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

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:

Cohen's d Value	Magnitude of effect
0	No effect
0.2	Small
0.5	Medium
0.8	Large

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

Receptor	Lurasidone	Cariprazine	Brexpiprazole
D2	Antag	PA	PA
5-HT2A	Antag	Wk antag	Antag
D3		PA	PA
5-HT7	Antag		Antag
H1		Weak antag	
M1	None	None	None

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

	SCZ	BD-Depn	BD-Mania	MDD
Lurasidone	X	X		
Cariprazine	X		X	
Brexpiprazole	X			X

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

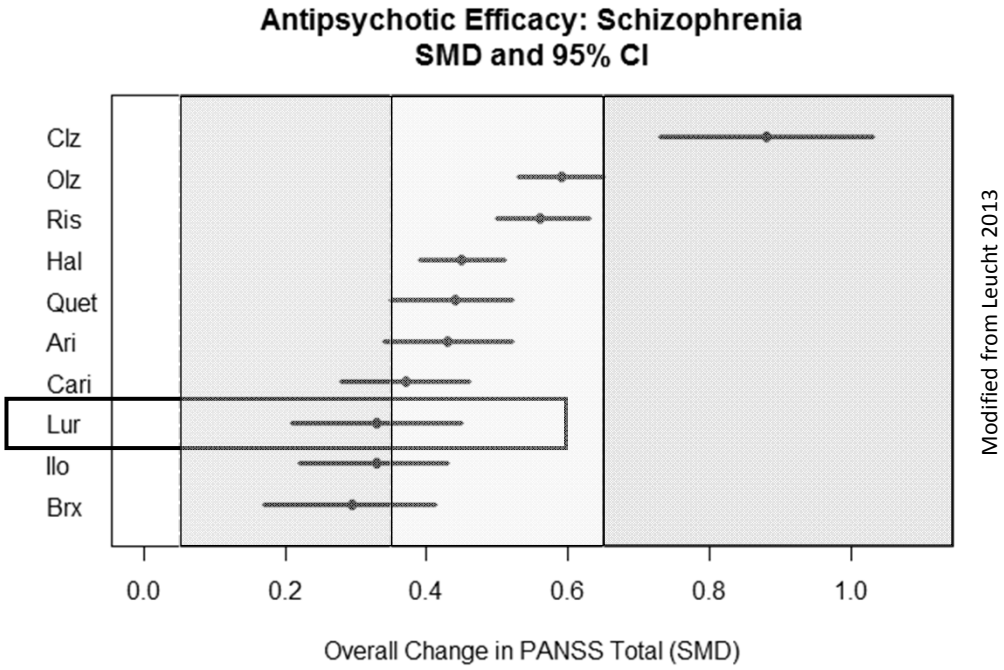
- Scz:
  - Start 40 mg/day
  - Max : 160 mg/day
- Bipolar depression:
  - Start 20 mg/day
  - Max: 120 mg/day
- Adjust dose with renal or hepatic impairment

