

Pharmacotherapy Updates:

## Managing Major Depression and Generalized Anxiety

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### Disclosure

- Chris Paxos has no actual or potential conflict(s) of interest in relation to this presentation.

### Objectives

- Compare and contrast practice guidelines for the treatment of major depressive disorder
- Describe the pharmacologic properties of modern antidepressants
- Compare and contrast practice guidelines for the treatment of generalized anxiety disorder
- Describe the pharmacologic properties of benzodiazepines and other anxiolytic medications

## Psychopharmacology Trivia

How many individuals over 12 years of age are prescribed an antidepressant in the U.S.?

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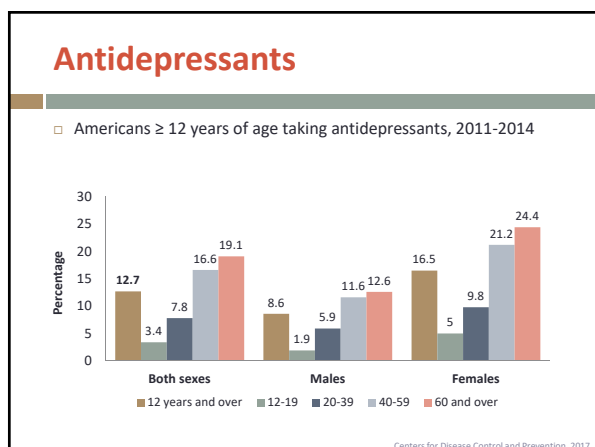
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## MDD Guidelines

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	Canadian Network for Mood and Anxiety Treatments, 2016	VA/DoD Clinical Practice Guidelines For the Management of MDD, 2016
1 <sup>st</sup> line	<b>Mild:</b> <ul style="list-style-type: none"> <li>Consider pharmacotherapy</li> <li>St. John's wort</li> </ul> <b>Moderate-to-severe:</b> <ul style="list-style-type: none"> <li>SSRI</li> <li>SNRI, not levomilnacipran</li> <li>Bupropion</li> <li>Mirtazapine</li> <li>Vortioxetine</li> </ul>	<b>Mild:</b> <ul style="list-style-type: none"> <li>St. John's wort</li> </ul> <b>Mild-to-moderate:</b> <ul style="list-style-type: none"> <li>SSRI, not fluvoxamine</li> <li>SNRI</li> <li>Bupropion</li> <li>Mirtazapine</li> </ul> <b>Severe or recurrent:</b> <ul style="list-style-type: none"> <li>Pharmacotherapy + psychotherapy</li> </ul>
2 <sup>nd</sup> line	<b>Non-response:</b> <ul style="list-style-type: none"> <li>Switch: SSRI, mirtazapine, venlafaxine</li> <li>Levomilnacipran, trazodone, vilazodone</li> <li>TCA, MAOI</li> <li>Omega-3 fatty acids</li> </ul> <b>Partial response:</b> <ul style="list-style-type: none"> <li>Adjunct second-generation antipsychotic</li> <li>Adjunct St. John's wort, SAME</li> <li>Adjunct omega-3 fatty acids</li> </ul>	<b>Switch:</b> <ul style="list-style-type: none"> <li>Alternate first-line agent</li> </ul> <b>Augment:</b> <ul style="list-style-type: none"> <li>Bupropion, buspirone, lithium, T3, second-generation antipsychotic</li> </ul> <b>Subsequent:</b> <ul style="list-style-type: none"> <li>Switch to agent with alternate mechanism</li> </ul>

VA/DoD Practice Guidelines, 2016;  
Can J Psychiatry. 2016;61(9):504-603.

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## Modern Antidepressants

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### Assessment Question #1

William is diagnosed with major depressive disorder (MDD) and started on escitalopram 10 mg once daily. The dosage is increased to 20 mg once daily after one week. Following 6 weeks of treatment, William reports minimal improvement in mood as well as new-onset sexual dysfunction, including erectile dysfunction. Which medication can the patient be switched to in order to resolve treatment emergent sexual dysfunction induced by prior SSRI treatment?

