**SULPIRIDE**

### Therapeutics

#### Brands
- Dolmatil
  *see index for additional brand names*

#### Generic?
Yes

#### Class
- Neuroscience-based Nomenclature: dopamine receptor antagonist (D-RAn)
- Conventional antipsychotic (neuroleptic, benzamide, dopamine 2 antagonist)

#### Commonly Prescribed for
(bold for FDA approved)
- Schizophrenia
- Depression

#### How the Drug Works
- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis
- Blocks dopamine 3 and 4 receptors, which may contribute to sulpiride’s actions
- Possibly blocks presynaptic dopamine 2 autoreceptors more potently at low doses, which could theoretically contribute to improving negative symptoms of schizophrenia as well as depression

#### How Long Until It Works
- Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior

#### If It Works
- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Continue treatment in schizophrenia until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis in schizophrenia
- For second and subsequent episodes of psychosis in schizophrenia, treatment may need to be indefinite

#### If It Doesn’t Work
- Consider trying one of the first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, amisulpride, asenapine, iloperidone, lurasidone)
- Consider trying another conventional antipsychotic
- If 2 or more antipsychotic monotherapies do not work, consider clozapine

#### Best Augmenting Combos for Partial Response or Treatment Resistance
- Augmentation of conventional antipsychotics has not been systematically studied
- Addition of a mood-stabilizing anticonvulsant such as valproate, carbamazepine, or lamotrigine may be helpful in both schizophrenia and bipolar mania
- Augmentation with lithium in bipolar mania may be helpful
- Addition of a benzodiazepine, especially short-term for agitation

#### Tests
- Since conventional antipsychotics are frequently associated with 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
- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- 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 antipsychotic
- Monitoring elevated prolactin levels of dubious clinical benefit
- 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 sulpiride 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
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- By blocking dopamine 2 receptors excessively in the mesocortical and mesolimbic dopamine pathways, especially at high doses, it can cause worsening of negative and cognitive symptoms (neuroleptic-induced deficit syndrome)
- Anticholinergic actions may cause sedation, blurred vision, constipation, dry mouth
- Antihistaminic actions may cause sedation, weight gain
- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- Mechanism of weight gain and any possible increased incidence of diabetes or dyslipidemia with conventional antipsychotics is unknown

#### Notable Side Effects
- Extrapyramidal symptoms, akathisia
- Prolactin elevation, galactorrhea, amenorrhea
- Sedation, dizziness, sleep disturbance, headache, impaired concentration
- Dry mouth, nausea, vomiting, constipation, anorexia
- Impotence
- Rare tardive dyskinesia
- Rare hypomania
- Palpitations, hypertension
- Weight gain

#### Life-Threatening or Dangerous Side Effects
- Rare neuroleptic malignant syndrome
- Rare seizures

#### Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

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

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

#### What to Do About Side Effects
- Wait
- Wait
- Wait
- For motor symptoms, add an anticholinergic agent
- Reduce the dose
- For sedation, give at night
- Switch to an atypical antipsychotic
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia

#### Best Augmenting Agents for Side Effects
- Benztropine or trihexyphenidyl for motor side effects
- Sometimes amantadine can be helpful for motor side effects
- Benzodiazepines may be helpful for akathisia
- Many side effects cannot be improved with an augmenting agent

#### DOSING AND USE

##### Usual Dosage Range
- Schizophrenia: 400–800 mg/day in 2 doses (oral)
- Predominantly negative symptoms: 50–300 mg/day (oral)
- Intramuscular injection: 600–800 mg/day
- Depression: 150–300 mg/day (oral)

##### Dosage Forms
- Different formulations may be available in different markets
• Tablet 200 mg, 400 mg, 500 mg
• Intramuscular injection 50 mg/mL, 100 mg/mL

How to Dose
• Initial 400–800 mg/day in 1–2 doses; may need to increase dose to control positive symptoms; maximum generally 2,400 mg/day

Dosing Tips
* Low doses of sulpiride may be more effective at reducing negative symptoms than positive symptoms in schizophrenia; high doses may be equally effective at reducing both symptom dimensions
* Lower doses are more likely to be activating; higher doses are more likely to be sedating
• Some patients receive more than 2,400 mg/day
• Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose
• Can be fatal; vomiting, agitation, hypotension, hallucinations, CNS depression, sinus tachycardia, arrhythmia, dystonia, dysarthria, hyperreflexia

Long-Term Use
• Apparently safe, but not well studied

Habit Forming
• No

How to Stop
• Recommended to reduce dose over a week
• Slow down-titration (over 6–8 weeks), especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
• Rapid discontinuation may lead to rebound psychosis and worsening of symptoms
• If antiparkinson agents are being used, they should be continued for a few weeks after sulpiride is discontinued

Pharmacokinetics
• Elimination half-life approximately 6–8 hours
• Excreted largely unchanged

Drug Interactions
• Sulpiride may increase the effects of antihypertensive drugs
• CNS effects may be increased if sulpiride is used with other CNS depressants
• May decrease the effects of levodopa, dopamine agonists
• Antacids or sucralfate may reduce the absorption of sulpiride

Other Warnings/Precautions
• If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued
• Use cautiously in patients with alcohol withdrawal or convulsive disorders because of possible lowering of seizure threshold
• Antiemetic effect of sulpiride may mask signs of other disorders or overdose; suppression of cough reflex may cause asphyxia
• Use with caution in patients with hypertension, cardiovascular disease, pulmonary disease, hyperthyroidism, urinary retention, glaucoma
• May exacerbate symptoms of mania or hypomania
• Use only with caution if at all in Parkinson’s disease or Lewy body dementia

SPECIAL POPULATIONS

Renal Impairment
• Use with caution; drug may accumulate
• Sulpiride 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

Do Not Use
• If patient has pheochromocytoma
• If patient has prolactin-dependent tumor
• If patient is pregnant or nursing
• In children under age 15
• If there is a proven allergy to sulpiride
Cardiac Impairment
- Use with caution

Elderly
- Some patients may tolerate lower doses better
- Although conventional 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 antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

Children and Adolescents
- Not recommended for use in children under age 15
- 14 and older: recommended 3–5 mg/kg per day

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
- Potential risks should be weighed against the potential benefits, and sulpiride should be used only if deemed necessary
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Atypical antipsychotics may be preferable to conventional antipsychotics or anticonvulsant mood stabilizers if treatment is required during pregnancy

Breast Feeding
- Some drug is found in mother’s breast milk
- Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for relapse of psychosis

Potential Advantages
- For negative symptoms in some patients

Potential Disadvantages
- Patients who cannot tolerate sedation at high doses
- Patients with severe renal impairment

Primary Target Symptoms
- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive functioning
- Depressive symptoms
- Aggressive symptoms

Pearls
- There is some controversy over whether sulpiride is more effective than older conventional at treating negative symptoms
- Sulpiride has been used to treat migraine associated with hormonal changes
- Some patients with inadequate response to clozapine may benefit from augmentation with sulpiride
- Sulpiride is poorly absorbed from the gastrointestinal tract and penetrates the blood-brain barrier poorly, which can lead to highly variable clinical responses, especially at lower doses
- Small studies and clinical anecdotes suggest efficacy in depression and anxiety disorders (“neuroses”) 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 a trial of augmentation with a conventional antipsychotic such as sulpiride or from switching to a conventional antipsychotic such as sulpiride
- 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
Suggested Reading


• 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 2 conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy.