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Depression in Primary Care: With a focus on first-line medications

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DEPRESSION IN PRIMARY CARE

…with a focus on first-line medications

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This lecture *will* cover

- An overview of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion and mirtazapine
- Appropriate selection and dose adjustments of first-line agents for depressive disorders in a primary care setting
- Monitoring and tapering first-line antidepressants
- Special considerations in treatment
- Future directions for antidepressant treatment

This lecture will *not* cover

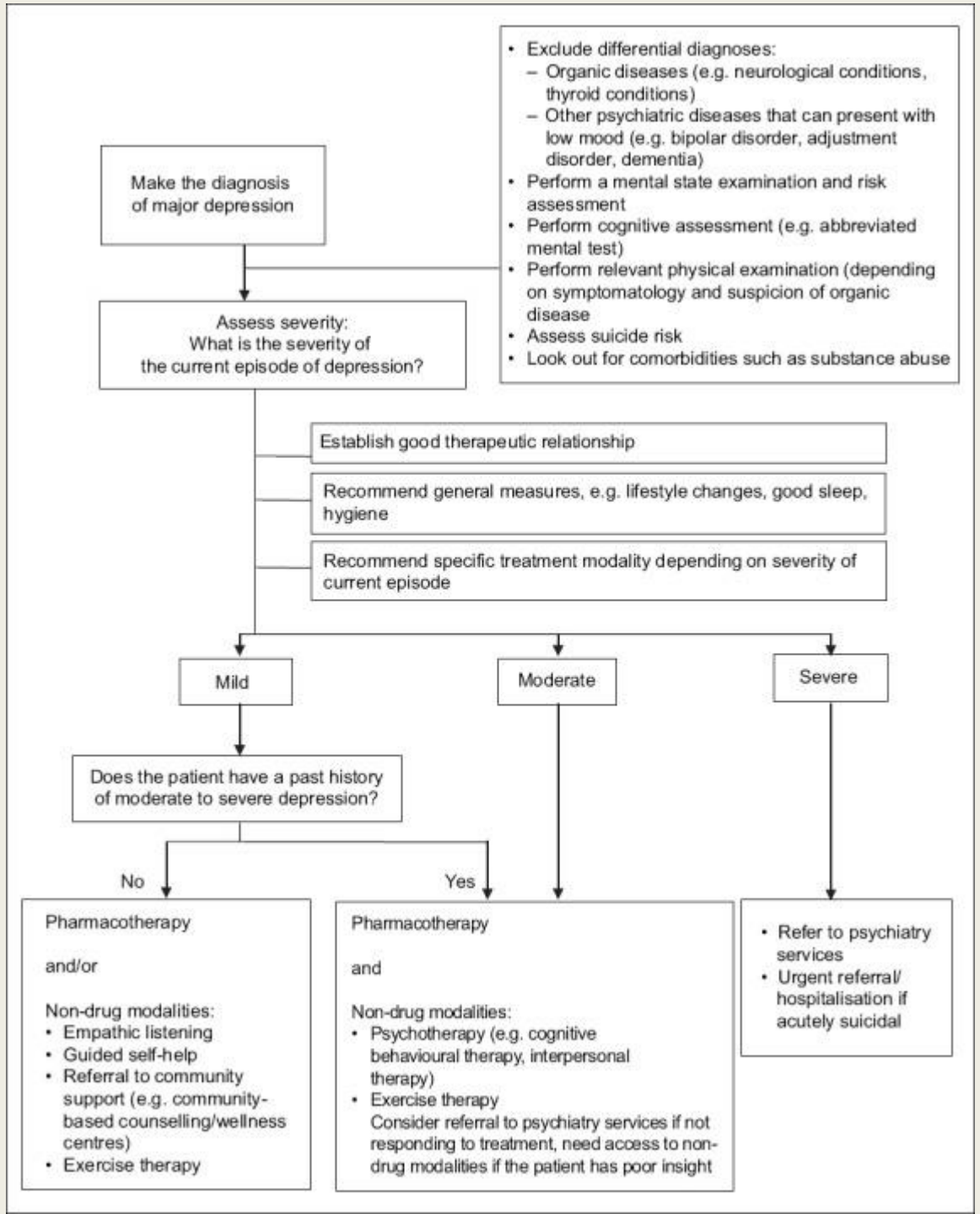
- In-depth initial diagnosis of different depressive disorders
- In-depth uses of antidepressants for conditions other than depression
- Medications other than SSRIs, SNRIs, mirtazapine, and bupropion
- Suggested adjunctive treatments to medication therapy

