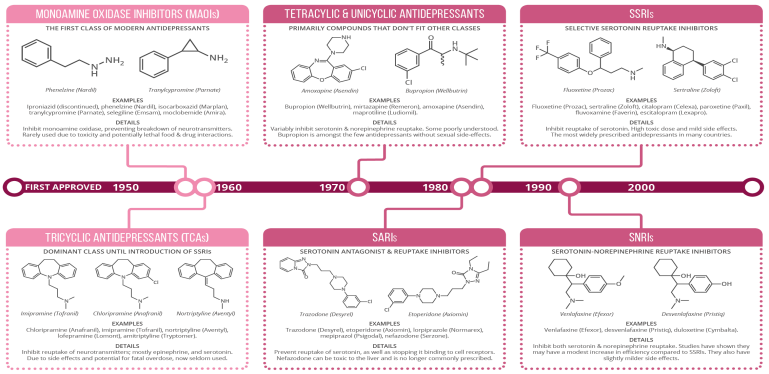
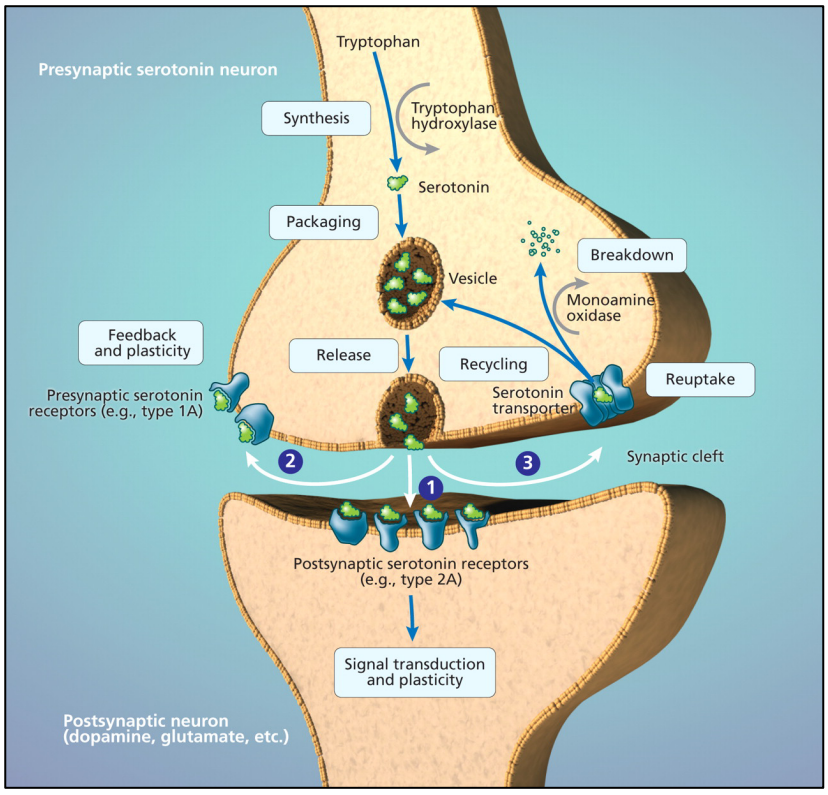
TREATMENT OF DEPRESSIVE DISORDERS

I. Overview: Classes of Antidepressants

A. Selective Serotonin Reuptake Inhibitors (SSRIs)
B. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
C. Tricyclic Antidepressants (TCAs)
D. Monoamine Oxidase Inhibitors (MAOIs)
E. Atypical Antidepressants



II. Mechanisms of Antidepressant Agents
(Monoamine vs Receptor Hypothesis)



Types of antidepressants

Catagories	Medications
SSRIs	- citalopram (Celexa) - fluvoxamine - escitalopram (Lexapro) - paroxetine (Paxil) - fluoxetine (Prozac) - sertraline (Zoloft)
SNRIs	- desvenlafaxine (Pristiq) - venlafaxine (Effexor) - duloxetine (Cymbalta) - milnacipran (Savella) - levomilnacipran (Fetzima)
Atypical	- bupropion (Wellbutrin) - mirtazapine (Remeron)
Serotonin modulators	- trazodone - vilazodone (Viibryd) - vortioxetine (Trintellix)
TCAs	- amitriptyline - imipramine - doxepin (Silenor) - nortriptyline (Pamelor) - desipramine (Norpramin)
MAOIs	- isocarboxazid (Marplan) - phenelzine (Nardil) - selegiline patch (Emsam) - tranylcypromine (Parnate)

III. Antidepressants: General Statements

A. All antidepressants are considered equal in efficacy, regardless of class.

B. Dual-acting antidepressants (e.g., SNRIs) tend to be more effective in severely depressed patients; however, other factors may be more important considerations, such as concomitant disorders (comorbidities), contraindications, and drug interactions.

C. Sertraline (Zoloft) and escitalopram (Lexapro) have the best efficacy to safety/tolerability ratio.

IV. Antidepressants: Factors to Consider

A. Past Medical History (PMH): The 1st factor to consider is the patient's response to previous antidepressant drug therapy.

B. Family History: If an immediate family member responded favorably to an antidepressant, that antidepressant may be a reasonable 1st choice in the initial treatment.

C. Concomitant Disorders and Medical Conditions

- TCAs, paroxetine (Paxil), and mirtazapine (Remeron) may cause significant weight gain → not good choices for obese patients and diabetics.
- Bupropion (Wellbutrin) should be avoided in patients with a history of seizure disorder.

D. Adverse Effects Profile (i.e., Side Effects) →

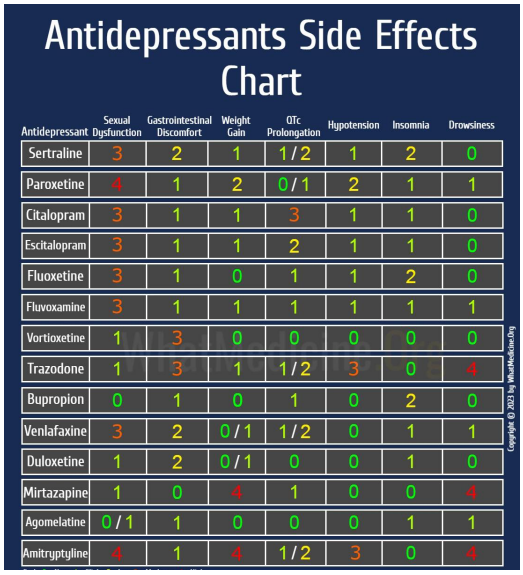
E. Drug-Drug Interactions

- Fluoxetine (Prozac) and paroxetine (Paxil) significantly inhibit cytochrome P-450 liver enzyme system; whereas citalopram (Celexa), escitalopram (Lexapro) and sertraline (Zoloft) have minimal effects on Cyt P-450.

