Analyzing Psychiatric Pharmacotherapy from Initiation and Beyond

GMCCP Spring Educational Event

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Selecting the Best Therapeutic Option – Antidepressants and Antipsychotics

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Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias this presentation

- The views expressed in this presentation reflect those of the author and not necessarily those of Concordia University Wisconsin

Learning Objectives

1. Recommend an antidepressant or antipsychotic for a patient with a mental health disorder based on its adverse effect profile, half-life, and/or drug interaction profile.

2. Design a pharmacologic treatment plan for a patient with a mental health disorder based on patient specific characteristics (age, comorbid conditions, concomitant medications, etc.)

Antidepressants

First-line Antidepressants

- Selective serotonin reuptake inhibitors (SSRIs)
  - Citalopram (Celexa®)
  - Escitalopram (Lexapro®)
  - Fluoxetine (Prozac®)
  - Fluvoxamine (Luvox®)
  - Paroxetine (Paxil®, Paxil CR®)
  - Sertraline (Zoloft®)
- Serotonin and norepinephrine reuptake inhibitors (SNRIs)
  - Desvenlafaxine (Pristiq®)
  - Duloxetine (Cymbalta®)
  - Levomilnacipran (Pristiq®)
  - Venlafaxine (Effexor®, Effexor XR®)
- Bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)
- Mirtazapine (Remeron®)

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Gelenberg A, Freeman M, Markowitz J, et al. APA practice guideline for the treatment of patients with major depressive disorder (3rd edition). American Psychiatric Association. 2010.

Patient Case

- A 56-year-old patient who recently suffered a myocardial infarction (MI) is now struggling with depression and is interested in starting an antidepressant. His past medical history is significant for treatment resistant hypertension, hyperlipidemia, coronary artery disease (h/o MI with drug eluting stent placement 2 months ago), and epilepsy. His current medications include aspirin, atorvastatin, clopidogrel, hydrochlorothiazide, lisinopril, metoprolol tartrate, and carbamazepine.

  Height: 6 feet

  Weight: 180 pounds

  Blood pressure: 144/88 mmHg

  Pulse: 60 beats per minute

  Electrocardiogram: QTc = 420 msec

  Which of the following antidepressants is the BEST initial option for this patient?

  a. Bupropion
  b. Escitalopram
  c. Fluoxetine
  d. Venlafaxine

Antidepressant Inhibition of CYP Enzymes

CYP Enzyme	Medication	Degree of Inhibition
2C9	Fluoxetine Sertraline	Moderate Moderate
2C19	Fluoxetine Sertraline	Moderate Moderate
2D6	Bupropion Fluoxetine Paroxetine Duloxetine Sertraline Citalopram Escitalopram Venlafaxine	Strong Strong Strong Moderate Weak to moderate Weak to moderate Weak to moderate Weak
3A4	Fluoxetine Sertraline	Moderate Weak to moderate

Gelenberg A, Freeman M, Markowitz J, et al. APA practice guideline for the treatment of patients with major depressive disorder (3rd edition). American Psychiatric Association. 2010.

Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* 1997; 32 (Suppl 1): 1-21.

Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 2002; 3: 13-37.

Devane CL. Differential pharmacology of newer antidepressants. *J Clin Psychiatry* 1998; 59 (Suppl 20): 85-93.

Adverse Effect	First-line Antidepressant(s) Most Associated with Adverse Effect
Activation/insomnia	• Bupropion • Fluoxetine
Anticholinergic effects	• Paroxetine
Decreased seizure threshold	• Bupropion
Diarrhea	• Sertraline
Elevated blood pressure	• SNRIs (venlafaxine)
Hepatotoxicity	• Duloxetine
QTc prolongation	• Citalopram • Escitalopram
Sedation	• Mirtazapine • Paroxetine
Weight gain	• Mirtazapine • Paroxetine

Product package inserts
Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. Drugs in Context 2015; 4: 212290.
Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. J Clin Psychiatry 2001; 3: 22-27.

SNRIs – Elevated Blood Pressure (BP)

- Most common with venlafaxine
  - Dose related
    - Minor elevations with doses of 75 to 300 mg daily
      - Approximately 3 to 7% of patients
    - Clinically significant elevations with doses > 300 mg daily
      - Up to 13% of patients
      - Majority of diastolic BP increases between 7 and 15 mmHg

Product package insert
Thase ME. Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. J Clin Psychiatry 1998; 59(10): 502-508.
Feighner JP. Cardiovascular safety in depressed patients: focus on venlafaxine. J Clin Psychiatry 1995; 56(12): 574-579.
Mbaya P, Alam F, Ashim S, Bennett D. Cardiovascular effects of high dose venlafaxine XL in patients with major depressive disorder. Human Psychopharmacology 2007; 22(3): 129-133.

Citalopram and Escitalopram – QTc Prolongation

- Citalopram and escitalopram cause dose-dependent QTc prolongation
- Assess risk factors for QTc prolongation and concomitant medications to determine clinical significance

Citalopram Dose (mg)	Change in QTc (90% CI) (ms)
20	8.5 (6.2, 10.8)
40*	12.6 (10.9, 14.3)
60	18.5 (16, 21)

Escitalopram Dose (mg)	Change in QTc (90% CI) (ms)
10	4.5 (2.5, 6.4)
20*	6.6 (5.3, 7.9)
30	10.7 (8.7, 12.7)

*Estimate based on relationship between blood concentration and QT interval
CI = confidence interval

US Food and Drug Administration. FDA drug safety communication: abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm. Accessed April 17, 2018.
US Food and Drug Administration. FDA drug safety communication: revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm. Accessed April 17, 2018.

Patient Case

- A 28-year-old female plans to initiate an antidepressant for treatment of major depressive disorder. The only medication she was taking was an oral contraceptive but she stopped it a few months ago because she hopes to become pregnant soon. She is concerned about how an antidepressant may affect the pregnancy and her ability to potentially breastfeed. She expresses a desire for the safest possible treatment. She admits she struggles to remember to take her medications and missed her oral contraceptive one to two times per week. Which of the following antidepressants is the BEST option for this patient?

  a. Fluoxetine
  b. Paroxetine
  c. Sertraline
  d. Venlafaxine

Compelling Indication	First-line Antidepressant(s) of Choice
Anxiety disorders	• SSRIs, SNRIs
Bulimia nervosa	• Fluoxetine
Cardiovascular disease	• SSRIs (escitalopram, fluoxetine, sertraline)
Fibromyalgia	• Duloxetine
Insomnia	• Mirtazapine
Lactation	• Paroxetine • Sertraline
Neuropathic pain/neuropathy	• Duloxetine
Poor medication adherence	• Fluoxetine
Premenstrual dysphoric disorder	• Fluoxetine • Paroxetine • Sertraline
Sexual dysfunction	• Bupropion • Mirtazapine
Smoking cessation	• Bupropion

Product package inserts
Schultz E, Malone D. A practical approach to prescribing antidepressants. Cleve Clin J Med 2013; 80(10): 625-631
Gelenberg A, Freeman M, Markowitz J, et al. APA practice guideline for the treatment of patients with major depressive disorder (3rd edition). American Psychiatric Association. 2010.

Pharmacokinetic Considerations

Antidepressant	Half-life (h)	Clinically Important Metabolites
Citalopram	35	
Escitalopram	27 to 32	
Fluoxetine	4 to 6 days	Norfluoxetine
Paroxetine	15 to 21	
Sertraline	26	
Desvenlafaxine	11	
Duloxetine	12	
Levomilnacipran	12	
Venlafaxine	5	O-Desmethylvenlafaxine
Bupropion	14 to 21	Several
Mirtazapine	20 to 40	

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Pregnancy and Lactation Considerations

- SSRIs have the most published data on safety and efficacy
  - Paroxetine – pregnancy category D
- SSRI use during pregnancy may be associated with:
  - Low birth weight
  - Premature birth
  - Withdrawal symptoms
- Untreated depression is associated with the same risk of low birth weight and premature birth
- Excreted in the breast milk but generally safe
  - Sertraline and paroxetine - lowest rates of excretion
  - Fluoxetine - highest rate of excretion

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Yonkers et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry* 2009; 31: 403-413.
Berle JØ, Spigset O. Antidepressant Use During Breastfeeding. Curr Womens Health Rev. 2011;7(1):28-34.