PRIMARY CARE OR PSYCHIATRY?

"It is often assumed that depressed patients in primary care settings are less severely depressed, have a milder course of illness, and are more likely to present with fatigue or other somatic symptoms compared to patients at psychiatry clinics. *However, there were few differences in demographics or symptom profiles between primary care and psychiatric clinic patients…"*

- Kennedy, 2013

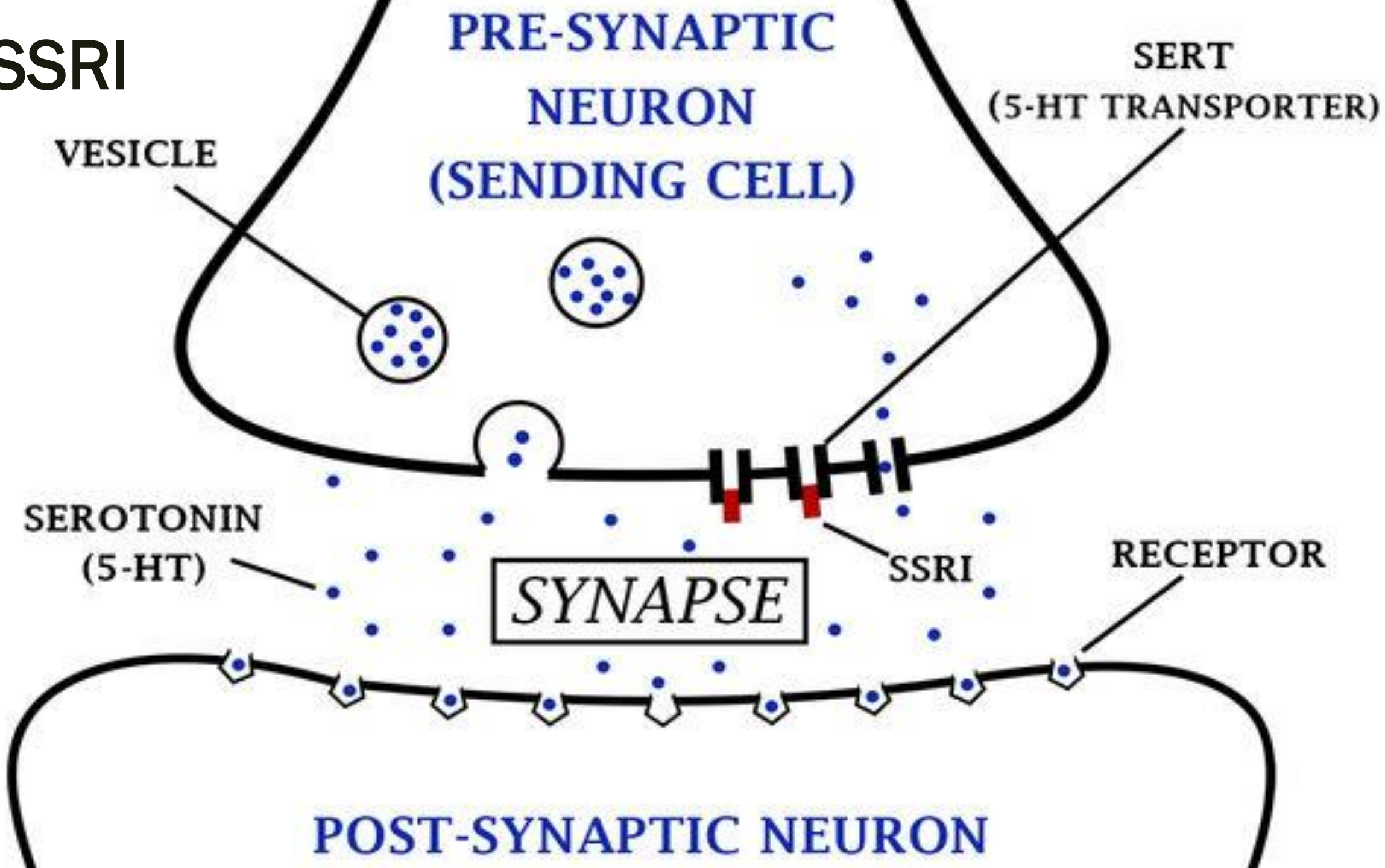
A framework for approaching depression



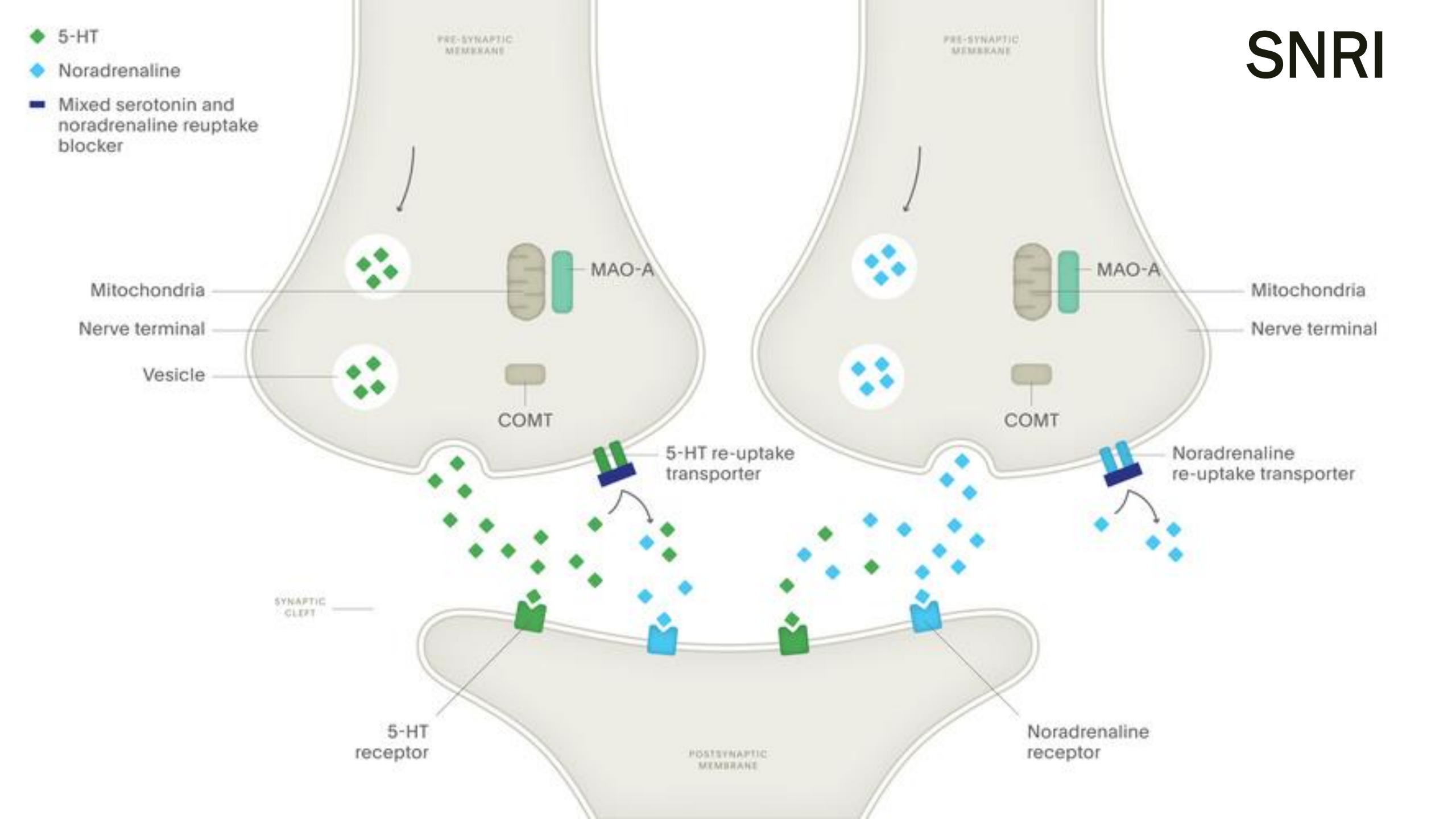
Flowchart courtesy Ng et al.

