Psychopharmacology for Collaborative Care Managers

Keep a Perspective

Treating patients with depression and anxiety:

- Three main tools
  - Biology – which may mean a psychiatric med.
  - Psychology – therapy of various kinds
  - Patient behavior and self management
- Which of these is more effective?
- Which is easier for the patient to do?
- The goal is to return a patient to functioning and normal emotional range – use all the tools

Scenario

Dr. Kim brings a patient to you and says, “Mr. M. here is an 70 yo man with hypertension and coronary artery disease. He recently moved to an assisted care facility; his family says he isn’t like himself anymore as he doesn’t want to do anything.

They think he’s depressed. Could you ask your psychiatrist if we should start an antidepressant?

What more information is needed?

Does the patient have an indicated condition to use an antidepressant?

- **Clinical history**
  - Does the chief complaint and history suggest a primary depressive or anxiety disorder according to DSM5 criteria?
  - Is there evidence that might suggest another reason for the way the patient is presenting?

- Symptom measures – like your blood pressure measure. A high level = look closer, not diagnose hypertension.
- Depression
  - **PHQ-9 ≥ 10**
- Anxiety
  - **GAD7 ≥ 10**

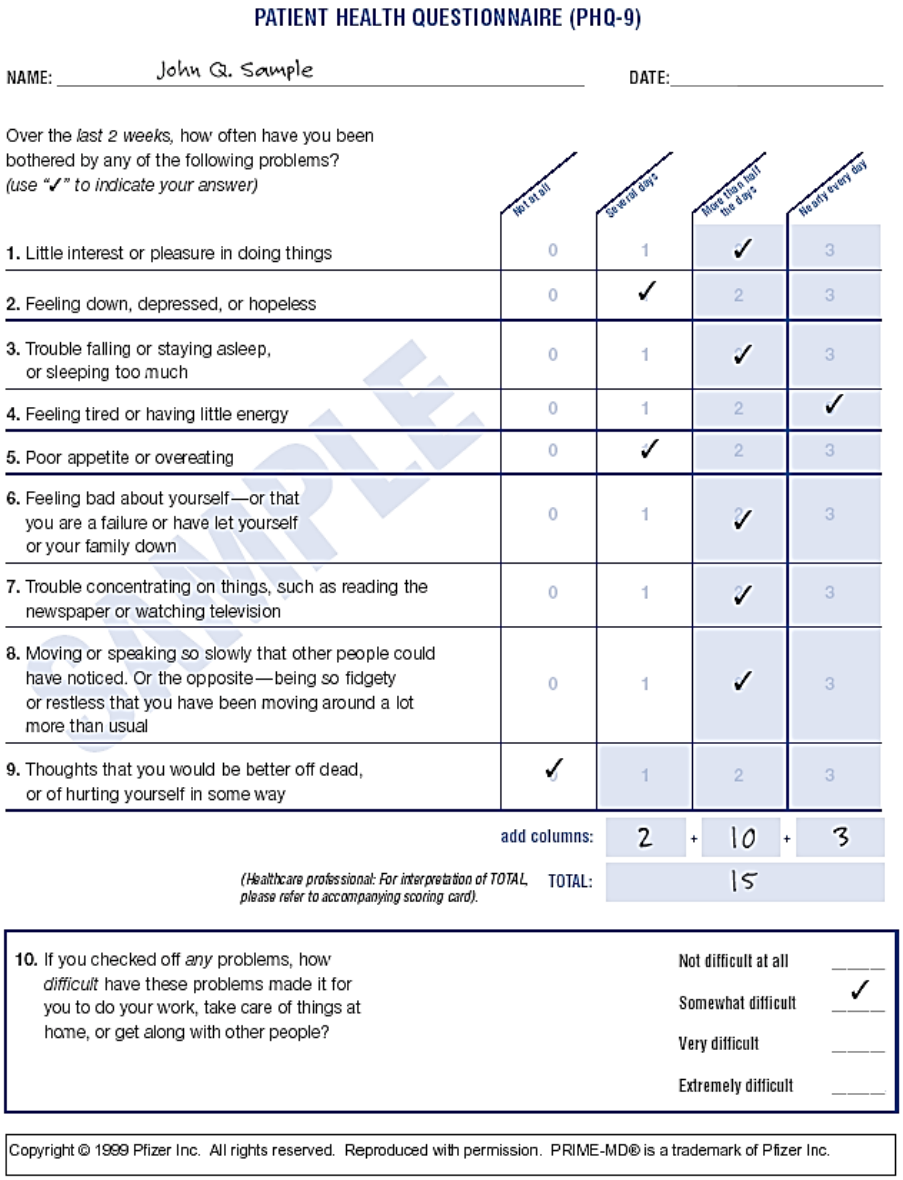
Depression

- Common
  - Lifetime prevalence of 16% (>20% in women)
  - 10-20 percent of primary care patients are depressed.
- Dangerous
  - Depression history = 2 X risk of CAD
  - Increases risk of HTN and stroke by 50%
  - Depression post MI = 6 X risk of death in 18 mos*

» Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after miocardial infarction Circulation 1995; 15;91;999-1005.