A. Esketamine  
 B. Levomilnacipran  
 C. Trazodone  
 D. Vortioxetine

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## Selective Serotonin Reuptake Inhibitors

- ❑ Adverse effects
  - ❑ GI distress, activating effects, sexual dysfunction, sleep disturbances
- ❑ Fluoxetine (Prozac®)
  - ❑ Activating (take in AM)
  - ❑ Long half-life (4-6 days)
- ❑ Paroxetine (Paxil®)
  - ❑ Weight gain, mildly antiACh
  - ❑ Discontinuation syndrome
- ❑ Sertraline (Zoloft®)
  - ❑ GI distress (diarrhea)
- ❑ Fluvoxamine (Luvox®)
  - ❑ Not approved for MDD
  - ❑ Sedating (take at bedtime)
- ❑ Citalopram (Celexa®)
  - ❑ QT interval prolongation
  - ❑ Max 20mg (liver dx, > 60)
- ❑ Escitalopram (Lexapro®)
  - ❑ Enantiomer of citalopram

Psychother Psychosom. 2016;85(5):270-88.  
Essential Psychopharmacology, 2013.

## Selective Serotonin Reuptake Inhibitors

	MDD	GAD	OCD	SAD	PTSD	PD	BN	PMDD	VSM
Fluoxetine	X		X			X	X	X	
Paroxetine	X	X	X	X	X	X		X	X
Sertraline	X		X	X	X	X		X	
Citalopram	X								
Escitalopram	X	X							
Fluvoxamine			X						

MDD, major depressive disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; SAD, social anxiety disorder; PTSD, posttraumatic stress disorder; PD, panic disorder; BN, bulimia nervosa; PMDD, premenstrual dysphoric disorder; VSM, vasomotor symptoms of menopause

Levi-Comp Online, 2019

## Serotonin/Norepinephrine Reuptake Inhibitors

- ❑ Adverse effects
  - ❑ Similar adverse effects to SSRIs; hyperhidrosis more common
  - ❑ SNRIs may increase blood pressure in a dose-dependent manner
- ❑ Venlafaxine (Effexor®)
  - ❑ Dual reuptake at high doses
  - ❑ Discontinuation syndrome
- ❑ Duloxetine (Cymbalta®)
  - ❑ Constipation, dry mouth
  - ❑ Several pain indications
  - ❑ Hepatotoxicity
- ❑ Desvenlafaxine (Pristiq®)
  - ❑ Venlafaxine metabolite
  - ❑ Tablet may appear in stool
- ❑ Levomilnacipran (Fetzima®)
  - ❑ Enantiomer of milnacipran
  - ❑ Most noradrenergic agent
  - ❑ Urinary hesitancy (4-6%)

Psychother Psychosom. 2016;85(5):270-88.  
Essential Psychopharmacology, 2013.

## Miscellaneous Antidepressants

- Bupropion (Wellbutrin®)
  - Activating (take in AM)
  - Low sexual dysfx, weight gain
  - Contraindications\*
- Trazodone (Desyrel®)
  - Sedating (take at bedtime)
  - Priapism (rare)
- Nefazodone (Serzone®)
  - Strong CYP3A4 inhibitor
  - Hepatotoxicity
- Mirtazapine (Remeron®)
  - Sedating (take at bedtime)
  - Appetite stimulation, weight gain
  - Agranulocytosis (rare)
- Vortioxetine (Trintellix®)
  - Nausea (21-32%)
  - Sexual dysfunction benefits
- Vilazodone (Viibryd®)
  - Nausea (23%), diarrhea (27%)
  - Take with food

Psychother Psychosom. 2016;85(S): 270-88.  
Essential Psychopharmacology, 2013.

