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

At the successful completion of this program, the participants should be able to do the following for each of these drugs: lurasidone, cariprazine, and brexpiprazole

- List the FDA approved indications
- Describe their pharmacological mechanisms of action
- Describe the efficacy compared to traditional therapeutic alternatives
- List common and/or dose-dependent side effects reported of each agent
- List anticipated drug interactions based on the known metabolism of each agent

INTRODUCTION

Things you need to know to understand this presentation

- Why I chose these three antipsychotics
- Interpretation of number needed to treat (NNT)/number needed to harm (NNH)
- Interpretation of standardized mean difference (SMD)
- Concerns with second or third generation antipsychotics
- Expected clinical effects of specific pharmacological effects

WHY THESE THREE ANTIPSYCHOTICS?

- They are *relatively* new
- They may have legitimate clinical advantages
- They are being heavily promoted and we need to know how to council patients about expectations and risks

NUMBER NEEDED TO TREAT/HARM[1]

- An easy-to-calculate estimate of how many patients need to be treated with a particular intervention for a particular amount of time in order to see 1 positive outcome OR prevent one negative outcome
- Can only be calculated for binary outcomes, i.e. yes/no, lived/died, response/non-response, etc.
- Calculation (Pr = proportion): $1/(Pr_{exp} - Pr_{ctrl})$
- NNT's less than 10 are effects that would be noticed on a day-to-day basis in clinical practice (difference potentially seen every day)
- In general, desirable NNTs are low and NNH's are high
- NNT and NNH provides a number that can be used to form an opinion

STANDARDIZED MEAN DIFFERENCE (SMD)[2]

- AKA Cohen's *d*, Hedge's g (with slight variation in calculation)
- An effect size measure for CONTINUOUS data
- Range: 0 – infinity
- Interpretation (one of several, and they are context-specific)

Value	Magnitude of effect
0	No effect
0.2	Small
0.5	Medium
0.8	Large

Having a "common language" e.g. the unitless SMD, allows us to compare outcomes from different studies that are measuring the same thing (e.g. comparing two studies, both of which measured depression, but used different rating scales). SMD's are recommended by the Cochrane Collaboration for pooling results of studies with continuous outcomes for meta-analyses[3].

CONCERNS WITH CURRENT ANTIPSYCHOTICS

- Extrapyramidal side effects (EPSE):
  - Akathisia: *compelling* restlessness, agitation, dysphoria, unease
  - Drug-induced Parkinson's Disease: characteristic symptoms of tremor, rigidity, bradykinesia, gait instability, et al
  - Dystonia: painful muscle spasms
  - Tardive dyskinesia: irregular, involuntary movements that occur after sustained, long term use of dopamine (DA) antagonists (i.e. antipsychotics)
- Metabolic syndrome
  - Wt gain
  - Worsening or new onset diabetes
  - Lipid abnormalities
- Prolactin elevation
  - DA suppresses prolactin release; blockade of DA receptors increases prolactin release
  - Can lead to sexual side effects, reduced bone mineral density, gynecomastia, menstrual irregularities, lactation
- QTc prolongation: lengthening of the cardiac QT interval predisposes to potentially fatal arrythymias

RECEPTOR EFFECTS

Receptor	Action	Theoretical Effects
D2	antagonist	Antipsychotic effects Antimanic effects Antiaggressive effects EPSE Prolactin Cognitive impairment
D2	agonist	N, V, insomnia, akathisia
D3	agonist	Reduced EPSE Impaired cognition[4] Worsening psychosis(?)
D3	antagonist	Antipsychotic(?) Improved negative symptoms Pro-cognitive (NOTE: D3 antag does NOT appear to induce EPSE)[4]
5-HT1A	partial agonist[5,6]	Anxiolysis Pro-cognitive Reduced EPSE Improved negative symptoms Improved depressive symptoms
5-HT2A	antagonist	Increased release of dopamine Improved negative symptoms Reduced EPSE
5-HT7	Antagonist	Improve or impair cognition?[7]
Alpha 1	antagonist	Orthostatic hypotension Dizziness Reflex tachycardia
H1 (histamine)	antagonist	Sedation Weight gain
M1 (muscarinic)	antagonist	Anticholinergic effects: confusion, memory dysfunction, dry eyes, blurred vision, exacerbation of angle closure glaucoma, dry mouth, tachycardia, dry skin, constipation, urinary retention
Partial agonists can act either as agonists or antagonists depending on the environmental conditions i.e. concentration of endogenous ligands like dopamine		

Receptor binding profiles[8]

