Antidepressants

Michigan Center for Clinical Systems Improvement (MI-CCSI)

Last Updated: April 2021

Objectives

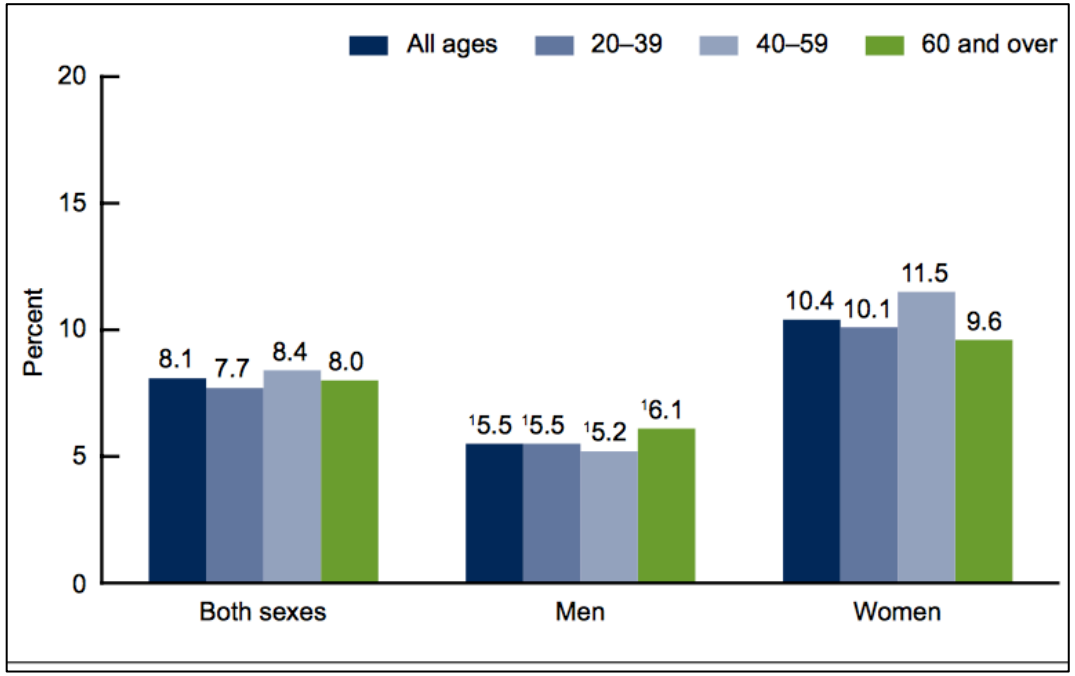
At the conclusion of this presentation, the participant will be able to:

- Describe the epidemiology, pathophysiologic processes, risk factors, clinical manifestations, and diagnostic criteria for depression.
- Identify medications available for the management of depression and their relative place in therapy.
- Recognize the potential for drug-drug interactions with medications used for the management of depression.
- Deploy strategies for management of side effects of antidepressants.

Epidemiology, Pathophysiology, Risk Factors, Clinical Manifestations, and Diagnostic Criteria

Epidemiology

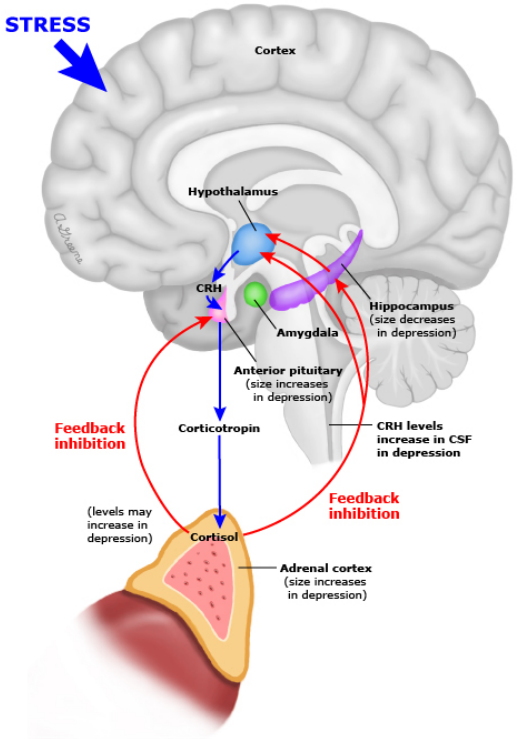
- 8.1% of Americans ≥ 20
- Twice as common in women
- Lowest among non-Hispanic Asian adults
- Decreased incidence as family income levels increase
- Incidence decreases with age



Brody DJ et al. Prevalence of Depression Among Adults Aged 20 and Over: United States, 2013-2016. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Health Statistics. Available from: https://www.cdc.gov/nchs/data/databriefs/db303.pdf. Published February 2018. Accessed July 7, 2020.

Krishnan R. Unipolar depression in adults: Epidemiology, pathogenesis, and neurobiology. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.

Pathophysiology



- Association with many neurobiological changes
- Likely an observable output of a wide range of disorders
- Final common pathway of different disease processes occurring across a biopsychosocial continuum

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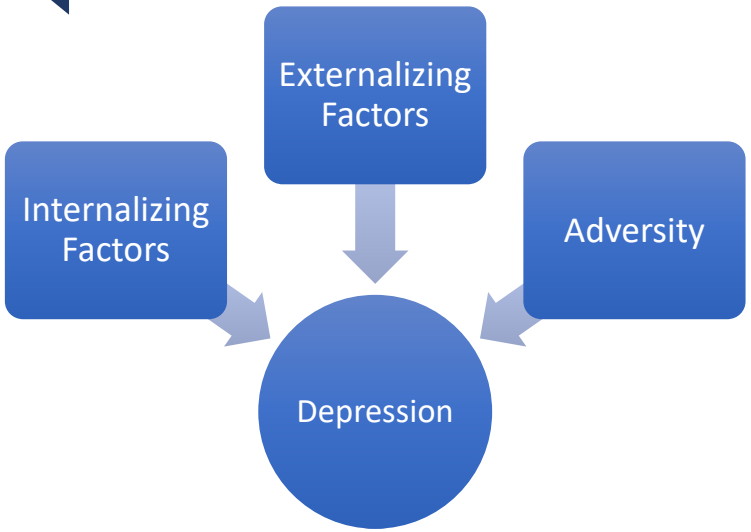
Pathophysiology



Internalizing Factors	Externalizing Factors	Adversity
• Genetics • Neuroticism • Low self-esteem • Early-onset anxiety disorder • History of major depression	• Genetics • Substance misuse • Conduct disorder	• Trauma during childhood or adulthood • Stressful life events in past year • Parental loss • History of divorce and/or marital problems • Low social support, education, and/or parental warmth

Krishnan R. Unipolar depression in adults: Epidemiology, pathogenesis, and neurobiology. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.

