2:45 – 3:45 PM

Medicines for the Mind: An Overview of Psychopharmacology

SPEAKER

Shirah Vollmer, MD

Disclosures

The following relationships have been disclosed related to this presentation:

- Shirah Vollmer, MD: No financial relationships to disclose.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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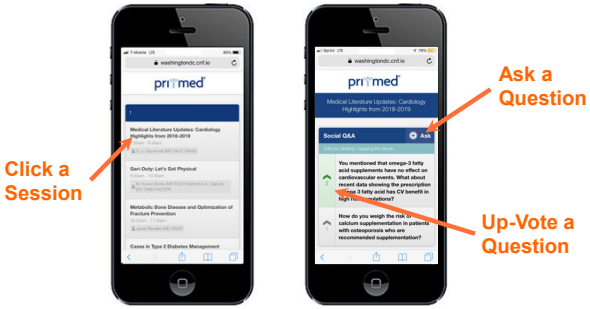


Who Am I?

Board Certified Adult and Child Psychiatrist

Clinical Professor of Psychiatry at the DGSOM

UCLA Extension Instructor

Graduate of LAPSI-NCP

Private Practice in Westwood

Blogger

Outline

- Introduction
- Sedatives/Hypnotics - Gina
- TCAs/SSRIs/Dual Uptake Inhibitors/Newer Agents/Machine Treatments - Leo
- Mood Stabilizers - Lydia
- Antipsychotics-typical and atypical - Sofia
- Stimulants - Olivia
- Summary

Psychotropics

Increasing utilization

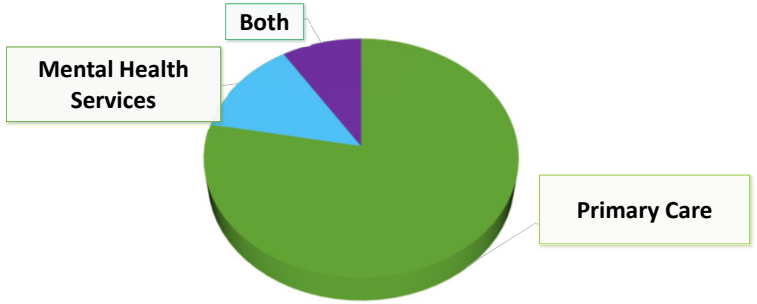
- More medications available
- Safer medications
- Increasing use by primary care clinicians
- Decreasing stigma and increased awareness of benefits
- Biological model of psychiatric illness
- 1/6 Americans reported taking a psychotropic drug at least once in 2013. *(JAMA Intern Med.* Published online December 12, 2016.)

COGNITION

AFFECT

BEHAVIOR

Approximately 78% of mental health disorders worldwide are managed in primary care settings



Gater et al. *Psychol Med*. 1991 Aug;21(3):761-74.

Case 1: Gina

28 yo college grad, living at home, not sure what to do with her life

Panic attacks 2-3 times per week, sometimes leading to trips to the ER

Poor sleep

Uses alcohol and MJ

History of child sexual abuse

Benzodiazepines and Barbiturates

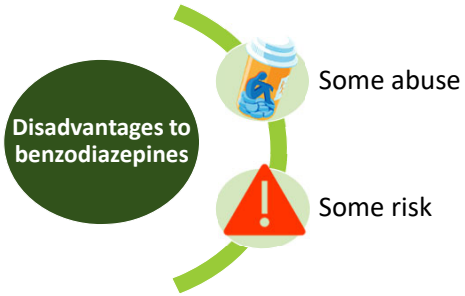
Mechanism of action

- Potentiates the effects of GABA
- Causes synaptic inhibition by membrane hyperpolarization

Benzodiazepines

- Hypnotic
- Anxiolytic
- Anticonvulsive
- Amnestic
- Muscle relaxant

Anxiolytics



Benzodiazepines

SSRI antidepressants
Atypical antidepressants
Tricyclic antidepressants
MAOI antidepressants
Older mood stabilizers
Newer mood stabilizers
Older antipsychotics
Newer antipsychotics
Anticholinergics
Benzodiazepines
Other anxiolytic/hypnotics
Stimulants
Meds for dementia
Meds for substance abuse
Psychiatric uses of antihypertensives

1957	Chlordiazepoxide (Librium)
1970s	Diazepam (Valium) top selling drug in the US
1986	Alprazolam (Xanax) top selling drug in the US
1990s	SSRIs replace some chronic benzodiazepine use for anxiety

Benzodiazepine Side Effects

- Drowsiness
- Ataxia
- Confusion
- Vertigo
- Impaired judgment

Benzodiazepines

Alprazolam (Xanax)	Short-mid
Chlordiazepoxide (Librium)	Long
Clonazepam (Klonopin)	Mid-long (serotonergic?)
Clorazepate (Tranxene)	Long
Diazepam (Valium)	Long
Estazolam (ProSom)	Mid
Flurazepam (Dalmane)	Long
Lorazepam (Ativan)	Short-mid (min DDI)
Oxazepam (Serax)	Short-mid (min DDI)
Temazepam (Restoril)	Mid (min DDI)
Triazolam (Halcion)	Short (common procedure presedate)

Benzodiazepine Withdrawal

This is a drug of abuse!!!

- Insomnia
- Anxiety
- Tremor
- Perspiration
- Loss of appetite
- Seizures

Other anxiolytic/hypnotics

Miscellaneous

- Buspirone (BuSpar) – subtle anxiolytic, slow response
- Chloral hydrate (Noctec) – hypnotic, rapid tolerance, toxicity in overdose
- Trazodone

Antihistamines

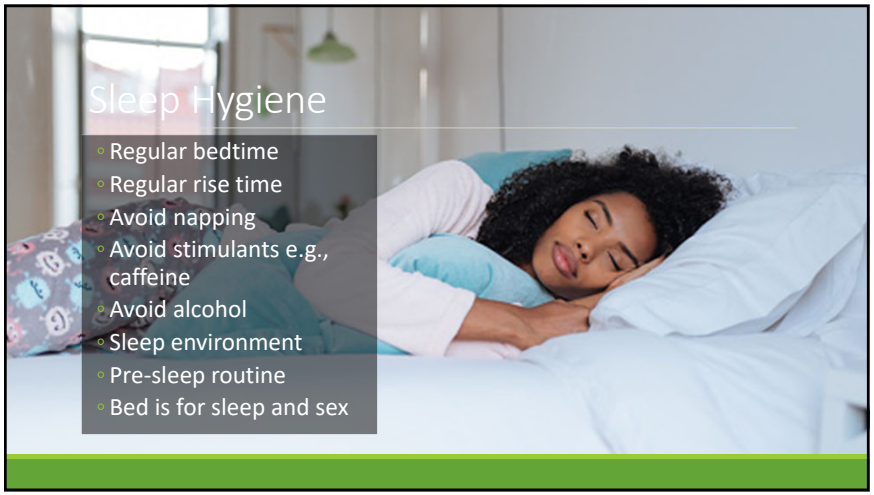
- Hydroxyzine pamoate (Vistaril)
- Diphenhydramine (Benadryl)

