Mind Matters ECHO

Module: Depression
Session 3: Effective Treatments for Depression: Pharmacology

July 13, 2022

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Mount Sinai Health Partners

Welcome!

- Pre-survey: bit.ly/depressionmeeting3
- Hub team introductions
- Disclosures
- Questions during presentations

Case Presentation

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Sisselman Medical Group

Patient Information

Demographic Information	• 20 year old cis-male • Lives with parents and extended family • Commercial insurance • Student/employed part-time
Medical History	• None
Current Medications	• None

Patient Information

Psychiatric and Social History	• Korean parents
Family Psychiatric and Social History	• None known
History of Trauma	• None known
Current Psychiatric Diagnoses	• Major depressive disorder • ADHD • Anxiety

Patient Information

Symptoms of Depression	• Energy • Lack of motivation • Feelings of hopelessness, helplessness, and/or guilt • Thoughts of suicide (thoughts of hanging himself with rope at home) • Symptoms for 3-6 months, sometimes severe
Symptoms of Anxiety/Panic	• None
Suicidality	• Access to lethal means • Past active ideation (thoughts with plan and/or intent) • Patient had rope at home; was told to bring it to the office which he did (and wanted to)

Patient & Case Information

Areas of Support and Consultation Being Sought	• Pharmacological consultation • Identify appropriate behavioral health referrals • Identify appropriate psychosocial referrals • Strategies for engaging the patient and/or their caregivers/family
Main Question	• Patient is 20 year old Korean male with depression and suicidal thoughts • Cultural barriers to support identified within family dynamic

Effective Treatments for Depression: Pharmacology & Side Effect Considerations

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SSRIs: Common Agents

- **Fluoxetine (Prozac)** – commonly used; *long half-life* (unlikely to cause withdrawal, may be used to assist with discontinuation of other agents), *activating*, evidence in eating disorder.

- **Escitalopram (Lexapro), citalopram (Celexa)** – usually well-tolerated, Celexa carries risk of QTc prolongation at doses over 40 mg.

SSRIs: Common Agents

- **Paroxetine (Paxil)** – good for anxiety, BUT weight gain, drug-drug interactions (strong 2D6 inhibitor), significant withdrawal syndrome.

- **Fluvoxamine (Luvox)** – good for OCD, BUT sedation, drug-drug interactions, BID dosing.

SSRIs: Common Risks and Side Effects

- 2004: FDA issued **BLACK BOX WARNING** for SSRIs in patients under age 24.
  - Based on meta-analyses that showed increased risk of suicidal thoughts and behaviors, aggression and hostility in children treated with SSRIs.
- SEXUAL: most common side effect with long-term use → decrease dose of SSRI, add bupropion or buspirone, sildenafil for ED.
- GASTRO: nausea, diarrhea, vomiting common with sertraline and fluvoxamine.

SSRIs: Common Risks and Side Effects

- Weight gain, especially on paroxetine
- Increased anxiety, insomnia, “activation” with fluoxetine, escitalopram
- Can inhibit platelet binding, leading to bruising – AVOID WITH BLEEDS
- **SEROTONIN SYNDROME** – potentially fatal; GI upset, autonomic instability, hyperthermia, myoclonus, delirium, coma!

SNRIs

- **Venlafaxine (Effexor)** >> 2D6 >> **desvenlafaxine (Pristiq)** – MDD, GAD, chronic pain, good for comorbid migraines, menopausal symptoms
  - Noradrenergic inhibition at doses > 150 mg (venlafaxine) → HTN
  - May increase anxiety at higher doses
  - Nausea, vomiting, insomnia, sweating
  - **DISCONTINUATION SYNDROME**: dizziness, insomnia, nausea, diarrhea, "brain zaps"
- **Duloxetine (Cymbalta)** - first FDA approved drug for neuropathic pain associated w/ DM! Also indicated for fibromyalgia.
  - Activating
  - May increase LFTs and HbA1c. HTN not dose dependent.

Bupropion (Wellbutrin)

- Inhibits reuptake of DA and NE. CYP2B6, 2D6.

