MANAGEMENT OF ANTIDEPRESSANT SIDE EFFECTS

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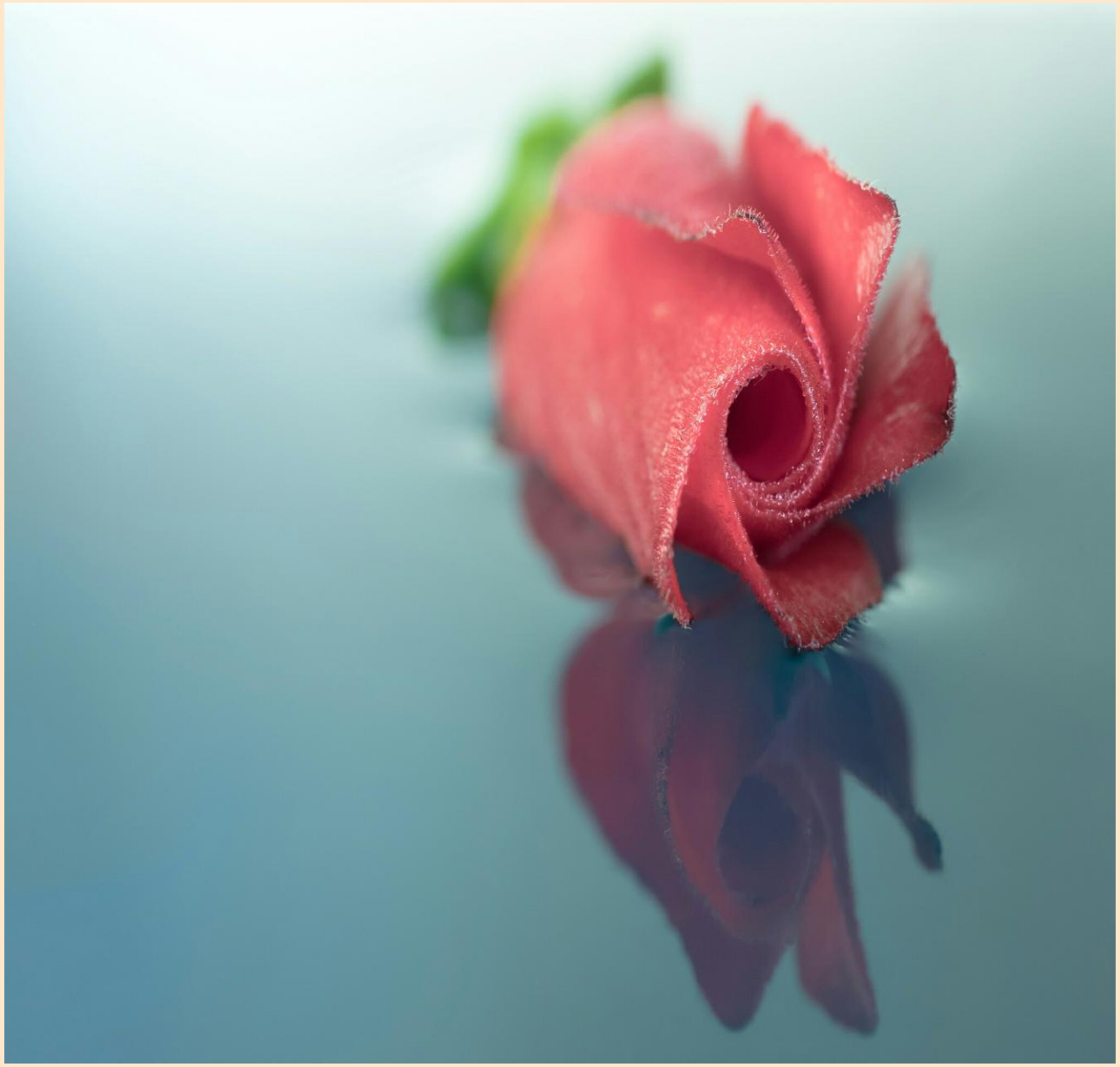

SSRI

SSRI side effects need to be considered in terms of **their onset, duration, and severity**.

For example, **nausea and jitteriness** are early, generally **mild, and time-limited** side effects.

Although **SSRIs share similar side effect profiles**, individual drugs in this class may cause a **higher rate** or carry a **more severe risk of specific side effects** depending on the patient.

The Maudsley prescribing guidelines in psychiatry. John Wiley & Sons; 2021

INSOMNIA AND SEDATION

The primary effect SSRIs exert in the area of insomnia and sedation is improved sleep resulting from the treatment of depression and anxiety.

25 % of persons taking SSRIs note trouble sleeping, excessive somnolence, or overwhelming fatigue.

Fluoxetine is the most likely to cause insomnia, for which reason it is often taken in the morning

Boland RJ, Verduin LN, Ruiz PK. Sadock's synopsis of psychiatry. Phlladelphia.2022.

- SSRIs had a **higher rate of sleepiness** than **bupropion and venlafaxine and duloxetine and moclobemide.**

- **Mirtazapine and trazodone** are associated with **greater rates of somnolence and fatigue** than SSRIs.

understanding and managing antidepressant side effects. Dialogues in clinical neuroscience. 2022

Many persons taking **SSRIs** report recalling extremely **vivid dreams** or nightmares.

Other sleep effects of the SSRIs include:

- ✓ **bruxism,**
- ✓ **restless legs,**
- ✓ **nocturnal myoclonus,**
- ✓ **and sweating**.

The Maudsley prescribing guidelines in psychiatry. John Wiley & Sons; 2021

- The differential of drowsiness should include:

- ✓ **residual symptoms** of depression,
- ✓ a primary sleep disorder such as obstructive sleep apnea or
- ✓ restless leg syndrome or altered sleep cycle,
- ✓ and substance-use disorders.

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Management of drowsiness

- sleep hygiene (avoidance of daytime napping),
- divided dosing
- Shifting from morning to nighttime
- slower release preparation,
- Insomnia: BNZ, trazodone
- psychostimulants, modafinil, bupropion,
- alternative remedies :methylfolate or S-adenosylmethionine
- graduated increase in exercise may also help reduce fatigue

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Sexual dysfunction

- ✓ **All** SSRIs cause sexual dysfunction.
- ✓ incidence of **between 50 and 80 percent**.
- ✓ **anorgasmia, inhibited orgasm, and decreased libido**.
- ✓ Some studies suggest that **sexual dysfunction is dose-related**, but this **has not been** established.

- ✓ **rarely resolves in the first few** weeks of use but usually continues **as long as the drug is taken**.
  In some cases, there **may be** an improvement **over time**

Libido, arousal, orgasm, and ejaculation,and may affect lubrication and erection.

In a study of **344** patients:

58% of patients reported SSRI-induced sexual dysfunction when **directly** inquired

compared with

only **14%** of those who spontaneously reported sexual dysfunction.

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closed-ended questions:

34% of patients reported sexual dysfunction.

