

Depression for Primary Care

Gabrielle Marzani-Nissen, MD

Associate Professor, Department of Psychiatry and
Neurobehavioral Sciences

- **Martha H is a 52 year old female with a history of neuropathic pain who presents to you.**
- **You have just started screening all your patients with a 2 question screening tool:**
 - 1. During the past month, have you often been bothered by feeling down, depressed or hopeless?**
 - 2. During the past month, have you often been bothered by little interest or pleasure in doing things?**
- *You are pleased with yourself (and you should be) as you know that there is a sensitivity and specificity of 97% and 67% respectively when tested in a primary care setting on patients who are not on antidepressant or any psychotropic medications.*
- **You download the 9 question Patient Health Questionnaire (PHQ-9) from [pfizer.com/phq-9](https://www.pfizer.com/phq-9)**
She scores a 16 indicating a moderately severe depression.
- **She is reporting depression for the first time in her life. She is postmenopausal.**
- **She has an atypical depression (contrasted with a “classic depression) – eating more, sleeping more, low energy. She is not suicidal. She has not been using alcohol to self medicate.**
- **You do some basic studies to make sure it is not due to her thyroid for example. It isn’t. Her neuropathic pain is not completely under control, but does not seem to be the reason for the depression.**
 - **What should you do?**

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(Use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Pearls

1. She has neuropathic pain.

- In selecting her antidepressant, you should know that Selective Serotonin Re-uptake Inhibitors (SSRI's) can make pain syndromes worse.
- You should select an Serotonin Norepinephrine Re-uptake Inhibitor (SNRI). Norepinephrine helps with pain.

2. She is menopausal.

- Post menopausal women respond better to SNRI's than SSRI's.
- So do men.
- Pre-menopausal women respond well to SSRI's (It's the presence of estrogen, we think),

Martha H - continued

- If she had a thyroid problem, you could still start her on a medication for depression. It can take a while to get the thyroid regulated so people will do this.
- You should use medication if it is a moderate to severe depression. You can offer/refer to therapy (combo works better than either alone), and it can be therapy alone if depression is mild, sometimes moderate, but not if severe.
- You can have her augment with folate. A study of folate (500mcg) added to fluoxetine (Prozac) showed improvement in both depression and homocysteine levels in women. Current recs are 800mcg for folate (one study says 5mg) and 1 mg of B12 (references in back)

Martha H

- If she doesn't respond well to antidepressants, it would be reasonable to consider HRT – studies show better outcomes and faster response rates (references in back)
- Some medications, like Venlafaxine (Effexor), are SSRI's at lower doses and SNRI's at higher doses. You should push up the dose and not assume that it has failed until you are at least 225mg. It takes 2-4 weeks to kick in – and usually at least 2 months to fully take effect. If you have hit a plateau then increase.
- There is a difference between the short and longer acting Venlafaxine. The side effects of the short acting version are much worse (nausea and GI) – which is why we used to call it 'Side Effexor'. This is one where you really want to use the XR.
- Check her Blood Pressure...
- **BY THE WAY:**
 - Duloxetine (Cymbalta) starts as an SNRI. Has potentially more drug interactions.
 - Desvenlafaxine (Pristiq) – is just the active metabolite of Venlafaxine.

Fred F -

- 24 year old man with a history of depression since childhood
- First depression as a teen (around puberty)
- Sleeping more, eating more, just wiped out and hard to get out of bed
- No psychotic symptoms
- Some alcohol, but fairly infrequently
- Maybe some ADD, a bit of a smoker
- Had done “OK” on Zoloft once before but stopped it – can’t remember why
- Screening is a 14 for depression on the PHQ-9 (scale is 1-27), cut off between mild/moderate is 10, mod/severe is 15

Fred

- You try another SSRI – use anything but paroxetine (Paxil), which “packs on the pounds” and has a very short $t_{1/2}$ life so causes a horrible and nasty discontinuation syndrome and also has lots of med side effects.
 - By the way, if your patient wants to get off paroxetine and can't because every time you get to 5mg he or she freaks out – which by the way is the drug discontinuation and not the person – start them on a low dose – say 10mg of fluoxetine (Prozac), as it has a really long $t_{1/2}$ life, and then after a few weeks you can pull them off the last of the paroxetine and then pull off the fluoxetine

You picked an SSRI because you read the STAR*D trial (reference in back) and citalopram was recommended as first line. But, we will get to that later....

