which symptoms may be related to serotonergic dysfunction
4. List the advantages and disadvantages of single mechanism antidepressants and multiple mechanism antidepressants
5. Evaluate clinical trial data between single mechanism antidepressants and multiple mechanism antidepressants

**Speaker:** Sarah E. Grady, PharmD, BCPS, BCPP, is an Associate Professor, Department of Clinical Sciences, College of Pharmacy and Health Sciences at Drake University. Her clinical practice site is the psychiatric unit at Broadlawns Medical Center in Des Moines, Iowa. Dr. Grady received her Doctor of Pharmacy from the University of Illinois in 1999. She then completed an ASHP-accredited pharmacy practice residency at the Chicago VA Healthcare System in 2000. After completing her residency, Dr. Grady obtained an academic appointment at Midwestern University Chicago College of Pharmacy, where she taught for nearly 8 years. She is currently a board-certified pharmacotherapy specialist and a board certified psychiatric pharmacist. Dr. Grady greatly enjoys teaching, research, and patient care.

**Speaker Disclosure:** Sarah Grady reports no actual or potential conflicts of interest in relation to this CPE activity. Off-label use of medications will be discussed during this presentation.
Are All Antidepressants Created Equal?

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Drake University College of Pharmacy & Health Sciences

Faculty Disclosure

- Sarah E. Grady reports she does not have actual or potential conflicts of interest associated with this presentation.
- Sarah E. Grady has indicated that off-label use of medication will be discussed during this presentation.

Learning Objectives

Upon completion of this activity, pharmacists (or pharmacy technicians) should be able to:

- Review the symptoms of major depressive disorder.
- Compare and contrast the subtypes of depression in terms of symptoms.
- Identify which symptoms of depression may be related to noradrenergic dysfunction and which symptoms may be related to serotonergic dysfunction.
- List the advantages and disadvantages of single mechanism antidepressants and multiple mechanism antidepressants.
- Evaluate clinical trial data between single mechanism antidepressants and multiple mechanism antidepressants.
Personal Learning Objectives
Upon completion of this activity, I would like to be able to:

1. 
2. 
3. 

Pre-Assessment Questions
- Which of the following is a symptom of depression?
  A. homicidal ideation
  B. pain
  C. paranoid delusions
  D. psychomotor agitation

Pre-Assessment Questions
- Which of the following symptoms of depression may be attributed to serotonergic dysfunction only?
  A. appetite disturbances
  B. concentration difficulties
  C. depressed mood
  D. fatigue or loss of energy
Pre-Assessment Questions

- When educating the patient about the average antidepressant time course, which of the following symptoms will likely improve first?
  A. loss of interest
  B. mood
  C. sleep disturbances
  D. suicidal ideation

Pre-Assessment Questions

- Which of the following antidepressants is least likely to improve painful physical symptoms of depression?
  A. amitriptyline
  B. duloxetine
  C. fluoxetine
  D. venlafaxine

Pre-Assessment Questions

- SSRIs are different from each other in which of the following ways:
  A. primary mechanism of action
  B. secondary mechanism of action
  C. side effect profile
  D. therapeutic effect profile
Major Depressive Disorder (MDD)

- One of the most common psychiatric conditions
- Characterized by cognitive, behavioral, & physical functioning dysfunction
- 50-100% of patients present with medically unexplained pain complaints
- Patients oftentimes have another psychiatric comorbidity
- This is a heterogeneous condition

Cardinal Symptoms of MDD

- S
- I
- G
- E
- C
- A
- P
- S
- + Depressed mood

DSM-IV-TR Criteria for Major Depressive Episode

- 5 or more symptoms present during same 2 week period & represent change from previous functioning
- At least 1 of the symptoms is:
  - Depressed mood or loss of pleasure
  - Symptoms do not meet criteria for mixed episode
  - Symptoms cause significant distress & impairment
  - Symptoms not caused by substances or medical conditions
  - Symptoms are not caused by bereavement
### Depressive symptoms

**Noradrenergic Dysfunction**
- Depressed mood
- Loss of interest
- Sleep disturbances
- Fatigue or loss of energy
- Concentration difficulties
- Psychomotor agitation or retardation

**Serotoninergic Dysfunction**
- Depressed mood
- Sleep disturbances
- Psychomotor agitation or retardation
- Appetite disturbances
- Suicidal ideation
- Feelings of guilt or worthlessness

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### Potential adverse effects by neurotransmitter system

**Serotonergic**
- Anxiety
- Insomnia
- Sexual dysfunction
- Weight changes
- GI problems

**Noradrenergic**
- Tremor,
- Tachycardia,
- Sweating,
- Jitteriness,
- ↑ BP

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### Subtypes of Depression

- Psychotic
- Melancholic
- Atypical
Psychotic
- Delusions or hallucinations
- Psychotic symptoms usually match depressive themes

Melancholic
- Loss of pleasure in activities
- Depressed mood in morning
- Early morning awakenings
- Loss of appetite
- Excessive guilt

Atypical
- Mood reactivity
- Weight gain
- Increased sleep
- Sensitivity to interpersonal rejection
Case

- 24 y/o woman presents to the clinic with c/o insomnia, hypophagia, low energy, decreased concentration, and depressed mood. She has been feeling this way for about 2 months. She reports missing several days of work over the past month. She also states, “I ache all over.”

- Her PMH is significant for seizures. She reports being managed well with levetiracetam for several years. She reports that her last seizure was 6 months ago. She states this seizure was most likely due to missing a few days of the levetiracetam plus drinking excessive alcohol around the same time. She states this incident scared her, and that she no longer drinks alcohol & misses very few doses of levetiracetam.