70% of patients:

did so by 2 weeks

80% experiencing it at

3 months

6000 individuals on SSRIs, bupropion, mirtazapine, and venlafaxine:

Bupropion immediaterelease and nefazodone were found to have the lowest rate

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Studies comparing SSRIs with mirtazapine are **inconclusive**,

some showing higher rates of sexual dysfunction with SSRIs and others with mirtazpine

Among the SSRIs**, paroxetine** has been found to have the **highest** rates of sexual dysfunction

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Prior to the introduction of sildenafil and similar agents, many methods and medications were used in an attempt to treat the sexual side effects of antidepressants.

These included dose reduction, timing of sexual activity toward the end of a dosing interval, several days' drug holiday, and antidote therapy with medicine such as psychostimulants , amantadine, pramipexole, bupropion, nefazodone, and yohimbine.

Management of sexual dysfunction

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A recent trial also demonstrated that **sildenafil is effective** at decreasing adverse sexual effects in women taking SSRIs,

including improvement in **desire, arousal-sensation, arousal-lubrication, orgasm, and enjoyment.**

Nevertheless, many patients **do not** respond sufficiently well to sildenafil and related agents or other attempted antidotes, and efforts to identify other remedies continue.

These include complementary and alternative treatments such as **maca root, arginine-containing compounds, and ginkgo biloba.**

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✓**switching** to agents with **lesser** degrees of sexual dysfunction, typically **bupropion**.

✓Nefazodone is another option, though its use has been limited by risk of rare but serious **hepatotoxicity**.

When sexual dysfunction persists despite efforts at dose adjustments and antidote therapy, the principal option is to consider

Gastrointestinal problems

- ✓ The most frequent GI complaints are nausea, diarrhea, anorexia, vomiting, flatulence, and dyspepsia.

- ✓ **Sertraline and fluvoxamine** produce **the most** intense GI symptoms.

Boland RJ, Verduin LN, Ruiz PK. Sadock's synopsis of psychiatry. Phlladelphia.2022.

- ✓ **Nausea and loose stools are usually dose-related and transient**, usually resolving **within a few weeks**.

- ✓ Sometimes **flatulence and diarrhea persist**, especially during **sertraline** treatment.

The Maudsley prescribing guidelines in psychiatry. John Wiley & Sons; 2021

Nausea and stomach upset, present in **17% to 26%** of patients taking it, **83%** of whom experienced it **by 2 weeks**, and **32 %** of whom continued to experience it at **3 months**

SSRIs was associated with a **higher rate of nausea** than **bupropion, moclobemide, mirtazapine.**

Venlafaxine has been found to have a **higher incidence** of nausea than SSRIs.

nausea from **venlafaxine and paroxetine** may be reduced using **controlled-release** formulations.

divided dosing

taking medications with a **small amount of food**, such as crackers or toast

ginger-containing foods

ranitidine or omeprazole

Adjunctive **promethazine, or ondansetron or mirtazepine**

management of nausea and vomiting

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Gastrointestinal problems

Diarrhea

Diarrhea

may be **a transient** effect and **resolve within weeks**,

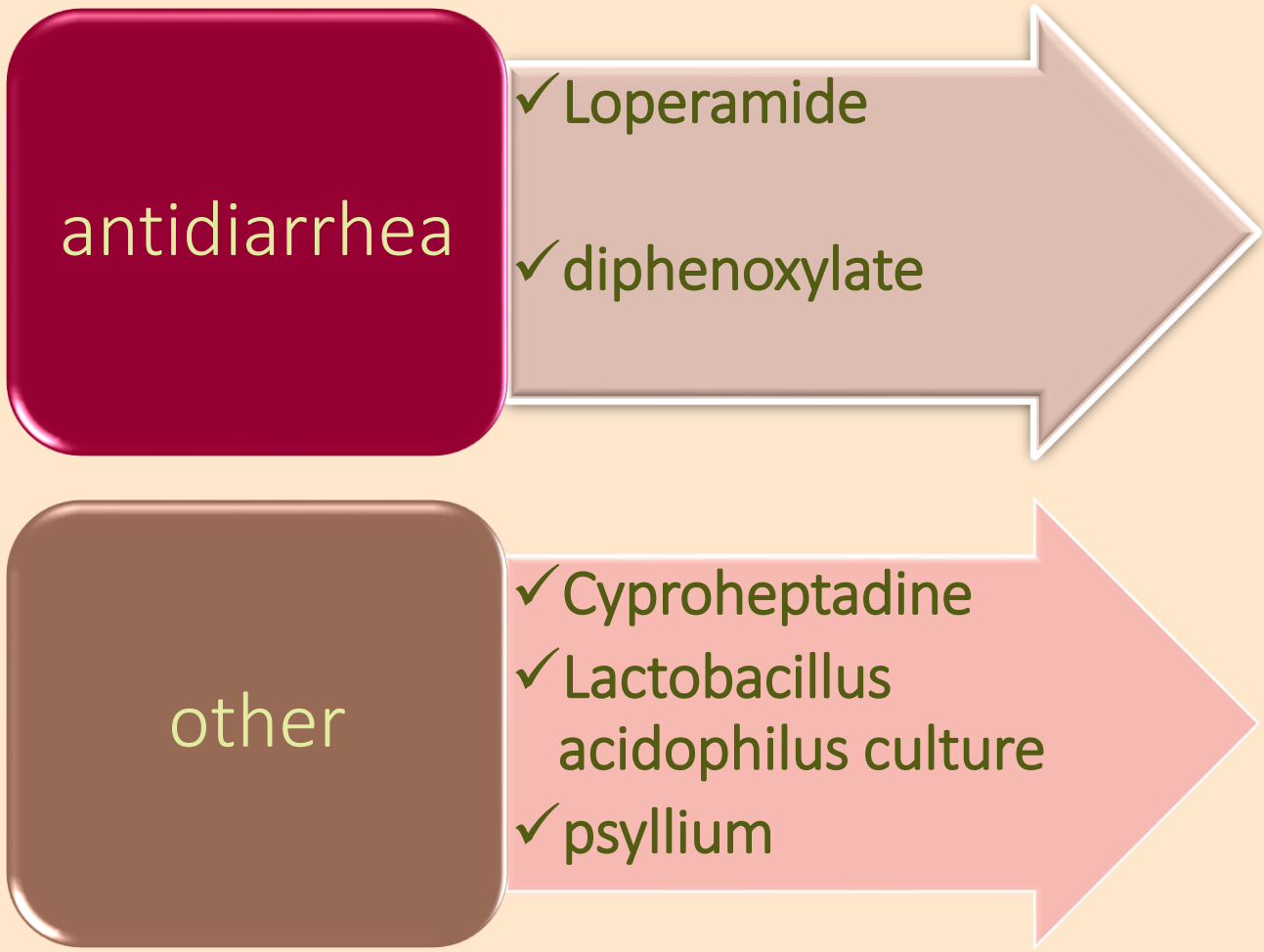
but it also may **persist** in some patients.

A meta-analysis of 84 trials:

16% of patients taking SSRIs experienced diarrhea.

15% of patients experienced diarrhea, **78%** of whom experienced it at **2 weeks** and **45%** of whom still experienced it at **3 months**

Management of diarrhea



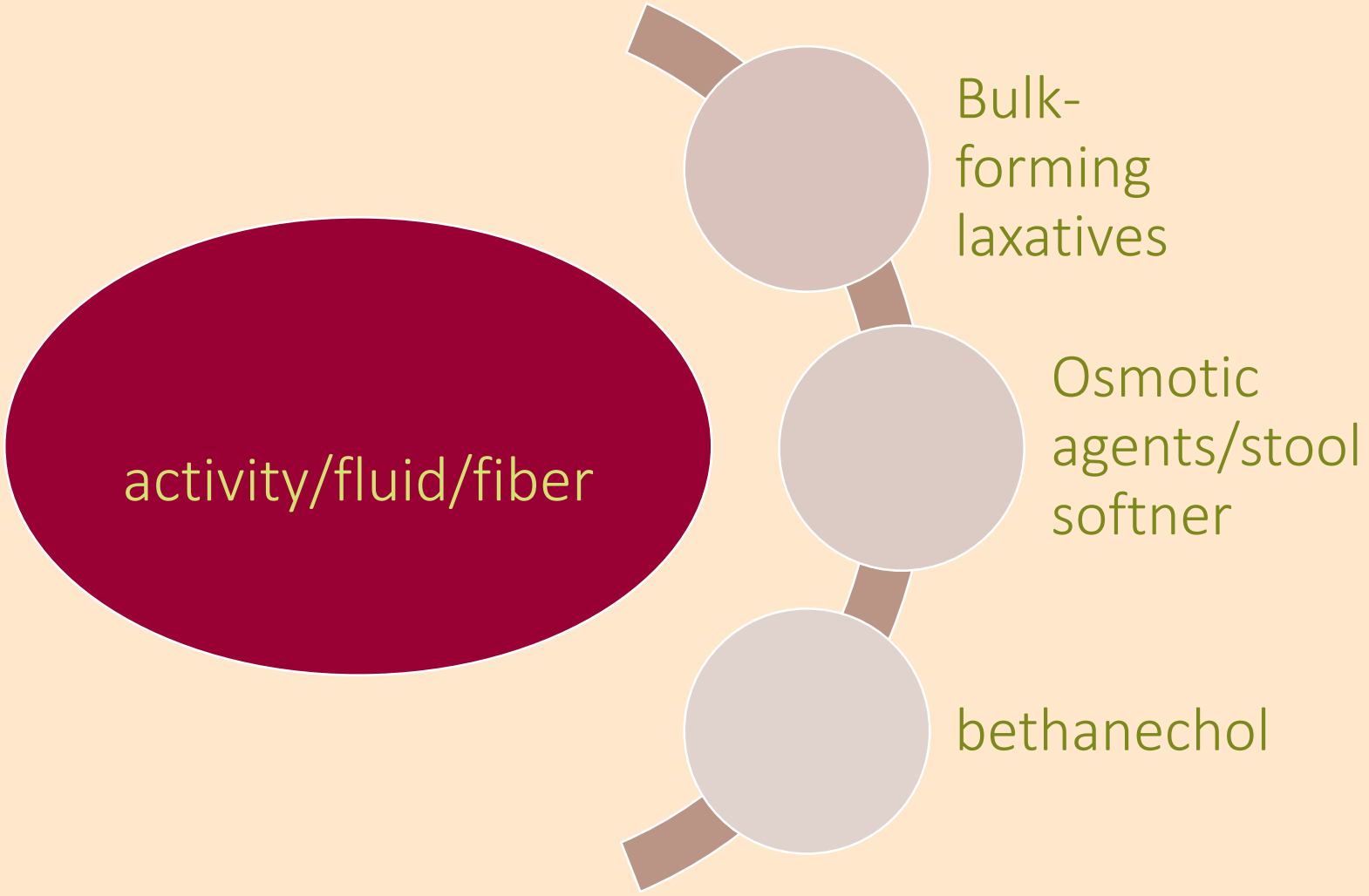
Gastrointestinal problems

Constipation

Of the SSRIs, **paroxetine** has been associated with the **highest** rates of constipation, presumably secondary to its **high affinity for muscarinic receptors**.

Overall, the rate of constipation has been found to be 11% to 12.5.

Management of Constipation



Weight gain

- ✓ **Initial anorexia** may also occur and is most frequent with **fluoxetine.** SSRI-induced appetite and **weight loss** begin **as soon as the drug is taken** and **peak at 20 weeks**, **after** which weight often **returns to baseline.**

- ✓ **Up to one-third** of persons taking SSRIs will **gain weight**, sometimes more **than 20 lb.**

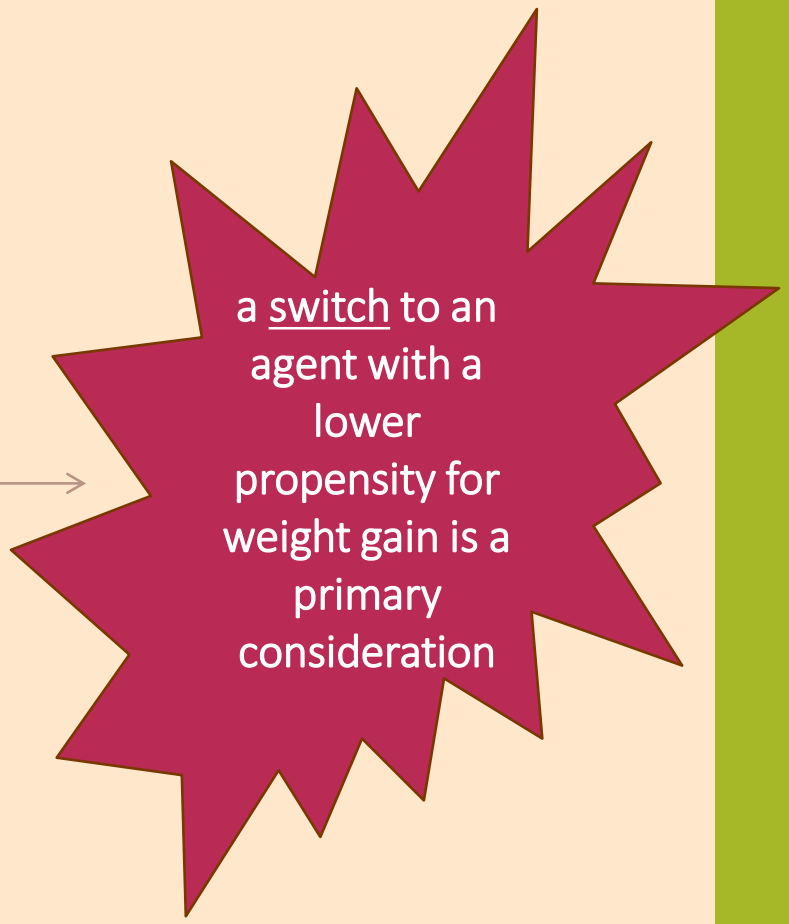
- ✓ This effect is mediated through a **metabolic mechanism**, an increase in **appetite, or both**.

- ✓ It happens gradually and is usually resistant to diet and exercise regimens.

Management of weight gain

The addition of **bupropion, topiramate, zonisamide, or sibutramine**

In the setting of unacceptable weight gain that is not responsive to dietary and behavioral modification



Cardiovascular Effects

- ✓ All SSRIs can lengthen the QT interval in healthy people and cause drug-induced long QT syndrome, especially when taken in overdose.

- ✓ The risk of QTc prolongation increases when an antidepressant and an antipsychotic are used ***in combination.***

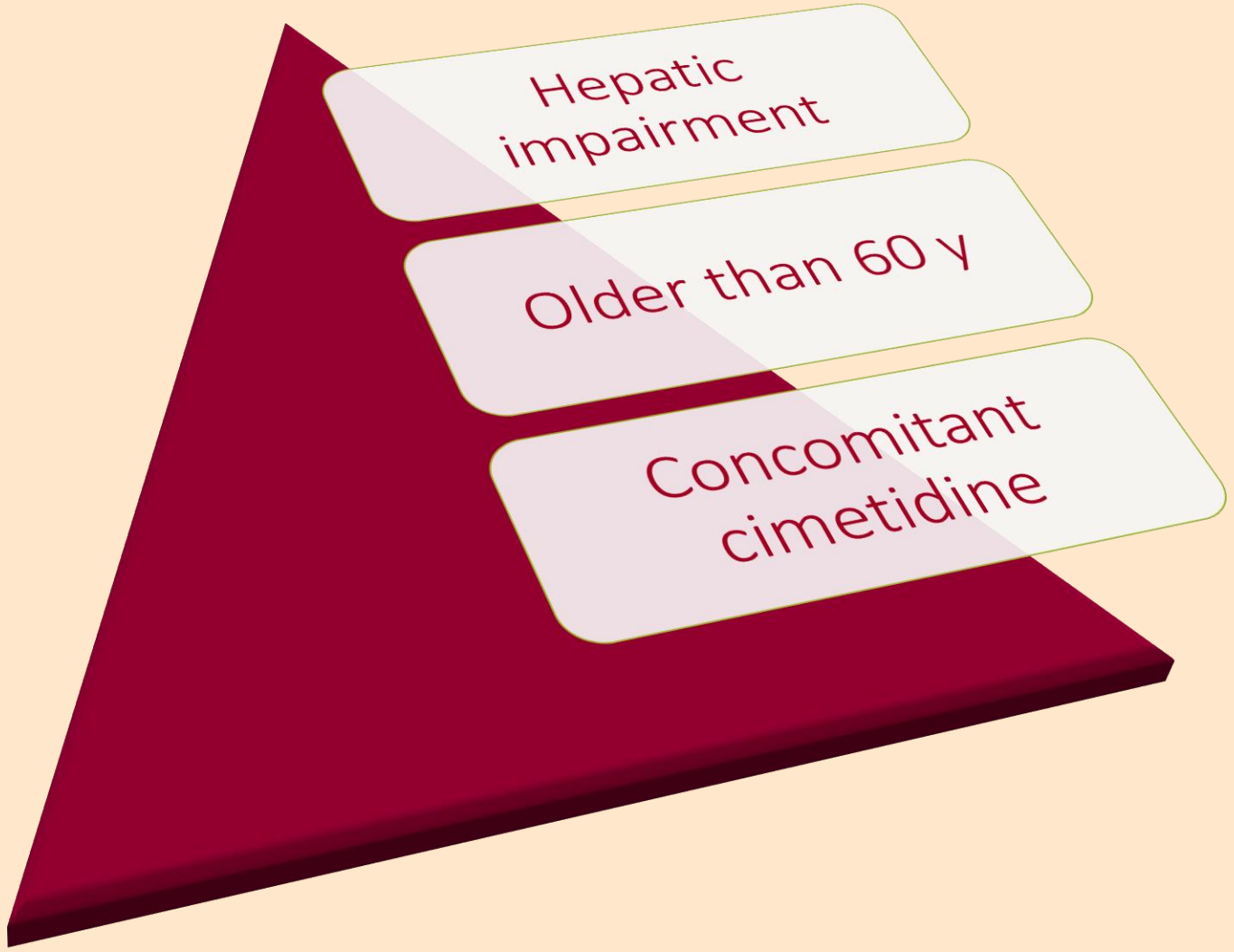
Cornett EM. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. Neurology International. 2021

Citalopram has the most pronounced effect on QT intervals.

FDA recomendation

- No longer prescribe at doses **greater than 40 mg**
- **Do not** use: congenital long QT syndrome
- Correct hypokalemia and hypomagnesemia
- Monitor electrolytes

20 mg a day is the **maximum** recommended dose



Headaches

- ✓ The incidence of headache in SSRI trials was 18 to 20 percent

- ✓ only one percentage point higher than the placebo rate.

- ✓ Fluoxetine is the most likely to cause headaches.

- ✓ On the other hand, all SSRIs are effective prophylaxis against both migraine and tension-type headaches in many persons

Electrolyte and Glucose Disturbances

- ✓ SSRIs may acutely decrease glucose concentrations; therefore, diabetic patients should be carefully monitored.
- ✓ Long-term use may be associated with increased glucose levels, although it remains to be proven whether this is the result of a pharmacologic effect.

Boland RJ, Verduin LN, Ruiz PK. Sadock's synopsis of psychiatry. Phlladelphia.2022.

SSRI-associated hyponatremia and SIADH have been seen in some patients, especially those who are older or treated with diuretics.

Boland RJ, Verduin LN, Ruiz PK. Sadock's synopsis of psychiatry. Phlladelphia.2022.