F. Safety in Overdose

- Cardiotoxicity Risk: MAOI > TCA > SNRI > SSRI

G. Patient Preference & Cost



V. Treatment Expectations

- Patients often show signs of clinical response in 1-2 weeks.
- Maximum improvement requires 6-8 weeks of treatment.
- Benzodiazepines (BZDs), such as lorazepam (Ativan) and alprazolam (Xanax), may be used short-term to alleviate symptoms.

VI. Selective Serotonin Reuptake Inhibitors (SSRIs)

A. Adverse Effects

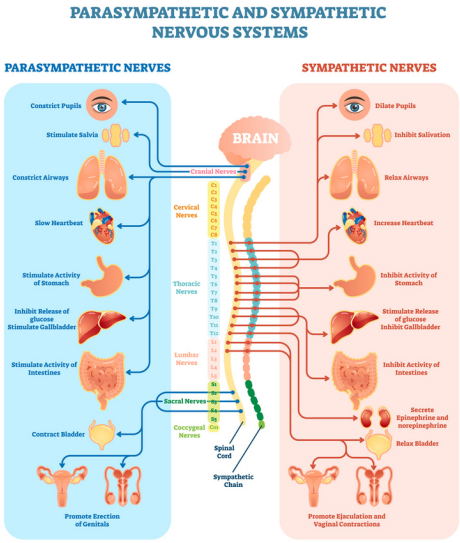
1. GI Complaints

- Nausea tends to diminish after 1st week of treatment.
  - Nausea is caused by 5-HT_3 activation in the CTZ (chemoreceptor trigger zone) and may be relieved with antiemetics: metoclopramide (Reglan), ondansetron (Zofran), prochlorperazine (Compazine).

- Diarrhea during the first few weeks of treatment.
  - Diarrhea is caused by 5-HT_3 stimulation (GI tract) → increases GI motility.
  - Diarrhea may be treated with OTC Imodium (loperamide) / Rx: Lomotil (diphenoxylate/atropine) → decrease GI motility.

A. SSRI: Adverse Effects (cont.)

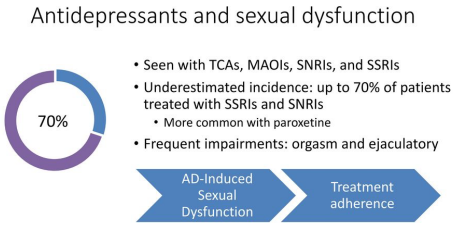
2. Anticholinergic Side Effects



- Paroxetine (Paxil) has mild anticholinergic properties and may cause constipation, drug mouth, blurred vision, urinary hesitancy, etc. … → avoid in patients with chronic constipation and in geriatrics.

3. Sexual Dysfunction (30-50%)

- Delayed orgasm and loss of libido are frequent complaints of SSRIs/SNRIs and often leads to medication noncompliance.
- Patients usually decide that improvements in mood outweigh limitation in sexual performance; others may stop the medication if the side effect is not addressed.
- Sexual dysfunction may be treated with the following approaches:
  i. decreasing the dose of the SSRI, since sexual dysfunction tends may be dose dependent.
  ii. drug holidays on weekends to restore sexual performance on weekends; however, drug holidays result in breakthrough symptoms of depression and withdrawal symptoms.



  iii. bupropion (Wellbutrin) as an adjunct at 150 mg PO daily → relieves delayed orgasm in approx. 50% of patients.
  iv. sildenafil (Viagra) in male patients was found to be effective in 54% of patients.

- Weight Gain
  - Some weight gain during treatment with an antidepressant may be in response to its therapeutic effect.
  - The incidence of SSRI weight gain is minimal, except with paroxetine (Paxil), which is rated 2+ for weight gain.

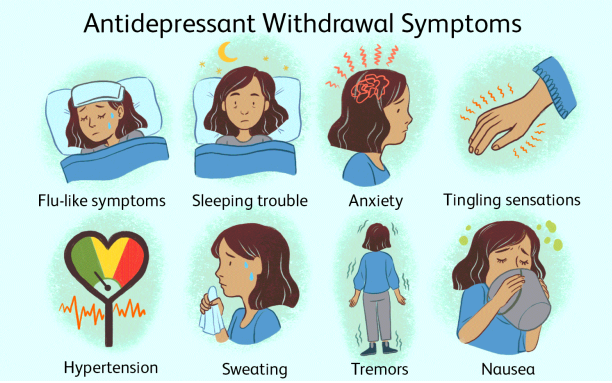
- Upper GI hemorrhage
  - A link between SSRIs and SNRIs with modest risk of upper GI bleeding exists due decreased platelet activation and aggregation.
  - SSRIs and SNRIs should be avoided in patients with active GI bleeds.
  - Concurrent use of high-dose NSAIDs and SSRI/SNRI in predisposed pts should be avoided.

B. Dose Titration of SSRIs

- If there is no improvement in depressive symptoms at 4 weeks, then switching the medication is necessary.
- If there is 25% or more improvement at 4 weeks, then treatment should continue for another 4 weeks for total of 8 weeks; then decide whether therapeutic response is acceptable.
- If the improvement is 25-30% at 8 weeks, then the clinician may increase the dose and continue to monitor for another 8 weeks.

C. Discontinuation of SSRIs

- Abrupt discontinuation of chronic SSRI (> 2 months) is associated with flu-like symptoms: dizziness, sweating, nausea, headache, anxiety, lethargy, dysphoria, tremors, and insomnia.
  - Onset of withdrawal symptoms: 36-72 hours
  - Duration of symptoms: approx. 1 week
- Recommendation: Taper SSRIs gradually over 6-8 weeks to reduce withdrawal symptoms and to observe for relapse of depressive symptoms.



D. Suicide Assessment

- TCAs and MAOIs are contraindicated in patients at risk for attempting suicide due to lethality in overdose (cardiotoxicity).
  - Overdose risk: MAOI > TCA > SNRI > SSRI

E. Antidepressants in Pregnancy and Lactation

- SSRIs are rated as "Class C" by the FDA (risk to fetus is not definitively known); however, paroxetine (Paxil) is rated "Class D" (risk for congenital heart defect).
- When assessing SSRI use during pregnancy, one must consider the "risks versus benefits" of maternal depression on the mother and fetus against the risks of teratogenicity. The important considerations must include the following:
  i. Untreated mother with sleep and appetite disturbances during pregnancy may adversely affect fetal development.
  ii. Untreated mother with risk of alcohol and substance abuse during pregnancy may present higher risks than SSRI use.
  iii. Untreated mother with depression during pregnancy is a very strong risk factor for postpartum depression.