Incidence of Sexual Dysfunction

Antidepressant	Decreased Libido	Impotence	Abnormal Ejaculation	Anorgasmia
Citalopram	2%	3%	6%	-
Escitalopram	3%	3%	9%	2%
Fluoxetine	1 to 11%	1 to 7%	2 to 7%	-
Paroxetine	6 to 15%	2 to 9%	13 to 28%	10%
Sertraline	4 to 7%	4%	3 to 8%	-
Desvenlafaxine	3 to 6%	3 to 11%	1 to 5%	1 to 8%
Duloxetine	3%	4%	2%	2%
Levomilnacipran	-	6 to 10%	5%	-
Venlafaxine	1 to 6%	2 to 6%	2 to 13%	2 to 3%
Bupropion	3%	3%	< 1%	-
Mirtazapine	1%	< 1%	< 1%	-

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Product package inserts

Antipsychotics

Patient Case

- A 38-year-old male was taking asenapine for the treatment of schizophrenia but he stopped it on his own two weeks ago because he didn't like the taste. He has a history of non-adherence with medications and also stopped ziprasidone and olanzapine in the past because he didn't think he needed them. His past medical history is significant for obesity, type II diabetes mellitus, hypertension, tobacco use disorder, and allergic rhinitis. Which of the following antipsychotics is the BEST option for this patient?

a. Aripiprazole
b. Lurasidone
c. Quetiapine
d. Risperidone

Second-Generation Antipsychotics (SGAs)

- Aripiprazole (Abilify®)
- Asenapine (Saphris®)
- Brexpiprazole (Rexulti®)
- Cariprazine (Vraylar®)
- Clozapine (Clozaril®)
- Iloperidone (Fanapt®)
- Lurasidone (Latuda®)
- Olanzapine (Zyprexa®)
- Paliperidone (Invega®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Ziprasidone (Geodon®)

Adverse Effect	SGA(s) Most Associated with Adverse Effect
Anticholinergic	• Clozapine • Olanzapine
Extrapyramidal symptoms	• Paliperidone • Risperidone
Hyperprolactinemia	• Paliperidone • Risperidone
Metabolic abnormalities (weight gain, hyperglycemia, hyperlipidemia)	• Clozapine • Olanzapine • Quetiapine • Risperidone
Orthostatic hypotension	• Clozapine • Iloperidone
QTc prolongation	• Ziprasidone
Sedation	• Clozapine • Olanzapine • Quetiapine

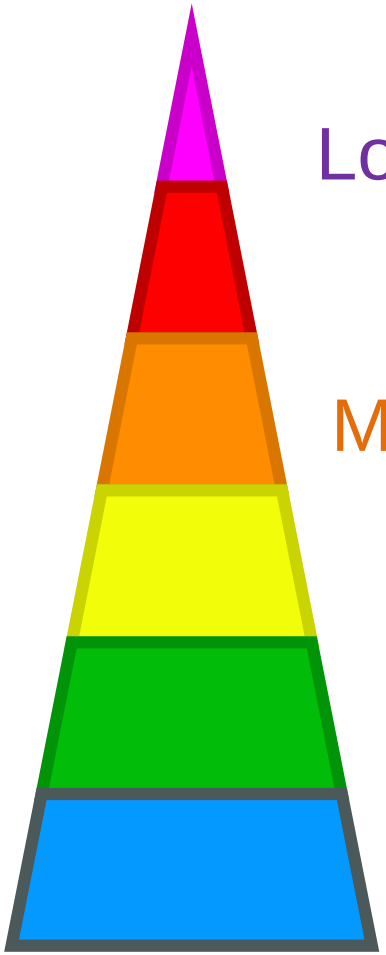
Product package inserts
Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. CNS Drugs 2007; 21(11): 911-936.
Lehman A, Lieberman J, Dixon L, et al. APA practice guideline for the treatment of patients with schizophrenia (2nd edition). American Psychiatric Association. 2004.

SGAs – Weight Gain

Risk of Weight Gain with Second Generation Antipsychotics		
Low	**Medium**	**High**
• Aripiprazole • Asenapine • Lurasidone • Ziprasidone	• Paliperidone • Risperidone • Quetiapine	• Clozapine • Olanzapine

Cooper SJ, Reynolds GP, et al. BAP guidelines on the management of weight gain, metabolic disturbances, and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J of Psychopharmacol* 2016; 30(8): 717-748.

SGAs – Relative Risk for Metabolic Side Effects



Low

Medium

High

- Cariprazine
- Brexpiprazole
- Lurasidone
- Asenapine
- Aripiprazole
- Ziprasidone
- Iloperidone
- Paliperidone
- Risperidone
- Quetiapine
- Olanzapine
- Clozapine

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Product package inserts

Antipsychotics - Risk of QTc Prolongation

Medication (n)	Dose (mg/day)	Mean Duration of Treatment (days)	Mean Change in Baseline QTc (msec)
Haloperidol (27)	15	18	7.1
Olanzapine (24)	20	20	1.7
Quetiapine (27)	750	17	5.7
Risperidone (25)	6 to 8	25	3.9
Thioridazine (30)	300	16	30.1
Ziprasidone (31)	160	15	15.9

No patient had a QTc interval ≥500 msec during the study.

Harrigan E, Miceli J, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharm* 2004; 24: 62-69.

SGAs – QTc Prolongation

Risk of QTc Prolongation with Second Generation Antipsychotics			
Minimal	**Low**	**Moderate**	**High**
• Aripiprazole	• Asenapine • Lurasidone • Olanzapine • Quetiapine	• Iloperidone • Paliperidone • Risperidone	• Ziprasidone

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Beach S, Celano C, Noseworthy P, et al. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics 2013; 54: 1-13.

Compelling Indication	SGA(s) of Choice
Diabetes/dyslipidemia/obesity	• Aripiprazole • Asenapine • Lurasidone • Ziprasidone
Hyperprolactinemia	• Aripiprazole
Insomnia	• Quetiapine • Olanzapine
Irritability/aggression with autism spectrum disorder	• Aripiprazole • Risperidone
Parkinson's Disease/movement disorders	• Clozapine • Quetiapine
Poor medication adherence	• Aripiprazole • Olanzapine • Paliperidone • Risperidone
Treatment resistant schizophrenia	• Clozapine

Product package inserts
Bostwick J, Guthrie S, Ellingrod V. Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy* 2009; 29: 64-73.
Cooper SJ, Reynolds GP, et al. BAP guidelines on the management of weight gain, metabolic disturbances, and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J of Psychopharmacol* 2016; 30(8): 717-748.
Chen JJ. Treatment of psychotic symptoms in patients with Parkinson disease. Ment Health Clin 2017; 6(2): 262-270.
Lehman A, Lieberman J, Dixon L, et al. APA practice guideline for the treatment of patients with schizophrenia (2nd edition). American Psychiatric Association. 2004.

Pharmacokinetic and Formulation Considerations

SGA	Brand Name	Half-life (days)	Dosing Interval
Aripiprazole lauroxil	Aristada®	53.9 to 57.2	Monthly OR every 6 weeks (882 mg) OR every 2 months (1064 mg)
Aripiprazole monohydrate	Abilify Maintena®	30 to 46.5	Monthly
Olanzapine pamoate	Zyprexa Relprevv®	30	2 or 4 weeks
Paliperidone palmitate	Invega Sustenna®	25 to 49	Monthly
Paliperidone palmitate	Invega Trinza®	84 to 95 (deltoid) 118 to 139 (gluteal)	3 months
Risperidone microspheres	Risperdal Consta®	3 to 6	2 weeks

Product package inserts

Summary

- First-line antidepressants are equally efficacious but have different adverse effect and drug interaction profiles
- SGAs, other than clozapine, are equally efficacious but have different adverse effect profiles and formulations
- Pharmacists should use patient specific information (e.g. comorbidities, concomitant medications) to guide antidepressant and antipsychotic selection

Identifying and Managing Serious Adverse Effects of Psychotropic Medications

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Conflict of Interest Statement and Disclosures

- The presenter has no conflicts of interest to disclose
- Off-label uses of the following medications will be discussed in accordance with available primary literature:
  - ✓ Amantadine
  - ✓ Bromocriptine
  - ✓ Chlorpromazine
  - ✓ Clonazepam
  - ✓ Cyproheptadine
  - ✓ Dantrolene
  - ✓ Olanzapine
  - ✓ Tetrabenazine

Objectives

- Describe signs and symptoms of serotonin syndrome, neuroleptic malignant syndrome (NMS), and tardive dyskinesia (TD)
- Design an appropriate treatment plan for serotonin syndrome, NMS, and TD

Select Package Insert Warnings for Antidepressants and Antipsychotics

- Increased suicidality (≤ 24 years)
- Serotonin syndrome
- QT prolongation
- SIADH/hyponatremia
- Bone fractures
- Bleeding
- Seizures
- Hypertensive crisis
- Increased mortality (elderly with dementia)
- Neuroleptic malignant syndrome (NMS)
- Extrapyramidal symptoms
- Tardive dyskinesia (TD)
- Blood dyscrasias
- Metabolic syndrome
- Orthostatic hypotension

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SEROTONIN SYNDROME

Serotonin Syndrome

- Potentially life-threatening reaction typically caused by combination of serotonergic agents stimulating variety of receptors (notably 5-$HT_{1A/2A}$)
  - Pharmacodynamic interactions with NE and DA receptors
- True incidence unknown due to diagnostic difficulties
- Classic triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities

Boyer EW, Shannon M. *N Engl J Med.* 2005;352(11):1112-20.