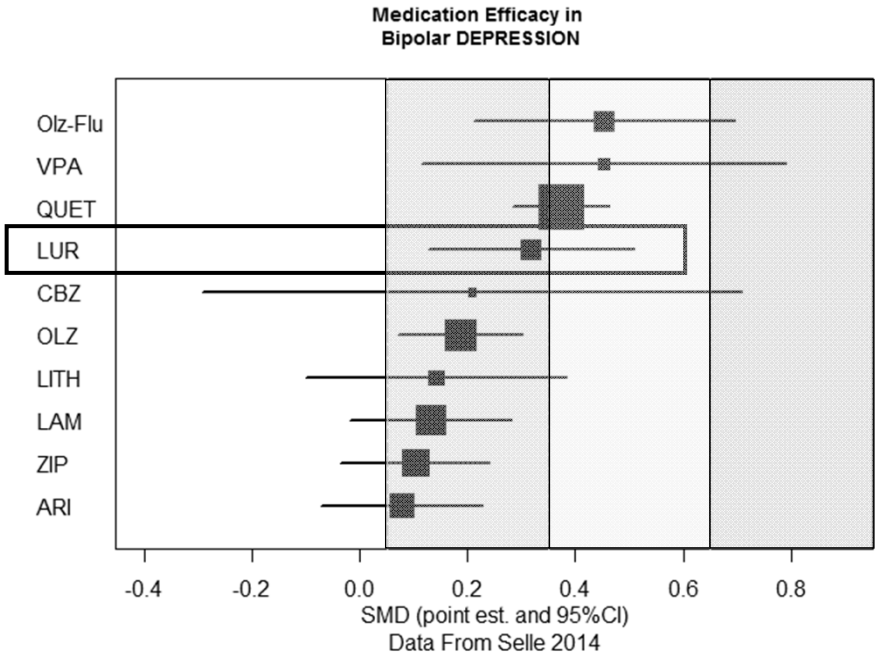
PK Highlights: Lurasidone

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

Comparative Efficacy

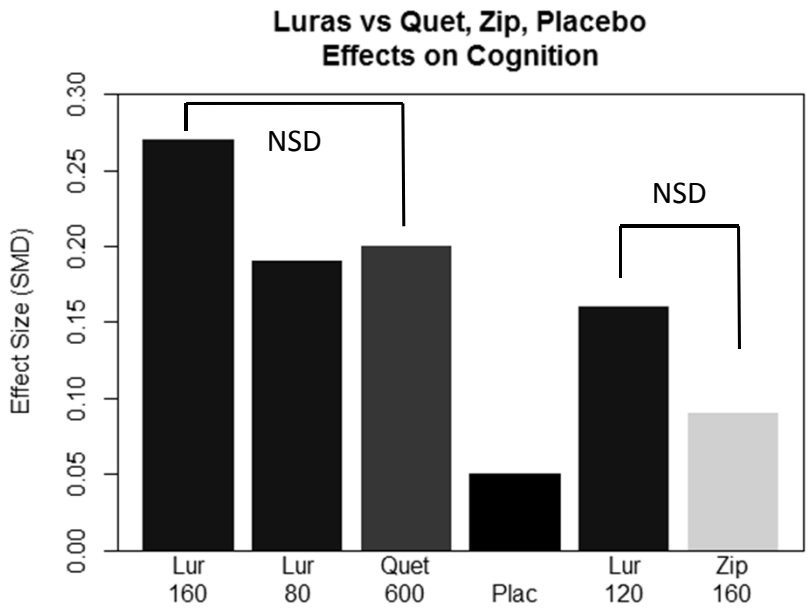
Lurasidone





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

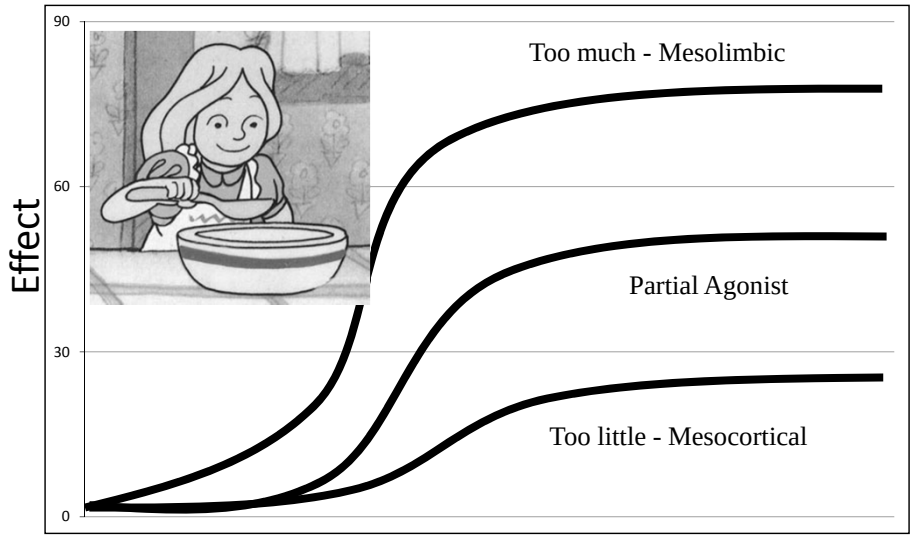
Drug Reviews

Cariprazine (Vraylar®)

