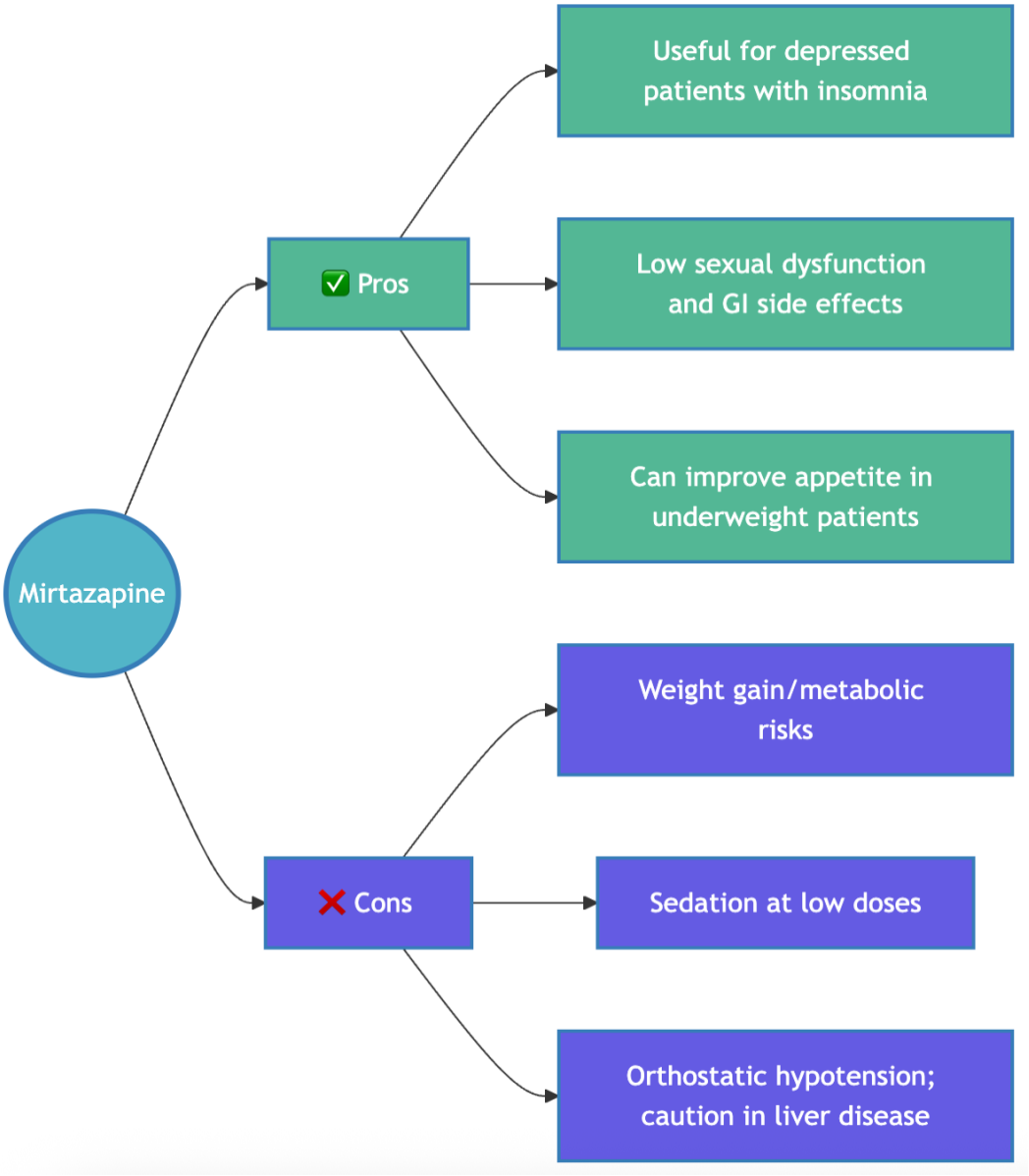
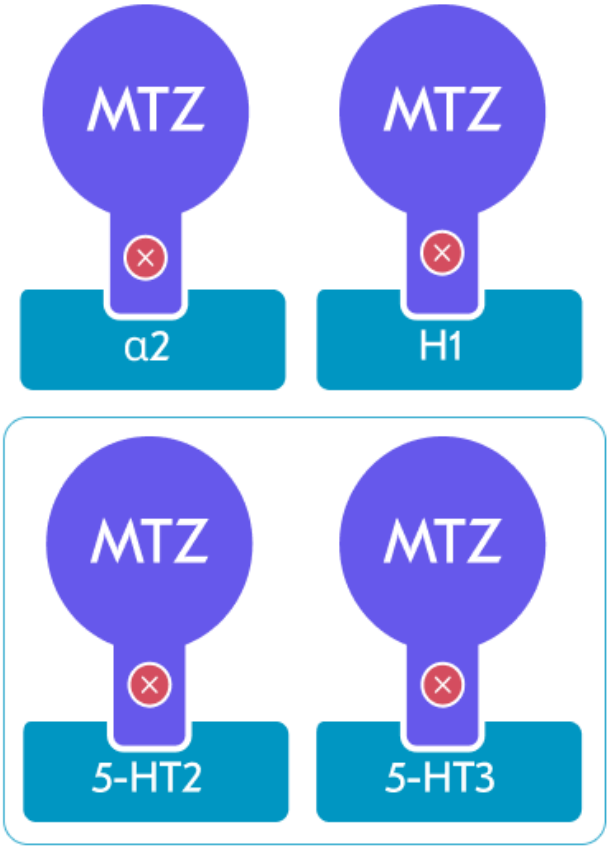
In a nutshell

