MI-CCSI
Center for Clinical Systems Improvement

Managing Depression

Today's Presenter

Mark Williams, MD

Mark D. Williams, M.D. is a psychiatrist at Mayo in Rochester, Minnesota. He is a Professor of Psychiatry at Mayo and has authored over 50 articles and book chapters mostly on topics related to integrated behavioral health. He has been a leader in the translation of evidence-based models of care coordination into primary care practices for adult and child depression, and patients with complex diseases both at Mayo and as a part of state and national initiatives.

MI-CCSI
Center for Clinical Systems Improvement

Disclosure

MI-CCSI, or the presenter, does not have any financial interest, relationships, or other potential conflicts, with respect to the material which will be covered in this presentation.

Outline

- What is clinical depression?
- How do we evaluate depression?
- Treatment options
- Self-management tools and approaches

Objectives

At the conclusion of this presentation the participant should…

- Be able to more clearly differentiate between reactive depression and Major Depression
- Demonstrate familiarity with comorbidities and other conditions that could look like Major Depression.
- Be familiar with the basic groups of antidepressants and be more able to explain them to patients

Depression – what do we mean by this word?

- *A state of feeling sad*
- *A mood disorder that is marked by varying degrees of sadness, despair, and loneliness and that is typically accompanied by inactivity, guilt, loss of concentration, social withdrawal, sleep disturbances, and sometimes suicidal tendencies.*
    - Merriam-Webster dictionary
- One of these definitions is experienced by everyone and overcome by time, moving forward, support from others, healthy behaviors, etc.
- The other can lead to hospitalization, disability, suicide, etc., and may require medications, therapy, and other interventions to recover.
    - Those who have less knowledge or experience may think the word only means the first definition – stigma and lack of support for those suffering.
        - Depression as we treat in health settings is not simply sadness

Clinical Settings: Depressive Disorders as defined by the Diagnostic and Statistical Manual (DSM)

- Major Depressive Disorder, Single and Recurrent Episodes
  - Seasonal Affective Disorder
- Persistent Depressive Disorder (Dysthymia)
- Premenstrual Dysphoric Disorder
- Substance/Medication-Induced Depressive Disorder
- Depressive Disorder Due to Another Medical Condition
- Unspecified Depressive Disorder

  - For this presentation, we are mostly concerned with how to address these conditions

Depression Can Affect Anyone

Many famous people have struggled with clinical depression:

- President Abraham Lincoln
- Rock star Bruce Springsteen
- Actress Kirsten Dunst (actress)
- Poet Sylvia Plath
- Statesman Winston Churchill
- Singer/actor Lady Gaga
- Athlete Michael Phelps

- Many more…all economic levels, races, etc.

Clinical 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.

Risk and Prognostic Factors

- Temperament – negative affectivity (neuroticism)
- Environment – adverse child experiences, income, education, racism, discrimination, etc.
- Genetics - 1st degree relatives of someone w Maj Dep have 2-4X risk.
- Physiology – women during hormonal changes – pre/post menstrual period and postpartum
- Other diagnoses that raise risk
  - Anxiety, trauma related, OCD, substance use, borderline personality
  - Diabetes, morbid obesity, cardiovascular disease

Mental Health and COVID-19: Early evidence of the pandemic's impact

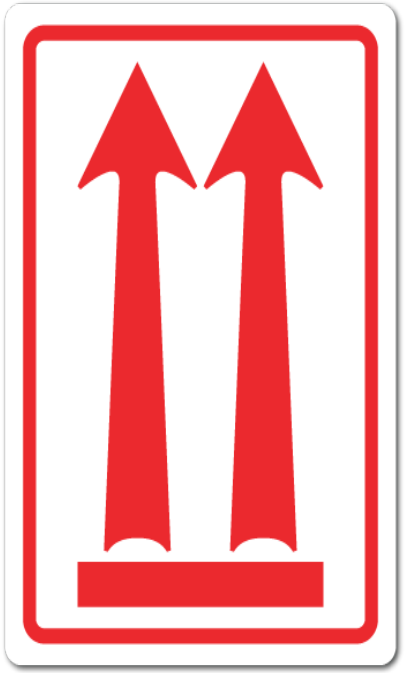
Scientific brief

2 March 2022

World Health Organization

27.6 %

MDD



25.6 %

Anxiety

Major Depressive Disorder – Symptoms (DSM5)

MI-CCSI
Center for Clinical Systems Improvement

5 or more of below in the same 2-week period. Must be a change from previous way of functioning. At least one of the first 2 symptoms must be present. Cannot be clearly from another medical condition.