MECHANISMS OF ACTION (IN BRIEF)

SSRI


PRE-SYNAPTIC
NEURON
(SENDING CELL)
VESICLE
SERT
(5-HT TRANSPORTER)
SEROTONIN
(5-HT)
SSRI
RECEPTOR
SYNAPSE
POST-SYNAPTIC NEURON

SNRI


5-HT
Noradrenaline
Mixed serotonin and noradrenaline reuptake blocker
PRE-SYNAPTIC MEMBRANE
PRE-SYNAPTIC MEMBRANE
Mitochondria
Nerve terminal
Vesicle
MAO-A
COMT
MAO-A
Mitochondria
Nerve terminal
COMT
5-HT re-uptake transporter
Noradrenaline re-uptake transporter
SYNAPTIC CLEFT
5-HT receptor
Noradrenaline receptor
POSTSYNAPTIC MEMBRANE

Mirtazapine is a bit harder to diagram…

- “Atypical” antidepressant
- Antagonizes central presynaptic alpha2-adrenergic receptors, increasing release of serotonin and norepinephrine
- Also antagonizes H1 histamine receptors (sedation/calming) and H-HT2A, 5-HT2C, and 5-HT3 serotonin receptors
  - Serotonin then interacts with the 5-HT1 receptor, leading to antidepressant effects

Bupropion

- Norepinephrine/dopamine reuptake inhibitor (NRDI)
- Weakly inhibits enzymes that are involved in reuptake of norepinephrine and dopamine in synaptic cleft

SELECTING A MEDICATION

Where to start

- Much of the selection of a first-line antidepressant is based off:
  - The patient's story
  - Side effect profile
- Evidence on "best" first-line options is somewhat limited
  - Often difficult to assess given differential responses to drugs
  - Significant publication bias
    - 2008 study by Turner et al. examined 74 studies, found that 97% of those with positive findings were published, but those with negative findings were either not published or published to portray some positive finding