Serotonergic Agents

Antidepressants	Antiemetic Agents (e.g. ondansetron)	Analgesics (e.g. tramadol, fentanyl)
Antimigraine Agents (e.g. sumatriptan)	Antibiotics (e.g. linezolid)	Mood Stabilizers (e.g. lithium, valproate)
OTC Cough and Cold Products (e.g. dextromethorphan)	Herbal Products (e.g. St. John's wort)	Illicit Substances (e.g. MDMA, cocaine)

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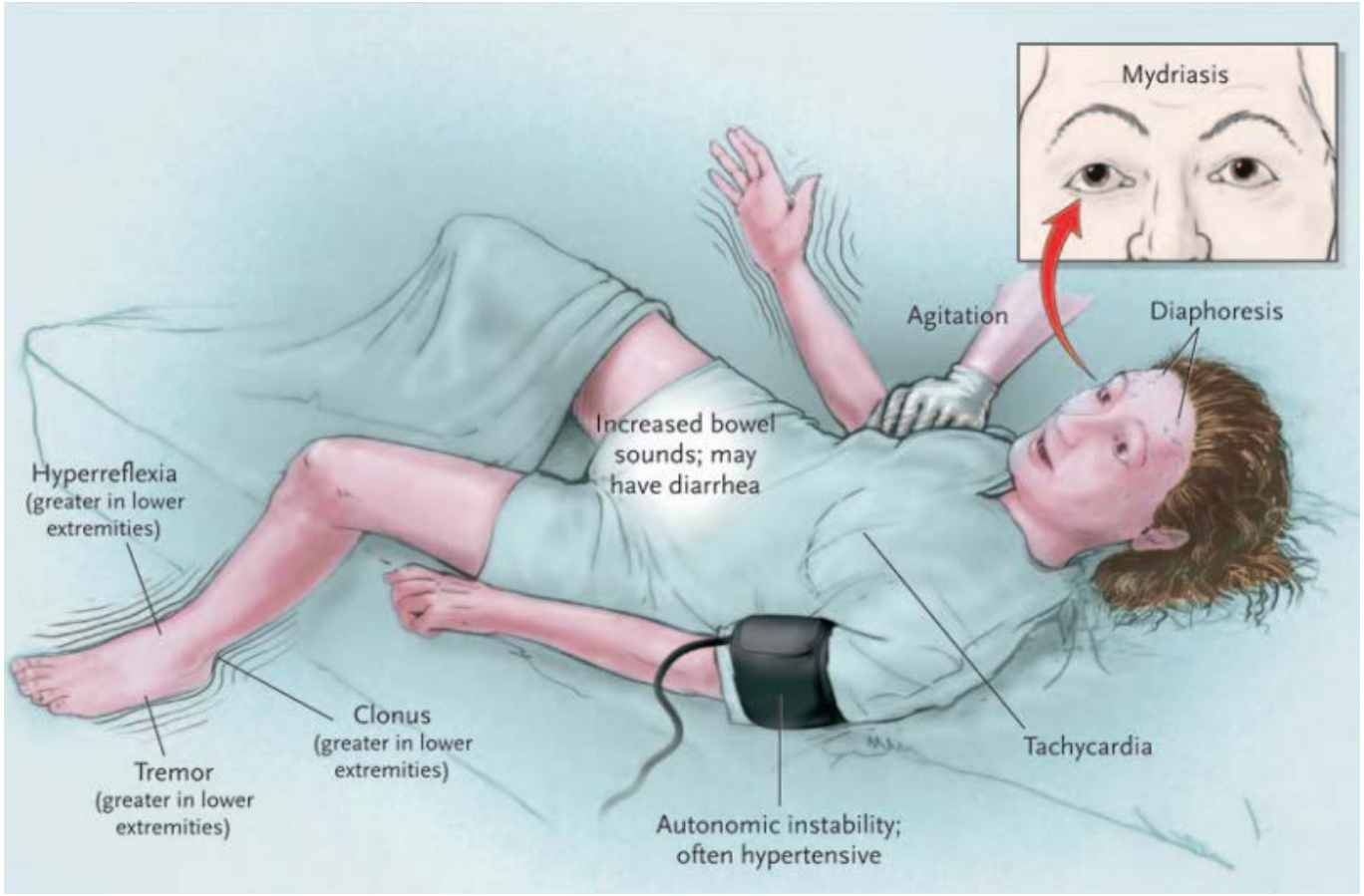
Boyer EW, Shannon M. *N Engl J Med.* 2005;352(11):1112-20.

Clinical Presentation



Boyer EW, Shannon M. *N Engl J Med.* 2005;352(11):1112-20.

Hunter Serotonin Toxicity Criteria

- Serotonergic agent received within past 5 weeks, **AND** at least 1 of the following symptoms:
  - Tremor and hyperreflexia
  - Spontaneous clonus
  - Muscle rigidity, temperature >38 C (100.4 F), and either ocular clonus or inducible clonus
  - Ocular clonus and either agitation or diaphoresis
  - Inducible clonus and either agitation or diaphoresis

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Dunkley EJ, et al. *QJM*. 2003;96(9):635-42.

Managing Serotonin Syndrome

Prevention: comprehensive medication review, prescriber education

Mild: remove offending agents, supportive care +/- benzodiazepines

Moderate: above actions + cyproheptadine

Severe: above actions + sedation, neuromuscular paralysis, and intubation

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Boyer EW, Shannon M. *N Engl J Med.* 2005;352(11):1112-20.

Select Pharmacologic Interventions

Benzodiazepines	• Sedation to control agitation and mild autonomic instability • No specific agents studied in humans, though many publications recommend IV lorazepam or diazepam
Cyproheptadine	• Potent antagonist at 5-$HT_{1A/2A}$ and H_1 receptors • Available as oral tablet (4mg) and syrup (2mg/5mL) • **Dosing:** 12mg PO initial, then 2mg PO q2h or 4-8mg PO q6h PRN
Alternative Route Options	• Chlorpromazine 50-100mg IM • Olanzapine 5-10mg sublingually *per case reports; efficacy/safety not well-established*

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Boyer EW, Shannon M. *N Engl J Med.* 2005;352(11):1112-20.
Volpi-Abadie J, et al. *Ochsner J.* 2013;13(4):533-40.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

Neuroleptic Malignant Syndrome

- Life-threatening emergency typically associated with neuroleptic agents (i.e. antipsychotics), likely due to sudden DA receptor blockade
  - Incidence ranges from 0.02-3.23%
  - Approximately 10-20% mortality rate
- Onset typically 1-2 weeks after drug initiation
- **Risk factors:** history of NMS, higher doses, faster titrations, more IM injections, neuroleptic-naïve, extreme agitation/catatonia, male gender, younger age

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Oruch R, et al. *Neuropsychiatr Dis Treat.* 2017;13:161-75.