Social and Psychological Factors

Social

- Isolation, poor social support, criticism from family members, etc. may lead to depression onset or perpetuate depressive episodes
- Onset it more likely in individuals who view their social support as poor

Psychological

- Individual psychologic factors have been identified as predisposing to depression
- For example, personality psychology has demonstrated the importance of personality traits in the onset and course of depression

Krishnan R. Unipolar depression in adults: Epidemiology, pathogenesis, and neurobiology. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.

Secondary Depression

Medical disorders

- Parkinson’s disease
- Multiple sclerosis
- Heart failure

Medications

- Glucocorticoids
- Interferons

Krishnan R. Unipolar depression in adults: Epidemiology, pathogenesis, and neurobiology. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.

Risk Factors

Younger Age	Prior Depressive Episode	Family History	Female Gender
Childbirth (e.g., Postpartum Depression)	Childhood Trauma	Stressful Life Events	Lower Income
Poor Social Support	Serious Medical Illness	Dementia	Substance Use Disorder

Williams J and Nieuwsma J. Screening for depression in adults. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2019.

Subtypes

- Anxiety
- Atypical
- Catatonic
- Melancholic
- Mixed features
- Peripartum
- Psychotic
- Seasonal

Lyness JM. Unipolar depression in adults: Clinical features. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.

Clinical Presentation

Mood Symptoms

- Sadness
- Emotional distress or numbness
- Anxiety or irritability

Neurovegetative Symptoms

- Loss of energy
- Changes in sleep, appetite, or weight

Somatic Symptoms

- Headache
- Abdominal or pelvic pain
- Back pain
- Other physical complaints

Williams J and Nieuwsma J. Screening for depression in adults. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2019.

Beyond Initial Presentation

- Most patients eventually experience remission
  - One-half within 1 year
  - Three-quarters within 2 years
- Some symptoms can persist after patients no longer technically meet the criteria for depression
  - Most commonly: insomnia > sad mood > decreased concentration
  - Persistent symptoms heighten the risk for recurrence
- Recurrence is common
  - 72% of patients report having more than one occurrence

Williams J and Nieuwsma J. Screening for depression in adults. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2019.

Patient Health Questionnaire-9 (PHQ-9)

	Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
PHQ-2	Little interest or pleasure in doing things	0	1	2	3
	Feeling down, depressed, or hopeless	0	1	2	3
	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
	Feeling tired or having little energy	0	1	2	3
	Poor appetite or overeating	0	1	2	3
	Feeling bad about yourself, or that you are a failure, or that you have let yourself or your family down	0	1	2	3
	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
	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.	0	1	2	3
	Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
	Total	--	+ __	+ __	+ __

Williams J and Nieuwsma J. Screening for depression in adults. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2019.

PHQ-9

- Somewhat more accurate than other screens
- Useful for monitoring response to treatment

PHQ-9 score ≥10: Likely major depression
Depression score ranges:
5 to 9: mild
10 to 14: moderate
15 to 19: moderately severe
≥20: severe

Williams J and Nieuwsma J. Screening for depression in adults. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2019.

Diagnostic Criteria

- ≥ 5 of the listed symptoms present during the same two-week period
- Symptoms must represent a change from previous functioning
- The symptoms:
  - Cause substantial distress or impair psychosocial functioning
  - Are not the direct result of the physiological effect of a substance or general medical disorder
  - Cannot be explained by response to significant loss

Williams J and Nieuwsma J. Screening for depression in adults. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2019.

Additional Considerations

- Patients who present with major depression may have either unipolar depression or bipolar depression.
  - The possibility of bipolar depression can be ruled out by ruling out a history of mania or hypomania
  - The distinction is important because approaches to treatment differ

Simon G. Unipolar depression in adults and initial treatment: General principles and prognosis. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2019.

Additional Considerations

- Assess all patients with depressive symptoms for suicidal and homicidal ideation and behavior
  - Suicidal or homicidal ideation, plan, and intent
  - Access to means for suicide and homicide, and the lethality of those means
  - Psychotic symptoms (e.g., delusions or command auditory hallucinations)
  - Severe anxiety
  - Substance-related disorders
  - History and seriousness of previous suicide and homicide attempts
  - Family history of or recent exposure to suicide and homicide

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Management of Depression

Initial Treatment – General Principles

- Goals include symptom remission and restoration of baseline function
- Combination pharmacotherapy and psychotherapy is preferred
- **Less than one-third of patients achieve remission with the first antidepressant tried**
- Antidepressant therapies take time to achieve maximal effect
- Switching between antidepressant therapies is a common and necessary strategy for most patients

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

Time to Max Effect

- Expect 4-8 weeks to see the max effect of a given dose
  - Some variation between classes
- Recommend a trial of 6-12 weeks before therapy switch

Choosing and Switching Antidepressants. Pharmacist's Letter. Published June 2018. Accessed July 10, 2020.
Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

Switching Therapy

- Lack of response
- Intolerable side effects
- Between or within classes
  - Once a patient has tried and failed two drugs in the same class, consideration may be given to a drug from a different class

