Antidepressants
Adverse Drug Events and Managing Patient Expectations

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Learning Objectives

Pharmacists

Identify common adverse drug events of different antidepressants.

For a given antidepressant, counsel on varying side effects and ways to mitigate these effects.

For a patient newly initiating an antidepressant, be able to counsel on expectations, including, side effects, efficacy, and timeline.

Technicians

Identify a patient who may have experienced common adverse drug events of antidepressants.

Recognize a patient who may not be aware of realistic expectations regarding side effects, efficacy, and timeline of antidepressants.

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Disclosures

No relevant financial relationships to disclose and has no actual or potential conflict of interest in relation to this activity or presentation

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Outline

Major Depressive Disorder

Treatment Goals of Antidepressants

Common adverse drug events of common antidepressant classes
- SSRIs
- SNRIs
- TCAs
- NDRI
- Serotonin modulators
- MAOIs

Counseling points on timeline and expectations

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Depression symptoms can vary from mild to severe

M	Mood decreased
S	Sleep changes
I	Interests decreased
G	Guilt/ hopelessness
E	Energy decreased
C	Concentration decreased
A	Appetite changes
P	Psychomotor retardation/agitation
S	Suicidality

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Clinical Course of Depression

Onset: average age is late 20s
- Sharp increase between 12-16 years
- Symptoms develop over days to weeks but may develop suddenly

Duration: Median time to recovery is 20 weeks with adequate treatment
- Untreated- episodes last 6 months or longer
- Function usually returns between episodes, but remission becomes shorter with each episode

Recurrence
- 1st episode- 50% will recover without recurrence
- Each subsequent episode is a risk factor for future recurrence

Untreated MDD has lifetime risk of ~20% for suicide
- Each episode of depression the risk of suicide becomes greater

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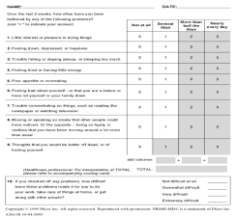
Patient Health Questionnaire (PHQ-9)

Sensitivity and Specificity of ~%94

Total Score	Depression Severity
1 – 4	Minimal depression
5 – 9	Mild depression
10 – 14	Moderate depression
15 – 19	Moderately severe depression
20 – 27	Severe depression



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Treatment

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Goals of Treatment

Resolution of current symptoms (i.e., remission) and the prevention of further episodes of depression (i.e., relapse or recurrence)

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Treatment Options

Pharmacotherapy

Psychotherapy

Refractory: Electroconvulsive Therapy (ECT), TMS, ketamine/esketamine

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Pharmacologic Treatment

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General Approach to Treatment

Three phases of treatment:

1. **Acute**
2. **Continuation**
3. **Maintenance**

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Acute Phase

Initial choice of antidepressant

- Patient preference
- Prior response
- Safety and tolerability
- Co-morbid disorders
- Drug-Drug- interactions and kinetic parameters
- Cost

Phase lasting approximately 6 to 12 weeks

- Goal is remission (i.e., absence of symptoms)
- Select agent or regimen until this is achieved

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Continuation Phase

Phase lasting 4 to 9 months after remission is achieved

- Goal to eliminate residual symptoms
- Prevent relapse (i.e., return of symptoms within 6 months of remission)

Relapse ranges from 20-85% without continuation of treatment

If depressive symptoms occur, consider:

- Poor adherence
- Substance use
- Psychosocial stressors

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Maintenance Phase

Phase lasting at least 12 to 36 months

- goal is to prevent recurrence (i.e., a separate episode of depression)
- Treatment may be indefinite and life-long

Consider this phase when

- History of 3 or more depressive episodes
- Patients with chronic depressive symptoms
- Continued psychosocial stressors
- Family history of chronic depression
- Severe depressive episodes
- Early age at onset or elderly

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Selective Serotonin Reuptake Inhibitors

SSRI	Dose	Half-Life	Metabolism/ Excretion
Sertraline	100-200mg	22-36 hrs	2D6 and 2C9
Citalopram	20-40mg	23-45 hrs	2D6, 2C19
Escitalopram	10-20mg	27-32 hrs	2D6, 2C19
Fluoxetine	10-80mg	4-6 days	2C9, 2D6*
Paroxetine	20-50mg	24-31hrs	2D6*
Fluvoxamine	100-200mg	15-26 hrs	*2D6, *3A4,*2C19, *1A2

* Indicate major substrate

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Common Adverse Effects of SSRIs