Screening , Monitoring Tool - PHQ-9

- Quick, many languages
- First 2 questions must have a positive score
- Score ≥ 10
  - For Major Depression
    - Sensitivity 88%
    - Specificity 88%
- Mild (5),mod (10), mod severe (15) severe depression (20)



PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: John Q. Sample DATE:

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	✓	3
2. Feeling down, depressed, or hopeless	0	✓	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	✓	3
4. Feeling tired or having little energy	0	1	2	✓
5. Poor appetite or overeating	0	✓	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	✓	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	✓	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	✓	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	✓	1	2	3
add columns:		2	+ 10	+ 3
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:			15	

10. 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 ____

*Patient Health Questionnaire (PHQ-9). Spitzer et al. Copyright Pfizer Inc. 1999

Could be something else…

Bereavement – feelings tied to loss	**Thyroid disease** – weight changes, energy changes	**Cancer** – weight and energy changes, pain
Substance induced mood disorder – tied to use patterns	**Bipolar disorder** – rapid improvement, mania/hypomania (earlier onset (mean age 24)	**Attention deficit** – concentration and irritability more than sadness or loss of interest
Dementia – lack of interest or initiative	**Pain disorders** – related to opiate use	**Persistent Depressive disorder** – last 2 years or more with no break

Could be Major depression plus…

- Among patients diagnosed with Major Depression
  - Anxiety (75% w features, 37% w diagnosis lifetime prev.)
  - Bipolar features (mixed features in 16%)
  - Personality Disorder (32% w diagnosis)
  - Substance abuse (58% w diagnosis)
- Insomnia/sleep apnea
- Pain, Thyroid disorder
- Social determinant – abuse, housing, finances, etc.

Hasin et al. Jama Psychiatry 2018

Information to gather as we decide on a medication

Medical

- Hypothyroid, pain, sleep issues, evidence of cognitive decline, fall risk, pregnancy, other medications…

Psychological/Social

- Pattern – when did this start? What was going on?
- Drinking or drug use?
- Life stressors and timing of mood changes
- Past history of depression – what happened?
  - Past medication trials – dose, duration, response?
- Other mental health problems
- Current life stressors, level of functionin and supports

Comorbid anxiety? GAD7

Over the last 2 weeks, how often have you been bothered by any of the following problems?
Please circle your answers.

GAD-7	**Not at all sure**	**Several days**	**Over half the days**	**Nearly every day**
1. Feeling nervous, anxious, or on edge.	0	1	2	3
2. Not being able to stop or control worrying.	0	1	2	3
3. Worrying too much about different things.	0	1	2	3
4. Trouble relaxing.	0	1	2	3
5. Being so restless that it's hard to sit still.	0	1	2	3
6. Becoming easily annoyed or irritable.	0	1	2	3
7. Feeling afraid as if something awful might happen.	0	1	2	3

- GAD should not be diagnosed when only occurring with a mood disorder or better explained by other anxiety disorder
- Other symptoms of GAD: muscle tension, fatigue, insomnia, poor concentration
- Several types of anxiety - panic, OCD, social anxiety, PTSD

How does the data gathering impact the decision?

- Examples:
  - If no history of mood problems and symptoms came up after a sad event
    - Might want to work on coping first
  - If also has pain
    - Might look at an antidepressant that also helps pain
  - If on a drug that could cause drug interactions
    - Think about that drug when choosing a med
  - Failed responding to several antidepressants
    - Is there a pattern? Maybe try a different class?

Evaluation for Antidepressant (or Anti-anxiety) Medication

Is there a reason not to use an antidepressant (contraindication)?

Only in rare cases are SSRIs absolutely contraindicated

Does the patient have?:

Depression/anxiety secondary to another condition

- **We address that condition and check back**
- **Substance use disorders are not contraindications to antidepressant treatment**

