Medication Selection for Depression: Picking the Best Treatment Option

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Objectives

1. List antidepressant medications and describe their mechanism of action, side effect profile and relative costs
2. Identify barriers and strategies to improve patient adherence to depression treatment plans
3. Formulate a Plan B for patients who do not want to take or do not have improvement from prescription antidepressants

Why is this topic important:

It's a common, recurrent, disabling problem that PCPs are being asked to treat

- Depression has a prevalence of 12% worldwide [1]
- In the US major depression ranks SECOND among all diseases and injuries as a cause of disability [2]
- Majority (67%) of depressed patients are obtaining prescriptions from primary care physicians rather than from psychiatrists [3]
- Risk of recurrence is >40% after single episode of major depression and patients with two episodes have 75% risk of recurrence [4]
- Nearly 50% of depressed primary patients do not initiate treatment i.e. do not attend first psychotherapy visit or fill antidepressant prescription [5]

Case 1

- Joe is a healthy 23 yo Male about to graduate with a degree in English from UW Madison. He shares an apartment with his girlfriend of 3 years who was just accepted to a law school out of state and then told him that she does not want him to move with her and he is devastated. He hasn't felt like going out for drinks with his coworkers at the restaurant where he is a part time server at the end of his shift. He isn't sleeping well. He just did poorly on an exam because he couldn't concentrate. He feels totally uncertain and "kind of" hopeless about his future. He denies thoughts of suicide but says sometimes he wishes he wouldn't wake up because he feels miserable and depressed so at the moment life does not seem worth living.
- What else do you need to ask him?

Case 1 Additional Information to Obtain

- Has he ever had a manic episode?
- Has he had an episode of depression before? Did he take an antidepressant in the past that was helpful?
- Is there a family history of depression or completed suicide?
- If he has a depressed family member does he know which medication is helpful to him/her?
- If he graduates will he still have health insurance? Will he have to pay for medication out of pocket?
- Does he have access to a gun?
- How many alcoholic beverages is he having in an average week?
- Would he prefer psychotherapy or antidepressant medication?
- How long has he been feeling this way?

What treatment would you like to offer Joe for his depression?

A. SSRI
B. SNRI
C. Bupropion
D. Mirtazapine
E. Watchful waiting- if his PHQ <15 because this is a situational depression and will likely improve over time without treatment
F. Psychotherapy referral – due to his age there is a risk that antidepressants will increase suicidal thoughts

What is the best treatment option for depression?

- Whatever your patient is willing to do
- It can be very time consuming to verify PHQ-9 depression screen, gather more information to confirm the diagnosis, but when it comes to formulating the management plan, a patient centered approach is essential
- If your patient does not fill the antidepressant medication prescription or does not take it after picking the bottle up there is a 0% chance of it helping them

No Antidepressant is clearly superior than the rest (except ECT) so selection is based on:

- Safety (is your patient going to overdose on it, cardiac arrhythmias)
- Tolerability based on side effect profile
- Ease of use- number of times a day patient must take it
- Patient preferences
- Cost of medication

SSRIs Selective Serotonin Reuptake Inhibitors

Medication	PROS cost, tolerability	CONS delayed orgasm, nausea, vomiting, antiplatelet
Citalopram	Middle of the pack half life	QT prolongation
Escitalopram	Ease of titration	Headache reported in 24%
Fluoxetine	Good for non-adherent, activating	Drug interactions, takes a long time to wash out
Sertraline	Ideal if patient has constipation	Diarrhea, multiple steps to titrate
Paroxetine	Has some sedation	Withdrawal, weight gain, drug interactions

SNRIs Serotonin-Norepinephrine Reuptake inhibitors

Medication	Pros 2 neurotransmitters	Cons- may only work on 2 neurotransmitters at higher doses
Venlafaxine	May help hot flashes	nausea, hypertension
Desvenlafaxine	Can dose adjust if patient has liver/kidney dysfunction	expensive
Duloxetine	Studied for pain	Can't use if ESRD or hepatic impairment
Levomilnacipran	It's sister drug has an indication for fibromyalgia	expensive

Others

- **Bupropion** noradrenergic dopaminergic reuptake inhibitor Risk of seizures, may cause insomnia, does not cause weight gain, does not have sexual side effects
- **Mirtazapine** noradrenergic weight gain, constipation, sedating so helps with sleep, improves nausea and appetite,