- GI-Nausea, diarrhea, constipation
- Headaches
- Sleep disturbances
- Anxiety- Jitteriness
- Sexual dysfunction
- Discontinuation syndrome

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Serotonin and Norepinephrine Reuptake Inhibitors

SNRI	Dose	Half-Life	Metabolism
Desvenlafaxine	50-400mg	11 hrs	3A4 2D6
Duloxetine	30-120mg	12 hrs	*2D6
Venlafaxine ER	75-225mg	10 hrs	2D6
Milnacipran	12mg-300mg	8 hrs	Glucuronidation
Levomilnacipran	20-120mg	12 hrs	*3A4, 2C19, 2D6

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Common Adverse Effects of SNRIs

- GI-Nausea, diarrhea, constipation
- Headaches
- Sleep disturbances
- Anxiety- Jitteriness
- Sexual dysfunction
- Discontinuation syndrome
- Hypertension*

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Serotonin Modulators

Modulators	Dose	Half-Life	Metabolism
Trazodone	50-200mg	6 hrs	3A4
Nefazodone	300-600mg	2-4hrs	N-dealkylation, hydroxylation

Medication	Dose	Half-Life	Metabolism
Vilazodone	20-40mg	25 hrs	3A4*, 2C19, 2D6
Vortioxetine	10-20mg	66 hrs	2D6*, 3A4/5, 2C19, 2C9, 2A6, 2C8, 2B6

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Common ADEs of Vortioxetine and Vilazodone

- GI- Nausea, diarrhea, constipation
- Headaches
- Sleep disturbances
- Anxiety- Jitteriness
- Sexual dysfunction
- Discontinuation syndrome

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Bupropion and Mirtazapine

Medication	Dose	Half-Life	Metabolism
Bupropion (IR,SR,XL)	IR: Max 450mg/day divided 3- 4 times. Do not exceed 150mg per dose 12hr: Max 200mg BID. Do not exceed 200mg per dose XL (24hr): Max 450mg daily	11hrs	2B6 2D6

Medication	Dose	Half-Life	Metabolism
Mirtazapine	30-45mg	20-40hrs	2D6, 1A2, 3A4

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Common ADEs of Bupropion

- Dry Mouth
- GI- Nausea, abdominal pain
- Insomnia
- Tremor
- Tinnitus
- Anxiety
- Weight loss

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Bupropion Contraindications

SEIZURE

Dose Range (mg/day)	Seizure Rate (%)
<300	0.1%
300-450	0.4%
450-600	Increase by almost 10-fold

OTHER CONTRAINDICATIONS

Bulimia nervosa or anorexia nervosa

Abrupt discontinuation of alcohol or sedatives

MAOI therapy

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Common Adverse Effects of Mirtazapine

- Increased appetite
- Increased weight gain
- Dry mouth
- Constipation
- Orthostasis
- Increased triglycerides
- Mania

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Tricyclic Antidepressants (TCAs)

Use limited as there is equally effective options that are safer in overdose and better tolerated

Tertiary Amines		
Amitriptyline	50-300mg	2D6 and 1A2
Imipramine	50-300mg	2D6 and 1A2
Clomipramine	100-250mg	2D6 and 1A2
Doxepin	75-300mg	2D6 and 1A2
Secondary Amines		
Nortriptyline	75-150mg	2D6
Desipramine	100-200mg	2D6 and 1A2
Protriptyline	16-60mg	2D6
Amoxapine	200-600mg	2D6

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ADEs of TCAs

- **Anticholinergic:** dry mouth, constipation, blurred vision, urinary retention, tachycardia
- **Antihistaminic**: sedation, weight gain
- **Alpha-antagonism**: Orthostatic hypotension
- **Cardiovascular:** Overdose can produce severe arrhythmias
- **Contraindications** acute recovery phase of a myocardial infarction.

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Monoamine Oxidase Inhibitors

MAOI	Usual Dose Range (mg/day)	Metabolism
Isocarboxazid	40-60	MAO
Phenelzine	6-90	MAO
Selegiline Transdermal	6-12	2B6, 2C9, 3A4/5,2A6
Tranylcypromine	40-60	MAO

MAO_A –Preferentially metabolizes NE and 5-HT

MAO_B- Preferentially metabolizes DA (though also trace amines as well).