Anticonvulsants – mildly sedating and calming

- Gabapentin (Neurontin)
- Pregabalin (Lyrica)
- Tiagabine (Gabatril)

Beta Blockers

- Drugs as **propranolol – atenolol**
- Act by blocking peripheral sympathetic system
- Reduce somatic symptoms of anxiety
- Decrease BP and slow HR
- Used in performance anxiety
- Are less effective for other forms of anxiety
- Should be used with caution in asthma, cardiac failure, peripheral vascular disorders



Sleep Hygiene

- Regular bedtime
- Regular rise time
- Avoid napping
- Avoid stimulants e.g., caffeine
- Avoid alcohol
- Sleep environment
- Pre-sleep routine
- Bed is for sleep and sex

Hypnotics

FDA requires stronger warnings about rare but serious incidents related to certain prescription insomnia medicines *Updated warnings for eszopiclone, zaleplon and zolpidem* Immediate Release: April 30, 2019

- Zaleplon: Gaba-a agonist (Sonata)*
- Zolpidem: Gaba-a agonist (Ambien CR)*
- Eszopiclone: Gaba-a agonist (Lunesta)*
- Ramelteon: melatonin agonist (Rozerem)

*Drugs without benzodiazepine chemical structure

Mendelson, WB. Pharmacological treatment of insomnia. *Psychiatric Annals*;2008;38:9:606-611

Suvorexant

Mechanism of action

- Antagonism of orexin receptors (presumed)
- Orexin neuropeptide signaling system is a central promoter of wakefulness
- Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive

Cervella

FDA Clears the Cervella Cranial Electrotherapy Stimulator for Treatment of Anxiety, Insomnia, and DepressionCARMEL, Ind., March 27, 2019 /PRNewswire/ -- Innovative Neurological Devices is pleased to announce receiving the FDA market clearance for the Cervella™ Cranial Electrotherapy Stimulator. The FDA cleared the Cervella medical device for treatment of anxiety, depression, and insomnia. Cervella works by delivering micro pulses of electrical current across patient's brain. According to clinical studies, this electrical stimulation results in reduction in anxiety levels, insomnia, and patient's depressive mood.

What About Gina's MJ use?

There is no data to understand how MJ impacts Gina's mental health

There is no data to understand how using CBD oil would impact Gina's mental health

Since MJ is still illegal in many states, the government has not allowed it to be studied in a randomized controlled trial

Case 2: Leo

35 yo African American Male who lost his job

Stays home on the couch, not motivated to look for a new job

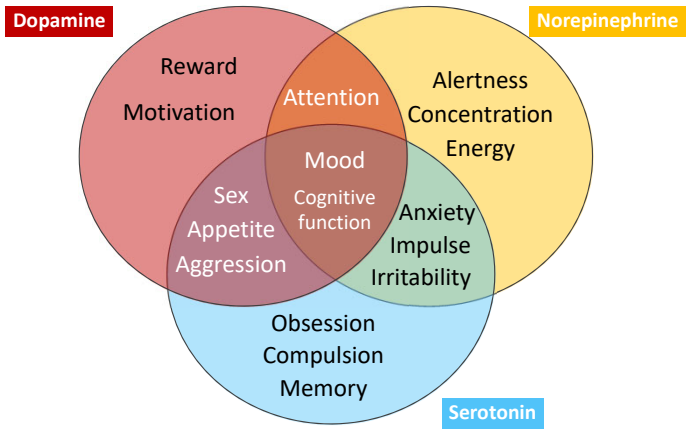
Eating and sleeping too much

No history of depressive episodes

Good relationship with his parents

No history of childhood physical, verbal or sexual abuse

Plays video games all day long. Mostly League of Legends



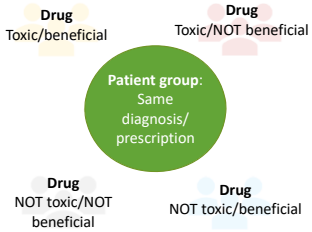
A Quick Psychopharmacology History

Iproniazid, "psychic energizer"
- 400,000 depressed patients treated in the first year
- Viral hepatitis (127 cases) – Iproniazid removed from market

1953	1957	1987	1989-94	1994	1995	1996
	Imipramine (Tofranil), the first "non-stimulating antidepressant"	**Fluoxetine** (Prozac)	**Bupropion** (Wellbutrin), **sertraline** (Zoloft), **paroxetine** (Paxil)	**Venlafaxine** (Effexor)	**Fluvoxamine** (Luvox), **Nefazodone** (Serzone)	**Mirtazapine** (Remeron)

Pharmacogenomics

- Do genetic polymorphisms determine outcome? ***Not yet***
- Hope is there…apoE4-good predictor of Alzheimer's Disease, but no link to drug response
- 5HT2A-might predict adverse effects to some antidepressants



Malhotra AK, Murphy GM, Kennedy JL. *Am J Psychiatry* 2004;161:780-796

Antidepressants

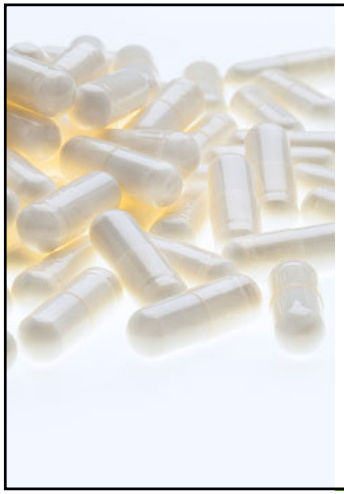
Tri-cyclics: traditional anti-depressants

- Imipramine (Tofranil)
- Amitryptilene (Elavil)
- Desipramine (Norpramin)
- Nortryptilene (Pamelar)
- Protryptilene (Aventyl)

Antidepressants

Disadvantages of tri-cyclics

- Fatal cardiac arrhythmias
- Status epilepticus
- Orthostatic hypotension
- Constipation
- Weight gain
- Blurred vision
- Memory impairment



Antidepressants

MAO inhibitors

- Tranylcypromine (Parnate)
- Phenelzine (Nardil)

Selegiline Pharmacology

Oral selegiline	Transdermal selegiline
• Low concentrations: inhibits MAO-B (Parkinson's disease) • Higher concentrations: **also** inhibits MAO-A (depression and ↑tyramine interaction)	• Inhibits MAO-A and –B in **CNS** (depression) • Inhibits MAO-B in **periphery** (↓tyramine interaction)

McGrath PJ et al. *J Clin Psychopharmacol*. 1989;9:310-11; Sunderland T, et al. Psychopharmacology (Berl). 1985;86:432-37.

