Drugs used in Depression- New groups

By

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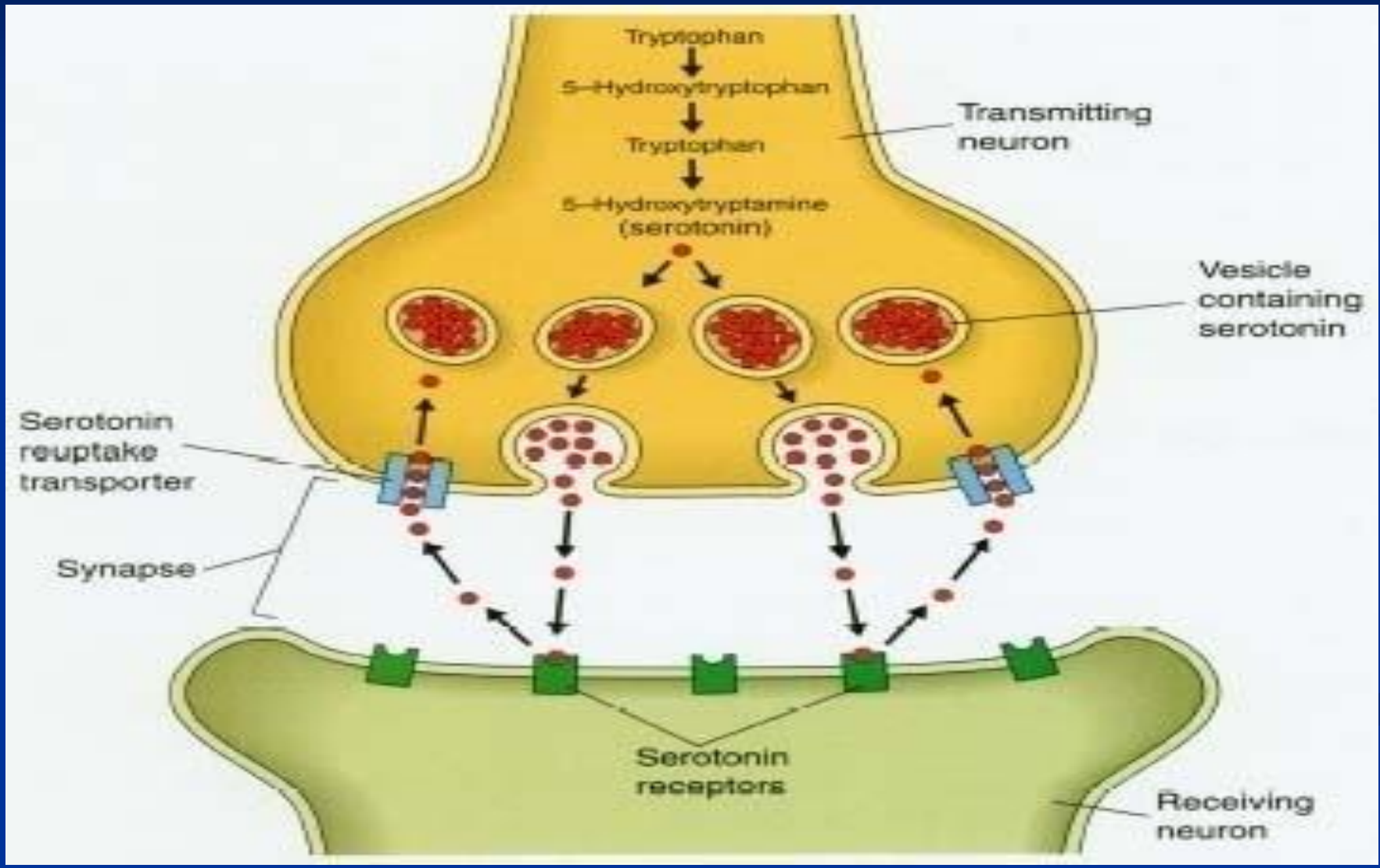
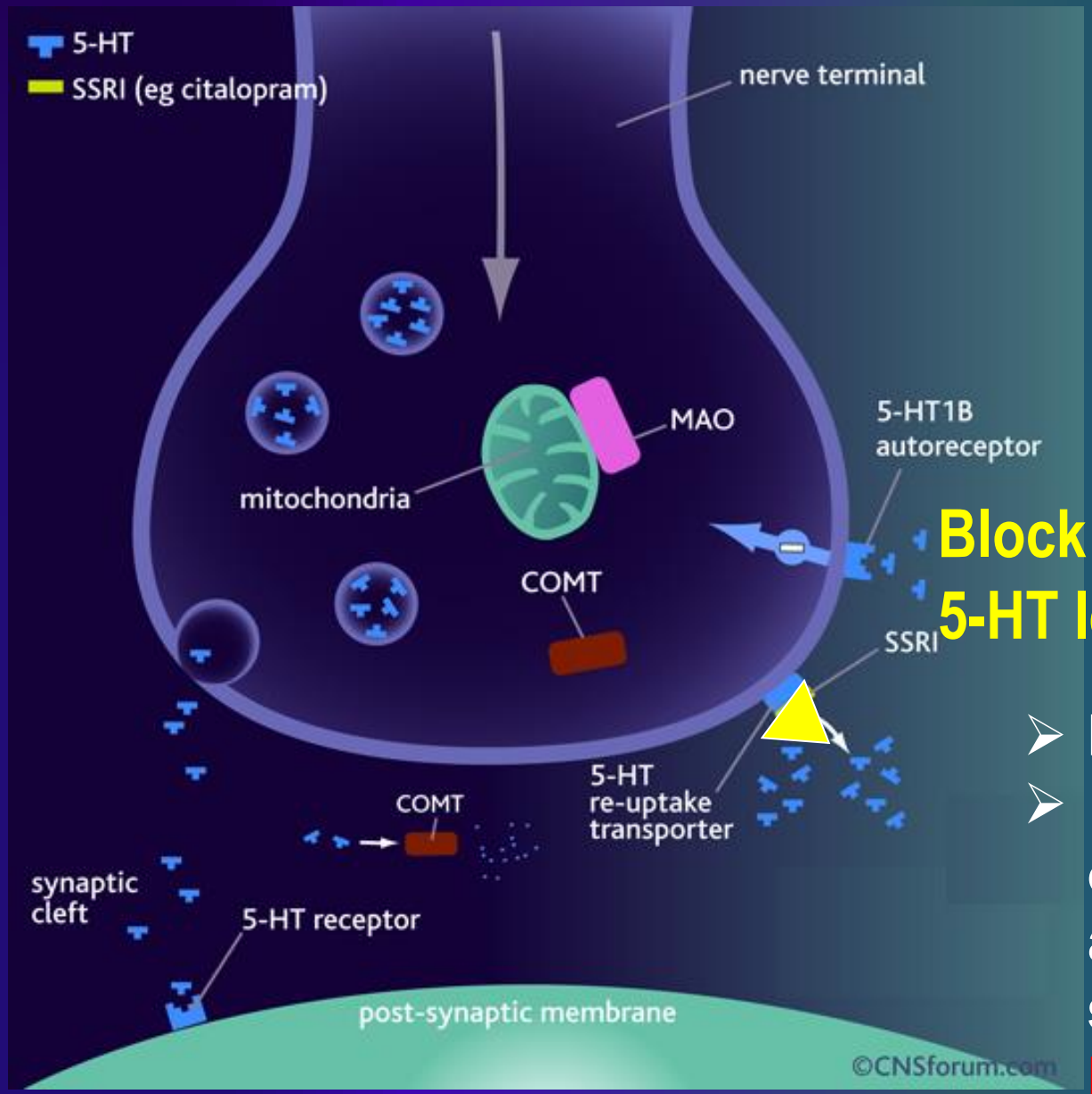
1. Selective Serotonin Reuptake Inhibitors (SSRIs)

- The SSRIs are currently the most widely utilized class of antidepressants in clinical practice.
- They act within the brain to increase the level of serotonin (5-HT) in the synaptic gap by inhibiting its re-uptake.
- SSRIs are described as 'selective' because they affect only the reuptake pumps responsible for serotonin.