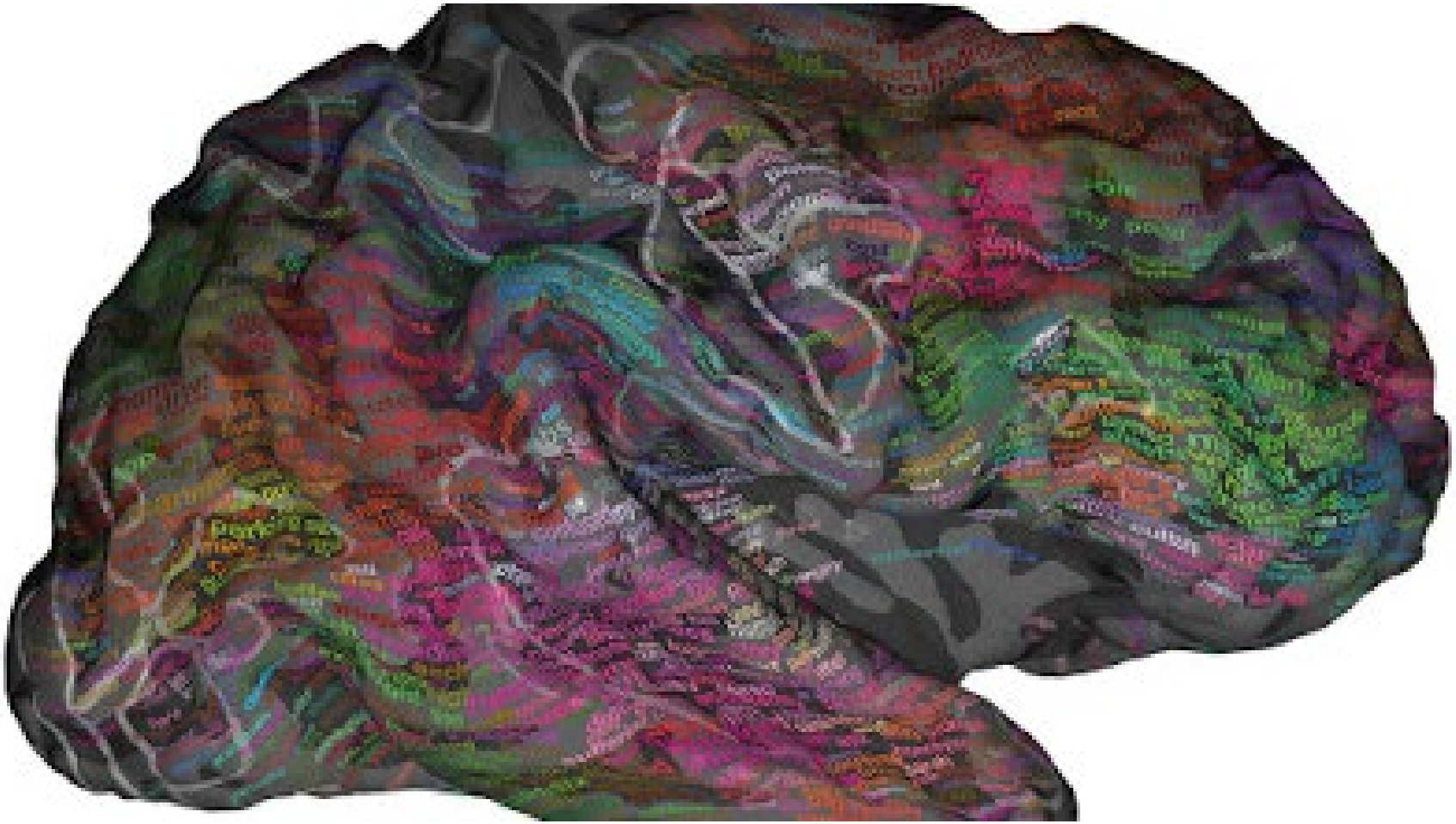
Bipolar disorder

- **<u>Antidepressants can lead to mood swings and/or mania if bipolar is the real issue</u>**
- **May still be effective for comorbid anxiety disorder**

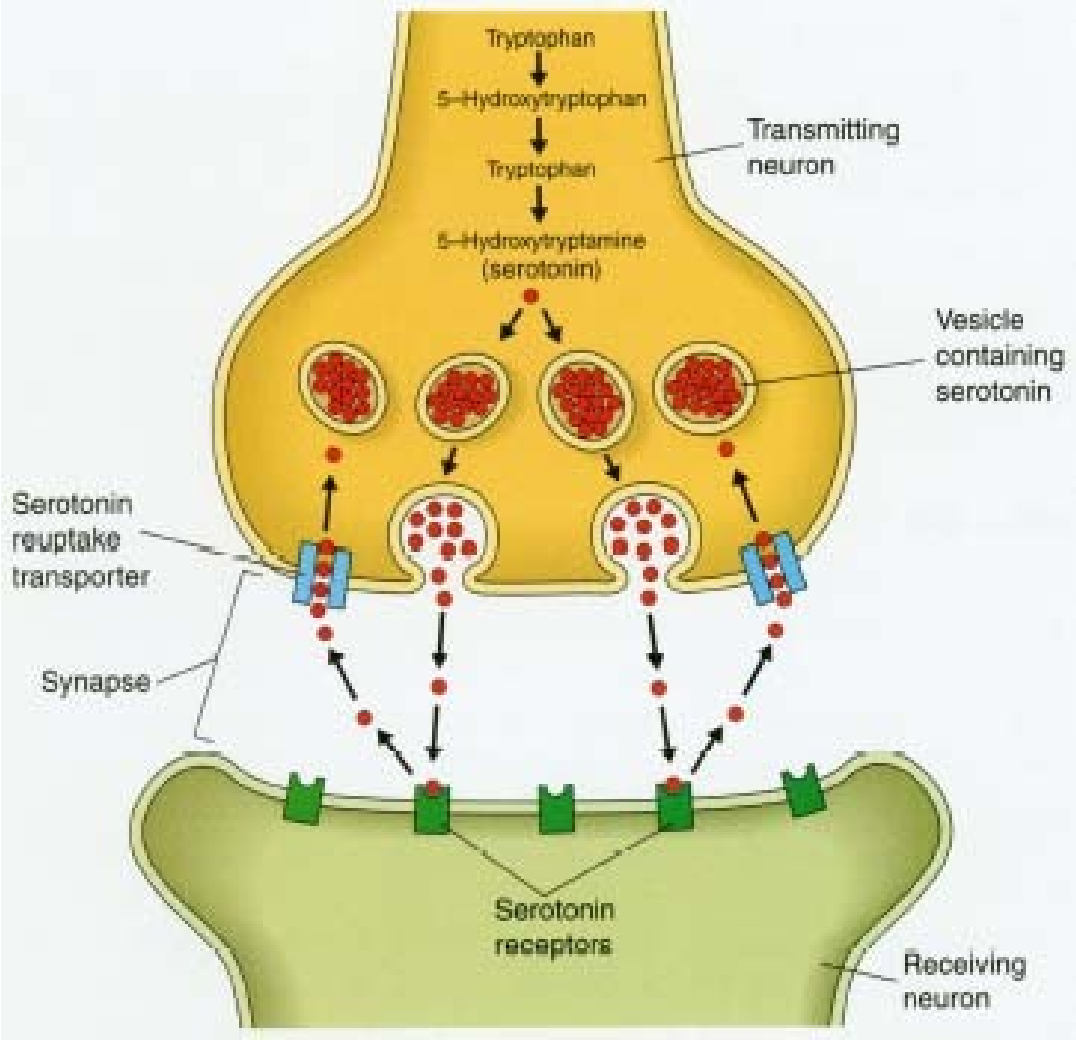
Medical condition or medications that would interact with antidepressant treatment