Antidepressants

Disadvantages of MAOIs

- Hypertensive crises
- Risk of strokes
- Rigid diet w/o tyramine
- Weight gain
- Orthostatic hypotension

Antidepressants

Selective serotonin re-up inhibitors advantages

- Safety, *safety,* ***safety***
- Better tolerated

Key Concepts on SSRI Antidepressants

- Now most widely used antidepressants, mainly because of their more benign side effect profile and because they are much safer
- As a group, they are essentially identical in their actions, except that fluoxetine (Prozac) has the longest duration of action
- Onset of action is delayed
- Useful in many other disorders

Key Concepts Regarding Antidepressants

- All antidepressants are equally effective in treating major depression, dysthymia, subclinical depression; approx. **60-70%** respond
- There is a latency of **2-4 weeks** before antidepressant action
- Adverse effects and potential drug interactions are prominent; the choice of antidepressant is based on tolerability
- Abuse, addiction, dependence, are not issues
- Mechanisms of therapeutic action are unknown

Indications for SSRIs

- Anxiety disorders:
  - GAD, panic disorder, OCD, social phobia, PTSD
- Dysthymia/Major depression
- PMDD
- Menopause
- Bulimia
- Neuropathic pain

Pharmacology: Better Living Through Chemistry
Starting Doses for SSRIs

Fluoxetine (Prozac)	5 mg approved for kids age 6 and older
Sertaline[1] (Zoloft)	12.5 mg approved for kids with OCD age 6 and up
Paroxetine (Paxil)	5 mg
Fluvoxamine (Luvox)	25 mg, Fluvoxamine ER (Luvox CR) Rx for one year
Citalopram* (Celexa)	5.0 mg NO ONE DOSE
Escitalopram (Lexapro)	2.5-5.0 mg approved for kids age 12-17

1. Cipriani A et al: Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 1/29/09

Beginning SSRI Treatment

CUT the lowest dose in HALF…Zoloft 12.5mg..for example

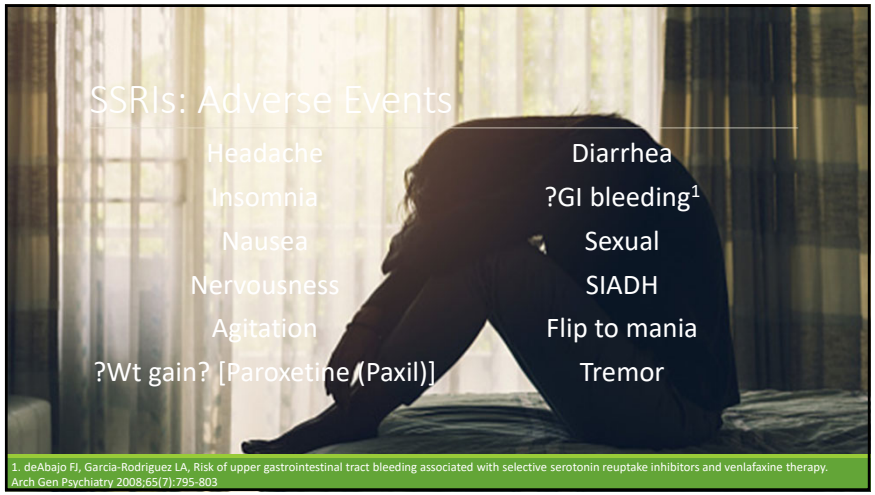
Start Low and Go Slow for EVERYBODY

Why? Ease their body into the medication so side effects do not make them MORE anxious

Citalopram (Celexa)
Warning 2011, Revised 2012

- Not to be used >40 mg/day because of the risk of QT prolongation
- Not >20mg/day for patients with hepatic impairment or >60 years, patients who are CYP2C19 poor metabolizers, or patients taking CYP2C19C19 inhibitors (cimetidine)
- Not for patients with congenital long QT syndrome, bradycardia, hypokalemia, hypomagnesemia, recent MI, uncompensated heart failure or those taking other drugs that prolong the QT interval.
- EKG monitoring is recommended for high risk groups
- d/c for QTc >500 ms.

www.fda.gov/safety/MedWatch



1. deAbajo FJ, Garcia-Rodriguez LA, Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy. Arch Gen Psychiatry 2008;65(7):795-803

Adolescents and SSRIs

The MOST dangerous population to treat with SSRIs

May cause of flip them into a MANIC episode, requiring psychiatric hospitalization and possible danger to self and others

Brain develops rapidly from 15-25 and so this is a very vulnerable age to expose them to neuroactive substances.

Drug Interactions

- CYP 2D6 transforms codeine into active metabolite morphine (and hydrocodone to hydromorphone)
- Antidepressants than inhibit 2D6 can impair analgesic effect
- Options: tramadol or oxycodone
- SSRIs can interact with warfarin by inhibition of metabolism AND increasing bleeding time by ↓ platelet aggregation

AmpliChip CYP450 Test

- Clinical test, FDA approved 12/04
- Aims to find the genotype of the patient that will determine metabolism
- 2D6 and 2C19
- 2D6-Four phenotypes: Poor, Intermediate, Normal, Ultrarapid
- First FDA approved pharmacogenetic test

SSRIs and Osteoporosis

- Cohort studies have suggested that SSRI use increases fracture risk and accelerates bone loss in older adults and in women
- No causation has been determined

Depression → Osteoporosis	Antidepressants → Osteoporosis	Osteoporosis → Depression
Lifestyle, Falls, Hypovitaminosis D, Hyperparathyroidism Hypercortisolism, Hypogonadism, Growth hormone suppression, Leptin elevation, Serotonin secretion (Brain oriented inhibits SNS, Gut oriented promotes osteoblast reduction), Cytokine release, Other mechanism	Medication	Chronic pain Impaired physical ability Loss of self-esteem Diminished quality of life

SSRIs and Osteoporosis. The Medical Letter 2007;1274(49):95-96; Takkouche B, Montes-Martinez A, et al. Drug Saf. 2007;30(2):171-184.

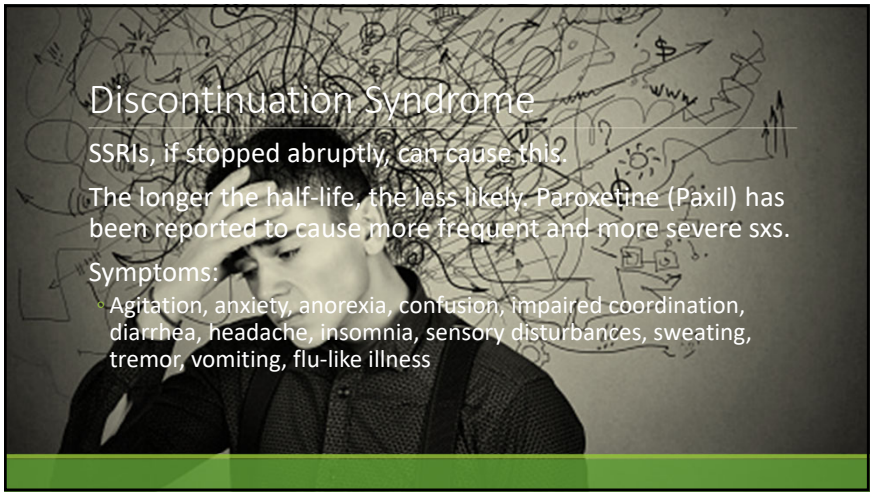
Serotonin Syndrome

- Serotonin syndrome is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system (CNS).
- May result from any combination of drugs that has the net effect of increasing serotonergic neurotransmission.
- Classically associated with the simultaneous administration of two serotonergic agents.
- Can occur after initiation of a single serotonergic drug or increasing the dose of a serotonergic drug in individuals who are particularly sensitive to serotonin.
- Also described following intentional overdose.