Clinical Features

- No clear diagnostic criteria exist for NMS
- **Symptoms:** altered mental status, “lead-pipe” muscle rigidity, tremor, hyperthermia, autonomic instability
- **Lab Findings:**
  - Elevations in CK, WBCs, LDH, AST/ALT, Alk Phos, K+
  - Decreases in Ca2+, Mg2+, and serum iron
  - Acute renal failure → rhabdomyolysis

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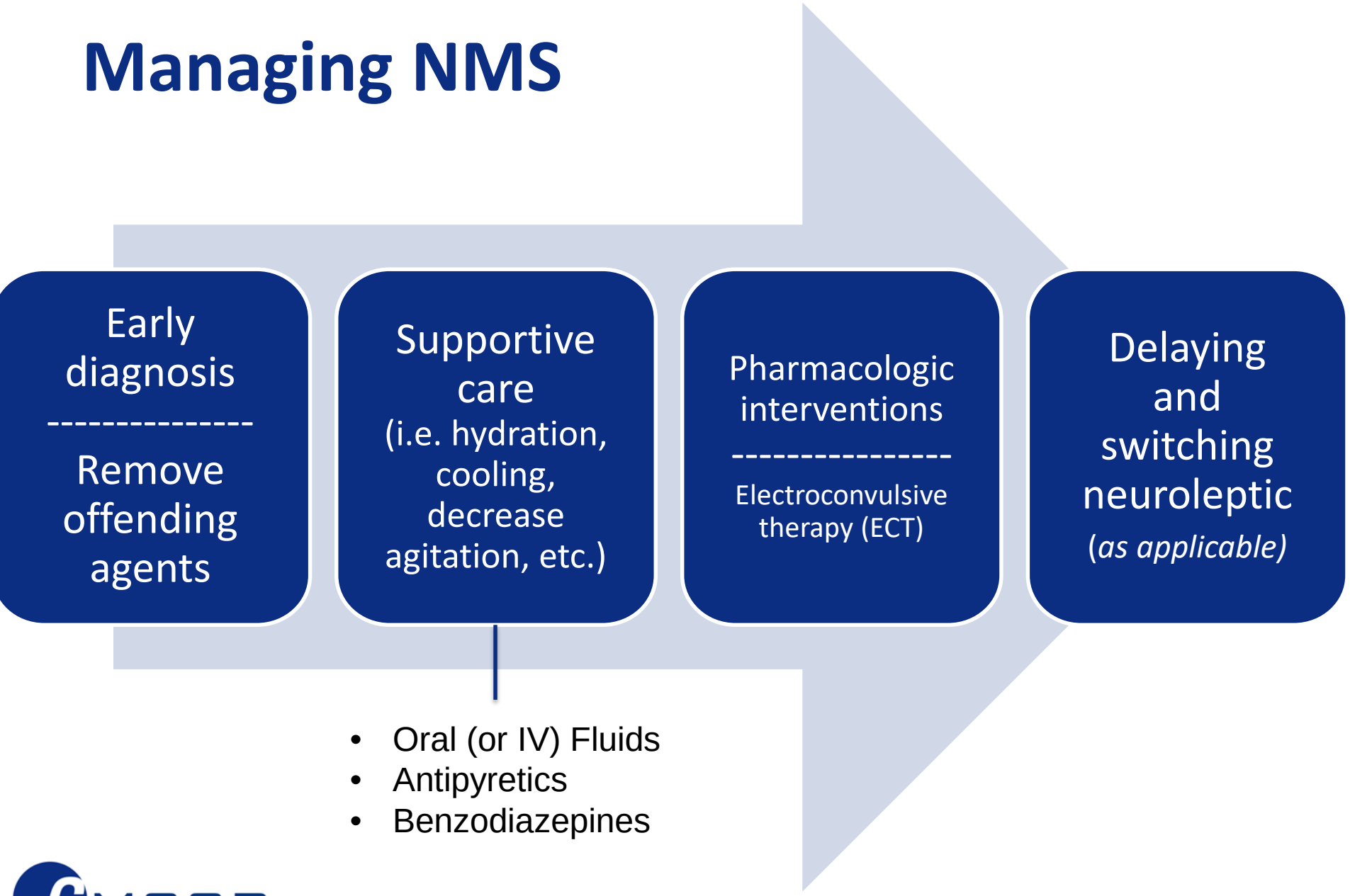
Oruch R, et al. *Neuropsychiatr Dis Treat.* 2017;13:161-75.

NMS vs. Serotonin Syndrome

	NMS	Serotonin Syndrome
Rigidity	+++	+
Hyperthermia	+++	+
GI Symptoms	-	+
Shivering	-	+
Hyperreflexia	-	+
Lab Changes	+ *(elevated CK)*	+/-

Managing NMS



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Pileggi DJ, Cook AM. *Ann Pharmacother.* 2016;50(11):973-81.

Select Pharmacologic Interventions

- Dantrolene (skeletal muscle relaxant)
  - Available as oral capsule (25mg, 50mg, 100mg) or IV solution (20mg, 250mg)
  - **Dosing:** 1-2.5mg/kg IV, repeated up to 10 mg/kg/day
  - Boxed warning for hepatotoxicity
- Bromocriptine (D_2 receptor agonist)
  - Available as oral tablet (0.8mg, 2.5mg) or capsule (5mg)
  - **Dosing:** 2.5mg PO q8-12h, increased to max of 45mg/day
  - May cause psychosis and hypotension
- Alternative option: amantadine 200-400 mg/day

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Pileggi DJ, Cook AM. *Ann Pharmacother.* 2016;50(11):973-81.

Knowledge Check #1

TP is a 52YO WF with a PMH of depression, migraines, and chronic pain who has been admitted to the hospital for osteomyelitis. A week into her stay, she begins to display agitation, loose stools, and hyperreflexia of her lower extremities. What is the most likely explanation of her new symptoms?

A. Neuroleptic malignant syndrome

B. Osteomyelitis

C. Serotonin syndrome

D. Substance withdrawal

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Knowledge Check #2

RL is a 27YO AAM with a PMH of schizophrenia who develops NMS after initiation of risperidone. Despite discontinuing the antipsychotic and supportive care measures (including lorazepam use), he develops more severe rigidity and a temperature of 104 F. What initial intervention is best to recommend?

A. Amantadine

B. Bromocriptine

C. Cyproheptadine

D. Dantrolene

TARDIVE DYSKINESIA (TD)

Antipsychotic-Induced Movement Disorders

- Extrapyramidal symptoms (EPS)
  - Include acute dystonia, akathisia, and parkinsonism
  - Occur within days to weeks of antipsychotic initiation
  - Usually reversible with treatment and adjustments to the antipsychotic regimen

- Tardive dyskinesia (TD) – *sometimes also considered EPS*
  - Occur after months to years of antipsychotic use
  - Potentially irreversible despite treatment/adjustments
  - Monitor with rating scales like AIMS and DISCUS

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Huffman JC, et al. "Side Effects of Psychotropic Medications." In: *Massachusetts General Hospital: Comprehensive Clinical Psychiatry*, 2nd ed. 2016.

Tardive Dyskinesia

- Repetitive, involuntary, non-rhythmic movements, most frequently of the orofacial region
  - Mechanism not fully understood, though potentially hypersensitivity of DA receptors from prolonged blockade
  - Incidence approximately 5% for first 5 treatment years

- **Risk factors:** first-generation antipsychotics (FGAs), lengthier exposure, early EPS, female gender, advanced age, diagnosis of mood disorder or organic brain disease

Huffman JC, et al. "Side Effects of Psychotropic Medications." In: *Massachusetts General Hospital: Comprehensive Clinical Psychiatry*, 2nd ed. 2016.

Managing TD

	American Academy of Neurology (2013)	Bhidayasiri R, et al (2018)
Level A		deutetrabenazine, valbenazine
Level B	clonazepam, ginkgo biloba	
Level C	amantadine, tetrabenazine	amantadine, tetrabenazine, deep brain stimulation
Level D		
Level U	withdraw agent, switch to second-generation antipsychotic (SGA), ECT, acetazolamide, baclofen, botulinum toxin, bromocriptine, buspirone, levetiracetam, melatonin, reserpine, thiamine, vitamin B6, vitamin E, zonisamide	

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Bhidayasiri R, et al. *Neurology.* 2013;81(5):463-9.
Bhidayasiri R, et al. *J Neurol Sci.* 2018;389:67-75.

