Mind Matters ECHO

Module: Depression
Session 4: Understanding and Managing the Side-Effects of SSRIs and Other Antidepressants

August 18, 2021

Project ECHO®

Mount Sinai Health Partners

Welcome!

- Pre-survey: bitly.com/mindmatters4
- Hub team introductions
- Disclosures
- Questions during presentations

Case Presentation

Dr. Danuta Jankowska

Internal Medicine

Patient Information

Demographic Information	• 45 year old cis-female • Lives alone • Commercial insurance • College Educated (4-year) • Employed full time (Hospital Clerk)
Medical History	• Diabetes (II) • Obesity • HTN
Current Medications	• Wellbutrin SR 150mg po Q12hr • Escitalopram 20mg po qd • Trulicity 0.75mg • Topamax 50mg po qd • Triamterene-HCTZ 75-50mg po qd
Past Psychiatric Medications	• Vivitrol Inj • Naltrexone 50mg po • Propranolol 60mg • Trazadone 50mg • Escitalopram 10mg

Patient Information

Current Psychiatric Diagnoses	• MDD • Anxiety • Insomnia • Alcohol Dependence (for 5+ years; precipitated by divorce)
Current Symptoms	**Depression** • Sleep difficulties for 3+ years • Appetite—For 5+ years, falls off diabetic dietary regimen intermittently during episodes of worsening of depression Energy—For 3+ years, fatigue for 4/7 days per week (average) corresponding with periods of low treatment compliance • Lack of motivation—stays in bed all day and feels unmotivated to perform basic hygiene tasks, ADLs and maintaining social connections (poor social supports at the present time) • No suicidality **Anxiety** • Palpitations • Sweating • Trembling • Chest Pain • Hot Flashes • GI Symptoms • Compulsive behaviors Symptoms in general manifest during the time patient misses on her performance at work, weekends. Difficulties with controlling automatic negative thoughts, feelings of resentment and guilt of non-compliance, that has a direct link to alcohol use which in turn causes missed days at work, and non-compliance with treatment.
Current Substance Use Concerns	• Continues to maintain sobriety on a day to day basis for the most part with a basic support system when compliant with treatments (ex. with counselor, psychotherapist, sponsor at AA, PMD) except during weekends or periods of feeling lonely • Feelings of depression and other lead to relapses→ misses her medical appointments and therapy sessions due to feeling unmotivated

Patient Information

Past Psychiatric History	• Completion of Rehab with a history of relapse, alongside feelings of guilt and resentment • Prior psychiatric hospitalization—following excessive alcohol use/ not attending work for a week/ found at home by neighbor
Family Psychiatric and Medical History	• MDD—Mother • Substance/Alcohol Use—Father
History of Trauma	• Verbal and emotional abuse as adult

Patient & Case Information

Current Treatment Plan for Psychiatric Conditions	• Control MDD and Anxiety with medications • Maintain compliance with visits • Maximize activity level • Improve sleep hygiene • Attend psychotherapy and support groups for maintaining sobriety • Follow up with psychiatrist (obstacle is financial barrier due to out-of-network providers)
Areas of Support and Consultation Being Sought	• Strategies for engaging the patient and/or their caregivers/family
Main Question	• How to engage the patient in treatment compliance?

Didactic Presentation

Dr. Yekaterina Angelova

Assistant Professor of Psychiatry,

Consultation-Liaison Psychiatry Division

Icahn School of Medicine at Mount Sinai

Effective Treatments for Depression: Pharmacology & Side Effect Considerations

Yekaterina (Katie) Angelova, MD
Assistant Professor of Psychiatry,
Consultation-Liaison Psychiatry Division
Icahn School of Medicine at Mount Sinai

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Disclosures

- I do not have conflicts of interest to disclose for this learning session.

- I affirm that all discussions of drug use will be consistent with either FDA or compendia (i.e. medical textbook, published medical literature, professional society guidelines) approved indications.

Picking Up Where We Left Off…

- Antidepressants: classes, when to consider, and side effect profiles.
- Can “side effects” be used to our advantage? I.e. sedation, increased appetite.
- Side effect management, and when to consider switching to alternative agent.

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 d/o.

- **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 sx.
  - 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 assoc. 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.