Mirtazapine enhances noradrenergic and serotonergic neurotransmission through alpha-2 receptor antagonism and 5-HT2/5-HT3 receptor blockade. It is particularly suitable for depressed patients with insomnia, anxiety, or decreased appetite. Unlike SSRIs/SNRIs, mirtazapine causes minimal sexual dysfunction and GI side effects. Lower doses (≤15 mg) are more sedating than higher doses.



- Choosing mirtazapine over other antidepressants:
    - Depression with prominent insomnia or poor appetite, given its H1 and 5-HT2/3 receptor blockade
    - When sexual dysfunction is a concern (switching from SSRIs/SNRIs)
    - For patients with poor appetite or weight loss
    - When GI side effects limit SSRI/SNRI use
- Prefer alternatives if:
    - Patients with obesity or metabolic syndrome
    - Concern about sedation affecting daytime functioning
    - Patients with hepatic impairment
    - History of orthostatic hypotension

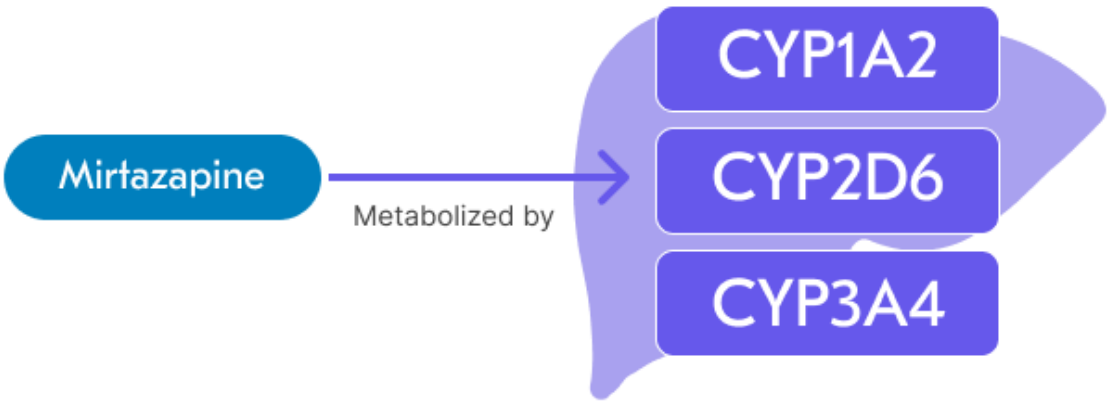
Pharmacodynamics and mechanism of action