Serotonin Syndrome

- Could be from concurrent use of triptans (serotonin-receptor agonists) and SSRIs
- Mental status changes
- Neuromuscular abnormalities
- Autonomic dysfunction
- GI disturbances
- 24 hours of taking 5HT

Soldin O, Tonning J. NEJM 2008;358:2185-2186; Sternbach H. Am J Psychiatry 1991;148(6):705-713; Mason PJ, et al. Medicine 2000, 79(4): 201-9



Discontinuation Syndrome

SSRIs, if stopped abruptly, can cause this.

The longer the half-life, the less likely. Paroxetine (Paxil) has been reported to cause more frequent and more severe sxs.

Symptoms:

- Agitation, anxiety, anorexia, confusion, impaired coordination, diarrhea, headache, insomnia, sensory disturbances, sweating, tremor, vomiting, flu-like illness

SSRIs and Suicide Warning

FDA Public Health Advisory
October 15, 2004

Suicidality in Children and Adolescents Being Treated With Antidepressant Medications

Wording of the Warning

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with MDD and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.

Venlafaxine (Effexor): *An SSRI-Like Antidepressant*

- Major use has been as an alternative to TCA or SSRI; new indication is GAD
- Blocks reuptake of both norepinephrine and serotonin
- Does not block alpha-adrenergic, cholinergic, or histamine receptors
- Side effect profile like SSRIs; but also some blood pressure elevation
- No cytochrome P-450 inhibition

Venlafaxine

- Dual Action Reuptake Inhibitor
- 5% get HTN on doses above 225 mg
- Discontinuation syndrome is a problem
- FDA approved for GAD
- Starting dose 37.5 mg XR
- Used for hot flashes in women undergoing perimenopause

Evans ML, et al. Obstet Gynecol 2005;105:161-166.

Desvenlafaxine (Pristiq)

- FDA approved for the Treatment of Major Depressive Disorder
- Only studies investigating its use are unpublished
- 50 mg dose, no titration
- Active metabolite of venlafaxine
- Htn
- Withdrawal symptoms
- Category C
- More expensive than most SSRIs

Desvenlafaxine for Depression. The Medical Letter 2008;50:37-39

Duloxetine (Cymbalta)

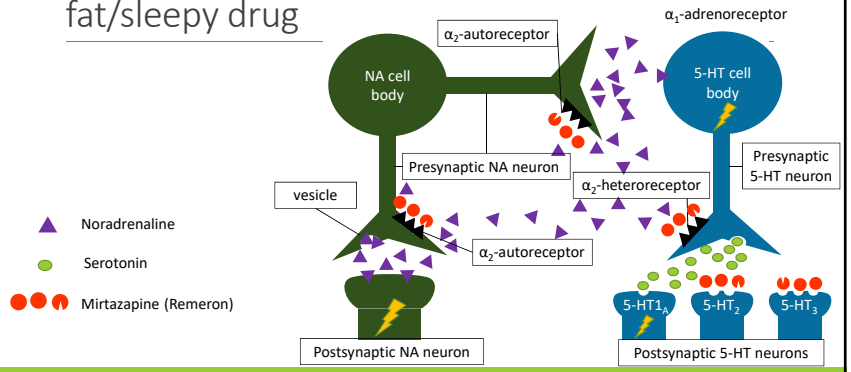
- FDA approval August 2004
- Based on preclinical data, duloxetine is a selective, balanced and potent dual reuptake inhibitor of both serotonin (5-HT) and norepinephrine (NE). Balanced as used here means that it has an approximately equal affinity for 5-HT and NE reuptake transporters.
- FDA approval for the treatment of fibromyalgia-6/08
- FDA approval for the management of chronic musculoskeletal pain in adults. 2/11. Mechanism not known
- Maximum recommended dosage is 60 mg/day

Hauser W, et al. JAMA 2009:301;198-209

Vilazodone

- FDA approval 1/11
- MDD in adults
- Better side effect profile
- SSRI and serotonin 1A partial agonist
- 10, 20, 40 mg tablets
- Maybe less sexual dysfunction

Mirtazapine (Remeron) fat/sleepy drug



Levomilnacipran (Fetzima)

Preliminary evidence suggests that levomilnacipran ER may be effective in improving not only depressive symptoms but also symptoms related to functioning:

- Social life
- Work
- Family life

Bruno A, Morabito P, Spina E, Muscatello MR. Current Neuropharmacology. 2016;14(2):191-199.

Levomilnacipran-Dosing/SE

Dosage & Administration

- Swallow whole
- Initially 20 mg once daily for 2 days, then increase to 40 mg once daily
- May increase dose in 40 mg increments at intervals of ≥2 days
- Max 120 mg once daily

- nausea
- vomiting
- constipation
- sweating
- increased heart rate, slowed heart rate, heart palpitations
- erectile dysfunction

Vortioxetine (Trintellix)

Multimodal-acting antidepressant
- Modulation of *several* 5-HT receptors

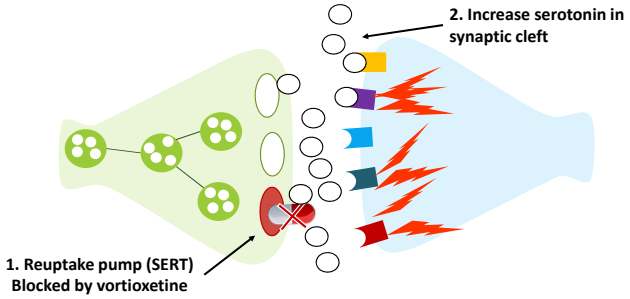
Serotonin 5-HT$_{1a/b}$ receptor agonist
- Coupled to G_i → inhibitory effects initially on 5-HT neurons
- Leads to downregulation of 5-HT$_{1A}$ over time → increased 5-HT neuronal activity

Serotonin 5-HT$_3$ receptor antagonist
- Ligand-gated ion channel on GABA interneurons → increased 5-HT and NE neuronal firing
- Present both in the peripheral and central nervous system
- Involved in GABA and dopamine regulation of neurotransmitter systems

Serotonin 5-HT$_7$ receptor antagonist
- Coupled to GS → located on GABA interneurons which regulate 5-HT neurons. Breaks taken off 5-HT neurons