1) **Mood down nearly daily with depression and hopelessness**
2) **Significant loss of interest and/or pleasure**
3) **Significant wt. loss/gain or appetite (up or down) nearly daily**
4) **Sleep disturbance – either too little or too much nearly daily**
5) **Psychomotor agitation or slowing nearly every day (observable)**
6) **Fatigue/loss of energy nearly every day**
7) **Guilt, negative self-talk, feeling like a failure nearly every day**
8) **Difficulty with concentration or indecisiveness nearly every day**
9) **Suicidal thoughts or nihilism**

Screening and Monitoring Tool - PHQ-9

- Quick, many languages
- Triggered by EPIC
- 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

PHQ-2

- First two questions on the PHQ-9
  - Depression
  - Anhedonia
    - Can help distinguish from medical concerns where sleep/appetite/energy might be issues
- <u>If both of these questions are negative, then cannot diagnose a major depression.</u>

What about diagnoses in this group

- Major Depressive Disorder, Single and Recurrent Episodes
  - Seasonal Affective Disorder - atypical symptoms in darker months
- Persistent Depressive Disorder (Dysthymia)- lower intensity ≥ 2 years
- Premenstrual Dysphoric Disorder – majority of menstrual cycles week before
- Substance/Medication-Induced Depressive Disorder – symptoms appear soon after intoxication or withdrawal from substance/medication
- Depressive Disorder Due to Another Medical Condition – evidence of direct physiologic link with a medical condition
- Unspecified Depressive Disorder – depressive symptoms causing clinically significant distress or impairment in social, occupational, or other area but do not meet full criteria for one of the above.

What also could be going on?

- 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

What else could this be?

- Bereavement – feelings tied to loss
- Thyroid disease – weight changes, energy changes
- Cancer – weight and energy changes, pain
- 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
- Personality disorder – chronic mood symptoms

