Session # B6

Psychopharmacology Review for Primary Care

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Faculty Disclosure

Thomas Salter, MD has NOT had any relevant financial relationships during the past 12 months.

Mark Williams, MD

- HealthStat – advisory board member on models of mental health care for employees – honorarium
- Neuroscience Educational Institute – peer review of presentations on psychopharmacology

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Conference Resources

Slides and handouts shared by our conference presenters are available on the CFHA website at https://www.cfha.net/page/Resources_2019 and on the conference mobile app.

3

Learning Objectives

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

- Identify and describe drug classes and examples of adverse effects of psychotropic medications and approach to common and challenging clinical situations
- Identify several psychopharmacology updates including newer treatment options and contemporary challenges.
- Identify and have access to at least three clinical tools/resources on psychopharmacology.

4

Bibliography / Reference

1. Byun, T. H., et al. (2019). "New Treatment Options for Depression: A Primer for Internists." Am J Med 132(6): 678-684
2. Benich, J. J., 3rd, et al. (2016). "Psychopharmacology in Primary Care Settings." Prim Care 43(2): 327-340.
3. Ahmed, A. T., et al. (2018). "Benefits of and Barriers to Pharmacogenomics-Guided Treatment for Major Depressive Disorder." Clin Pharmacol Ther 103(5): 767-769.
4. McCarron, R. M., et al. (2016). "Depression." Ann Intern Med 165(7): ITC49-ITC64
5. Brenner, C. J. and S. I. Shyn (2014). "Diagnosis and management of bipolar disorder in primary care: a DSM-5 update." Med Clin North Am 98(5): 1025-1048.

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Learning Assessment

- A learning assessment is required for CE credit.
- A question and answer period will be conducted at the end of this presentation.

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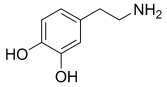
Overview

Note: Primary focus is Adult population

- 1-Introduction –Why is Psychopharmacology so complicated?
- 2-Overview of drug classes and adverse effects
- 3-Pharmacologic approach to treating depression and treatment resistant depression
- 4-Psychoharmacology rapid review: illustrative cases, pearls, challenges, new topics
- 5-The role of collaborative and integrated health team in psychopharmacology
- 6-Summary and review of resources
- Questions and Discussion



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Why is Psychopharmacology so complicated?

- Psychotropic medication complexity
- Other prescribed medications and medical complexity
- Over the counter medications
- Drugs of abuse, illicit
- Alcohol, tobacco/nicotine, caffeine
- Polypharmacy
- New medications
- Partial efficacy is the norm
- Heterogeneous presentations
- Drug-drug interactions
- Stigma, adherence, cost
- Others?

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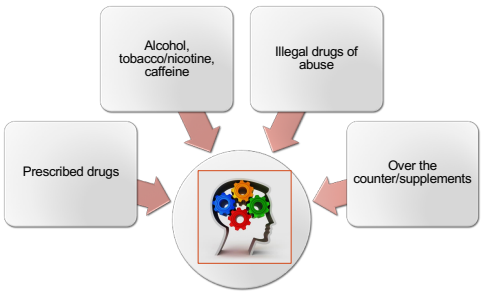

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Introduction

- Psychopharmacology review/update in 60 minutes?
- Emphasis on overview, general strategies, updates and new topics in psychopharmacology and use of resources
- Focus is primarily adult populations
- Concepts "Allopathic compulsion" (Harvard's Dr. Baldessarini) and "Subtraction"
- Communication and expectations when prescribing
- Cultural psychiatry aspects of psychopharmacology (illness beliefs; historical mistrust)
- Role of collaborative and integrated health teams in psychopharmacologic treatments

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Some Pharmacology terminology

- **Adverse effect**: undesired, potentially harmful side effects of drugs ***Distinguish vs Allergy***
- **Agonist:** drug that binds to and activates a receptor (full and partial types)
- **Antagonist**: drug that binds to a receptor and does not active receptor or blocks/reduces effect of an agonist
- **Pharmacodynamics**: study of what the drug does to the body; site of action effects; drug receptor status, genetic factors, drug interactions, tolerance
- **Pharmacokinetics**: study of what the body does to the drug (absorption, distribution, metabolism, excretion)
- **Half-Life (T ½):** time it takes for concentration of the drug to decline to 50% of original level
- **Narrow therapeutic window:** when there is only a small difference in concentration of dug that is safe and therapeutic and that which leads to serious toxicity or harmful adverse effects
- **Monoamine:** refers to neurotransmitters such as dopamine, norepinephrine, serotonin

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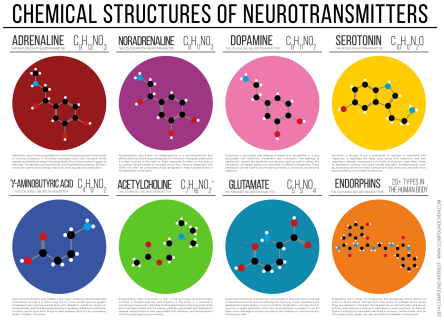

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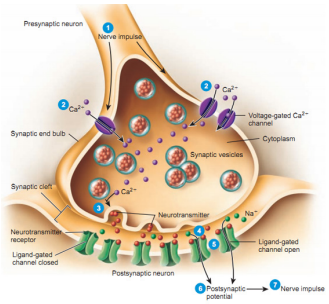

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Overview of drug classes and adverse effects

- SSRI
- Atypical Antidepressants
- Serotonin Modulators
- SNRI
- Antipsychotics (first-generation)
- Antipsychotics (second-generation)
- Mood Stabilizers
- Sedative/Hypnotics and Benzodiazepines
- Drugs for addictions
- Drugs for anxiety and drugs with cardiac/adrenergic effects
- NMDA effects-Ketamine
- Cannabinoid-Medical Cannabis

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How common is antidepressant use? Very Common

Summary

During 2011–2014, about one in eight Americans aged 12 and over reported taking antidepressants in the previous month. Antidepressant use increased with age and was twice as common among females as males. Non-Hispanic white persons were more likely to take antidepressants than non-Hispanic black, Hispanic, and non-Hispanic Asian persons.

Long-term antidepressant use was common. One-fourth of all people who took antidepressants in the past month reported having taken them for 10 years or more.

Antidepressant use increased nearly 65% over a 15-year time frame, from 7.7% in 1999–2002 to 12.7% in 2011–2014. This increase was similar among males and females. At every time point, females were about twice as likely as males to report antidepressant use in the past month.

National Health and Nutrition Examination Survey (NHANES)
NCHS Data Brief No. 283, August 2017. Pratt, Brody, and Gu
https://www.cdc.gov/nchs/products/databriefs/db283.htm

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SSRI	Atypical/ Serotonin modulators	SNRI	TCA
fluoxetine	bupropion	venlafaxine	amitriptyline
sertraline	mirtazapine	duloxetine	imipramine
citalopram	trazodone		clomipramine
escitalopram		desvenlafaxine	doxepin
paroxetine	vilazodone	milnacipran	nortriptyline
fluvoxamine	vortioxetine	leveomilnacipran	desipramine

Understand differences including properties, indications, adverse effects helps guide choice.

What would you choose if also need to target…

Pain?
Sleep?
Poorly adherent patient?
Weight loss/poor appetite?
Tobacco cessation?
Migraine prevention?

Avoid use or caution in…

Seizures/seizure risk?
Significant cardiac disease?
Pregnancy?
Prolonged QT interval?
Weight gain concerns?
Poorly adherent patient?
Suicide risk/overdose?

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Antidepressants Adverse Effects

Early	• GI with loose stools, diarrhea, nausea • Jitteriness/anxiety/insomnia (in some, sedation, fatigue)
Common/persistent	• Sexual dysfunction • Weight gain • Excessive sweating
Serious	• **S**erotonin syndrome, **S**lippery platelets (Bleeding risk) • **S**uicidal ideation (young patients); **S**eizures (buproprion) • **R**educed sodium (hyponatremia-most antidepressants) • **I**ncreased QT interval (citalopram, TCAs cardiac and QTc effects, lethal in OD)

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Adverse effects of non-SSRI antidepressants

- TCA
  - Anticholinergic (dry mouth, blurry vision, urinary retention)
  - Cardiac toxicity including prolonged QTc
  - Weight gain
- Atypical antidepressants
  - mirtazapine-weight gain, sedation (more so at lower doses)
  - trazodone-orthostatic hypotension
- MAOI
  - Still used?
  - Tyramine-induced hypertensive crisis. Though traditional dietary advice may have been unnecessarily restrictive.
  - Serotonin syndrome; wash-out periods

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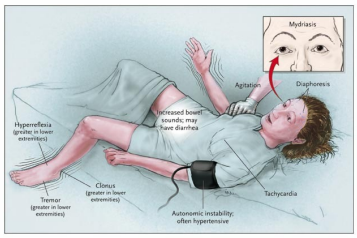
Serotonin syndrome



Boyer and Shannon. N Engl J Med 2005; 352:1112-1120. March 17, 2005.
https://www.nejm.org/doi/full/10.1056/NEJMra041867

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Consider using template when you take psychotropic treatment history.

May help you reveal a drug class or augmentation approach you had not considered.