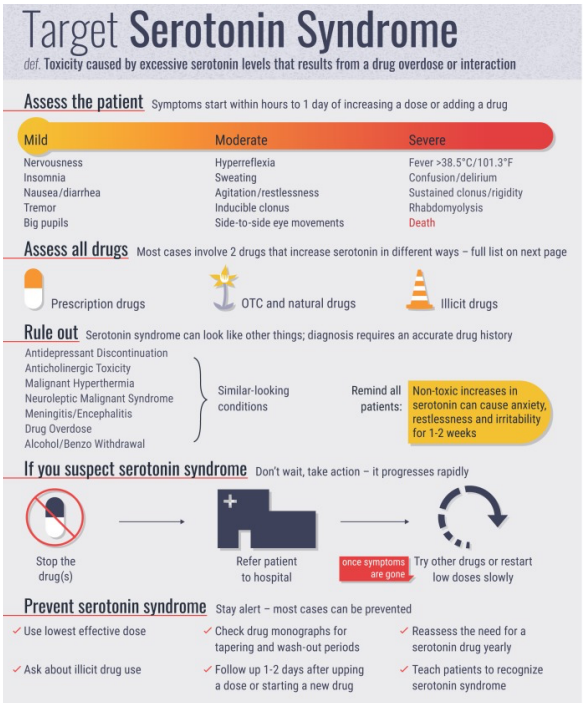
FDA Pregnancy categories

Category	Definition	Explanation
A	Generally acceptable	Controlled studies in pregnant women show no evidence of fetal risk.
B	May be acceptable	Either animal studies show no risk but human studies not available or animal showed minor risks and human studies were done and showed no risk.
C	Use with caution if benefits outweigh risks	Animal studies show risk and human studies not available or neither animal nor human studies were done.
D	Use in life-threatening emergencies when no safer drug is available	Positive evidence of human fetal risk.
X	Do not use in pregnancy	Risks involved outweigh potential benefits. Safer alternatives exist.

- SSRI use during pregnancy may result in "neonatal serotonin withdrawal syndrome," characterized by restlessness, tremor, shivering, etc... for 4 days after delivery, then symptoms subsides.
- Lactation: Low concentrations of SSRI were measured in breast milk, with scant reports of infant irritability.
  - Fluoxetine (Prozac) and TCAs has been associated with highest concentration in breast milk in infants and should be avoided.
  - Sertraline (Zoloft) is associated with lowest concentration in breast milk.
  - FDA recommendation: Use lowest doses of SSRI during lactation.

F. Serotonin Syndrome

- Although most cases of SS are mild-moderate, it's a potentially fatal interaction due to excessive serotonin concentrations within the synapse, resulting in hyper-excitatory adverse effects: anxiety, agitation, tremor, hyperreflexia, increased BP and HR, fever, and rhabdomyolysis.
  - Moderate-severe symptoms of serotonin syndrome are managed with …
    (1) supportive care to normalize vitals: oxygen to maintain O_2 sat > 94%, IV fluids to treat volume depletion and hyperthermia, and cardiac monitoring,
    (2) sedation to control agitation/restlessness: lorazepam (Ativan) 2-4 mg IV, and/or
    (3) administration of serotonin antagonist: cyproheptadine (Periactin): 12 mg PO once then 2 mg Q2H until clinical response.
- MAOI plus SSRI → absolutely contraindicated due to high risk of serotonin syndrome.

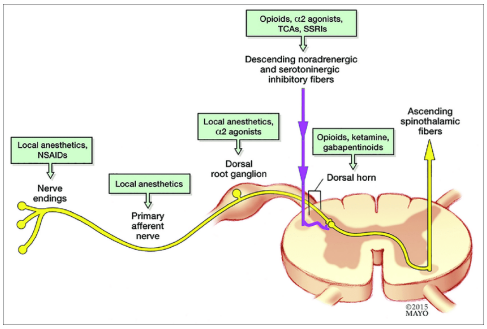


- Other risk factors of serotonin syndrome include SSRI/SNRI combinations with the following agents: tryptophan, meperidine (Demerol), dextromethorphan (Robitussin DM), linezolid (Zyvox), and tramadol (Ultram).
- OTC Herbal products may also precipitate a serotonin syndrome: e.g., SAM-E and Saint John's-Wort in combination with a SSRI/SNRI.
- Patients taking multiple SSRIs may also be at risk of serotonin syndrome, although not considered fatal.
- Trazodone (Desyrel) is commonly used in patients taking SSRIs for treatment of insomnia, with no confirmed cases of serotonin syndrome.

VII. SNRIs: Venlafaxine (Effexor) and Duloxetine (Cymbalta)

A. General Considerations

- Approx 50-70% of patients who are unresponsive or intolerant to an SSRI will experience a therapeutic response to a different SSRI.
- When a patient fails to respond to two SSRIs, it is recommended to try an antidepressant from a different class, such as an SNRI.
- All SNRIs have a risk of increasing blood pressure and heart rate due to the increase in NE (norepinephrine) activity, especially at higher doses.
- Since many patients with chronic pain syndromes are also clinically depressed, SNRIs and TCAs offer a dual benefit in treating depressive symptoms and relieving chronic pain symptoms associated with diabetic neuropathy, postherpetic neuralgia, and low back pain.



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SNRIs: Venlafaxine and Duloxetine (cont.)

B. Venlafaxine (Effexor)

- At doses < 150 mg/day, venlafaxine blocks serotonin (SE) reuptake → therapeutic and side effects similar to SSRIs.
- At doses > 150 mg/day, venlafaxine blocks NE and SE reuptake → may cause tachycardia, hypertension, and insomnia.