- Mirtazapine is a tetracyclic antidepressant that acts as an antagonist at central presynaptic α2-adrenergic autoreceptors and heteroreceptors [1]
    - This mechanism enhances both noradrenergic and serotonergic neurotransmission

    - It has also been characterized as a noradrenergic and specific serotonergic antidepressant (NaSSA) [2]
    - No direct serotonin or norepinephrine reuptake inhibition
- Serotonergic effects:
    - Potent antagonist at 5-HT2 and 5-HT3 receptors [1,3]
    - Mirtazapine increases noradrenergic and 5-HT1A-mediated serotonergic neurotransmission, despite showing no significant intrinsic affinity for 5-HT1A and 5-HT1B receptors [1,4]
    - This unique profile may explain its low rate of sexual dysfunction and GI side effects compared to SSRIs [5]
- Antihistaminergic effects:
    - Potent H1 receptor antagonism [1,3,6]
    - Shows inverse dose-response relationship with sedation - lower doses (≤15 mg) are more sedating than higher doses due to noradrenergic effects counteracting histamine blockade at higher doses [7–9]
- Additional receptor binding:
    - Moderate antagonism at peripheral α1-adrenergic receptors [3]
    - Weak muscarinic receptor antagonism [6]
    - This may contribute to side effects like orthostatic hypotension and mild anticholinergic effects.

Pharmacokinetics



Psychopharmacology Institute

Metabolism

- Primarily metabolized through CYP1A2, CYP2D6 and CYP3A4 [1,10]
- Mirtazapine levels potentially increased by:
    - Strong CYP3A4 inhibitors (e.g., ketoconazole): Increases peak plasma levels ~40% and AUC ~50% [1]
    - Cimetidine (CYP1A2, CYP2D6, CYP3A4 inhibitor): Increases AUC >50% [10]
    - Consider decreasing mirtazapine dose when using these inhibitors
- Mirtazapine levels potentially decreased by:
    - Strong CYP3A4 inducers:
        - Carbamazepine: Decreases plasma concentrations ~60% [1]
        - Phenytoin: Decreases plasma concentrations ~45% [1]
    - Smoking: Reduces concentrations due to CYP1A2 induction [1]
    - Consider increasing mirtazapine dose when using inducers and monitor therapy in patients who smoke
- Mirtazapine should be used cautiously with other QT-prolonging drugs like haloperidol, as concurrent use may increase the risk of QT interval prolongation.
- The concomitant use of warfarin with mirtazapine may result in increased INR [1]
    - Monitor INR during concomitant use of warfarin
- Serotonergic agents:
    - Concurrent use requires careful consideration.
    - Monitor for serotonin syndrome with other serotonergic medications (SSRIs, SNRIs, triptans, tricyclic antidepressants)
    - Also applies to tramadol, tryptophan, St. John's Wort
- Contraindicated with MAOIs [11]
    - A 14-day washout period is required after discontinuation before starting an MAOI
    - A 14-day washout period is required after discontinuing an MAOI before initiating mirtazapine

Half-life

- Mirtazapine's half-life is approximately 20-40 hours, with women exhibiting significantly longer elimination half-lives than men [10]
- The (–) enantiomer has an elimination half-life approximately twice as long as the (+) enantiomer [1]

Dosage forms

Dosage forms

- Immediate-release:
  - Tablets
    - 7.5 mg, 15 mg (scored), 30 mg (scored), 45 mg
    - Generic, Remeron
  - Orally disintegrating tablets
    - 15 mg, 30 mg, 45 mg
    - Generic, Remeron SolTab
    - Formulation considerations
      - Must remain in blister pack until ready to use
      - Cannot be split or crushed
      - Contains phenylalanine (component of aspartame)

Indications

FDA-Approved Indications

Major Depressive Disorder (MDD)