Antidepressants	SSRI	Atypical AD	SNRI	NDRI	TCA	MAOI	
	fluoxetine	bupropion	venlafaxine	amitriptyline	phenelzine		
	sertraline	mirtazapine	duloxetine	imipramine	trazodone		
	citalopram	trazodone		clomipramine	selegiline		
	escitalopram			desipramine	doxepin		
	paroxetine	vilazodone	milnacipran	nortriptyline			
	fluvoxamine	vortioxetine	levomilnacipran	imipramine			

Augmentation/MDD: bupirone, lithium, atypical antipsychotics, thyroid hormone, stimulant, Omega-3 fatty acids, SAMe, l-methylfolate, pramipexole

ADHD/ wakefulness promoting	amphetamine salts	methylphenidate	melatonin/melatonin	modafinil	armodafinil	
Antipsychotics (2nd generation)	ziprasidone	aripiprazole	quetiapine	risperidone	olanazpine	clozapine
	cariprazine	asenapine	lloperidone	paliperidone		
Antipsychotics (1st generation)	haloperidol	fluphenazine	thiothixene	trifluoperazine	pephenazine	chlorpromazine
Mood stabilizers	lithium	valproate	lamotrigine	Carbamazepine oxcarbazepine	gabapentin	pregabalin
Benzos	lorazepam	clonazepam	alprazolam	diazepam	temazepam	

Non-Benzo Anxiety:	hydroxyzine	buspirone	Others: "antidepressants" above, gabapentin, pregabalin, propranolol, atypical antipsychotics			
Sedative-hypnotics	zolpidem	eszopiclone	zaleplon			
Dopamine agonist	pramipexole	ropinirole	bromocriptine			
Alcohol use disorder	naltrexone	acamprosate	disulfiram	topiramate	gabapentin	
Opioid addiction	buprenorphine	methadone				
Smoking cessation	Nicotine replacement	varenicline	bupropion			
Cardiovascular	prazosin	Clonidine	guanfacine	propranolol		
Cognitive enhancers	donepezil	rivastigmine	galantamine		memantine	
OTC	melatonin	diphenhydramine	CBD oil			
Endocannabinoid	cannabis					
NMDA	ketamine					
Neuromodulatory	ECT	TMS	DBS	VNS		light box

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Benzodiazepines

lorazepam	clonazepam	alprazolam	diazepam	temazepam

Uses:

- Anxiety disorders
- Seizure disorders
- Alcohol withdrawal
- Tremor
- Agitation/Akathisia

Notes:

- Enhance effects of GABA (inhibitory)
- Short term vs long term use
- Significant adverse effects to consider-addiction, sedation, falls, cognitive effects
- Avoid use with opioid analgesics-risk of respiratory suppression, overdose, death
- Prescribers need to find their comfort level

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Sedative-Hypnotics (non-benzodiazepine)

zolpidem (Ambien)	eszopiclone (Lunesta)	zaleplon (Sonata)

Uses:

- Short-term treatment of insomnia
- Relative to benzos-less anxiolytic, anticonvulsant, muscle relaxant effects

Notes:

- Adverse effects drowsiness, dizziness, memory difficulties
- **2019 Black Box Warning**: rare but serious sleep behaviors, including **sleepwalking, sleep driving, and engaging in other activities while not fully awake**. These complex sleep behaviors have also resulted in **deaths**

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Antipsychotics (aka neuroleptics)

First-generation (older)
- Examples: haloperidol, chlorpromazine
- Blocks dopamine D2 receptor
- **Neurologic adverse effects**
  - **Akathisia, Parkinsonism, Acute dystonic reactions**
  - **Tardive dyskinesia**

Second-generation (newer)
- Examples: risperidone, aripiprazole, quetiapine
- Effects at D2 receptor but many others (serotonin, cholinergic, histaminergic effects)
- **Metabolic adverse effects:**
  - **Weight gain, glucose increase/diabetes, hyperlipidemia**

- Others: Cardiovascular effects, prolonged QT interval, orthostatic hypotension/falls, sedation, prolactin elevation, sexual dysfunction, seizures, neuroleptic malignant syndrome (NMS), anticholinergic effects, agranulocytosis, increased mortality (increased risk stroke, MI, death in older patients with dementia)

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Antipsychotics-strongly consider adverse effects

- Wide use in prescribing for numerous disorders, many off-label
- Significant adverse effect profile
- Concerns about overuse in prescribing practices
- APA Choosing Wisely campaign-potential inappropriate use, warns:
  - Do not prescribe without appropriate monitoring
  - Avoid prescribing 2 or more antipsychotics
  - Avoid using antipsychotics for insomnia
  - Not using antipsychotics first-line in children without a psychotic disorder

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Antipsychotics

Table 6
Antipsychotic appropriateness per indication

Appropriateness	Indication
Appropriate	• Schizophrenia/schizoaffective disorder • Hallucinations/delusions • Severe bipolar
Potentially appropriate	• Mild bipolar • Delirium
Potentially inappropriate	• Behavioral symptoms with dementia • Children or adolescents for any indication except psychotic disorders • Depression or anxiety
Inappropriate	• Insomnia • Posttraumatic stress syndrome • Intractable nausea and vomiting

Benich, Bragg, Freedy. Psychopharmacology in Primary Care Setting. Prim Care Clin Office Pract 2016

Table 7
Recommended neuroleptic monitoring tests

Test	Baseline	Weekly	Monthly	Every 3 mo	Every 6 mo	Annually
Personal and family history	x	—	—	—	—	x
Fasting glucose	x	—	—	x	—	x
Blood pressure	x	—	—	x	—	x
Fasting lipid profile	x	—	—	x	—	x
CBC	x	x[a]	x[a]	—	—	—
Liver and renal function	x	—	—	—	x	x
Thyroid[b]	x	—	—	—	x	x
Eye examination	x	—	—	—	—	x
Abnormal involuntary movement scale	x	x[c]	—	—	x	—

Abbreviation: CBC, complete blood count.
[a] Clozapine absolute neutrophil count (ANC)/white blood cell count weekly for 6 months, then every other week for 6 months, then monthly; monitor other agents weekly to monthly if having a low ANC.
[b] Only quetiapine.
[c] Weekly until on a stable dose for greater than 2 weeks.
Data from Lexicomp Online. Copyright © 1978-2015 Lexicomp, Inc. All Rights Reserved. Available at: http://www.wolterskluwercdi.com/lexicomp-online/.

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Clozapine

- Important treatment option for treatment-resistant schizophrenia, but well-established risk of life threatening agranulocytosis
- Requires careful monitoring with frequent blood draws and use of registry Clozapine REMS
- Other important adverse effects:
  - Metabolic, seizures, anticholinergic, life threating GI hypomotility, myocarditis, DVT/PE,
  - Unique: sialorrhea (excessive drooling)
- Metabolism through CYP1A2

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Pharmacotherapy for addictions

Naltrexone
Acamprosate
Disulfaram

Methadone*
Buprenorphine**

Varenicline, nicotine replacement therapy
bupropion

A Primary Care Approach to Substance Misuse

BRAD SHAPIRO, MD; DIANA COFFA, MD; and ELINORE F. McCANCE-KATZ, MD, PhD
University of California, San Francisco, School of Medicine, San Francisco, California

Substance misuse is common among patients in primary care settings. Although it has a substantial health impact, physicians report low levels of preparedness to identify and assist patients with substance use disorders. An effective approach to office-based treatment includes a coherent framework for identifying and managing substance use disorders and specific strategies to promote behavior change. Brief validated screening tools allow rapid and efficient identification of problematic drug use, including prescription medication misuse. After a positive screening, a brief assessment should be performed to stratify patients into three categories: hazardous use, substance abuse, or substance dependence. Patients with hazardous use benefit from brief counseling by a physician. For patients with substance abuse, brief counseling is also indicated, with the addition of more intensive ongoing follow-up and reevaluation. In patients with substance dependence, best practices include a combination of counseling, referral to specialty treatment, and pharmacotherapy (e.g., drug tapering, naltrexone, buprenorphine, methadone). Comorbid mental illness and intimate partner violence are common in patients with substance use disorders. The use of a motivational rather than a confrontational communication style during screening, counseling, and treatment is important to improve patient outcomes. (*Am Fam Physician.* 2013;88(2):113-121. Copyright © 2013 American Academy of Family Physicians.)