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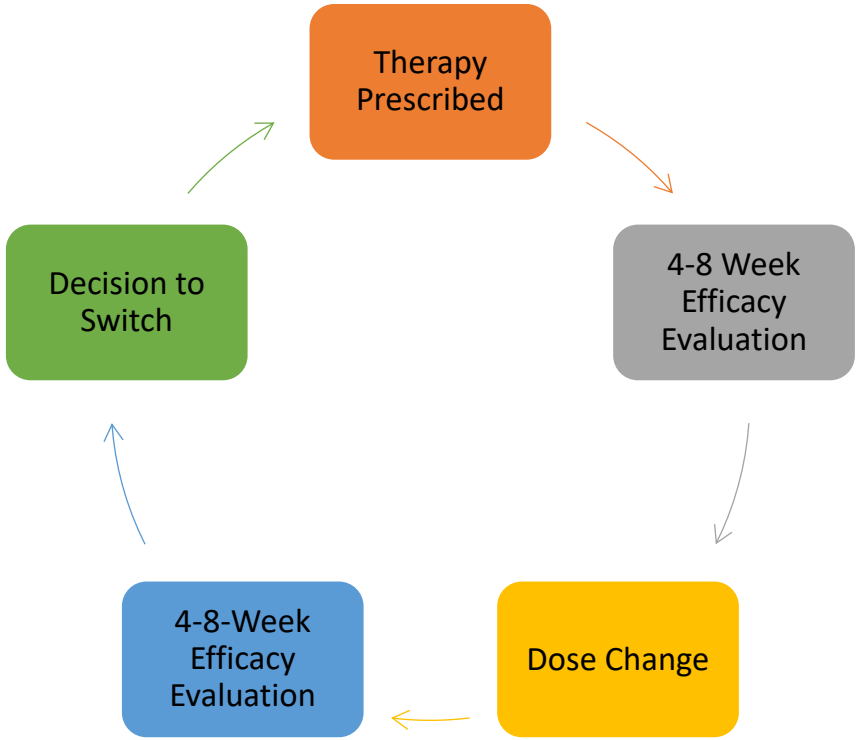
Initial Therapy Selection

- Can be a long process!
  - Set appropriate expectations!
  - Remember: **Less than one-third of patients achieve remission with the first antidepressant tried**



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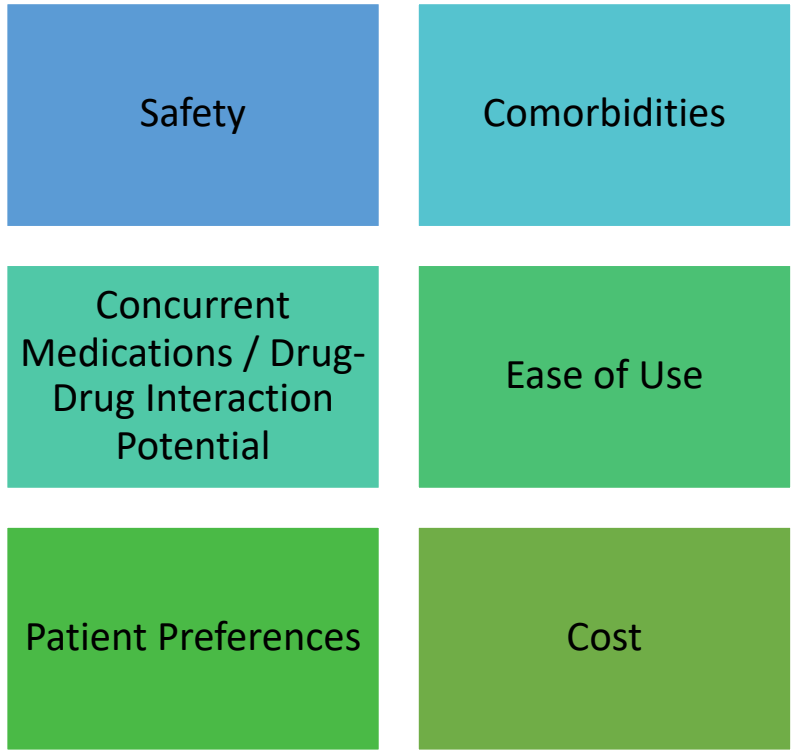
Initial Therapy Selection

- The efficacy of different antidepressants is generally comparable across and within classes
- Decisions about choice of therapy are based on other factors



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Treatment Options

First-Generation	Second-Generation
• Tricyclic Antidepressants (TCAs) • Monoamine Oxidase Inhibitors (MAOIs)	• Selective Serotonin Reuptake Inhibitors (SSRIs) • Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) • Atypical Antidepressants • Serotonin Modulators

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

First Generation Therapy Options (TCAs/MAOIs)

- Typically, not used as initial therapy due to side effect profiles
- May have a role in treating treatment-resistant depression

TCAs	MAOIs
• Risk of cardiac effects and sudden death – screen prior to therapy initiation • Anticholinergic and/or antihistaminic effects • ↓ seizure threshold • Generally taken in the evening due to sedating side effects	• Risk for hypertensive crisis and/or serotonin syndrome • Dietary restrictions and monitoring for drug-drug interactions

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.
Hirsch M and Birnbaum RJ. Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.
Hirsch M and Bimbaum RJ. Monoamine oxidase inhibitors (MAOIs) for treating depressed adults. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

TCAs

Drug	Usual Total Starting Dose Per Day (mg)	Usual Total Dose Per Day (mg)	Extreme Daily Dose Range (mg)
Amitriptyline	25	150-300	10-300
Amoxapine	25	200-300	25-400
Clomipramine	25	100-250	25-300
Desipramine	25	150	300
Doxepin	25	100-300	10-300
Imipramine	25	150-300	10-300
Maprotiline*	25	100-225	25-225
Nortriptyline	25	50-150	10-150
Protriptyline	10	15-60	5-60
Trimipramine	25	150-300	25-300

** Tetracyclic antidepressant*

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MAOIs

Drug	Usual Total Starting Dose Per Day (mg)	Usual Total Dose Per Day (mg)
Isocarboxazid	10	10-40
Phenelzine	15	15-90
Selegiline (transdermal)	6 mg/24 hr patch	6-12 mg/24 hr patch
Tranylcypromine	10	30-60

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.
Hirsch M and Bimbaum RJ. Monoamine oxidase inhibitors (MAOIs) for treating depressed adults. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