VMAT2 Inhibitors

*Conversion table provided for tetrabenazine to deutetrabenazine

	Valbenazine (Ingrezza®)	Deutetrabenazine (Austedo®)
Approval	April 11, 2017	August 30, 2017
Dosages	Oral capsule (40mg, 80mg)	Oral tablet (6mg, 9mg, 12mg)
Dosing	40mg daily x1 week, then increase to 80mg daily	6mg twice daily (may increase weekly up to 24mg twice daily)*
Adverse Effects	Somnolence, dry mouth, dizziness, headache, akathisia, vomiting, arthralgia	Nasopharyngitis, insomnia, depression, akathisia
Select Evidence	• **KINECT 2:** 6-week, DB, PC, titratable RCT (N=102) • **KINECT 3:** 6-week, DB, PC, fixed RCT (N=234)	• **ARM-TD:** 12-week, DB, PC, titratable RCT (N=117) • **AIM-TD:** 12-week, DB, PC, fixed RCT (N=298)

DB=double-blind, PC=placebo-controlled, RCT=randomized controlled trial

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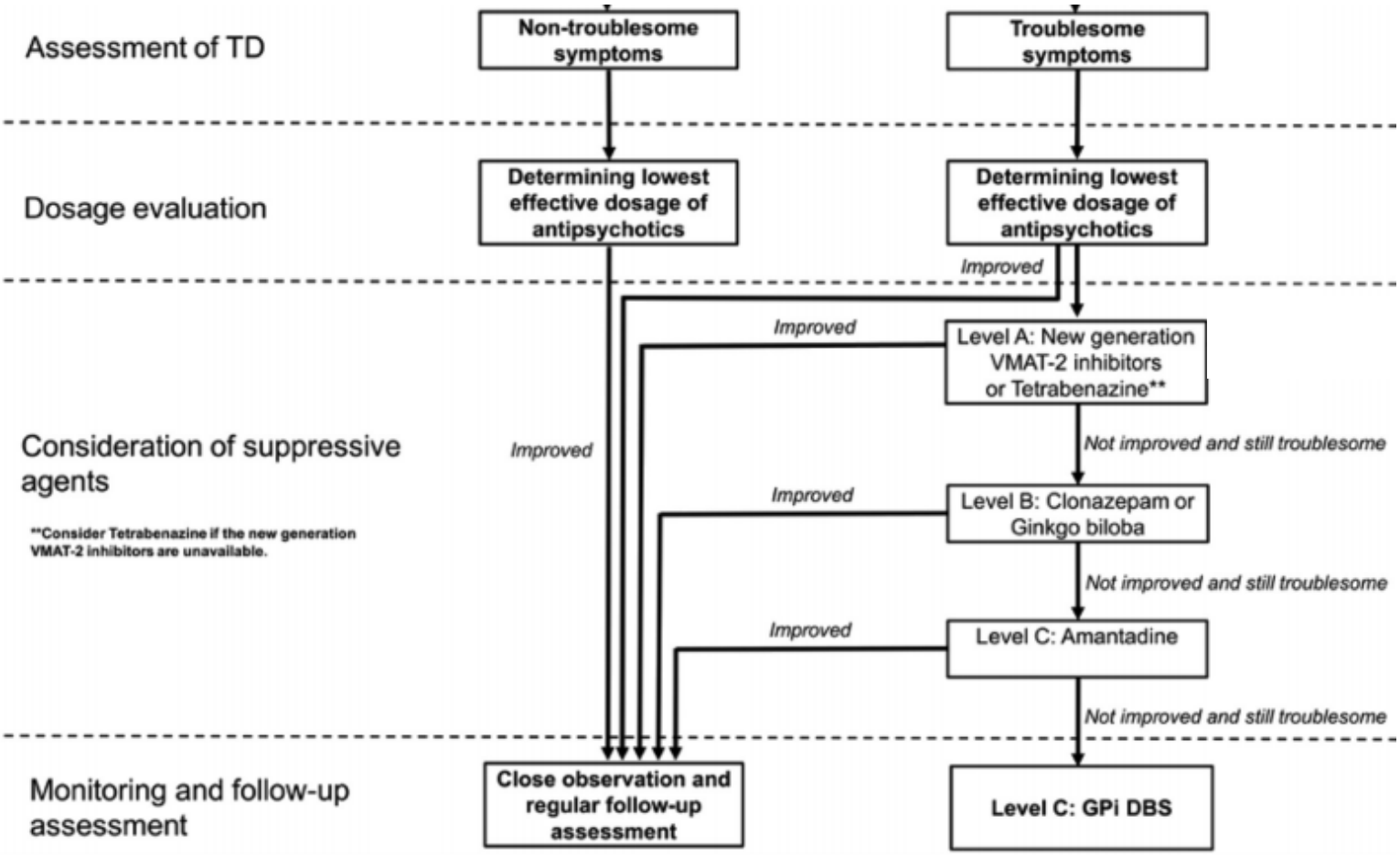
Valbenazine [package insert]. 2017.
O'Brien CF, et al. *Mov Disord.* 2015;30(12):1681-7.
Hauser RA, et al. *Am J Psychiatry.* 2017;174(5):476-84.

Deutetrabenazine [package insert]. 2017.
Fernandez HH, et al. *Neurology.* 2017;88(21):2003-10.
Anderson KE, et al. *Lancet Psychiatry.* 2017;4(8):595-604.

Proposed TD Treatment Algorithm



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Bhidayasiri R, et al. *J Neurol Sci*. 2018;389:67-75.

Knowledge Check #3

PW is a 66YO WF with a PMH of treatment-resistant schizophrenia and bothersome TD maintained on long-acting fluphenazine injections every 2 weeks. She has not tolerated antipsychotic switches or dose reductions. Her provider would like to try an effective medication for TD but is concerned about adherence. What do you recommend?

A. Clonazepam

B. Deutetrabenazine

C. Tetrabenazine

D. Valbenazine

Take-Home Points

- ✓ When it comes to serious adverse events of psychotropics, prevention (or early detection) is key
- ✓ Labs can assist in differentiating syndromes, but they are ultimately clinical diagnoses
- ✓ New medications are FDA-approved for tardive dyskinesia, though long-term data and cost are still significant considerations

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Therapy Modifications: Avoiding Withdrawal Effects