*Must be dispensed at a certified opioid treatment program (methadone clinic) as federal law prohibits prescribing it to treat opioid use disorder
**Requires 8 hours course to prescribe, federal law

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Cardiac medications/Drugs with adrenergic effects

Prazosin (alpha-1-antagonist)	**Clonidine** (alpha-2-agonist)	**Guanfacine** (alpha-2-agonist)	**Propranolol** (beta-blocker)
Uses: **PTSD-related nightmares and sleep disruption** Can start 1 mg qhs and titrate 1 mg every few days to every 1 week. Efficacy can take weeks Disadvantage: -hypotension, syncope	Uses: ADHD (extended release)* many off-label uses hyper-arousal states -PTSD -opioid withdrawal -ODD/Tics -insomnia/akathisia Disadvantages: -sedation -hypotension -rebound HTN -TID dosing	Uses: ADHD (extended release)* Off label uses similar to clonidine PDD-pediatrics Disadvantages: -sedation	Uses: -Akathisia -Tremor -Anxiety (performance) -Migraine prophylaxis -some patients with POTS (orthostatic intolerance) -**Some recent small studies for Autism Spectrum Disorder** Disadvantages: -must consider cardiac comorbidities, heart block, bronchospasm

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Ketamine

- Described as paradigm-shifting, revolutionary and breakthrough in psychopharmacology
- Common **dissociative anesthetic** in human/veterinary medicine (FDA approved 1970); abused "Special K"
- NMDA antagonist glutamate receptor
- Role in pain management
- Used in acute settings for behavioral dyscontrol
- Anesthetic doses: dissociative effects
- Sub-anesthetic ketamine IV doses: rapid acting antidepressant dosing
- Ketamine clinics
- Treatment for MDD (treatment resistant)
- March 2019: FDA approved intranasal esketamine (Spravato) for adults with treatment-resistant depression
  - Still requires monitoring for transient dissociative symptoms, tachycardia, HTN, etc

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Ketamine

Pros	Challenges
• Rapid alleviation of depression for some • May alleviate suicidal ideation • Novel treatment and future research • FDA approval intranasal form eskatmine	• Immediate side effects (dissociative) • Cost • Logistical (monitoring period, can't drive) • Long term efficacy and adverse effects? • Still need to be on standard/maintenance antidepressants

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Medical Cannabis

- Complex history and story
- **Younger patients-more risk of psychosis**
- Different states, different laws
- Effects on motivation, psychosis?
- Major knowledge gaps, need for further study
- Qualifying conditions in Minnesota→

- Thoughts/Experiences?

Qualifying Conditions:

- Cancer associated with severe/chronic pain, nausea or severe vomiting, or cachexia or severe wasting
- Glaucoma.
- HIV/AIDS
- Tourette Syndrome
- Amyotrophic Lateral Sclerosis (ALS)
- Seizures, including those characteristic of Epilepsy
- Severe and persistent muscle spasms, including those characteristic of Multiple Sclerosis.
- Inflammatory bowel disease, including Crohn's disease
- Terminal illness, with a probable life expectancy of less than one year*
- Intractable pain
- Post-Traumatic Stress Disorder
- Autism
- Obstructive Sleep Apnea

Patients can be certified beginning on July 1, 2019:

- Alzheimer's Disease

*To qualify for the program, you must suffer from cancer or a terminal illness

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Table 7
Mood stabilizers and FDA-approved indications in BD

Medication	AED	Antipsychotic	Maintenance	Mania	Depression
Aripiprazole (ABILIFY)		X	X	X	
Asenapine (SAPHRIS)		X		X	
Carbamazepine extended-release (Tegretol XR)	X			X	
Haloperidol (Haldol)		X		X	
Lamotrigine (Lamictal)	X		X		
Lithium			X	X	
Lurasidone (LATUDA)		X			X
Olanzapine (Zyprexa)		X	X	X	
Olanzapine-fluoxetine (Symbyax)		X			X
Paliperidone (INVEGA)		X		X	
Quetiapine (SEROQUEL)		X	Adjunctive	X	X
Risperidone (RISPERDAL)		X		X	
Valproate (Depakote)	X			X	
Ziprasidone (GEODON)		X		X	

Brenner, C. J. and S. I. Shyn (2014). "Diagnosis and management of bipolar disorder in primary care: a DSM-5 update." Med Clin North Am 98(5): 1025-1048.

Treatments and indications in Bipolar Disorder

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Table 8
Mood stabilizers and guidelines for dosing and monitoring

Medication	Dosing	Monitoring Guidelines	Side Effects	Additional Notes
Atypical antipsychotics		Monitoring guidelines for metabolic indices are nicely summarized in a review by Hasnain and colleagues[45]; some of these recommendations include obtaining baseline weight, waist circumference, blood pressure, fasting glucose, fasting lipids; repeat at 3 mo, then fasting glucose Q y & fasting lipids Q 5 y.	Sedation, orthostatic hypotension, extrapyramidal side effects, neuroleptic malignant syndrome, metabolic syndrome, hyperprolactinemia, sexual side effects	Recent literature suggests that some of the metabolic risks may be mitigated by concurrent use of metformin,[45,46] even without a diagnosis of diabetes, and this intervention has been incorporated into the American Psychiatric Association (APA) practice guidelines[3]
Aripiprazole (ABILIFY)	15–30 mg/d		Lower metabolic risks	Partial dopamine (D_2) agonist; available as soluble tablet & Q 4-wk depot injection
Asenapine (SAPHRIS)	5–10 mg SL BID		Lower metabolic risks	Must be absorbed sublingually; oral ingestion reduces absorption
Lurasidone (LATUDA)	20–120 mg/d		Lower metabolic risks	
Olanzapine (Zyprexa)	5–20 mg/d		Higher metabolic risks	Available as a soluble tablet & Q 4-wk depot injection
Olanzapine-fluoxetine (Symbyax)	6/25–18/75 mg/d		Higher metabolic risks	
Paliperidone (INVEGA)	6–12 mg/d		Moderate metabolic risks	Available as Q 4-wk depot injection
Quetiapine (SEROQUEL)	300–800 mg/d		Moderate metabolic risks	
Risperidone (RISPERDAL)	1–6 mg/d		Moderate metabolic risks	Available as soluble tablet & Q 2-wk depot injection

Brenner, C. J. and S. I. Shyn (2014). "Diagnosis and management of bipolar disorder in primary care: a DSM-5 update." Med Clin North Am 98(5): 1025-1048.

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Table II
(*continued*)

Medication	Dosing	Monitoring Guidelines	Side Effects	Additional Notes
Ziprasidone (GEODON)	40–80 mg BID		Lower metabolic risks; EKG at baseline and with dose adjustments if patient has preexisting cardiac issues (given possible QTc prolongation)	Administer with food to maximize absorption
Typical antipsychotics				
Haloperidol (Haldol)	0.5–10 mg/d	Check prolactin if clinically indicated	Sedation, extrapyramidal side effects, neuroleptic malignant syndrome, hyperprolactinemia	
Antiepileptic drugs				
Carbamazepine extended release (Tegretol XR)	200–1600 mg/d	Check for HLA-B1502 before starting in East Asian patients because of Stevens-Johnson syndrome risk;[58] adjust to target serum level of 4–12 μg/mL (more for limiting toxicity than for any correlation with therapeutic benefit[59]), including 1 mo after initiation because of auto-induction of CYP3A4	Agranulocytosis, Stevens-Johnson syndrome	Concurrent antipsychotics (as well as carbamazepine itself) may require dose increase after about 1 mo given CYP3A4 induction
Lamotrigine (Lamictal)	200 mg/d		Stevens-Johnson syndrome	Slow titration (ie, Q 2 wks for each step, starting with 25 mg orally Q morning) to minimize Stevens-Johnson syndrome risk; doses should be halved if there is concurrent valproic acid, which can cause a drug-drug interaction[60]; best to avoid if there is a concurrent estrogen-based oral contraceptive with variable dosing caused by drug-drug interaction

Brenner, C. J. and S. I. Shyn (2014). "Diagnosis and management of bipolar disorder in primary care: a DSM-5 update." Med Clin North Am 98(5): 1025-1048.

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Valproate (Depakote)	500–2500 mg/d	Adjust to target serum level of 50–120 μg/mL,[61] although the default convention of aiming for the higher end of this range (ie, levels >75 or 80) does not appear to have a clear correlation with greater therapeutic effect[62]	Alopecia, sedation, polycystic ovarian syndrome (young females), thrombocytopenia, transaminitis, tremor, weight gain	Typically prescribed in its divalproex formulation; may have superiority to lithium in mixed presentations[62] and in mania when there is an additional history of a substance use disorder;[24] caution with this agent is appropriate in women of reproductive age (given teratogenicity, eg, up to 5%–10% of first trimester exposures result in neural tube defects, and associations with polycystic ovarian syndrome)[63,64] and in patients with preexisting hepatic issues.
Other				
Lithium	900–1200 mg/d	Check baseline and then Q 6 mo TSH, Cr; adjust to target serum level of 0.6–1.2 mEq/L	Diabetes insipidus, diarrhea, nausea, hypothyroidism, polyuria, renal failure (chronic), sedation, thirst	Often favored among available options because of its broader spectrum of activity and low cost but does have a narrow therapeutic window and should generally be avoided in patients in whom the potential for renal impairment is prohibitive; avoid combining with NSAIDs (aspirin and sulindac safer)

Abbreviations: BID, twice a day; Cr, creatinine; CYP, cytochrome P450; EKG, electrocardiogram; HLA, human leukocyte antigen; NSAID, non-steroidal anti-inflammatory drug; Q, each/every; SL, sublingual; TSH, thyroid stimulating hormone.
Data from Refs.[59–62]

Brenner, C. J. and S. I. Shyn (2014). "Diagnosis and management of bipolar disorder in primary care: a DSM-5 update." Med Clin North Am 98(5): 1025-1048.

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Clinical approach to "Depression"

- Depression heterogeneous-multiple diagnosis
- For purposes of next several slides depression = unipolar depression/MDD
- Mild cases may not require antidepressant medications (role of psychology, social work, behavioral activation)
- STAR-D trial and newer studies
- Nearly all antidepressants have similar efficacy, so….
- For first trial, no clear front runner. **Match medication with patient preferences and other factors** (side effects, medical problems)

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Jim, age 35, has partly responded (65%) to an antidepressant but has residual insomnia and agitation. He does not have bipolar disorder, but has soft signs and a family history. You are looking for next steps augment, **which might be your best choice for next step**?

