Pharmacy Grand Rounds
Review of Lurasidone, Cariprazine, and Brexpiprazole
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Objectives

For each of the three antipsychotics:
• List FDA approved indications
• Describe pharmacology
• Describe efficacy compared to existing antipsychotics
• List anticipated side effects
• List drug interactions
Abbreviations

- NNT = number needed to treat
- NNH = number needed to harm
- ARR = absolute risk reduction
- SMD = standardized mean difference
- DA = dopamine
- 5-HT = serotonin
- SGA = second generation antipsychotic

Introduction: Necessary background information

- Why these 3 antipsychotics?
- Number needed to treat/harm (NNT/NNH)
- Standardized mean difference (SMD)
- Concerns with current antipsychotics
- Receptor pharmacology
Why these antipsychotics?

Why, why, why?!

- Relatively new
- *May* have legitimate advantages
- Heavily promoted
- Need to be prepared to answer questions from patients
NNT/NNH

Number Needed to Treat/Harm (NNT/NNH)

• Def: the number of people you would have to treat with the intervention of interest over a specified time period to have one more success (or failure) compared to the comparison group treatment

• Calculation:
  • NNT = 1/ARR
  Where ARR = proportion in experimental group – proportion in control group
Example: NNT

Results of a study show:
• Response in experimental group = 65%
• Response in control group = 45%

• ARR = 0.65 – 0.45 = 0.2
• NNT = 1/ARR = 1/0.2 = 5

• Interpretation: you would need to treat 5 patients with the experimental treatment to see one more response compared to the control group

NNT/NNH: Characteristics

• Can only be calculated for dichotomous/binary data (lived/died, side effect? yes/no, etc)
• <10 is probably clinically meaningful NNT
• Smaller is desirable for NNT (< 10)
• Larger is desirable for NNH (preferably in the 100’s for serious side effects)
Standardized Mean Difference

SMD

• AKA Cohen’s d, Hedge’s g, Glass’s delta
• An effect size measure for *continuous* data (e.g. change in rating scale score from baseline)
Cohen’s d or Hedge’s g: Interpretation

• Most common reporting:

<table>
<thead>
<tr>
<th>Cohen’s d Value</th>
<th>Magnitude of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No effect</td>
</tr>
<tr>
<td>0.2</td>
<td>Small</td>
</tr>
<tr>
<td>0.5</td>
<td>Medium</td>
</tr>
<tr>
<td>0.8</td>
<td>Large</td>
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SMD

• SMD gives us a common unit by which to compare results from different studies
• It is often used as the measure of effect size in sample size calculations
• SMD is recommended by the Cochrane Collaboration for meta-analyses
Problems with current Antipsychotics

• Extrapyramidal side effects (EPSE)
• Metabolic syndrome
• Prolactin elevation (prl)
• QTc prolongation

EPSE

• Akathisia
• Drug-induced Parkinson’s Disease
• Dystonia
• Tardive dyskinesia
Metabolic syndrome

• Weight gain
• Worsening or new onset diabetes
• Lipid abnormalities

Prolactin (PRL) elevation

• DA suppresses secretion of prl
• DA antagonists result in increased secretion of prl
• Increased prl results in:
  • Sexual side effects
  • Reduced bone mineral density
  • Gynecomastia
  • Menstrual irregularities
  • Lactation
QTc Prolongation

• Increase in duration of the QT interval corrected for heart rate
• Predisposes to potentially fatal arrhythmias (e.g. torsades de pointe)

Summary: Problems

• Current antipsychotics have significant problems
• We need more effective drugs that are better tolerated with fewer side effects to treat psychoses
Symptoms of Schizophrenia

• Positive: delusions, hallucinations, et al
• Negative: withdrawal, amotivation, et al
• Cognitive: impaired executive function – planning, problem solving, etc

Cognition:
Receptor Pharmacology

Current SGA pharmacology

• Most are serotonin-dopamine antagonists (SDA)
  • D2 antagonists
  • 5-HT2A antagonists
• Aripiprazole = D2 partial agonist
D2 receptor blockade

- Beneficial effects on positive symptoms (delusions, hallucinations, etc)
- May worsen negative symptoms (withdrawal, amotivation, etc)
- Causes EPSE
- Results in prl elevation
- May impair cognition

5-HT2A receptor blockade

- Increases DA release in prefrontal cortex and nigrostriatal DA tracts theoretically improving negative symptoms and EPSE, respectively
Cognitive-enhancing receptor actions

(all theoretical)
• D3 antagonism
• 5-HT1A partial agonism
• 5-HT7 antagonism
• Reduced H1 binding
• Reduced M1 binding

