Psychiatric Medications: What you need to know

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Disclosures

- Lindsay McCoy has nothing to disclose.
Objectives

- Discuss the prescribing considerations with recently approved drug therapies in the treatment of mood disorders.
- Recognize and manage potential drug-drug and drug-disease interactions.
Atypical Antipsychotics

Aripiprazole
Brexpiprazole
Cariprazine
Lurasidone
Comparing binding profiles


<table>
<thead>
<tr>
<th>Receptor</th>
<th>Aripiprazole</th>
<th>Brexpiprazole</th>
<th>Cariprazine</th>
<th>Therapeutic effects</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>D&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.34</td>
<td>0.30</td>
<td>0.49</td>
<td>Antipsychotic</td>
<td>EPS, tardive dyskinesia, akathisia, NMS hyperprolactinemia</td>
</tr>
<tr>
<td>D&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.8</td>
<td>1.1</td>
<td>0.085</td>
<td>Antipsychotic (including negative symptoms), antimanic, antidepressant</td>
<td></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>1.7</td>
<td>0.12</td>
<td>2.6</td>
<td>Antidepressant, anxiolytic</td>
<td></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>3.4</td>
<td>0.47</td>
<td>18.8</td>
<td>Anti-EPS</td>
<td></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt;</td>
<td>15</td>
<td>34</td>
<td>134</td>
<td>Antidepressant</td>
<td></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;7&lt;/sub&gt;</td>
<td>29</td>
<td>3.7</td>
<td>111</td>
<td>Antidepressant</td>
<td></td>
</tr>
<tr>
<td>H&lt;sub&gt;1&lt;/sub&gt;</td>
<td>61</td>
<td>19</td>
<td>23.2</td>
<td>Anxiolytic, anti-insomnia</td>
<td>Weight gain sedation</td>
</tr>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt;</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>Opposes EPS</td>
<td></td>
</tr>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;</td>
<td>57</td>
<td>3.8</td>
<td>155</td>
<td>Antihypertensive</td>
<td></td>
</tr>
</tbody>
</table>

Comparing the three partial D<sub>2</sub> agonists:
(1) Aripiprazole has the greatest affinity for 5-HT<sub>2C</sub>R; it has the weakest affinity for H<sub>1</sub>R. Theoretically, this suggests it may be less associated with metabolic symptoms and perhaps elevate monoamines for better antidepressant effects, therapeutically speaking. It may be the least sedating.
(2) Brexpiprazole shows the greatest affinity for D<sub>3</sub>R, 5-HT<sub>1A</sub>R, 5-HT<sub>2A</sub>R, 5-HT<sub>7</sub>R, H<sub>1</sub>R, and α<sub>1</sub>R; it has the weakest affinity for D<sub>2</sub>R. This suggests the possibility that it can both inhibit and enhance dopamine activity to a higher degree, treating either psychosis or depression. The serotonin modulation is highly suggestive of antidepressant activity.
(3) Cariprazine shows the greatest affinity for D<sub>3</sub>R; it is the weakest in affinity for D<sub>2</sub>R, 5-HT<sub>1A</sub>R, 5-HT<sub>2A</sub>R, 5-HT<sub>7</sub>R, and α<sub>1</sub>R. This may promote a fair amount of dopamine activity and act as an antidepressant. The serotonin modulation is highly suggestive of antidepressant activity. EPS, extrapyramidal symptoms; NMS, neuroleptic malignant syndrome.
Aripiprazole

- Indications/dosing (adult):
  - Schizophrenia – 10-15 mg/day (max 30mg)
  - Bipolar mania – monotherapy – 15 mg/day (max 30mg)
  - Bipolar mania – adjunct to lithium or valproate – 15 mg/day (max 30mg)
  - Major depressive disorder – adjunct to antidepressant – 5-10 mg/day (max 15mg)

- Common side effects: akathisia, tremor, extrapyramidal symptoms, somnolence, insomnia

- Mechanism of action: D2 and 5-HT$_{1A}$ partial agonist; 5-HT$_{2A}$ antagonist

Abilify(R) [package insert]. Rockville, MD: Otsuka America Pharmaceutical; 2014
<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP450 2D6 and 3A4 inhibitors</td>
<td>Reduce usual dose by half</td>
</tr>
<tr>
<td>Strong CYP450 3A4 inducers</td>
<td>Double usual dose over 1-2 weeks</td>
</tr>
<tr>
<td>Known 2D6 poor metabolizers</td>
<td>Reduce usual dose by half</td>
</tr>
<tr>
<td>Antihypertensive medications</td>
<td>Monitor BP closely; adjust if necessary</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Monitor sedation, BP; adjust if necessary</td>
</tr>
<tr>
<td>Known 2D6 poor metabolizer AND 3A4 inhibitor</td>
<td>Reduce usual dose to ¼</td>
</tr>
<tr>
<td>Strong 3A4 inhibitor with 2D6 inhibitor</td>
<td>Reduce usual dose to ¼</td>
</tr>
</tbody>
</table>
Brexpiprazole