## SNRIs & Miscellaneous Antidepressants

	MDD	GAD	SAD	PD	FM	DPN	CMP	SeAD	SC	WL
Venlafaxine	X	X	X	X						
Desvenlafaxine	X									
Duloxetine	X	X			X	X	X			
Levomilnacipran	X									
Bupropion	X							X	X	X
Mirtazapine	X									
Trazodone	X									
Nefazodone	X									
Vilazodone	X									
Vortioxetine	X									

MDD, major depressive disorder; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PD, panic disorder; FM, fibromyalgia; DPN, diabetic peripheral neuropathy; CMP, chronic musculoskeletal pain; SeAD, seasonal affective disorder; SC, smoking cessation; WL, weight loss (with naltrexone)

Levi-Comp Online, 2019

## Second Generation Antipsychotics

	Aripiprazole	Brexipiprazole	Quetiapine
Brand	Abilify®	Rexulti®	Seroquel XR®
Indication	Adjunctive therapy to antidepressants for major depressive disorder		
FDA Approval	2007	2015	2009
Initial Dose	2-5 mg	0.5-1 mg	50 mg
Target Dose	5-10 mg	2 mg	150-300 mg
Max Dose	15 mg	3 mg	300 mg
Side Effects	akathisia (25%), fatigue, insomnia	akathisia (9%), headache, weight gain	somnolence (43%), dry mouth, fatigue
Wt Gain (≥ 7%)	5.2%	2-5%	3-7%

DailyMed.nlm.nih.gov

## Brexanolone (Zulresso®)

### U.S. Approval

- March 2019

### Pharmacology

- Neuroactive steroid
- Allopregnanolone
- GABA<sub>A</sub> modulation

### DEA Schedule

- C-IV medication

### Dosage Form

- Single-dose vial
- 100 mg / 20 mL

DailyMed.nlm.nih.gov

## Brexanolone (Zulresso®)

### Indication

- Postpartum depression

### Warnings

- Excessive sedation
- Sudden loss of consciousness
- Suicidal thoughts, behaviors
- REMS program

### Monitoring

- Sedation
- Pulse oximetry
- Patient-child interactions

### Lactation

- Unknown effects; RID = 1-2%

### Dosing

- 60-hour (2.5 day) infusion

Hours	Dose
0-4	30 mcg/kg/hr
4-24	60 mcg/kg/hr
24-52	90 mcg/kg/hr
52-56	60 mcg/kg/hr
56-60	30 mcg/kg/hr

DailyMed.nlm.nih.gov

## Esketamine (Spravato®)

### Nasal Spray Device



Each device delivers two sprays containing a total of 28 mg of esketamine.

### Indicator

One device contains 2 sprays. (1 spray for each nostril)

2 green dots (0 mg delivered)

Device full

1 green dot

One spray delivered

No green dots

Two sprays (28 mg) delivered

Device empty

### U.S. Approval

- March 2019

### Pharmacology

- S-enantiomer
- NMDA antagonist

### DEA Schedule

- C-III medication

### Dosage Form

- Nasal spray
- 28 mg per device

DailyMed.nlm.nih.gov

## Esketamine (Spravato®)

**About 45°**

**Instruct the patient to:**

- Recline head at about 45 degrees during administration to keep medication inside the nose.

**Instruct the patient to:**

- Close opposite nostril.
- Breathe in through nose while pushing plunger all the way up until it stops.

**Instruct the patient to:**

- Sniff gently after spraying to keep medication inside nose.

**Instruct the patient to:**

- Switch hands to insert tip into the second nostril.

**5 MIN REST**

**Instruct the patient to:**

- Rest in a comfortable position (preferably, semi-reclined) for 5 minutes after each device.
- If liquid drips out, dab nose with a tissue.

56mg, 84mg

**Administration**

- Confirm number of devices
- Blow nose before first device only
- Do not prime devices
- Administer per instructions
- Take device(s) from patient
- Dispose of device(s) properly

DailyMed.nlm.nih.gov

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## Esketamine (Spravato®)

**Indication**

- Treatment-resistant depression
- With oral antidepressant

**Contraindications**

- Intracerebral hemorrhage
- Aneurysmal vascular disease

**Monitoring**

- Blood pressure before and after
- ≥ 2 hours after administration

**Boxed warnings**

- Sedation and dissociation
- Potential for abuse and misuse
- Suicidal thoughts, behaviors
- Ulcerative or interstitial cystitis
- REMS program