- A. Switch to antidepressant to mirtazapine
- B. Augment with bupropion
- C. Switch antidepressant to lithium
- D. Augment with atypical antipsychotic
- E. Check pharmacogenomic panel to rule out slow metabolizer phenotype

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Adherence to the Treatment (Medications)?

- Based on review of 13 studies, about 50% of patients discontinue antidepressant therapy prematurely.
  - Similar rates in primary and specialty settings.
- Choosing an antidepressant
  - For first trial, no clear front runner. Match medication with patient preferences.
    - Mayo shared decision aid
      - https://depressiondecisionaid.mayoclinic.org/index
    - Bostwick JM. A generalist's guide to treating patients with depression with an emphasis on using side effects to tailor antidepressant therapy. *Mayo Clinic Proc.* 2010;85:538-550

Sansone, R et al., Innov Clin Neurosci, 2012

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Partial Response: Are We Treating **the Right** Problem? Differential diagnosis for depression

- Psychiatric
  - Bereavement – feelings tied to loss
  - Bipolar disorder – rapid improvement, mania/hypomania
  - Attention deficit – concentration and irritability more than sadness or loss of interest
  - Many others
- Medical
  - Obstructive sleep apnea—fatigue, low energy predominates
  - Thyroid disease – weight changes, energy changes
  - Cancer – weight and energy changes, pain
  - Dementia—apathy, cognitive, personality, memory changes
- Substance or Medication-Induced Depression
  - Alcohol, Opioids, Sedatives
  - Corticosteroids (prednisone), beta-blockers, hormones, interferons

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Are We Treating More than One Related Problem?

- Among patients diagnosed with Major Depression
  - Anxiety (75% w features, 37% w diagnosis lifetime prev.)
  - Bipolar features (mixed features in 16%)
  - Personality Disorder (32% w diagnosis)
  - Substance abuse (58% w diagnosis)
- Insomnia/sleep apnea
- Pain, Thyroid disorder
- Social determinant – abuse, housing, finances, etc.
- Life circumstances; depression vs unhapiness

Hasin et al. Jama Psychiatry 2018

40

Treatment of depression

- Response – e.g. 50% reduction on the PHQ-9
- Remission – e.g. PHQ-9 score under 5 sustained for 2 months
- How long to wait for improvement?
  - SSRI – response at 2 weeks is predictive
    - Are you dosing correctly?
  - Do not expect further medication improvement after 8-12 weeks
    - Often making changes in 4-6 weeks

Acute Phase 6-12 weeks → Continuation Phase 4-9 months → Maintenance Phase 12 months and beyond

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Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

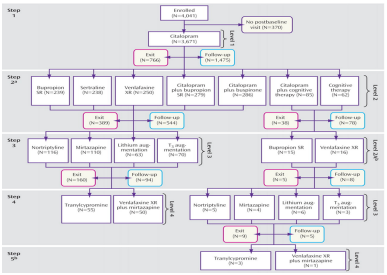
2006

Start with citalopram

Next CBT alone or change drugs/augment

Single drugs:
- Bupropion
- Sertraline
- Venlafaxine
- Nortriptyline
- Mirtazapine
- Tranylcypromine

Augmentation offered
- CBT
- Bupropion
- Buspirone
- Lithium
- T3
- Mirtazapine with venlafaxine



42

Augment/Combination or Switch?

- Adequate dose and duration of current treatment?
  - Antidepressants – 8-12 weeks at therapeutic dose
  - Psychotherapy – CBT 8-12 sessions for remission
    - Adherence to either or both?
- How much improvement?
  - At least 60% may suggest augmentation
  - Less may suggest a new approach
  - Treatment resistant – 2 failed trials of adequate dose/duration.
- Side effect burden/adherence/cost also involved in choice

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Augmentation/Combination

ADVANTAGES

- Novel mechanisms
- Treat residual symptoms
- No need to taper or washout first agent
- Treat comorbid disorders
- Avoid period of worsening while switching agents

DISADVANTAGES

- Increased potential for side effects
- Increased potential for drug interactions
- Increased cost
- Decreased compliance
- Potentially off-label use

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Augmentation/Combinations

- Antidepressant from a 2nd class
  - Bupropion, Mirtazapine, TCA, SSR
  - **OR**
- Add medication from non-antidepressant class
  - Lithium
  - Thyroid hormone (T3)
  - Atypical antipsychotic
  - Buspirone
  - Stimulants

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Canadian CANMET guidelines 2016

Can J Psychiatry. 2016 Sept; 61(9): 540-560.

Table 1.

Criteria for Level of Evidence and Line of Treatment.

Level of evidence[a]	Criteria
1	Meta-analysis with narrow confidence intervals and/or 2 or more RCTs with adequate sample size, preferably placebo controlled
2	Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size
3	Small-sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies
4	Expert opinion/consensus

Table 11.

Recommendations for Adjunctive Medications for Nonresponse or Partial Response to an Antidepressant.

Recommendation	Adjunctive Agent	Level of Evidence	Dosing
First line	Aripiprazole	Level 1	2-15 mg
	Quetiapine	Level 1	150-300 mg
	Risperidone	Level 1	1-3 mg
Second line	Brexpiprazole[a]	Level 1	1-3 mg
	Bupropion	Level 2	150-300 mg
	Lithium	Level 2	600-1200 mg (therapeutic serum levels)
	Mirtazapine/mianserin	Level 2	30-60 mg
	Modafinil	Level 2	100-400 mg
	Olanzapine	Level 1	2.5-10 mg
	Triiodothyronine	Level 2	25-50 mcg
Third line	Other antidepressants	Level 3	Various
	Other stimulants (methylphenidate, lisdexamfetamine, etc.)	Level 3	Various
	TCAs (e.g., desipramine)	Level 2	Various
	Ziprasidone	Level 3	20-80 mg bid
Experimental	Ketamine	Level 1	0.5 mg/kg, single intravenous dose[b]
Not recommended	Pindolol	Level 1 (lack of efficacy)	Not applicable

TCA, tricyclic antidepressant.

[a]Newly approved since the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.

[b]For acute treatment.

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Augmentation Aside From Medications

- **Bright Light Therapy** (5,000 lux for 30+ min)
  - Non-seasonal depression, Meta-analysis
    - Moderate effect size (0.5)
- **Psychotherapy**
  - CBT, ACT, IPT, DBT, etc.
    - May reduce risk of relapse
  - Behavioral Activation
- **Exercise**

Penders et al, Primary Care Companion, 2016

47

How to Choose?

- **Specific benefit**
  - Residual insomnia or anxiety
  - Sexual side effects/weight gain/fatigue
  - Soft bipolar signs
  - Personality traits/coping style/life events impacting mood
- **Avoiding side effect or problem**
  - Weight issues/metabolic syndrome/QTc prolongation
  - Cost/access
  - Parkinsonian side effects
  - Contraindications to lithium

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Depression Seems More Complicated Than I Thought….

- **System based suggestions**
  - Use decision support, access to psychiatry is poor
- **Consider a Care Coordination program in Primary care**
  - Doubled improvement rates in initial RCT trial
  - Involves care coordinator and psychiatry reviewing cases weekly and providing input to PCP
  - Currently billing codes available (CoCM) Medicare
    - Private insurances are covering in many areas
  - Collaborative model has over 90 RCTs supporting positive results (Archer J et al 2012 Cochrane review)

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Jim, age 35, has partly responded (65%) to an antidepressant but has residual insomnia and agitation. He does not have bipolar disorder, but has soft signs and a family history. You are looking for next steps augment, **which might be your best choice for next step**?

- A. Switch antidepressant to mirtazapine
- B. Augment with bupropion
- C. Switch antidepressant to lithium
- **D. Augment with atypical antipsychotic**
- E. Check pharmacogenomic panel to rule out slow metabolizer phenotype

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Pearls!
Augmentation in Treatment Resistant Depression

- Depression can be difficult to get into remission
  - About 1/3 of patients in first trial, 2/3rds after 4 trials
  - Need to follow up to see what really happened
- Augmentation when a response is 60% or greater
  - Match augmentation to patient
  - Medications, psychotherapy, exercise all can help
  - If collaborative care is an option for your clinic, consider advocating for this option to achieve better access to psychiatry and better outcomes for your patients

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Newer treatment options: Antidepressants approved in past decade (Newer usually means more cost, but usually *not* more efficacious)

- Desvenlafaxine (SNRI)
- Levomilnacipran (SNRI)
- Vilazodone (SPARI)
- Vortioxetine (Serotonin modulator)

- Aripiprazole (atypical antipsychotic)
- Brexpiprazole (atypical antipsychotic)

- Esketamine (nasal spray; still requires oral antidepressant; cost)

- L-methylfolate ("medical food")

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Table Comparison of Newer Antidepressant Drugs