We also may find patients who have had bad reactions to antidepressants

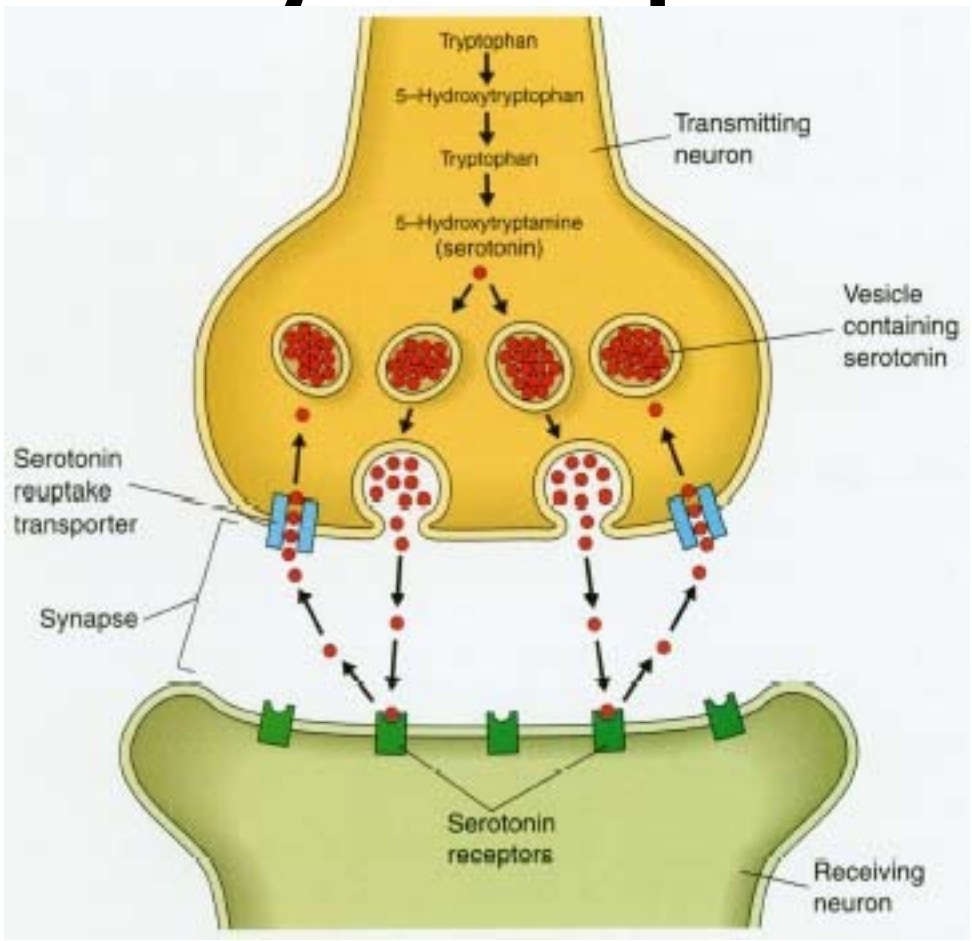
Mechanisms of Psychopharmacology



Neurotransmission



Psychotropic Sites of Action



Increase release

Decrease reuptake

Decrease breakdown

Direct receptor activation

Receptor modulation

Direct receptor blockade

Things to think about with medications

Half life – how long does it take for half of the medicine to leave my body

- Impacts how long to feel a benefit
- Impacts how likely we will see withdrawal

Does the medication impact the cytochrome p450 system?