Primarily binds to the serotonin reuptake transporters (SERT)

SERT Blockade



Vortioxetine-Dosing/SE

- 5 mg starting dose
- 5, 10, 20 mg tablets
- 20 mg max dose

Dosing:

Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were:
- Nausea
- Constipation
- Vomiting

Buproprion-Dosing/SE

- Generic: Bupropion
- Form: oral immediate-release
- 5 mg, 100 mg
- oral extended-release
- Tablet strengths:
  - 100 mg, 150 mg, 200 mg, 300 mg

Common side effects:
- Dry mouth
- Nausea
- Stomach pain
- Headache
- Dizziness
- Ringing in ears
- Vision changes
- Loss of interest in sex
- Sore throat
- Muscle pain
- Mild itching or skin rash
- Increased seating
- Increased urination
- Changes in appetite
- Weight loss or gain

Bupropion Contraindications

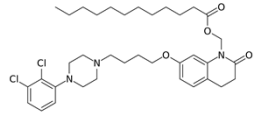
- History of seizures
- Eating disorder
- Bipolar
- Use of MAOI: phenelzine (Nardil), tranylcypromine (Parnate), moclobemide (Manerix), Selegiline (Eldepryl)
- Alcoholism
- Severe liver problems

Aripipizole

Public release date: 20-Nov-2007

FDA approves ABILIFY(R) (aripiprazole) as the first medication for add-on treatment of MDD

ABILIFY used with another antidepressant can help adults living with depression who have failed to achieve adequate symptom relief



Abilify-THINK TWICE

Although FDA approved as an adjunct for depression..please consider…

Metabolic side effects include Type II diabetes, truncal obesity, HTN, and unwanted weight gain

It is NOT clear if this should be a primary care medication…

Ketamine

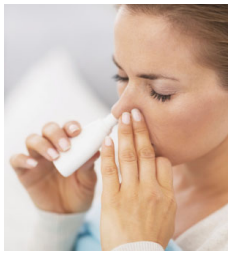
- NMDA receptor antagonist, “Special K”
- Rapid antidepressant effect
- NIMH director Dr. Thomas Insel remarked:

"To my knowledge, this is the first report of any medication or other treatment that results in such a pronounced, rapid, prolonged response with a single dose. These were very treatment-resistant patients."

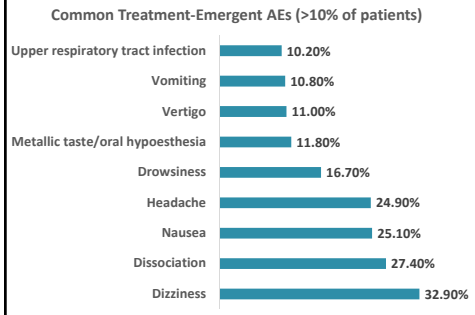
Zarate CA, Singh JB, Carlson PJ, et al. (August 2006). *Archives of General Psychiatry* 63 (8): 856–64

Esketamine-March 5, 2019, Spravato

- Nasal spray
- Novel mechanism of action
- Glutamate receptor modulator thought to help restore synaptic connections in brain cells in people with major depressive disorder
- U.S. FDA granted Breakthrough Therapy Designations for esketamine for treatment-resistant depression and major depressive disorder with imminent risk for suicide
- Restricted distribution system, risk evaluation and mitigation strategy (REMS)



Esketamine-side effects



55/802 (6.9%) had 68 serious treatment-emergent adverse events

Of these, 5 serious treatment-emergent adverse events from 4 patients were assessed by the investigator to be related to esketamine

There were 2 deaths, which the investigator determined to be unrelated to esketamine nasal spray/oral antidepressant use

www.prnewswire.com/news-releases/long-term-phase-3-study-shows-esketamine-nasal-spray-plus-an-oral-antidepressant-delayed-time-to-relapse-in-patients-with-treatment-resistant-depression-300657458.html

July 1, 2019, Assembly Bill (AB) 2193 requires licensed health care practitioners who provide prenatal or postpartum care for a patient to screen or offer to screen mothers for maternal mental health conditions.

Brexanolone IV-Post-Partum Depression

March 19, 2019

The U.S. Food and Drug Administration today approved Zulresso (brexanolone) injection for intravenous (IV) use for the treatment of postpartum depression (PPD) in adult women. This is the first drug approved by the FDA specifically for PPD.

Zulresso will be available only through a restricted program called the Zulresso REMS Program that requires the drug be administered by a health care provider in a certified health care facility. The REMS requires that patients be enrolled in the program prior to administration of the drug. Zulresso is administered as a continuous IV infusion over a total of 60 hours (2.5 days).

Brexanolone is a synthetic form of allopregnanolone, a hormone produced by progesterone in the brain that may help ease depression and anxiety by dampening neural activity,

Other Rx for Depression

- ECT
- SunBox-light box-not FDA approved
- Vagus Nerve Stimulation-FDA approved
- rTMS-FDA approved-10/7/08 www.NeuroStarTMS.com
  5 days a week, up to 6 weeks, 40 minutes a session[1]
- Deep Brain Stimulation[2]-not FDA approved

1. Dowd et al. Current Psychiatry vol 7 (12): 27-35
2. Kringelbach ML, Jenkinson N, Owen SLF, Aziz TZ (2007). *Nature Reviews Neuroscience*. 8:623–635

Magnetic Pulse to Ease Depression

- Transcranial magnetic stimulation (or TMS) uses magnetic pulse to stimulate mood-controlling brain cells
- Short pulses of magnetic energy are focused at the limbic system structures, which are thought to control emotional/behavior patterns
- The pulses trigger electrical charges that cause neurons to become active

Three-Minute TMS Device

ITBS:

- 3 pulses at 50 Hz and repeated at 5 Hz, 2 s on and 8 s off, leading to 600 pulses at ~3 min
- This short protocol generates similar extent in the excitatory effects on cortex, measured both electrophysiological responses and functional imaging. Limited studies argued for the use of iTBS in depression treatments including treatment resistant depression.