Selegiline
- <10mg= irreversible inhibitor of MAO_B
- >10mg= irreversible of both MAO_A and MAO_B

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Common ADEs of MAOIs

- Orthostatic hypotension
- Dizziness
- Mydriasis
- Edema
- Sexual dysfunction
- Insomnia
- Weight gain

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Side Effects of MAOIs

- Sedation
- Serotonin syndrome
- Hypertensive crisis
- Mania

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Drug Interactions

Serotonergic		Sympathomimetic Agents
SSRIs SNRIs TCAs Vilazodone Vortioxetine Antihistamines • Chlorpheniramine • Brompheniramine Opioids • Fentanyl • Methadone • Tramadol • Meperidine	Other • Carbamazepine • Cyclobenzaprine • Dextroamphetamine • Linezolid • Methylene blue	Decongestants • Phenylephrine • Oxymetazoline • Ephedrine • Pseudoephedrine Stimulants Norepinephrine reuptake inhibitors • TCAs • SNRIs • Atomoxetine • Bupropion Appetite suppressants • Phentermine

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MAOI Diet

Class of food and Beverage	Tyramine-Rich Foods and Beverages to Avoid	Acceptable Foods, Containing No or Little Tyramine
Meat, Poultry, and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring	Fresh meat, poultry and fish, including processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese and yogurt
Beverages	All varieties of tap beer, and beers that have not been pasteurized so as to allow for ongoing fermentation	Avoid with all antidepressants, but MAOIs in particular. (Bottled and canned beers and wines contain little or no tyramine)
Miscellaneous	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (including soy sauce and tofu); OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain-restaurant pizzas prepared with cheeses low in tyramine

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Expectations

TIMELINE

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Overview

- **Week 1**
  - Tolerability
  - No efficacy
- **Week 2**
  - Improvement in most ADEs
  - Improvement in MDD symptoms
- **Week 3 and 4**
  - Minimal to no ADEs
  - Improvement in most symptoms

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Week 1- Tolerability

SIDE EFFECTS	DEPRESSION SYMPTOMS
Headache Nausea Diarrhea Stomach upset Anxiety – "might feel more jittery" Insomnia or sedation	None

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Week 2- Ancillary Function

SIDE EFFECTS	DEPRESSION SYMPTOMS
Improvement or resolution in: ◦ Headache ◦ Nausea ◦ Diarrhea ◦ Stomach upset ◦ Anxiety – "might feel more jittery" ◦ Insomnia or sedation	Some improvement in: ◦ Sleep ◦ Appetite ◦ Executive function

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Week 3 and 4

SIDE EFFECTS

Resolution or Tolerability

* Dose increases can reset potential risk of causing symptoms

DEPRESSION SYMPTOMS

Improvement in:
- Energy
- Memory
- Self-care
- Depression

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Side Effect Management

SELF LIMITING

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GI

NAUSEA AND VOMITING

Usually transient
- Resolves in 1-2 weeks after initiation or increasing dose

Split into smaller doses

Take with food

Change agents if intolerable or does not subside

DIARRHEA

Usually transient
- Resolves in 1-2 weeks after initiation or increasing dose

Increase dietary fiber or OTC Metamucil

Change agents if intolerable or does not subside

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Jitteriness

Usually transient
- Resolves in 1-2 weeks after initiation or increasing dose

Avoid caffeine or other stimulants

Recommended decrease dose, then increase at a slower rate

Switch medications
- Nefazodone and mirtazapine have lower incident

Adjunct with beta-blocker

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Insomnia

Avoid caffeine, alcohol, or tobacco at bedtime

Consider CBT-I

Change timing of medication

Decrease dose of antidepressant

Switch medications or adjunct:
- Mirtazapine, nefazodone, TCA (doxepin), trazodone

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Withdrawal Syndrome

SYMPTOMS

Increased anxiety, depression or mood swings

Flu-like symptoms, headache, fatigue, dizziness, vertigo

Electric shock sensation (or "brain zaps")

MANAGEMENT

Not directly life threatening- risk depends on ½ life of medication

Adherence

Switch to medication with longer ½ life

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Case Break

AJ is a 39yoM with MDD who regularly picks up his prescriptions at your community pharmacy. He comes to the pickup window where you, the pharmacy technician, are helping him. He asks for his prescription, and you note that it is not in the bin. When looking at the computer you note the following prescriptions:

Prescriptions	Last filled
Duloxetine 60mg #30 1 tablet by mouth daily	April 30, 2022
Hydroxyzine 50mg #90 1 tablet by mouth 3 times daily as needed	March 15, 2022
Duloxetine 60mg #30 1 tablet by mouth daily	March 15, 2022
Duloxetine 60mg #30 1 tablet by mouth daily	January 12, 2022
Duloxetine 30mg #30 1 tablet by mouth daily	December 20, 2022

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Case Break

Which of the following concerns may be playing a role in AJ's fill history?