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Learning Objectives

1. Identify potential withdrawal effects from discontinuing antidepressants, antipsychotics, and benzodiazepines.

2. Develop a treatment plan for a patient switching psychotropic medications.

Reasons to Modify Therapy

Inefficacy

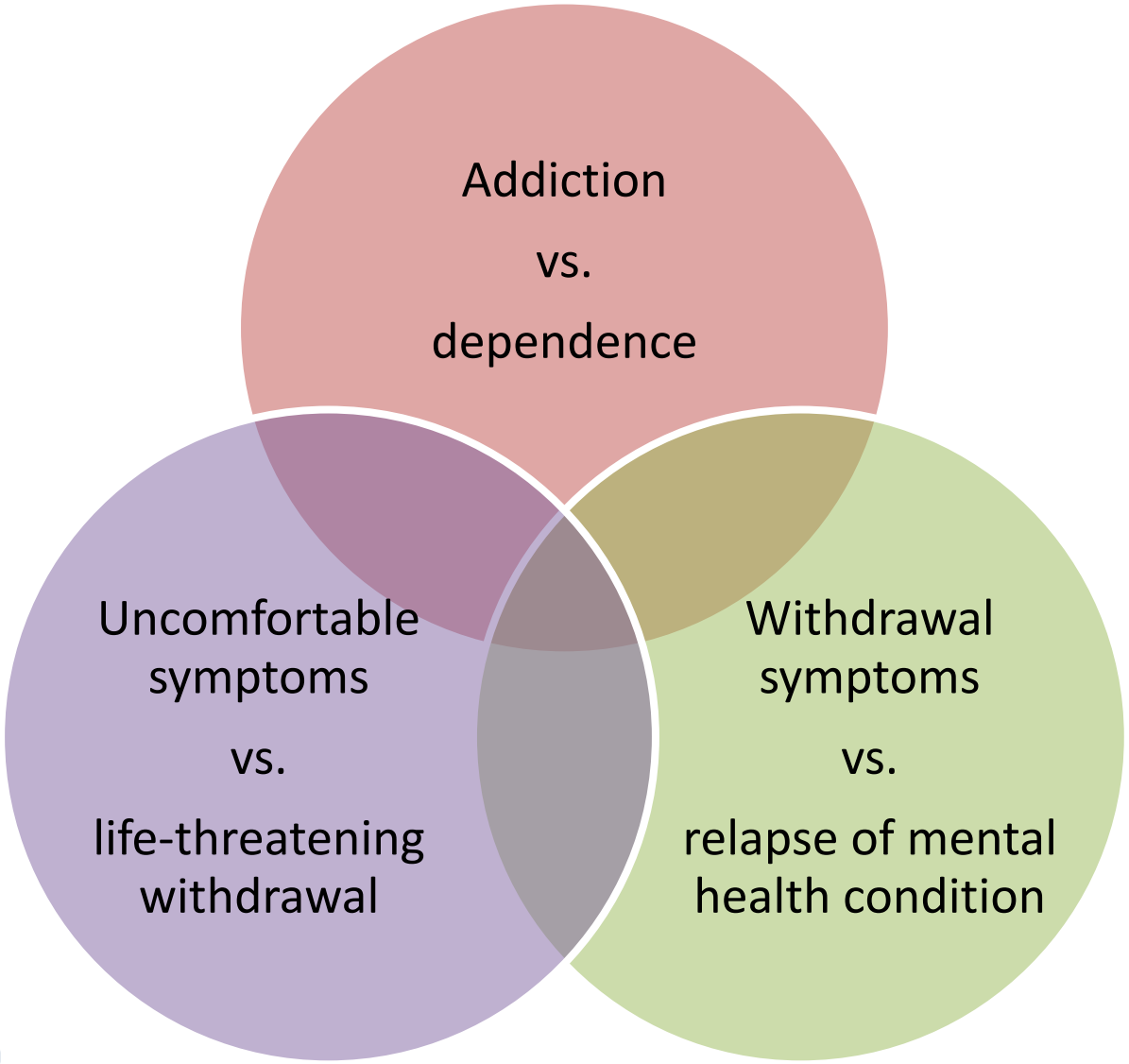
Intolerability

Safety concerns

- Change in renal/hepatic function
- Age
- Drug interactions

Medication indicated for short term use or no longer needed

Important Distinctions



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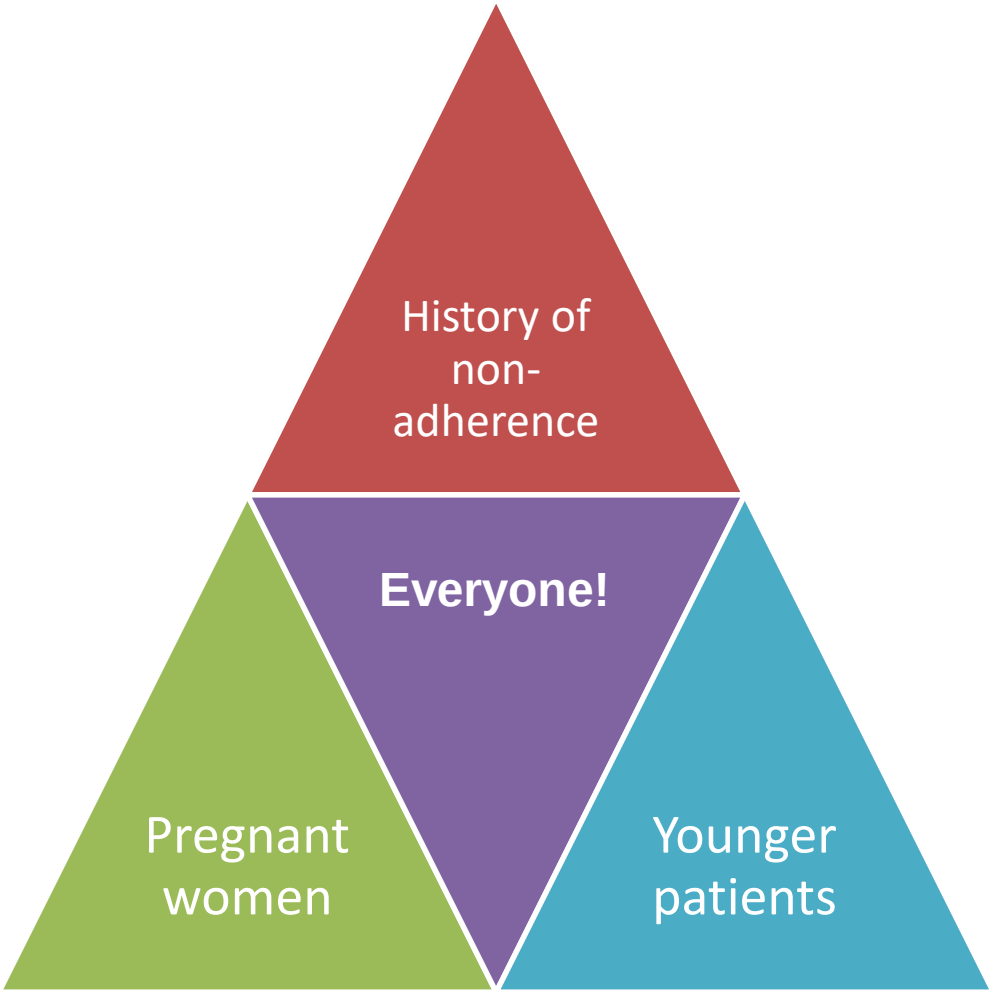
Patients at Risk for Withdrawal



Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant Discontinuation Syndrome. *Am Fam Physician*. 2006;74(3):449-56.
Muzina D. Discontinuing an Antidepressant? Tapering tips to ease distressing symptoms. *Curr Psychiatry*. 2010;9:50-61.

Active Learning

Kanye West is admitted to your inpatient psychiatry unit with another "breakthrough." He reports he stopped taking his medication about 3 days ago but is unable to remember the name of it. He is currently experiencing symptoms of insomnia, "brain zaps," and nausea. Which of the following medications was Kanye MOST likely taking?

A. Alprazolam (Xanax®)
B. Bupropion (Wellbutrin®)
C. Paroxetine (Paxil®)
D. Quetiapine (Seroquel®)

Antidepressants

Antidepressant Withdrawal

- Occurs in ~20% of patients after abrupt discontinuation of antidepressant medications after a period of use (6-8 weeks)
- Not life-threatening and usually mild
- Symptoms generally occur within 3 days and may last 1-2 weeks
- "FINISH"
  - Flu-like symptoms
  - Insomnia
  - Nausea
  - Imbalance
  - Sensory disturbances
  - Hyperarousal

Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant Discontinuation Syndrome. *Am Fam Physician*. 2006;74(3):449-56.
Berber MJ. FINISH: remembering the discontinuation syndrome. Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances, and Hyperarousal (anxiety/agitation). J Clin Psychiatry. 1998;59(5):255.

Antidepressant Withdrawal

- Risk of withdrawal depends on half-life of antidepressant and presence of active metabolites
- Lower incidence with agents with longer half life and/or active metabolites (fluoxetine)
  - Self-tapering
- More common with agents with shorter half lives and immediate release formulations (paroxetine, venlafaxine)
  - Tapering is recommended

Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant Discontinuation Syndrome. *Am Fam Physician*. 2006;74(3):449-56.
Gelenberg A, Freeman M, Markowitz J, et al. APA practice guideline for the treatment of patients with major depressive disorder (3rd edition). American Psychiatric Association. 2010.

Antidepressant Tapering Strategies

- Suggested taper rates vary widely
  - Taper over 4-6 months
  - Taper ove
  - Reduce dosag
  - 50% dose red 0% reduction x3 days, then
- Some recommendatio t for specific agents
  - Reduce dose of venlafaxine by 75 mg per week