General class considerations: SSRIs

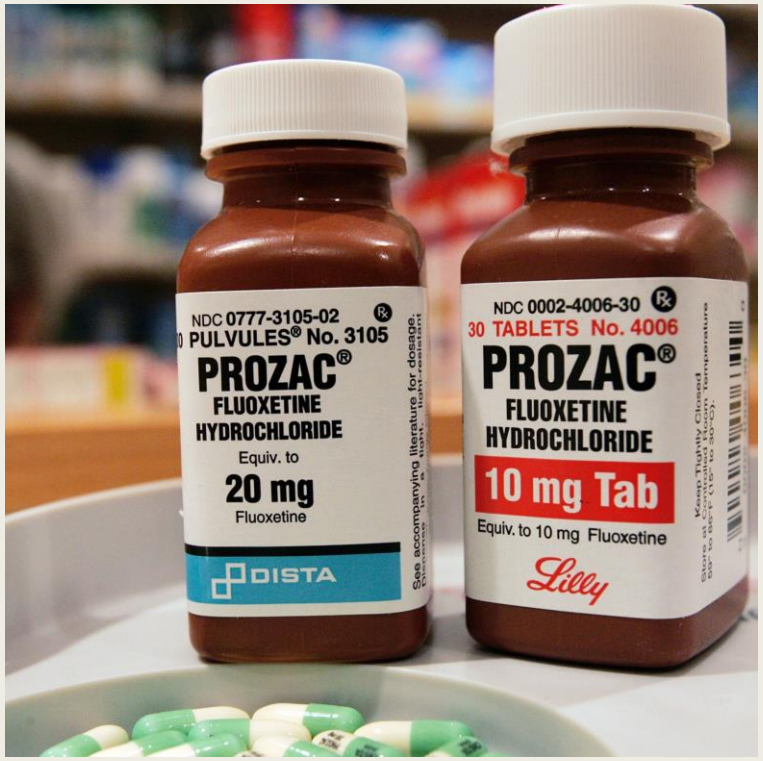
- Common side effects:
  - QTc prolongation
  - Sexual dysfunction
  - GI upset
- There is an increased risk of GI bleeding with SSRI use, especially in patients on antiplatelet, anticoagulation, and NSAIDs
- Hyponatremia is a risk, generally in older adults
- Dose adjustments are generally necessary for patients with liver disease
- Geriatric dosing: “start low and go slow” – generally consider 50% dose reduction

Case 1

SH is a 30 year old nurse with no significant past medical history. He presents to your clinic with complaints of depressed mood and anhedonia. He is “incredibly fatigued” and can barely get through a day at work. You diagnose major depression. What might be a good first choice antidepressant for SH?

Fluoxetine

- Most **activating** SSRI
- **Longest half-life** of any SSRI (7-15 days)
- Potent CYP inhibitor (mostly 2D6) – use with caution in medically complex individuals
- Adult dosing: start at **20mg daily**, can up-titrate in a few weeks to maximum 80mg daily



Fluoxetine

- Good choice for:
  - Patients who might forget to take medications every day
  - Patients who do not take many other medications
  - Patients who complain of excessive fatigue
- Less ideal for:
  - Patients who may not fare well with initial activation
  - Patients on beta blockers, antiarrhythmics, calcium channel blockers, warfarin, traditional antipsychotics, and certain benzodiazepines
  - Older patients
  - Patients with severe liver disease

Case 2

HD is a 75 year old female with a history of a-fib on warfarin, HFrEF (EF 45%), hypertension, and hyperlipidemia. She has been attempting to undergo talk therapy for depression, but is now willing to try a medication. What might be her best options?

Citalopram and escitalopram

- **Mildly** sedating (c), **neither** sedating nor activating (e)
- Half life: 27-32h (e), 36h (c)
- Minimal CYP inhibition
- Adult dosing:
  - C: 20mg starting dose, may increase in no less than one week to max 40mg
  - E: 10mg starting dose, may increase in no less than one week to max 20mg

Citalopram and escitalopram

- Good choice for:
  - Older adults
  - Adults with complex medical issues on medications metabolized by CYP450 enzymes
  - Patients with GI sensitivity (e)
- Less ideal for:
  - Patients with excessive fatigue/apathy as a presenting symptom
  - Patients with severe renal disease (CrCl <20)
    - Partially renally excreted

Case 3

VC is a 55 year old male with a history of hypertension, hyperlipidemia, and asthma presenting to clinic for a routine physical exam. In the process, his PHQ-9 reveals a score of 15 and he reveals he has had low energy and his mood is down. He feels as though he is moving slowly lately. Which might be a good first-choice medication for him?