A. Nausea

B. Erectile dysfunction

C. Antidepressant withdrawal syndrome

D. Increased anxiety

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Case Break

After discussing with AJ, he reports he will occasionally get anxious and feel like his duloxetine is making him more depressed. He will even have days where he will feel more tired and will get headaches. He tells you that it is random and that he is open to talking to the pharmacist about it. You refer him to the consult window. What would you like to tell the pharmacist?

A. "Hey, a patient has a question for you"

B. "A patient might be experiencing side effects to duloxetine, which he does not always fill on time"

C. " Hey, a patient might be experiencing serotonin syndrome from duloxetine, which he takes too much of."

D. Run!

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Case Break

AJ describes the above symptoms to you, the pharmacist. What could be a question to ask for further clarification?

A. "Why are you always refilling your duloxetine late?"

B. "How often do you forget to take a dose of the duloxetine"

C. "Did you tell your PCP about these symptoms?"

D. "Can you wait for the technician to come back; I am going on break?"

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Case Break

AJ tells you that he will miss a dose maybe every two weeks and that is usually when he notices these side effects. What is the likely side effect he is experiencing and what counseling can you give?

A. Withdrawal syndrome- counsel on not life threatening and adherence will help

B. Serotonin syndrome- counsel to stop taking the medication right away

C. Increased jitteriness- counsel on symptoms are transient and will go away in 2 weeks

D. Increased jitteriness- counsel on asking his PCP for a benzodiazepine prescription to help

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Side Effect Management

LONG-TERM OR SEVERE ADES

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Warnings and Precautions With All Antidepressants

[US Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders; consider risk prior to prescribing.

Serotonin Syndrome

Increased risk of bleeding

Activation of mania/ hypomania

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Suicidality

- Counsel that it is rare but to watch for worsening ideation or gestures, especially the beginning of treatment and among younger patients (<25 years of age).
- Discuss the possibility that adverse events may occur, including behavioral agitation or anger, and encourage patients to seek help should this occur.
- Deal with the subject of suicide directly.

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Serotonin Syndrome

Mild	Moderate	Life Threatening
Mydriasis Shivering Mild tachycardia	Altered mental status Autonomic hyperactivity Neuromuscular abnormalities	Delirium Hypertension Hyperthermia Muscle rigidity Tachycardia
Management		
Discontinue serotonergic agents Observe for improvement over 6 hours Benzodiazepine PRN	Admit to hospital Cardiac monitoring Cyproheptadine	ICU Esmolol or nitroprusside Cooling measures Sedation, paralysis, ventilation

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Common Serotonergic Agents

Antidepressants/ Others	Opioids	Stimulants	Hallucinogens/ Dissociative	Antibiotics
SSRI	Tramadol	Amphetamine salts	dextromethorphan	Linezolid
SNRI	Methadone	Methamphetamine	LSD	
MAOI	Meperidine			
TCAs	Fentanyl			
Trazodone				
Buspirone				
Lithium				

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Sexual Dysfunction

Symptoms	Treatment
Decreased libido	Switch agent, add bupropion or trazodone, cyproheptadine
Difficulty attaining orgasm	Switch agent, add PDE-5 inhibitor, or medication above
Difficulty maintaining arousal	Switch agent, add PDE-5 inhibitor, or medication above

Can also consider:

- Wait to see if tolerance develops
- Decrease the antidepressant dose
- Drug holidays

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Mania/Hypomania

D	Distractibility
I	Impulsivity
G	Grandiosity
F	Flight of ideas
A	Activities increased
S	Sleep decreased
T	Talkative

~ 50% of patients with bipolar disorder present with bipolar depression

~60% of patients with bipolar disorder are misdiagnosed with MDD

Management:

Hold the antidepressant

Get a hold of the prescriber

Curr Psychiatry Rep. 2012
J Clin Psychiatry. 2003

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Summary

Untreated depression is a chronic remitting disease

- Leads to decreased quality of life
- And increases risk of suicide

Pharmacotherapy is just as efficacious as psychotherapy

- It will require approximately at least 1 year of continued treatment
- Based on patient preference and tolerability

Transparency is key to success with pharmacotherapy

- Providing counseling on realistic expectations
- Monitoring and checking in with side effects can increase their success

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Thank you

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