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Tackling Unresolved Challenges in The Treatment of Schizophrenia: Negative Symptoms, Cognitive Deficits, and Partial Treatment Response

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Disclosure Information

- Dr. Harvey has served as a consultant in the past year to:
  - Alkermes; Boehringer-Ingelheim; EMA Wellness; Karuna Therapeutics; Minerva Pharma, Sunovion Pharmaceuticals;
  - CSO i-Function
  - Royalties from WCG-Verasci
- No nonpublic information is being presented in this lecture

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What is the biggest problem in schizophrenia and bipolar disorder?

- It's not
  - Suicide (10-15%)
  - Hallucinations (30%)
  - Delusions (30%)
- It is
  - Disability
    - Social (65%)
    - Vocational (60-90%)
    - Residential (40-60%

What Predicts Everyday Disability in Schizophrenia?

- The usual suspects include:
  - Cognition
  - Social Cognition
  - Negative Symptoms
  - Functional Capacity
- An additional issue is Failures in Treatment response
  - Treatment Resistance
  - Partial Response

Important Domains of Cognitive Dysfunction In Schizophrenia

- Attention/vigilance
- Processing Speed
- Working Memory
- Executive Functioning
- Episodic Memory

What are the current symptoms that are included in the Negative Symptoms construct?

- Reduced Motivation: Avolition
- Reduced Pleasure Sensitivity: Anhedonia
- Reduced Social Engagement: Asociality
- Reduced Communication: Alogia
- Reduced Emotional Expression Affective Blunting

- There are other concepts that are linked, but may be subsumed: Amotivation

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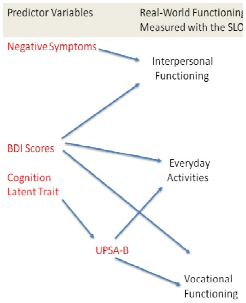
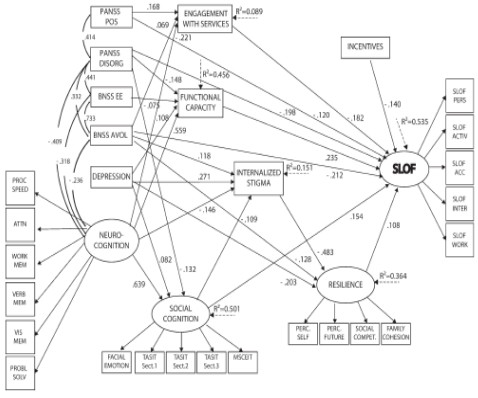
Important Features of Cognitive Impairments

- Functional relevance
  - Social and everyday living skills
  - Adherence to treatment
- Potential vulnerability factors
- Markers for endophenotypes

Predictive Models:



Strassnig et al., 2015; n=821



Galderisi et al., 2014; n=921

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Features of the Cognitive Enhancement Research Design

- Use of a consensus-derived cognitive battery
  - The MATRICS Consensus Cognitive Battery or 'equivalent'
- Use of a co-primary outcomes measure
  - Either a performance-based assessment of functional skills or a structured interview
- Enrollment of clinically stable patients
  - To rule out 'pseudospecificity'
- Long trial duration

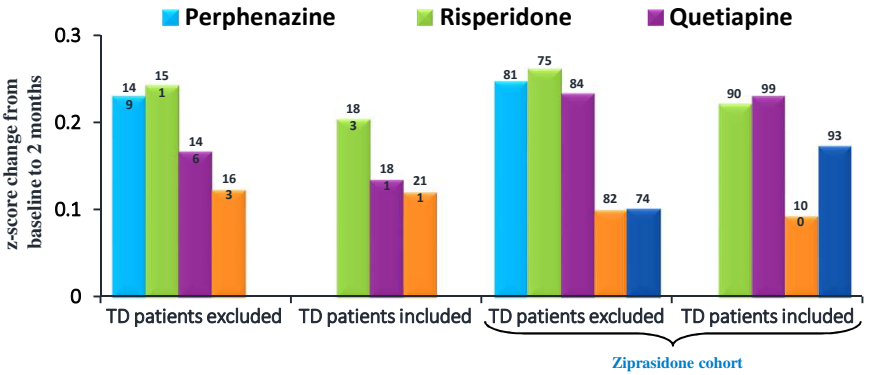
Buchanan RW, *et al. Schizophr Bull* 2005;31:5–19;
Buchanan RW, *et al. Schizophr Bull* 2011;37:1209–17.

