Psychopharmacology for Non-Prescribers in Integrated Care Settings

Paul N. Pfeiffer, MD
Susan Crumpacker Brown Research Professor Depression
University of Michigan, Department of Psychiatry
&
Medical Director, Primary Care Mental Health
Ann Arbor VA Medical Center

Objectives/Outline

- Review general approach to evaluating patients for antidepressant medication
- Understand how different psychotropic medications work differently in the brain
- Be familiar with the common antidepressant medications and their relative advantages/disadvantages
- Very brief summary of other commonly used psychotropic medications
- Review common patient concerns and how to address them

Evaluation for Antidepressant Medication

Scenario

- Dr. Kim brings a patient to you and says, “Mr. M. here is an 85 year old man, he recently moved to an assisted care facility, family says he isn’t like himself anymore, doesn’t want to do anything. They think he’s depressed. Should I start him on an antidepressant?”

- What more information is needed?

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

- Major depressive disorder or persistent depressive disorder (dysthymia)
  - **PHQ-9 ≥ 10**
- Anxiety disorder (GAD, Panic, Social anxiety, OCD)
  - **GAD7 ≥ 10**
- PTSD
  - **PCL5 ≥ 40**

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

Only in rare cases are SSRIs absolutely contraindicated

Does the patient have?:

- **Bipolar disorder**
  - Antidepressants may induce mania in the absence of a mood stabilizer
  - May still be effective for comorbid anxiety disorder
- **Other primary psychiatric illness (e.g., PTSD) or substance use disorder**
  - Additional or other treatments may be more effective
- **Potential medical cause of depression**
- **Medical condition or medications that would interact with antidepressant treatment**

Medical Conditions and Depression

Medical Causes of Depression

- Obstructive sleep apnea
- Hypothyroidism, endocrine disorders
- Anemia
- Infectious disease: HIV, TB, Mono
- Cancer
- Neurologic disorders (e.g., dementia, stroke, Parkinson's)
- Autoimmune disorders (e.g., lupus)
- Medications: beta blockers, interferon, steroids, hormones, antibiotics, statins, anticonvulsants

Medical conditions where caution with antidepressants is needed

- Pregnancy, seizures, bleeding, liver disease, kidney disease
- Medication use: triptans (migraines), anything where the level is critical: arrhythmia, seizure, HIV, anticoagulation
- Allergies to similar medications

Case Follow-up

- You assess Mr. M. and the medical record documentation
- His PHQ9 is 18, depression started 1 month ago after moving
- No history of mania, substance use, or trauma
- 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 you consider starting an antidepressant at this point appropriate?
- What might be further areas of focus in this patient prior to starting antidepressant treatment?

Collaborative Care

Antidepressant treatment of depression in primary care is more effective with care manager involvement:

- Assessment of side effects and adherence
- Measurement-based care (e.g., PHQ-9)
- Self-management support using evidence-based approaches
- Feedback to PCP regarding prescribing guidelines
- Psychiatrist consultation/supervision
- Registry-based population management

Mechanisms of Psychopharmacology

How is this information useful?

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

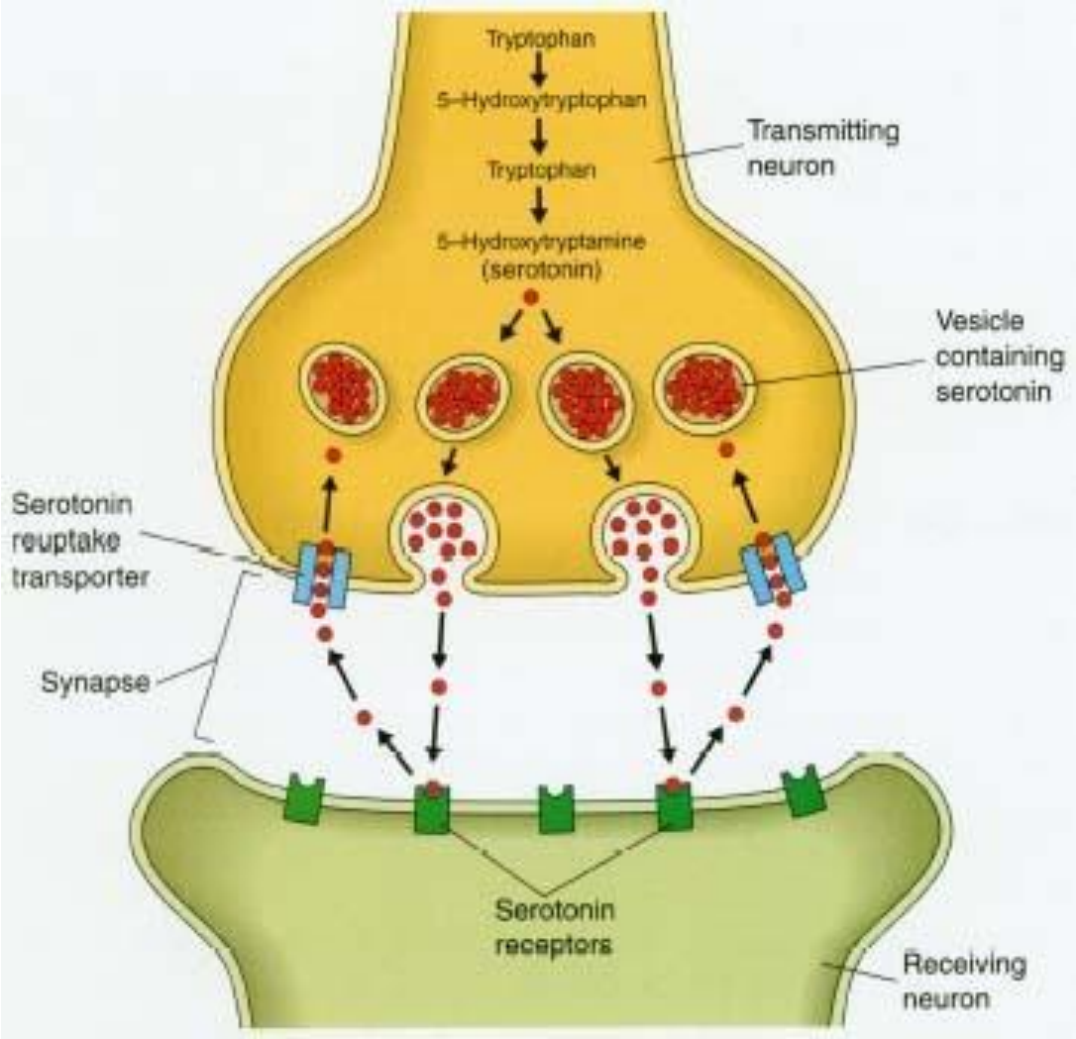
Establishes classes of medications (e.g. SSRIs)

