**THERAPEUTICS**

**Brands**
- Remeron
  
  *see index for additional brand names*

**Generic?**
- Yes

**Class**
- Neuroscience-based Nomenclature:
  - serotonin, norepinephrine receptor antagonist (SN-RAn)
- Alpha 2 antagonist; NaSSA (noradrenaline and specific serotonergic agent); dual serotonin and norepinephrine agent; antidepressant

**Commonly Prescribed for**
- (bold for FDA approved)
  - Major depressive disorder
  - Panic disorder
  - Generalized anxiety disorder
  - Posttraumatic stress disorder

**How the Drug Works**
- Boost neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks alpha 2 adrenergic presynaptic receptor, thereby increasing norepinephrine neurotransmission
- Blocks alpha 2 adrenergic presynaptic receptor on serotonin neurons (heteroreceptors), thereby increasing serotonin neurotransmission
- This is a novel mechanism independent of norepinephrine and serotonin reuptake blockade
- Blocks 5HT2A, 5HT2C, and 5HT3 serotonin receptors
- Blocks H1 histamine receptors

**How Long Until It Works**
- *Actions on insomnia and anxiety can start shortly after initiation of dosing*
- Onset of therapeutic actions in depression, however, is usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

**If It Works**
- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

**If It Doesn’t Work**
- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- SSRIs, bupropion, reboxetine, atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- Venlafaxine (“California rocket fuel”; a potentially powerful dual serotonin and norepinephrine combination, but observe for activation of bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
• Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression or treatment-resistant depression
• Benzodiazepines
• Hypnotics or trazodone for insomnia

**Notable Side Effects**
- Dry mouth, constipation, increased appetite, weight gain
- Sedation, dizziness, abnormal dreams, confusion
- Flu-like symptoms (may indicate low white blood cell or granulocyte count)
- Change in urinary function
- Hypotension

**Life-Threatening or Dangerous Side Effects**
- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

**Weight Gain**
- Many experience and/or can be significant in amount

**Sedation**
- Many experience and/or can be significant in amount

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- Switch to another drug

**Best Augmenting Agents for Side Effects**
- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Trazodone or a hypnotic for insomnia
- Many side effects cannot be improved with an augmenting agent

**SIDE EFFECTS**

**How Drug Causes Side Effects**
- Most side effects are immediate but often go away with time
  ✴ Histamine 1 receptor antagonism may explain sedative effects
  ✴ Histamine 1 receptor antagonism plus 5HT2C antagonism may explain some aspects of weight gain

**Tests**
- None for healthy individuals
- May need liver function tests for those with hepatic abnormalities before initiating treatment
- May need to monitor blood count during treatment for those with blood dyscrasias, leucopenia, or granulocytopenia
- Since some antidepressants such as mirtazapine can be associated with significant weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI >25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
  ✴ Monitor weight and BMI during treatment
  ✴ While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant

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How to Stop

- Taper is prudent to avoid withdrawal effects, but tolerance, dependence, and withdrawal effects not reliably reported

Pharmacokinetics

- Half-life 20–40 hours
- Substrate for CYP450 2D6, 3A4, and possibly also CYP450 1A2
- Food does not affect absorption

Other Warnings/Precautions

- Drug may lower white blood cell count (rare; may not be increased compared to other antidepressants but controlled studies lacking; not a common problem reported in postmarketing surveillance)
- Drug may increase cholesterol
- May cause photosensitivity
- Avoid alcohol, which may increase sedation and cognitive and motor effects
- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately

DOSING AND USE

Usual Dosage Range

- 15–45 mg at night

Dosage Forms

- Tablet 15 mg scored, 30 mg scored, 45 mg
- SolTab disintegrating tablet 15 mg, 30 mg, 45 mg

How to Dose

- Initial 15 mg/day in the evening; increase every 1–2 weeks until desired efficacy is reached; maximum generally 45 mg/day

Dosing Tips

- Sedation may not worsen as dose increases
- Breaking a 15-mg tablet in half and administering 7.5 mg dose may actually increase sedation
- Some patients require more than 45 mg daily, including up to 90 mg in difficult patients who tolerate these doses
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Rarely lethal; all fatalities have involved other medications; symptoms include sedation, disorientation, memory impairment, rapid heartbeat

Long-Term Use

- Safe

Habit Forming

- Not expected

Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- No significant pharmacokinetic drug interactions
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing mirtazapine

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 Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of mirtazapine
MIRTAZAPINE (continued)

- Monitor patients for activation of suicidal ideation, especially children and adolescents

**Do Not Use**
- If patient is taking an MAOI
- If there is a proven allergy to mirtazapine

### SPECIAL POPULATIONS

**Renal Impairment**
- Drug should be used with caution

**Hepatic Impairment**
- Drug should be used with caution
- May require lower dose

**Cardiac Impairment**
- Drug should be used with caution
- The potential risk of hypotension should be considered

**Elderly**
- Some patients may tolerate lower doses better
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

**Children and Adolescents**
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Safety and efficacy have not been established

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

**Breast Feeding**
- Unknown if mirtazapine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

### THE ART OF PSYCHOPHARMACOLOGY

**Potential Advantages**
- Patients particularly concerned about sexual side effects
- Patients with symptoms of anxiety
- Patients on concomitant medications
- As an augmenting agent to boost the efficacy of other antidepressants

**Potential Disadvantages**
- Patients particularly concerned about gaining weight
- Patients with low energy
primary target symptoms
- Depressed mood
- Sleep disturbance
- Anxiety

**Pearls**

* Adding alpha 2 antagonism to agents that block serotonin and/or norepinephrine reuptake may be synergistic for severe depression
* Adding mirtazapine to venlafaxine or SSRIs may reverse drug-induced anxiety and insomnia
* Adding mirtazapine’s 5HT3 antagonism to venlafaxine or SSRIs may reverse drug-induced nausea, diarrhea, stomach cramps, and gastrointestinal side effects
* SSRIs, venlafaxine, bupropion, phentermine, or stimulants may mitigate mirtazapine-induced weight gain
* If weight gain has not occurred by week 6 of treatment, it is less likely for there to be significant weight gain
* Has been demonstrated to have an earlier onset of action than SSRIs
* Does not affect the CYP450 system, and so may be preferable in patients requiring concomitant medications
* Preliminary evidence suggests efficacy as an augmenting agent to haloperidol in treating negative symptoms of schizophrenia
* Anecdotal reports of efficacy in recurrent brief depression
* Weight gain as a result of mirtazapine treatment is more likely in women than in men, and before menopause rather than after
* May cause sexual dysfunction only infrequently
* Patients can have carryover sedation and intoxicated-like feeling if particularly sensitive to sedative side effects when initiating dosing
* Rarely, patients may complain of visual “trails” or after-images on mirtazapine

suggested reading