FINALLY! Let’s talk about drugs...
New Antipsychotics

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Lurasidone</th>
<th>Cariprazine</th>
<th>Brexpiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td>Antag</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>5-HT2A</td>
<td>Antag</td>
<td>Wk antag</td>
<td>Antag</td>
</tr>
<tr>
<td>D3</td>
<td>PA</td>
<td>PA</td>
<td></td>
</tr>
<tr>
<td>5-HT7</td>
<td>Antag</td>
<td></td>
<td>Antag</td>
</tr>
<tr>
<td>H1</td>
<td></td>
<td>Weak antag</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Antag = antagonist
PA = partial agonist

Cognitive-enhancement issues

• Existing drugs have same receptor effects
• Relationship w/ D2 block and other receptors is same for old and new drugs
• Conflicting data from animal studies
• Partial agonists can act in either direction depending on endogenous neurotransmitter concentration
• Reducing H1 and M1 binding alone may improve cognition
“Although it is fair to say that the latter 5-HT mechanisms cannot be ruled out [5-HT1A & 5-HT7], the complete lack of anticholinergic and antihistaminergic properties provides a potentially much more parsimonious explanation for a relatively more cognition sparing effect of these drugs when compared to existing antipsychotics.”

Source: Wallace et al. 2011

Commenting on the possible difference in “cognition enhancement” between lurasidone and other antipsychotics

### FDA approved indications

<table>
<thead>
<tr>
<th></th>
<th>SCZ</th>
<th>BD-Depn</th>
<th>BD-Mania</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Scz = schizophrenia
BD-Depn = bipolar depression
BD-Mania = bipolar mania
MDD = major depressive disorder
Drug Reviews
*Lurasidone (Latuda®)*

Lurasidone: Pharmacology

- SDA
- Plus 5-HT7 antagonist
- Lacks effects at H1 and M1 receptors
Lurasidone: Dosing

• Scz:
  • Start 40 mg/day
  • Max: 160 mg/day
• Bipolar depression:
  • Start 20 mg/day
  • Max: 120 mg/day
• Adjust dose with renal or hepatic impairment

PK Highlights: Lurasidone

• Give with at least 350 calories of food
• CYP3A4 substrate
• AVOID coadministration with strong CYP3A4 inducers/inhibitors
Comparative Efficacy

*Lurasidone*

Antipsychotic Efficacy: Schizophrenia

*SMD and 95% CI*

Overall Change in PANSS Total (SMD)

Modified from Leucht 2013
Lurasidone – Cognition

• Studies with active comparators quetiapine and ziprasidone showed equal effect on total cognitive measures with lurasidone and the comparators
Side Effects

*Lurasidone*
Lurasidone Side Effects

• May be less well-tolerated than other antipsychotics
• GI: 20 – 25%; NNH = 13.5
• Akathisia: 10 – 15%; NNH = 16.5 (and worse than Ari.)
• Sedation: ≈ 10%; NNH 15 – 18
• Modest effects on prolactin
• Little → no:
  • Insomnia, metabolic effects, QTc effect, anticholinergic effects

Lurasidone: Summary

• Good:
  • Metabolic profile
  • QTc, antihistaminic, anticholinergic effects
• Dosing issues: Food, CYP3A4, renal, hepatic issues
• Tolerability questions (akathisia, GI, prolactin)
• Questions how well it works for schizophrenia
• About as effective as alternatives for bipolar depression
• Cognitive benefits remain to be clarified
• Very expensive compared to generic antipsychotics
Drug Reviews

Cariprazine (Vraylar®)

Cariprazine: Pharmacology

• D3 > D2 partial agonist
• Weak H1 and basically no M1 binding
• 5-HT1A partial agonist – cognitive benefits?
Cariprazine: Dosing

• Schizophrenia AND Bipolar mania
  • Start: 1.5 mg/day
  • Max = 6 mg/day

• Target dose ranges:
  • Scz: 1.5 – 6 mg/day
  • Mania: 3 – 6 mg/day

• Reduce dose with CYP3A4 inhibitors (next slide)

• No major concerns with food
PK Highlights: Cariprazine

• Metabolized primarily by CYP3A4
• Give half the dose in presence of strong CYP3A4 inhibitors
• T-1/2 parent = 2 – 5 days
• T-1/2 metabolite = 1 – 3 WEEKS!