No Medication Works if Your Patient Does not take it

- Intolerable side effects
- Too expensive
- Not provided with education about how long it takes to work

Improving Adherence to Antidepressants

- Education
- Collaborative care with psychiatrist embedded in primary care clinic and a Case Manager (nurse with mental health background)
- Telemedicine based collaborative care
- Follow up with a clinician within 4 weeks of initial presentation with depression

Document Meaningful Evidence of Clinical Improvement to Reassess at Follow Up

- Helpful to have a collateral informant i.e. spouse, parent
- "Joe antidepressants take 4-6 weeks to work, so sometimes the improvement is so gradual it can be hard for the patient to notice that it is working. When I see you again, how will we be able to tell that your medication is helping you?"

✓I will care about my future again and have applied for some jobs

✓I will be able to actually enjoy going out with my friends

✓It won't take me 90 minutes to fall asleep because of negative thoughts

✓I will be looking forward to graduation instead of dreading it because I feel so unsure about myself

Case 1 Continued

- Joe has never been depressed before or taken an antidepressant. He has been depressed for 3 weeks and it's not getting better. He has only drank alcohol once in past 3 weeks. He cannot describe a manic episode. His insurance coverage is not good so medication cost is a concern and he may only have partial coverage for 4 psychotherapy visits a year. He does not have a gun. No one in his family has committed suicide and he does not think anyone has been treated for depression but he knows his mom was prescribed venlafaxine for her hot flashes and said it's a terrible medication because it did not help and made her throw up.

Walmart $4 for 30 days, $10 for 90

- Citalopram 20mg or 40mg
- Fluoxetine 20mg or 40mg
- Lithium 300mg
- Nortriptyline 50mg
- Paroxetine 20mg, 30mg, 40mg
- Amitriptyline 100mg

Walgreens Savings Club Member

Tier 1 $5 for 30 days $10 for 90 days	Tier 2 $10 for 30 days $20 for 90 days	Tier 3 $15 for 30 days $30 for 90 days
Fluoxetine 20mg	Citalopram 20mg or 40mg	Sertraline 50mg or 100mg
	Fluoxetine 40mg	Nortriptyline 75mg
	Lithium 300mg	Lithium 600mg
	Mirtazapine 15mg	
	Paroxetine 20mg	Paroxetine 30mg

Sam's Plus Members (fee to join)but largest "extra value drug list"

Escitalopram, citalopram, paroxetine, sertraline, fluoxetine
Venlafaxine
Mirtazapine
Bupropion
Lithium
Imipramine, amitriptyline, nortriptyline

STAR*D Sequenced Treatment Alternatives to Relieve Depression NIMH trial 1998-2005

- Prospective multicenter study of 3671 outpatients with unipolar major depression , 12 weeks at each level

1. Citalopram
2. Switch bupropion, Cognitive Therapy, Sertraline, Venlafaxine OR Augment Bupropion, buspirone, cognitive therapy
3. Switch nortriptyline or mirtazapine OR Augment Lithium or triiodothyronine
4. Switch Tranylcypromine, Venlafaxine + mirtazapine

What Did We Learn from STAR*D

- PCPs can prescribe tricyclics and MAOIs
- We probably do not treat patients long enough to get to remission, the 12 weeks was sometimes extended to 14 weeks
- Remission should be the goal rather than partial response because it may decrease the risk of relapse
- We need to push the dosages higher in some patients: citalopram in this study went up to 60mg, mirtazapine up to 60mg, nortriptyline up to 150mg, lithium 450-900mg, venlafaxine XR 300mg qday
- Some patients who do not respond to one SSRI citalopram will respond to another sertraline

Case 1

- Joe is started on citalopram and titrated up to 40mg daily. 3 months after initial visit he is doing pretty well. He has had some job interviews. He is enjoying going out with friends. He has gone out on some dates with women and discovered he really likes the sexual side effects of his citalopram because he can "last longer." However, he does not feel totally back to his normal self. It is taking him about 45 minutes to fall asleep because he finds himself dwelling on having been rejected by his long term girlfriend which causes him to doubt his own desirability. An EKG shows a QTc of 432msec. What is your next step in treatment?