- First-line antidepressant treatment option for MDD [12,13]
- Particularly effective for depression with sleep disturbances and anxiety symptoms due to its unique receptor profile [6]
- May be a good option for patients with poor appetite or weight loss due to depression [6]
- Dosing:
  - Starting dose: 15 mg once daily at bedtime (due to sedating properties) [1]
    - Sensitive patients: 7.5 mg daily in anxiety-prone patients [14]
  - Increase dose in 15 mg increments at intervals of 1-2 weeks
  - Target dose: 15-45 mg/day
  - Maximum dose: 45 mg/day (though doses up to 60 mg have been studied) [15]

Off-Label Uses

Panic Disorder

- Alternative agent for patients who are nonresponsive to SSRIs [16]
- Two open-label studies have shown efficacy in panic disorder [17,18]

- Dosing:
    - Starting dose: 15 mg once daily at bedtime
    - Increase in 15 mg increments at ≥1 week intervals
    - Target dose: 30 mg/day (average in clinical trials)
    - Maximum dose: 45 mg once daily [19]

Sexual Dysfunction Associated with SSRIs

- Meta-analysis showed significantly lower rates compared to SSRIs [20] and other antidepressants [21]
- Two potential strategies for management:
    - Strategy 1: Switch to mirtazapine
        - Before switching, consider watchful waiting for 2-8 weeks, as sexual side effects may resolve spontaneously [21]
        - When switching, use appropriate schedule (cross-taper over 1-2 weeks or immediate switch) [22]
        - Initiate and titrate mirtazapine to therapeutic dose based on the primary indication
    - Strategy 2: Add-on therapy
        - Low-dose mirtazapine (15-30 mg/day) as an adjunct to ongoing SSRI treatment has shown effectiveness in reducing sexual dysfunction [23,24]

Side Effects

Common side effects

- Somnolence (54% incidence)
    - Most common side effect and cause of discontinuation, particularly at lower doses [1]
    - Inverse dose-relationship: Lower doses (≤15 mg) cause more sedation than higher doses (>15 mg) [7,8]
        - Mechanism: Primarily due to H1 antihistamine effects at lower doses; higher doses activate noradrenergic transmission which partially offsets sedation [7–9]
    - Tolerance typically develops within a few days [25,26]
- Weight gain (12% incidence)
    - Among antidepressants with the greatest impact on weight [27]
        - Short-term (4-12 weeks): Average gain of 1.74 kg
        - Long-term (≥4 months): Average gain of 2.59 kg
    - Substantial long-term impact:
        - 22% of patients experience >7% weight gain at 9 months [28]

        - Highest risk among antidepressants in 10-year follow-up (rate ratio: 1.50; 95% CI: 1.45-1.56) [29]
    - Mechanism: Related to H1 antihistamine blockade and 5-HT2C receptor effects [30]
    - Monitor weight regularly, especially in the first months of treatment
    - Consider alternative antidepressants in:
        - Patients with obesity or metabolic syndrome
        - Cases where weight gain could worsen comorbid conditions
- Increased appetite (17% incidence) [1,31]
    - May be used therapeutically in elderly or cancer patients needing appetite stimulation [32,33]
    - Occurs early in treatment [34]
- Dry mouth (25% incidence) [1]
- Constipation (13% incidence) [1]
- Dizziness (7% incidence) [1]
- Dyslipidemia
    - Increased cholesterol (15% incidence) [1]
    - Elevated triglycerides (6% incidence)
    - Studies support the hypothesis that mirtazapine has direct pharmacological effects on lipid metabolism, independent of weight gain [35]
    - Consider baseline and periodic lipid monitoring
- Hyponatremia (3-4% incidence) [36]
    - Ranking of risk [37]:
        - MAOIs > SNRIs > SSRIs > TCAs > **Mirtazapine**
        - Often considered the antidepressant of choice for hyponatremia-prone patients [36]