YAWNING

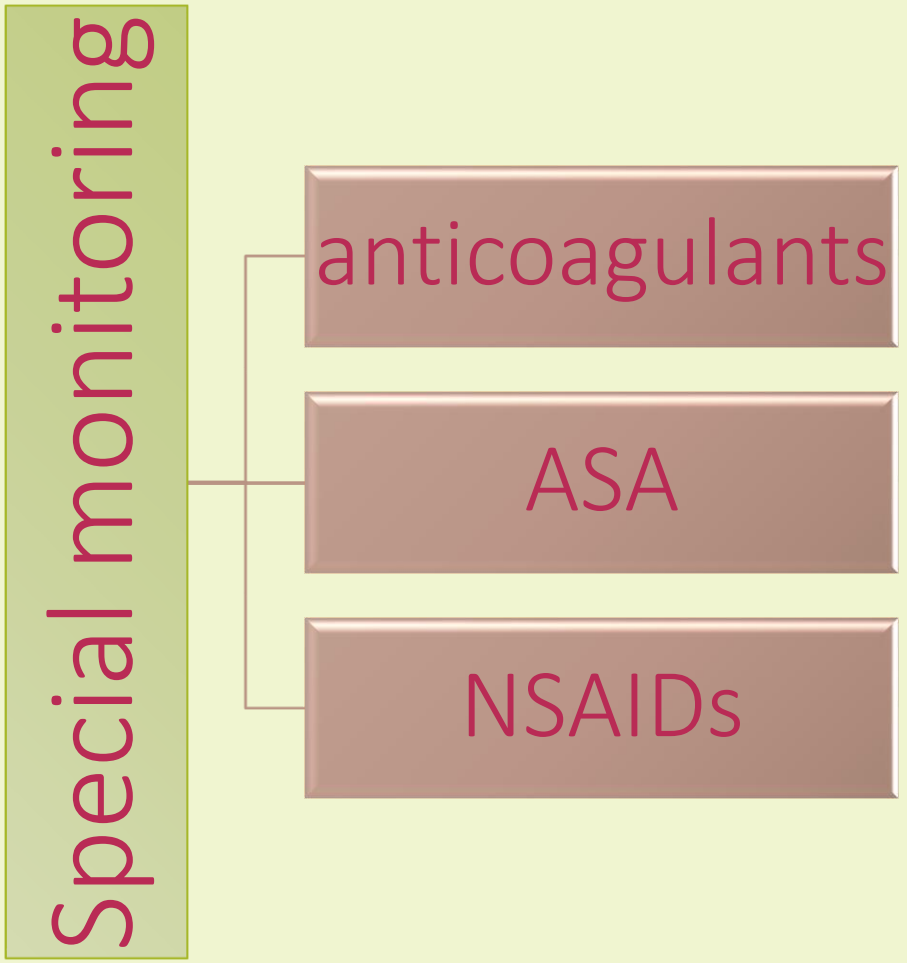
This side effect **is not** a reflection of **fatigue or poor nocturnal sleep** but is the result of SSRI effects on the **hypothalamus.**

EXTRAPYRAMIDAL SYMPTOMS.

- ✓ The SSRIs may **rarely** cause a**kathisia, dystonia, tremor, cogwheel rigidity, torticollis, opisthotonos, gait disorders, and bradykinesia**.
- ✓ occurred **within 30 days** of treatment **initiation or dose increase;**
- ✓ **Rare** cases of **tardive dyskinesia** have been reported.
- ✓ Some people with well-controlled Parkinson disease may experience **acute worsening** of their motor symptoms when they take SSRIs.

Hematologic Adverse Effects

- ✓ functional impairment of **plt aggregation** but **not** a reduction in plt **number.**
- ✓ **easy bruising and excessive or prolonged bleeding**.
- ✓ numerous studies reported the risk of bleeding associated with SSRIs and venlafaxine



Serotonin Syndrome

Serotonin syndrome

✓potentially fatal consequence of serotonergic overactivity in the peripheral and central nervous systems

The majority of cases involve **a combination** of serotonergic drugs,
though **SSRI monotherapy** may also lead to serotonin syndrome.

Concurrent administration of an SSRI with an **MAOI, L-tryptophan, or lithium**
can raise plasma serotonin concentrations to toxic levels

Cornett EM. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. Neurology International. 2021

Table 21-17
Serotonin Syndrome Symptoms

Diarrhea	Myoclonus
Diaphoresis	Hyperactive reflexes
Tremor	Disorientation
Ataxia	Lability of mood

Treatment of serotonin syndrome

removing the offending agents and comprehensive **supportive care**

1. nitroglycerine,
2. cyproheptadine
3. methysergide
4. cooling blankets,
5. chlorpromazine
6. dantrolene
7. benzodiazepines,
8. anticonvulsants,
9. mechanical ventilation,
10. paralyzing agents.

Cornett EM. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. Neurology International. 2021

Sweating

sweating is **independent** of the temperature

Nocturnal sweating may drench bed sheets and require a change of nightclothes.

Terazosin (1 or 2 mg/day, is often dramatically effective)

SNRI

venlafaxine

- causes a **lower frequency** of anticholinergic, sedating, and cardiovascular side effects
- but a **higher** incidence of gastrointestinal complaints, sleep impairment, and sexual dysfunction than TCAs.

impair **sexual function**.

Sexual dysfunction can sometimes be ameliorated **by lowering the dose or instituting drug-free weekends and holidays** in appropriate patients.

Singh D. Venlafaxine. InStatPearls [Internet] 2021 StatPearls Publishing.

Venlafaxine Common side effects

- Headache
- Nausea
- Insomnia, dizziness, hypotension, anorexia, somnolence
- Xerostomia
- Asthenia
- HTN
- Impotence, decreased libido, and/or anorgasmia

- Constipation
- Weight loss
- Abnormal dreams
- Diarrhea, abdominal pain
- Blurred vision
- Anxiety, tremor
- Hypercholesterolemia
- Hyponatremia
- Serotonin syndrome
- Seizures

Singh D. Venlafaxine. InStatPearls [Internet] 2021 StatPearls Publishing.

venlafaxine

- ✓ Caution is advisable in
- ✓ **heart failure** patients,
- ✓ hyperthyroidism,
- ✓ those with **recent myocardial infarctions**
- ✓ as it can **raise blood pressure** and **increase heart rate**

Singh D. Venlafaxine. InStatPearls [Internet] 2021 StatPearls Publishing.

Duloxetine

duloxetine should also **be avoided** in:

- ✓ **liver failure**
- ✓ **severe renal dysfunction.**

Clinicians should also avoid using duloxetine in patients receiving treatment with **linezolid** due to an increased risk of serotonin syndrome.

Dhaliwal, "Duloxetine." (2019). StatPearls [Internet].