Receptor	Brexpiprazole	Cariprazine	Lurasidone
D2	PA	PA	ANTAG
D3	PA	PA	
5-HT1A	PA	PA	PA
5-HT2A	ANTAG	WEAK ANTAG	ANTAG
5-HT7	ANTAG		ANTAG
Alpha1	ANTAG		
H1		WEAK ANTAG	None
M1			None
PA = partial agonist ANTAG = antagonist			

Considering the theoretical association between receptor binding and effects on cognition, I am skeptical of some of the claims for these new agents. Existing drugs have similar affinities for the receptors of interest. Perhaps more important, existing drugs have the same relationship between the "cognitive enhancing" receptors and D2 receptors which are of primary importance in reducing positive symptoms of schizophrenia. There are conflicting data regarding the effect of some pharmacological actions e.g. 5-HT7 antagonism, on cognitive processes in animal studies. Partial agonists can act in either direction, increasing or decreasing neurotransmission depending on concentration of endogenous neurotransmitter and anatomical location. Finally, lack of significant effect at histamine and muscarinic receptors may account for the small improvements seen in cognitive outcomes with these new drugs, which as noted above may not differ from current first line antipsychotics.

FDA-APPROVED INDICATIONS

	Scz	BD-depression*	BD-mania*	MDD*
lurasidone	X	X		
cariprazine	X		X	
brexpiprazole	X			X
Scz = schizophrenia BD-depression* = bipolar disorder, current episode depressed, as monotherapy, or adjunct to lithium/VPA BD-mania* = bipolar disorder, current episode manic or mixed MDD* = major depressive disorder as *adjunct* to antidepressants				

Lack of FDA approval does not mean that a drug is ineffective for a given indication, merely unstudied. That is certainly the case for the three drugs being discussed today.

DRUG REVIEWS

LURASIDONE (LATUDA®)

PHARMACOLOGY/CHARACTERISTICS [9-12]

- Serotonin-dopamine antagonist (SDA) with 5-HT_7 antagonism which may confer cognitive and memory benefits (? – other SGA's do this, too)[7,12], and lack of effect at H1 and M1 receptors may account for lack of cognitive effects[13]
- Dosing:
  - Schizophrenia: start = 40 mg QD with food; Max dose = 160 mg/day; Max dose 80 mg/day with renal or mild-mod hepatic impairment; 40 mg/day max in severe hepatic impairment (Child-Pugh = 10 – 15)
  - Bipolar depression: start = 20 mg/day with food; Max dose = 120 mg/day
  - per Drug Labeling at http://www.latuda.com/LatudaPrescribingInformation.pdf [accessed 6/18/17]

PHARMACOKINETICS

- Food increases AUC, Cmax, and Tmax almost 3-fold; Give with at least 350 calories[9,14]
- F: 9 – 19% [Drugbank DB08815; accessed 5/26/17]
- Highly protein bound (99.8%) to albumin and α1-glycoprotein [ibid]
- Metab: CYP3A4; avoid coadministration with strong CYP3A4 inducers or inhibitors[14,15]
- T-1/2: 18 hrs? 29 – 37?[8,9]

EFFICACY COMPARED TO EXISTING AGENTS

- Schizophrenia: In lower end of the range of efficacy demonstrated by other antipsychotics; perhaps less effective than clozapine, olanzapine, risperidone, and paliperidone[16]
- Bipolar depression: In middle of the "pack" compared to mood stabilizers and other SGA
- Cognition: Claims for better effects on cognitive symptoms of schizophrenia versus other antipsychotics[17], but theoretical advantages have not resulted in robust evidence in studies. Other antipsychotics appear to have similar effects on cognition in patients with schizophrenia[17,18]

SIDE EFFECTS[10,19-21]

- There is evidence that lurasidone may be poorly tolerated compared to other antipsychotics in terms of akathisia, EPSE, discontinuation due to adverse effects, and all-cause discontinuation [16,22,23]
- GI (including nausea, vomiting, dyspepsia): 20 – 25%; median NNH = 13.5
- Akathisia (dose-dependent): rates appear high, and higher than aripiprazole[22]; 10 – 15%; median NNH = 16.5
- Sedation/Somnolence (dose-dependent): about 10%; median NNH = 15 - 18
- Insomnia: inconsistently reported
- Little risk of metabolic effects[16,24]
- Little or no effect on QTc interval[16]
- Modest effects on prolactin; not as bad as risperidone/paliperidone, but worse than placebo
- Little interaction w/ alpha-1, H_1, or M_1 receptors, so reduced risk of orthostatic hypotension, weight gain, and anticholinergic side effects. Less H1 should = less sedation, but it's still reported

LURASIDONE: SUMMARY

- Good metabolic profile (weight change, lipids, diabetes)
- Good profile regarding QTc
- Good profile regarding antihistaminic and anticholinergic side effects
- Dosing issues: Give with food, CYP3A4 drug interactions, adjustment in renal or hepatic impairment
- Worrisome signal regarding side effect tolerability (akathisia, GI, prolactin, et al)
- Probably works as well as some other antipsychotics for schizophrenia and bipolar depression, but cognitive benefits aren't obvious in clinical trials
- May have a niche due to low rates of metabolic syndrome, but it's a very expensive drug entering a crowded market.