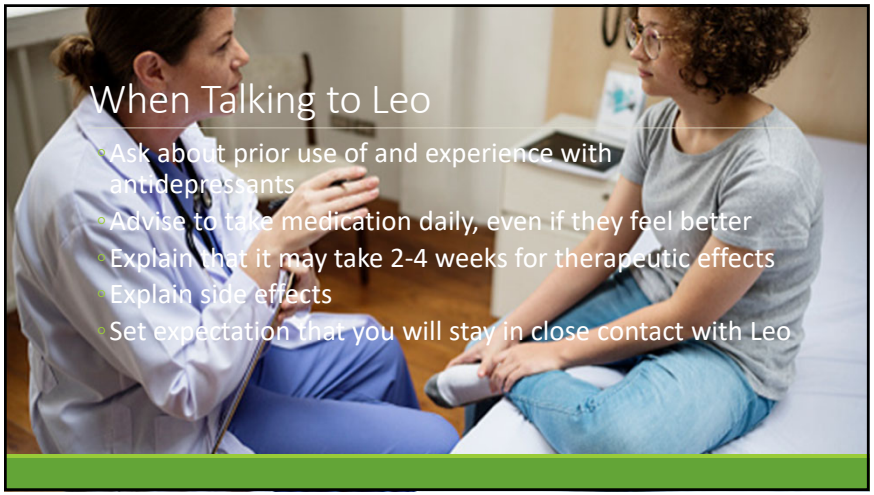
ADVERSE EFFECTS:

- Groups were similar–more than half subjects reported headache the most common AEs following TMS therapy
- Nausea, dizziness, fatigue, etc. had comparable occurrence rates between the two groups
- More "painful" experience in iTBS group, (and a higher self-reported pain score) but not with more dropout rate in these patients. This suggested that the iTBS is tolerable in daily treatment and does not accompany more AEs
- The painful feeling still worth more evaluation for other types of patients in future practices

Huang et al., 2005; Duprat et al., 2017; Li et al., 2018; Blumberger et al., 2018
Blumberger, D. M., Vila-Rodriguez, F., Thorpe, K. E., Feffer, K., Noda, Y., Giacoble, P., et al. (2018). Lancet 391, 1683–1692.

Treatment Guidelines-How to help Leo

- Titrate agent to achieve therapeutic dose or remission
- Full effect may take 4-6 weeks
- Treat for 4-9 months after full remission
- Continue medication indefinitely for recurrent depression
- Close Follow up!!!



When Talking to Leo

- Ask about prior use of and experience with antidepressants
- Advise to take medication daily, even if they feel better
- Explain that it may take 2-4 weeks for therapeutic effects
- Explain side effects
- Set expectation that you will stay in close contact with Leo

Case 3: Lydia

33 yo woman who reports she has bipolar disorder

No history of psychosis

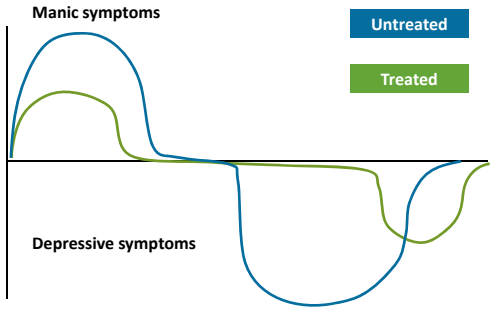
No history of Psychiatric hospitalization

Mood swings are reported to occur after relationship break-ups

She works in Public Relations and has a good job

She is lonely and has problems finding a significant other

Cycling



What Is Bipolar Disorder?

1 % of the population

Equal in men and women

A family history is almost always present

Patient has a history of psychiatric hospitalization and/or psychosis

Onset is typically 15-25

Drugs for Bipolar Disorder: *The Mood-Stabilizing Agents*

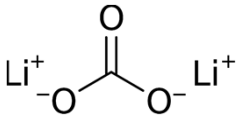
Key concepts

- Mood-stabilizing agents are prescribed for bipolar disorder
  - Lithium, carbamazepine (Tegretol), and valproate (Depakote, Depakene)
- They are effective against both manic and depressive stages of bipolar disorder, but they are not effective in major depression
- Adverse effects are prominent
- Mechanisms of action are completely unknown

Mood Stabilizers

Time frame

- Lithium was first recognized as treatment for mania by John Cade in 1949
- It came into use in the U.S. for bipolar disorder in the 60s

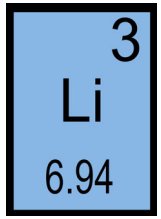


AJPjan98: Mood Stabilizer combinations: A review of safety and efficacy. Marlene P. Freeman, MD, and Andrew L. Stoll, MD.

Lithium

Indications:

- Acute manic episodes of bipolar disorder
- Acute depressive episodes of bipolar disorder
- Long term prophylaxis of recurrent bipolar disorder
- Long term prophylaxis of recurrent mania
- Augmentation of antidepressant action in treatment resistant major depression



Lithium Dosing

Pre-dosing

- CBC (Li causes leukocytosis)
- TSH (Li can cause hypothyroidism)
- Creatinine (long-term use can cause renal problems, including iatrogenic diabetes insipidus)

Dosing: 0.5-0.6/0.7 in women/men

- Rule of thumb: 70 kg - 300 mg tid or Eskalith 450CR bid

Target range: 0.8-1.2 mEq/L = “therapeutic”

Lithium

Efficacy: positive response in 50-70% of patients in acute episode

- 40% of lithium-treated show relapse within one year; 55-65% show relapse within two years

Predictors of poor response to lithium include

- Rapid cycles
- Family Hx
- Mixed symptomology
- Hx of drug abuse

Mood Stabilizers

Time frame

- Carbamazepine was first used for bipolar disorder in the 70s
- Valproate was just recently approved by the FDA for use in bipolar disorder

AJPjan98: Mood Stabilizer combinations: A review of safety and efficacy. Marlene P. Freeman, MD, and Andrew L. Stoll, MD.

Common Adverse Effects of Valproate

- CNS
  - Sedation, tremor
- GI
  - Nausea, vomiting, diarrhea
- Coagulopathies
- Infertility, teratogenic in pregnancy
- Rare
  - Hepatotoxicity, pancreatitis, agranulocytosis
- Key drug interactions: NSAIDs
- Valproate is an inhibitor of P-450 enzymes

Therapeutic Principles for Use of Mood Stabilizers

- All equally effective in acute phase; lithium best documented for maintenance phase
- All require 1-2 weeks full effect
- If no early response to single agent, may need to add adjunctive agent (benzodiazepine or neuroleptic) or combo lithium and anticonvulsant
- Lifetime maintenance probably required

Mood Stabilizers

Classic Drug

- Lithium

Inositol Depletion hypothesis

Newer Agents

Anticonvulsants

- Valproate
- Carbamazepine
- Lamotrigine

SGAs

- Aripiprazole
- Asenapine
- Lurasidone
- Olanzapine
- Quetiapine
- Risperidone
- Ziprasidone

Case 4: Sofia

54 yo Caucasian female who has been mentally ill since college

In college she reported hallucinations and delusions and she dropped out and has been unable to hold a job since then.