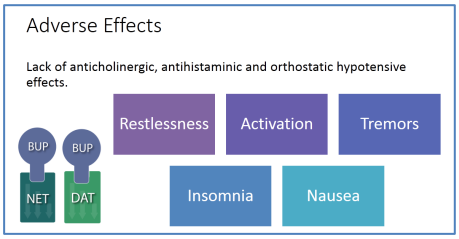
C. Duloxetine (Cymbalta)

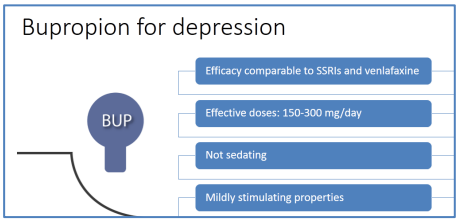
- Unlike venlafaxine, duloxetine reuptake blocking effects on NE are not dose dependent.
- Duloxetine has been shown to slightly increase LFTs (liver function tests); therefore, duloxetine should be avoided in patients with frequent alcohol use and patients with chronic liver disease.

VIII. Atypical Antidepressants: Bupropion (Wellbutrin), Mirtazapine (Remeron), Trazodone (Desyrel)

A. Bupropion (Wellbutrin)

- The therapeutic effect of bupropion is due primary to blocking the reuptake of dopamine (DA), with mild NE reuptake blocking effect and negligible serotonin (SE) reuptake blocking effect.
- Due to its unique DA reuptake blocking effect, bupropion may be used as an adjunct in patients who have not fully responded to SSRI/SNRI.
- Stimulatory DA effect may cause nausea, insomnia, agitation, and jitteriness → prominent side effects associated with bupropion.
- Bupropion does <u>not</u> cause sexual dysfunction (rated: 0) and drowsiness (rated: 0)
  - Bupropion may be added to SSRI or SNRI in patients who experience sexual dysfunction.

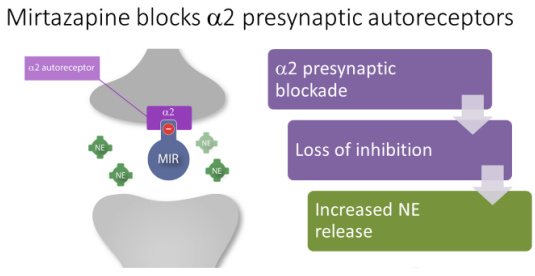




- Bupropion may decrease appetite and may promote weight loss; however, it should be avoided in patients with a history of anorexia or bulimia.
- Bupropion increases the risk of seizure activity in patients with history of seizure disorder; therefore, it should be avoided in patients with seizure disorders.
- Bupropion (Zyban) ER 150 mg PO BID is indicated for tobacco cessation, since bupropion is effective in decreasing cravings for nicotine and mitigating withdrawal symptoms.

B. Mirtazapine (Remeron)

- Mirtazapine is a novel antidepressant that works as an alpha-2 presynaptic antagonist. It also mildly inhibits SE reuptake activity.
- Most common side effects of mirtazapine are sedation (4+) and weight gain (4+).
- Mirtazapine is often used as a hypnotic agent, similar to trazodone, due to its potent histamine-1 blocking effect → Mirtazapine 15-45 mg PO QHS.



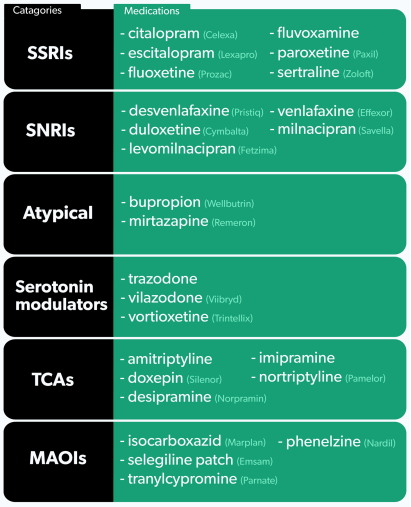
- A significant increase in total cholesterol and triglycerides is associated with mirtazapine; therefore it is not recommended in diabetics and patients with hypercholesteremia.
- Mirtazapine is added to patients who are poor responders to SSRI/SNRI, offering enhanced effect with its unique mechanism of blocking alpha-2 presynaptic receptors.

IX. Atypical Antidepressants (cont.)

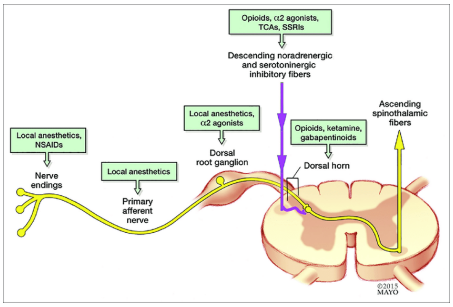
C. Trazodone (Desyrel)

- Trazodone is a weak SE reuptake inhibitor with potent histamine-1 (H-1) blocking activity. Potent H-1 blocking effect induces a high level of sedation (4+).
- Trazodone 25 – 150 mg PO QHS is used off-label as a "hypnotic agent" for management of insomnia. It may also be dosed trazodone 25-150 mg PO HS "PRN" insomnia.
- For "antidepressant effects," trazodone requires a higher dosage: 150-300 mg PO QHS.
- Trazodone exerts alpha-1 blocking effect on blood vessels → orthostatic hypotension (3+).
- Trazodone has been rarely associated with priapism, which requires treatment in the ED with phenylephrine 100-500 mcg intra-cavernosal every 3-5 minutes. Phenylephrine is an alpha-1 agonist on blood vessels → promotes vasoconstriction.

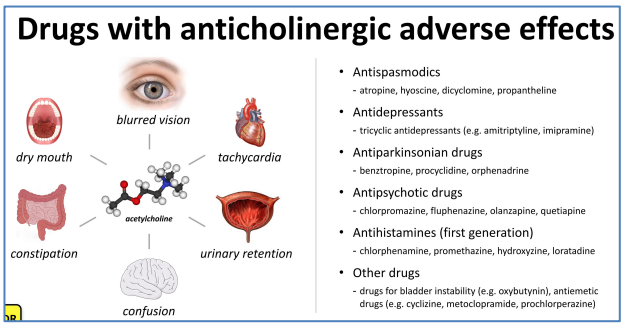
X. Tricyclic Antidepressants (TCAs): Amitriptyline (Elavil)



- TCAs inhibit reuptake of SE and NE, functionally like SNRIs; but TCAs also have significant effects on blocking acetylcholine (ACh), histamine-1 (H-1), and alpha-1 receptors.
- SSRIs are recommended over TCAs in the treatment of mood disorders for the following reasons:
  (1) lower side effect burden
  (2) safety in overdose
  (3) less dosage titration
  (4) patient preference
- TCAs are more commonly used at low doses in other indications that are comorbid with depression, such as chronic pain syndromes (diabetic neuropathy, postherpetic neuralgia, low back pain).
  - SNRIs and TCAs exert pain relieving effects by inhibiting the propagation of pain impulses via the descending "noradrenergic" pathway in the CNS.