Cariprazine: Pharmacology

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

DA Concentration vs Effect



Cariprazine: Dosing

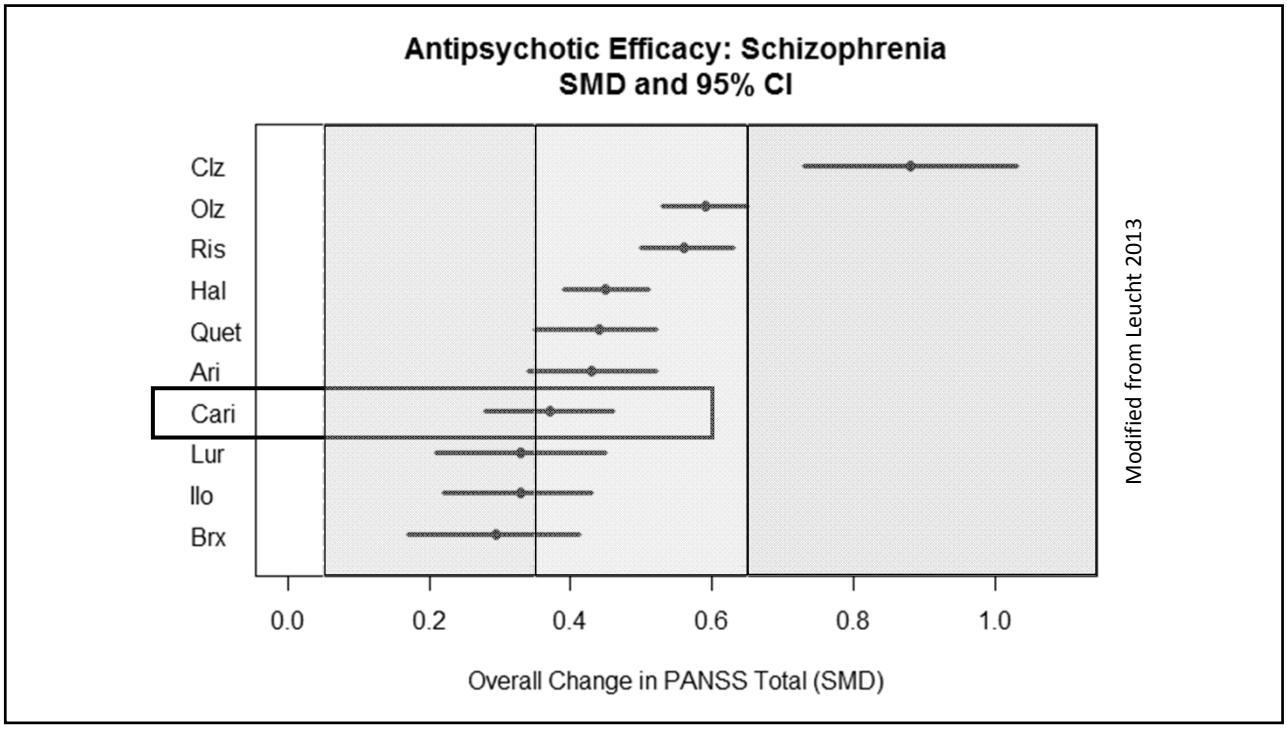
- Schizophrenia AND Bipolar mania
  - Start: 1.5 mg/day
  - Max = 6 mg/day
- Target dose ranges:
  - Scz: 1.5 – 6 mg/day
  - Mania: 3 – 6 mg/day
- Reduce dose with CYP3A4 inhibitors (next slide)
- No major concerns with food