Her mother is schizophrenic, and she was raised by her dad and step-mom

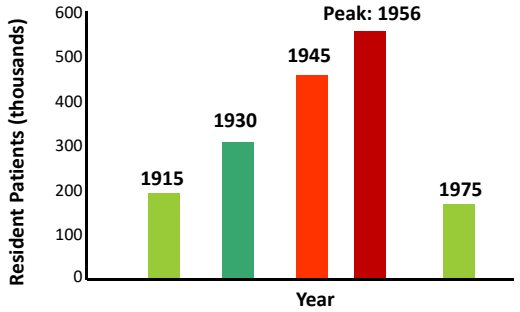
Sofia is often homeless, but at the moment, she is living with her dad and step-mom

Schizophrenia: *Core Symptom Clusters*

B Target Symptoms for Antipsychotic Treatment

- Hostility
- Agitation/anxiety
- Insomnia
- Suspiciousness
- Poor self-care habits
- Mutism
- Social withdrawal
- Loose associations
- Inappropriate affect
- Delusions
- Hallucinations
- Preoccupations

Patient Populations in Mental Institutions 1900 to 1975



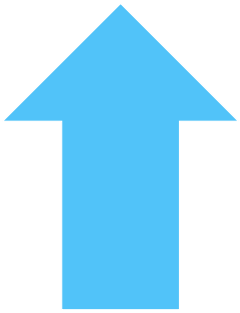
Bassuk and Gerson, 1978

Antipsychotics

Side effects of typicals

- Tremors
- Stiffness
- Cogwheeling
- Acute muscle dystonia
- Tardive dyskinesia
- Ineffective for negative SXs

Antipsychotics



Advantages of atypicals

- Reduced tremor
- Reduced stiffness
- Reduced cogwheeling
- Reduced muscle dystonia
- Reduced tardive dyskinesia
- Effective for negative SXs

Newer Antipsychotics

Terminology

- Atypical antipsychotics, second generation antipsychotics, serotonin-dopamine antagonists

Mechanism

- Adds serotonin (5HT 2A) activity
- Binds more loosely to dopamine receptors
- Clozapine initially rejected as an antipsychotic because of its seemingly reduced dopamine impact and lack of EPS

Indications/uses

- Schizophrenia & other psychotic disorders
- Acute bipolar mania & maintenance
- Augmentation of antidepressants & mood stabilizers
- Aggression & impulsivity

Newer Antipsychotics

Aripiprazole (Abilify)	• Unique complex mechanism • Can be either activating or sedating, nausea common
Clozapine (Clozaril)	• Most effective antipsychotic • Risk of agranulocytosis (decreased neutrophil WBCs) • CBC weekly × 6mos, then monthly • Multiple other side effects & DDI • Levels reduced by smoking
Olanzapine (Zyprexa, Zydis)	• Significant weight, diabetes, and lipid abnormality risk • Levels reduced by smoking

Tolerability of Antipsychotic Drugs

Traditional concerns	• Extrapyramidal symptoms (EPS) • Excess sedation • Cognitive slowing
Evolving concerns	• Cerebrovascular risks • Mortality • Weight or adiposity change • Insulin resistance • Dyslipidemia • Glucose intolerance

ADA Consensus Conference on Antipsychotic Drugs and Obesity and Diabetes: Baseline Screening

- Personal/family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease
- Weight and height to calculate BMI
- Waist circumference at umbilicus
- Blood pressure
- Fasting plasma glucose
- Fasting lipid profile

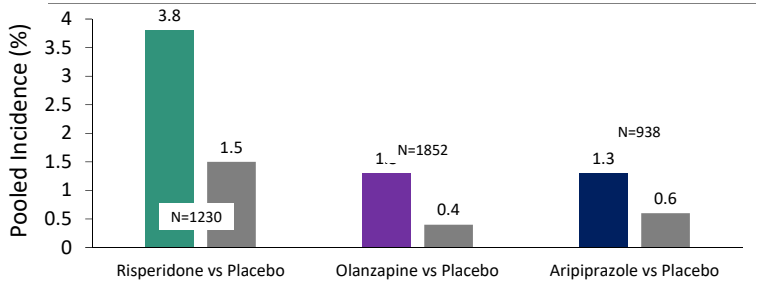
Diabetes Care. 2004;27:596-601.

Hyperprolactinemia and Risperdal

- Risperdal is a D2 antagonist-D2 inhibits PRL secretion causes hyperprolactinemia
- Causes hypogonadism
- This causes low bone mineral density
- ? Screen all patients on antipsychotics for their Prolactin levels

Kleinberg DL, Davis JM, De Coster R et al. J Clin Psychopharmacology 1999;19(1):57-61.

Cerebrovascular Adverse Events



Risk factors for CVAE may play a contributing role **CVAE = Cerebrovascular Adverse Event**

Based on Health Canada Therapeutics Products Directorate, Risperidone warning letter, October 2002. Data on file Janssen Pharmaceutica; Based on Eli Lilly and Company medical letter 2004; Based on Brisol-Myers Squibb Company medical letter, 2005.

Newest Antipsychotics Disadvantages

Iloperidone	Asenapine	Lurasidone
Dose-dependent QTc prolongation	Not absorbed once swallowed; must be administered sublingually	EPS and akathisia, but seems to be reduced if taken at night
Slow titration	Common side effect: oral hypoesthesia	Will require confirmation from real world clinical experience
Use caution with patients sensitive to orthostasis (young, elderly, CV problems)	Patients may not eat or drink for 10 min after administration to increase bioavailability	
In presence of 2D6 inhibitors (paroxetine, fluvoxamine, duloxetine) reduce dose by half	Somnolence/sedation/EPS	
Weight gain/metabolic profile comparable to risperidone	Inhibits 2D6 and is a substrate for 1A2	

CATIE Study

- Clinical Antipsychotic Trials of Intervention Effectiveness
- 74% patients d/c'd their medication within 18 months
- Naturalistic study

Lieberman JA, Stroup TS, McEvoy JP, et al. NEJM 2005;353:1209-1223

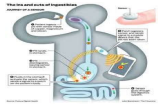
Long-acting Injectable Antipsychotics

WHERE DO THEY FIT IN THE TREATMENT PLAN?

Abilify MyCite

November 13, 2017

Abilify MyCite, a pill with a sensor that digitally tracks if patients have ingested their medication Abilify MyCite (aripiprazole tablets with sensor) has an ingestible sensor embedded in the pill that records that the medication was taken.The system works by sending a message from the pill's sensor to a wearable patch. The patch transmits the information to a mobile application so that patients can track the ingestion of the medication on their smart phone. Patients can also permit their caregivers and physician to access the information through a web-based portal.



Weight Gain Problem

- ? Metformin
- N=40
- 12 week rct
- 750 mg metformin/day
- Adding metformin changed the insulin resistance and prevented weight gain

Wu R, et al: *JAMA* 2008;299:185-193.

Atypicals and Risk of Sudden Cardiac Death

- Dose-related increased risk of sudden cardiac death
- Adjusted incidence ratio of 1.99

Ray WA, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *NEJM*. 2009;360:225-35.