Mechanism of Action of SSRIs





Fluoxetine
Citalopram
Escitalopram
Paroxetine

Block 5HT transport➔ ↑ 5-HT levels in synapse

- **No effect on NET**
- **No block to mAch, H, or α_1 Adrenoceptor ➔ so no antimuscarinic nor sedative effects Except Paroxetine**

- **They are nearly of comparable efficacy but of preferential response in each individual**

Advantages of SSRIS

- The Most commonly prescribed antidepressants

- Lacks cardiovascular and anticholinergic side effects compared to TCA

- In contrast to MAOI, they do not cause ‘cheese’ reaction

- Safer (low risk of overdose)

- Acute toxicity is less than that of MAOI or TCA

Pharmacokinetics

t1/2 :

➔Too long (3-11 days): Fluoxetine (Prozac)

➔ Moderate length (~24hr): Sertraline, Paroxetine, Citalopram.

Metabolism: P450 then conjugation

- **They are enzyme inhibitors**
- **➔ Weak inhibitors :Sertraline, Citalopram ➔↓ interaction**
- **➔ Strong inhibitors > Fluoxetine, Paroxetine ➔↓ metabolism of TCA, neuroleptic, some antiarrhythmic, β-blockers.**

- **Fluoxetine** differs from others members of this class in:

  1- It has a longer $t_{1/2}$ (50hrs).

  2- Available ➔ as sustained release preparations

  ➔once weekly.

  3- Metabolite **norfluoxetine** = potent as parent drug $t_{1/2}$

  10 days.

Adverse effects of SSRIs:

- GIT symptoms: Nausea vomiting (due to 5-HT3 stim. & diarrhea.
- Changes in appetite (5-HT3)---weight loss
- Sleep disturbances: Drowsiness with Fluvoxamine.
- Anxiety & Tremors.
- Sexual dysfunction: Loss of libido , delayed ejaculation (stim of 5-HT2A).

Discontinuation syndrome:

- Symptoms are headache ,malaise & flu like symptoms, agitation , irritability & nervousness

Side effects of SSRIs

Drug	Cardiotoxicty	Nausea	Anticholinergic effects	Sedation
Fluoxetine	-	++	_	_
Fluvoxamine	_	+++	_	+
Paroxetine	_	++	+	+
Sertraline	_	++	_	_

Therapeutic Uses of SSRIs

Same as for TCA, in addition effective in the following conditions

- Anxiety Disorder.
- Eating disorders- bulimia nervosa (fluoxetine), Anorexia nervosa (restricting eating).
- Post traumatic stress disorder.
- Attention Deficit Hyperkinetic Disorder.
- Treatment of premature ejaculation (via stim of 5-HT2A).

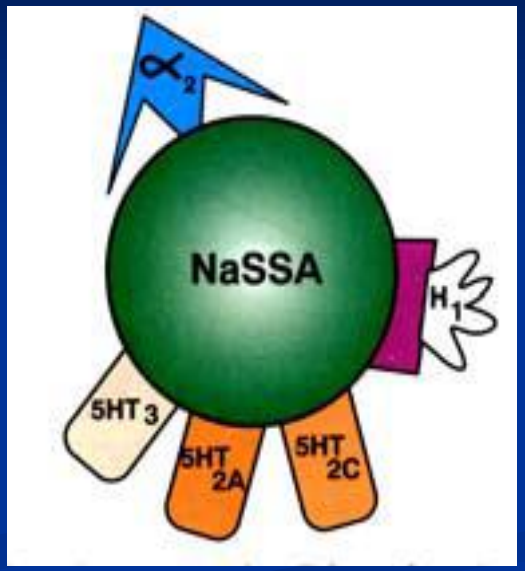
Drug interactions of SSRIs

- **SSRIs are potent inhibitors of liver microsomal enzymes. Therefore they should not be used in combination with TCAs because they can inhibit their metabolism increasing their toxicity.**

