Medications associated with/exacerbating depressive symptoms:

1. Isotretinoin **(acne treatment)**
2. Levetiracetam, topiramate, vigabatrin **(anticonvulsants)**
3. Triptans **(antimigraine)**
4. B-blocks, clonidine, reserpine, methyldopa **(cardiovascular meds)**
5. Gonadotropin-releasing hormone, OCPs, steroids, tamoxifen **(hormonal meds)**
6. Interferons **(immunologic meds)**
7. Varenicline **(smoking cessation meds)**

Medical conditions associated with depression:

1. Stroke
2. Parkinson's disease
3. Traumatic brain injury
4. Hypothyroidism
5. Withdrawal from stimulant drugs (e.g., cocaine)

Phases of depression therapy:

1. The **acute phase** lasting 6 - 12 weeks in which the goal is **remission** (absence of symptoms).

2. The **continuation phase** lasting 4 - 9 months after remission in which the goal is to **eliminate residual symptoms or prevent relapse** (return of symptoms within 6 months of remission).

3. The **maintenance phase** lasting 12 - 36 months in which the goal is to **prevent recurrence** (a separate episode of depression).

For the maintenance phase, <u>lifelong treatment is recommended for:</u>

1) Patients older than 40 years with 2 or more prior episodes.
2) Patients of any age with 3 or more prior episodes.

Approaches to major depression therapy:

1. Non-pharmacologic approach:
    a. Psychotherapy (not useful alone)
    b. Cognitive therapy
    c. Electroconvulsive therapy (for severe disease)
2. Pharmacologic approach:
    a. **Selective serotonin reuptake inhibitors (SSRIs)**
        - E.g., Citalopram, **Escitalopram**, Fluoxetine, Fluvoxamine, **Sertraline**
        - Has the best adverse effect profile out of all antidepressant medication (least likely to cause adverse effects)
        - **Escitalopram** & **sertraline** has the best effect and safety profile.
        - Has less anticholinergic and cardiovascular adverse effects compared to TCAs and is *not associated with significant weight gain*.
        - Can cause withdrawal syndrome when discontinued. Thus, gradual tapering of the drug is recommended.
        - Useful in patients with **anxiety** and **cognitive difficulties**.

- **General adverse effects of SSRIs:**
  - GI side effects. (Nausea, vomiting, diarrhea)
  - Sexual dysfunction. (Both males and females)
  - Headache.
  - Insomnia.
- **Specific adverse effects of some SSRIs:**
  Dose-dependent prolongation of QT interval with the use of **citalopram** and **escitalopram**.

b. **Norepinephrine-dopamine reuptake inhibitors (NRDI)**
E.g., Buproprion
- May be used in smoking cessation programs.
- Side effects of NRDIs:
  - Nausea, vomiting, tremor, insomnia, dry mouth
  - Dose-dependent seizures
  - Contraindicated in patients with eating disorders (bulimia and anorexia) because they are prone to electrolyte abnormalities and increased risk for seizures.

c. **Serotonin-Norepinephrine reuptake inhibitors (SNRIs)**

i. Tricyclic antidepressants (TCAs)

- E.g., **Amitriptyline**, Nortriptyline, Imipramine.
  - Adverse effects of TCAs:
    - Dose-related anticholinergic effects (dry mouth, constipation, blurred vision, urinary retention, dizziness, tachycardia, memory impairment, and **delirium** at high doses) m.c.
    The anticholinergic effects affect patient adherence for long term maintenance therapy.
      - Weight gain
      - Sexual dysfunction
      - Orthostatic hypotension
      - Cardiac conduction delays & heart block
      - Severe cardiac arrhythmias and increased risk of death with TCA overdose.

ii. **Newer-generation SNRIs**
E.g., Venlafaxine
- Adverse effects of newer-generation SNRIs:
  - Sexual dysfunction (m.c.)
  - Nausea and vomiting (m.c.)
  - Dose-related increase in BP.
  - Anticholinergic effects (dry mouth, constipation, decreased appetite, insomnia, and increased sweating)

d. **Mixed serotonergic drugs:**
E.g., Trazadone

- Mechanism of action:

  1. 5-HT2 antagonist and 5-HT reuptake inhibitor
  2. 5-HT1A mediated neurotransmission
  3. Alpha-1 adrenergic and histaminergic receptor blocking.