- Patient compliance issues are common due to the side effect profile of TCAs.
  (1) Anticholinergic side effects include dry mouth, constipation, blurred vision, urinary hesitancy, etc. …



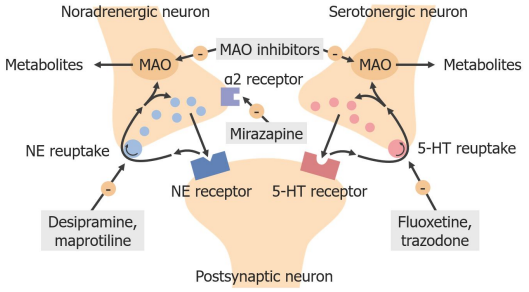
  (2) Histamine-1 (H-1) blocking effect of TCAs causes excessive sedation, which requires dosing at bedtime to minimize functional impairment.
    - TCA's impair concentration and alertness, increasing risk of falls in geriatric patients.
  (3) Alpha-1 blocking effect of TCAs potentiates orthostatic hypotension.
    - In addition to the sedative effect imposed by H-1 blocking activity of TCAs, orthostatic hypotension further increases risk of falls in geriatric patients → increases risk of bone fractures and lacerations in the elderly.

Tricyclic Antidepressants (cont.)

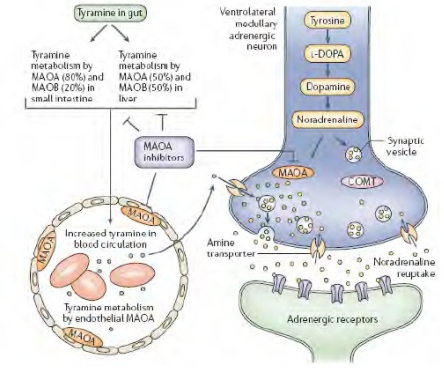
- Among the class of TCAs, nortriptyline (Pamelor) has the lowest potential risk for inducing orthostatic hypotension (1+), anticholinergic effects (2+), and sedation (2+).
- TCA's should be avoided in patients with pre-existing cardiac conduction abnormalities (e.g, atrial fibrillation and SVT), since anticholinergic cardiac effects may induce tachycardia and interfere with rhythmic control.

XI. MAOI (Monamine Oxidase Inhibitors): phenelzine (Nardil), Tranylcypromine (Parnate)

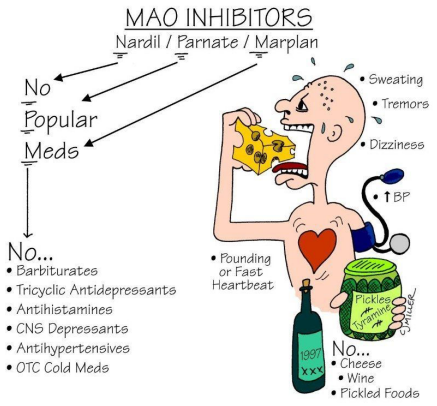
- MAOIs are last-line agents for patients who have failed multiple antidepressant trials with SSRIs, SNRIs, TCAs, and atypical antidepressants.
- There are two isoenzymes of MAO: MAO-A and MAO-B. MAOI-A metabolizes SE, DA, and NE; whereas MAO-B breaks down DA.
    - Phenelzine and tranylcypromine are non-selective MAOIs, which inhibit MAO-A and MAO-B.
    - Selegiline (Eldepryl, Emsam Patch) is a selective MAO-B inhibitor at lower doses and non-selective at higher doses. Selegiline is also used as a MAO-B inhibitor in the treatment of Parkinson Disease to preserve DA levels in the substantia nigra.



The mechanism of potentiation of cardiovascular effects of tyramine: the cheese effect



- MAOIs inhibit MAO in the brain, but also inhibit MAO-A in the gut and liver responsible for breaking down tyramine in certain foods.
    - The "cheese rection" is a hypertensive crisis caused when foods high in tyramine (e.g., aged cheese, red wine, meats, fava beans) are ingested by patients taking MAOIs.
    - In the presence of MAOIs, more tyramine is absorbed and very high concentrations are achieved in the circulation → increases production of DA, SE, NE → HTN crisis.
    - Selegiline patch (Emsam) applied once daily avoids inhibiting MAO in GI tract, but higher doses (> 6 mg/24 hours) still imposes a risk of drug-food interactions.



- Candidates for treatment with MAOIs are chosen carefully by psychiatrists who are meticulously managing their care, since MAOIs are also associated with very serious drug-drug interactions with sympathomimetic agents, such as pseudoephedrine and phenylephrine (OTC decongestants); phentermine (appetite suppressant); tramadol (Ultram); and SSRIs/SNRIs.
- When switching from an SSRI/SNRI to a MAOI, a 14-day washout period is required.
- Side effects of MAOIs include weight gain, edema, sexual dysfunction, orthostatic hypotension, insomnia, agitation, and anticholinergic side effects.

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	0	1+	0	0	2+	unknown	1+
Duloxetine	0	0	1+	0	0	2+ ¶	0-1+	1+
Levomilnacipran ¥	0 ‡	0	0-1+	0-1+	0	2+ ¶	0	1+
Milnacipran ¥	0	1+	0	0	0	2+ ¶	0	1+
Venlafaxine ¥	0	1+	1+	0	1+	2+	0-1+	3+
Serotonin modulators								
Nefazodone ¶¶	1+	2+	0	1+	0	2+	0	0
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+
Vortioxetine	0	0	0	0	0	3+	0	1+
Tricyclic and tetracyclic antidepressants (TCAs) ΔΔ								
Amitriptyline	4+	4+	0	3+	3+	1+ (all TCAs see ΔΔ)	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.

‡ Levomilnacipran has dose dependent effects on urinary hesitancy.

† 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.

ΔΔ Gastrointestinal forms of anticholinergic side effects include: dry mouth, constipation, epigastric distress, decreased esophagogastric tone. Refer to "Anticholinergic" data for frequency rankings.