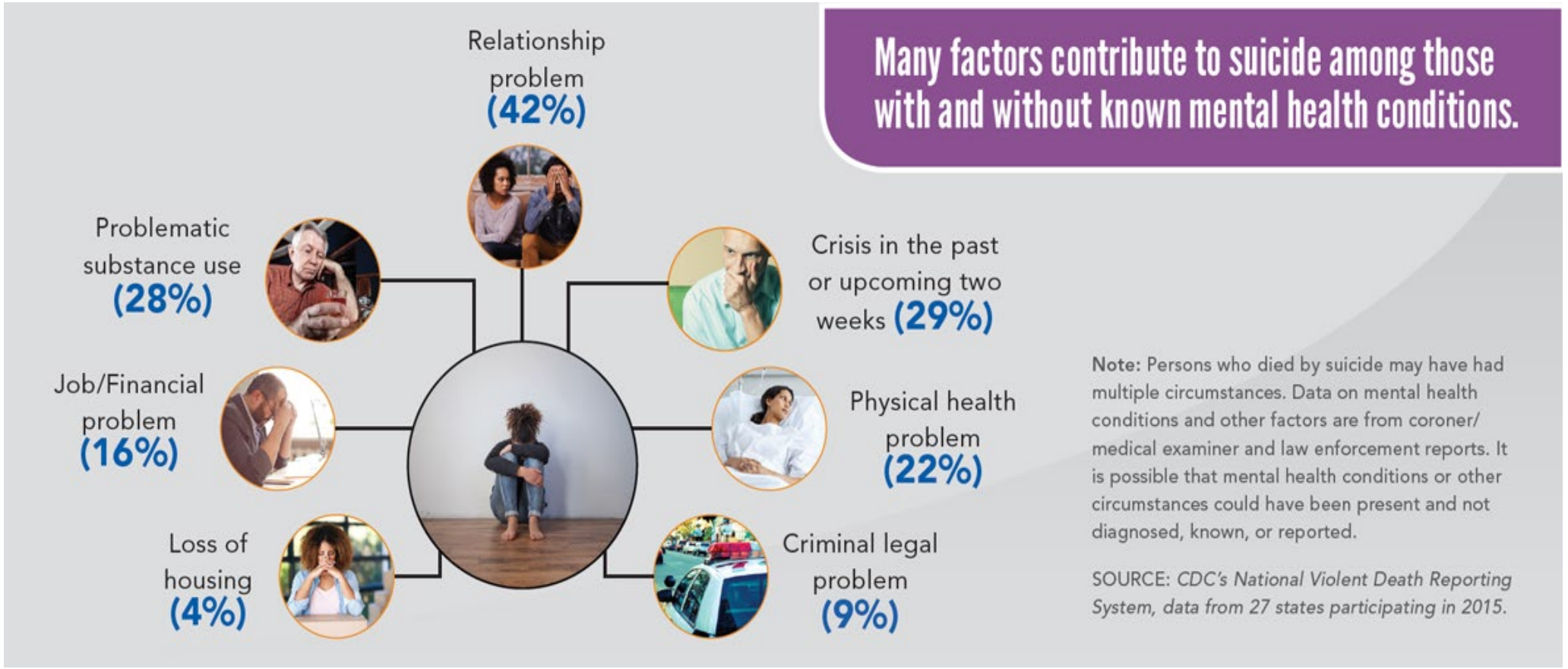
Evaluating someone with depression

- **Question often asked**
  - What are the symptoms of concern?
  - Timeline?
  - Impact on functioning?
  - Recent events/current situation/stressors?
  - Associated symptoms (anxiety, psychosis)
  - Attempts at treatment up to now – what has/has not helped?
  - Past psychiatric history?
  - Substance abuse issues?
  - Family history – bipolar is good to ask about
  - Past medical history
    - Thyroid, neurologic, new meds, pain, etc.
  - Ask about suicidality and, if positive guns.

Suicide Rates rising – Report by KFF Aug 2023

- From 2011 to 2022, over half a million lives lost to suicide in US
  - An adjusted suicide rate increase of 16%
  - 2022 had the highest number of suicides on record
    - Highest number of gun-related suicides on records (this cause driving the increase)
- Rates vary by state from less than 13.5/100,000 (11 states) up to 20.4 – 32.3/100,000 (12 states)
- More deaths in American Indian/Alaskan Native, males, and those in non-metro areas.
- Increased rates of suicide attempts in young females and the overall suicide death rate in adolescents went up 48%

Factors Elevating Suicide Risk



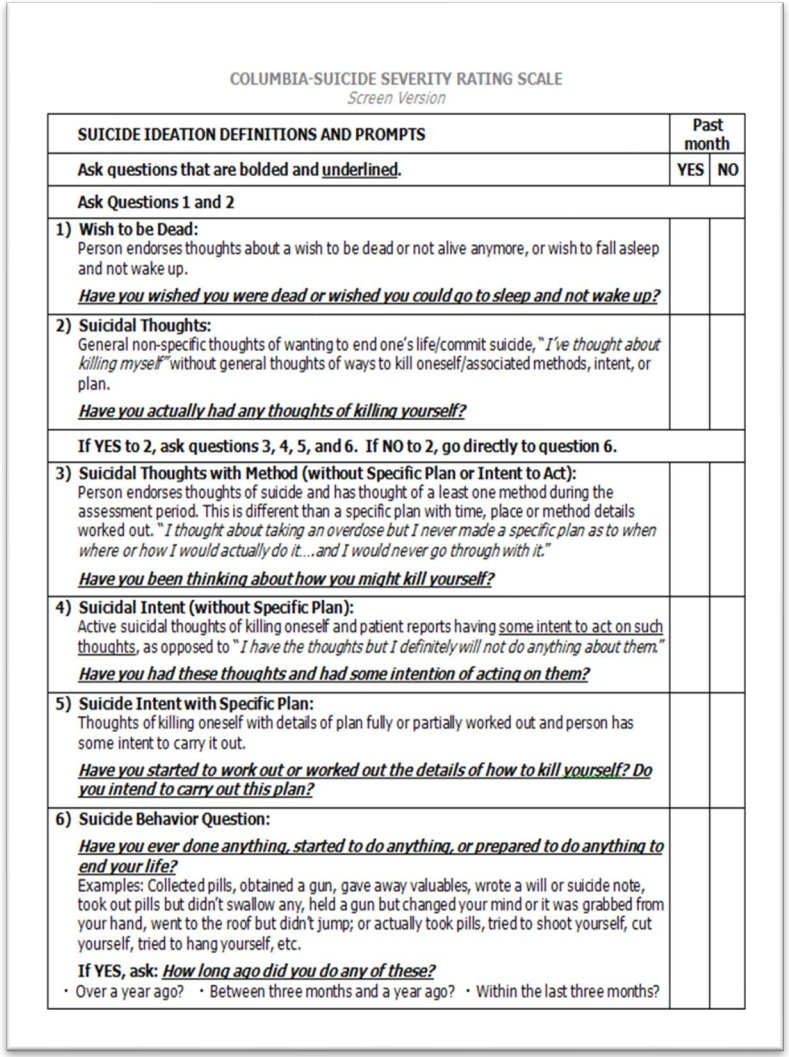
Bipolar disorder, or bipolar symptoms increase the risk of suicide