SSRIs

- Most widely prescribed class of antidepressants
- Frequently the initial therapy class of choice
- May inhibit liver enzymes responsible for metabolizing other medications
  - Citalopram and escitalopram have less drug-drug interaction potential
- Common side effects include sexual dysfunction, drowsiness, weight gain, insomnia, anxiety, dizziness, headache, and dry mouth
- Black box warning: ↑ risk of suicidality for children, adolescents, and young adults

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.
Hirsch M and Birnbaum RJ. Selectice serotonin reuptake inhibitors: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

SSRIs

Drug	Usual Total Starting Dose Per Day (mg)	Usual Total Dose Per Day (mg)	Extreme Daily Dose Range (mg)
Citalopram	20	20-40	10-40
Escitalopram	10	10-20	5-30
Fluoxetine	20	20-60	10-80
Fluvoxamine	50	50-200	25-300
Fluvoxamine CR	100	100-200	100-300
Paroxetine	20	20-40	10-50
Paroxetine CR	25	25-50	12.5-62.5
Sertraline	50	50-200	25-300

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SNRIs

- A reasonable alternative to SSRIs
- Nausea is the most common side affect – administration with food may reduce this effect
- Other side effects include constipation, dizziness, dry mouth, and sweating, sexual dysfunction, and substantial weight gain
- SNRIs, except for duloxetine, have the potential to increase blood pressure
- Black box warning: ↑ risk of suicidality for children, adolescents, and young adults

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.
Nelson C. Serotonin-norepinephrine reuptake inhibitors (SNRIs): Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

SNRIs

Drug	Usual Total Starting Dose Per Day (mg)	Usual Total Dose Per Day (mg)	Extreme Daily Dose Range (mg)
Desvenlafaxine	25-50	50-100	50-400
Duloxetine	30-60	60	30-120
Levomilnacipran	20	40-80	20-120
Milnacipran	12.5	100-200	50-300
Venlafaxine	37.5-75	75-375	75-375
Venlafaxine XR	37.5-75	75-225	75-375

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

Atypical Antidepressants

- Option for initial treatment
- Frequently used in patients who have had an inadequate response or intolerable side effects after first-line treatment with SSRIs
- Be especially mindful of the following when patients are receiving a medication from this class
  - The potential for drug-drug interactions (e.g., bupropion)
  - The dosage form of bupropion, which can impact dosing
- Medication specific adverse effects
- Black box warning: ↑ risk of suicidality for children, adolescents, and young adults

Hirsch M and Birnbaum RJ. Atypical antidepressants: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

Atypical Antidepressants

Drug	Usual Total Starting Dose Per Day (mg)	Usual Total Dose Per Day (mg)	Extreme Daily Dose Range (mg)
Bupropion	200	300 (max single dose 150 mg)	100-450
Bupropion SR 12 hour	150	300 (max single dose 200 mg)	150-400
Bupropion XL 24 hour	150	300	150-450
Bupropion hydrobromide 24 hour	174	348	174-522
Mirtazapine	15	15-45	7.5-60

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

Serotonin Modulators

- Nefazodone, trazodone, vilazodone, vortioxetine
- Medication specific adverse effects:
- Black box warning: ↑ risk of suicidality for children, adolescents, and young adults

Hirsch M and Birnbaum RJ. Serotonin modulators: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

Serotonin Modulators

Drug	Usual Total Starting Dose Per Day (mg)	Usual Total Dose Per Day (mg)	Extreme Daily Dose Range (mg)
Nefazodone	200	300-600	50-600
Trazodone	100	200-400	100-600
Vilazodone	10	40	10-40
Vortioxetine	10	20	5-20

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Therapy Discontinuation

- Go slow!
  - Even slower when the patient has been on therapy for an extended period
- In general, consider tapering any antidepressant taken for more than **one week**
  - Taper over several weeks unless there is a clinical reason not to
  - Fluoxetine and bupropion may be discontinued without a taper

Choosing and Switching Antidepressants. Pharmacist's Letter. Published June 2018. Accessed July 13, 2020.

Therapy Discontinuation

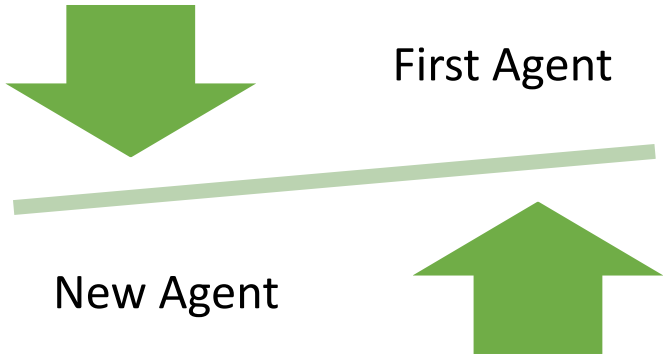
- Abrupt discontinuation may result in symptom recurrence and discontinuation syndromes
- Withdrawal symptoms can include:
  - Tingling/prickling sensations
  - Irritability
  - Insomnia
  - Dizziness
  - Vivid dream

Choosing and Switching Antidepressants. Pharmacist's Letter. Published June 2018. Accessed July 13, 2020.

Therapy Discontinuation and Switching

- Guidelines are available for specific therapies
- Remain in close contact with the patient throughout the taper
  - Adjustments may be necessary
- Dosage form considerations may impact the taper
- Consult a pharmacist!

Cross-Tapering



Choosing and Switching Antidepressants. Pharmacist's Letter. Published June 2018. Accessed July 13, 2020.

