AGOMELATINE

<table>
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<th>THERAPEUTICS</th>
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| **Brands** • Valdoxan  
*see index for additional brand names*  
| **Generic?** No  
| **Class** • 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  

**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 at initiation of treatment, then around 3, 6, 12, and 24 weeks after treatment, and thereafter when clinically indicated  
• When increasing the dose, liver function tests should be performed at the same frequency as when initiating treatment  

• For second and subsequent episodes of depression, treatment may need to be indefinite
AGOMELATINE (continued)

How Drug Causes Side Effects
• Adverse reactions usually mild to moderate and occur within the first two weeks of treatment
• Actions at melatonergic receptors and at 5HT2C 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
• Reported but not expected

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 reach 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
• Therapeutically 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
AGOMELATINE

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

Drug Interactions
- Use of agomelatine with potent CYP450 1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin) 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 or who take medication associated with risk of hepatic injury
- 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 increase to 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

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

Pregnancy
- No controlled studies in humans
- Not generally recommended for use during pregnancy, especially during first trimester
AGOMELATINE (continued)

**Potential Advantages**
- Patients particularly concerned about sexual side effects

**Potential Disadvantages**
- Patients with hepatic impairment

**Primary Target Symptoms**
- Depressed mood, anhedonia
- Daytime functioning

**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
- Agomelatine may improve sleep quality by promoting proper maintenance of circadian rhythms underlying a normal sleep-wake cycle

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**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

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**The Art of Psychopharmacology**

**Potential Advantages**
- Patients with lack of energy, anhedonia, anxious comorbidity, and sleep-wake disturbances

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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

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Antidepressants: Fifth Edition
Stephen M. Stahl
Excerpt

More information
Suggested Reading


AMISULPRIDE

**Brands** • Solian

*see index for additional brand names*

**Generic?** No

**Class**

- Atypical antipsychotic (benzamide; possibly a dopamine stabilizer and dopamine partial agonist)

**Commonly Prescribed for**

(bold for FDA approved)

- Schizophrenia, acute and chronic (outside of U.S., especially Europe)
- Dysthymia

**How the Drug Works**

- Theoretically blocks presynaptic dopamine D2 receptors at low doses
- Theoretically blocks postsynaptic dopamine D2 receptors at higher doses
- May be a partial agonist at dopamine D2 receptors, which would theoretically reduce dopamine output when dopamine concentrations are high and increase dopamine output when dopamine concentrations are low
- Blocks dopamine D3 receptors, which may contribute to its clinical actions
- Unlike other atypical antipsychotics, amisulpride does not have potent actions at serotonin 2A or serotonin 1A receptors
- Does have antagonist actions at serotonin 7 receptors and serotonin 2B receptors, which may contribute to antidepressant effects

**How Long Until It Works**

- Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition and affective stabilization
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients require up to 16–20 weeks to show a good response, especially on cognitive symptoms

**If It Works**

- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
- Continuation treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment indefinitely to avoid subsequent episodes

**If It Doesn’t Work**

- Try one of the other first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, iloperidone, lurasidone)
- If two or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
- Consider initiating rehabilitation and psychotherapy such as cognitive remediation
- Consider presence of concomitant drug abuse

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Valproic acid (valproate, divalproex, divalproex ER)
- Augmentation of amisulpride has not been systematically studied
**AMISULPRIDE (continued)**

- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

**Tests**

- Although risk of diabetes and dyslipidemia with amisulpride has not been systematically studied, monitoring as for all other atypical antipsychotics is suggested

**Before starting an atypical antipsychotic**

- Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- Get waistline circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if patient is overweight (BMI 25.0–29.9), obese (BMI ≥30), has pre-diabetes (fasting plasma glucose 100–125 mg/dL), has diabetes (fasting plasma glucose >126 mg/dL), has hypertension (BP >140/90 mm Hg), has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

**Monitoring after starting an atypical antipsychotic**

- BMI monthly for 3 months, then quarterly
- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic

**SIDE EFFECTS**

- Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness and clouding of sensorium, even coma
- EKGS may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and amisulpride should be discontinued at the first sign of decline of WBC in the absence of other causative factors

**How Drug Causes Side Effects**

- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects, especially at high doses
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- Mechanism of weight gain and possible increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