Presence of firearm in the house raises risk by 4X

Suicide Protective Factors

- **Social:** Family; having children; support system; connectedness
- **Access:** Clinical care for health problems
- **Personal:** Pregnancy, Cultural, religious/spiritual beliefs; purpose
- **Life Skills:** Coping; problem-solving
- **Psychological:** Fears of dying

C-SSRS Screener - suicide



COLUMBIA-SUICIDE SEVERITY RATING SCALE
Screen Version

SUICIDE IDEATION DEFINITIONS AND PROMPTS	Past month YES	NO
Ask questions that are bolded and underlined.		
Ask Questions 1 and 2		
1) Wish to be Dead: Person endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?***		
2) Suicidal Thoughts: General non-specific thoughts of wanting to end one's life/commit suicide, "*I've thought about killing myself*" without general thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?***		
If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.		
3) Suicidal Thoughts with Method (without Specific Plan or Intent to Act): Person endorses thoughts of suicide and has thought of a least one method during the assessment period. This is different than a specific plan with time, place or method details worked out. "*I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it....and I would never go through with it.*" ***Have you been thinking about how you might kill yourself?***		
4) Suicidal Intent (without Specific Plan): Active suicidal thoughts of killing oneself and patient reports having some intent to act on such thoughts, as opposed to "*I have the thoughts but I definitely will not do anything about them.*" ***Have you had these thoughts and had some intention of acting on them?***		
5) Suicide Intent with Specific Plan: Thoughts of killing oneself with details of plan fully or partially worked out and person has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***		
6) Suicide Behavior Question: ***Have you ever done anything, started to do anything, or prepared to do anything to end your life?*** Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc. **If YES, ask:** ***How long ago did you do any of these?*** · Over a year ago? · Between three months and a year ago? · Within the last three months?		

- The **screening version** of the CSSRS contains six questions:
- 1-5 reflect five types of ideation of increasing severity
- Question 6 is a suicidal behavior subscale – more proximal, more risk
- Questions 1, 2, and 6 are always asked; regardless of preceding negative responses
- A positive response on Question 3 indicates moderate level of risk. A positive response on either Question 4 or 5 indicates a high level of risk.

http://mayoweb.mayo.edu/sp-forms/mc1800-mc1899/mc1887-178.pdf

Depression Treatment options

- Mild depression with no past history
  - Watch and wait
    - Improve healthy coping, behavioral activation, remove alcohol, etc.
- Moderate depression
  - Consider therapy or medications
    - Equally effective – how to find evidence-based providers…
- Serious depression
  - Possible need for medications AND therapy
    - follow up in some way – high reoccurrence rate
- With all – attend to comorbidities and encourage healthy life behaviors.

Realistic expectations?