Taper regimens should be individualized to the patient

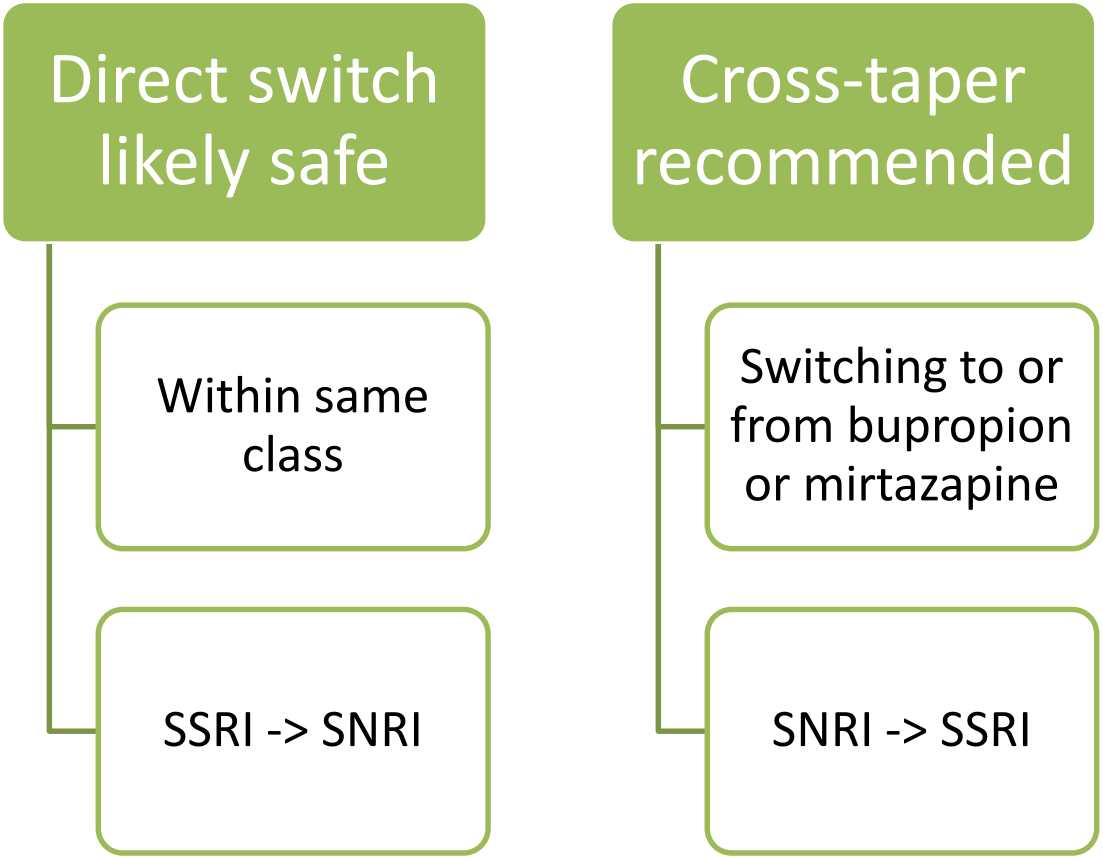
Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant Discontinuation Syndrome. *Am Fam Physician*. 2006;74(3):449-56.
Stahl, SM. Prescriber's Guide. 5th ed. New York, NY: Cambridge University Press; 2014.
Bauer M, Pfennig A, Severus E, et al. World Federation of Societies of Biological Psychiatry (WFSBP): Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders. *World J Biol Psychiatry*. 2013;14(5):334-385.

Antidepressant Tapering Strategies

- Taper as tolerated
  - If withdrawal symptoms occur, consider restarting at original dose and tapering at a slower rate
- Decrease dose to lowest possible dose
- Decrease frequency if necessary
- Consider switching to an agent with a longer half-life
  - e.g. Fluoxetine 10 mg x1-2 weeks

Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant Discontinuation Syndrome. *Am Fam Physician*. 2006;74(3):449-56.
Gelenberg A, Freeman M, Markowitz J, et al. APA practice guideline for the treatment of patients with major depressive disorder (3rd edition). American Psychiatric Association. 2010.
Stahl, SM. Prescriber's Guide. 5th ed. New York, NY: Cambridge University Press; 2014.

Switching Antidepressants



Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry, 11th ed. 2012. West Sussex, UK: Wiley-Blackwell.

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin/norepinephrine reuptake inhibitor

Antipsychotics

Antipsychotic Withdrawal Effects

- Symptoms usually occur within 1-2 weeks
- Not life-threatening and generally mild
- Symptoms may include:
  - Rebound psychosis
  - Dyskinesias/dystonias
  - Pseudoparkinsonism
  - Akathisia
  - Anxiety, insomnia
  - Cholinergic rebound (gastrointestinal effects, diaphoresis)

A Roadmap to Key Pharmacologic Principles in Using Antipsychotics. *Prim Care Companion J Clin Psychiatry*. 2007;9(6):444-454.
Alphs LD, Lee HS. Comparison of withdrawal of typical and atypical antipsychotic drugs: a case study. *J Clin Psychiatry*. 1991;52(8):346-348.
Luchins DJ, Freed WJ, Wyatt RJ. The role of cholinergic supersensitivity in the medical symptoms associated with withdrawal of antipsychotics drugs. *Am J Psychiatry*. 1980;137(11):1395-1398.
Gilbert PL, Harris MJ, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenia patients: a review of the literature. *Arch Gen Psychiatry*. 1995;52(3):173-188.

Antipsychotic Withdrawal Effects

- Management of withdrawal effects
  - Restart original antipsychotic
  - More gradual taper rate
  - Short term use of medications to treat extrapyramidal symptoms
    - Anticholinergic medications
    - Benzodiazepines
    - Propranolol

Antipsychotic Tapering Strategies

- No specific guidelines
  - Reduce dose by 1/5 to 1/3 every 1-2 months
  - Decrease dose by 5-25% [illegible] 1-3 weeks
  - Decrease dose by 25 [illegible]

Taper regimens should be individualized to the patient

A Roadmap to Key Pharmacologic Principles in Using Antipsychotics. *Prim Care Companion J Clin Psychiatry*. 2007;9(6):444-454.
Gilbert PL, Harris MJ, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenia patients: a review of the literature. *Arch Gen Psychiatry*. 1995;52(3):173-188.

Switching Antipsychotics

- 6-8 week cross-tapers are generally recommended

Strategy #1

- Slowly decrease dose of antipsychotic #1 while titrating dose of antipsychotic #2

Strategy #2

- Maintain therapeutic dose of antipsychotic #1 while titrating dose of antipsychotic #2, once dose of antipsychotic #2 is therapeutic start taper of antipsychotic #1

  - Risk of polypharmacy, additive adverse effects, nonadherence

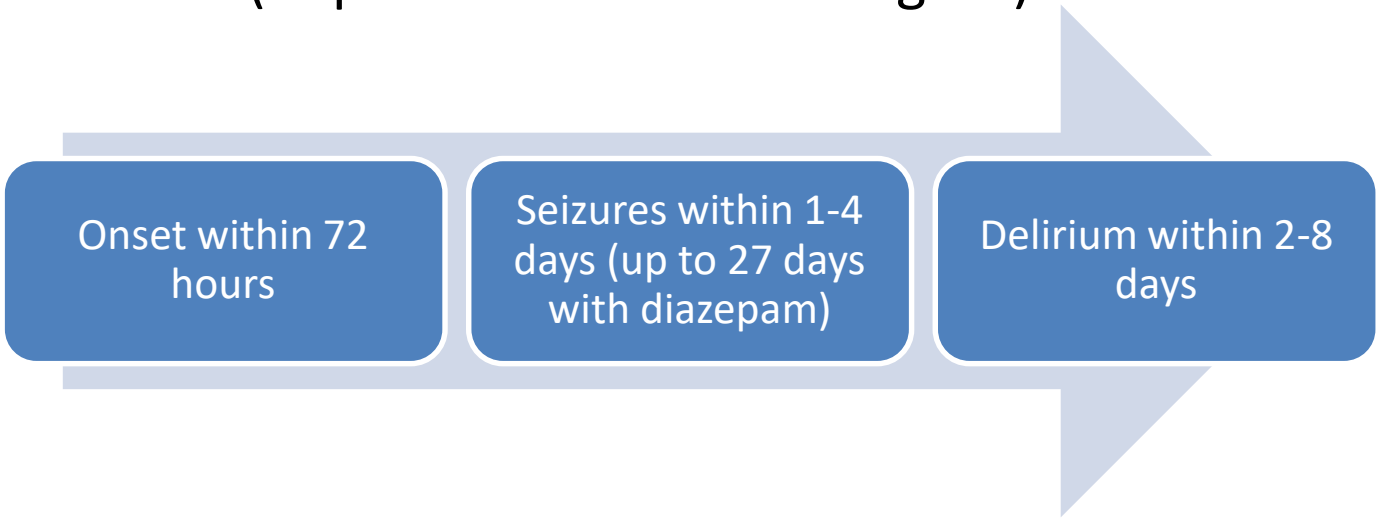
- Do not need to cross taper between risperidone and paliperidone
- Do not need to cross taper with long-acting injectable antipsychotics

A Roadmap to Key Pharmacologic Principles in Using Antipsychotics. *Prim Care Companion J Clin Psychiatry*. 2007;9(6):444-454.
Gilbert PL, Harris MJ, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenia patients: a review of the literature. *Arch Gen Psychiatry*. 1995;52(3):173-188.