**Notable Side Effects**

- Extrapyramidal symptoms
- Galactorrhea, amenorrhea
- Atypical antipsychotics may increase the risk for diabetes and dyslipidemia, although the specific risks associated with amisulpride are unknown
- Insomnia, sedation, agitation, anxiety
- Constipation, weight gain
- Rare tardive dyskinesia
**AMISULPRIDE**

### How to Dose
- Initial 400–800 mg/day in 2 doses; daily doses above 400 mg should be divided in 2; maximum generally 1200 mg/day
- See also the Switching section below, after Pearls

### Dosing Tips
- **Efficacy for negative symptoms in schizophrenia may be achieved at lower doses, while efficacy for positive symptoms may require higher doses**
- **Patients receiving low doses may only need to take the drug once daily**
- **For dysthymia and depression, use only low doses**
- **Dose-dependent QTc prolongation, so use with caution, especially at higher doses (>800 mg/day)**
- **Amisulpride may accumulate in patients with renal insufficiency, requiring lower dosing or switching to another antipsychotic to avoid QTc prolongation in these patients**
- **Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³**
- **Sedation, coma, hypotension, extrapyramidal symptoms**

### Life-Threatening or Dangerous Side Effects
- Rare neuroleptic malignant syndrome
- Rare seizures
- Dose-dependent QTc prolongation
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

### Weight Gain
- Occurs in significant minority

### Sedation
- Many experience and/or can be significant in amount, especially at high doses

### What to Do About Side Effects
- Wait
- Wait
- Lower the dose
- For motor symptoms, add an anticholinergic agent
- Take more of the dose at bedtime to help reduce daytime sedation
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

### Best Augmenting Agents for Side Effects
- Benztropine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent

### Pharmacokinetics
- Elimination half-life approximately 12 hours
- Excreted largely unchanged

### Drug Interactions
- Can decrease the effects of levodopa, dopamine agonists
- Can increase the effects of antihypertensive drugs

### Usual Dosage Range
- Schizophrenia: 400–800 mg/day in 2 doses
- Negative symptoms only: 50–300 mg/day
- Dysthymia: 50 mg/day

### Dosage Forms
- Different formulations may be available in different markets
- Tablet 50 mg, 100 mg, 200 mg, 400 mg
- Oral solution 100 mg/mL

### Overdose
- Sedation, coma, hypotension, extrapyramidal symptoms

### Long-Term Use
- Amisulpride is used for both acute and chronic schizophrenia treatment

### Habit Forming
- No

### How to Stop
- See Switching section of individual agents for how to stop amisulpride
- Rapid discontinuation may lead to rebound psychosis and worsening of symptoms

### More information
AMISULPRIDE (continued)

• CNS effects may be increased if used with a CNS depressant
• May enhance QTc prolongation of other drugs capable of prolonging QTc interval
• Since amisulpride is only weakly metabolized, few drug interactions that could raise amisulpride plasma levels are expected

Other Warnings/Precautions
• Use cautiously in patients with alcohol withdrawal or convulsive disorders because of possible lowering of seizure threshold.
• If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued.
• Because amisulpride may dose-dependently prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis).
• Because amisulpride may dose-dependently prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or hypomagnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracacside).
• Use only with caution if at all in Parkinson’s disease or Lewy body dementia, especially at high doses.

Do Not Use
• If patient has pheochromocytoma.
• If patient has prolactin-dependent tumor.
• If patient is pregnant or nursing.
• If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide; thioridazine; selected antiarrhythmics such as quinidine, disopyramide, amiodarone, and sotalol; selected antibiotics such as moxifloxacin and sparfloxacin).
• If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure.
• If patient is taking cisapride, intravenous erythromycin, or pentamidine.
• In children.
• If there is a proven allergy to amisulpride.

SPECIAL POPULATIONS

Renal Impairment
• Use with caution; drug may accumulate.
• Amisulpride is eliminated by the renal route; in cases of severe renal insufficiency, the dose should be decreased and intermittent treatment or switching to another antipsychotic should be considered.

Hepatic Impairment
• Use with caution, but dose adjustment not generally necessary.

Cardiac Impairment
• Amisulpride produces a dose-dependent prolongation of QTc interval, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering amisulpride.
• Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval.
• Avoid amisulpride in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure.

Elderly
• Some patients may be more susceptible to sedative and hypotensive effects.
• Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis.
• Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events.

Children and Adolescents
• Efficacy and safety not established under age 18.

Pregnancy
• Although animal studies have not shown teratogenic effect, amisulpride is not recommended for use during pregnancy.