- May be used in low doses to induce sleep in depressed patients taking other antidepressant medications.
- Side effects of mixed serotonergic medications:
  - Sedation cognitive slowing, and dizziness **(m.c.)**
  - Orthostatic hypotension
  - Minimal anticholinergic adverse effects
  - Priapism (rare)

e. Serotonin & alpha-2 adrenergic antagonist

- E.g., Mirtazapine
- Adverse effects of serotonin-alpha-2 adrenergic antagonists:
  - Somnolence
  - Weight gain
  - Dry mouth
  - Constipation

f. Monoamine oxidase inhibitors (MAOIs)
E.g., Phenelzine, selegiline, tranylcypromine

- Side effects of MAOIs:
  - Postural hypotension (more with phenelzine than tranylcypromine)
  - Weight gain
  - Sexual dysfunction
  - Fever, myoclonic jerks, brisk deep tendon reflexes
  - Hypertensive crisis with foods high in tyramine or certain drugs.
  - **Phenelzine** has sedating effects while **tranylcypromine** may exert a stimulating effect (insomnia)

Serotonin syndrome

- Any antidepressant that increases serotenergic neurotransmission can cause serotonin syndrome.
- Triad of symptoms: **mental status changes**, **autonomic instability**, and **neuromuscular abnormalities.**
- Presence of the following symptom clusters is highly diagnostic of serotonin syndrome:

1. Tremor & hyperreflexia
2. Spontaneous clonus
3. Muscle rigidity + temp >38c + ocular clonus/inducible clonus
4. Ocular clonus + agitation or diaphoresis
5. Inducible clonus + agitation or diaphoresis

Pharmacokinetic drug interactions with antidepressant medications:

1. Inhibits metabolism of other co-administered drugs by antidepressants

Examples: Duloxetine, fluoxetine, paroxetine, and sertraline inhibit **CYP2D6**
Fluvoxamine inhibits CYP1A2

2. Displacement of highly protein bound drugs from their binding sites.
3. Drugs that decrease hepatic blood flow may reduce the metabolism of some antidepressants.

Pharmacodynamic drug interactions with antidepressant medications:

1. SSRI+ other drugs that increase serotonin at synapse (e.g., linezolid) -> serotonin syndrome
   * TCAs, SNRIs, and SSRIs can cause serotonin syndrome by themselves.
2. Increased risk of upper GI bleeding and intracranial hemorrhage when combined with NSAIDs. (due to serotonin effects on platelet aggregation)
3. MAOI+ other drug that increase vasopressor response -> hypertensive crisis.

Therapy in special populations:

1. **Elderly patients:**
   - Depression can be mistaken for dementia.
   - SSRI are first line choice in elderly.
   - Buproprion and venlafaxine may be used because milder anticholinergic effects and less frequent Cardiovascular adverse effects.
   - Mirtazapine can also be used.
2. **Pediatric patients:**
   - Only **Fluoxetine** and **escitalopram** are approved for patients younger than 18.
   - Increased risk for suicidal ideation and behavior due to taking antidepressants in children.
   - Sudden death due to cardiac causes in children and adolescents taking antidepressants such as desipramine.
3. **Pregnancy:**
   - Maternal depression adversely affects child development.
   - Prenatal exposure to SSRI was associated with increased risk of low birth weight.
   - High risk of persistent pulmonary hypertension of newborn infants exposed to SSRI after 20^{th} week of gestation.
   - SSRI is the best treatment for depression in pregnancy.