Case 5: Olivia

50 yo African American woman who complains that she cannot get things done

Problem has persisted since childhood

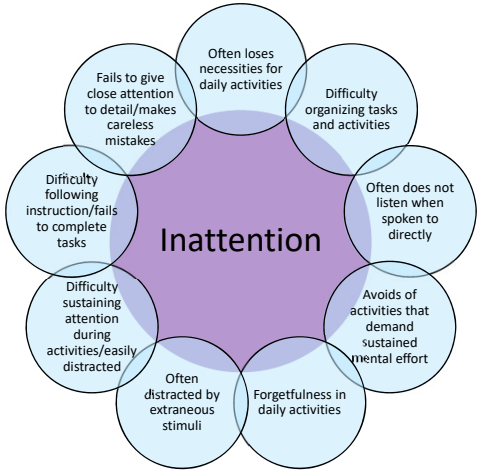
She was never diagnosed with ADHD

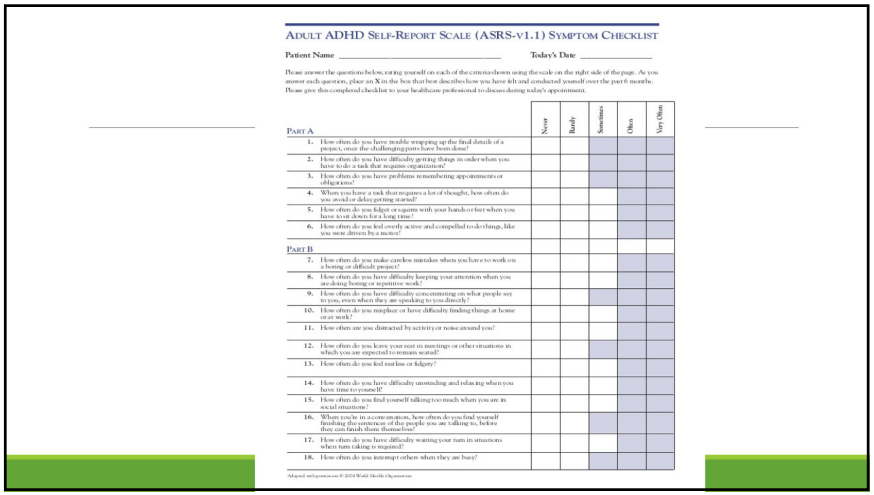
She reports that it is hard for her to keep her apartment clean and organizing her paperwork is very difficult

She reports problems in her relationships because she knows she is a "bad listener".

ADHD in Adults

Afraid of Prescribing Stimulant Medications?





ADULT ADHD SELF-REPORT SCALE (ASRS-V1.1) SYMPTOM CHECKLIST

Patient Name _____ Today's Date _____

Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.

		Never	Rarely	Sometimes	Often	Very Often
PART A						
1.	How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?					
2.	How often do you have difficulty getting things in order when you have to do a task that requires organization?					
3.	How often do you have problems remembering appointments or obligations?					
4.	When you have a task that requires a lot of thought, how often do you avoid or delay getting started?					
5.	How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?					
6.	How often do you feel overly active and compelled to do things, like you were driven by a motor?					
PART B						
7.	How often do you make careless mistakes when you have to work on a boring or difficult project?					
8.	How often do you have difficulty keeping your attention when you are doing boring or repetitive work?					
9.	How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?					
10.	How often do you misplace or have difficulty finding things at home or at work?					
11.	How often are you distracted by activity or noise around you?					
12.	How often do you leave your seat in meetings or other situations in which you are expected to remain seated?					
13.	How often do you feel restless or fidgety?					
14.	How often do you have difficulty unwinding and relaxing when you have time to yourself?					
15.	How often do you find yourself talking too much when you are in social situations?					
16.	When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?					
17.	How often do you have difficulty waiting your turn in situations when turn taking is required?					
18.	How often do you interrupt others when they are busy?					

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Stimulants

Short-term effectiveness of stimulants for ADHD is well-documented

Over 200 published RCTs, including studies with preschoolers and adults

- Methylphenidate best studied, followed by dextroamphetamine and mixed amphetamine salts
- **65-75%** response rate compared to **5-30%** placebo response
- All stimulants equally effective, although methylphenidate more effective with comorbid autism

FDA approval for ADHD treatment

- Age 6 for all, age 3 for DEX
- FDA black box warning for amphetamine salts due to cardiotoxicity → REMOVED

Extended release preparations

- Transdermal methylphenidate
- D-threo methyphenidate
- Lisdexamfetamine

(Meth)amphetamine meanings?

Generic Name	Trade Name	Approved Age
Amphetamine (extended release)	Adderall/Adderall XR	≥3
Methylphenidate (long acting)	Concerta	≥6
Pemoline*	Cylert	≥6
Methylphenidate	Daytrana (patch)	≥6
Dextroamphetamine	Dexedrine/Dextrostat	≥3
Dexmethylphenidate	Focalin	≥6
Methylphenidate (extended release)	Metadate ER/Metadate CD	≥6
Methylphenidate extended release long acting	Ritalin Ritalin SR Ritalin LA	≥6
Atomextine	Strattera	≥6
Guanfacine hydrochloride	Tenex, Intuniv**	≥12
Lisdexamfetamine	Vyvanse	≥6

FDA approves Adhansia XR for ADHD March 1, 2019

*Pemoline should not ordinarily be considered as first-line drug therapy for ADHD because of its potential for serious side effects
**Tenex is short-term preparation and Intuniv is the long-term preparation brand name

Methylphenidate/Mixed Amphetamine Salts-Side Effects

Decreased appetite

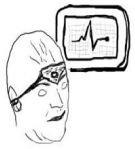
Sleep problems

Increased HR

BP increased-usually minor

TNS-Trigeminal Nerve Stimulation

For Immediate Release: April 19, 2019The U.S. Food and Drug Administration today permitted marketing of the first medical device to treat attention deficit hyperactivity disorder (ADHD). The prescription-only device, called the Monarch external Trigeminal Nerve Stimulation (eTNS) System, is indicated for patients ages 7 to12 years old who are not currently taking prescription ADHD medication and is the first non-drug treatment for ADHD granted marketing authorization by the FDA.

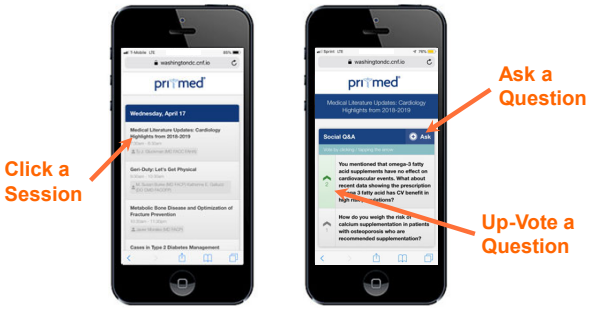


Summary

- Clinicians are now managing psychotropic drugs adding on to your wide toolbox of treatments
- Sedative/Hypnotics are good in small dosages with limited refills
- Treatment for Depression/Anxiety has expanded beyond SSRIs to include esketamine and TMS
- Mood Stabilizers-more choices than Li, but diagnosing bipolar disorder is tricky
- Antipsychotics-move to the atypicals-think of the metabolic syndrome-use as last resort
- Stimulants-consider Adult ADHD

ASK QUESTIONS USING OUR NEW SOCIAL Q&A FEATURE!

Navigate to www.longbeach.cnf.io



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