Severe side effects

- Hematologic abnormalities
    - Agranulocytosis and severe neutropenia
        - Rare but serious adverse effect
        - Onset ranged from 1 day to 8 months after initiation, with the majority of cases occurring within 1 month after starting mirtazapine [38]
        - Mechanism poorly understood, proposed pathways involve immune-mediated neutrophil destruction and direct toxic effects on bone marrow precursor cells [38,39]
        - Monitor for signs of infection (fever, sore throat, flu-like symptoms) [1]
        - Discontinue if white blood cell count drops significantly [1]

    - Drug-induced immune thrombocytopenia [40,41]
        - Non-dose-dependent
        - Immunologic mechanism involves drug-dependent antibodies that bind to platelet glycoprotein IIb/IIIa complexes [42]
- Serotonin syndrome
    - Risk increases with other serotonergic drugs
    - Has also been reported rarely in monotherapy at therapeutic doses [43]
        - Some clinicians argue that mirtazapine's receptor binding profile, which does not significantly increase synaptic serotonin levels, makes it mechanistically improbable for the drug to cause true serotonin toxicity, suggesting reported cases may represent misclassification of other adverse effects [44,45]
    - Use caution when combining mirtazapine with serotonergic medications, especially during treatment initiation or dose adjustments [1]
- Activation of mania/hypomania
    - Although rare, cases with mirtazapine have been reported [46,47]
    - May present atypically with dysphoria and agitation [48]
- QT prolongation
    - Risk increases with higher doses
    - Doses up to 45 mg generally considered to have minimal clinical impact on QT interval [1,49]
    - Use caution in patients with cardiovascular disease [1]
- Discontinuation syndrome
    - SNRIs, paroxetine, and mirtazapine have the highest risk among antidepressants [50]
    - Symptoms may include dizziness, nausea, anxiety, and sleep disturbances [1,51]
    - Rare manifestations involve withdrawal-induced mania/hypomania and pruritus [52,53]
    - Mechanism attributed to sudden removal of 5-HT2/5-HT3 receptor blockade, H1-receptor rebound may cause dizziness [54]
    - Gradual tapering recommended to minimize risk [1]

Other side effects

- Orthostatic hypotension
    - Infrequently reported adverse effect [1,55]
    - Mechanism: α1-adrenergic and H1 receptor antagonism [6]
    - Consider monitoring blood pressure in high-risk patients

- Drug-induced movement disorders
    - Akathisia
        - More common at higher doses (30 mg/day) [[56]; [57,58]
        - Lower doses have been used to treat antipsychotic-induced akathisia , potentially due to 5-HT2A receptor blockade [59]
        - Mechanism likely related to α2-adrenoreceptor blockade [57]
        - Onset varies from immediate (single dose) to delayed (up to 20 years of treatment) [56]
    - Dystonia and dyskinesia
        - More common at lower doses (15 mg/day) [58]
        - Related to 5-HT2 receptor inhibition and noradrenergic-dopaminergic imbalance [60,61]
    - Restless leg syndrome (RLS)
        - Associated with serotonergic modulation [62]

Use in special populations

Pregnancy

- First-trimester safety
    - Congenital malformations risk
        - No increased risk of congenital malformations according to multiple studies, including a nationwide medical birth register [63,64]
- Pregnancy complications
    - Possible increased preterm birth risk (13% vs 2% in controls) [65]
    - No increased risk of:
        - Stillbirth or neonatal death [64]
        - Low birth weight [65]
        - Preeclampsia [66]
    - Neonatal adaptation
        - Poor neonatal adaptation in about one-third of exposed infants [67]
        - Generally mild and self-limiting effects [68,69]

Breastfeeding

- Mirtazapine is present in breast milk [1,70]
- Generally considered acceptable during breastfeeding due to minimal infant exposure [71]
    - Drug levels in breastmilk are low [1]
    - Infant serum levels typically <1% of maternal levels [70]

    - No reported serious adverse effects in breastfed infants [69]
- Breastfed infants should be monitored for [71]
    - Sedation
    - Poor feeding patterns.
    - Weight gain adequacy.
    - Development
- When initiating antidepressant therapy in treatment-naive patients:
    - SSRIs are typically first-line options [72]
    - Mirtazapine may be considered if maternal history suggests better tolerability [69]