**Dosing**

Weeks	Dose	Frequency
1 – 4	56 mg, 84 mg	2x per week
5 – 8	56 mg, 84 mg	1x per week
≥ 9	56 mg, 84 mg	1x per week 1x Q 2 weeks

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# GAD Guidelines

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	Anxiety Disorders Assoc. of Canada, 2014	British Assoc. for Psychopharmacology, 2014	Psychopharm. Project at Harvard South Shore, 2016
1 <sup>st</sup> line	SSRI: escitalopram, paroxetine, sertraline SNRI: duloxetine, venlafaxine XR Pregabalin	SSRI: escitalopram, paroxetine, sertraline SNRI: venlafaxine BZD: alprazolam, diazepam TCA: imipramine Buspirone Hydroxyzine	SSRI: escitalopram, paroxetine, sertraline Alternatives: duloxetine, buspirone, hydroxyzine, pregabalin, bupropion Augmentation: BZD, hydroxyzine, pregabalin
2 <sup>nd</sup> line	BZD (short-term use) Bupropion XL Buspirone Hydroxyzine Imipramine Quetiapine XR Vortioxetine	Switch to another evidence-based treatment after non-response to initial treatment	Switch to another first-line option after non-response to initial treatment
3 <sup>rd</sup> line	SSRI: citalopram, fluoxetine SGA augmentation Divalproex Mirtazapine Trazodone	Consider use of a BZD after non-response to SSRI and SNRI treatment	TCA: imipramine SGA: quetiapine, risperidone Valproate (treatment-resistant male patients only)

Harv Rev Psychiatry. 2016;24(4):243-56.  
BMC Psychiatry. 2014;14 Suppl 1:S1.  
J Psychopharmacol. 2014;25(8):409-39.

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## Anxiolytic Medications

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## Psychopharmacology History

*Apr 27, 1958      Rx 5-0690/1      See 144.*

*Run strong tablet at 8:30*  
*Slightly softer than the others 10-11.*  
*Appetite not improved. Clearcut.*

*1:35 Slightly uneasy.*  
*2:50 Sleeping.*  
*4:00 Pretty sleeping.*  
*5:30 Slight dizziness.*  
*6- No effect*  
*8:30 ..*

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## Assessment Question #2

A patient is most likely to experience breakthrough anxiety between doses with which of the following benzodiazepines?

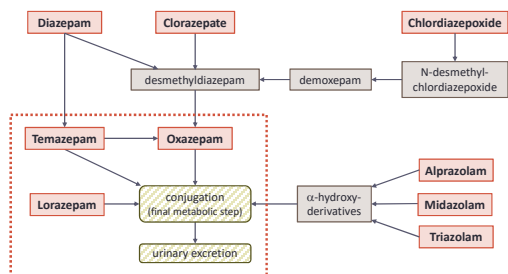
- A. Alprazolam
- B. Chlordiazepoxide
- C. Clorazepate
- D. Diazepam

## Benzodiazepines

Generic	Brand	Half-life [Parent drug] (hours)	Half-life [Metabolites] (hours)	Approximate Equivalency (mg)
Alprazolam	Xanax®	12-15	—	0.5
Chlordiazepoxide	Librium®	24-48	> 100	10
Clonazepam	Klonopin®	30-40	—	0.25
Clorazepate	Tranxene®	—	> 100	7.5
Diazepam	Vallium®	20-80	> 100	5
Lorazepam	Ativan®	10-20	—	1
Oxazepam	Serax®	5-20	—	15

Lexi-Comp Online, 2019.  
Pharmacotherapy, Principles and Practice, 2019.

## Benzodiazepines



Applied Therapeutics: The Clinical Use of Drugs, 2009.

## Benzodiazepines

- Withdrawal patterns
  - Affected by dose, half-life, duration of use, and discontinuation speed
  - Short BZD half-life – arises sooner, shorter in total duration, more intense
  - With 4 weeks of routine use, dependence develops in 50% of patients
- Withdrawal symptoms

Anxiety	Insomnia	Restlessness jitteriness	Muscle tension	Irritability
Blurred vision	Diaphoresis	Tinnitus	Psychosis	SEIZURES

Pharmacist toolkit: benzodiazepine taper, 2018.  
N Engl J Med. 2017;376(12):1147-57.  
Stahl's Essential Psychopharmacology, 2013.

