**How the Drug Works**

- **Partial agonism at dopamine 2 receptors**
- Theoretically reduces dopamine output when dopamine concentrations are high, thus improving positive symptoms and mediating antipsychotic actions
- Theoretically increases dopamine output when dopamine concentrations are low, thus improving cognitive, negative, and mood symptoms
- Partial agonist at 5HT1A receptors, which may be beneficial for mood, anxiety, and cognition in a number of disorders
- Blockade of serotonin type 2A receptors may contribute at clinical doses to cause enhancement of dopamine release in certain brain regions, thus reducing motor side effects and possibly improving cognitive and affective symptoms
- Blockade of alpha 1B receptors may reduce motor side effects such as akathisia
- Blockade of alpha 2C receptors may contribute to antidepressant actions
- Actions at dopamine 3 receptors could theoretically contribute to brexpiprazole’s efficacy
- Blocks serotonin 7 receptors, which may be beneficial for mood, cognitive impairment, and negative symptoms in schizophrenia, and also in bipolar disorder and major depressive disorder

**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
- For psychosis, 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 impairment and functional outcome
- For depression, onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks

**If It Works (for Schizophrenia)**

- 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 Works (for Depression)
• 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 stopped
• Continue treatment until all symptoms are gone (remission) or significantly reduced
• Once symptoms are 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 (for Schizophrenia)
• Try one of the other atypical antipsychotics do not work, consider clozapine
• 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
• Consider initiating rehabilitation and psychotherapy
• Consider presence of concomitant drug abuse

Best Augmenting Combos for Partial Response or Treatment Resistance
• For depression, brexpiprazole is itself an augmenting agent
• Valproic acid (valproate, divalproex, divalproex ER)
• Mood stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
• Lithium
• Benzodiazepines

Tests
Before starting any 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 mmHg)
  • 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 any 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

If It Doesn’t Work (for Depression)
• Some patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
• Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
• 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
• 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 leukopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and brexpiprazole should be discontinued at the first sign of decline in WBC in the absence of other causative factors.

**SIDE EFFECTS**

**How Drug Causes Side Effects**

• By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension.

• Partial agonist actions at dopamine 2 receptors in the striatum can cause motor side effects, such as akathisia.

• Partial agonist actions at dopamine 2 receptors and 5HT1A receptors can also cause nausea, occasional vomiting, and activating side effects.

• Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown.

**Notable Side Effects**

• Weight gain
• Akathisia (dose dependent), restlessness (dose dependent), anxiety
• Sedation, headache
• Theoretical risk of tardive dyskinesia

**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**

• Occurs in a significant minority.

**Sedation**

• Occurs in a significant minority.

**What to Do About Side Effects**

• Wait
• Wait
• Wait
• 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.

• Beta blockers or sometimes benzodiazepines for akathisia.

• Many side effects cannot be improved with an augmenting agent.

**DOSING AND USE**

**Usual Dosage Range**

• Schizophrenia: 2–4 mg once daily.

• Depression: 2 mg once daily.

**Dosage Forms**

• Tablet 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg.

**How to Dose**

• Schizophrenia: Initial 1 mg once daily for days 1–4; increase to 2 mg once daily for...
days 5–7; increase to 4 mg once daily on day 8; maximum dose 4 mg once daily
• Depression: Initial 0.5–1 mg once daily; increase in weekly intervals up to 1 mg once daily and then up to 2 mg once daily; maximum dose 3 mg once daily

Dosing Tips
• Can be taken with or without food

Overdose
• Limited experience

Long-Term Use
• Safety and efficacy demonstrated in schizophrenia in a maintenance study lasting over 1 year
• Should periodically reevaluate long-term usefulness in individual patients, but treatment may need to continue for many years in patients with schizophrenia or treatment-resistant depression

Habit Forming
• No

How to Stop
• Because clinical experience is lacking, down-titration may be prudent, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
• However, the long half-life suggests that it may be possible to stop brexpiprazole abruptly
• The method for stopping brexpiprazole can vary depending on which agent is being switched to; see switching guidelines of individual agents for how to stop brexpiprazole
• Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms, but less likely with brexpiprazole due to its long half-life

Pharmacokinetics
• Mean half-life 91 hours (brexpiprazole) and 86 hours (major metabolite DM-3411)
• Metabolized primarily by CYP450 2D6 and CYP450 3A4

Drug Interactions
• In patients receiving a strong/moderate CYP450 3A4 inhibitor (e.g., ketoconazole), brexpiprazole should be administered at half the usual dose
• In patients receiving a strong CYP450 3A4 inducer (e.g., carbamazepine), brexpiprazole should be administered at double the usual dose
• In patients with schizophrenia who are receiving a strong/moderate CYP450 2D6 inhibitor (e.g., quinidine) or who are known CYP450 2D6 poor metabolizers, brexpiprazole should be administered at half the usual dose
• However, clinical trials in major depressive disorder took into account the potential concomitant administration of strong CYP450 2D6 inhibitors (e.g., paroxetine, fluoxetine), so the dose of brexpiprazole does not need to be adjusted in these cases
• In patients receiving both a strong/moderate CYP3A4 inhibitor and a strong/moderate CYP450 2D6 inhibitor, brexpiprazole should be administered at one quarter the usual dose
• In patients receiving a strong/moderate CYP3A4 inhibitor who are known CYP450 2D6 poor metabolizers, brexpiprazole should be administered at one quarter the usual dose
• May increase effects of antihypertensive agents
• May antagonize levodopa, dopamine agonists

Other Warnings/Precautions
• Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
• Dysphagia has been associated with antipsychotic use, and brexpiprazole should be used cautiously in patients at risk for aspiration pneumonia

Do Not Use
• If there is a proven allergy to brexpiprazole
In animal studies, brexpiprazole did not demonstrate teratogenicity. 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. Brexpiprazole 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 brexpiprazole is secreted in human breast milk, but all psychotropics are assumed to be secreted in breast milk. Recommended either to discontinue drug or bottle feed unless the potential benefit to the mother justifies the potential risk to the child. Infants of women who choose to breast feed while on brexpiprazole should be monitored for possible adverse effects.

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

For patients who do not tolerate aripiprazole

Potential Disadvantages

Expensive

Primary Target Symptoms

Positive symptoms of psychosis
Negative symptoms of psychosis
Cognitive symptoms
Unstable mood and depression
Aggressive symptoms

Pearls

Approved as an adjunct treatment for depression
• Animal data suggest that brexpiprazole may improve cognitive impairment in schizophrenia
• Brexpiprazole is also being studied in clinical trials in attention deficit hyperactivity disorder, post-traumatic stress disorder, and agitation associated with Alzheimer dementia
• Not approved for mania, but almost all atypical antipsychotics approved for acute treatment of schizophrenia have proven effective in the acute treatment of mania as well
• Pharmacological differences from aripiprazole suggest less akathisia with brexpiprazole, but no head-to-head trials
• Compared to aripiprazole, brexpiprazole has more potent binding of several receptor sites relative to dopamine 2 receptor binding, namely 5HT1A, 5HT2A, and alpha 1 receptors; however, the clinical significance of these differences is still under investigation

THE ART OF SWITCHING

Switching from Oral Antipsychotics to Brexpiprazole

• It is advisable to begin brexpiprazole 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