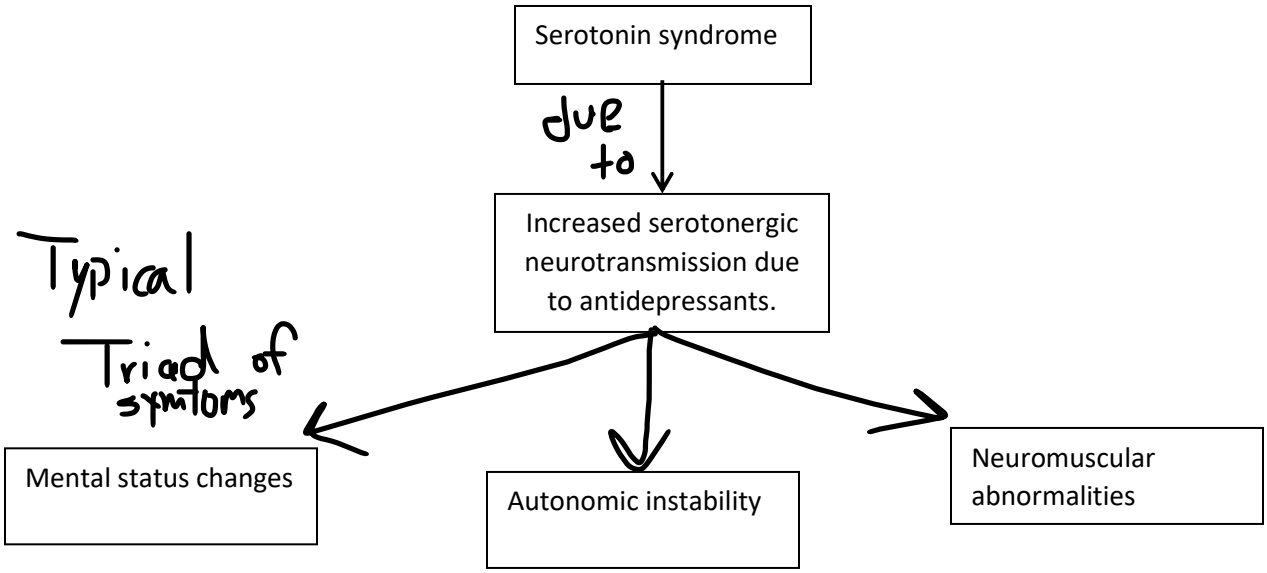
Treatment resistant depression

Treatment-resistant depression is depression that has not achieved remission even after two optimal antidepressant trails.

Management of treatment-resistant depression:

1. Switching to another agent
2. Augmenting current agent with another drug such as lithium or another antidepressant (combination therapy)
3. Augmenting current agent with atypical antipsychotic agent. Aripiprazole and quetiapine slow release have been recommended as first line agents to augment antidepressant medication.

Antidepressant Type	Examples	Adverse Effects
SSRIs	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline	• General adverse effects: GI side effects, Sexual dysfunction, Headache, Insomnia. • Specific adverse effects: Dose-dependent prolongation of QT interval with citalopram and escitalopram.
NRDIs	Bupropion	Nausea, vomiting, tremor, insomnia, dry mouth. Dose-dependent seizures. Contraindicated in patients with eating disorders.
SNRIs	Venlafaxine	Sexual dysfunction, Nausea and vomiting. Dose-related increase in BP. Anticholinergic effects.
TCAs	Amitriptyline, Nortriptyline, Imipramine	Dose-related anticholinergic effects, Weight gain, Sexual dysfunction, Orthostatic hypotension, Cardiac conduction delays and heart block, Severe cardiac arrhythmias and increased risk of death with TCA overdose.
Mixed serotonergic drugs	Trazadone	Sedation cognitive slowing and dizziness. Orthostatic hypotension. Minimal anticholinergic adverse effects, Priapism (rare).
Serotonin & alpha-2 adrenergic antagonist	Mirtazapine	Somnolence, Weight gain, Dry mouth, Constipation.
MAOIs	Phenelzine, Selegiline, Tranylcypromine	Postural hypotension (more with phenelzine than tranylcypromine) Weight gain. Sexual dysfunction. Fever, myoclonic jerks, brisk deep tendon reflexes. Hypertensive crisis with foods high in tyramine or certain drugs. Phenelzine has sedating effects while tranylcypromine may exert a stimulating effect (insomnia).



Sxs clusters diagnostic of SS.