◇◇ None of the SNRIs have anticholinergic activity. However, SNRIs can produce anticholinergic-like effects (which appear to be mediated by noradrenergic effects on the autonomic nervous

Unipolar depression in adults: Antidepressant doses*

Drug	Usual total starting dose per day (mg) ¶	Usual total dose per day (mg)	Extreme daily dose range (mg) ¶
Selective serotonin reuptake inhibitors			
Citalopram	20	20 to 40 Δ	10 to 40 Δ
Escitalopram	10	10 to 20	5 to 30
Fluoxetine	20	20 to 60	10 to 80
Fluvoxamine	50	50 to 200	25 to 300
Fluvoxamine CR	100	100 to 200	100 to 300
Paroxetine	20	20 to 40	10 to 50
Paroxetine CR	25	25 to 50	12.5 to 62.5
Sertraline	50	50 to 200	25 to 300
Serotonin-norepinephrine reuptake inhibitors			
Desvenlafaxine	25 to 50	50 to 100	50 to 400 ◇
Duloxetine	30 to 60	60 to 120	30 to 120 §
Levomilnacipran	20	40 to 80	20 to 120
Milnacipran	12.5	100 to 200	50 to 300
Venlafaxine	37.5 to 75	75 to 375	75 to 375
Venlafaxine XR	37.5 to 75	75 to 225	75 to 375
Atypical agents			
Agomelatine § (not available in United States)	25	25 to 50	25 to 50
Bupropion	200	300 (maximum single dose 150 mg)	100 to 450
Bupropion SR 12 hour	150	300 (maximum single dose 200 mg)	150 to 400
Bupropion XL 24 hour	150	300	150 to 450 (United States) 150 to 300 (Europe)
Bupropion hydrobromide 24 hour	174	348	174 to 522
Mirtazapine	15	15 to 45	7.5 to 60
Serotonin modulators			
Nefazodone ‡	200	300 to 600	50 to 600
Trazodone	100	200 to 400	100 to 600
Vilazodone	10	40	10 to 40
Vortioxetine	10	20	5 to 20
Tricyclics and tetracyclics †			
Amitriptyline	25	150 to 300	10 to 300
Amoxapine	25	200 to 300	25 to 400
Clomipramine	25	100 to 250	25 to 300
Desipramine	25	150 to 300	25 to 300
Doxepin	25	150 to 300	25 to 300
Imipramine	25	150 to 300	10 to 300
Maprotiline	25	100 to 225	25 to 225
Nortriptyline	25	50 to 150	10 to 150
Protriptyline	10	15 to 60	5 to 60
Trimipramine	25	150 to 300	25 to 300
Monamine oxidase inhibitors †			
Isocarboxazid	10	10 to 40	10 to 60
Phenelzine	15	15 to 90	7.5 to 90
Selegiline transdermal	6 mg/24 hour patch	6 to 12 mg/24 hour patch	6 to 12 mg/24 hour patch
Tranylcypromine	10	30 to 60	10 to 60

* Total daily oral doses shown in table may need to be given as two or three equally divided doses per day, depending on specific antidepressant and other factors. For additional detail, refer to individual Lexicomp drug monographs included with UpToDate.

¶ Lower end doses may be useful for initiating or maintaining elderly, medically compromised (eg, renal or hepatic illness), or drug sensitive patients, as well as patients with a low body mass index. High doses may be used for medications that are well tolerated but ineffective at lower doses.

Δ Maximum recommended dose of citalopram is 20 mg for patients >60 years of age, with significant hepatic insufficiency, or taking interacting medications that can increase citalopram levels. For more information refer to the UpToDate topic on unipolar depression in adults and selective serotonin reuptake inhibitors.

◇ Although desvenlafaxine doses up to 400 mg per day have been studied, there is no evidence that doses >50 mg per day provide any additional benefit.

§ Although duloxetine doses up to 120 mg per day have been used, there is no evidence that doses >60 mg per day provide any additional benefit in treatment of depression.

¥ Agomelatine may be hepatotoxic and is contraindicated with any degree of liver impairment. Transaminase monitoring is required according to the product information.

‡ Caution: can cause liver failure. Not available in Europe, Canada, and several other countries.

† Conservative starting doses shown in table are lower than starting doses shown in some other references. For additional information, refer to UpToDate topics on unipolar depression in adults and cyclic antidepressants and monoamine oxidase inhibitors for treatment of adults with depression.

Data from:

Pharmacology of Antidepressant Medications

Medication	Serotonin	Norepinephrine	Dopamine	Bioavailability (Oral)	Protein Binding	Half-Life (hours) (Active Metabolite)
Selective Serotonin Reuptake Inhibitors						
Fluoxetine	++++	0/+	0	80%	95%	24–72 (146)
Sertraline	++++	0/+	+	>44%	95%	26 (66)
Paroxetine	++++	+	0	64%	99%	24
Citalopram	++++	0	0	80%	<80%	33
Escitalopram	++++	0	0	80%	56%	27–32
Serotonin Norepinephrine Reuptake Inhibitors						
Venlafaxine	++++	+++	0	92%	25%–29%	4 (10)
Desvenlafaxine	+++	+++	0	80%	30%	11 (0)
Duloxetine	++++	++++	0	50%	>90%	12 (8–17)
Levomilnacipran	+	++++	0	92%	22%	12
Dopamine/Norepinephrine Reuptake Inhibitors						
Bupropion	0/+	+	++	>90%	85%	10–21
Tricyclic Antidepressants						
Desipramine	+	++++	0/+	51%	90%	12–28
Nortriptyline	++	+++	0	46%–56%	92%	18–56
Amitriptyline	++++	++++	0	37%–49%	95%	9–46 (18–56)
Imipramine	+++	++	0/+	19%–35%	95%	6–28 (12–28)
Doxepin	+++	+	0	17%–37%	68%–85%	11–23
Others						
Mirtazapine	+++	++++	0	50%	85%	20–40
Nefazodone	+++	+	0	20%	99%	5
Vilazodone	++++	0	0	72%	98%	25
Vortioxetine	++++	0	0	75%	99%	60

0, negligible; +, very low; ++, low; +++, moderate; ++++, high.