Sertraline

- Tends to be **activating**
- Half-life: 22-36 hours
- Minimal CYP inhibition
- Adult dosing: 50mg starting dose, may increase in 25mg increments weekly, max dose 200mg daily

Sertraline

- Good choice for:
  - Patients with medical issues; those on other drugs
  - Patients who might benefit from activation
  - Patients who might benefit from the wide dose range
- Less ideal for:
  - Patients who may not fare well with initial activation

Case 4

JK is a 31 year old G1P0 currently at 9 weeks. During her initial prenatal visit, you note that she has a history of major depression on paroxetine, as well as mild intermittent asthma on PRN symbicort. She asks if either of these medications are problematic for her pregnancy. What do you tell her?

Paroxetine

- Tends to be more sedating (and constipating) – higher **anticholinergic activity**
- Half life: 21-24h
- Potent CYP inhibition (especially 2D6)
- More anticholinergic activity at higher doses
- Adult dosing: starting dose 20mg daily, may increase in 10mg increments weekly, max dose 50mg

Paroxetine

- Good choice for:
  - Patients who may not do well with initial insomnia/activation
- Less ideal for:
  - Patients on beta blockers, antiarrhythmics, calcium channel blockers, warfarin, traditional antipsychotics, and certain benzodiazepines
  - Older patients (especially at higher doses)
  - Patients who are overweight/obese
  - Pregnant patients (risk of birth defects?)
  - Patients who might require higher doses

General class considerations: SNRIs

- Common side effects:
  - Overall similar to SSRIs
  - Sometimes more nausea
  - Dose dependent blood pressure increases (especially diastolic)

Case 5

AU is a 59 year old largely healthy female with a known diagnosis of MDD, previously treated with fluoxetine. She self-discontinued the medication as she did not feel it was working. She comes to the office today noting significant hot flashes and vaginal dryness, consistent with menopause. She would also like to discuss her mood symptoms, which have worsened recently. What antidepressant might be a good choice?

Venlafaxine

- Can have some activation at higher doses
- **Very short half-life** (3—7 hours, 9-13 for active metabolite
- Adult dosing:
  - IR: starting dose 75mg/day dosed q8h-q12h, may increase in 75mg increments after no less than four days to max ~375mg/day
  - ER: starting dose 37.5-75mg daily, may increase in 75mg increments after no less than four days to max ~225mg/day
- Dose reductions required in hepatic/renal impairment (50% and 25% respectively)

Venlafaxine

- Good choice for:
  - Patients who have not had success with other SSRIs
  - Patients who also have menopausal vasomotor symptoms
- Less ideal for:
  - Patients with hypertension
  - Patients at risk for abrupt discontinuation of therapy
  - Patients with significant GI disturbance at baseline

Case 6

AL is a 71 year old male with metastatic prostate cancer. Recently, he states that his mood has been down as he has learned his cancer is worsening. He has lost 15 pounds over the past 6 months. He reports that he is anxious and restless. What might be a good antidepressant option for AL?

Mirtazapine

- Induces sleep (at *lower* doses)
- Weight gain **common**
- Can be helpful for nausea
- Half life: 20-40h
- No significant CYP interactions
- Dosing:
  - For sleep – 7.5 mg nightly
  - Depression – 15 mg starting dose, increase in 15mg increments q1-2 weeks, max dose 45mg

Mirtazapine

- Good choice for:
  - Patients having difficulty sleeping or poor appetite
  - Patients with cancer
- Less ideal for:
  - Patients with excessive fatigue
  - Patients who are overweight or would not benefit from weight gain
  - Patients with neutropenia

Case 7

SH from Case 1, the 30 year old healthy male, returns to the office. He was hopeful the fluoxetine would help, but couldn't tolerate the sexual side effects and self-discontinued it. He is unwilling to restart any medication that might cause the same effects. His mood is still down and his energy levels low. What can you offer him?