Benzodiazepines

Benzodiazepine Withdrawal Effects

- Occur in ~50% of patients receiving therapeutic doses of benzodiazepines (BZDs)
- Symptoms may be serious and can be life-threatening; some patients may require hospitalization
- Time course (depends on half-life of agent):



Noyes RJ, Garvey MJ, Cook BL, Perry PJ. Benzodiazepine withdrawal: a review of the evidence. *J Clin Psychiatry*. 1988;49(10):382-389.
Perry PJ, Alexander B, Liskow BI, DeVane CL. Psychotropic drug handbook. 8th ed. 2007. Lippincott Williams & Wilkins.

Benzodiazepine Withdrawal Effects

Common:

- Rebound symptoms
  - Insomnia, anxiety, restlessness, irritability
- GI effects (nausea, vomiting)
- Tremor, muscle twitches
- Incoordination, weakness
- Blurred vision
- Sweating
- Anorexia

Serious:

- Tonic-clonic seizures
- Hallucinations
- Delirium
- Death

Noyes RJ, Garvey MJ, Cook BL, Perry PJ. Benzodiazepine withdrawal: a review of the evidence. *J Clin Psychiatry*. 1988;49(10):382-389.
Perry PJ, Alexander B, Liskow BI, DeVane CL. Psychotropic drug handbook. 8th ed. 2007. Lippincott Williams & Wilkins.

Benzodiazepines Taper Strategies

- Always taper if patient taking for ≥2 weeks
  - Consider switching to a long-acting BZD for ease of taper
    - Clonazepam, diazepam
  - Duration of therapy d uration of the taper

Dur	aper
<6	eeks
6	
>1 year	2-4 months

Taper regimens should be individualized to the patient

  - General tapering strateg
    - 25% reduction weekly x2 weeks
    - May need to hold at current dose for weeks to months
    - Then reduce dose by 10-25% of current dose every 1-2 weeks

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Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *J Clin Psychiatry*. 2004;65 Supple 5:7-12.

Alternatives to Benzodiazepines

For anxiety:

- Maintenance anxiolytic medication
  - SSRI, SNRI, mirtazapine
- Hydroxyzine
- Propranolol
- Gabapentin, pregabalin (if appropriate)

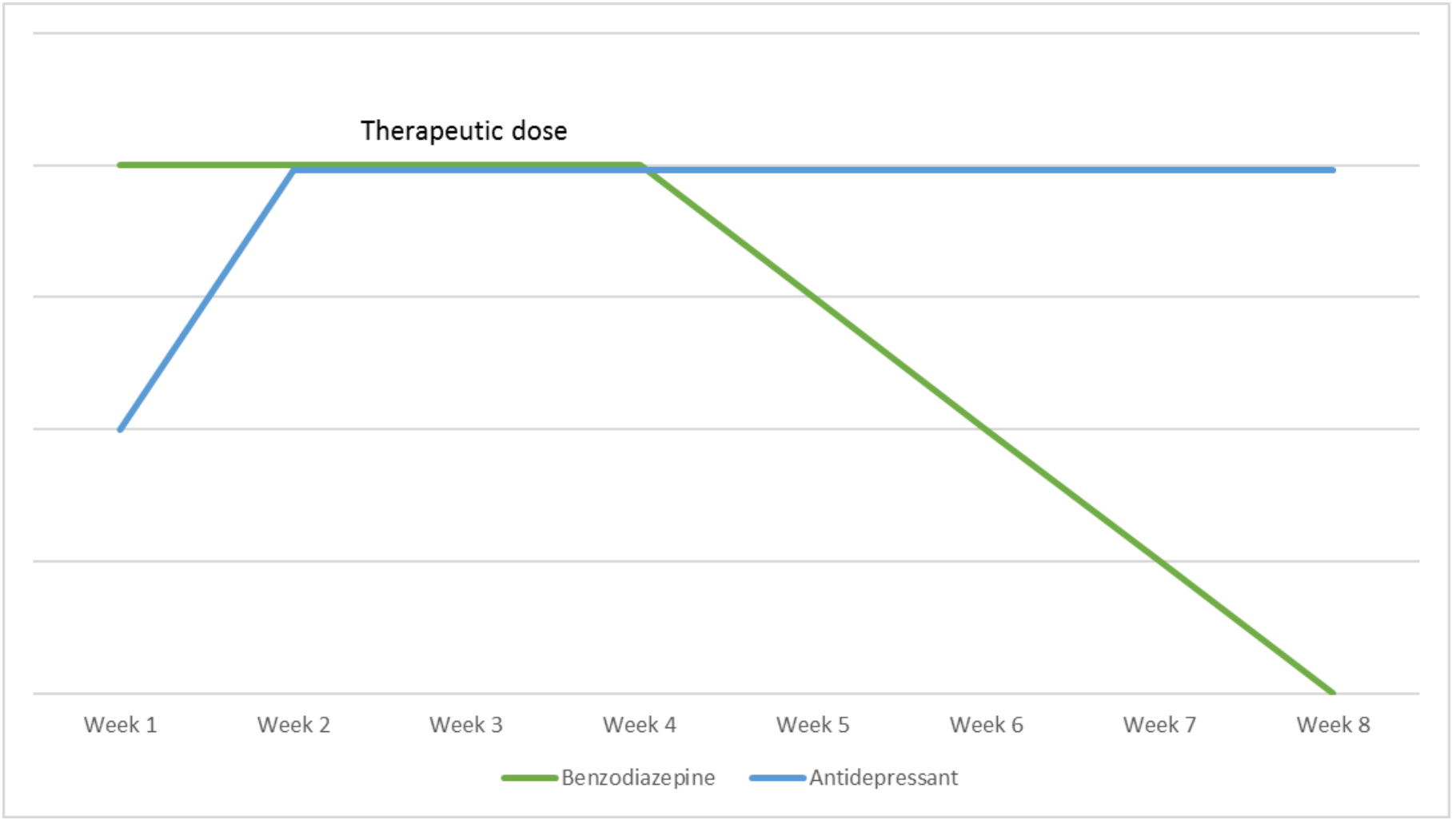
For insomnia:

- Non-pharmacologic therapies
  - Cognitive behavioral therapy for insomnia (CBT-I), sleep hygiene
- Melatonin, ramelteon
- Doxepin (low dose)
- Mirtazapine, trazodone
- Z-hypnotics

Active Learning

Channing Tatum was started on clonazepam (Klonopin®) 1 mg BID when he divorced his wife Jenna Dewan in March 2018. His prescriber is requesting pharmacist input on how to stop the benzodiazepine and switch to a more appropriate maintenance medication for anxiety. Develop a treatment plan for this patient.

Active Learning



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Active Learning

Considerations for benzodiazepine tapers:

- Does he need to taper the clonazepam?
- If so, how long should the taper last?

Duration of Therapy	Duration of Taper
<6 months	2-3 weeks
6 months - 1 year	4-8 weeks
>1 year	2-4 months

- Should we consider switching to a longer-acting agent?
- Design an appropriate dosing schedule:
    - Week 1: 0.5 mg po qAM, 1 mg po qPM (25% dose reduction)
    - Week 2: 0.5 mg po BID (50% dose reduction)
    - Week 3: 0.5 mg po qHS (75% dose reduction)

Active Learning

<u>Considerations for benzodiazepine tapers:</u>

- What should you do if the patient experiences withdrawal symptoms?
    - If serious, consider hospital admission for observation
    - Return to previous tolerated dose
    - Taper more slowly
    - Consider adding a medication short-term to help with withdrawal symptoms
        - Hydroxyzine for anxiety
        - Melatonin, doxepin, trazodone for insomnia

Tapering Resources

- Lexicomp
  - "Discontinuation of therapy" section
- Stahl's Essential Pharmacology: Prescriber's Guide
  - Each medication has a "how to stop" section
- APA guidelines
- https://switchrx.com/

Take Home Messages

- Counsel on discontinuation/withdrawal effects when starting medications
- Ask if patients recently stopped any medications
- When in doubt, taper!
- Write out clear directions for the patient
- Provide support and reassurance to the patient
- Consider short term alternative agents when necessary

Questions?