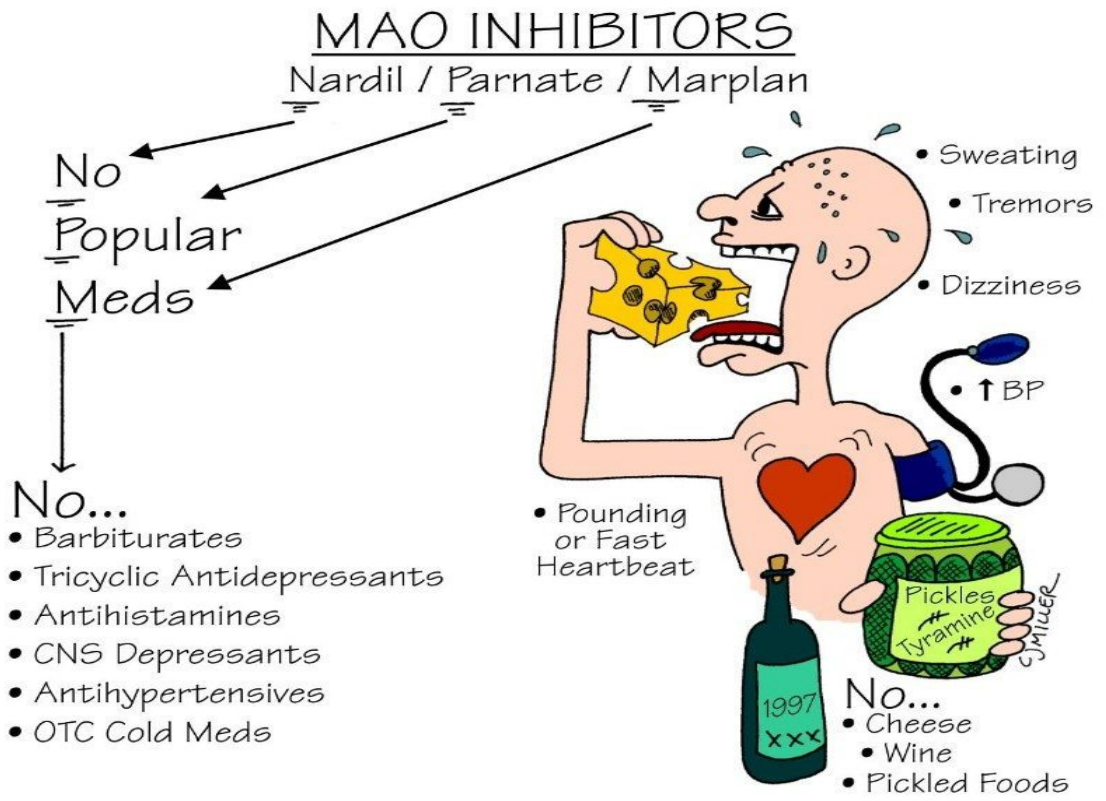
PROS	CONS
Used in MDD, bipolar depression (less likely to trigger mania), smoking cessation, ADHD, comorbid cocaine d/o. Activating, weight-neutral, no sexual side effects.	Seizure risk is 2% with 600 mg and 0.1% with 300-450 mg. *BUT, contraindicated in patients with seizure disorders and eating disorders*. 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)
- Consider reassessing diagnosis, e.g. bipolar depression vs. unipolar depression.
- TAPER antidepressants / cross-titrate with another agent.

STAR*D Study, 2000-2004 (FYI)

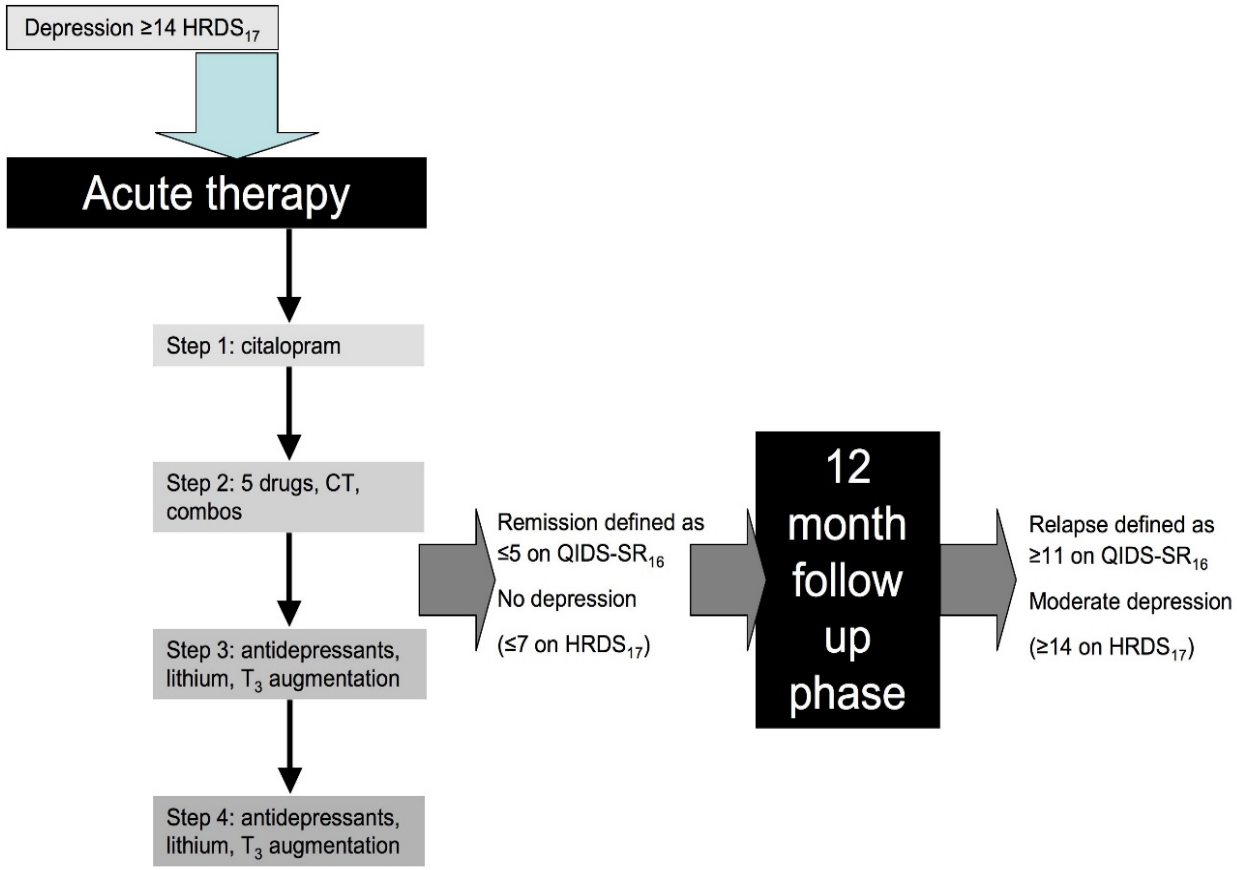


TABLE 2

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

Academy of Consultation-Liaison Psychiatry

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.