Bupropion

- Most **activating** antidepressant
- Lowers seizure threshold
- Low risk of sexual dysfunction
- Half-life: 12-30 hours
- Concern for CYP inhibition (2D6)
- Three forms of bupropion available:
  - Immediate release (~TID)
  - Sustained release (BID)
  - XL (daily)

Bupropion

- Dosing varies by formulation:
  - IR: starting dose 100mg q12h, can increase to q8h after four days. If no improvement within several weeks, can increase to 150mg q8h.
  - SR: starting dose 150mg daily, can increase to q12h after three days. If no improvement, can increase to 200mg q12h after four weeks
  - XL: starting dose 150mg PO daily, can increase to 300mg daily after four days. If no improvement, can increase to 450mg after four weeks
- Some psychiatrists choose not to increase beyond 300mg daily

Bupropion

- Good choice for:
  - Patients who can’t tolerate sexual side effects of SSRIs
  - Depressed patients with bipolar disorder (less likely to switch to mania)
  - Patients with low energy
  - Patients who are actively smoking
- Less ideal for:
  - Patients with a contraindication to use: seizure disorder, history of head trauma, and eating disorders
  - Anxious patients who would not tolerate significant activation

Is one antidepressant more effective?

Lancet. 2018 Apr 7; 391(10128): 1357–1366.
doi: 10.1016/S0140-6736(17)32802-7
PMCID: PMC5889788
PMID: 29477251

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

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- 2018 meta analysis in *The Lancet*
- Weighed efficacy in treating depression vs. acceptability to patients
- Found *all* antidepressants superior to placebo
- Escitalopram, mirtazapine, paroxetine, sertraline found to have “relatively higher response and lower dropout” than other antidepressants

The caveat…

“Our assessment overall found few differences between antidepressants when all data were considered, while there was more diversity in the range of efficacy and dropout patterns seen across the head-to-head comparisons than the meta-analysis of antidepressants versus placebo.”

Summary: selecting an antidepressant

- As of now, there is not a single “best” option
- Selection driven by patient and their symptoms
- Must consider certain factors when choosing a medication
  - Activation vs. sedation
  - Drug interactions
  - Side effects
- A wide range of options currently exist
  - …including some not covered in this talk (duloxetine, desvenlafaxine, etc.)

MONITORING, DISCONTINUING, AND TAPERING MEDICATIONS

Monitoring efficacy

- Generally, should wait **at least four weeks** after starting an antidepressant to assess
  - …and, realistically, as long as two months
- Should monitor symptoms with some objective measure
  - e.g. PHQ-9
- May need to titrate dose up to achieve response
- Must also account for patient perceptions of efficacy
- If an SSRI fails to improve mood, can try another. If this fails, may try SNRI or alternative option.

Addressing side effects

- Sexual side effects are *very* common with SSRIs
  - May switch agents or consider augmentation with bupropion or mirtazapine
  - For male sexual dysfunction, can also consider sildenafil
- May be necessary to switch within drug classes to improve side effects (e.g. activation/sedation)

Duration of therapy

- Current guidelines suggest **four to twelve months** for an initial episode of depression
- Risk factors for relapse can help guide longer durations:
  - Recurrent depression
  - Other psychiatric illness
  - Persistent symptoms
  - Presence of other medical illness
- ~60 percent of Americans on antidepressants have been taking for > two years
  - …and ~14 percent have been on them for > 10!