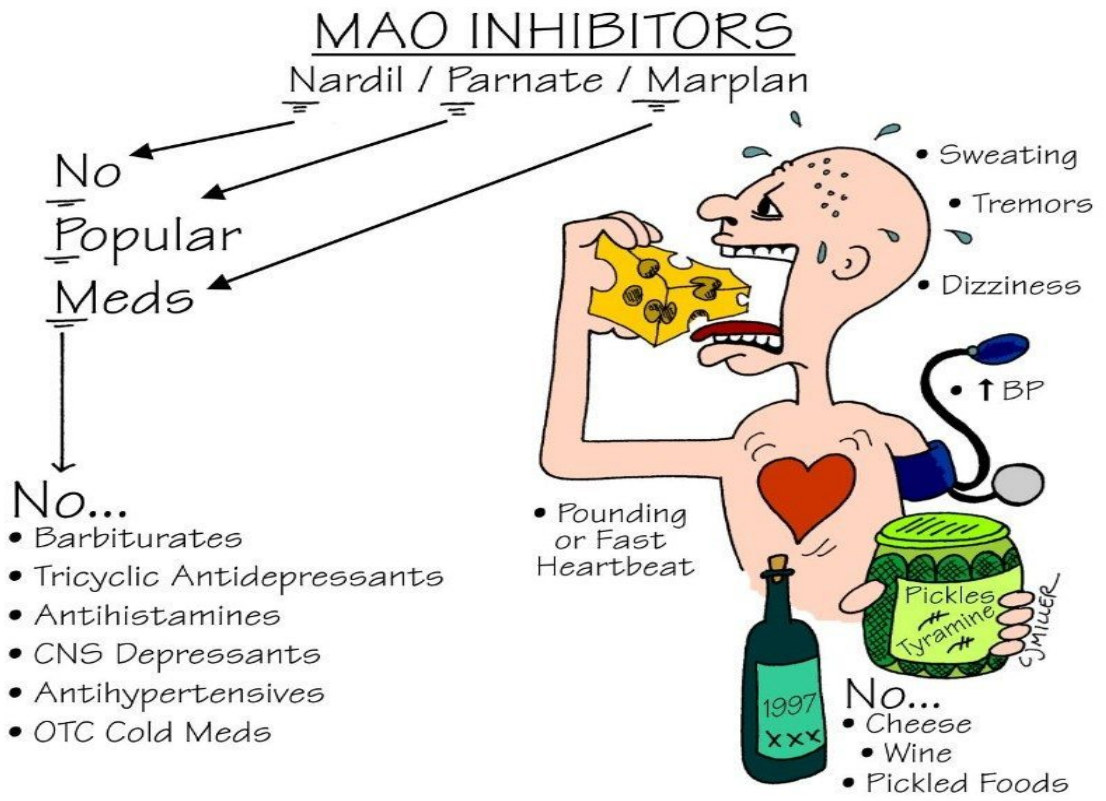
PROS	CONS
Used in MDD, bipolar depression (less likely to trigger mania), smoking cessation, ADHD, comorbid cocaine d/o. Activating, weight-neutral, no sexual side effects.	Seizure risk is 2% with 600 mg and 0.1% with 300-450 mg. *BUT, contraindicated in patients with seizure disorders and eating disorders*. Headache, insomnia, dry mouth, tremor, nausea. Can worsen anxiety, psychosis.

Mirtazapine (Remeron)

- "Tetracyclic antidepressant"; unique mechanism: blocks 5HT2A, 5HT2C and 5HT3 → all serotonin directed to 5HT1A receptor (main site for antidepressant effects)
  - Hence, increases NE and DA transmission (5HT2C normally inhibits DA)
  - Strong histamine affinity → sedation, weight gain (can be used to our advantage – oncology pts, nausea/vomiting)
  - Less sexual and GI side effects, minimal anticholinergic effect
  - Dose > 30 mg → higher NE effect, less sedation (*the lower the dose, the more sedating*)
  - May cause **AGRANULOCYTOSIS** (rare)!