- Easier to remember than learning each individually

Helps understand new medications

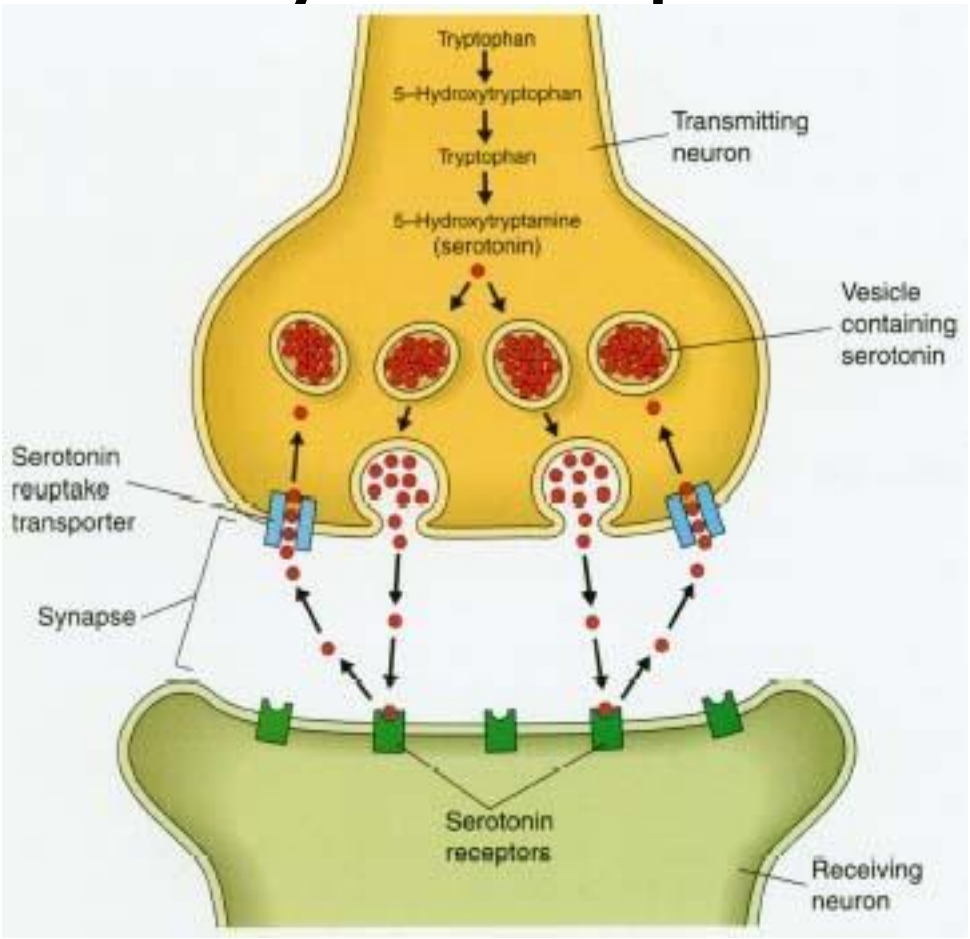
- Really new or “me too”?

Neurotransmission



http://www.humanillnesses.com/Behavioral-Health-Fe-Mu/Medications.html

Psychotropic Sites of Action



http://www.humanillnesses.com/Behavioral-Health-Fe-Mu/Medications.html

Increase release

Decrease reuptake

Decrease breakdown

Direct receptor activation

Receptor modulation

Direct receptor blockade

Neurotransmitters: Monoamines

Serotonin:

mood, anxiety, sleep, anger/aggression

sexual functioning, gastrointestinal functioning

Norepinephrine:

mood, anxiety

heart rate, blood pressure, “fight or flight”

Dopamine:

motivation, mood, psychosis, attention, cognition,

motor activity, inhibits lactation, addiction

Histamine & Melatonin: sleep

Neurotransmitters: Other

GABA:

major inhibitory role, anxiety

sedation, cognition

Glutamate:

major excitatory role, cognition, mood

psychosis

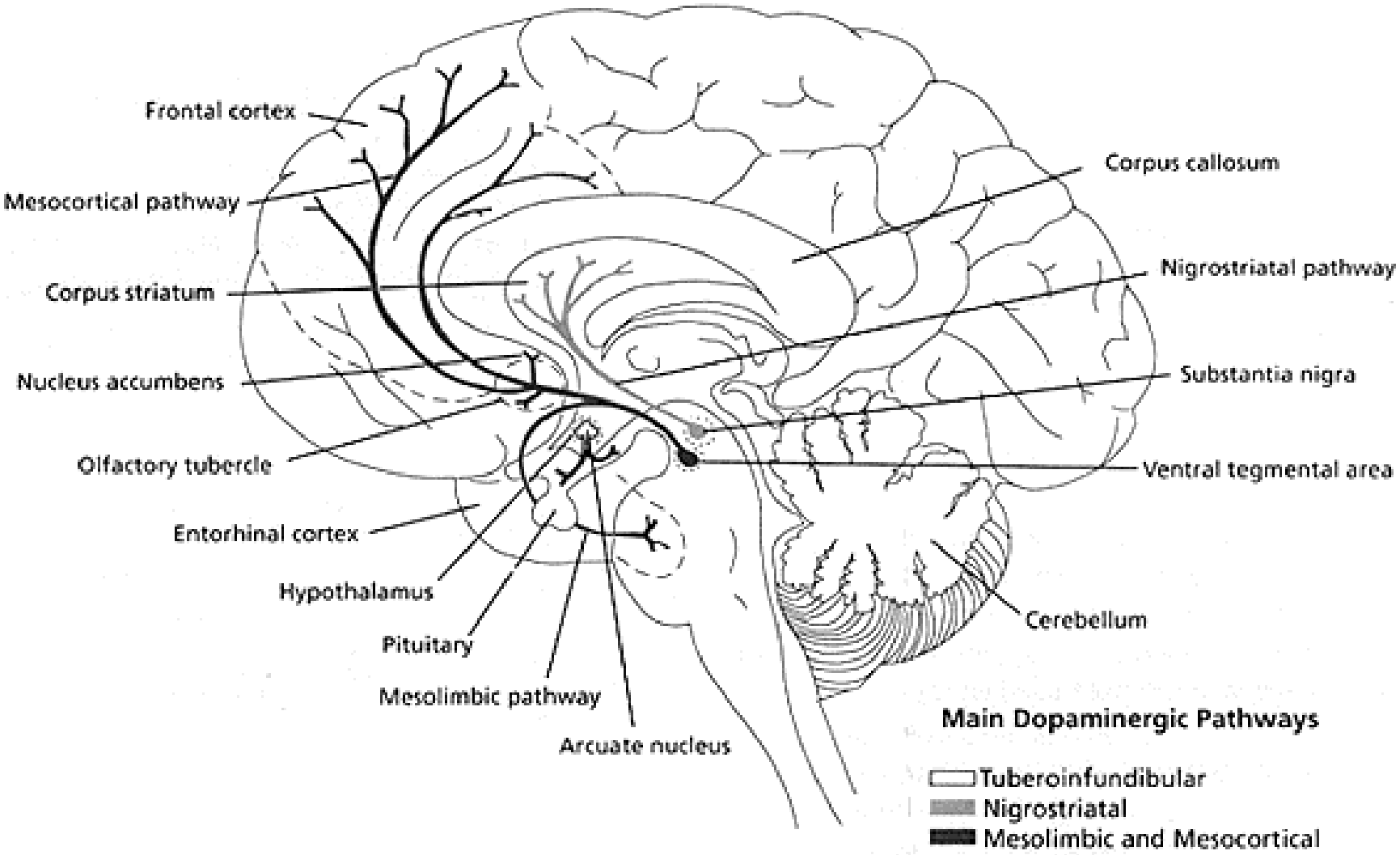
Acetylcholine:

cognition

heart rate, bladder, gastrointestinal: “rest & digest”

“anticholinergic” side effects

Neurotransmitter Pathways



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
    - Amitriptyline (Elavil) and Nortriptyline (Pamelor)
  - Should not be first choice for depression/anxiety

Modern Antidepressants

- SSRIs
- SNRIs
- Bupropion (Wellbutrin)
- Mirtazapine (Remeron)
- Other/new

SSRIs

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

- FDA approved for major depressive disorder

- 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

- Dosages vary: e.g. 20-60mg for fluoxetine, 50-200mg for sertraline
- Citalopram 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
- Paroxetine may have greater anticholinergic side effects and worse discontinuation syndrome

SNRIs

- **Venlafaxine (Effexor) & Desvenlafaxine (Pristiq)**
- **Duloxetine (Cymbalta)**
- **Levomilnacipran (Fetzima) -- NEW (2013)**
- 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)

- Novel 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

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) – New (2011)**
  Vortioxetine (Trintellix) – New (2013)
- Serotonin reuptake inhibitor and partial serotonin receptor activator
- Advantages/disadvantages vs. existing antidepressant not well known

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 PTSD

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

Choice of Antidepressant

- 55 year-old woman with depression, anxiety, insomnia, and weight loss

A) Fluoxetine
B) Duloxetine
C) Bupropion
D) Mirtazapine

Choice of Antidepressant

- 25 year-old woman with depression, no major anxiety disorder, smokes cigarettes, anorexic, seizure history

