**ILOPERIDONE**

**THERAPEUTICS**

**Brands** • FANAPT
*see index for additional brand names*

**Generic?** No

**Class**
- Neuroscience-based Nomenclature: dopamine and serotonin receptor antagonist (DS-RAn)
- Atypical antipsychotic (serotonin-dopamine antagonist; second-generation antipsychotic; also a mood stabilizer)

**Commonly Prescribed for**
(bold for FDA approved)
- Schizophrenia
- Schizophrenia maintenance
- Acute mania/mixed mania
- Other psychotic disorders
- Bipolar maintenance
- Bipolar depression
- Treatment-resistant depression
- Behavioral disturbances in dementia
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control

**How the Drug Works**
- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms
- Blockade of central alpha 1 adrenergic receptors may contribute to low potential for EPS

**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
- Slow titration may delay antipsychotic effects during the first 1 to 2 weeks compared to some other antipsychotic drugs that do not require similar titration

**If It Works**
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients may require up to 16–20 weeks to show a good response, especially on cognitive symptoms
- Most often reduces positive symptoms but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenia 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

**If It Doesn’t Work**
- Try one of the other atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone, amisulpride)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no first-line 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 (a depot formulation of iloperidone is in clinical testing)
• 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)
- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

**Tests**

**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 waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the 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% of 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
- 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 iloperidone should be discontinued at the first sign of decline in WBC in the absence of other causative factors
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

**SIDE EFFECTS**

**How Drug Causes Side Effects**

- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- 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
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

**Notable Side Effects**

- Orthostatic hypotension
- Sedation, dose-dependent dizziness, fatigue
- Dry mouth, nasal congestion
- Dose-dependent weight gain
- May increase risk for diabetes and dyslipidemia
- Dose-dependent tachycardia
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)
Life-Threatening or Dangerous Side Effects
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures

Weight Gain
- Many experience and/or can be significant in amount
- May be less than for some antipsychotics, more than for others

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

What to Do About Side Effects
- Anticholinergics may reduce motor side effects when present
- 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

Dosage Forms
- Tablet 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

How to Dose
- Initial 2 mg in 2 divided doses on day 1; 4 mg in 2 divided doses on day 2; 8 mg in 2 divided doses on day 3; 12 mg in 2 divided doses on day 4; 16 mg in 2 divided doses on day 5; 20 mg in 2 divided doses on day 6; 24 mg in 2 divided doses on day 7
- Maximum dose studied is 32 mg/day

Dosing Tips
- May titrate even slower in patients who develop side effects, especially orthostasis, or when adding or switching from another drug with alpha 1 antagonist properties
- Patients most vulnerable to side effects during titration would be those sensitive to orthostasis (e.g., the young, the elderly, those with cardiovascular problems, those taking concomitant vasoactive drugs)
- Slow dosing could lead to delayed onset of antipsychotic effects
- Once daily use seems theoretically possible because the half-life of iloperidone is 18–33 hours
- Some patients may respond to doses greater than 24 mg/day if tolerated
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³
- If treatment is discontinued for more than 3 days, it may need to be restarted following the initial titration schedule in order to maximize tolerability
- Iloperidone should be discontinued in patients with persistent QTc measurements of more than 500 msec

Overdose
- Sedation, tachycardia, hypotension

Long-Term Use
- Not studied, but long-term maintenance treatment is often necessary for schizophrenia

Habit Forming
- No

DOSING AND USE

Usual Dosage Range
- 12–24 mg/day in 2 divided doses
ILOPERIDONE (continued)

How to Stop
- Down-titration, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms

Pharmacokinetics
- Half-life 18–33 hours
- Metabolized by CYP450 2D6 and 3A4
- Food does not affect absorption

Drug Interactions
- May increase effects of antihypertensive agents
- May antagonize levodopa, dopamine agonists
- May enhance QTc prolongation of other drugs capable of prolonging QTc interval
- Inhibitors of CYP450 2D6 (e.g., paroxetine, fluoxetine, duloxetine, quinidine) may increase plasma levels of iloperidone and require a dosage reduction by one-half of iloperidone
- Inhibitors of CYP450 3A4 (e.g., nefazodone, fluvoxamine, fluoxetine, ketoconazole) may increase plasma levels of iloperidone and require a dosage reduction by one-half of iloperidone

Other Warnings/Precautions
- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Dysphagia has been associated with antipsychotic use, and iloperidone should be used cautiously in patients at risk for aspiration pneumonia
- Iloperidone prolongs QTc interval more than some other antipsychotics, an effect that is augmented by concomitant use of drugs that inhibit iloperidone metabolism
- Priapism has been reported with iloperidone

Do Not Use
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)

If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If there is a proven allergy to iloperidone

SPECIAL POPULATIONS

Renal Impairment
- Dose adjustment not generally necessary

Hepatic Impairment
- Not recommended for patients with hepatic impairment

Cardiac Impairment
- Drug should be used with caution because of risk of orthostatic hypotension
- Not recommended for patients with significant cardiovascular illness

Elderly
- Some patients may tolerate lower doses better
- 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
- Safety and efficacy have not been established
- Children and adolescents using iloperidone may need to be monitored more often than adults

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 (PLL 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
• 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
• Iloperidone may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
• National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/

Breast Feeding
• Unknown if iloperidone is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk

✽ Recommended either to discontinue drug or bottle feed
• Infants of women who choose to breast feed while on iloperidone should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• Some cases of psychosis and bipolar disorder refractory to treatment with other antipsychotics
• Patients wishing to avoid EPS

Potential Disadvantages
• Patients requiring rapid onset of antipsychotic action without dosage titration
• Patients noncompliant with twice daily dosing
• Cognitive symptoms

• Unstable mood (both depression and mania)
• Aggressive symptoms

Primary Target Symptoms
• Positive symptoms of psychosis
• Negative symptoms of psychosis

Pearls
• Not approved for mania, but all atypical antipsychotics approved for acute treatment of schizophrenia have proven effective in the acute treatment of mania as well
• Seems to have placebo-level EPS, including little or no akathisia
• Potent alpha 1 blocking properties suggest potential utility in PTSD (e.g., nightmares, as for prazosin)
• Binding properties suggest theoretical efficacy in depression, but studies and clinical experience are required to confirm this
• QTc warning similar to that for ziprasidone, where this has not materialized into a significant clinical problem
• A 4-week depot preparation is in clinical testing
• Early studies indicate iloperidone’s efficacy may be linked to pharmacogenomic markers such as ciliary neurotrophic factor (CNTF), and others
• 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
• 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
Switching from Oral Antipsychotics to Iloperidone

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible.
- Clinical experience has shown that quetiapine, olanzapine, and asenapine 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.

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Suggested Reading