Drug	Mechanism of Action	Dosing	Notable Adverse Effects	Other Considerations	Cost for 30-day Supply (Dose)[a]
Monotherapy					
Desvenlafaxine	SNRI	Start at 50 mg/d Can increase, although additional benefit of dosages >50 mg is limited For moderate-severe hepatic impairment: maximum dosage is 100 mg/d For CKD stage 4 or greater: maximum dosage is 50 mg/d	Nausea, insomnia, dizziness, dry mouth, and decreased appetite Must monitor periodically for increased blood pressure	Improves menopausal hot flashes No benefit for neuropathic pain	$150 (50 mg)
Levomilnacipran	SNRI	Start at 20 mg/d for 2 days, then increase to 40 mg/d Titrate every 2+ days based on response to maximum dosage of 120 mg/d	Headache, nausea/vomiting, hyperhidrosis, constipation, tachycardia, urinary hesitancy, erectile dysfunction, ejaculatory disorders May cause small increase in blood pressure (3-4 mm Hg) and triaminicous	Consider with concomitant fibromyalgia Good for patients with negative symptoms of depression Weight neutral No QT prolongation	$340 (40 mg)
Vilazodone	SPARI	Start at 10 mg/d and double every 7 days to 40 mg/d Limit dosage to 20 mg/d if used in combination with strong CYP3A4 inhibitors Has not been studied for use with severe renal or hepatic dysfunction	GI symptoms, insomnia, headache, dizziness, dry mouth	Additional benefit for anxiety May have faster onset of antidepressant effect Less sexual dysfunction Weight neutral	$220 (40 mg)
Vortioxetine	SSRI	Start at 10 mg/d Can increase to 20 mg/d if needed Do not exceed 10 mg/d for CYP2D6 poor metabolizers	GI symptoms, headache, dizziness	No increase in blood pressure, heart rate, QT interval. Limited benefit for anxiety	$330 (10 mg)
Adjunctive therapy					
Aripiprazole	Second-generation antipsychotic	Start at 2-5 mg/d Titrate every 7+ days based on response to maximum dosage of 15 mg/d	Headache, extrapyramidal symptoms, akathisia, sedation, insomnia, weight gain, metabolic syndrome, anticholinergic effects, tremor	Not for use as monotherapy	$75 (5 mg)
Brexpiprazole	Second-generation antipsychotic	Start at 0.5-1 mg/d Titrate every 7+ days based on response to maximum dosage of 3 mg/d	Akathisia, metabolic syndrome, weight gain, headache, extrapyramidal symptoms, dizziness	Not for use as monotherapy	$984 (2 mg)
L-Methylfolate	Medical food	15 mg/d	No substantial known adverse effects	Not for use as monotherapy	$143 (15 mg)

CKD = chronic kidney disease; GI = gastrointestinal; SNRI = serotonin-norepinephrine reuptake inhibitor; SPARI = serotonin partial agonist-reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Byun, T. H., et al. (2019). "New Treatment Options for Depression: A Primer for Internists." Am J Med 132(6): 678-684

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Navigating competing concepts of drugs and antidepressants

- Often vastly different meaning for provider, patient.
  - Yours-basic sciences, pharmacology, RCTs, familiarity, relatively safe, routine
  - vs
  - Patient-Big pharma, historical distrust, chemical, mind-altering, zombie, addictive, dangerous, scary, indicative of weakness, message boards, overestimate of risk

- How might you phrase this?

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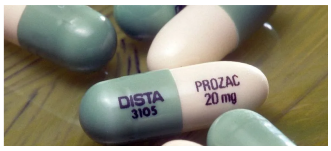
NEWS IN BRIEF

Antidepressant Can't Believe It's Expected To Fix This Mess All On Its Own

10/29/14 12:39pm • SEE MORE: SCIENCE & TECHNOLOGY



SEATTLE— Stunned and dismayed that it will have no assistance in treating the serious mood disorder, the antidepressant Prozac cannot believe that it is being asked to fix this mess entirely on its own, sources said Wednesday. "I'm seriously supposed to go in there and turn around years of hopelessness without any backup whatsoever," said the exasperated twice-daily 10-milligram SSRI, adding it simply could not believe it would have no support from moderate exercise, a healthy diet, or a dedicated psychotherapy program. "The plan is for me, all by myself, to do this without any aid from mature coping skills or a support system of loved ones—is this what you're telling me? Oh, and let me guess, I'm not gonna get an assist from a reasonable sleep schedule either." At press time, the drug was getting more help than it needed from alcohol.

theonion.com. 10/29/14

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Case:

- 25-year-old male with bipolar disorder presents to primary care. Patient has reduced sleep, increased energy and mood, is working 70 + hours per week and is more distractible. He went off his lithium a few months ago and refuses to restart it due to emotional blunting. He is not psychotic or suicidal. He does not want to be admitted to the hospital. He is generally healthy. He only substance use is 2-4 beers per week.
- How do you proceed?
  - A) Restart lithium
  - B) Add atypical antipsychotic such as olanzapine
  - C) Check TSH
  - D) Trazodone

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Stabilize the manic patient until further follow-up can be arranged.

- 25-year-old male with established diagnosed of bipolar disorder presents to primary care. Patient has reduced sleep, increased energy and mood, is working 70 + hours per week and is more distractible. He went off his lithium a few months ago and refuses to restart it due to emotional blunting. He is not psychotic or suicidal. He does not want to be admitted to the hospital. He is generally healthy. He only substance use is 2-4 beers per week.
- How do you proceed?
  - A) Restart lithium
  - **B) Add atypical antipsychotic such as olanzapine**
  - C) Check TSH
  - D) Trazodone
- **Also:**
  - **Arrange close follow-up and/or psychiatric follow-up**
  - **Baseline metabolic status (weight, labs for glucose metabolism and lipids)**
  - **Non-pharmacologic options: care coordination, psychotherapy follow-up**

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Pharmacologic management of Bipolar is complicated

- Different treatment states (acute mania, depression, mixed, maintenance)
- Drugs with more side effects, more monitoring required (previous slides)
- Controversies and complicated treatment algorithms
- Consider developing strategy for acute stabilization:
  - Triage: outpatient vs ED
  - Rule-outs: non-adherence, substance or alcohol abuse
  - Mania: Consider atypical antipsychotic +- mood stabilizer.
  - Bipolar depression: FDA-approved treatments: Lurasidone, quetiapine, olanzpaine-fluoxetine. Many other non-FDA-approved approaches.
- The challenge of treating the bipolar depressed patient and not making them worse

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Case:

- 35-year-old man with schizophrenia that was difficult to control
- Has found good control of positive symptoms on risperidone 4 mg/day.
- Sedentary lifestyle and does not socialize or work
- His labs return with Hemoglobin A1C of 9.5% and abnormal lipid panel.

- Next steps?
  - A) Change risperidone to olanzapine for better metabolic profile
  - B) Continue risperidone and manage metabolic conditions
  - C) Immediate taper off risperidone and observe
  - D) Letter for emotional support animal

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Case: **Manage patient with schizophrenia with metabolic adverse effects**

- 35-year-old man with schizophrenia that was difficult to control
- Has found good control of positive symptoms on risperidone 4 mg/day.
- Sedentary lifestyle and does not socialize or work
- His labs return with Hemoglobin A1C of 9.5% and abnormal lipid panel.

- Next steps?
  - A) Change risperidone to olanzapine for better metabolic profile
  - **B) Continue risperidone and manage metabolic conditions**
  - C) Immediate taper off risperidone and observe
  - D) Letter for emotional support animal

- **Patient was continued on risperidone (benefit felt to > risk).**
- **Metformin and a statin were added to his regimen.**
- **Sleep apnea was also diagnosed and patient started on CPAP.**
- **Ongoing efforts toward behavioral activation, dietary education, psychosocial programs.**

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Schizophrenia

- Typically life-long antipsychotic treatment needed
- Adherence challenges extremely common, often need to consider long-acting injectable medications
- **Mortality gap of 20-25 years for schizophrenia** and related conditions
- High rate of cardiovascular disease, tobacco use
- Antipsychotics, especially atypical antipsychotics, associated with **weight gain, diabetes, dyslipidemia, metabolic syndrome**
  - **Lower risk**: lurasidone, ziprasidone, aripiprazole
  - **Higher risk:** quetiapine, risperidone, olanzapine, clozapine

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Case

- 45-year-old male with alcohol use disorder and depression.
- Sober 2 month but having intense cravings.
- Attends AA and outpatient CD
- Early onset drinking and positive family history. BMP normal.

PCP asks, if it is safe to start a mediation for his alcohol use disorder, "I've never started any of these medications." Psychiatrist suggested:

- A) naltrexone
- B) disulfiram
- C) gabapentin
- D) PCP should NOT be prescribing medications for alcohol use disorder

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Case: psychopharmacology for alcohol use disorder in the appropriate clinical setting.

- 45-year-old male with alcohol use disorder and depression.
- Sober 2 month but having intense cravings.
- Attends AA and outpatient CD
- Early onset drinking and positive family history. BMP normal.