- Enzymes that help break down medications
- Basis for drug interactions

Can the medication do more than one thing?

- Sleep and mood for example

Is this medication covered by insurance?

Makes my head spin, what do I tell patients?

Antidepressants aim to address the chemicals we all have in our brain to return you to normal mood

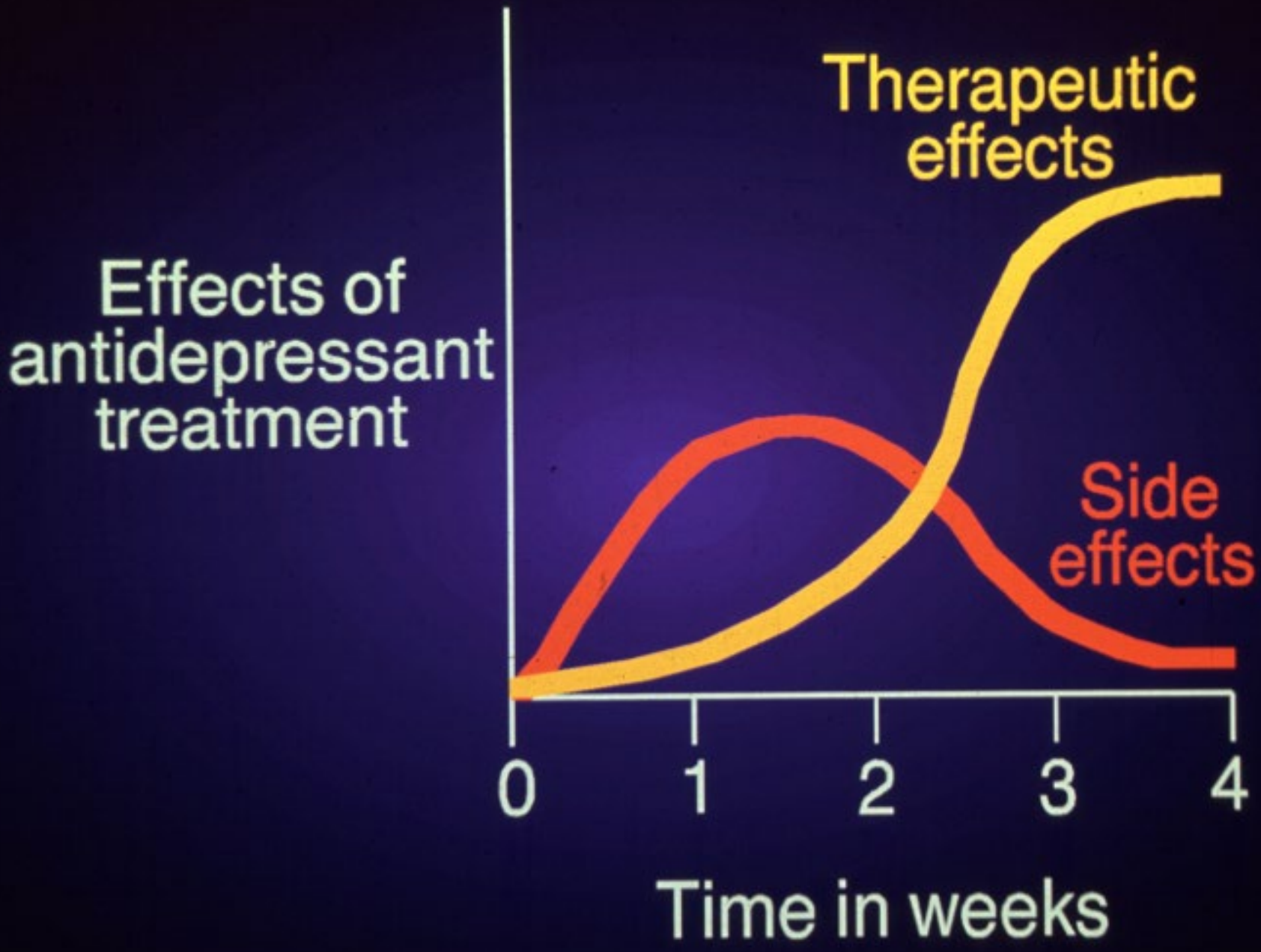
- Not to make you into someone else.
- They are NOT addictive

The initial effects on your body from the medicine are to increase those chemicals

- So you may see side effects at the start

The benefit comes from your body adjusting to that increase

- So we need to stay on the medicine to reach benefit


Therapeutic effects
Effects of antidepressant treatment
Side effects
0
1
2
3
4
Time in weeks

How long to wait?