Education about a broader approach than medications alone

Social determinants

Depression versus unhappiness

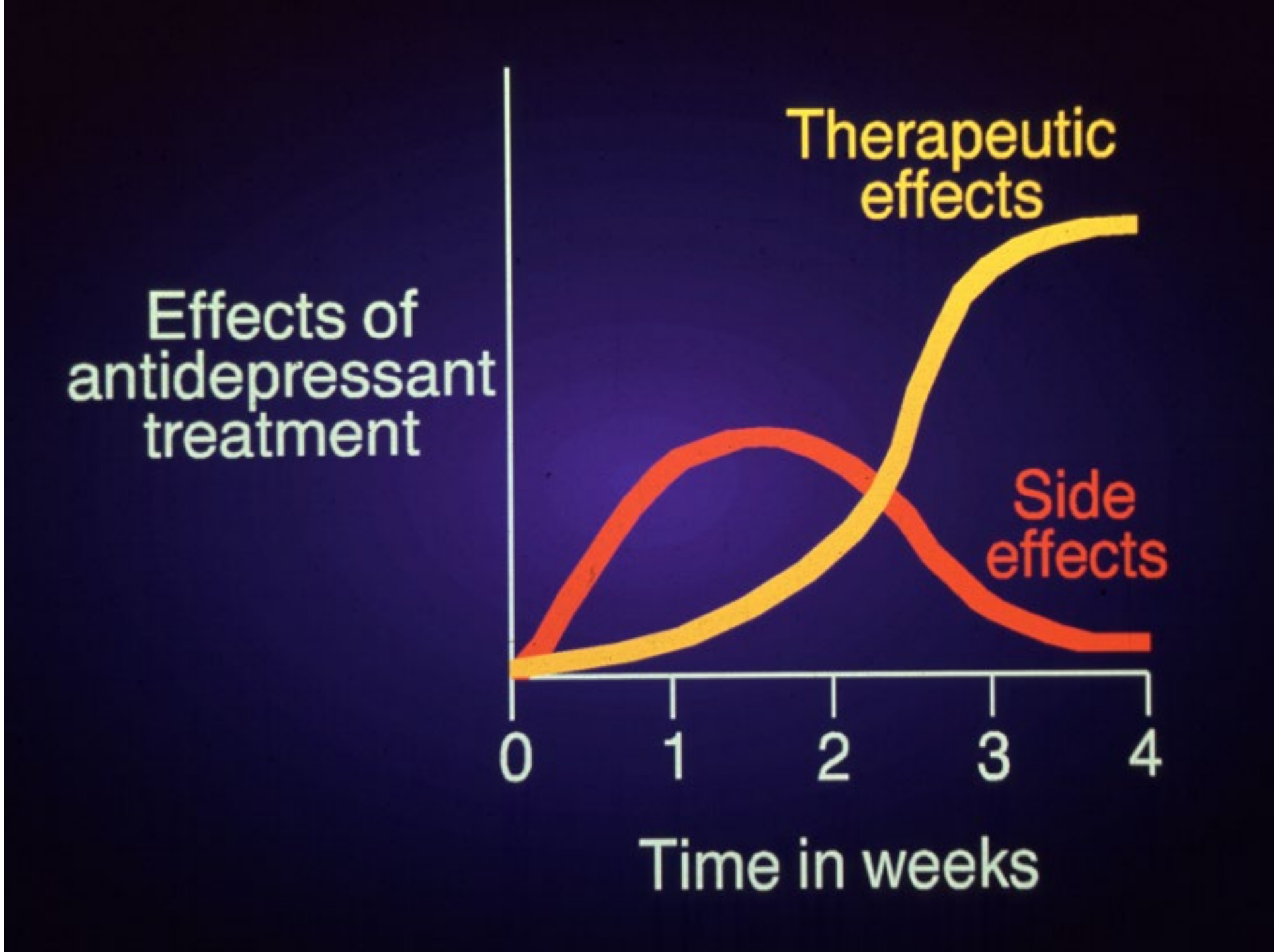
Goals of treatment using PHQ-9

- Response – e.g. 50% reduction on the PHQ-9
- Remission – e.g. PHQ-9 score under 5 sustained for 2 months

- How long to wait for improvement?
  - SSRI – response at 2 weeks is predictive
    - Are you dosing correctly?
  - Plateau of any medication improvement at 8-12 weeks
    - Often making changes in 4-6 weeks

How do antidepressant biological treatments work?

- Most commonly used impact monamines
  - 5HT (serotonin)
  - NE (norepinephrine)
  - DA (dopamine)
- Newer approaches targeting glutamate, GABA receptors
  - Ketamine
  - Brexanolone
- Neuromodulation
  - ECT and TMS
- Investigational
  - Psilocybin


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

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

MI-CCSI
Center for Clinical Systems Improvement

SSRIs

- **Fluoxetine (Prozac)**
- **Sertraline (Zoloft)**
- **Paroxetine (Paxil)**
- **Citalopram (Celexa) & Escitalopram (Lexapro)**
- **Fluvoxamine (Luvox)***
- FDA approved for major depressive disorder

  *Fluvoxamine only FDA approved for OCD
- 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

HINT: Try to differentiate what was already a problem before the medicine versus after

SSRIs & Serotonin Syndrome

- Serotonin Syndrome: uncommon but dangerous consequence of excessive serotonin activity
  - Symptoms: muscle rigidity, fever, agitation – can be serious if not addressed
- 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

MI-CCSI
Center for Clinical Systems Improvement

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:
- Improvement 60% or more
  - Increasing dose
  - Adding a second “augmenting” antidepressant from other class
    - SSRI + bupropion or mirtazapine are common choices
  - Augmenting with an antipsychotic or other medication
    - VA trial found augmentation with aripiprazole (Abilify) was more effective than switch to bupropion.
- Improvement less than 60% despite adequate dose and duration
  - Switching to another antidepressant

- After 2 failures, scrutinize diagnosis, consider intensifying treatment

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)

MI-CCSI
Center for Clinical Systems Improvement

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

MI-CCSI
Center for Clinical Systems Improvement

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

MI-CCSI
Center for Clinical Systems Improvement

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

MI-CCSI
Center for Clinical Systems Improvement

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.