- Indications/dosing (adult):
  - Adjunct to antidepressant in MDD: 2 mg/day (max 3 mg)
  - Schizophrenia: 2-4 mg/day (max 4mg)

- Mechanism of action: D2 and 5-HT$_{1A}$ partial agonist; 5-HT$_{2A}$ antagonist

- Most common side effects: akathisia, increased weight

- Drug interactions:
  - CYP$_{450}$ 2D6 and 3A4 inhibitors/inducers
  - CYP$_{450}$ 2D6 poor metabolizers
**Brexpiprazole**

**[Drug Interactions]**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Dosage Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP450 2D6 OR 3A4 inhibitors</td>
<td>Reduce usual dose by half</td>
</tr>
<tr>
<td>Strong CYP450 3A4 inducers</td>
<td>Double usual dose and adjust based on response</td>
</tr>
<tr>
<td>Known 2D6 poor metabolizer AND strong/moderate 3A4 inhibitor</td>
<td>Reduce usual dose to ¼</td>
</tr>
<tr>
<td>Strong/moderate 3A4 AND strong/moderate 2D6 inhibitor</td>
<td>Reduce usual dose to ¼</td>
</tr>
</tbody>
</table>
Cariprazine

- Indications:
  - Schizophrenia – 1.5 - 6 mg/day (max 6 mg/day)
  - Acute manic or mixed episodes associated with bipolar I disorder – 3 – 6 mg/day (max 6 mg/day)

- Common side effects: extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, restlessness

- Mechanism of action: D2 and 5-HT$_{1A}$ partial agonist; 5-HT$_{2A}$ antagonist

- Drug interactions: CYP450 3A4 inhibitors/inducers
Cariprazine

- Positive outcomes vs placebo for
  - Schizophrenia
  - Bipolar (mania and depression)
  - Major Depressive Disorder

- High rates of akathisia (2.8% to 22.3%)
- Low rates of metabolic disturbances

Lurasidone

- Indications:
  - Schizophrenia – 40 – 160 mg/day
  - Depressive episode associated with Bipolar I Disorder (bipolar depression), monotherapy or adjunctive therapy with lithium or valproate – 20 – 120 mg/day
- Common side effects: Somnolence, akathisia, extrapyramidal symptoms
- Mechanism of Action: D2 and 5-HT$_{2A}$ antagonist

Lurasidone
[Drug Interactions]

- Avoid use with strong CYP450 3A4 inhibitors and inducers
- Reduce dose by half with moderate CYP450 3A4 inhibitors and inducers
Atypical Antipsychotics
[Metabolic Adverse Effects]

Table 5. Summary of potential for metabolic adverse effects with atypical antipsychotics.\textsuperscript{2-33}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight gain</th>
<th>Acute Hyperglycemia/ Diabetes</th>
<th>Worsening lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (Clozaril\textsuperscript{®})</td>
<td>High</td>
<td>High*</td>
<td>High</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa\textsuperscript{®})</td>
<td>High</td>
<td>High*</td>
<td>High</td>
</tr>
<tr>
<td>Quetiapine (Seroquel\textsuperscript{®})</td>
<td>Moderate</td>
<td>Moderate*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Risperidone (Risperdal\textsuperscript{®})</td>
<td>Moderate</td>
<td>Low to moderate*</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Iloperidone (Fanapt\textsuperscript{®})</td>
<td>Moderate</td>
<td>Low/NR</td>
<td>Low/NR</td>
</tr>
<tr>
<td>Asenapine (Saphris\textsuperscript{®})</td>
<td>Low</td>
<td>Low/NR</td>
<td>Low/NR</td>
</tr>
<tr>
<td>Paliperidone (Invega\textsuperscript{®})</td>
<td>Low</td>
<td>Low/NR</td>
<td>Low/NR</td>
</tr>
<tr>
<td>Lurasidone (Latuda\textsuperscript{®})</td>
<td>Low</td>
<td>Low/NR</td>
<td>Low/NR</td>
</tr>
<tr>
<td>Aripiprazole (Abilify\textsuperscript{®})</td>
<td>Low</td>
<td>Low*</td>
<td>Low</td>
</tr>
<tr>
<td>Ziprasidone (Geodon\textsuperscript{®})</td>
<td>Low</td>
<td>Low*</td>
<td>Low</td>
</tr>
<tr>
<td>Cariprazine (Vraylar\textsuperscript{®})</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

NR = not reported

*Agents with existing case reports of acute hyperglycemia

https://doi.org/10.9740/mhc.n366834
Vraylar\textsuperscript{®} [package insert]. Madison, NJ: Allergan; 2018
Antidepressants

Vortioxetine
Vilazodone
Vortioxetine

- Indicated for the treatment of major depressive disorder
- Mechanism of action........

Vortioxetine (Mechanism of action)

The clinical relevance of the pharmacologic activity is unknown.

https://www.trintellixhcp.com/clinical-pharmacology
**Vortioxetine [Key Points]**

- **Dose:** 5 to 20 mg daily
- **Side effects:** 
  - Nausea, headache, diarrhea, dry mouth
- **Major drug interactions:**
  - Strong CYP450 2D6 inhibitors
    - Bupropion
    - Fluoxetine
    - Paroxetine
    - Reduce dose by half
  - CYP Inducers: consider dose increase, max 3 times original dose
- **Poor 2D6 metabolizers:** max 10mg/day
• Indicated in the treatment of major depressive disorder

• Mechanism of action:
  • Selective inhibition of serotonin reuptake
  • 5-HT$_{1A}$ partial agonist
Vilazodone
[Key Points]

- **Recommended dose:** 40mg daily
  - Initial titration: 10mg x 7 days, then 20mg x 7 days, then 40mg daily
  - Take with food

- **Side effects:** Diarrhea, nausea, dry mouth, vomiting

- **Drug interactions:**
  - CYP450 3A4 inhibitors: reduce dose to max 20mg daily
  - CYP450 inducers: not studied for package insert
    - May be prudent to increase dose to 80 mg daily

Comparative Efficacy of 21 Anti-depressants

Cipriani et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet 2018;391(10128):1357-1366. DOI: https://doi.org/10.1016/S0140-6736(17)32802-7
Comparative Acceptability of 21 Anti-depressants

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| Agomelatine | Amitriptyline | Amoxapine | Bupropion | Citalopram | Clomipramine | Duloxetine | Escitalopram | Fluoxetine | Fluvoxamine | Mirtazapine | Nefazodone | Paroxetine | Reboxetine | Sertraline | Sertindole | Trazodone | Venlafaxine | Vortioxetine |
|-------------|---------------|-----------|-----------|------------|--------------|------------|-------------|------------|-------------|-------------|------------|-------------|------------|------------|----------|----------|----------|-----------|------------|
| 0.72 (0.55–0.92) | 0.80 (0.64–1.08) | 0.89 (0.68–1.17) | 0.52 (0.42–0.67) | 0.62 (0.50–0.78) | 0.97 (0.74–1.27) | 0.85 (0.68–1.05) | 0.69 (0.51–0.97) | 0.81 (0.69–0.94) | 0.80 (0.68–0.93) | 0.71 (0.60–0.85) | 0.98 (0.91–1.06) | 1.02 (0.94–1.11) | 0.74 (0.62–0.90) | 0.97 (0.89–1.07) | 0.76 (0.65–0.88) | 0.74 (0.61–0.89) | 1.04 (0.86–1.26) | 0.67 (0.57–0.79) |
| 1.21 (0.97–1.51) | 1.71 (1.57–1.85) | 0.82 (0.76–0.89) | 1.49 (1.43–1.56) | 1.27 (1.21–1.33) | 1.41 (1.34–1.49) | 0.89 (0.84–0.94) | 0.89 (0.84–0.94) | 0.80 (0.75–0.84) | 0.82 (0.77–0.87) | 0.93 (0.88–0.98) | 0.80 (0.75–0.84) | 0.90 (0.85–0.96) | 0.82 (0.75–0.89) | 0.80 (0.75–0.84) | 0.82 (0.77–0.87) | 0.82 (0.77–0.87) | 0.80 (0.75–0.84) | 0.82 (0.77–0.87) |

"Drugs are reported in alphabetical order. Data are ORs (95% CrI) in the column-defining treatment compared with the row-defining treatment. For efficacy, ORs higher than 1 favour the column-defining treatment (ie, the first in alphabetical order). For acceptability, ORs lower than 1 favour the first drug in alphabetical order. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored."
A 37 yo F with Major Depressive Disorder is currently stabilized on sertraline 100mg daily and aripiprazole 10mg daily. She begins to complain about sexual side effects and would like to switch to bupropion. Which of the following is correct:

- A. Discontinue sertraline and start bupropion at the patient’s request.
- B. Discontinue both sertraline and aripiprazole to start bupropion.
- C. Cross titrate sertraline and bupropion to reduce side effects; make no changes to aripiprazole
- D. Cross titrate sertraline and bupropion to reduce side effects and reduce the dose of her aripiprazole by half
One potential benefit of D2 partial agonists (such as aripiprazole, brexpiprazole, and cariprazine) over other atypical antipsychotics is:

- A. Reduced drug interactions
- B. Reduced risk of akathisia
- C. Reduced risk of metabolic side effects
- D. Increased efficacy
A 32 yo M with history of irritable bowel syndrome presents with a new diagnosis of depression. Which of the following would be the least appropriate initial treatment option?

- A. Citalopram 20 mg daily
- B. Bupropion SR 100 mg daily
- C. Vilazodone 20 mg daily
- D. Escitalopram 10 mg daily