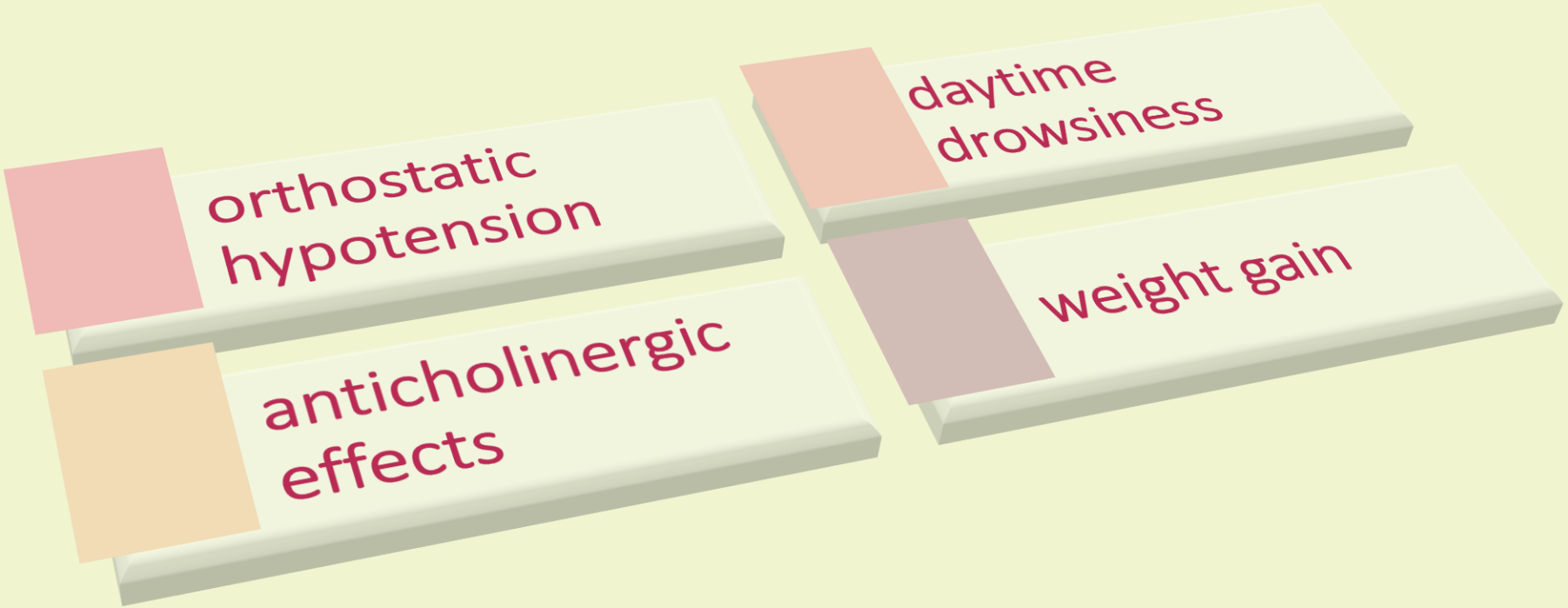
BUPROPION

- Headache,
- insomnia,
- dry mouth
- tremor
- nausea
- Restlessness
- agitation
- irritability

Patients with **severe anxiety** or **panic disorder** should **not** be prescribed bupropion.

Most likely, because of its potentiating effects on dopaminergic neurotransmission, bupropion can **cause psychotic symptoms**, including **hallucinations, delusions, and catatonia**, as well as **delirium.**

absence of significant drug-induced



Hypertension may occur in some patients, but bupropion causes no other significant cardiovascular or clinical laboratory changes.

Bupropion exerts indirect sympathomimetic activity, producing positive inotropic effects in the human myocardium, an effect that may reflect catecholamine release.

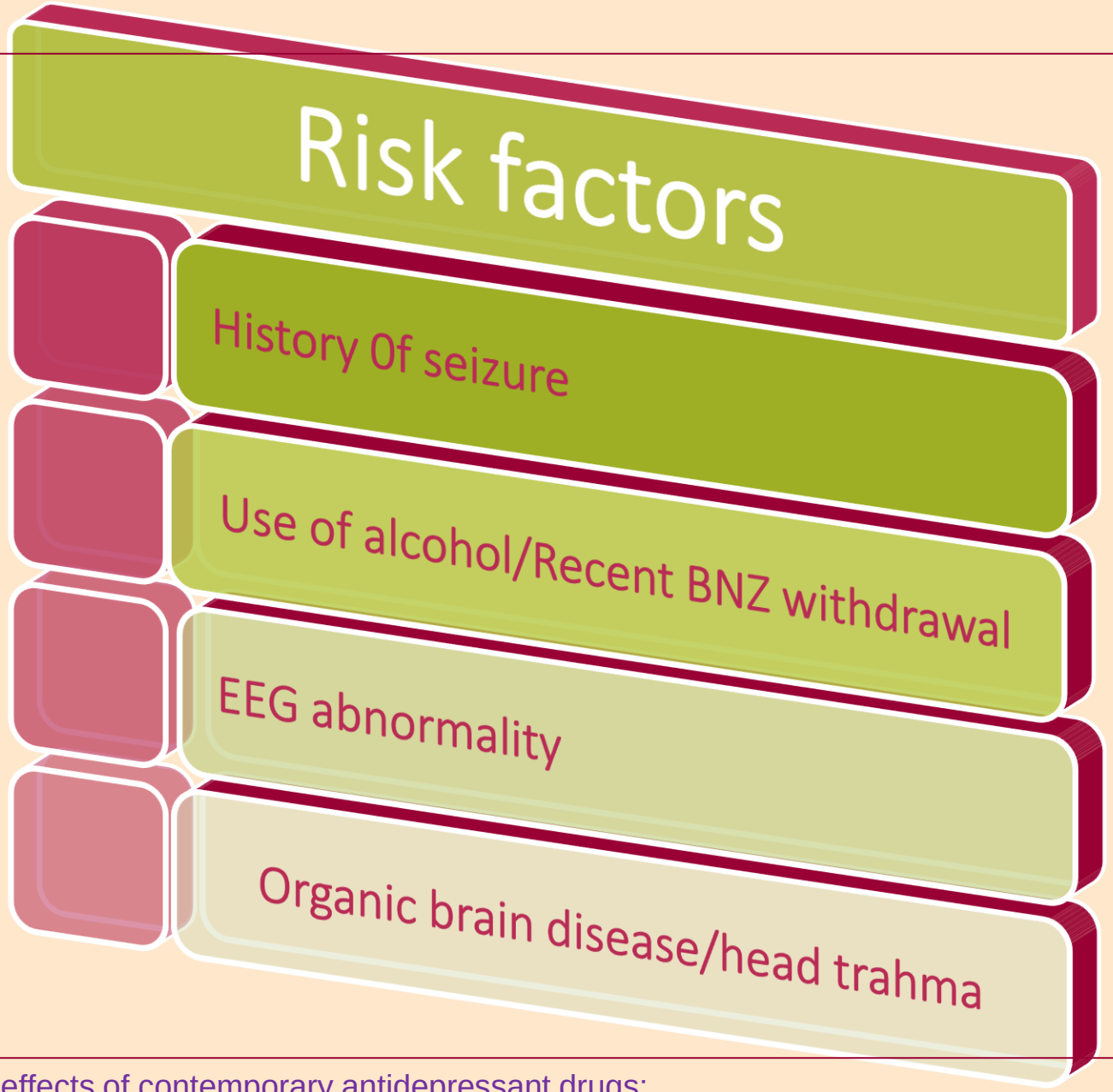
Some patients experience cognitive impairment, most notably word-finding difficultie

BUPROPION AND SEIZURE

The risk of seizure is dose-dependent.

The risk of seizures increases to about 0.1 percent with dosages of 400 mg a day.

. Addressing the side effects of contemporary antidepressant drugs:
a comprehensive review. Chonnam medical journal. 2018.