## Benzodiazepines

- Examples of tapering strategies
  - Decrease 25% in the first and second week, then 10% each week
  - Decrease 10-25% every 2-4 weeks if on high doses or long use history
  - Decrease no higher than 10% each week in patients with panic disorder
- Tapering pearls
  - Data on switching to a long-acting BZD for tapering are lacking
  - Avoid PRN or "as needed" doses during the tapering process
  - Avoid increasing the dose once a taper has been initiated

Pharmacist toolkit: benzodiazepine taper, 2018.  
N Engl J Med. 2017;376(12):1147-57.  
American Psychiatric Association, 2009.

## Assessment Question #3

A patient with generalized anxiety disorder has failed several trials of antidepressant medications secondary to either inefficacy or adverse effects. The prescriber initiates **pregabalin** after reviewing the Anxiety Disorders Association of Canada practice guidelines. What should the prescriber monitor throughout pregabalin therapy?

## Buspirone (BuSpar®)

- Mechanism of action
  - Partial 5HT<sub>1A</sub> receptor agonist
- Indication
  - Generalized anxiety disorder
  - Considered a 2nd line agent
- Distinguishing characteristics
  - Not a controlled substance
  - Serotonergic medication
  - Delayed onset of action
  - Requires routine dosing
- Adverse effects
  - Dizziness, HA, nervousness
- Interactions
  - Pro-serotonergic agents
  - CYP3A4 inhibitors or inducers
  - Grapefruit juice
- Dosing
  - Dosed 2-3 times per day
  - Initial: 15 mg/day
  - Maximum: 60 mg/day

DailyMed.nlm.nih.gov

## Pregabalin (Lyrica®)

- Mechanism of action
  - Alpha-2 delta ligand
  - Schedule V controlled substance
- Indications
  - Numerous pain indications
  - \*Off-label for anxiety disorders
- Treatment guidelines
  - Endorsed by several guidelines
  - Treatment option for GAD
- Adverse effects
  - Dizziness, sedation, edema
- Dosing
  - Dosed 2-3 times per day
  - Initial: 150 mg/day
  - Maximum: 600 mg/day
- Monitoring
  - Renal function
- Gabapentin (Neurontin®)
  - \*Off-label for anxiety
  - Alternative to pregabalin
  - Data less robust

DailyMed.nlm.nih.gov  
Harv Rev Psychiatry. 2016;24(4):243-56.  
BMC Psychiatry. 2014;14 Suppl 1:51

## Additional Anxiolytics

<b>Hydroxyzine</b> (Vistaril®)	– FDA approved for anxiety; considered a 2nd line agent – Antihistamine; sedation and anticholinergic effects – Dosage: 25-100 mg four times daily
<b>Beta-blockers</b>	– Performance-related social anxiety disorder; *off-label use – Propranolol often used; most lipophilic beta-blocker – Given 1-2 hours before performance
<b>Antipsychotics</b>	– Treatment refractory anxiety disorders; *off-label use – Used as augmenting agents; monotherapy data with quetiapine – FDA concerns regarding metabolic effects, TD, sudden death

Pharmacotherapy: Principles and Practice, 2019  
CNS Drugs. 2014;28(6):519-33.

## Summary

- SSRIs, SNRIs, bupropion, and mirtazapine are first-line options for major depressive disorder. Esketamine and brexanolone are the first FDA approved medications for treatment-resistant and postpartum depression, respectively.
- Modern antidepressants share similarities; however, they differ with regard to adverse effect profiles and other pharmacologic properties
- SSRIs and SNRIs are broadly regarded as first-line options for the treatment of generalized anxiety disorder
- Benzodiazepines differ by pharmacokinetic properties and require gradual tapering after periods of extended use

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OHIO ASSOCIATION OF ADVANCED PRACTICE NURSES

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Pharmacotherapy Updates:

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