TCAs, MAOIs

- Low tolerability
- Toxic in overdose
- MAOIs require strict dietary restrictions (tyramine)



Talking to your patient about antidepressant therapy

- Set expectations, but be positive ☺
- Start low, go slow; increase every 2 weeks if tolerated
- 4-6 weeks until benefit
- Adequate trial = at least 4-8 weeks on effective dose!
- Discuss common side effects, encourage patience
- Daily adherence important!

When to switch agents

- Intolerable side effects, even with reasonable treatment
- Medical contraindication, e.g. newly dx seizure disorder, bleed, etc.
- If no improvement of depression/anxiety, assess adequacy of duration and dose, adherence, and comorbidities (substance use?)
- Consider reassessing diagnosis, e.g. bipolar depression vs. unipolar depression
- TAPER antidepressants / cross-titrate with another agent

STAR*D Study, 2000-2004 (FYI)

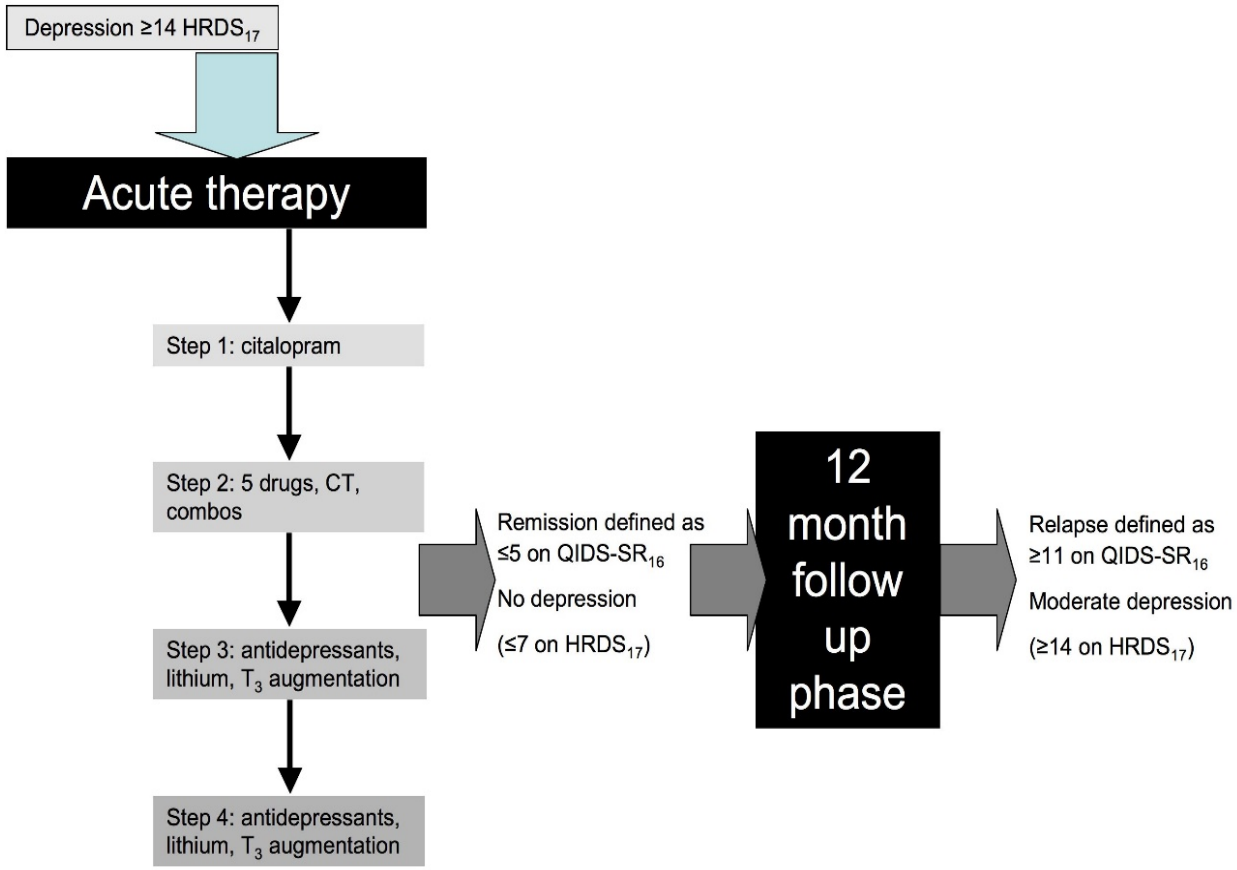


TABLE 2

KEY STAR*D LEARNING POINTS

- Nearly one-third of depressed patients will remit with optimized use of an initial SSRI treatment.
- Likelihood of remitting decreases with each subsequent treatment required.
- Maximally tolerated dosing is often required for full remission.
- Time to remission may take as long as 14 weeks.
- Switching to a different SSRI or to a non-SSRI are both reasonable options following inadequate response with an initial SSRI.
- Augmentation with bupropion or buspirone are both reasonable options (though bupropion may be slightly preferable) following inadequate response with an initial SSRI.
- Full remission is associated with lower relapse rates.
- Disease management strategies are feasible in both primary care and specialty care settings.
- Self-report assessments, such as the QIDS-SR_{16}, can be easily incorporated into clinical practice to monitor response and guide dosing.