Therapy Selection – Clinical Pearls

- Comparable efficacy across and within classes
- TCAs and MAOIs typically avoided as initial therapy
- Escitalopram and sertraline may provide the best combination of efficacy and tolerability
- Bupropion useful when seeking to avoid sexual dysfunction or treat comorbid alcohol dependence
- Citalopram and escitalopram less likely to cause drug-drug interaction
- Diarrhea more common with sertraline
- Nausea and vomiting more common with venlafaxine than with SSRIs
- Weight gain more likely with mirtazapine than with fluoxetine, paroxetine, trazodone, or venlafaxine

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

Monitoring

- Following initiation of therapy, follow-up should occur (at a minimum):
  - At 1-2 weeks
  - Every 2-4 weeks for the first two months
  - At variable intervals based on clinical urgency and other patient-specific factors
- At each follow-up, assess for:
  - Response to therapy
  - Patient's ability to tolerate/maintain therapy
  - Adherence

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Treatment Resistant or Refractory Depression

- 45-65% experience an unsatisfactory response to initial treatment
- Risk factors:
  - General medical or psychiatric comorbidity
  - Severe depressive symptoms
  - Adverse life events
- 67% of patients experience remission after additional drug trials
  - ↓ probability of remission with each subsequent trial failure
  - ↑ withdrawal symptoms with each sequential trial
- Allow 6-12 trial
  - May limit to 4-6 for patients experiencing little improvement (reduction in baseline symptoms ≤25%)

Thase M and Connolly KR. Unipolar treatment resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.
Thase M and Connolly KR. Unipolar depression in adults: Choosing treatment for resistant depression. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.
Thase M and Connolly KR. Unipolar depression in adults: General principles of treating resistant depression. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.

Treatment Resistant or Refractory Depression

- Mild-to-moderate treatment resistant depression
  - Augmentation of initial therapy with a second medication and/or psychotherapy is preferred over switching agents
  - Switching agents is a reasonable alternative
  - Patients who cannot tolerate an adequate dose of the initial antidepressant should be switched to another agent

Thase M and Connolly KR. Unipolar treatment resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.
Thase M and Connolly KR. Unipolar depression in adults: Choosing treatment for resistant depression. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.
Thase M and Connolly KR. Unipolar depression in adults: General principles of treating resistant depression. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2019.

Care Coordination

- In care as usual, the primary care clinician will typically refer a patient with major depression to a psychiatrist or other mental health clinician under the following circumstances:
  - Suspicion of bipolar disorder (e.g., history of mania or hypomania)
  - Management of unipolar major depression with mixed features
  - Severe depression (e.g., PHQ score ≥20 or patient has a suicide plan)
  - Complicating features are present (e.g., psychotic features such as delusions or hallucinations)
  - Comorbid psychiatric disorders (e.g., personality or substance use disorders) are present.
  - Patient preference for psychotherapy, either as the primary treatment or in combination with antidepressant medication
- With the Collaborative Care Model, the BHCM can review specific cases at the Systematic Case Review weekly meeting with the psychiatrist
  - The psychiatrist can assist in determining diagnosis and or the need for a consultation

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Drug-Drug Interactions

General Principles

- Older age and polypharmacy are risk factors for clinically significant drug interactions
  - > 80% of patients taking seven or more drugs are at risk of a drug interaction
- Drug interactions may:
  - Apply across an entire medication class
  - Be drug specific
- Not all drug interactions are **clinically** significant
- Always consult a drug interaction tool or a pharmacist

Lynch T and Price A. The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects. *Am Fam Physician.* 2007 Aug 1;76(3):391-396.
Hirsch M and Birnbaum RJ. Selectice serotonin reuptake inhibitors: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

General Principles

- An accurate medication list is critical
  - Prescription, over the counter, and herbal
  - Not only the directions but also **how the patient is taking each product**
- Be especially mindful of the potential for interactions with drugs with:
  - Serious dose-dependent adverse effects
  - Narrow therapeutic indexes
- Educate patients on communicating any changes in their medication list
  - All members of the care team

Lynch T and Price A. The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects. *Am Fam Physician.* 2007 Aug 1;76(3):391-396.
Drug Interactions: A Practical Approach. Pharmacist's Letter. Published February 2017. Accessed January 28, 2021.

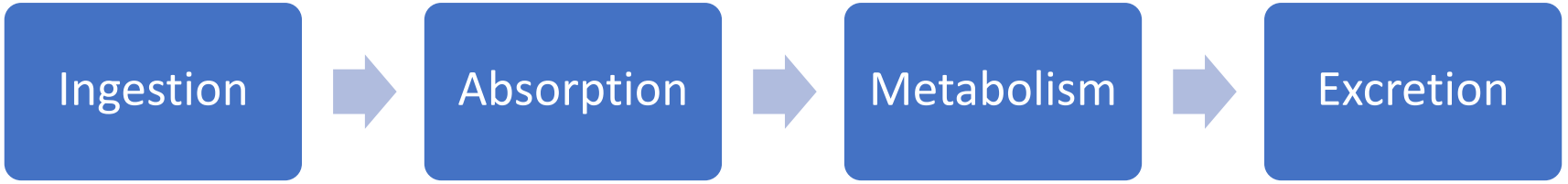
General Principles

- Once medication is absorbed into the body, metabolism begins to occur
- Most medications are metabolized, to some extent, in the liver via cytochrome P450 enzymes (CYP enzymes)
  - Over 50 CYP enzymes exist
  - 6 CYP enzymes metabolize 90% of drugs
  - The two most significant enzymes are CYP 3A4 and CYP 2D6
- CYP enzymes can be induced or inhibited by drugs
  - Induced = the enzyme works faster
  - Inhibited = the enzyme works slower
- Induction or inhibition of CYP enzymes can result in drug-drug interactions

Lynch T and Price A. The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects. *Am Fam Physician.* 2007 Aug 1;76(3):391-396.

Example

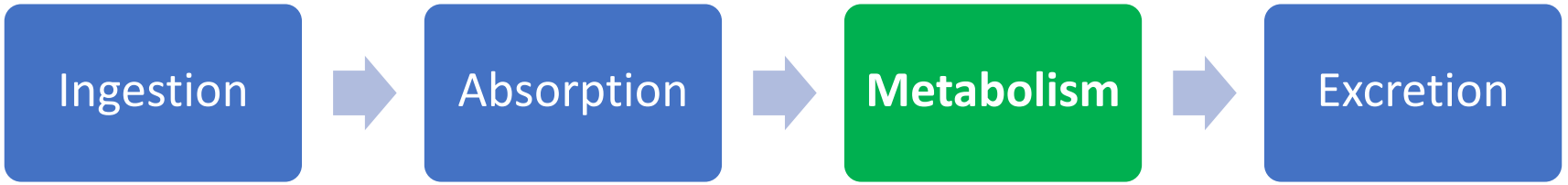
- Patient John Doe has been taking Drug A for 3 years
- Drug A is the only medication John Doe takes and is metabolized via CYP 3A4 in the liver
- In this scenario, Drug A takes the following path



Lynch T and Price A. The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects. *Am Fam Physician.* 2007 Aug 1;76(3):391-396.