A) Citalopram
B) Desvenlafaxine
C) Bupropion
D) Mirtazapine

Choice of Antidepressant

- 45 year-old woman with depression, chronic headaches, fibromyalgia, excessive sleep, and weight gain

A) Fluoxetine
B) Duloxetine
C) Bupropion
D) Mirtazapine

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
    - SSRI to other SSRI is as good as switching to bupropion
  - Augmenting with an antipsychotic or other medication
- 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
- 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

"Z" Drugs -- Hypnotics

- **Zolpidem (Ambien)**
- **Eszopiclone (Lunesta)**
- **Zaleplon (Sonata)**

- Act at same GABA site as benzodiazepines
- Indicated for initial insomnia (less effective for maintaining sleep)
- Potentially less abuse, dependence, withdrawal concerns than for benzodiazepines
- Care when combining with other sedating medications (e.g., opiates, benzos)
- Have been associated with rare disordered behaviors during sleep (e.g., sleep walking)

Controlled Substance Prescribing

Benzo use doubles risk of opiate overdose

- MAPS report now required prior to prescribing
- Only 30-day supply at a time
- 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)**
  - Serotonin agonist, not effective for depression
  - 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)
- **Gabapentin (Neurontin)**
  - 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

Other Hypnotics ("Sleep Aids")

- **Diphenhydramine (Benadryl, other OTCs)**
  - Stops working quickly, anticholinergic side effects
- **Melatonin**
  - Generally safe, not very effective
- **Ramelteon (Rozerem): melatonin agonist**
  - Limited effectiveness
- **Belsomra (suvorexant): new 2015**
  - Orexin antagonist
- **Antidepressants: Trazodone, Mirtazapine, TCAs**
- **Antipsychotics**
  - Should generally not be used for sleep given side effect potential

Break

- Questions so far?
- Any thing need review?

Second-generation Antipsychotics

- **Aripiprazole (Abilify)**
- **Quetiapine (Seroquel)**
- **Olanzapine (Zyprexa)**
- **Risperidone (Risperdal)**
- **Clozapine (Clozaril)**

Lurasidone (Latuda)
Cariprazine (Vraylar)
Iloperidone (Fanapt)
Paliperidone (Invega)

- Mechanism: block dopamine and serotonin
- Indicated for schizophrenia, bipolar disorder, and treatment-resistant depression
- Quetiapine often used for sedating properties
- Associated with weight gain, diabetes, and cardiac arrhythmias
- Much less likely than older antipsychotics to cause muscle contractions (dystonias) or long-term movement disorders (tardive dyskinesias)

Mood Stabilizers

- **Lithium**
- **Valproate (Depakote)**
- **Lamotrigine (Lamictal)**
- **Carbamazepine (Tegretol)**

- Various/complex/unknown mechanisms
- Indicated for bipolar disorder and schizoaffective disorder
- Most have serious side effects and are typically managed by a psychiatrist
  - Lithium: kidney damage, birth defects
  - Valproate: liver failure, birth defects
  - Lamotrigine: life threatening rash
  - Carbamazepine: severe anemia

Stimulants

- **Methylphenidate (Ritalin, Concerta)**
- **Dextroamphetamine/amphetamine (Adderall)**
- **Lisdexamfetamine (Vyvanse)**

- Mechanism: increases dopamine in synapse
- Indicated for ADHD
- Generally safe: rare cardiac side effects
- Effective immediately
- Common side effects: insomnia, loss of appetite
- Potential for abuse: avoid in patients with substance use disorder history (consider atomoxetine instead)

Medical-assisted Therapy (MAT) for Addiction

- **Methadone / Suboxone**
  - Opiate agonist therapy (OAT), reduces craving for opiates
- **Narcan (Naloxone)**
  - Reverse opiate overdose, blocks opiate receptors
- **Naltrexone / Campral / Antabuse**
  - Used for alcohol use disorders
- **Chantix (Varenicline) / Wellbutrin / Nicotine replacement**
  - Used for nicotine use disorders

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**
- If the first antidepressant doesn't work out, there are many other options

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 and have no dangerous withdrawal syndromes. Patients may experience some unpleasant side effects but these are typically mild when discontinued over several days.