STAR*D=Sequenced Treatment Alternatives to Relieve Depression; SSRI=selective serotonin reuptake inhibitor; QIDS-SR_{16}=16-item Quick Inventory of Depressive Symptomatology-Self Report.

Ziffra MS, Gilmer WS. *Primary Psychiatry.* Vol 14, No 1. 2007.

First Line Medication Treatment

Medication	Dose Range	P450 inhibitor	Substrate
Fluoxetine (Prozac)	10mg-40mg	2D6(s), 2C19(s), 3A4(w)	2C9,2C19,2D6
Mirtazapine (Remeron)	15mg-60mg	-----	1A2, 2D6
Bupropion (Wellbutrin)	150mg-450mg	2D6(s)	2B6,
Sertraline (Zoloft)	25mg-200mg	2D6(w), 2C9(w)	2C9,2C19,2D6
Paroxetine (Paxil)	20mg-60mg	2D6(s), 2C9(m), 2C19(w)	2D6
Citalopram (Celexa)	20mg-40mg	2D6(w)	2C19,2D6
Escitalopram (Lexapro)	10mg-40mg	2D6(w)	2C19 ,2D6
Duloxetine (Cymbalta)	20mg-60 mg	2D6(m)	1A2, 2D6
Venlafaxine (Effexor)	75mg-300mg	2D6(w)	2C19,2D6
Trazodone (Desyrel)	50mg-600mg	-----	3A4, 2D6

(s)= strong inhibitor, (m)= moderate inhibitor, (w) weak inhibitor

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SSRIs (Trade name)	1A2	2C9/10	2C19	2D6	3A3/4
Citalopram (Celexa)	•	•	•	++	•
Escitalopram (Lexapro)	•	•	•	++	•
Fluoxetine (Prozac)	•	++	++	+++	+
Fluvoxamine (Luvox)	+++	+++	+++	•	++
Sertraline (Zoloft)	•	•	•	+	•
Paroxetine (Paxil, Paxil CR)	•	•	•	+++	•
SNRIs	**1A2**	**2C9/10**	**2C19**	**2D6**	**3A3/4**
Duloxetine (Cymbalta)	•	•	•	++	•
Venlafaxine ER (Effexor XR)	•	•	•	•	•
Newer Antidepressants	**1A2**	**2C9/10**	**2C19**	**2D6**	**3A4/4**
Bupropion (Wellbutrin)	?	?	?	+++	?
Nefazodone (Serzone)	•	•	•	•	+++

* Percent increase in plasma levels of a coadministered drug dependent on this CYP enzyme for its clearance: •=no or minimal effect (< 20%); ++=moderate effect (50–150%); +=mild effect (20–50%); +++=substantial effect (>150%); ?=unknown.

DDI=drug-drug interaction; CYP=cytochrome P450; SSRIs=selective serotonin reuptake inhibitors; SNRIs=selective norepinephrine reuptake inhibitors; CR=controlled release; XR=extended release.

Preskorn SH, Flockhart D. *Primary Psychiatry.* Vol 13, No 4. 2006.

THANK YOU!

ANY QUESTIONS?