Example

- John Doe is diagnosed with a new medical condition and prescribed Drug B
- Drug B is an inducer of CYP 3A4
- In this scenario, the metabolism of Drug A will be impacted by the introduction of Drug B



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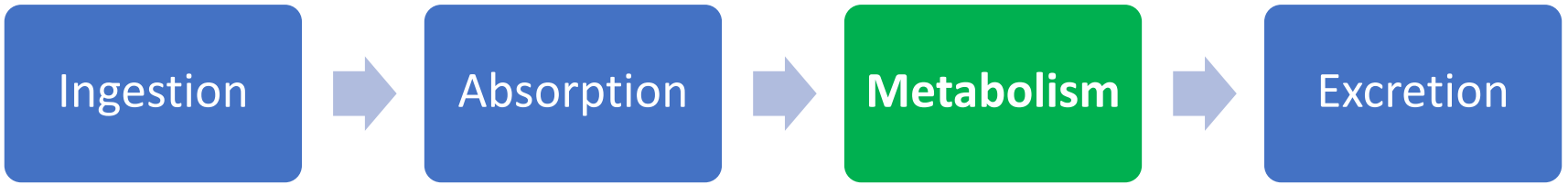
Example

- Drug B is “inducing”, or speeding up, the CYP 3A4 enzyme
  - This impacts the metabolism of Drug A
  - Drug A will be metabolized more quickly, which could result in a clinically significant impact on (1) the condition it was intended to treat and/or (2) the likelihood that John Doe will experience side effects
  - The intensity of the impact will be influenced by the level of induction as well as the therapeutic index of Drug A



Lynch T and Price A. The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects. *Am Fam Physician.* 2007 Aug 1;76(3):391-396.

SSRIs

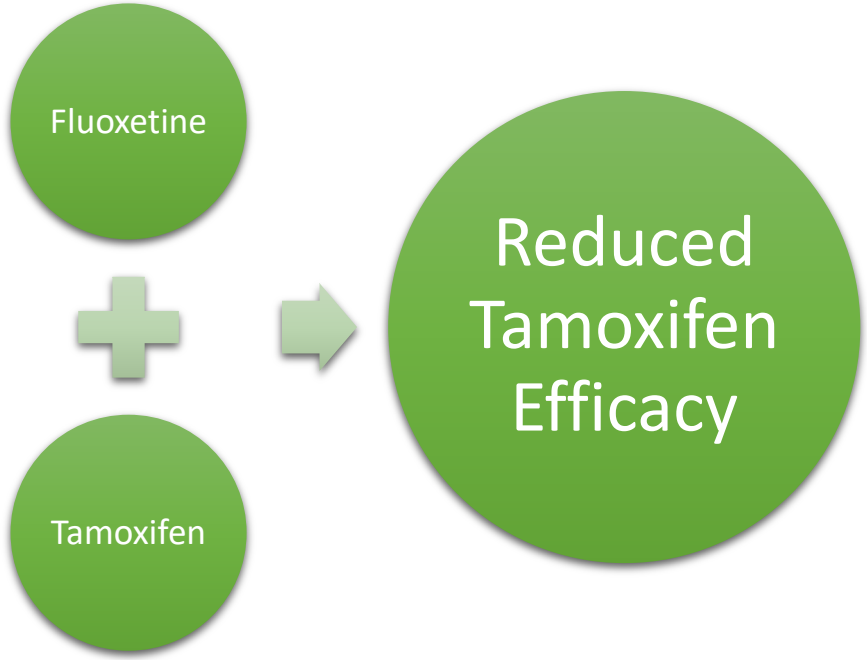
- All weakly inhibit one or more CYP 450 enzyme
  - Weak inhibition is unlikely to be clinically significant
- Citalopram and escitalopram are the SSRIs of choice when drug-drug interactions are of particular concern
  - Sertraline is a reasonable alternative

Drug	CYP Inhibition
Citalopram	• Weak inhibition only
Escitalopram	• Weak inhibition only
Fluoxetine	• Potent 2D6 inhibition • Moderate 2C19 inhibition
Fluvoxamine	• Potent 1A2 inhibition • Moderate 2C19 inhibition
Paroxetine	• Potent 2D6 inhibition
Sertraline	• Weak inhibition only

Hirsch M and Birnbaum RJ. Selectice serotonin reuptake inhibitors: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

SSRIs: Drug-Drug Interaction Example

- Tamoxifen
  - Used for the treatment or prevention of recurrent breast cancer
  - Prodrug that must be metabolized by CYP 2D6 to its active metabolite (no metabolism = no activity)
- Fluoxetine
  - Commonly prescribed SSRI
  - Potent inhibitor of CYP 2D6



Hirsch M and Birnbaum RJ. Selectice serotonin reuptake inhibitors: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