Comparative Efficacy

Cariprazine
Tamoxifen is off

The chart ➔
Cariprazine: Cognition

- Inadequately studied
- Claims for improved cognitive outcomes are theoretical
- Insufficient data to draw conclusion
- In one study cognitive effects were equal between cariprazine and risperidone

Side Effects

Cariprazine
Cariprazine Side Effects

• Patients with bipolar mania may be at greater risk for side effects, especially akathisia
• Akathisia: probably dose-dependent, 10 – 30%; median NNH = 8 (all doses, all conditions)
• Other EPSE: carip < risp; NNH = 19
• GI (N, V, D, dyspepsia): median NNH = 8
• Little effect on weight or prolactin

Cariprazine: Summary

• Questions about effect in schizophrenia
• Concerns about akathisia & GI side effects
• Claims of less EPSE appear unfounded
• Claims of improved cognition currently unsupported
• Desirable profile for weight, prolactin, and QTc
Drug Reviews

Brexpiprazole (Rexulti®)

Brexpiprazole: Pharmacology

• D2 partial agonist like aripiprazole but with less intrinsic agonist activity
  • Less akathisia, insomnia, nausea
• D2 antag effects < “pure” SDA = less EPSE, prl effect
• 5-HT2A antagonist = improved neg sxs; less EPSE
• 5-HT1A partial agonist – cognitive benefits?
• These actions should put BRX between aripiprazole and SDA antipsychotics in efficacy and adverse effects
Brexpiprazole: Dosing

• Requires titration
• Schizophrenia
  • Initial 1 mg/day; increase slowly to target of 2 – 4 mg/day; Max = 4 mg/day
• MDD
  • Initial 0.5 – 1 mg/day; Max 3 mg/day

Brexpiprazole: Dosage adjustments

• Liver impairment
• Renal impairment
• When used in presence of strong inducers or inhibitors of CYP3A4 or CYP2D6
PK Highlights: Brexpiprazole

• No effect from food
• Metabolized by CYP3A4 and CYP2D6

Comparative Efficacy

*Brexiprazole (Rexulti®)*
Brexpiprazole: Efficacy – Schizophrenia

- 1 failed trial with aripiprazole
- 1 trial w/ quetiapine, quetiapine > plac, not brexpiprazole
- 1 trial: 1 and 2 mg/day didn’t separate from placebo; 4 mg/day did
- 1 trial both 2 and 4 mg/day separated from placebo

Modified from Leucht 2013
Brexpiprazole: Efficacy in MDD

• In one trial, met prespecified sample size and brex vs plac was statistically significant, but not CLINICALLY significant by authors’ definition of “significant”
• Had < 3 point* change in MADRS scores
  
• 3 point change is considered clinically significant

Brexpiprazole: Cognition

• In a trial with aripiprazole, neither drug showed a statistically significant result on cognitive composite score
Brexpiprazole: Side Effects

- Low risk of EPSE
- Akathisia: inconsistent results across studies; brex < aripiprazole; NNH = 25
- EPSE (other than akathisia): NNH = 24
- Weight gain: most patients don’t gain wt; some gain quite a lot
- Nausea and dizziness: probably dose-dependent
- Little effect on QTc
- Little effect on prolactin but prl not consistently decreased as with aripiprazole
Brexpiprazole: Summary

- Appears well tolerated RE akathisia, QTc, weight, EPSE and prolactin
- Lots of dosage adjustments (liver, renal, CYP)
- Uninspiring performance in studies
Brexpiprazole: Summary

- Few side effects
- Few beneficial effects

Summary: SEs & Dosing

<table>
<thead>
<tr>
<th></th>
<th>Lurasidone</th>
<th>Cariprazine</th>
<th>Brexpiprazole</th>
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</thead>
<tbody>
<tr>
<td>EPSE</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Akathisia</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Metab synd</td>
<td>—</td>
<td>+ (weight)</td>
<td>+</td>
</tr>
<tr>
<td>Prolactin</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>QTc</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dose issues</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>Liver Renal CYP3A4 CYP2D6</td>
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</table>
Major Metabolic Routes

<table>
<thead>
<tr>
<th></th>
<th>3A4</th>
<th>2D6</th>
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<tbody>
<tr>
<td>Lurasidone</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
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</tr>
<tr>
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<td>X</td>
</tr>
</tbody>
</table>

Conclusions

- Each agent has potential advantages
- Each may find a niche
- Head-to-head trials reveal no compelling advantages
- Cognitive advantages require more study
- We need more data
Cohen’s d: formula

• Cohen’s d:
  1 = treatment group
  2 = control group
  M = mean
  SD = standard deviation (pooled)

\[
Cohen's \ d = \frac{M_1 - M_2}{SD_{pooled}}
\]