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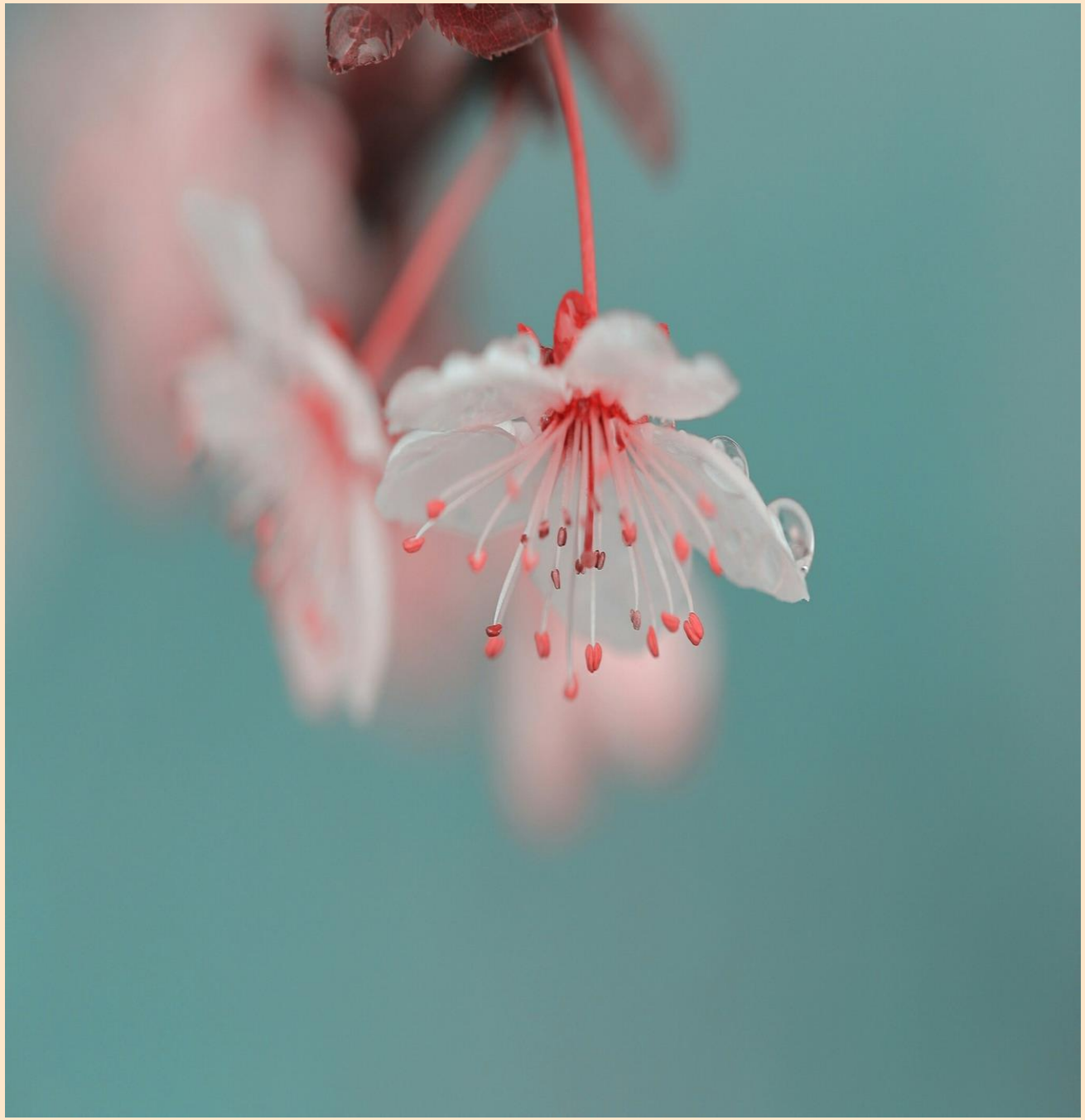
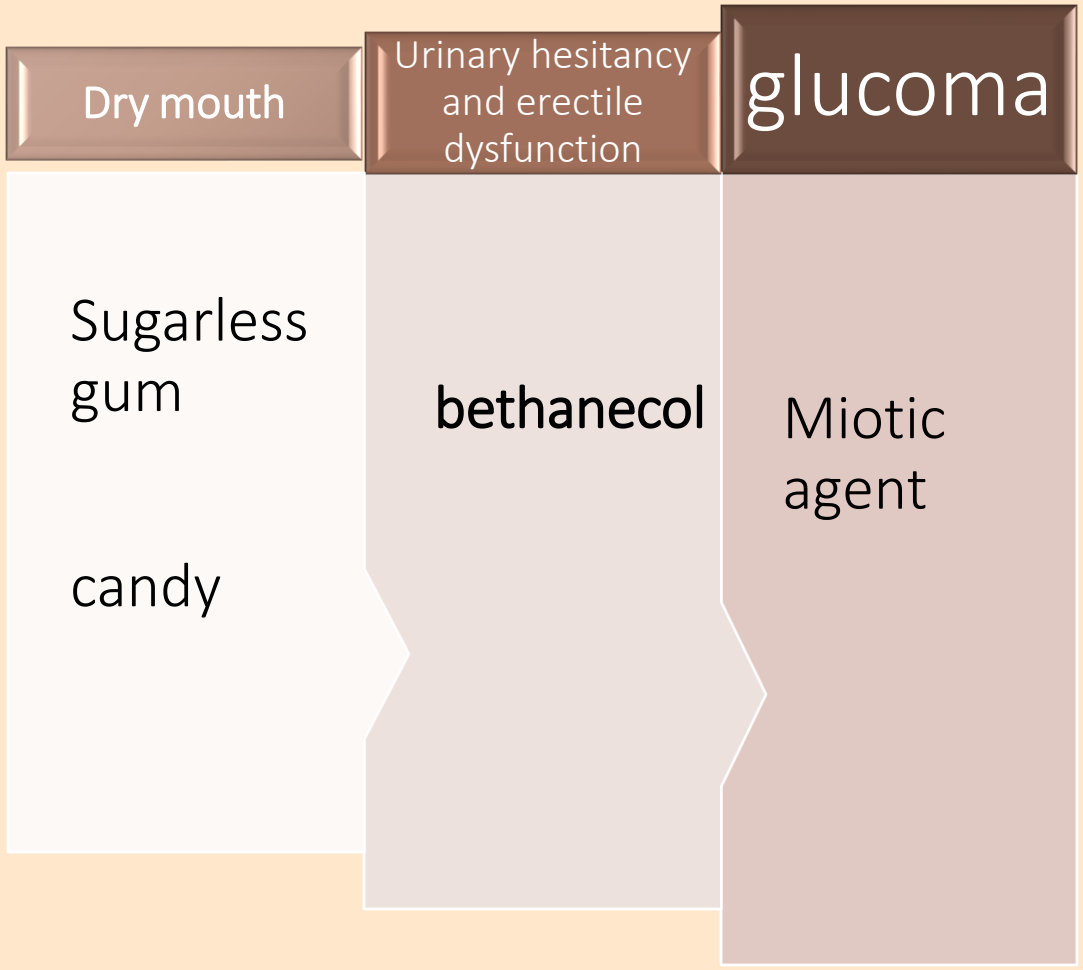


TRICYCLICS AND TETRACYCLICS

- switch to mania or hypomania.
- exacerbate psychotic disorders
- confusion or delirium.

In susceptible individuals

Boland RJ, Verduin LN, Ruiz PK. Sadock's synopsis of psychiatry. Phlladelphia.2022.



Managegement of Anticholinergic Effects.

Cardiac Effects

- All of the TCAs can cause tachycardia, which may persist for months

- tachycardia,
- flattened T waves,
- prolonged QT intervals,
- and depressed ST
- Orthostatic hypotension

Because the drugs prolong conduction time, their use in persons with preexisting conduction defects is contraindicated.