Fred takes it. On visit 2, he is back and you increase his citalopram (it's what you gave him). He goes home and comes back...

Fred comes back

- It would be too strong to say that he hates you, but he isn't pleased.
- He remembers why he didn't like this medication.
- It caused him to not care about anything and he is having sexual problems
- You screen him for a history of panic attacks, anorexia and bulimia. (I'll tell you why in a sec...) All neg. By the way, all his labs were neg too.
- Is there a reason why he just doesn't care?

Yes, there is!

- Fred doesn't care because he has an amotivation syndrome which is a consequence of his SSRI. It's not his depression.
If he were in another set of circumstances, you would DECREASE the dose of the medication as it helps with the amotivation syndrome
- But, because of this plus his sex drive, and that possible ADD and definite smoking story, you want to try Bupropion (Wellbutrin) SR or XL would be fine – good for you!
- You start it and it works. He'll need to be on meds for 3-5 years
- If he was otherwise getting better, but the sex drive was affecting him, could you just augment with Bupropion? Yes, you could.
- If he had a history of depression and anxiety, could you use Bupropion? Yes, the issue is that it can trigger panic attacks.
- Seizure worries? The data was with the short acting IR and doses up to 450mg. At lower and longer acting form, risk is similar to an SNRI. (see references)

Mark D -

- Mark D, age 45, comes to you
- It's winter and he is really down. Winters are bad for him.
- Depressions since childhood, like age 6. Has been a bunch of meds in the past, none have worked great, Zoloft wasn't awful..
- He screens 24 on the PHQ-9 – no suicidal thoughts
- Pretty happy in the spring/summer
- He is on Carbamazepine for a seizure disorder and a low dose of Elavil for sleep – his neurologist started this.
- You start him on Sertraline (Zoloft)
- He comes back and isn't feeling great. Just not “right”
- What should you check?

Answer...

- Check his sodium
- (His sodium is low – 128)
- Who knew that Carbamazepine is a tri-cyclic like medication? The addition of the SSRI prompted the three drugs to cause a plummeting in his sodium
- How could you have avoided this?

Check for Drug Interactions

- Please check to make sure you don't have drug interactions with these meds and other ones.
- The older meds work through p 450 2D6, newer ones work through 3A4. The system is active in the liver and in the gut. By the way, women have more 3A4 activity in the gut than do men, which is, in part, why metabolism is different.
- **BY THE WAY – use of SNRIs and SSRIs DECREASE tamoxifen levels and have led to breast cancer recurrence!**
- Use Micromedix or your source of choice.
- I personally like to look at Indiana University's site:
- *Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007).*
 - medicine.iupui.edu/clinpharm/ddis/main-table

Something else you may want to know about

- The vast majority of serotonin hangs out in platelets
- Serotonergic antidepressants appear to be involved in bleeding events
- The first literature (in the Netherlands) noted that patients on these agents required more blood transfusions intra-operatively during hip and knee surgeries. Some debate now (see references).
- Literature is noting an increase in upper GI bleeds, but mainly with elderly and especially with non-selective NSAIDs and/or aspirin (see references).
- Consider the other medications that individuals are on; consider an SSRI a form of blood thinner.

Here are a few hints to know about Mark

- It is not typical to develop depression in early childhood. Depression tends to hit around puberty. That isn't to say that it doesn't happen, particularly if the had some form of trauma in childhood. If someone has a childhood (5, 6, 7) onset of depression, they have a much higher incidence of bipolar disorder, particularly if the depression had psychotic features.
- Men who present with atypical features (eat more, sleep more, etc) also appear to have a higher incidence of bipolar illness. There is some literature to suggest that Seasonal Affective Disorder may be on this continuum.
- Mark also happens to be on a mood stabilizer. If hadn't been the antidepressant might have triggered a mixed, hypomanic or manic state. If someone presents with a long history of intractable depression with this kind of story, they might have a bipolar depression which will require a mood stabilizer.
- It is one of the reasons we need to follow closely when we start new meds. New panic attacks, racing thoughts, sleeplessness and restlessness may be hints.

How long to treat?

