

AGOMELATINE

THERAPEUTICS

Brands • Valdoxan
see index for additional brand names

Generic? No



Class

- Neuroscience-based Nomenclature: melatonin multi-modal (Mel-MM)
- Agonist at melatonergic 1 and melatonergic 2 receptors
- Antagonist at 5HT2C receptors

Commonly Prescribed for

(bold for FDA approved)

- Depression



How the Drug Works

- Actions at both melatonergic and 5HT2C receptors may be synergistic and increase norepinephrine and dopamine neurotransmission in the prefrontal cortex; may resynchronize circadian rhythms that are disturbed in depression
- No influence on extracellular levels of serotonin

How Long Until It Works

- Daytime functioning, anhedonia, and sleep can improve from the first week of treatment
- Onset of full therapeutic actions in depression is usually not immediate, but often delayed 2–4 weeks
- 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 is stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms 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

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 as early as 2 weeks after initiating treatment if response is insufficient (decision on dose increase has to be balanced with a higher risk of transaminase elevation; any dose increase should be made on an individual patient benefit/risk basis and with strict respect of liver function tests monitoring)
- Consider 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 (excluding fluvoxamine), SNRIs, bupropion, reboxetine, atomoxetine (use combinations of antidepressant with caution as this may activate 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

Tests

- Liver function tests before initiation of treatment and then after around 3 weeks, 6 weeks, 12 weeks, 24 weeks, and thereafter when clinically indicated
- When increasing the dose, liver function tests should be performed at the same frequency as when initiating treatment
- Liver function tests should be repeated within 48 hours in any patient who develops raised transaminases

AGOMELATINE (continued)

SIDE EFFECTS

How Drug Causes Side Effects

- Adverse reactions usually mild to moderate and occur within the first 2 weeks of treatment
- Actions at melatonergic receptors and at 5HT_{2C} receptors could contribute to the side effects described below

Notable Side Effects

- Nausea and dizziness are most common
- Other adverse reactions are somnolence, fatigue, insomnia, headache, anxiety, diarrhea, constipation, upper abdominal pain, vomiting, hyperhidrosis
- Increase of transaminase levels



Life-Threatening or Dangerous Side Effects

- * Rare hepatitis, hepatic failure
- Theoretically rare induction of mania (class warning)
- 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) (class warning)

Weight Gain



- Occurs in significant minority
- Cases of weight decrease have been reported

Sedation (Somnolence)



- Occurs in significant minority
- Generally transient
- May be more likely to cause fatigue than sedation

What to Do About Side Effects

- Wait
- Wait
- Stop if transaminase levels exceed 3 times the upper limit of normal
- 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 time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Many side effects cannot be improved with an augmenting agent
- Therotically 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 agomelatine (class warning)

DOSING AND USE

Usual Dosage Range

- 25–50 mg/day at bedtime

Dosage Forms

- Tablet 25 mg

How to Dose

- Initial 25 mg/day at bedtime; after 2 weeks can increase to 50 mg/day at bedtime



Dosing Tips

- 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

- Drowsiness and epigastralgia; fatigue, agitation, anxiety, tension, dizziness, cyanosis, or malaise have also been reported

Long-Term Use

- Treatment up to 12 months has been found to decrease rate of relapse

Habit Forming

- No

How to Stop

- No need to taper dose

Pharmacokinetics

- Half-life 1–2 hours
- Metabolized primarily by CYP450 1A2

**Drug Interactions**

- Use of agomelatine with potent CYP450 1A2 inhibitors (e.g., fluvoxamine) is contraindicated
- Tramadol increases the risk of seizures in patients taking an antidepressant (class warning)

**Other Warnings/
Precautions**

- Use with caution in patients with hepatic injury risk factors, such as obesity/overweight/non-alcoholic fatty liver disease, diabetes, patients who drink large quantities of alcohol and/or have alcohol use disorder, or who take medication associated with risk of hepatic injury. Doctors should ask their patients if they have ever had liver problems.
- If symptoms or signs of potential liver injury (dark urine, light-colored stools, yellow skin/eyes, pain in upper right belly, sustained new-onset and unexplained fatigue) are present, agomelatine should be discontinued immediately
- Use caution in patients with pre-treatment elevated transaminases ($>$ the upper limit of the normal range and ≤ 3 times the upper limit of the normal range)
- Discontinue treatment if serum transaminases exceed 3 times the upper limit of normal; liver function tests should be performed regularly until serum transaminases return to normal
- Agomelatine should be administered at bedtime
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children off label (an unapproved use), 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
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately

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

Do Not Use

- If patient has hepatic impairment
- If patient has transaminase levels > 3 times the upper limit of normal
- If patient is taking a potent CYP450 1A2 inhibitor (e.g., fluvoxamine, ciprofloxacin)
- If patient is taking an MAO inhibitor (MAOI)
- If patient has galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
- If there is a proven allergy to agomelatine

SPECIAL POPULATIONS**Renal Impairment**

- Drug should be used with caution

Hepatic Impairment

- Contraindicated

Cardiac Impairment

- Dose adjustment not necessary

Elderly

- Efficacy and safety have been established (< 75 years old)
- Dose adjustment not necessary
- Should not be used in patients age 75 years and older
- Should not be used in elderly patients with dementia

**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
- Safety and efficacy have not been established and it is not recommended

**Pregnancy**

- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester

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- 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 agomelatine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Therefore, breast feeding or drug needs 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 reinstituted late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with lack of energy, anhedonia, anxious comorbidity, and sleep-wake disturbances
- Patients particularly concerned about sexual side effects

Potential Disadvantages

- Patients with hepatic impairment

Primary Target Symptoms

- Depressed mood, anhedonia
- Functioning
- Anxiety within depression



Pearls

- Agomelatine represents a novel approach to depression through a novel pharmacologic profile, agonist at melatonergic MT1 / MT2 receptors and antagonist at 5HT2C receptors acting synergistically
- This synergy provides agomelatine with a distinctive efficacy profile, different from conventional antidepressants with potentially an early and continuous improvement over time
- Agomelatine improves anhedonia early in treatment
- Improves anxiety in major depressive disorder
- May be fewer withdrawals/discontinuations for adverse events than with other antidepressants
- No significant effect on cardiac parameters such as blood pressure and heart rate
- Some data suggest that agomelatine may be specially efficacious in achieving functional remission
- Agomelatine may improve sleep quality by promoting proper maintenance of circadian rhythms underlying a normal sleep-wake cycle



Suggested Reading

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