MI-CCSI
Center for Clinical Systems Improvement

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"

Resources Related to Medications

ICSI (Institute for Clinical Systems Improvement), Depression, Adult in primary care depression (2016)	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)

Psychotherapy – highly effective

- Evidence-based psychotherapies – partial list
  - CBT (cognitive-behavioral therapy)
    - GOOGLE workbooks on CBT and depression
  - ACT (acceptance and commitment therapy)
    - Book – “The Happiness Trap”
  - IPT (interpersonal therapy)
- Patients needing support/counseling (situational issue) – if employee consider EAP
- Tell patients that these treatments work as well as medications if they put in the time for 8-12 sessions and they reduce risk of relapse.
- We now have many on-line options and apps that can help

Antidepressants Plus Psychotherapy Meta-Analysis 2018

- 6 RCTs
  - Antidepressants alone versus with add-on psychotherapy
  - 635 patients with treatment resistant depression
  - Cognitive behavioral therapy, Intensive short-term dynamic therapy, interpersonal therapy, and group dialectic behavioral therapy were represented
- Remission nearly twice as likely (RR 1.92, 95% CI 1.5-2.5)
  - Discontinuation comparable between groups
  - Evidence of moderate quality
- How to find evidence-based psychotherapy for your patient?

Ijaz, S, Cochrane Database Syst Rev. 2018;5:CD010558. Epub 2018 May 14.

Challenges in Reaching and Sustaining Remission: Remission Rates - STAR*D Study

• Step 1: citalopram only	(3,671)	36.8%
• Step 2: augment or switch	(1,439)	30.6%
• Step 3: augment or switch	(390)	13.7%
• Step 4: switch medications	(123)	13.0%
• Step 5b: switch medications	(3)	

Overall remission rate in multi year study 67%

Those reaching remission later had higher relapse rate

Rush AJ et al, Am J Psychiatry 2006 Nov, 163(11):1905-17.

Herbal medicines

Purity of herbal medications is a concern

Drug interactions and side effects

- St. John's Wort
    - Studies mixed, but recent review favors efficacy for mild to moderate depression.
- Omega-3 fatty acids
    - Small study showed improved depressive sx.
- S-adenosyl-L-methionine (SAM-e)
    - possibly effective for short-term treatment

What can a patient do to help themselves?

- Behavioral activation
  - Depression makes one want to sit alone on the couch
    - Giving into those impulses will feed the depression
      - Get up and do something productive and/or pleasurable
- Isolation increases depression – we are social beings
- Exercise – moderately vigorous exercise a few times per week
- Get adequate sleep – time for brain recovery
- Healthy diet – your brain is an organ of your body as well
- Avoid addictive substances – alcohol is a depressant
- Work/life balance – explore ways to take healthy breaks
- Seek help in facing challenges and fears – e.g. a financial advisor, couples counseling, etc.
- Get into nature

References

- Use of antidepressants in primary care and Canadian article on guidelines for mood and anxiety
  - Bostwick JM. A generalist's guide to treating patients with depression with an emphasis on using side effects to tailor antidepressant therapy. *Mayo Clinic Proc.* 2010;85:538-550
  - Kennedy SH et al, CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016 Sep;61(9):540-60.
- Articles on psychotherapy
  - Ijaz, S, Cochrane Database Syst Rev. 2018;5: Epub 2018, May 14
  - Farah WH, Non-pharmacological treatment of depression: a systematic review and evidence map. Evid Based Med. 2016 Dec;21(6):214-221.

Other guidelines for depression

- Kaiser Permanente guidelines 2021:
  - https://wa.kaiserpermanente.org/static/pdf/public/guidelines/depression.pdf
- NICE guidelines from UK for adults 2022
  - https://www.nice.org.uk/guidance/ng222

Thank You