- She also takes an oral contraceptive daily. She has also taken this for years.

- She reports having obsessions with germs since she was a child, but has started washing her hands and taking 1 hour long showers in the course of the past few months. She also checks her doors, alarm clock, and oven several times a day.

- All labs & toxicology screens are normal.

- She has prescription insurance coverage through work.

What antidepressant do you recommend?

Antidepressant Pharmacotherapy

- All agents proven effective
- 60-80% response rate according to some references
- Response: 50% reduction in symptoms from baseline
- Therapeutic effects seen weeks after initial-dose taken
  - Week 1: improved sleep, appetite, energy
  - Weeks 2-4: improved mood, anhedonia, suicidal ideation
- Adverse effects may show up after initial dose is taken

Antidepressant Progression

- TCA & MAOIs
- SSRIs
- SNRIs, bupropion, mirtazapine
Are 2 Antidepressant Mechanisms Better Than 1?

- TCAs
  - Multiple mechanisms = side effects
  - Single mechanism = less side effects but loss of efficacy?
- SSRIs
  - SSRI = single mechanism

Are 2 Antidepressant Mechanisms Better Than 1? – The debate

- Clinicians debate whether remission rates are higher with SNRIs compared to SSRIs
- Clinicians debate whether SNRIs are more helpful in patients who fail to respond to SSRIs

Evidence for advantage of dual-action over single-action

- Delgado et al. performed serotonin & norepinephrine depletion studies
  - When patients who responded to serotonergic medications were diet depleted of serotonin -- symptoms returned
  - Same result seen for noradrenergic group
  - When patients who responded to serotonergic medications were diet depleted of norepinephrine -- symptoms did not significantly increase
  - Same result seen for noradrenergic group
  - Studies concluded that addressing BOTH serotonergic & noradrenergic aspects of depression might lead to broader antidepressant effects in an individual patient

Delgado et al. Serotonin function and the mechanism of antidepressant action: reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. Arch Gen Psychiatry 1990

Miller et al. Clinical and biochemical effects of catecholamine depletion on antidepressant-induced remission of depression. Arch Gen Psychiatry 1996
SSRIs vs. TCAs

- Anderson published a meta-analysis of 25 different studies comparing SSRIs and TCAs
  - Dual-action TCAs were superior to SSRIs in reducing symptoms of depression
  - SSRIs were better tolerated than TCAs

SSRIs vs. SNRIs

- Thase et al. published a pooled analysis of 8 studies comparing venlafaxine & various SSRIs
  - Authors found that SSRIs needed 8 weeks to separate from placebo while venlafaxine needed only 2 weeks
  - Venlafaxine found to be superior in final remission rates: Venlafaxine (45%), SSRIs (35%), placebo (25%)
- Smith et al. analyzed 32 studies in which venlafaxine was compared to various antidepressants
  - Venlafaxine more effective than SSRIs
  - Venlafaxine had no advantage over TCAs
- Goldstein et al. compared duloxetine & fluoxetine for MDD
  - Duloxetine was superior in producing remission

Antidepressants and pain

- TCAs may be more effective than SSRIs for painful physical symptoms
- Studies have demonstrated effectiveness of medium to high doses of venlafaxine & duloxetine for painful physical symptoms
Treatment Guidelines – American Psychiatric Association 2010

- Prescriber may choose between:
  - Pharmacotherapy
  - Psychotherapy
  - Combination of pharmacotherapy + psychotherapy
  - Somatic therapies


SSRI – Indications

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<th>Diagnosis</th>
<th>Citalopram</th>
<th>Escitalopram</th>
<th>Fluoxetine</th>
<th>Fluvoxamine</th>
<th>Paroxetine</th>
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SSRIs: 6 unique drugs or 1 class of 6 drugs?

- What they have in common:
  - Primary mechanism of action
  - Therapeutic profiles
  - Side effect profiles

- How they differ:
  - Structure
  - Secondary mechanisms of action

Same individuals often react very differently to one SSRI versus another.

Stahl’s Essential Psychopharmacology 2008
SSRIs vs. SNRIs

- Thase et al. concluded that remission rates for patients treated with venlafaxine ER or SSRIs did not differ significantly after 6 months of treatment.
- Signorovitch et al. concluded that patients treated with escitalopram were significantly more likely to have remission without concurrent AEs compared to those taking SNRIs.
- Kornstein et al. concluded in a pooled analysis that escitalopram is at least as effective as SNRIs and is better tolerated.

Thase et al. Remission with venlafaxine ER or SSRIs in depressed patients: a randomized, open-label study. Prim Care Companion 2011
Signorovitch et al. Remission of MDD w/out adverse events: a comparison of escitalopram vs. SNRIs. Curr Med Res Opin 2011
Kornstein et al. Escitalopram vs. SNRI antidepressants in acute treatment of MDD: integrative analysis of 4 double-blind, randomized trials. CNS Spect 2009

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- All labs & toxicology screens are normal.
- She has prescription insurance coverage through work.

What antidepressant do you recommend?

Antidepressant selection

- Current symptoms
- H/O drug response (if any)
- Patient preference
- Adverse effect profile
- Potential drug interactions
- Concurrent medical or psychiatric conditions
- Potential for overdose
- Cost

Pharmacotherapy: Principles & Practice 2010
Conclusions

- Dual-action antidepressants may have better efficacy and may be appropriate for some patients
- The important thing to keep in mind is the need to attain remission in all patients, and to do this with any antidepressant that works and the patient can tolerate
- Treatment needs to be individualized

Post-Assessment Questions

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