SNRIs

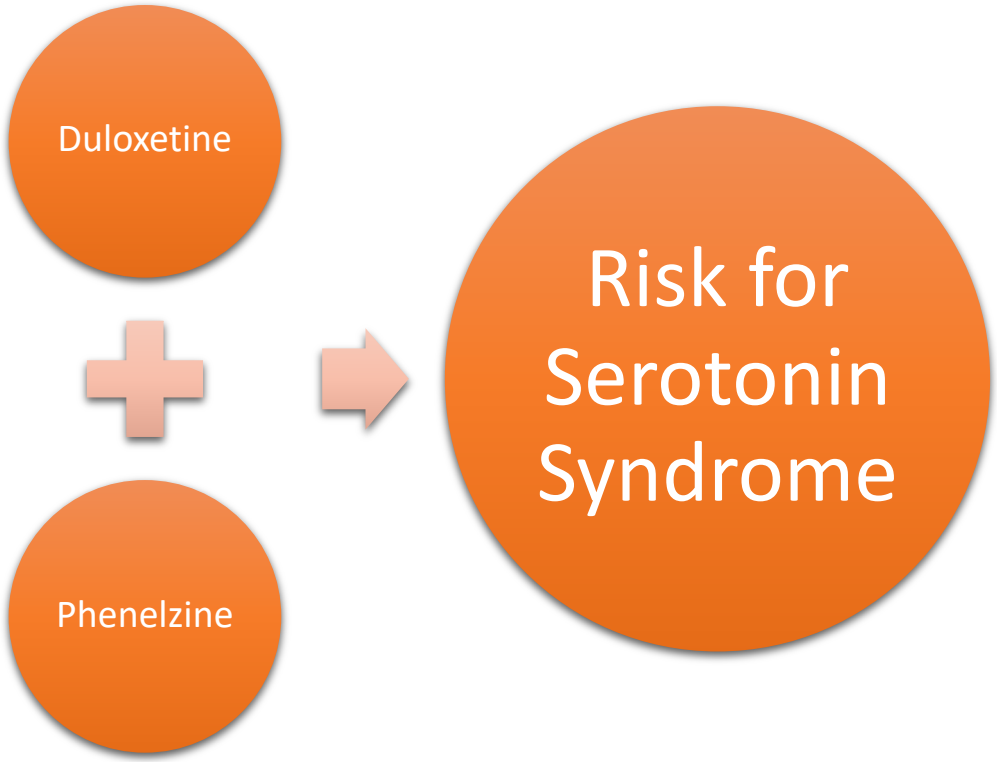
- Duloxetine should be avoided in situations where drug interactions are of particular concern
- Contraindicated in patients who have received MAOIs in the previous two weeks

Drug	CYP Inhibition
Desvenlafaxine	No clinically meaningful effects
Duloxetine	Moderately potent inhibitor of 2D6
Levomilnacipran	No clinically meaningful effects
Milnacipran	No clinically meaningful effects
Venlafaxine	No clinically meaningful effects

Nelson C. Serotonin-norepinephrine reuptake inhibitors (SNRIs): Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

SNRIs: Drug-Drug Interaction Example

- Duloxetine
  - SNRI
- Phenelzine
  - MAOI



Hirsch M and Birnbaum RJ. Selectice serotonin reuptake inhibitors: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

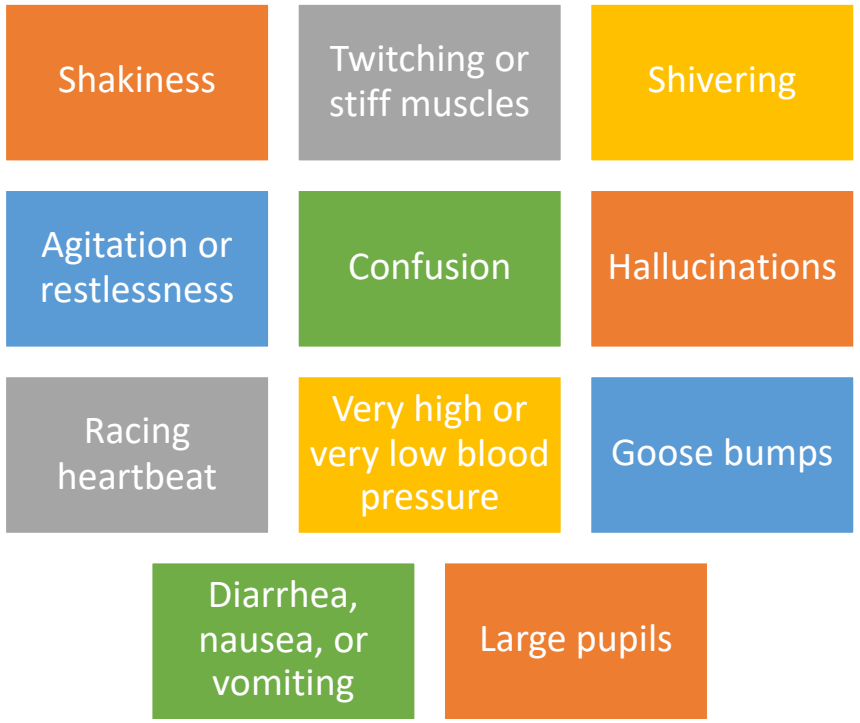
Serotonin Syndrome

- Can occur as a result of therapeutic medication use, inadvertent interactions between drugs, and intentional self-poisoning
- Risk with medications that increase serotonin
  - Prescription medications for depression, pain, etc.
  - Over the counter medications (e.g., dextromethorphan)
  - Herbal medications containing St. John's wort

Boyer EW. Serotonin syndrome (serotonin toxicity). In: UpToDate, Grayzel J (Ed), UpToDate, Waltham, MA, 2020.
What You Should Know About Serotonin Syndrome. Pharmacist's Letter. Published September 2016. Accessed July 13, 2020.

Serotonin Syndrome

- A potentially life-threatening condition associated with increased serotonergic activity in the central nervous system (CNS)
- Majority of cases present within 24 hours, and most within six hours, of a change or initiation of a drug
- Diagnosis is clinical – there is no laboratory test to confirm the diagnosis and serotonin concentrations do not correlate with clinical findings
- Patients should be counseled to watch for symptoms listed to the right



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What You Should Know About Serotonin Syndrome. Pharmacist's Letter. Published September 2016. Accessed July 13, 2020.

Atypical Antidepressants and Serotonin Modulators

Drug	Drug Class	Notes on CYP Metabolism
Bupropion	Atypical Antidepressant	2D6 inhibitor
Mirtazapine	Atypical Antidepressant	No clinically meaningful effects
Nefazodone	Serotonin Modulator	• Seems to undergo extensive metabolism by 3A4 (more data needed) • Strong 3A4 inhibitor
Trazodone	Serotonin Modulator	Extensively metabolized by 3A4
Vilazodone	Serotonin Modulator	Extensively metabolized by 3A4
Vortioxetine	Serotonin Modulator	Extensively metabolized by 2D6

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.
Hirsch M and Birnbaum RJ. Atypical antidepressants: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.
Hirsch M and Birnbaum RJ. Serotonin modulators: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

CYP 3A4 Modulation

- The list of medications that impact metabolism via CYP 3A4 is extensive and includes many common therapies
- For example:
  - Fluconazole – moderate inhibitor
  - Cimetidine – moderate inhibitor
  - St. John's Wort - moderate inducer
  - Phenytoin – strong inducer
- Caution is always warranted whenever a new medication is prescribed or discontinued
- Consult a drug interaction tool or pharmacist!

