AMISULPRIDE

THERAPEUTICS

Brands • Solian
see index for additional brand names

Generic? No

Class

- Neuroscience-based Nomenclature: dopamine receptor antagonist (D-RAn)
- Atypical antipsychotic (benzamide; possibly a dopamine stabilizer and dopamine partial agonist)

Commonly Prescribed for

(bold for FDA approved)

- Schizophrenia, acute and chronic (outside of USA, especially Europe)
- Dysthymia

How the Drug Works

- Theoretically blocks presynaptic dopamine 2 receptors at low doses
- Theoretically blocks postsynaptic dopamine 2 receptors at higher doses
- ✻ May be a partial agonist at dopamine 2 receptors, which would theoretically reduce dopamine output when dopamine concentrations are high and increase dopamine output when dopamine concentrations are low
- Blocks dopamine 3 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
- Continue 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

✻ 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

SIDE EFFECTS

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

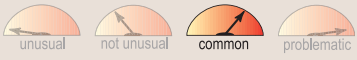
Life-Threatening or Dangerous Side Effects

- 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
- 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

DOSING AND USE

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

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/mm^3

Overdose

- Sedation, coma, hypotension, extrapyramidal symptoms

Long-Term Use

- Amisulpride is used for both acute and chronic schizophrenia treatment

Habit Forming

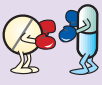
- No

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

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

- 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 magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- 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

- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary

Breast Feeding

- Unknown if amisulpride is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk

✻ Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Not as clearly associated with weight gain as some other atypical antipsychotics
- For patients who are responsive to low-dose activation effects that reduce negative symptoms and depression

Potential Disadvantages

- Patients who have difficulty being compliant with twice daily dosing
- Patients for whom elevated prolactin may not be desired (e.g., possibly pregnant patients; pubescent girls with amenorrhea; postmenopausal women with low estrogen who do not take estrogen replacement therapy)
- Patients with severe renal impairment

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Depressive symptoms

Pearls

✻ Efficacy has been particularly well demonstrated in patients with predominantly negative symptoms

✻ The increase in prolactin caused by amisulpride may cause menstruation to stop

- Some treatment-resistant patients with inadequate responses to clozapine may benefit from amisulpride augmentation of clozapine
- Risks of diabetes and dyslipidemia not well studied, but does not seem to cause as much weight gain as some other atypical antipsychotics
- Has atypical antipsychotic properties (i.e., antipsychotic action without a high incidence of extrapyramidal symptoms), especially at low doses, but not a serotonin dopamine antagonist
- Mediates its atypical antipsychotic properties via novel actions on dopamine receptors, perhaps dopamine stabilizing partial agonist actions on dopamine 2 receptors
- May be more of a dopamine 2 antagonist than aripiprazole, but less of a dopamine 2 antagonist than other atypical or conventional antipsychotics
- Low-dose activating actions may be beneficial for negative symptoms in schizophrenia
- Very low doses may be useful in dysthymia
- Compared to sulpiride, amisulpride has better oral bioavailability and more potency, thus allowing lower dosing, less weight gain, and fewer extrapyramidal symptoms
- Compared to other atypical antipsychotics with potent serotonin 2A antagonism, amisulpride may have more extrapyramidal symptoms and prolactin elevation, but may still be classified as an atypical antipsychotic, particularly at low doses
- Patients have very similar antipsychotic responses to any conventional antipsychotic, which is different from atypical antipsychotics where antipsychotic responses of individual patients can occasionally vary greatly from one atypical antipsychotic to another
- Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and, if low, a dosage increase even beyond the usual prescribing limits
- Patients with inadequate responses to atypical antipsychotics may also benefit from a trial of augmentation with a

AMISULPRIDE (continued)

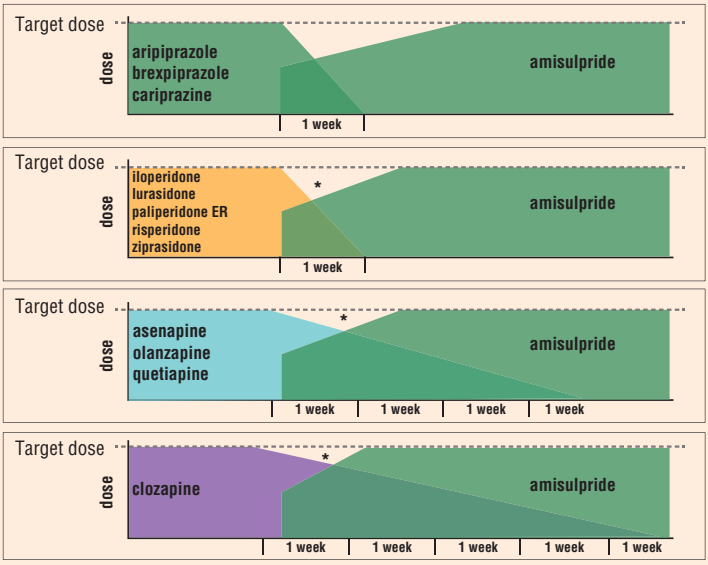
conventional antipsychotic or switching to a conventional antipsychotic
- However, long-term polypharmacy with a combination of a conventional antipsychotic with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either
- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic
- Although a frequent practice by some prescribers, adding two conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy

THE ART OF SWITCHING

Switching from Oral Antipsychotics to Amisulpride

- It is advisable to begin amisulpride at an intermediate dose and build the dose rapidly over 3–7 days
- Clinical experience has shown that asenapine, quetiapine, and olanzapine should be tapered off slowly over a period of 3–4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha-1 receptors
- Clozapine should always be tapered off slowly, over a period of 4 weeks or more

* Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis



Suggested Reading

Burns T, Bale R. Clinical advantages of amisulpride in the treatment of acute schizophrenia. J Int Med Res 2001;29(6): 451–66.

Curran MP, Perry CM. Spotlight on amisulpride in schizophrenia. CNS Drugs 2002;16(3): 207–11.

Komossa K, Rummel-Kluge C, Hunder H, et al. Amisulpride versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2010;(1):CD006624.

Leucht S, Pitschel-Walz G, Engel RR, Kissling W. Amisulpride, an unusual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. Am J Psychiatry 2002;159 (2):180–90.