- **SSRIs should not be used in combination with MAOIs because of the risk of life-threatening "serotonin syndrome" (tremors, hyperthermia, cardiovascular collapse and death). Both drugs require a "*washout*" period of 6 weeks before the administration of the other.**

2. Noradrenergic and specific Serotonergic Antidepressant (NaSSA)

Mirtazapine



- α2 receptor antagonist
- Increase NE and 5HT levels
- Blocks 5HT2A, 5HT3 and thus reduces side effects of anxiety, and sexual dysfunction

- Blocking 5HT2C, and H1 receptors cause side effects: sedation, and weight gain.

Mirtazapine

Preferred in cancer patients because:

1. Improves appetite
2- ↓nausea & vomiting (5-HT_3 blocking)
3- ↑ body weight
4- Sedation (potent antihistaminic)
5- Less sexual dysfunction (5-HT_2 blocking)
6- Has no anti-muscarinic effect .

3. Serotonin-2A Antagonist and serotonin Reuptake Inhibitors (SARI)

Trazodone, Nefazodone

- **Blocks 5HT uptake selectively but in a less potent manner than tricyclics. This reduces depression.**
- **However, they are powerful 5HT2A antagonists, blockade of 5HT2A receptors stimulates 5HT1A receptors, which may help reduce depression.**
- **5HT2A antagonism also reduces the risk of anxiety, sedation or sexual dysfunction which is normally associated with SSRIs.**
- **Nefazodone: Structurally related to trazodone but has less sedative effect, however; it likes most SSRI inhibit P450 3A4 isoenzyme.**

4. Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

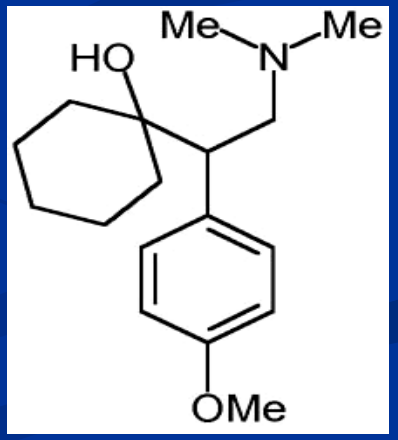
Venlafaxine (Effexor)

- It is used primarily for the treatment of depression, generalized anxiety disorder, and social anxiety disorder in adults. Venlafaxine is the first and most commonly used SNRI.

- Selective 5HT and NE uptake blockers combines the action of SSRI and NRI.

- But without α1, M1 cholinergic or H receptor blocking properties.

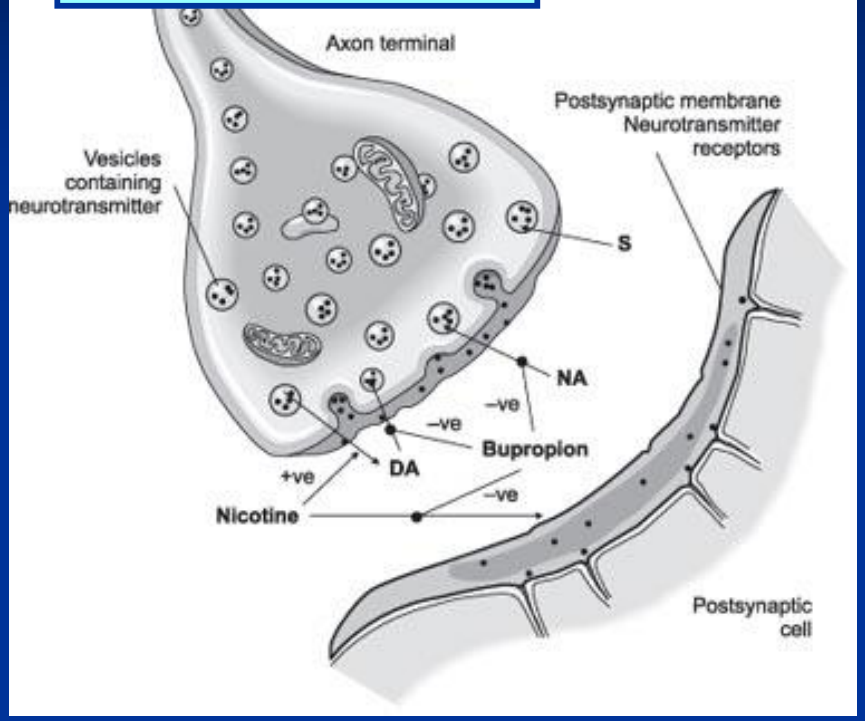
- Desvenlafaxine is a metabolite of Venlavaxine