Hepatic impairment

- Mirtazapine should be used with caution in patients with impaired hepatic function [1]
- Mild to moderate cirrhosis (Child-Pugh Class A/B)
    - Starting dose: Administer 50% of the normal indication-specific starting dose [73,74]
    - Maximum dose: 30 mg/day
    - Monitor closely for adverse effects
- Child-Pugh Class C [75]
    - Consider alternative agents
    - If use is required:
        - Start at 50% of usual dose
        - Maximum: 30 mg/day
        - Close monitoring essential

Renal impairment

- ClCr ≥30 mL/minute [1]
    - No dosage adjustment necessary
- ClCr <30 mL/minute and hemodialysis/peritoneal dialysis [1,76]
    - Initial: 7.5 to 15 mg once daily
    - Titrate slowly with close monitoring
    - Clearance reduced by ~50% in severe impairment

Elderly

- Consider lower starting doses (7.5 mg once daily) [1]
    - Clearance reduced (40% lower in elderly males and 10% lower in elderly females) [1]

- Elderly patients may be at increased risk of hyponatremia with mirtazapine, though the incidence is lower compared to other antidepressants [1,37]

Patients with Phenylketonuria

- Mirtazapine orally disintegrating tablets (Remeron SolTab) contains phenylalanine (from aspartame) [1]

Brand names

- US: Remeron, Remeron SolTab
- Canada: APO-Mirtazapine, Auro-Mirtazapine, Auro-Mirtazapine OD, MYLAN-Mirtazapine, NRA-Mirtazapine, PMS-Mirtazapine, PRO-Mirtazapine, Remeron, Remeron RD, SANDOZ Mirtazapine, TEVA-Mirtazapine
- Other countries/regions: Actizipine, ADCO Mirteron, Alpreak, Amirel, Amiron, Aprimertaz, Arintapin, Auromirta oro, Aurozapine, Avanza, Bilanz, Calixta, Ciblex, Combar, Comenter, Contrelmin, Conalpin, Depreram, Dinertone, Deprezapina, Divaril, Elaxine, Esprital, Exania, Epilfarmo, Farmapina, Itazpam, Jeta, Jewell, Kang duo ning, M zap, Matiz, Maz, Mazipine, Melinton, Mira, Miramind, Mirap, Miradep, Miraz, Mirazagen, Mirazep, Mirdep, Mirfast, Miro, Miron, Mirnite, Mirpine, Mirsol, Milta, Milta od, Mipine, Mirt, Mirtabene, Mirtachem, Mirtalab, Mirtalich, Mirtagen, Mirtagamma, Mirtamerck, Mirtamylan, Mirtamor, Mirtan, Mirtapax, Mirtaril, Mirtatsapiini ennapharma, Mirtatsapiini Teva, Mirtastad, Mirtastadin, Mirtawin, Mirtax, Mirtel, Mitaprex, Mitapin, Mitocent, Mitpin, Mitraford, Mitrazac, Mzapine, Mirzaten, Mirzaten Q Tab, Mirzagen, Mirastad, Multapine, Mirzentac, Mirzentac od, Nasdep, Noxibel, Ociples, Ociplos, Odonazin, Orzap, Pai di sheng, Psidep, Rapine, Ramizipine, Rapizapine, Rejoy, Reflex, Remedrint, Remeron, Remergil, Remirta, Remirta oro, Remeron soltab, Rezam, Redepra, Remixil, Ramure, Saxib, Segmir, Shakes, Sypine, Sinmaron, Smilon, Tazepin, Tazamel, Tasomin, Terladep, Tazip, Tizapine, Trimazimyl, U Mirtaron, U-Zepine, Valdren, Velorin OD, Vastat, Vastat flas, Zapsy, Zania, Zatimar, Zemer, Zapimert, Zapex, Zestat, Zimvaken, Zispin, Zismirt, Zispin soltab, Zulin, Zuleptan, Zamir 15, Zamir 30, Zymron, Zipdep, Zapmir

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