Hirsch M and Birnbaum RJ. Serotonin modulators: Pharmacology, administration, and side effects. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.

Managing Side Effects

General Principles

- Class effects and drug-specific adverse effects are possible
- Starting with a low dose can help
- Individual patients respond differently
  - Genes may play a role
- Most side effects will subside or disappear quickly (1-2 weeks)
- Involve the patient in treatment decisions
- Counsel on the risk for serotonin syndrome

Simon G. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Solomon D (Ed), UpToDate, Waltham, MA, 2020.
Improving Care in Patients with Depression. Pharmacist's Letter. Published June 2018. Accessed January 27, 2021.

Common Side Effects

- Gastrointestinal Issues
- Weight Gain
- Fatigue
- Insomnia
- Dry Mouth
- Dizziness
- Agitation/Anxiety
- Sexual Side Effects

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Antidepressants: Get tips to cope with side effects. Mayo Clinic. Available from: https://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20049305. Last Updated September 12, 2019. Last Accessed January 28, 2021.

Gastrointestinal Issues

Side Effect	Offending Agents or Classes	Management Strategies
Nausea	• More common with venlafaxine (33%) than SSRI class (22%)	• Take with food • Eat frequent small meals • Use sugar-free hard candy • Drink fluids, preferably water or flat ginger ale • Use an antacid or a product containing bismuth subsalicylate • Consider a dose change or switch to a slow-release formulation
Diarrhea	• More common with sertraline (16%) • Less common with bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine (8%)	• Stay hydrated, preferably with water • Consider a diet dense with boiled starches and cereal if the diarrhea is watery • Crackers, bananas, soup, and boiled vegetables may also help • Avoid high-fat foods and dairy products
Constipation	• TCAs	• Stay hydrated, preferably with water • Eat foods high in fiber (or take a fiber supplement) • Engage in regular exercise • Consider a stool softener if needed

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LaRocque R and Harris JB. Approach to the adult with acute diarrhea in resource-rich settings. In: UpToDate, Bloom A (Ed), UpToDate, Waltham, MA, 2020.

Weight Gain

- May be related to fluid retention, lack of physical activity, or increased appetite due to depression symptom relief
- More common with some medications than others
  - Greater likelihood with mirtazapine (1.75-6.6 lbs after 6-8 weeks of treatment)
  - Less likely with fluoxetine, paroxetine, trazodone, or venlafaxine
  - Less likely with SNRIs than SSRIs, TCAs, or MAOIs
- Management strategies
  - Keep a food diary and engage in regular physical activity
  - Seek advice from a registered dietician
  - Eat a diet dense in nutritious fruits and vegetables and limit sweets and sugary drinks
  - Consider switching to an alternative therapy if weight gain is of particular concern

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Antidepressants: Get tips to cope with side effects. Mayo Clinic. Available from: https://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20049305. Last Updated September 12, 2019. Last Accessed January 28, 2021.

Fatigue

- Common during initial weeks of treatment
- Management strategies
  - Take at bedtime
  - Regular physical activity
  - Nap briefly as needed
  - Avoid driving or operating heavy machinery
  - Consider a dose adjustment

More Likely (42%)	Less likely (25%)
• Trazodone	• Bupropion • Fluoxetine • Mirtazapine • Paroxetine • Venlafaxine

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Insomnia

- More likely to occur with fluoxetine, sertraline, and immediate release bupropion
- Management strategies
  - Take in the morning
  - Avoid caffeine, especially later in the day
  - Regular exercise, preferably early in the day
  - Consider additional therapy for insomnia or switching to an alternative antidepressant

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Improving Care in Patients with Depression. Pharmacist's Letter. Published June 2018. Accessed January 27, 2021.
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Dry Mouth

- Most likely to occur with TCAs
- Uncommon with second-generation agents
- Management strategies
  - Take in the morning
  - Sip or swish water frequently
  - Use sugar-free gum or candies
  - Avoid caffeine, alcohol, and tobacco
  - Breath through the nose
  - Maintain consistent oral hygiene
  - Consider additional therapy for dry mouth or switching to an alternative antidepressant

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Dizziness

- More common with TCAs and MAOIs due to the risk of low blood pressure
- Management strategies:
  - Rise slowly
  - Use assistive devices, handrails, etc.
  - Avoid driving or operating heavy machinery
  - Avoid caffeine, tobacco, and alcohol
  - Maintain hydration, preferably with water
  - Take at bedtime

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Agitation/Anxiety

- Can result from the stimulating effects of certain antidepressant products
- With Collaborative Care, the care manager will regularly monitor the patient and counsel patients to report symptoms to the BHCM (who can then review the information with the psychiatrist)
- Management strategies:
  - Regular exercise
  - Practice deep-breathing exercises and/or yoga
  - Consider an alternative therapy

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Sexual Side Effects

- More likely to occur with SSRIs
- Side effects may include:
  - Reduced sex drive
  - Difficulty reaching orgasm
  - Erectile dysfunction
- Management strategies:
  - Select a medication that requires once-daily dosing and engage in sexual activity prior to that dose
  - Adjust sexual routines
  - Consider switching antidepressant therapy or the addition of a medication for erectile dysfunction
  - Avoid over the counter herbal supplements advertised to increase sexual desire and function

More Likely (16%)	Less likely (6%)
• Escitalopram • Fluoxetine • Paroxetine • Sertraline	• Bupropion

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Summary

- Depression occurs along a continuum of severity with heterogeneous manifestations
- Less than one-third of patients achieve remission with the first antidepressant tried
- Drug interactions occur frequently, especially in the elderly and in patients taking seven or more medications
- More side effects of antidepressant therapies subside or disappear after the initial weeks of therapy

Thank you!

Any questions regarding the content of this presentation can be submitted to sue.vos@miccsi.org or claire.nolan@miccsi.org

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