Venlafaxine

5. Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)

Bupropion



Is unique in possessing significant potency as NE and DA reuptake inhibitor, with no direct action on 5HT.

Therapeutic uses:

1- Treatment of major depression

2- Can be used for smoking cessation. As it reduces the severity of nicotine craving & withdrawal symptoms

Advantages: No sexual dysfunction ➔ given in young (combination with SSRIs to avoid sexual dysfunction)

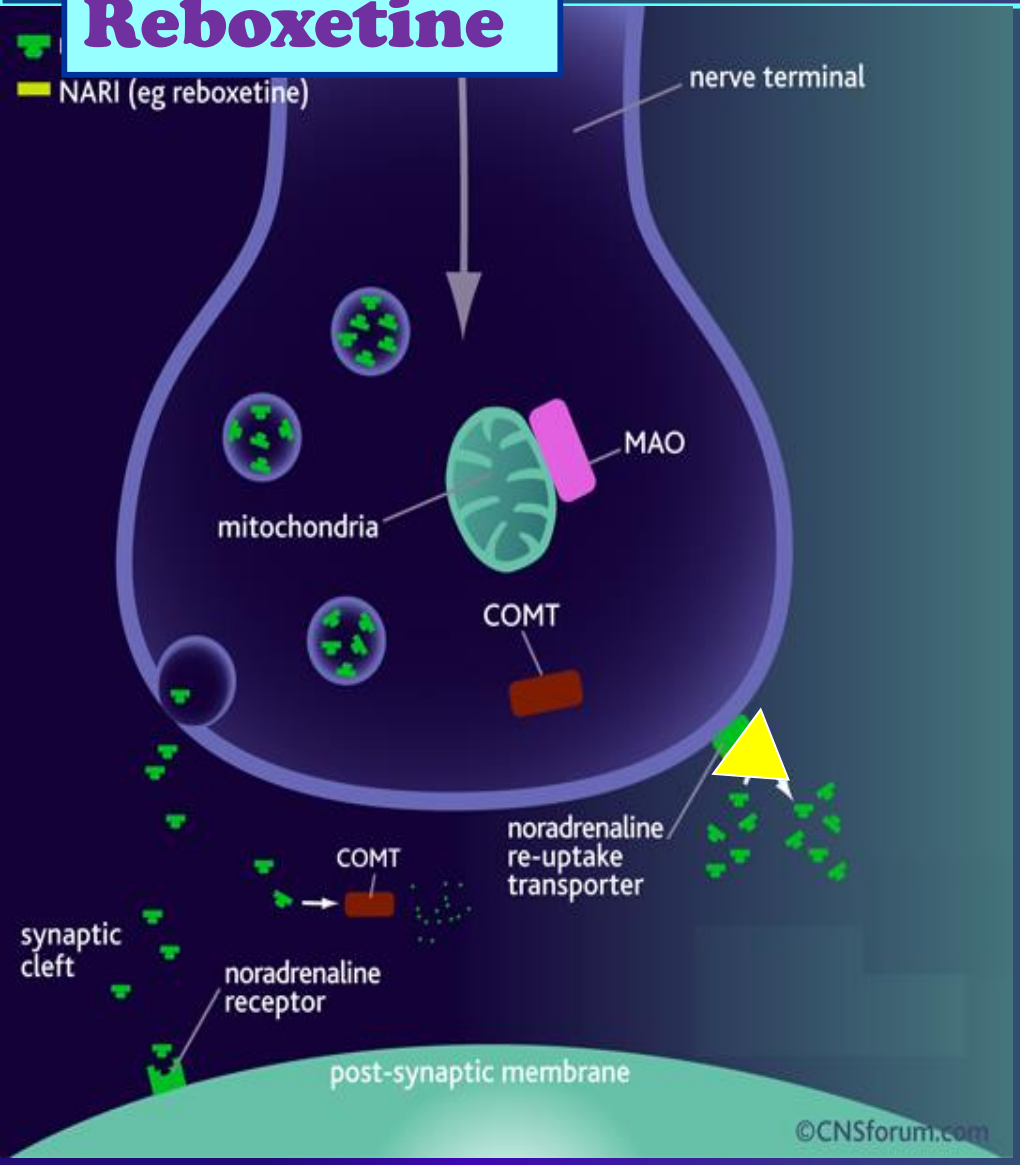
No weight gain [No 5HT effect]