The MCCB

- MATRICS battery (Measurement and Treatment Research to Improve Cognition in Schizophrenia)[1]
  - Speed of processing
    - Category fluency
    - Trail making test, part A
    - Symbol-coding
  - Attention/vigilance
    - Continuous performance test - identical pairs (CPT-IP)
  - Working memory
    - Letter-number span
    - Spatial span
  - Verbal learning
    - Hopkins verbal learning test – revised (HVLT-R)
  - Visual learning
    - Brief visuospatial memory test – revised (BVMT-R)
  - Reasoning and problem solving
    - Mazes
  - Uses mean of t-scores for an estimate of global neuropsychological performance

Nuechterlein KH, *et al. Am J Psychiatry* 2008;165:203–13.

CATIE Results:Change in neurocognitive composite score after 2 months of treatment



N above histogram. No significant differences between treatments (p=0.20). TD, tardive dyskinesia.
Keefe RSE, *et al. Arch Gen Psychiatry* 2007; 64: 633–47.

The long list of Failed Add-On Pharmacotherapy for Cognition(Small font Required)

- Cholinesterase Inhibitors
- l-Dopa
- AMPA-Kine
- Memantine
- Modafinil/armodafinil
- H-3
- PDE-9
- Bitopertin (Gly T-1 Agonist)
- Pimavanserin
- Roluperidone
- SKF38393 (Does not penetrate BBB; works with intracranial delivery)
- Alpha-7 partial agonists (maybe; hold the thought)
- Guanfacine (worked in SPD)
- Dihydrexidine (worked in SPD)

What Did work?

- Lisdexamfetamine (Development suspended)
- Amphetamine (single dose studies)
- Computerized Cognitive Training
- Computerized Social Cognitive Training

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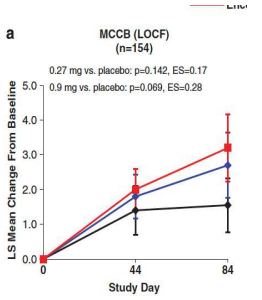
Encenicline effects phase 2

Table 4 SCoRS items that responded to treatment with encenicline 1.0 mg compared to placebo: Effect sizes (ES) presented as Cohen's d.

SCoRS Item	Interviewer ES (p-Value)	Informant ES (p-Value)	Patient ES (p-Value)
1. Remembering the names of people you know or meet	0.32 (.027)	0.55 (.001)	
2. Remembering how to get places	0.27 (.058)	0.48 (.005)	
3. Following a TV show	0.44 (.003)	0.49 (.004)	0.38 (.008)
4. Remembering where you put things	0.32 (.024)	0.56 (.001)	
7. Remembering information recently given to you		0.36 (.035)	
13. Staying Focused	0.28 (.048)	0.44 (.011)	
16. Doing things quickly	0.28 (.054)	0.37 (.029)	
20. Following conversations in a group	0.37 (.010)	0.36 (.033)	
Total score	0.37 (.011)	0.57 (.001)	



European Neuropsychopharmacology (2015) 25, 176-184

ELSEVIER www.elsevier.com/locate/euroneuro

Reliability, validity and treatment sensitivity of the Schizophrenia Cognition Rating Scale

Richard S.E. Keefe[a,b,*], Vicki G. Davis[b], Nathan B. Spagnola[b], Dana Hilt[c], Nancy Dgetluck[c], Stacy Ruse[b], Thomas D. Patterson[d], Meera Narasimhan[e], Philip D. Harvey[f]

Randomized, Double-Blind, Placebo-Controlled Study of Encenicline, an α7 Nicotinic Acetylcholine Receptor Agonist, as a Treatment for Cognitive Impairment in Schizophrenia

Richard SE Keefe[1], Herbert A Meltzer[2], Nancy Dgetluck[1], Maria Gawryl[3,4], Gerhard Koenig[3], Hans J Moebius[3], Ilise Lombards[3,5] and Dana C Hilt[3,5]

[1]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA; [2]Department of Psychiatry and Behavioral Sciences Psychiatry, Northwestern University, Feinberg School of Medicine, USA; [3]FORUM Pharmaceuticals Inc., Waltham, MA, USA

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Why Did Encenicline Fail in phase 3?