Get to a minimal therapeutic dose

- Good sign if seeing some improvement in 2 weeks
- Leveling off of benefit in 6-8 weeks

Good to have a list of the medications and the dose ranges

- What is the minimal effective dose of each medicine?
- What is the usual maximum dose?

Neurotransmitters: Monoamines

Serotonin: CALM – Reduce strong negative emotions

- mood, anxiety, sleep, anger/aggression
- sexual functioning, gastrointestinal functioning

Norepinephrine: Can help with focus and pain

- mood, anxiety
- heart rate, blood pressure, “fight or flight”

Dopamine: enhancing versus blocking

- motivation, mood, psychosis, attention, cognition, reward
- motor activity, inhibits lactation

Histamine & Melatonin: sleep

Neurotransmitters: Other

GABA: Think of the Valium drugs here as well as gabapentin

- major inhibitory role, anxiety
- sedation, cognition

Glutamate: This is a work in progress but think ketamine

- major excitatory role, cognition, mood
- psychosis

Acetylcholine: blocking versus enhancing

- cognition and memory
- heart rate, bladder, gastrointestinal: “rest & digest”
- “anticholinergic” side effects

How to use this information

Explaining it to clients:

- Example: “This medication affects the level of a chemical called serotonin in the brain”

Helps to understand what are expected side effects

Establishes classes of medications (e.g. SSRIs or SNRIs)

- Easier to remember than learning each individually

Helps understand new medications

- Really new or “me too”?

Antidepressant Medications

Old-school Antidepressants

Monoamine Oxidase Inhibitors (MAOIs)

- Require strict dietary restrictions to avoid dangerous side effects, rarely used anymore

Tricyclic antidepressants (TCAs)

- Significant anticholinergic side effects
- Dangerous in overdose (cardiac arrhythmias)
- Still used for migraine headaches, nerve pain, sleep
  - Amitriptyline (Elavil), Nortriptyline (Pamelor), Doxepin (Sinequan)
- Generally not first choice for depression/anxiety
- Often see low dose at night added to another antidepressant but watch for drug interactions

More commonly used Antidepressants

SSRIs – serotonin recycling blocker

SNRIs – impacts serotonin AND norepinephrine

Bupropion (Wellbutrin) – serotonin not involved – impacts norepinephrine and dopamine

Mirtazapine (Remeron)

Trazodone – also serotonin in another way but is so sedating that used mostly for sleep

Others

SSRIs

- **Fluoxetine (Prozac)**
- **Sertraline (Zoloft)**
- **Paroxetine (Paxil)**
- **Citalopram (Celexa) & Escitalopram (Lexapro)**
- **Fluvoxamine (Luvox)**

- FDA approved for major depressive disorder
- This group is often picked when also having anxiety
- Some also approved for:
  - Posttraumatic stress disorder
  - Generalized anxiety disorder
  - Obsessive compulsive disorder
  - Social anxiety disorder

SSRIs: Common Side Effects

Gastrointestinal upset (nausea, diarrhea), usually transient over the first few days
Sexual side effects – difficulty with libido, erection, orgasm, reversible upon stopping medication
“Early activation” – transient period of increased anxiety, restlessness upon initiating treatment
Discontinuation syndrome – “Brain zaps”, electric shock-like sensations in the neck and head
Insomnia or somnolence
Weight gain, average about 1% per year

SSRIs & Serotonin Syndrome

- Serotonin Syndrome: uncommon but dangerous consequence of excessive serotonin activity
  - Symptoms: muscle rigidity, fever, agitation
- Causes: overdose of SSRI antidepressants or combination of medications that affect serotonin
- Other pro-serotonin drugs include:
  - Tramadol and other opiates
  - Triptans for migraine headaches
  - Stimulants and drugs of abuse: cocaine, ecstasy (MDMA)
  - Anti-nausea medications, some antibiotics
  - St. John's Wort, some herbal supplements

SSRIs: Differences within class

- Citalopram, escitalopram, and sertraline have the fewest interactions with other medications
  - Good for older patients on lots of medications
- Fluoxetine has the longest half-life
  - Possible better for patients apt to miss doses
  - Also most weight neutral
- Paroxetine may have greater anticholinergic side effects and worse discontinuation syndrome
  - Also more concerns in pregnancy

SNRIs

Venlafaxine (Effexor) & Desvenlafaxine (Pristiq)

Duloxetine (Cymbalta)

Levomilnacipran (Fetzima) – rarely used until generic

Block reuptake of serotonin and norepinephrine

Efficacy and side effects generally similar to SSRIs

Advantage vs. SSRIs: also effective for neuropathic pain (e.g. from diabetes, fibromyalgia)

Disadvantage vs. SSRIs: greater hypertensive effects

Bupropion (Wellbutrin)

- Mechanism: Inhibits norepinephrine and dopamine reuptake
- Effective for major depression and smoking cessation
- Common side effects: headache, insomnia
- Advantages vs. SSRIs: Less weight gain or sexual dysfunction
- Disadvantage vs. SSRIs: not effective for anxiety disorders
- Avoid in patient with a seizure history

Mirtazapine (Remeron)

- Complex mechanism: blocks some serotonin receptors while increasing serotonin and norepinephrine release
- Effective for major depression
- Common side effects: sedation and weight gain
- Advantage vs. SSRIs: useful if insomnia and weight loss are present, less sexual side effects
- Disadvantage vs. SSRIs: weight gain, not proven effective for comorbid anxiety disorders

SRI plus Serotonin Modulator

Vilazodone (Viibryd) – (2011)
Vortioxetine (Trintellix) – (2013)

Serotonin reuptake inhibitor and partial serotonin receptor activator

Might not be covered by insurance

Vilazodone may have less sexual side effects

Vortioxetine may help with cognitive issues in depression

No clear reason to expect these are better by being new.