Guidelines for switching between specific antidepressants

↓ FROM / TO →	citalopram escitalopram paroxetine sertraline (SSRIs)	fluoxetine	fluvoxamine	vortioxetine	agomelatine	desvenlafaxine duloxetine venlafaxine (SNRIs)	mianserin mirtazapine	reboxetine	amitriptyline imipramine nortriptyline doxepin dothiepin trimipramine (TCAs)	clomipramine	moclobemide	phenelzine tranylcypromine (MAOIs)
citalopram escitalopram paroxetine sertraline (SSRIs)	taper drug, start alternative SSRI at low dose*	taper and stop drug, then start fluoxetine at 10 mg§	taper and stop drug, then start fluvoxamine at 50 mg§	taper drug, start vortioxetine at 5 mg*	taper drug, start agomelatine*	taper drug, then start SNRI at low dose*	taper drug, then start above drug at low dose*	taper drug, start reboxetine*	taper SSRI, start above drug at low dose (usually 25 mg)*	taper and stop drug, then start clomipramine at 25 mg§	taper and stop drug for 7 days washout before starting moclobemide at low dose§	taper and stop drug for 7 days washout before starting MAOI at low dose§
fluoxetine	stop fluoxetine (or taper if dose >40 mg/day), wait 7 days for washout, then start above SSRI at low dose†§		stop fluoxetine (or taper if dose >40 mg/day), wait 14 days for washout, then start fluvoxamine at 50 mg†§	stop fluoxetine (or taper if dose >40 mg/day), wait 7 days for washout, then start vortioxetine at 5 mg†§	stop fluoxetine (or taper if dose >40 mg/day), start agomelatine	taper and stop fluoxetine, wait 7 days for washout, then start SNRI at low dose†§	stop fluoxetine (or taper if dose >40 mg/day), start above drug at low dose	stop fluoxetine (or taper if dose >40 mg/day), start reboxetine at 4 mg	stop fluoxetine (or taper if dose >40 mg/day), wait 14 days for washout, then start above drug at 25 mg and continue low dose for further 3 weeks‡	stop fluoxetine (or taper if dose >40 mg/day), wait 14 days for washout, then start clomipramine at 25 mg and continue this dose for further 3 weeks‡	stop fluoxetine (or taper if dose >40 mg/day), then wait 5–6 weeks for washout before cautiously commencing low-dose moclobemide§	stop fluoxetine (or taper if dose >40 mg/day), then wait 5–6 weeks for washout before cautiously commencing low-dose MAOI§
fluvoxamine	taper and stop fluvoxamine, then start above SSRI at low dose§	taper and stop fluvoxamine, then start fluoxetine at 10 mg§		taper and stop fluvoxamine, start vortioxetine at 5 mg§	taper and stop fluvoxamine, wait 7 days for washout, then start agomelatine§	taper and stop fluvoxamine, then start SNRI at low dose§	taper and stop fluvoxamine, then start above drug at low dose§	taper fluvoxamine, start reboxetine at 4 mg*	taper fluvoxamine, start above drug at 25 mg*	taper and stop fluvoxamine, start clomipramine at 25 mg§	taper and stop fluvoxamine, wait 7 days for washout before cautiously commencing low-dose moclobemide§	taper and stop fluvoxamine, wait 7 days for washout before cautiously commencing low-dose MAOI§
vortioxetine	taper vortioxetine, start above SSRI at low dose*	taper and stop vortioxetine, start fluoxetine at 10 mg§	taper and stop vortioxetine, start fluvoxamine at 50 mg§		taper vortioxetine, start agomelatine at 25 mg*	taper vortioxetine, start SNRI at low dose*	taper vortioxetine, start above drug at low dose*	taper vortioxetine, start reboxetine*	taper vortioxetine, start above drug at low dose (usually 25 mg)*	taper and stop vortioxetine, start clomipramine at 25 mg§	taper and stop vortioxetine for 14 days washout before starting moclobemide at low dose§	taper and stop vortioxetine for 21 days washout before starting MAOI at low dose cautiously§
agomelatine	stop agomelatine, then start above SSRI	stop agomelatine, then start fluoxetine	stop agomelatine, then start fluvoxamine*	stop agomelatine, then start vortioxetine		stop agomelatine, then start SNRI	stop agomelatine, then start above drug	stop agomelatine, then start reboxetine	stop agomelatine, then start above drug at low dose (usually 25 mg)*	stop agomelatine, then start clomipramine	stop agomelatine, then start moclobemide	stop agomelatine, then start MAOI
desvenlafaxine duloxetine venlafaxine (SNRIs)	taper SNRI, start above SSRI at low dose*	taper and stop SNRI, start fluoxetine at 10 mg§	taper and stop SNRI, start fluvoxamine at 50 mg§	taper SNRI, start vortioxetine at 5 mg*	taper SNRI, start agomelatine*	taper SNRI, start alternative SNRI at low dose*	taper SNRI, start above drug at low dose*	taper SNRI, start reboxetine at 4 mg*	taper SNRI, start above drug at 25 mg*	taper SNRI, start clomipramine at 25 mg*	taper and stop SNRI, wait 7 days for washout before cautiously commencing low-dose moclobemide§	taper and stop SNRI, wait 7 days for washout before cautiously commencing low-dose MAOI§
mianserin mirtazepine	taper drug, start above SSRI*	taper drug, start fluoxetine*	taper drug, start fluvoxamine*	taper drug, start vortioxetine*	taper drug, start agomelatine*	taper drug, start SNRI*	taper drug, start drug above at low dose*	taper drug, start reboxetine at 4 mg*	taper drug, start above drug at 25 mg*	taper drug, start clomipramine at 25 mg*	taper and stop drug, wait 7 days for washout before cautiously commencing low-dose moclobemide§	taper and stop drug, wait 14 days for washout before cautiously commencing low-dose MAOI§
reboxetine	taper reboxetine, start above SSRI*	taper reboxetine, start fluoxetine*	taper reboxetine, start fluvoxamine at 50 mg*	taper reboxetine, start vortioxetine at 5 mg*	taper reboxetine, start agomelatine*	taper reboxetine, start SNRI at low dose*	taper reboxetine, start above drug*		taper reboxetine, start above drug at 25 mg*	taper reboxetine, start clomipramine at 25 mg*	taper and stop reboxetine, then wait 7 days for washout before cautiously commencing low-dose moclobemide§	taper and stop reboxetine, then wait 7 days for washout before cautiously commencing low-dose MAOI§
amitriptyline imipramine nortriptyline doxepin dothiepin trimipramine (TCAs)	taper first drug and start above drug at low dose*	taper and stop first drug before starting fluoxetine§	taper drug, start fluvoxamine at 50 mg*	taper drug, start vortioxetine at 5 mg*	taper drug, start agomelatine*	taper drug, start SNRI at low dose*	taper drug, start above drug at low dose*	taper drug, start reboxetine at 4 mg*	taper first drug, start alternative TCA at 25 mg*	taper drug, start clomipramine cautiously at 25 mg*	taper and stop drug, then wait 7 days for washout before starting moclobemide§	taper and stop drug, then wait 14 days (21 days for imipramine) before starting MAOI§
clomipramine	taper and stop clomipramine, then start above SSRI at low dose§	taper and stop clomipramine, then start fluoxetine at 10 mg§	taper and stop clomipramine, then start fluvoxamine at 50 mg§	taper and stop clomipramine, then start vortioxetine at 5 mg§	taper clomipramine, start agomelatine*	taper and stop clomipramine, then start SNRI at low dose§	taper clomipramine, then start above drug at low dose*	taper clomipramine, then start reboxetine at 4 mg*	taper clomipramine, then start drug at 25 mg*		taper and stop clomipramine, then wait 7 days for washout before starting moclobemide§	taper and stop clomipramine, then wait 21 days for washout before starting MAOI§
moclobemide	taper and stop moclobemide, then wait 24 hours for washout before starting above drug§	taper and stop moclobemide, then wait 24 hours for washout before starting fluoxetine§	taper and stop moclobemide, then wait 24 hours for washout before starting fluvoxamine§	taper and stop moclobemide, then wait 24 hours for washout before starting vortioxetine§	taper moclobemide, start agomelatine	taper and stop moclobemide, then wait 24 hours for washout before starting SNRI§	taper and stop moclobemide, then wait 24 hours for washout before starting above drug§	taper and stop moclobemide, then wait 24 hours for washout before starting reboxetine§	taper and stop moclobemide, then wait 24 hours for washout before starting above drug§	taper and stop moclobemide, then wait 24 hours for washout before starting clomipramine§		taper and stop moclobemide, then wait 24 hours for washout before starting MAOI§
phenelzine tranylcypromine (MAOIs)	taper and stop MAOI, then wait 14 days for washout before starting above drug§	taper and stop MAOI, then wait 14 days for washout before starting fluoxetine§	taper and stop MAOI, then wait 14 days for washout before starting fluvoxamine§	taper and stop MAOI, then wait 14 days for washout before starting vortioxetine§	taper and stop MAOI, start agomelatine*	taper and stop MAOI, then wait 14 days for washout before starting SNRI§	taper and stop MAOI, then wait 14 days for washout before starting above drug§	taper and stop MAOI, then wait 14 days for washout before starting reboxetine§	taper and stop MAOI, then wait 14 days for washout before starting above drug§	taper and stop MAOI, then wait 21 days for washout before starting clomipramine§	taper and stop MAOI, start moclobemide while maintaining MAOI dietary restrictions for 14 days§	taper and stop MAOI, wait 14 days for washout before starting other MAOI§