No orthostatic hypotension.

Side effects: Seizures; it ↓ threshold of neuronal firing

6. NE Selective Reuptake Inhibitors (NRIs)

Reboxetine



Block only NET

No affinity for 5HT, DA, ADR, H, mAch receptors

So, has positive effects on the concentration and motivation in particular.

Safe to combine with SSRIs

Minimal side effects only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy

Clinical uses of Antidepressant Drugs.

A. Endogenous Depression (SSRIs (first Choice) New generation and Tricyclics can be used

B. Panic Disorders (Imipramine or SSRIs)

C. Obsessive Compulsive Disorders (SSRIs and Clomipramine) & Chronic pain (**Amitriptyline**)

D. Anorexia nervosa and Bulemia (SSRIs)

E. Schizo-Afective Disorders (Amoxapine or SSRI + Haloperidol)

F. Premature ejaculation (SSRI)

Clinical Uses of Antidepressants (Continue…)

G. Anxiety disorders (**Amitriptyline**)

H. Migraine and Anxiety & IBS (**Amitriptyline**)

I. Nocturnal Enuresis in children e.g. Imipramine

Self reading

Side effects of antidepressant medications

Drug	Anticholinergic	Drowsiness	Insomnia/agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs)¶								
Citalopram	0	0	1+	1+	1+Δ	1+ (all SSRIs: see¶)	1+	3+
Escitalopram	0	0	1+	1+	1+	1+	1+	3+
Fluoxetine	0	0	2+	1+	1+	1+	1+	3+
Fluvoxamine	0	1+	1+	1+	0 to 1+	1+	1+	3+
Paroxetine	1+	1+	1+	2+	0 to 1+	1+	2+	4+
Sertraline	0	0	2+	1+	0 to 1+	2+◇	1+	3+
Atypical agents								
Agomelatine§ (not available in United States)	0	1+	1+	0	0	1+	0	0 to 1+
Bupropion	0	0	2+ (immediate release) 1+ (sustained release)	0	1+	1+	0	0
Mirtazapine	1+	4+	0	0	1+	0	4+	1+
Serotonin-norepinephrine reuptake inhibitors (SNRIs)¶								
Desvenlafaxine¥	0	1+	2+	0	0	2+ (initially)¶ 1+ (after 1 week)	0	3+
Duloxetine	0	0	2+	0	0	2+¶	0	3+
Milnacipran¥	1+	1+	0	0	0	2+¶	0	0
Venlafaxine¥	0	1+	2+	0	1+	2+ (immediate release)¶ 1+ (extended release)¶	0	3+
Serotonin modulators								
Trazodone	0	4+	0	1+ (hypnotic dose) 3+ (antidepressant dose)	1+ (hypnotic dose) 2+ (antidepressant dose)	1+ (hypnotic dose) 3+ (antidepressant dose)	0 (hypnotic dose) 1+ (antidepressant dose)	1+‡
Vilazodone	0	0	2+	0	0	4+†	0	2+
Nefazodone**	1+	2+	0	1+	0	2+	0	0
Tricyclic and tetracyclic antidepressants (TCAs)¶¶								
Amitriptyline	4+	4+	0	3+	3+	1+ (all TCAs see¶¶)	4+	3 to 4+
Amoxapine	2+	2+	2+	2+	2+	0	2+	ND
Clomipramine	4+	4+	1+	2+	2+	1+	4+	4+
Desipramine	1+	2+	1+	2+	3+	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+	3+	0	2+	ND
Nortriptyline	2+	2+	0	1+	3+	0	1+	ND
Protriptyline	2+	1+	1+	2+	3+	1+	1+	3 to 4+