CARIPRAZINE (VRAYLAR®)

AKA: RGH-188, MP-214

CLAIMS

- Low H1 binding → less weight gain and sedation.
- D3 > D2 binding → reduced EPSE; improved cognition
- 5HT1A partial agonism → improved negative symptoms and cognition

PHARMACOLOGY/CHARACTERISTICS[25]

- Dopamine partial agonist: D3 > D2; (D3: Emax = 70.9%; D2: Emax = 30%)[26]
- Dose [from Prescribing Information accessed 6/18/17]:
  - Schizophrenia: Start 1.5 mg/day; Target dose range: 1.5 – 6 mg/day; Max = 6 mg/day
  - Bipolar mania: Start 1.5 mg/day; Target: 3 – 6 mg/day; Max = 6 mg/day

PHARMACOKINETICS[8,27]

- Absorption rapid; absorption delayed but extent not affected by food
- F: 52-63% (rats); 64-80% (dogs); information not available for humans
- Highly protein bound (91 – 97%) [Drugbank DB06016; accessed 6/1/17]
- Metab: CYP3A4 (major – ½ the dose [Vraylar package insert]) and CYP2D6 (minor – no dose adjustment necessary) to two active metabolites
- T-1/2: parent = 2-5 days; metabolite = 1-3 weeks

EFFICACY COMPARED TO EXISTING AGENTS

- Schizophrenia: Appears to work as well as aripiprazole[28] for symptoms represented by the PANSS Total score, perhaps NOT as well as risperidone[29] (?)
- Bipolar mania: Appears to work fairly well. Effect sizes in 4 studies ranged from 0.41 to 0.59 with 3 studies between 0.5 and 0.6. However, patients with bipolar disorder may be more sensitive to side effects from cariprazine.
- Cognition: Cognitive effects have not been adequately studied. Theoretical claims about benefits for cognition and EPSE are either not mentioned in package insert (cognition), or not borne out in clinical trials (EPSE)

SIDE EFFECTS[28-34]

- Akathisia; carip > ari[28], carip = risp[29]; possibly greater frequency in patients with bipolar disorder than patients with schizophrenia; Relative risk vs placebo = 3.4[35]; median NNH = 8
- EPSE (other than akathisia) significant but maybe slightly less than risperidone; more frequent in bipolar disorder; median NNH = 19
- Gi side effects (nausea, vomiting, diarrhea, "dyspepsia"): median NNH = 8
- Little effect on prolactin
- Slight effect on weight
- Dizziness and sedation inconsistently reported so probably not a big problem.

CARIPRAZINE: SUMMARY

- Questions about effectiveness in schizophrenia
- Concerns about akathisia, particularly in patients with bipolar disorder
- Concerns about GI side effects
- Claims of reduced risk of EPSE appear unfounded (carip = risperidone)
- Claims of improved cognition appear unfounded (carip = risperidone)
- Appears to have desirable profile for prolactin, weight, and QTc

BREXPIPRAZOLE (REXULTI®) (OTSUKA & LUNDBECK)

AKA OPC-34712

CLAIMS[5,36,37]

- Less intrinsic D2 agonism compared to aripiprazole → reduced akathisia, insomnia, restlessness, nausea
- Less D2 antagonist effect compared to pure D2 antagonists → less EPSE, hyperprolactinemia, TD
- 5-HT2A antagonist → Improved effect on negative symptoms; less EPSE
- 5-HT1A partial agonist → cognitive effects (helpful or harmful?)
- Low H1 antagonist properties → less sedation, weight gain
- Alpha 2 antagonist → antidepressant effects (think mirtazapine)