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. People will often have a friend or relative that "acts like a zombie" but this is likely due to depression itself or other more sedating medications.

Qualitative Study

- 1,747 New Zealanders prescribed an antidepressant were asked to complete “In my life antidepressant have been … “

Sidebar: Qualitative Study

N 1747

Positive experiences of antidepressants		Negative experiences of antidepressants		Mixed experiences of antidepressants	
54 % (*n* 939)		16 % (*n* 273)		28 % (*n* 489)	
Positive themes	Example of coded data	Negative themes	Example of coded data	Mixed themes	Example of coded data
Necessary for disease treatment	*No different to a diabetic taking their insulin.*	Ineffective	*Useless despite trying several different kinds.*	Benefits vs side effects	*Very unfortunate side effects in terms of weight gain and sexual dysfunction which lead to me stopping the treatment despite its benefits for my mood and anger issues.*
A life saver	*Antidepressants have been a lifeline, without them I would be dead.*	Unbearable side effects	*A major cost to my sex life*	Calmer but not myself	*Good at removing my anxiety and fear but it made me feel dead inside.*
Meeting social obligations	*The medication I'm on is assisting me to function as an individual and to work and contribute to the community and society and to cope with things in my workplace.*	Loss of authenticity/ Emotional numbing	*Feel alienated from myself and my emotions.*	Fear of dependence versus stopping medication	*Very useful but I am now too scared to come off them and constantly worry about long term effects of being on citalopram 20mg per day*
Getting through difficult times	*Helpful for getting through a busy, tiring and stressful time in my life.*	Masks real problems	*A distraction that means I don't address the real issue.*	Finding one that works	*Useless until I found the one that worked for me.*
A stepping stone to further help	*Provided the 'lift' I've needed to get started with other things like CBT, regular exercise etc.*	Loss of control	*A sign of failing to cope.*		

Content category: Other 2 % (*n* 46)

Gibson, BMC Psychiatry 2016

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”

Antidepressant FAQ

- Q. How am I going to remember to take my medication at the same time every day?

- A. Several strategies to offer:
  - Consider location of pill bottle
  - Consider how pill is incorporated into routine (e.g., brushing teeth, dinner, etc.)
  - Use a pill organizer
  - Use a timer or alarm

Special Populations

Pregnancy

- Evidence is mixed regarding risks of antidepressants and birth defects when taken during pregnancy, but overall risk is considered low
- Antidepressants may increase risk for neonatal complications, including pulmonary hypertension
- Antidepressants are secreted in breast milk, but no clear negative effects on infants
- The risks of untreated depression are generally felt to outweigh the risk of antidepressant treatment during and after pregnancy
- Medications for bipolar disorder such as lithium, depakote, and tegretol have greater associations with birth defects

Older Adults

- Antidepressants are effective for late-life depression
  - Motto for prescribing: "Start low, go slow, don't stop"
- Avoid medications with sedating or anticholinergic properties such as benzodiazepines and TCAs
- Second-generation antipsychotics have increased risk of death in patients with dementia
- Pay extra attention to dementia, delirium, and comorbid medical conditions when making the diagnosis and treatment decisions
  - Consider geriatric-specific screening tool such as Geriatric Depression Scale (short form)

Medical Comorbidity

- Patient with severe liver or kidney impairment may need reductions in the starting dose of medications
- SSRIs are generally safe in patients with cardiac disease
- SSRIs may increase the risk of bleeding
- Many psychotropic medications may increase the risk of seizures, including Wellbutrin
- Second-generation antipsychotics and mirtazapine can lead to obesity, diabetes, and cholesterol problems
- Potential drug interactions should always be considered, citalopram and then sertraline have fewest interactions.

Conclusion

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

Keys are:

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

Resources

Antidepressant Treatment Algorithm

- https://www.jpshealthnet.org/sites/default/files/tmap_depression_2010.pdf

General Information on Integrated Care

- http://www.integration.samhsa.gov/

Patient handout

- http://www.nimh.nih.gov/health/publications/depression-easy-to-read/index.shtml