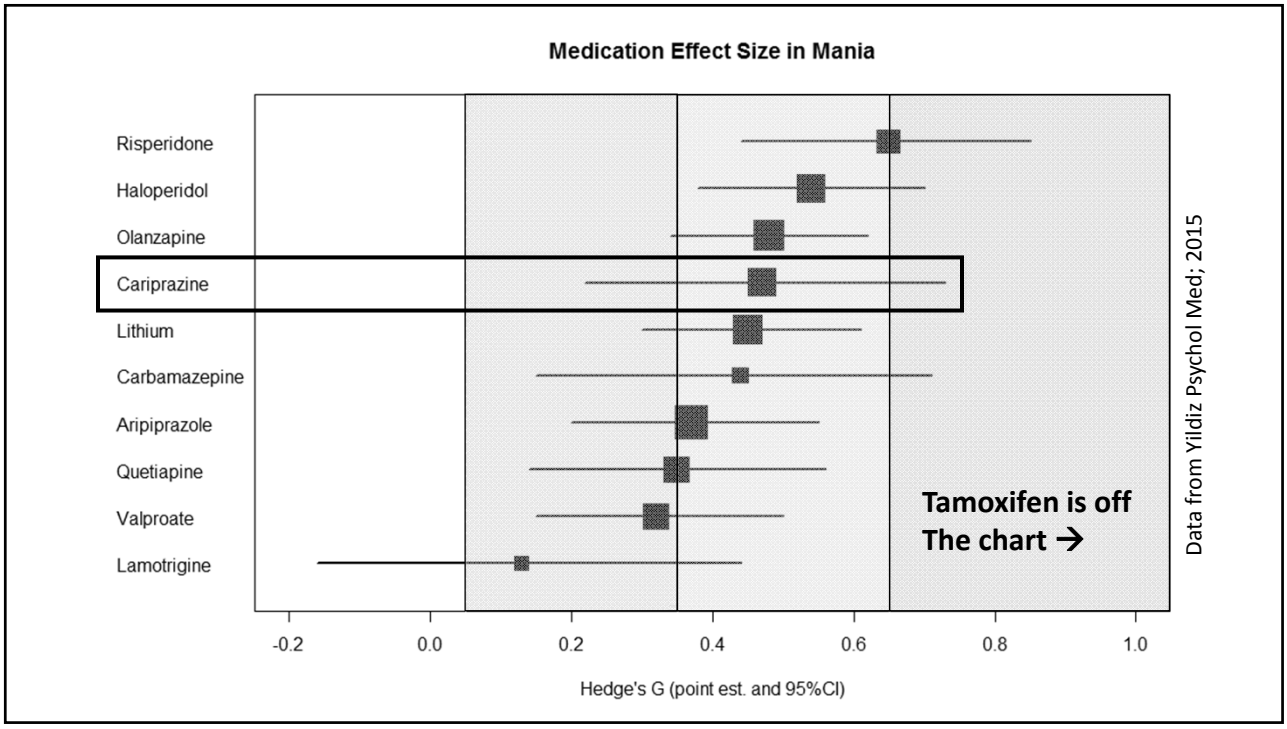
PK Highlights: Cariprazine

- 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


Antipsychotic Efficacy: Schizophrenia
SMD and 95% CI
Clz
Olz
Ris
Hal
Quet
Ari
Cari
Lur
Ilo
Brx
0.0
0.2
0.4
0.6
0.8
1.0
Overall Change in PANSS Total (SMD)
Modified from Leucht 2013


Medication Effect Size in Mania
Risperidone
Haloperidol
Olanzapine
Cariprazine
Lithium
Carbamazepine
Aripiprazole
Quetiapine
Valproate
Lamotrigine
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
Hedge's G (point est. and 95%CI)
Tamoxifen is off
The chart →
Data from Yildiz Psychol Med; 2015