Avoiding FInISH: tapering antidepressants

- Abrupt discontinuation can lead to **discontinuation syndrome**
  - FInISH: FIu-like symptoms, Insomnia, Imbalance, Sensory disturbances, hyperarousal
- Shorter half-lives (**venlafaxine**) and **paroxetine** are especially prone to this syndrome
- Fluoxetine has a long half-life and tapering is less of a concern
- Depending on the antidepressant, may be beneficial to taper “old” agent while switching to the “new” one

Summary: monitoring

- Antidepressants should be given ~two months for full efficacy
- Up-titrating may be necessary
- Ideal therapy duration for first occurrence is ~one year, but many people require longer
- Tapering medications can help avoid discontinuation syndrome

SPECIAL CONSIDERATIONS

Serotonin Syndrome

- Serotonin “overload”
  - *Agitation, tremors, hyperreflexia, hypertension, vomiting, arrhythmias, etc.*
- To avoid:
  - Monitor the list at right and avoid too many combinations
  - Take special caution with fluoxetine!
    - Its metabolite can persist for up to 2.5 weeks

Table 2. Medications that May Contribute to Serotonin Syndrome

Class	*Drugs*
Amphetamines and derivatives	3,4-methylenedioxymethamphetamine (“Ecstasy”)
	Dextroamphetamine
	Methamphetamine
Analgesics	Buprenorphine
	Cyclobenzaprine (Flexeril)
	Fentanyl
	Hydrocodone
	Meperidine (Demerol)
	Morphine
	Oxycodone
	Pentazocine (Talwin)
	Tramadol
Antidepressants/ mood stabilizers	Buspirone (Buspar)
	Lithium
	Monoamine oxidase inhibitors
	Olanzapine (Zyprexa)
	Selective serotonin reuptake inhibitors
	Serotonin 2A receptor blockers
	Serotonin-norepinephrine reuptake inhibitors
	St. John’s wort
	Tricyclic antidepressants
Antiemetics	Droperidol
	Metoclopramide (Reglan)
	Ondansetron (Zofran)
Antimigraine drugs and antiepileptics	Carbamazepine (Tegretol)
	Ergot alkaloids
	Triptans
	Valproic acid (Depakene)
Other medications	Chlorpheniramine
	Cocaine
	Dextromethorphan
	Ginseng
	5-hydroxytryptophan
	Linezolid (Zyvox)
	L-tryptophan
	Nutmeg
	Reserpine
	Ritonavir (Norvir)
	Yohimbe

Adapted with permission from Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. Am Fam Physician. *2010;81(9):1140, with additional information from reference 25.*

Breastfeeding and antidepressants

- Most antidepressants are transferred to breastmilk in low concentrations
  - Fluoxetine and venlafaxine highest in infant serum samples
- May find some level of discontinuation syndrome (irritability)
- Little evidence to support true adverse events

Antidepressants in adolescents

- Fluoxetine is approved for depression in children 8 years of age or older, escitalopram in those 12 or older
- Better outcomes when medications combined with talk therapy
- FDA black box warning for SI in pediatric/adolescent patients, but no evidence of increased rates of completed suicide

When to refer to psychiatry

- Treatment-resistant depression
- Difficult cross-tapering
- Medical complexity with multiple drug interactions

THE FUTURE OF ANTIDEPRESSANTS

Genetic testing: a panacea?

- Specific genes have been associated with MDD
- Current research has focused on identifying specific genetic variants that predict responses to antidepressants

› Am J Psychiatry. 2018 Sep 1;175(9):873-886. doi: 10.1176/appi.ajp.2018.17111282.
Epub 2018 Apr 25.

Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing

Zane Zeier [1], Linda L Carpenter [1], Ned H Kalin [1], Carolyn I Rodriguez [1], William M McDonald [1], Alik S Widge [1], Charles B Nemeroff [1]

The current state of affairs…

"[A]t present, there are insufficient data to support the widespread use of combinatorial pharmacogenetic testing in clinical practice, although there are clinical situations in which the technology may be informative, particularly in predicting side effects.

Summary: overall

- Treating with first-line antidepressants is within the scope of practice of family medicine physicians
- A wide range of medication options exist, and treatment is patient-directed
- Careful monitoring for side effects and efficacy is critical
- Tapering should be considered at time of discontinuation of therapy
- The future of antidepressant therapy may be individualized medicine

Questions?

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