- They decided to rush to complete recruitment
  - If you compared separation from placebo, it separates under the first CEO, not the second
- Participants did not take it
  - Participants with any detectable level of the medication separated

BI GLYt-1 Inhibitor: Iclepertin

Efficacy and safety of the novel glycine transporter inhibitor BI 425809 once daily in patients with schizophrenia: a double-blind, randomised, placebo-controlled phase 2 study

W Wolfgang Fleischhacker, Jana Podhorna, Martina Gröschl, Sanjay Hake, Yihua Zhao, Songqiao Huang, Richard S E Keefe, Michael Desch, Ronald Brenner, David P Walling, Emilio Mantero-Atienza, Kazuyuki Nakagome, Stephane Pollentier

MCCB neurocognitive composite T-score at week 12*				
n	79	80	82	83
Adjusted mean change from baseline	2·16 (0·88 to 3·43)	2·08 (0·83 to 3·33)	3·59 (2·39 to 4·79)	3·48 (2·28 to 4·67)
Adjusted mean difference versus placebo	0·45 (−1·09 to 1·99)	0·37 (−1·14 to 1·88)	1·88 (0·41 to 3·35)	1·77 (0·29 to 3·24)
SCoRS interviewer-rated total score at week 12†				
n	77	80	82	83
Adjusted mean change from baseline	−1·64 (−2·81 to −0·46)	−3·65 (−4·81 to −2·50)	−3·08 (−4·22 to −1·94)	−3·89 (−5·02 to −2·75)
Adjusted mean difference versus placebo	1·18 (−0·26 to 2·61)	−0·84 (−2·26 to 0·58)	−0·26 (−1·67 to 1·14)	−1·07 (−2·47 to 0·33)

Back to the Past

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia

Stephen K. Brannan, M.D., Sharon Sawchak, R.N., Andrew C. Miller, Ph.D., Jeffrey A. Lieberman, M.D., Steven M. Paul, M.D., and Alan Breier, M.D.

Two successful phase-3 trials since this one

Which May Also Impact Positively on Cognition, as you'd expect

Translational Psychiatry www.nature.com/tp

ARTICLE OPEN Check for updates

Effectiveness of KarXT (xanomeline-trospium) for cognitive impairment in schizophrenia: post hoc analyses from a randomised, double-blind, placebo-controlled phase 2 study

Colin Sauder[1 ✉], Luke A. Allen[2], Elizabeth Baker[2], Andrew C. Miller[1], Steven M. Paul[1] and Stephen K. Brannan[1]

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Table 2. KarXT treatment effect on cognitive performance by baseline impairment subgroup.

Sample	LS means change from baseline at day 35		95% confidence interval			
	Treatment	Estimate (SE)	Lower	Upper	*p* value	Cohen's *d*
Minimally impaired	KarXT ($n = 37$)	−0.18 (0.13)	−0.44	0.09	0.19	0.22
	Placebo ($n = 28$)	−0.22 (0.15)	−0.52	0.08	0.15	0.28
	KarXT vs. placebo	0.04 (0.16)	−0.28	0.37	0.79	0.05
Impaired	KarXT ($n = 23$)	0.57 (0.19)	0.18	0.95	0.01	0.61
	Placebo ($n = 37$)	0.07 (0.13)	−0.19	0.33	0.59	0.09
	KarXT vs. placebo	0.50 (0.22)	0.04	0.95	0.03	0.50

LS means and *p* values are derived from post hoc ANCOVA models described earlier, with covariates of site, gender, age, and baseline performance. *ANCOVA* analysis of covariance, *LS* least squares.

Quick, Interim, Summary

- Large scale phase 3 BI trial ongoing
- Smaller scale Neurocrine Study ongoing
  - Luvadaxistat: DAO[1] inhibitor designed to reverse NMDA hypo-function
  - Failed for Negative Symptoms
- KarXT Trial likely

[1] Inhibition of DAO leads to the increase of D-serine levels which act as agonists at the NMDAR.

Treatment Efforts for Negative symptoms

- Couple of Previous negative outcomes
  - Bitopertin
  - Neurocrine
    - GlyT-1 Agents
  - Multiple previous studies focusing on Glutamate
    - Glycine; D-Serine; D-Cycloserine

Couple of Potentially Important Developments

Efficacy and Safety of MIN-101: A 12-Week Randomized, Double-Blind, Placebo-Controlled Trial of a New Drug in Development for the Treatment of Negative Symptoms in Schizophrenia

Michael Davidson, M.D., Jay Saoud, Ph.D., Corinne Staner, M.D., Nadine Noel, Ph.D., Elisabeth Luthringer, R.N., Sandra Werner, Ph.D., Joseph Reilly, M.S., Jean-Yves Schaffhauser, Pharm.D., Jonathan Rabinowitz, Ph.D., Mark Weiser, M.D., Remy Luthringer, Ph.D.