Trazodone

Weak serotonin reuptake inhibitor, blocks and partially activates some serotonin receptors

Used most often for its primary side effect in low doses: sleep

Rare side effect: priapism (erection that won't go away)

Other common side effect: hangover

Choice of Antidepressant

- 38 year-old woman with depression and anxiety

A) Sertraline
B) Venlafaxine
C) Bupropion
D) Mirtazapine

- What if she also has ADHD symptoms but no anxiety?
- What if she also has chronic neuropathic pain?
- Remember, the patient has to keep taking the med (50% stop)
- There is no best antidepressant – choice is based on side effects, preferences, cost, comorbidities
  - Mayo antidepressant shared decision aid for a first medication choice
  - https://depressiondecisionaid.mayoclinic.org/index

What if initial treatment fails?

Up to 2/3^{rds} of patients fail initial treatment

Options for the next step include:

- Increasing dose
- Adding a second “augmenting” antidepressant from other class
  - SSRI + bupropion or mirtazapine are common choices
- Switching to another antidepressant (< 60% improvement)
  - SSRI to other SSRI is as good as switching to bupropion
- Augmenting with an antipsychotic or other medication
  - VA trial found augmentation with aripiprazole (Abilify) was more effective than switch to bupropion.

After 2 failures, scrutinize diagnosis, consider intensifying treatment

Other Common Psychotropic Medications

Benzodiazepines

- **Alprazolam (Xanax)**
- **Clonazepam (Klonopin)**
- **Lorazepam (Ativan)**
- **Diazepam (Valium)**

- Mechanism: act on GABA receptors to enhance GABA effects
- Indicated for panic disorder, generalized anxiety disorder
  - Also used to treat alcohol withdrawal
- Best if used short-term (in primary care)
- Not effective for depression or PTSD
- Potential for abuse and dependence
- Caution with driving, not to be mixed with alcohol
- Sudden withdrawal syndrome: anxiety, shakes, insomnia, seizures
- Can worsen cognition in elderly and may increase fall risk

Controlled Substance Prescribing

Benzo use doubles risk of opiate overdose

MAPS report required prior to prescribing

Only 30-day supply at a time (+/- refills)

Consider also:

- Urine drug screen for other substance use
- Patient contract
  - Only one doctor at a time
  - No early refills or replacement for lost medications
  - Attend all appointments

Other (non-addictive) anti-anxiety

- **Buspirone (Buspar) – indication is GAD**
  - Serotonin agonist, not effective for depression – but can augment
  - Takes weeks to work, significant GI side effects
- **Hydroxyzine (Atarax, Vistaril)**
  - Anti-histamine (like Benadryl), can be taken PRN, works immediately
  - Avoid in elderly (confusion, falls). Can impact EKG (QTc)
- **Gabapentin (Neurontin), Pregabalin (Lyrica) – also GABA system**
  - Works immediately, safe
  - Good for alcohol withdrawal and related anxiety & neuropathic pain
- **Prazosin (Minipress)**
  - Anti-hypertensive medication, increased dose gradually
  - Evidence primarily for PTSD-related nightmares
  - Effectiveness has been questioned recently

“Z” Drugs -- Hypnotics

Zolpidem (Ambien)

Eszopiclone (Lunesta)

Zaleplon (Sonata)

Act at same GABA site as benzodiazepines

Care when combining with other sedating medications (e.g., opiates, benzos)

Typically want to use for short term if possible

Higher doses (above max range) can be addictive

Have been associated with rare disordered behaviors during sleep (e.g., sleep walking)

Other Hypnotics ("Sleep Aids")

CBT for Insomnia recommended 1st line for chronic insomnia

- **Diphenhydramine (Benadryl, other OTCs)**
  - Stops working quickly, anticholinergic side effects
- **Melatonin**
  - Generally safe, not very effective long term
- **Sedating antidepressants: Doxepin, Trazodone, Mirtazapine**
- **Ramelteon (Rozerem): melatonin agonist**
  - Limited effectiveness
- **Belsomra (suvorexant): (2015)**
  - Orexin antagonist

Talking with Patients about Antidepressants

The nuts and bolts

- Antidepressants need to be taken **daily, NOT as needed**
- All antidepressant **take 2-4 weeks to see a benefit**
- Most side effects resolve in a few days, serious side effects are rare
- Antidepressant should be **continued for at least 6 months. Longer if recurrent serious episodes**
- If the first antidepressant doesn't work out, there are many other options – generally 60% rule (change/add)

Antidepressant FAQ

Q: Are antidepressants just a placebo?