Taper means gradual dose reduction, with lowering by increments every few days, usually over a period of 4 weeks, modified by patient experience, drug, illness and other factors.

All switches from one antidepressant to another may result in serious complications. Switches must be undertaken cautiously and under close observation.

The recommendations in this table are based on clinical experience, product information, empirical evidence and recommendations from other guidelines. It may be necessary to modify the switching process depending on patient, illness and interacting drug variables, determined by the patient's clinical progress. In appropriate circumstances expert prescribers may use less conservative switch strategies if justified by harm–benefit considerations arising from factors such as illness severity.

MAOI monoamine oxidase inhibitor
TCA tricyclic antidepressant
SNRI serotonin noradrenaline reuptake inhibitor
SSRI selective serotonin reuptake inhibitor

* A washout period of 2–5 half-lives (most frequently 2–5 days) between cessation of previous drug and the introduction of a new drug is the safest switching strategy from the point of view of drug interactions. In the indicated instances a washout period is not essential if switching is carried out cautiously and under close observation, and clinical considerations such as illness severity support harm–benefit considerations. Cautious cross taper (when the dose of the first drug is being reduced and the dose of the second drug is being increased at the same time so that the patient is taking both antidepressants) may be used in the indicated instances if appropriate and safe. (See Table 1 of original article for drug half-lives.)

† Fluoxetine may still cause interactions 5 or 6 weeks after cessation (especially from higher doses) due to long half-life of drug and active metabolite.

‡ Fluoxetine is likely to continue to elevate TCA concentrations for several weeks.

§ Co-prescription of the two antidepressants in this instance is not recommended.

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Australian Prescriber

COMPARISON OF BENZODIAZEPINES

Benzodiazepine	Onset of Action[2]	Peak Onset (hrs)	Half-life parent (hrs)	Half-life metabolite (hrs)	Comparative Oral Dose
Long Acting					
Chlordiazepoxide (Librium®)	Int. (po)	2-4(po)	5-30	3-100	10 mg
Diazepam[1] (Valium®)	Rapid (po, IV)	1(po)	20-50	3-100	5 mg
Flurazepam (Dalmane®)	Rapid	0.5-2	inactive	47-100	30 mg
Intermediate Acting					
Alprazolam[1] (Xanax®)	Int.	0.7-1.6	6-20	-	0.5mg
Clonazepam[1] (Klonopin ®)	Int.	1-4	18-39	-	0.25mg
Lorazepam[1] (Ativan®)	Int. (po), Rapid (sl, IV)	1-1.5 (po)	10-20	-	1mg
Oxazepam[1] (Serax®)	Slow	2-3	3-21	-	15mg
Temazepam[1] (Restoril®)	Slow	0.75-1.5	10-20	-	30mg
Short Acting					
Midazolam[1] (Versed®)	Most Rapid IV	0.5-1 (IV)	1-4	-	-
Triazolam (Halcion®)	Int.	0.75-2	1.6-5.5	-	0.5mg

[1] formulary drug
[2] Rapid onset = within 15 minutes, Intermediate = 15-30 minutes, Slow = 30-60 minutes

General Considerations of Benzodiazepines

Patients taking BZDs and opioids are at 10 times higher risk of overdose than those taking opioids OR BZDs.

- flumazenil (Romazicon) 0.2 mg to 0.3 mg IV every 1 min as needed for 3 doses/hour

BZDs are indicated for “short-term” use in treating phobias and panic disorders --> “exposure therapy;” and, for generalized anxiety disorder (GAD).

BZDs, mainly lorazepam (Ativan) and chlordiazepoxide (Librium), are used to suppress alcohol withdrawal symptoms (e.g., N/V, tremors, anxiety, agitation) --> CIWA protocol (“Clinical Institute Withdrawal Assessment” of Alcohol Scale).

BZDs (e.g., lorazepam, diazepam) are used to treat seizure disorders, such as status epilepticus.

There is no evidence that BZDs are effective for PTSD (post-traumatic stress disorder).

BZDs may lead to cognitive and memory impairments with long-term use.

Interdependent and Interacting Factors in Blood Pressure Regulation