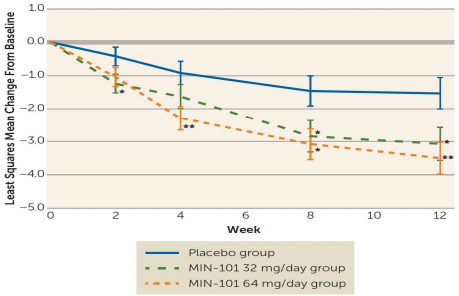
Similar drugs
Different
Strategies

Pimavanserin for negative symptoms of schizophrenia: results from the ADVANCE phase 2 randomised, placebo-controlled trial in North America and Europe

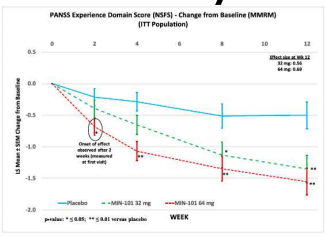
Dragana Bugarski-Kirola, Celso Arango, Maurizio Fava, Henry Nasrallah, I-Yuan Liu, Brandon Abbs, Srdjan Stankovic

Roluperidone Efficacy

FIGURE 1. Change From Baseline in the Five-Factor PANSS Negative Subscale Scores in Patients With Schizophrenia Treated With MIN-101 or Placebo[a]



Harvey PD, Saoud JB, Luthringer R, et al. Effects of Roluperidone (MIN-101) on two dimensions of the negative symptoms factor score: Reduced emotional experience and reduced emotional expression. *Schizophr Res.* 2020;215:352-356.



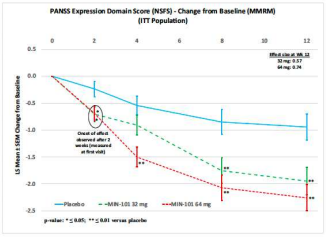
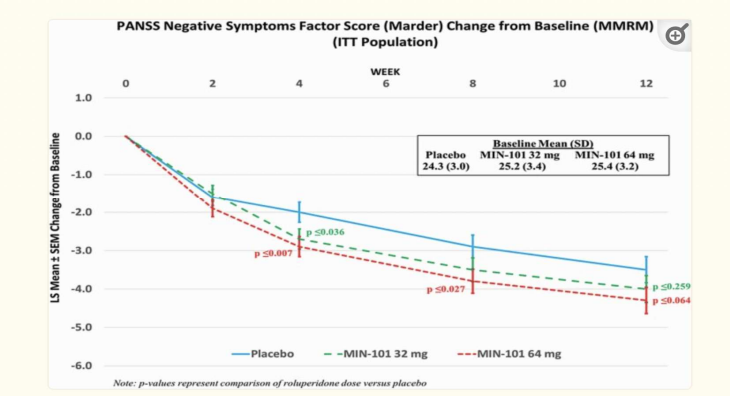


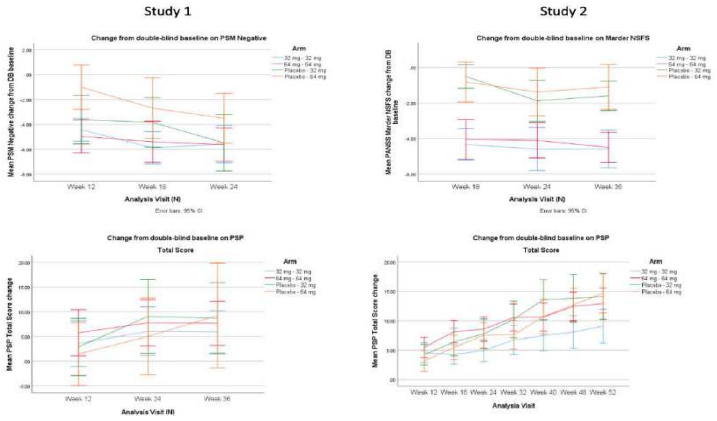
Fig. 1. Treatment response of the PANSS Reduced Emotional Experience and Reduced Emotional Expression Factors.

Phase 3 Roluperidone



Davidson M, Saoud J, Staner C, et al. Efficacy and Safety of Roluperidone for the Treatment of Negative Symptoms of Schizophrenia. *Schizophr Bull*. 2022;48(3):609-619.

Roluperidone Long Term Efficacy



Rabinowitz J, Staner C, Saoud J, et al. Long-term effects of Roluperidone on negative symptoms of schizophrenia *Schizophr Res*. 2023;255:9-18.