Neurologic Effects.

Sedation

fine, rapid tremor

Myoclonic twitches and tremors of the tongue and the upper extremities are common

Seizure

- maprotiline
- clomipramine

Modest weight gain

amenorrhea

SIADH

MIRTAZAPINE

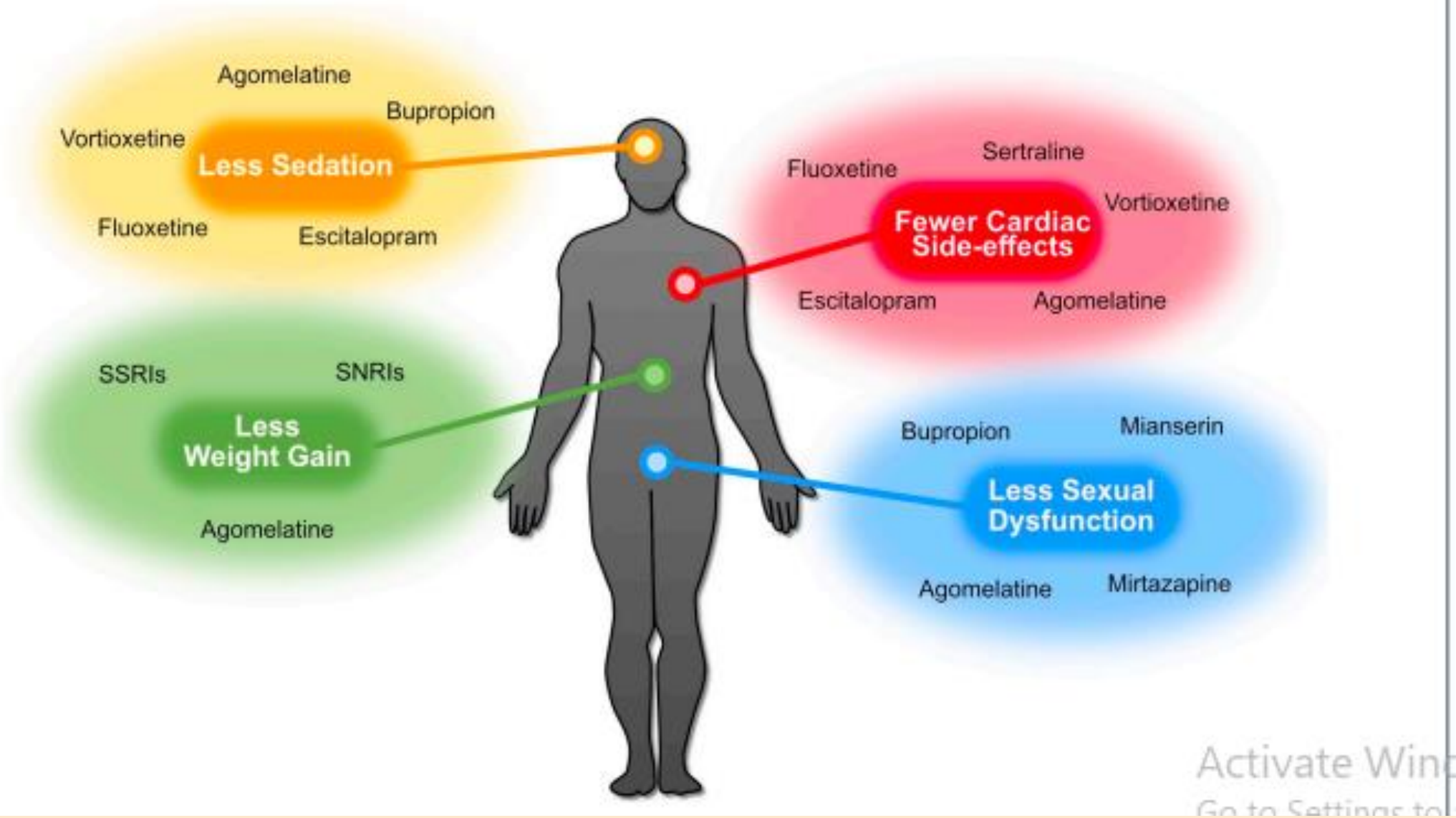
Table 21-18
Adverse Reactions Reported with Mirtazapine

Event	Patients (%)
Somnolence	54
Dry mouth	25
Increased appetite	17
Constipation	13
Weight gain	12
Dizziness	7
Myalgias	5
Disturbing dreams	4

Boland RJ, Verduin LN, Ruiz PK. Sadock's synopsis of psychiatry. Phlladelphia.2022.

Thank you for your attention

Figure 23. Antidepressant side effects.



Side effects of antidepressant medications[1-7]

Drug	Anticholinergic	Drowsiness	Insomnia/agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Selective serotonin reuptake inhibitors¶								
Citalopram	0	0	1+	1+	3+Δ	1+¶	1+	3+
Escitalopram	0	0	1+	1+	2+	1+¶	1+	3+
Fluoxetine	0	0	2+	1+	1+	1+¶	0	3+
Fluvoxamine	0	1+	1+	1+	1+	1+¶	1+	3+
Paroxetine	1+	1+	1+	2+	0 to 1+	1+¶	2+	4+
Sertraline	0	0	2+	1+	1 to 2+	2+¶◇	1+	3+

Drug	Anticholinergic	Drowsiness	Insomnia/agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Tricyclic and tetracyclic antidepressants								
Amitriptyline	4+	4+	0	3+	1 to 2+	1+◇◇	4+	3 to 4+
Amoxapine	2+	2+	2+	2+	1+	0◇◇	2+	ND
Clomipramine	4+	4+	1+	2+	3+	1+◇◇	4+	4+
Desipramine	1+	2+	1+	2+	1 to 2+	0◇◇	1+	ND
Doxepin	3+	3+	0	2+	3+	0◇◇	4+	3+
Imipramine	3+	3+	1+	4+	3+	1+◇◇	4+	3+
Maprotiline	2+	3+	0	2+	1+	0◇◇	2+	ND
Nortriptyline	2+	2+	0	1+	1 to 2+	0◇◇	1+	ND
Protriptyline	2+	1+	1+	2+	1+	1+◇◇	1+	3 to 4+
Trimipramine	4+	4+	1+	3+	1+	0◇◇	4+	ND

Class	Drugs	SE	Considerations
TCA	Imipramine Amitriptyline Doxepin Desipramine Nortriptyline	Weight gain, sedation, dry mouth, nausea, blurred vision, constipation, tachycardia	Generally not first-line therapy due to increased anticholinergic and cardiotoxic SE
MAOI	Isocarboxazid Phenelzine Tranylcypromine Selegiline	Weight gain, fatigue, sexual dysfunction, hypotension	Generally not first-line therapy due to serotonin syndrome and hypertensive crises
SSRI	Fluoxetine Paroxetine Sertraline Citalopram Escitalopram	Headaches, GI distress, insomnia, fatigue, anxiety, sexual dysfunction, weight gain	Often first-line treatment due to safer SE profile. Subtle SE differences must be weighed by the prescriber