PCP asks, if it is safe to start a mediation for his alcohol use disorder, "I've never started any of these medications." Psychiatrist suggested:

- **A) naltrexone**
- B) disulfiram
- C) gabapentin
- D) PCP should NOT be prescribing medications for alcohol use disorder

63

Case

- Social worker (LCISW) sees 28 y/o woman with borderline personality disorder with past overdoses and hospitalizations for brief urgent triage requested by PCP for suicidal ideation and anxiety and nausea.
- Patient has a psychiatrist at a different practice.
- Complex medication list of 12 different medications including oxycodone.
- Outside provider recently added back clonazepam for anxiety and patient would like more clonazepam.
- **Recommendations?**
  - A) Taper off clonazepam
  - B) Add lorazepam for nausea
  - C) Add buspirone for anxiety
  - D) Keep current medications but add DBT

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Case: **Recognize and manage polypharmacy in borderline personality disorder**

- Social worker (LCISW) sees 28 y/o woman with borderline personality disorder with past overdoses and hospitalizations for brief urgent triage requested by PCP for suicidal ideation and anxiety and nausea.
- Patient has a psychiatrist at a different practice.
- Complex medication list of 12 different medications including oxycodone.
- Outside provider recently added back clonazepam for anxiety and patient would like more clonazepam.
- **Recommendations?**
  - **A) Taper off clonazepam**
  - B) Add lorazepam for nausea
  - C) Add buspirone for anxiety
  - D) Keep current medications but add DBT

- **Known risk of overdose, respiratory depression with combined benzodiazepines + opioids**
- **Collaboration among integrated team (SW curbsides psychiatrist, then recs to PCP)**
- **Check prescription monitoring systems/outside records to see what else patient prescribed**

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Treating the anxious patient without using benzodiazepines

Challenges:

- Convincing patient that "antidepressants" are indicated/often first-line for their anxiety
- Benzos have often been extremely effective for patient in past
- Time for efficacy (weeks) for antidepressants
- They are often already on benzos

Suggestions:

- Have several non-benzo options in prescriber tool box (next slide)
- If on benzos, taper slowly (weeks to months), anticipate anxiety, "I'm not ready" and "After I get through this next stressor" and "I can't do this."
- Non-pharmacologic approaches (next slide)
- Some situations might warrant sensible, careful prescribing of short-term benzo

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Non-benzodiazepine treatments for anxiety

Pharmacologic	Nonpharmacologic
SSRIs/SNRIs	Cognitive-behavioral therapy
Buspirone	Acceptance and commitment therapy
Atypical antipsychotics[a]	Dialectical behavioral therapy
Mirtazapine[a]	Psychodynamic psychotherapy
TCAs	Interpersonal psychotherapy
MAOIs	Progressive muscle relaxation
Gabapentin/pregabalin[a]	Deep breathing exercises
Antihistamines (diphenhydramine,[a] hydroxyzine)	Mindfulness and meditation
Propranolol[a]	Diet
Anticonvulsants (lamotrigine, topiramate)[a]	Exercise

[a]Off-label use

MAOIs: monamine oxidase inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Weber, Samuel R., and Anne-Marie Duchemin. "BENZODIAZEPINES: Sensible prescribing in light of the risks: Understand the risks and consider alternative treatments, especially in high-risk patients." *Current Psychiatry*, vol. 17, no. 2, 2018, p. 22+. *Gale OneFile: Health and Medicine*, Accessed 5 Oct. 2019.

67

Antidepressant management after Roux-en-Y Gastric Bypass Surgery

Challenges:

- Reduced absorption of antidepressant medications
- Psychosocial stressors of surgery and major life/dietary changes
- Limited clinical guidelines to direct management
- Increased rates of alcohol abuse after surgery
- Potential mal-absorption of vitamins

Suggestions:

- Try to avoid extended release formulations
- Screen for alcohol abuse
- Rule out vitamin/mineral deficiencies (ex: Vitamin B12)
- In some situations, could consider pre-surgical antidepressant levels
- TCAs often have more defined therapeutic serum levels for depression, but can cause weight gain

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Medication-sensitive, anxious patient

- Prone to adverse effects even at low doses
- Anxious about serious but rare adverse effects

Challenges:

- Unable to tolerate at dose/duration for adequate trial

Suggestions:

- Reassurance and encouragement
- Car analogy
- Low and slow
- Consider liquid formulations for ultra low dosing
- Consider p450 genetic testing
- Psychotherapy to challenge beliefs

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Patient requesting "genetic testing" to find out which medication will work

Challenges:

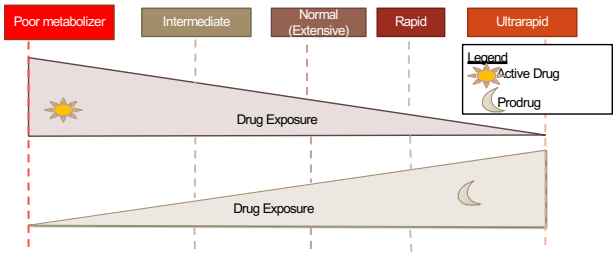
- Pharmacogenomic (cytochrome P450 testing) genetic testing is available and provides phenotypes, metabolizer status; but the story is much more complex

Suggestions:

- Educate and correct patient misconceptions: - test will not tell us which meds will "work"
- Clinical judgement outweighs lab result
- Discuss limited evidence testing translates to better outcomes for patients
- Consider in right clinical setting
- Have a plan for psychiatry or pharmacy review to help patient/PCP interpret results
- What might most likely change management? poor or ultra-rapid metabolizers at CYP2D6 or 2C19
- Guidance: PDR website (pdr.net) and FDA.gov has some information

70

Metabolizer status & drug exposure

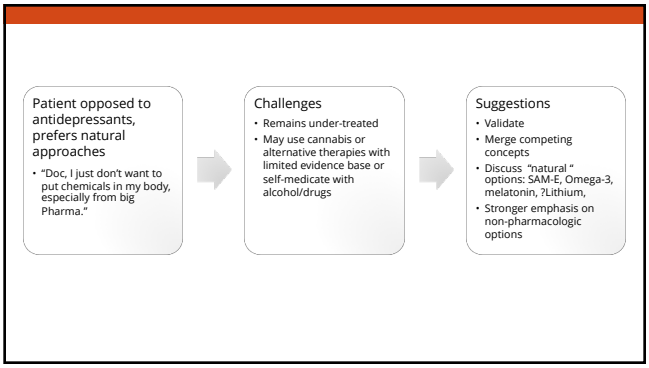


71

Helpful websites for pharmacogenomics

- https://www.pharmgkb.org/
- https://drug-interactions.medicine.iu.edu/MainTable.aspx

72


Patient opposed to antidepressants, prefers natural approaches
• "Doc, I just don't want to put chemicals in my body, especially from big Pharma."
Challenges
• Remains under-treated
• May use cannabis or alternative therapies with limited evidence base or self-medicate with alcohol/drugs
Suggestions
• Validate
• Merge competing concepts
• Discuss "natural" options: SAM-E, Omega-3, melatonin, ?Lithium,
• Stronger emphasis on non-pharmacologic options

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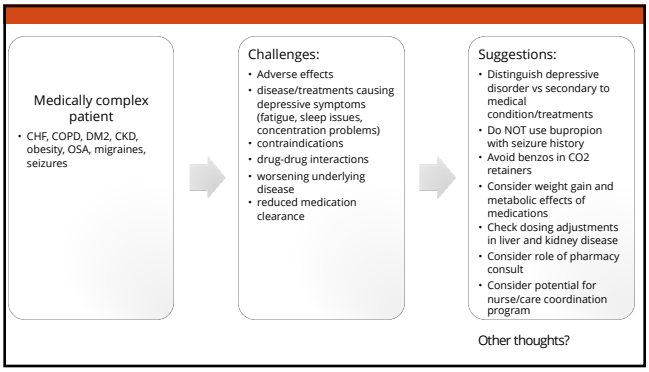
Medically complex patient
• CHF, COPD, DM2, CKD, obesity, OSA, migraines, seizures
Challenges:
• Adverse effects
• disease/treatments causing depressive symptoms (fatigue, sleep issues, concentration problems)
• contraindications
• drug-drug interactions
• worsening underlying disease
• reduced medication clearance
Suggestions:
• Distinguish depressive disorder vs secondary to medical condition/treatments
• Do NOT use bupropion with seizure history
• Avoid benzos in CO2 retainers
• Consider weight gain and metabolic effects of medications
• Check dosing adjustments in liver and kidney disease
• Consider role of pharmacy consult
• Consider potential for nurse/care coordination program
Other thoughts?