- Martha, single episode - six months to one year
- Fred, had a recurrence - 3-5 years
- Mark, more than three episodes - medications for life.
- The reason is that there can be treatment failures if you stop the medication and restart it or the dose may need to be raised.
- Risk of relapse is greatest during first 6 months of recovery

Differential Diagnosis -selective

- Medications
- Hypothyroidism, Obstructive Sleep Apnea (common)
- Vitamin D deficiency
- Pancreatic CA (board question, for a new dx)
- Undiagnosed neurologic pathology: tumors/ multiple sclerosis/Delirium/Dementias (Parkinson's Disease/Multi-infarct Dementia (requires an MRI not CT)
- Metabolic disorders, acute intermittent porphyria, renal failure, anemia, heavy metals, SLE, RA
- Labs that need to be considered: CBC, U/A, TFT's, VDRL, B12/Folate, Vitamin D, Chemistries, EKG, MRI

Factors with increase risk of suicide

- Demographics: male, recent loss, never married, older
- Symptoms: severe depression, substance abuse, anxiety
- hopelessness, psychosis (esp. command hallucinations), severe illness
- History: h/o suicide attempts (SA), FH of SA/suicide
- Suicidal thinking, plan, means, absence of factor that would stop patient from completing plan, rehearsal

Reference Material – Typical v Atypical

Melancholic/Classic

“classic depression”,
Don't sleep, don't eat
guilt early am awakening
Depression worse in am
Affects males more than females

Atypical

Mood reactivity (mood brightens in response to actual or potential positive events)
Two or more: weight gain, increase in appetite and/or sleep, leaden paralysis,
long standing pattern of rejection sensitivity (even when not depressed)
Women and bipolar individuals affected most

Seasonal Affective Disorder – (lights helpful, use 10,000 Lux)

Screening Tests – Use one to see how things are progressing as well as for screening

- **Beck Depression Inventory for Primary Care (BDI-PC) – 97% sensitive and 99% specific - 21-question multiple choice self report inventory – need to purchase it**
- **The Patient Health Questionnaire (PHQ-9) – a subcomponent of PRIME-MD – has a sensitivity/specificity of up to 88%, free**
- **Quick Inventory of Depressive Symptomatology (QIDS) – 16 items – both s & s about 80%, may be more helpful for atypical depression**
- **The WHO-5 Wellbeing Index (performed as well as PHQ-9) both sensitive and specific up to 88%, free**

Evidence based screening tests –

- **3 Gold Standard Rating Scales For Depression (just so you have them)**
- The Beck Depression Inventory (BDI) [27] (patient-rated)
- Inventory of Depressive Symptomatology (IDS or QIDS) [35] (patient-rated or clinician administered)
- The Hamilton Rating Scale for Depression (HAM-D or HRSD) [2] (clinician administered) – used in research a lot

Sequenced Treatment Alternatives to Relieve Depression STAR*D Trial

- <http://www.edc.gsph.pitt.edu/stard/>

Level 1 -- Citalopram (Celexa) , 12 to 14 weeks. If symptom free – follow up for 12 m. on med

Level 2 -- those who had intolerable side effects or not symptom free, option to switch or add to citalopram

- *Switch group -- randomly assigned to sertraline (Zoloft), bupropion-SR (Wellbutrin), or venlafaxine-XR (Effexor).*
- *Add on group -- randomly assigned either the non-SSRI antidepressant bupropion-SR (Wellbutrin), or buspirone (BuSpar),*
- If symptom free – follow up for 12 months on med/s

Level 3 -- those who had intolerable side effects or not symptom free option of either switching or adding on.

- *Switch group -- randomly assigned to either mirtazapine (Remeron) or to nortriptyline (Aventyl or Pamelor) for up to 14 weeks.*
- *Add on - randomly prescribed either lithium or triiodothyronine (T3)*

Level 4 -- described as treatment resistant, taken off all meds, then

- *randomly switched to (MAOI) tranylcypromine (Parnate) or combination of venlafaxine extended release (Effexor XR) with mirtazapine (Remeron).*

References for screening tests:

- *For the 2 screening questions:*
 - *Arroll B, Khin N, Kerse N. Screening for depression in primary care with two verbally asked questions: cross sectional study. BMJ. 2003;327:1144-1146.*
- *Lowe B, Kroenke K, Herzog W, Grafe K. Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). J Affect Disord. 2004;81:61-66.*
- *Henkel V, Mergl R, Kohnen R, et al. Identifying depression in primary care: a comparison of different methods in a prospective cohort study. BMJ. 2003; 326, 200.*
- *Steer RA, Cavalieri TA, Leonard DM., et al. Use of the beck depression inventory for primary care to screen for major depression disorders. Gen Hosp Psychiatry 1999; 21, 106. Mar / Apr.*
- *Rush, et al. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biological Psychiatry. 2003; 54 (5) 573-583*

References on Folate & Vit B12

- Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. *J Affect Disorders*. 2000 Nov;60(2):121-30.
- Papakostas GI, et al. Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 1: predictors of clinical response in fluoxetine-resistant depression. *J Clin Psychiatry*. 2004 Aug;65(8):1090-5.
- Venkatasubramanian R, Kumar CN, Pandey RS. A randomized double-blind comparison of fluoxetine augmentation by high and low dosage folic acid in patients with depressive episodes. *J Affective Disord*. 2013 Sep 5;150(2):644-8.

References for treatment of women around the menopause

- Cohen LS, Soares CN, Joffe H. Diagnosis and management of mood disorders during the menopausal transition. *Am J Med.* 2005 Dec 19;118 Suppl 12B:93-7.
- Soares CN, et al. Treatment of menopause-related mood disturbances. *CNS Spectr.* 2005 Jun;10(6):489-97.
- Graziottin A, Serafini A. Depression and the menopause: why antidepressants are not enough? *Menopause Int.* 2009 Jun;15(2):76-81.

Risk of Bleed and SSRIs – from Pub Med

This is the study from the Netherlands :

Movig et al. Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. Arch Intern Med. 2003 Oct 27;163(19):2354-8.

- **“CONCLUSIONS:** Use of serotonergic antidepressants is associated with an increased risk of bleeding and subsequent need for blood transfusion during orthopedic surgery. The bleeding could be attributed to inhibition of serotonin-mediated platelet activation.”

This is a later study with different conclusions:

Van Haelst IM, et al. Use of serotonergic antidepressants and bleeding risk in orthopedic patients. Anesthesiology. 2010 Mar;112(3):631-6.

- **“CONCLUSIONS:** Patients undergoing total hip arthroplasty who continue the use of serotonergic antidepressants show a significantly higher, but clinically unimportant, intraoperative blood loss, without an increase in perioperative transfusion requirements.”

Risk of Bleed and SSRI's –

From Pub Med

Yuan Y, Tsoi K, Hunt RH. Selective serotonin reuptake inhibitors and risk of upper GI bleeding: confusion or confounding? Am J Med. 2006 Sep;119(9):719-27

- “CONCLUSIONS: Only a few epidemiology studies have investigated the association between SSRIs and UGIB. They provide weak evidence to support the hypothesis of a link between SSRIs and UGIB at a population level. Available evidence shows that concurrent use of NSAIDs or aspirin with SSRIs greatly increases the risk of UGIB. The preventive strategy should be considered in those SSRI users at high risk, especially the elderly or those with a history of UGIB and taking nonselective NSAIDs or aspirin.”

Seizure Risk and antidepressants

- Montgomery SA. Antidepressants and seizures: emphasis on newer agents and clinical implications. Int J Clinical Pract. 2005. Dec;59(12):1435-40.
- **Has a nice chart.**
- Rate of seizure in Bupropion SR is actually lower (0.1%) than fluoxetine (0.2%) and citalopram (0.3%). The rate of IR (short acting Bupropion is 0.4% at doses up to 450mg).
- Notes that although Venlafaxine has a 0.3% chance of seizure, Venlafaxine ER has a zero percent of seizure...which is interesting as I personally caused one after giving this drug to a woman in my clinic, a woman who had no prior history of seizure until low and behold, seizure history undiagnosed, but right there on her EEG...

Other Resources:

1. The American Psychiatric Association's Clinical Practice Guidelines. <http://www.psychiatry.org/practice/clinical-practice-guidelines> & psychiatryonline.org/guidelines.aspx
2. Some nice commentary and data on treatment of depression:

Prim Care Companion J Clin Psychiatry. 2007; 9(3): 214–223. Preventing Recurrent Depression: Long-Term Treatment for Major Depressive Disorder