PHARMACOLOGY/CHARACTERISTICS

- D2 partial agonist similar to aripiprazole but it's more potent at 5HT1A (partial agonist) and 5HT2A (antagonist) receptors and has less intrinsic activity at D2 (partial agonist) receptors compared to aripiprazole[37,38]
- Brexpiprazole's actions should fall somewhere between aripiprazole and other antipsychotics in terms of efficacy, risk of EPSE, and prolactin elevation[37,39]
- Dose:
  - Requires titration:
  - Schizophrenia: 1 mg/day x 4 days, then 2 mg x 3 days, then 4 mg if necessary depending on response and tolerability. Target 2 – 4 mg/day
  - Adjunct for MDD: 0.5 - 1 mg/day increasing dose at weekly intervals depending on response and tolerability to max of 3 mg [*Rexulti* package insert; Accessed 2/2/16]
  - Dosage adjustments recommended for both liver and renal impairment and when administered w/ strong inducers or inhibitors of CYP3A4 or CYP2D6

PHARMACOKINETICS:

- Food has no effect on Cmax or AUC[40] [Drugbank DB09128 accessed 6/8/17]
- F = 95%
- Highly protein bound (>99%) to albumin and α1-acid glycoprotein [Drugbank DB09128 accessed 6/8/17]
- Metab: CYP3A4 and CYP2D6[40,41]
- T-1/2 = 91 hours

EFFICACY COMPARED TO EXISTING AGENTS

- Schizophrenia: Questions exist regarding efficacy of brexpiprazole in schizophrenia. Of four comparative trials, one was a failed trial with aripiprazole as internal comparator [NCT00905307, clinicaltrials.gov]; in a trial with quetiapine, quetiapine separated from placebo but brex did not [NCT01810380; available from clinicaltrials.gov]; in a RDBPCT only the 4 mg/day dose of brex separated from placebo, 1 and 2 mg/day did not[42]; and in one study both 2 and 4 mg/day doses of brex separated from placebo[43].
- Major depressive disorder: In one of the depression studies[44], even though they met their pre-specified sample size of > 660 patients, neither brexpiprazole dose group reached the 3 point change in MADRS score that is believed to be clinically significant. That was in a group of per final protocol patients so this was the best case scenario. It was statistically significant but not clinically significant by the authors own definition of clinically significant.
- Cognition: In a trial with aripiprazole as active control and a cognitive test battery as a secondary outcome, neither drug had a statistically significant effect on the test battery composite score at endpoint [NCT02054702 from clinicaltrials.gov accessed 6/8/17]

SIDE EFFECTS

- Theoretically (beware!) lower D2 antagonist action → reduced risk of EPS or prolactin elevation. Current studies support this advantage[42,43,45]
- Akathisia: inconsistent values in studies; dose-dependent; less than aripiprazole: 15% at doses > 4 mg/day; NNH = 10[45]. All-dose NNH = 25[46]
- Extrapyramidal side effects: 6.5%, dose-dependent; NNH = 24[45]
- Weight gain: 6.5%. About 3 lb increase on average over 6 weeks.[42-44,47] (probably dose-dependent[45]): Pooled NNT for weight gain compared to placebo = 22[45]. Most patients don't experience weight gain, but there are outliers who gain substantial weight.[45] May see more weight increase with prolonged treatment. The short term studies may be underestimating the risk.[48]
- Nausea (probably dose-dependent): 6.5%; NNH = 34[45]; overall NNH = 25
- Dizziness (probably dose-dependent): 5.4%; Brx > 4 mg/day: NNH = 27[45]
- Little if any effect on QTc[42]
- Little effect on prolactin[45], but doesn't consistently decrease prolactin like aripiprazole

BREXPIPRAZOLE SUMMARY

- Appears reasonably well tolerated with low rates of akathisia, QTc prolongation (as with aripiprazole), weight increase (with exceptions), EPSE and prolactin elevation
- Dosing issues: CYP3A4 and 2D6 drug interactions, adjustment in renal or hepatic impairment
- *Probably* effective vs schizophrenia and as adjunct in MDD, but uninspiring performance. Set response expectations low.

Summary of common second generation antipsychotic side effects and dosing issues

	Lurasidone	Cariprazine	Brexpiprazole
EPSE	+	++	+
Akathisia	++	++	+
Metabolic syndrome	—	+ (weight)	+
Prolactin	+	—	—
QTc prolongation	—	—	—
Dose considerations	Avoid!: CYP3A4	Adjust: CYP3A4	Must Titrate Adjust: CYP3A4 & 2D6 Renal impairment Hepatic impairment

CONCLUSIONS

- The three medications discussed here have certain advantages unique to each agent.
- They may each find a specific niche in treating patients with conditions for which they are approved
- Head-to-head studies with existing agents with similar pharmacology reveal no compelling clinically meaningful differences that are unique to these agents
- Advantages related to cognitive improvements are inadequately studied but existing data do not support overwhelming superiority of these agents over existing agents.
- We clearly need more head to head studies with similar antipsychotics before making final conclusions about safety and efficacy of these agents

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