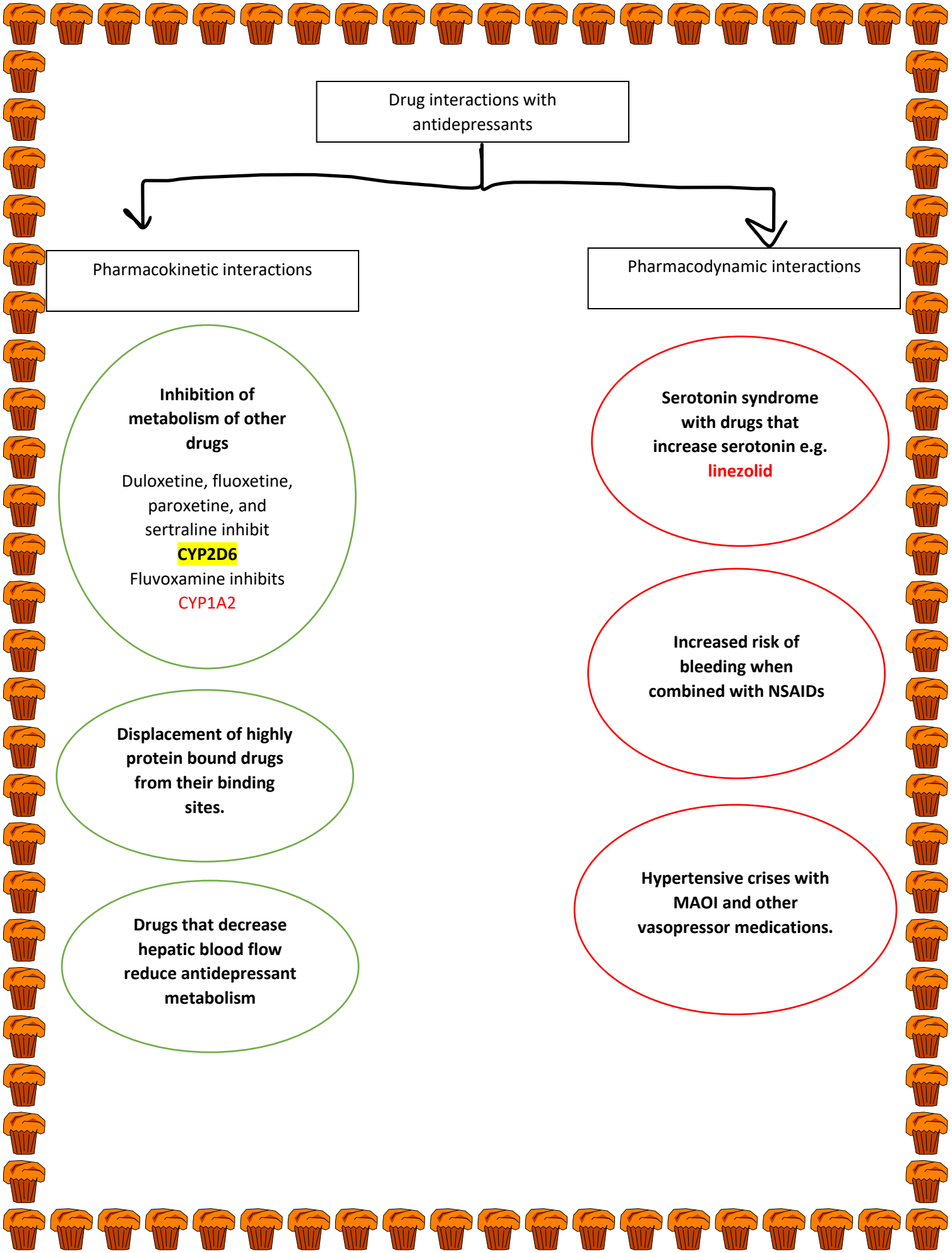
1. Spontaneous clonus

2. Tremor + Hyperreflexia

3. Muscle rigidity + temp >38 +Ocular clonus or inducible clonus

4. Ocular clonus + Agitation or diaphoresis

5 Inducible clonus + Agitation or diaphoresis


Drug interactions with antidepressants
Pharmacokinetic interactions
Pharmacodynamic interactions
Inhibition of metabolism of other drugs
Duloxetine, fluoxetine, paroxetine, and sertraline inhibit CYP2D6
Fluvoxamine inhibits CYP1A2
Displacement of highly protein bound drugs from their binding sites.
Drugs that decrease hepatic blood flow reduce antidepressant metabolism
Serotonin syndrome with drugs that increase serotonin e.g. linezolid
Increased risk of bleeding when combined with NSAIDs
Hypertensive crises with MAOI and other vasopressor medications.

Therapy in special populations

Elderly

SSRI first choice

Bupropion and venlafaxine have milder anticholinergic and less cardiovascular effects.

Mirtazapine can be used as well.

Pediatrics

Fluoxetine and escitalopram only

Increased risk of suicidal ideation due to antidepressants

Might cause sudden death due to cardiac causes (e.g., desipramine)

Pregnancy

SSRI best tolerated during pregnancy
However, SSRIs increase risk of LBW and persistent pulmonary hypertension if exposed after 20th week of gestation

Treatment resistant depression

1. Stop current antidepressant and switch to another (switching)
2. Augment antidepressant with another antidepressant or another agent e.g., lithium
3. Augment antidepressant with atypical antipsychotics. Aripiprazole and quetiapine are first line.