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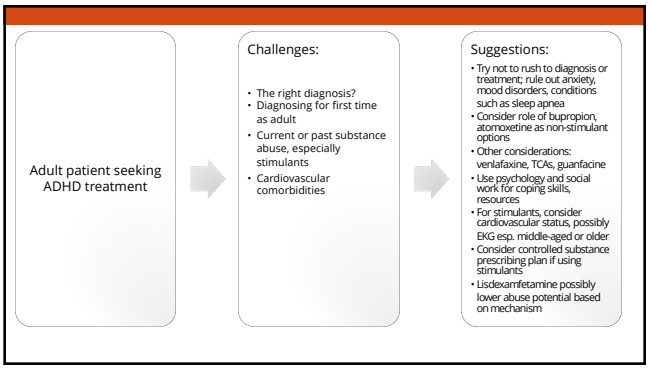
Adult patient seeking ADHD treatment
Challenges:
• The right diagnosis?
• Diagnosing for first time as adult
• Current or past substance abuse, especially stimulants
• Cardiovascular comorbidities
Suggestions:
• Try not to rush to diagnosis or treatment; rule out anxiety, mood disorders, conditions such as sleep apnea
• Consider role of bupropion, atomoxetine as non-stimulant options
• Other considerations: venlafaxine, TCAs, guanfacine
• Use psychology and social work for coping skills, resources
• For stimulants, consider cardiovascular status, possibly EKG esp. middle-aged or older
• Consider controlled substance prescribing plan if using stimulants
• Lisdexamfetamine possibly lower abuse potential based on mechanism

75

Psychopharmacology in the geriatric patient

Challenges:
- Possibly more stigma, more somatic presentations
- Ruling out delirium, dementia, and other medical problems
- Pharmacokinetic changes with aging

Suggestions:
- Start low, go slow…but still ensure adequate trial
- Provide written summary/patient instructions
- Consider 3 D's (dementia, delirium, depression) and medical problems
- Often already on sedating/inappropriate meds for elderly (Beers Criteria/List)
- Avoid/caution w/ benzos-risk cognitive impairments, falls, delirium, fractures
- Hyponatremia with ADs
- Black box warning antipsychotics
- Mirtazapine often considered for sleep, appetite promoting effects
- Do not forget to consider ECT for severe depression, psychosis, suicidality, malnutrition

CLINICAL INVESTIGATIONS

American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults

*By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel**

https://onlinelibrary.wiley.com/doi/full/10.1111/jgs.15767

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Psychotropic medication use during pregnancy

Example: depressed/anxious but failed 2 or 3 SSRIs including sertraline, can she safely take an SNRI such as venlafaxine?

Challenges:
- Psychopharmacology risks/benefits in the pregnant woman
- Limited data on most medications
- Perception of risk of medication vs untreated psychiatric disorder

Suggestions:
- Beyond scope of this talk, but…
- Must consider risk of untreated psychiatric disorder
- Some medication are clearly contra-indicated (valproate, carbamazepine)
- Many medications can be considered pending careful risk-benefit discussion
- Sertraline often recommended as one of most studied
- Re-consider role of psychotherapy
- Use perinatal resources

Resources:

Mental Health Task Force (Harvard):
https://www.mhtf.org/topics/perinatal-mental-health/

American College of Obstetricians and Gynecologists (ACOG):
https://www.acog.org/Womens-Health/Depression-and-Postpartum-Depression?IsMobileSet=false

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Patient seeking or already taking medical marijuana

Challenges:
- Many unknowns/lack of research
- Access/Cost/Availability
- Different states with different qualifying medical conditions
- Worsening of psychosis, low motivational states
- Effects on psych drugs , effects on P450 system?

Considerations:
- We struggle with this question, we still have a lot to learn
- Consider
  - Well-established adverse effects
  - Limited evidence benefit in psych disorders
  - But, many remain treatment resistant, suffering despite our current best treatments
- Recent review on topic below

Clinical Psychology Review

Review

Medical cannabis and mental health: A guided systematic review

Zach Walsh*, Raul Gonzalez*, Kim Crosby*, Michelle S. Thiessen*, Chris Carroll*, Marcel O. Bonn-Miller*

Lowe, D. J. E., et al. (2019). "Cannabis and mental illness: a review." Eur Arch Psychiatry Clin Neurosci **269**(1): 107-120.

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How do I switch from one antidepressant to another?

Challenges:

- Avoiding withdrawal, discontinuation side effects
- While not confusing patient
- While avoiding serotonin overload, serotonin syndrome
- Getting patient on therapeutic dose, response

Considerations:

- Many "common sense" aspects
- Know **fluoxetine**-long half-life
- Know **venlafaxine**-discontinuation symptoms common and symptomatically very bothersome
- Use a antidepressant change/cross-taper tool, example next page

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General strategies for switching antidepressants

A) ***Direct switch:*** stop the first antidepressant abruptly and start new antidepressant the next day. This is recommended only when patient is on a low dose of an antidepressant.
B) ***Taper & switch immediately:*** gradually taper the first antidepressant, and then start the new antidepressant immediately after discontinuation.
C) ***Taper & switch after a washout:*** gradually withdraw the first antidepressant, and then start the new antidepressant after a washout period.
D) ***Cross-tapering:*** taper the first antidepressant (usually over 1-2 week or longer), and build up the dose of the new antidepressant simultaneously.

Note: The table below is meant to provide a general guideline for discontinuation of SSRIs and SNRIs.

Switch From	To	SSRI (except Fluoxetine)	Fluoxetine	SNRIs
SSRI (except Fluoxetine)	→	Taper and switch immediately	Taper and switch immediately	Taper and switch immediately
Fluoxetine	→	Stop and switch after washout (4-7 days)		Stop and switch after washout (4-7 days) then start new SNRI at low dose and increase slowly
SNRIs	→	Cross taper with low dose SSRI	Cross taper with low dose Fluoxetine	Taper then switch immediately

Mayo pharmacy committee

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Young adult patient with Autism presents with multiple symptoms (depression, inattention, anxiety, anger) for medication management.

Any FDA-approved treatment options for Autism?

Challenges:

- Prescribers often feel poorly equipped, trained to mange patients with ASD including medications
- Diagnostic clarity
- Lack of well-defined pharmacotherapy approaches
- What is the target? cognitive, behavioral, social, mood/anxiety

Considerations:

- Define the target symptoms or behavior
- Involve the entire health team for behavioral/social ideas/resources
- Diverse medication classes being studied, many in child-adolescent patients, most off-label
- Only FDA-approved are risperidone and aripiprazole (for irritability aspects of ASD)
- One recent review article below

Pharmacological Therapies for Autism Spectrum Disorder: A Review

Sheena LeClerc, PharmD; and Deidra Easley, PharmD, BCPS

LeClerc, S. and D. Easley (2015). "Pharmacological therapies for autism spectrum disorder: a review." P T **40**(6): 389-397

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Approach to Common Antidepressant Adverse Effects

first, consider general approaches for adverse effects: dose reduction, drug holiday, different medication, therapy still indicated? and non-pharmacologic strategies

Sexual dysfunction
- Consider switch to bupropion, mirtazapine, vortioxetine
- Consider add-on with: bupropion, PDE-5 inhibitor (sildenafil), buspirone, stimulant
- Ask about sexual dysfunction *before* starting/changing antidepressants

Weight gain:
- Consider fluoxetine as weight neutral or bupropion-some weight loss
- Avoid mirtazapine, TCAs given association with weight gain

Excessive sweating
- Add mirtazapine?
- Limited evidence: benztropine, cyproheptadine, glycopyrolate, terazosin

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Approach, considerations, next steps?

Non-verbal 30 year-old patient with autism on Haloperidol and several others psychotropic medications presents with increase in anxiety and self-injury.
- Thoughts?

Patient with schizoaffective disorder on stable medications wants to quit smoking with varencilcine, but her PCP would not start varencilcine.
- Thoughts?

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Rethinking varenicline and neuropsychiatric adverse effects in patient with psychiatric disorders

Varenicline for smoking cessation: a narrative review of efficacy, adverse effects, use in at-risk populations, and adherence

Burke, M. V., et al. (2016). "Varenicline for smoking cessation: a narrative review of efficacy, adverse effects, use in at-risk populations, and adherence." Patient Prefer Adherence **10**: 435-447.

Davies, N. M. and K. H. Thomas (2017). "The Food and Drug Administration and varenicline: should risk communication be improved?" Addiction **112**(4): 555-558.

Varenicline can be an effective pharmacologic option for smoking cessation. Previous boxed warning for neuropsychiatric effects. Important to offer, consider treatment approaches, risks/benefits for tobacco cessation, especially in populations with increased cardiovascular and mortality risk.

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Serious drug-drug interactions, toxicities, and syndromes
What is the concern with the following?

- Clozapine and CYP1A2?
- TCAs?
- Lamotrigine and valproic acid?
- Serotonin syndrome?
- Neuroleptic malignant syndrome?
- SSRIs and hydrochlorothiazide?
- Clozapine and 3 ways adverse effects could be lethal?
- Lithium and these three common classes of medications?
- Starting sildenafil for SSRI-related sexual side effects, must ask about?
- Benzodiazepines and opioids?