Case 1- Partial Response

A. Push the citalopram to 60mg daily
B. Add bupropion
C. Add quetiapine XR
D. Add aripiprazole
E. Add lithium
F. Refer for cognitive behavioral or interpersonal therapy
G. Add mirtazapine

FDA Approved to Augment Antidepressant

- Quetiapine XR
- Aripiprazole
- Olanzapine in combination with fluoxetine for treatment resistant depression

Bauer M, Fortshoff A, Baethge C, et al. Lithium Augmentation therapy in refractory depression- Update 2002. Eur Arch Psychiatry Clin Neurosci (2003) 253:132-139

- "Summarizing all open and controlled studies, approximately 50% of patients responded to lithium augmentation within 4 weeks. In conclusion lithium is the foremost and most well-documented augmentation strategy in refractory depression. Therefore, it should be considered a first-line treatment strategy in patients with major depression who do not adequately respond to standard antidepressants."
- Standard dose 600-800mg a day (range 250mg to 1200mg daily) level 0.6

Barowsky J and Schwartz TL. An Evidence-based approach to augmentation and combination strategies for treatment resistant depression. Psychiatry 2006 July 3(7):42-61

- Table 1 Relative Efficacy of Augmentation Strategies based on Strength of evidence (double blind placebo controlled RCTs to case reports)

Lithium	1
Antipsychotics	0.51
Thyroid hormone	0.43
Buspirone	0.35
Pindolol	0.25
Omega 3 Fatty Acids	0.25
Modafinil	0.22
Stimulants	0.22
yohimbine	0.22
lamotrigine	0.09 (published 2006)

Case 2

- Mrs. Jones is a 48 year old female with a remote hx of post partum depression who presents with headaches, irritable bowel symptoms, poor sleep, irritability. Symptoms started after her husband told her she should not accept a job promotion because it would mean needing to travel. She feels guilty like she is selfish for wanting to focus on her career while her youngest child is still at home. She is having a hard time focusing at work. She denies suicidality. She is agreeable to starting treatment for depression but cannot recall which medication she took in the past. She does not want to gain weight because she is already struggling with feeling unattractive, and if she has sexual side effects and cannot achieve orgasm "the one activity I still enjoy will be ruined." She took one of her 17 year olds ADHD stimulants the other day and it seemed to help.

What treatment do you want to offer Mrs. Jones?

A. Whatever stimulant her son has because it helped
B. Vilazodone
C. Desipramine
D. Bupropion
E. Psychotherapy
F. A prescription for exercise

Tricyclic /Tetracyclic Antidepressants, MAOIs

- **Nortriptyline**
- **Desipramine**
- Amitriptyline, amoxapine, doxepin, imipramine, protriptyline, trimipramine, clomipramine, maprotiline

- Selegiline, isocarboxaid, phenelzine, tranylcypromine

Serotonin Modulators SSRI + partial agonism at other serotonin receptors

- Vilazodone- GI side effects, no weight gain, does not seem to have the sexual dysfunction
- Vortioxetine GI side effects, some trials in geriatric patients $317.90 a month at Sam's Club

"I won't take psych drugs for my depression"

- Alternative Medications: St John's Wort, SAMe
- Psychotherapy Cognitive Behavioral Therapy or Interpersonal
- Exercise

Psychotherapy

- SilverCloud online cognitive behavioral therapy
- https://www.psychologytoday.com

Verified checked that they have valid unrestricted license to practice in state

Search by zip code

Check insurance/sliding scale for uninsured

Age range, language spoken, Type of therapy

- CBT Cognitive Behavioral Therapy, DBT Dialectical Behavior Therapy, or Interpersonal Therapy

Exercise Rethorst CD, Trivedi MH. Evidence-based recommendations for the prescription of exercise for major depressive disorder. J Psychiatr Pract 2013; 19:204.

- Data for both aerobic exercise and resistance training being helpful
- 3-5 times a week
- 45-60 minutes per session
- Aerobic exercise at 50-85% of maximum heart rate
- Resistance training: 3 sets of 8 reps of 80% of the maximum weight that can be lifted for a single repetition
- Patients should be willing to participate in exercise for 10 weeks

SUMMARY: Take Home Points

1. The best treatment option is whatever your patient is willing to do so take a patient centered approach
2. The benefits of antidepressant medications have such a gradual onset that they can be hard to perceive, so document a list of concrete markers of meaningful improvement that you can assess when the patient follows up with you
3. Add a tricyclic to to your repertoire: nortriptyline or desipramine
4. Lithium is probably the most cost effective augmentation strategy for patients having a partial response to an antidepressant
5. For patients who are unwilling to take antidepressant medications consider referral for CBT psychotherapy, alternative medications such as St John's Wort, SAMe or exercise

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