Trimipramine	4+	4+	1+	3+	1+	0	4+	ND
Monoamine oxidase inhibitors								
Isocarboxazid	1+	1+	2+	2+	0	1+	1+	4+
Phenelzine	1+	2+	1+	3+	0	1+	2+	4+
Selegiline	1+	0	1+	1+	0	0	0	0
Tranylcypromine	1+	1+	2+	2+	0	1+	1+	4+

Scale: 0 = none; 1+ = slight; 2+ = low; 3+ = moderate; 4+ = high; ND = inadequate data.

* Risk of QTc prolongation or torsades de pointes is also elevated with advanced age, female sex, heart disease, congenital long QT syndrome, hypokalemia or hypomagnesemia, elevated serum drug concentrations (eg, drug overdose, interacting drugs, organ failure) and combination of drugs with QTc prolonging effects. Refer to topic on acquired long QT syndrome.
¶ All SSRIs and SNRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.
Δ Based upon reports of dose related QTc prolongation and arrhythmia, the maximum recommended dose of citalopram is 20 mg for patients at increased risk of elevated citalopram serum concentrations.
◇ Sertraline is associated with higher rates of diarrhea.
§ Agomelatine may be hepatotoxic and is contraindicated with any degree of liver impairment. Transaminase monitoring is required.
¥ May cause persistent dose-related increases in blood pressure (primarily diastolic) and heart rate. Monitor blood pressure regularly.
‡ Trazodone is associated rarely with priapism, which is considered a medical emergency. Refer to UpToDate topic on Serotonin modulators.
† Vilazodone is associated with higher rates of nausea, vomiting, and diarrhea.
** Caution: can cause liver failure. Not available in Europe, Canada, and several other countries.
¶¶ Gastrointestinal forms of anticholinergic side effects include: dry mouth, constipation, epigastric distress, decreased esophagogastric tone. Refer to "Anticholinergic" data for frequency rankings.

Created with data from:

1. *Nelson JC. Tricyclic and tetracyclic drugs. In: The American Psychiatric Publishing Textbook of Psychopharmacology, 4th ed, Schatzberg AF, Nemeroff CB (Ed), American Psychiatric Publishing, Washington, DC 2009. p.263.*
2. *Lexicomp Online. Copyright © 1978-2015 Lexicomp, Inc. All Rights Reserved.*
3. *Wenzel-Seifert K, Wittmann M, Haen E: QTc prolongation by psychotropic drugs and the risk of torsade de pointes. Dtsch Arztebl Int 2011; 108:687.*
4. *Serretti A, Chiesa A. Sexual side effects of pharmacological treatment of psychiatric disease. Clin Pharm Ther 2011; 89:142.*
5. *Howland RH. A benefit-risk assessment of agomelatine in the treatment of major depression. Drug Saf 2011; 34:709.*