A: Antidepressants trials consistently show superiority to placebo: about 30% will get better with a placebo compared to 40% with an antidepressant

- Placebo response is high with depression, some consider this part of antidepressant treatment

Antidepressant FAQ

Q: Do antidepressants cause suicide?

A: Although the FDA warns against an increase in suicidal thoughts and behaviors in those under 24 years old, there is no convincing evidence antidepressants result in an increase in suicide death. Epidemiologic studies suggest antidepressant use is associated with fewer suicides

Antidepressant FAQ

Q: Are antidepressants addictive?

A: Antidepressants are very rarely abused (no real street value) and have no dangerous withdrawal syndromes. Withdrawal occurs in some patients with short acting drugs – more uncomfortable than dangerous

Antidepressant FAQ

Q: Do antidepressants turn people into zombies?

A: Most antidepressants are not sedating nor cause problematic slowing of cognition. Some people report feeling overall less emotional on antidepressants. This may be a dose issue or a need to try another medicine. The goal is not lacking emotions but having normal range.

Antidepressant FAQ

Q: Am I going to be on this medication forever?

A: Recommend at least 6 months after achieving remission if first episode, indefinitely if multiple episodes. Message to patients is, “It’s up to you how long you take this medication, and whether you find the benefits outweigh the costs”

Conclusion

Antidepressants are effective, generally safe, and preferred by many patients

Keys are:	
	Rule out other causes of depression, including bipolar disorder and medical conditions
	Provide education to patients about antidepressant treatment, expected response time, and side effects
	Follow-up with patients to assess treatment response and to ensure changes are made when response is inadequate

Resources Related to Medications

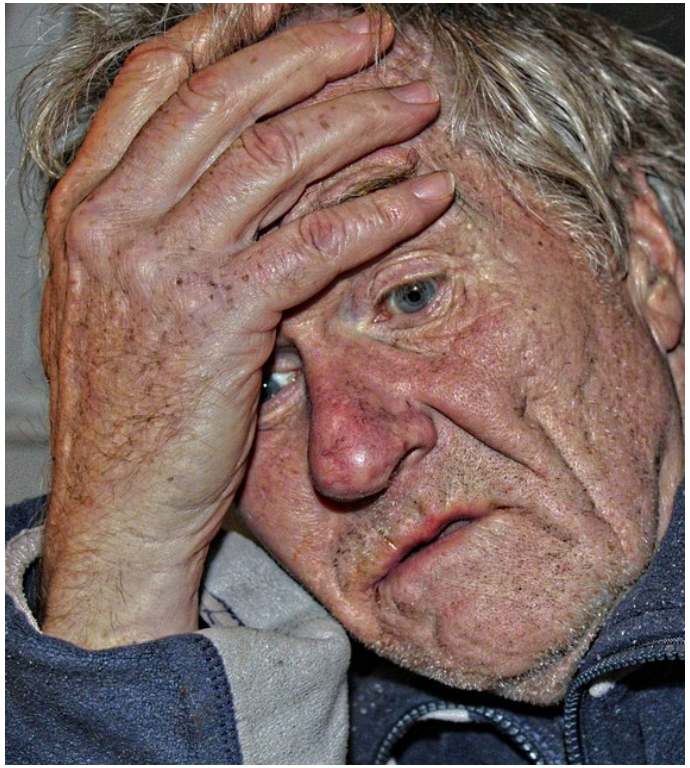
ICSI (Institute for Clinical Systems Improvement), Depression, Adult in primary care depression	https://www.icsi.org/guideline/depression/
APA (American Psychiatric Association) Practice Guidelines	https://psychiatryonline.org/guidelines
American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults	https://onlinelibrary.wiley.com/doi/full/10.1111/jgs.15767
Mayo antidepressant shared decision aid	https://depressiondecisionaid.mayoclinic.org/index
Psychopharmacology and Psychiatry Updates Psychopharmacology Institute (Podcasts)	https://podcasts.apple.com/us/podcast/psychopharmacology-and-psychiatry-updates/id1425185370 (free access to short and preview podcasts)

See Handout – Section 6

Case Follow-up

You assess Mr. M. and the medical record documentation

- His PHQ9 is 18, loss of interest started 1 month ago after moving
- No history of mania, substance use, or trauma. No past depression.
- Medical history positive for a heart attack 10 years ago with bypass surgery, has hypertension and high cholesterol, treated with medications (beta blocker, ace inhibitor, statin, and aspirin)
- All lab work is normal



Would starting an antidepressant at this point be appropriate?

What might be further areas of focus in this patient prior to starting antidepressant treatment?

  - Cognitive functioning
  - Recent change in medications, medical condition
  - Problems related to environment, socializing

Questions?

See Resource #7 Mental Health Apps