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

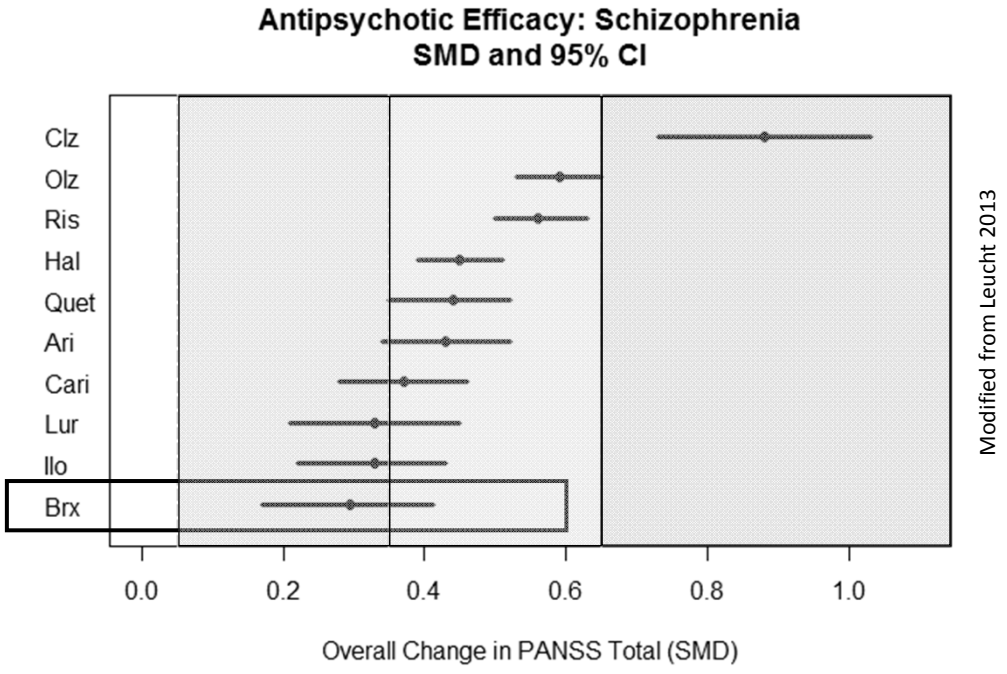
- No effect from food
- Metabolized by CYP3A4 and CYP2D6

Comparative Efficacy

Brexpiprazole (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



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

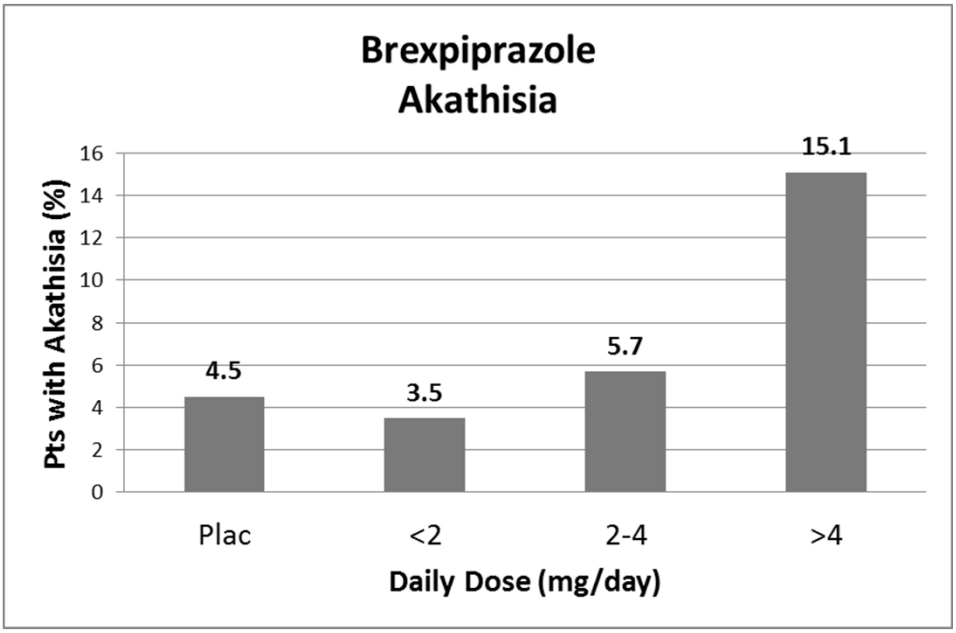
- In a trial with aripiprazole, neither drug showed a statistically significant result on cognitive composite score

Side Effects

Brexpiprazole

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

	Lurasidone	Cariprazine	Brexpiprazole
EPSE	+	++	+
Akathisia	++	++	+
Metab synd	—	+ (weight)	+
Prolactin	+	—	—
QTc	—	—	—
Dose issues	CYP3A4	CYP3A4	Liver Renal CYP3A4 CYP2D6

Major Metabolic Routes

	3A4	2D6
Lurasidone	X	
Cariprazine	X	
Brexpiprazole	X	X

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

The End

Cohen's d: formula

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

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