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Role of ECT/TMS in Depression

- ECT
  - More effective
  - Requires anesthesia (if outpatient, patient can't drive themselves)
  - Memory side effects
  - Stigma-requires education
- TMS
  - Less effective
  - No anesthesia (patient theoretically could get over their lunch hour)
  - No memory side effects
  - Seizure is possible side effect and also contraindication
  - Less known-requires education

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Looking forward

TABLE 1
Example substances tested in humans with novel antidepressant mechanisms across three major pharmacological classes

Compound	Pharmacodynamic mechanisms	Outcome parameter	Phase	N	Dosage	Placebo control	Results	Rapid-acting[a]	Refs
Glutamatergic modulators									
Ketamine	NMDA antagonist, μ- and κ-opioid agonist, D_2 agonist, mAch antagonist, weak SERT, DAT, NET reuptake inhibition, 5-HT2 affinity	HAM-D	IV	99	0.1, 0.2, 0.5 and 1.0 mg/kg	Midazolam 0.045 mg/kg	+	Y	[65]
Nitrous oxide	NMDA antagonist	HAM-D	II	40	50% N_2O/50% O_2 for 1 h	50% N/50% O_2	+	Y	[69]
Sarcosine	Glycine transporter-I inhibitor	HAM-D	II	40	500 mg to 1500 mg	Citalopram 20 mg	+	N	[70]
GABAergic modulators									
Brexanolone (SAGE-547)	GABA$_A$ PAM, nAch, and 5-HT$_3$ NAM	HAM-D	II	21	30–90 μg/kg/h	Yes	+	Y	[77]
SAGE-217	agonist at mPR	HAM-D	III	89	30 mg	Yes	+	Y	NCT03864614 [78]
Opioids									
ALKS 5461	Combination of a μ- and κ-opioid partial agonist and μ-opioid antagonist	MADRS	III	790	High-dose or low-dose (sublingual)	Yes	+	N	[85]
Buprenorphine	μ-receptor partial agonist, κ-opioid, δ-opioid antagonist	MADRS	III	13	0.2 mg to 1.6 mg (sublingual)	No	+	N	[82]
Serotonergic hallucinogens									
Psilocybin	5-HT$_{2A}$, 5-HT$_{1A}$, 5-HT$_{2C}$ agonist	QIDS	II	12	10 mg and 25 mg	No	+	Y	[90]
DMT	5-HT$_{2A}$, 5-HT$_{1A}$, 5-HT$_{2C}$ agonist	HAM-D	II	35		Yes	Ongoing	N/A	NCT03219359
LSD	5-HT$_{2A}$, 5-HT$_{1A}$, 5-HT$_{2C}$ agonist	BDI	II	80	100 or 200 μg	25 μg LSD	Ongoing	N/A	NCT03866252

Abbreviations: 5-HT$_{1A}$, serotonin 1A receptor; 5-HT$_{2A}$, serotonin 2A receptor; 5-HT$_{2C}$, serotonin 2C receptor; 5-HT$_{3A}$, serotonin 3A receptor; D_1, delta; D_2, dopamine receptor 2; DAT, dopamine transporter; DMT, N-dimethyltryptamine; GABA, gamma aminobutyric acid; HAM-D, Hamilton Depression Rating Scale; IDS, Inventory of Depressive Symptomatology; κ, kappa; LSD, lysergic acid diethylamide; μ, mu; mAch, muscarinic acetylcholine; MADRS, Montgomery-Asberg Depression Rating Scale; mPR, membrane progesterone receptor; mg, milligrams; μg, micrograms; NAM, negative allosteric modulator; NET, norepinephrine transporter; nAch, nicotinic acetylcholine receptor; NMDA, N-methyl-D-aspartate; PAM, positive allosteric modulator; QIDS, Quick Inventory of Depressive Symptomatology; SERT, serotonin transporter.
[a]Rapid-acting was defined as response (>50% baseline scores) within 1 week of treatment.

Kraus, C., et al. (2019). "The influence of ketamine on drug discovery in depression." Drug Discov Today

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Beyond serotonin, norepinephrine, dopamine:
SAGE-217: oral, synthetic neurosteroid and modulator of GABA$_A$ receptors

ORIGINAL ARTICLE

Trial of SAGE-217 in Patients with Major Depressive Disorder

Handan Gunduz-Bruce, M.D., Christopher Silber, M.D., Inder Kaul, M.D., Anthony J. Rothschild, M.D., Robert Riesenberg, M.D., Abdul J. Sankoh, Ph.D., Haihong Li, Ph.D., Robert Lasser, M.D., Charles F. Zorumski, M.D., David R. Rubinow, M.D., Steven M. Paul, M.D., Jeffrey Jonas, M.D., et al.

N Engl J Med 2019; 381:903-911
DOI: 10.1056/NEJMoa1815981
Sept 5, 2019

Improved depressive symptoms at day 15
RCT, phase II study
Favorable side effect profile
Oral agent
Faster acting than standard antidepressants

Exciting finding, but further study ahead; excluded treatment resistant depression; history suicide attempts

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The role of collaborative/integrated behavioral health team in psychopharmacology

Psychologist:
- Help the patient understand realistic beliefs about medications, balance pharmacologic and non-pharmacologic approaches
- Often feeds back to prescriber if patient not doing well
- Often has good sense when a medication change would be helpful
- In some states-they are the presciber, too!

RN Care Coordinator
- Extremely important role in education on medications side effects, importance of adherence, time to efficacy
- Frequent or weekly meetings with psychiatrist, much of discussion is medication related
- Conveying medication recommendations back to PCP
- They know a lot of pharmacology-they usually have a favorite antidepressant!

Social Worker (Therapist)
- Similar to psychology, often picks up on patients not taking medication or relays patients concerns
- Helps with social/cost barriers to medications,
- Also, can pick up patients not satisfied with PCP or when psychiatric curbside or formal consultation may be helpful
- Examples from clinic

Examples from out practice... **Examples from your practice?**

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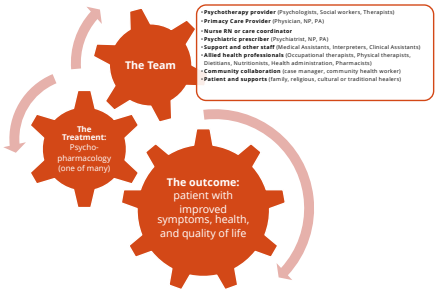
The role of collaborative/integrated behavioral health team in psychopharmacology

Examples from out practice... **Examples from your practice?**



- **Psychotherapy provider** (Psychologists, Social workers, Therapists)
- **Primacy Care Provider** (Physician, NP, PA)
- **Nurse RN or care coordinator**
- **Psychiatric prescriber** (Psychiatrist, NP, PA)
- **Support and other staff** (Medical Assistants, Interpreters, Clinical Assistants)
- **Allied health professionals** (Occupational therapists, Physical therapists, Dietitians, Nutritionists, Health administration, Pharmacists)
- **Community collaboration** (case manager, community health worker)
- **Patient and supports** (family, religious, cultural or traditional healers)

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Psychopharmacology at our integrated behavioral health practice in Rochester

Gone well	Ongoing challenges
• Discuss tough cases with colleagues • Monthly prescriber meetings • Weekly huddle meetings with entire behavioral health team • Weekly Acute Care Clinic with MD and social worker • Pharmacist availability	• Usual limitations/access challenges • Currently no care coordination (DIAMOND) programs other than for unipolar depression • Population health, reaching all struggling patients • Standardizing and following monitoring guidelines especially antipsychotics

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Resources

ICSI (Institute for Clinical Systems Improvement), Depression, Adult in primary care depression	https://www.icsi.org/guideline/depression/
APA (American Psychiatric Association) Practice Guidelines	https://psychiatryonline.org/guidelines
Black Dog Institute (Australian website with patient and provider topics)	https://www.blackdoginstitute.org.au/
Mayo antidepressant shared decision aid	https://depressiondecisionaid.mayoclinic.org/index
Depression Management Toolkit for Primary Care (44 page document, appears last update 2009)	https://www.integration.samhsa.gov/clinical-practice/macarthur_depression_toolkit.pdf

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Resources

Psychopharmacology and Psychiatry Updates Psychopharmacology Institute (Podcasts)	https://podcasts.apple.com/us/podcast/psychopharmacology-and-psychiatry-updates/id1425185370 (free access to short and preview podcasts)
American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults	https://onlinelibrary.wiley.com/doi/full/10.1111/jgs.15767
Depression Management Toolkit for Primary Care (44 page document, appears last update 2009)	https://www.integration.samhsa.gov/clinical-practice/macarthur_depression_toolkit.pdf

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Take home points

- **1) Psychopharmacology is often an essential part of treatment for our patients:**
  - But is increasingly complex and with potential for harm--utilize your resources
- **2) Develop strategies you are comfortable with for stabilizing acute presentations:**
  - Example, manic patient, depressed patient, anxious patient, until next phase of care
- **3) Evidence-based but individualized:**
  - Drugs in same class often have similar efficacy, therefore patient factors/preference, adverse effects, medical and psychiatric comorbidity often drive treatment decisions
- **4) Think broadly:**
  - Must consider social determinant factors, health disparities (cardiovascular, tobacco, preventive screening) in managing patients with psychiatric diagnoses
- **5) Team-based approach**:
  - We all contribute to ensure the pharmacology treatments are optimal and that they are coupled with non-pharmacologic and psychosocial approaches

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Questions, Discussion, Cases?

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SSRI	Atypical AD or serotonin modulator	SNRI	TCA	MAOI
fluoxetine	bupropion	venlafaxine	amitriptyline	phenelzine
sertraline	mirtazapine	duloxetine	imipramine	tranylcypromine
citalopram	trazodone		clomipramine	selegiline
escitalopram		desvenlafaxine	doxepin	
paroxetine	vilazodone	milnacipran	nortriptyline	
fluvoxamine	vortioxetine	levomilnacipran	desipramine	
Augmentation in MDD with non-antidepressant: buspirone, lithium, atypical antipsychotics, thyroid hormone, stimulant, Omega-3 fatty acids, SAMe, l-methylfolate, pramipexole				

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Session Survey

Use the CFHA mobile app to complete the survey/evaluation for this session.

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Join us next year in Philadelphia, Pennsylvania! Thank you!

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