Pimavanserin Efficacy

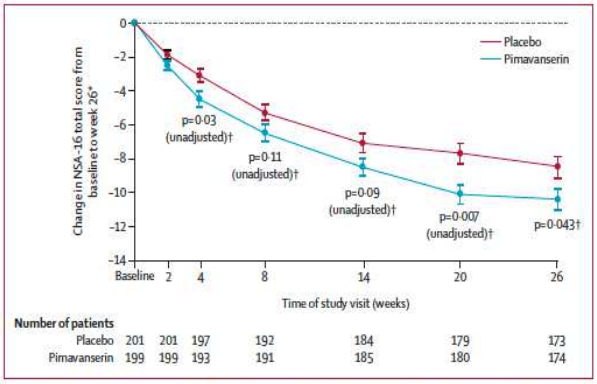


Figure 2: Least squares mean change in the NSA-16 total score from baseline to week 26 on the full analysis set

And Another interesting Finding

Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial

György Németh, István Laszlovszky, Pál Czobor, Erzsébet Szalai, Balázs Szatmári, Judit Harsányi, Ágota Barabássy, Marc Debelle, Suresh Durgam, István Bitter, Stephen Marder, W Wolfgang Fleischhacker

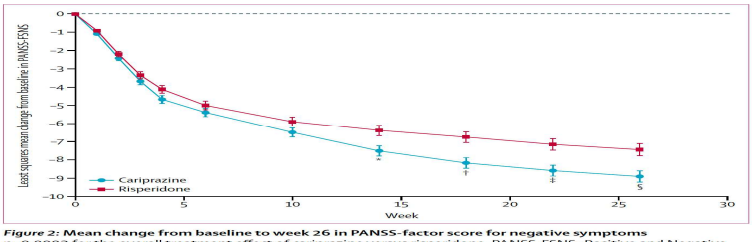


Figure 2: **Mean change from baseline to week 26 in PANSS-factor score for negative symptoms**
p=0·0092 for the overall treatment effect of cariprazine versus risperidone. PANSS-FSNS=Positive and Negative Syndrome Scale factor score for negative symptoms. *p=0·0079. †p=0·0011. ‡p=0·0016. §p=0·0022.

And there do seem to be Functional Gains as well

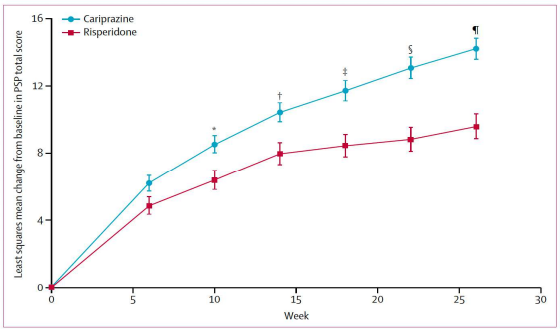


Figure 3: **Mean change from baseline to week 26 in PSP total score**

There have been some regulatory challenges

- FDA did not accept the Cariprazine data for label language
- FDA gave Minerva a refusal to file decision

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Partial Treatment Response

- First episode patients with schizophrenia commonly have a good response to treatment (~75%)
- There are some non responders from day 1
- Treatment resistance also develops across successive relapses

Treatment Resistance

- Clozapine provides a good strategy for many patients
- Some patients fail to respond, constituting an "Ultra-Treatment Resistant" group.
- It is important to differentiate non response or partial response from nonadherence

Partial Response or Partial Adherence?

- Confirmation of adherence can be tricky
  - Most patients will you that they are adherent, particularly if you have a study for them
- Blood levels is one strategy
- Extrapolating from response to Long- Acting Antipsychotics is another, probably simpler, strategy

Remission with LAI Treatment Compared to Oral Medications

- Estimates of remission with LAI treatment range from 33% to 75%; response is higher
- In an analysis of the large cohort of patients we discussed previously (Strassnig et al.), 18% of patients treated with oral medications met criteria for remission, even though we only recruited participants who reported that they were prescribed and adherent to antipsychotic treatments
- In a screening run-in for the Acadia partial response study 8 consecutive patients who produced a prescription for antipsychotics and insisting that they took their medication yesterday had 0.0 blood levels of any antipsychotic medication.

Augmentation Strategies

- Several studies have examined augmentation strategies for partial treatment response without success
  - Pimavanserin
  - Bitopertin
  - Multiple other historical add-on Therapies ranging from SSRI to Benzodiazipines

A newly available Possible Mechanism

- Stimulation of the cholinergic M4 receptor has been shown in animal and human studies to downregulate dopamine signaling, in critical areas
- If this actually happens in humans, then M4 compounds could, at least theoretically, down-relate striatal DA activity
- Monotherapy with xanomeline, although not tolerable, had efficacy for psychosis in schizophrenia and AD.

Two Cholinergic Compounds

- KARxT, shown in three trials to separate from placebo in acute psychosis
  - Very unlikely that this is an M1 effect.

- Krystal JH, Kane JM, Correll CU, et al. Emraclidine, a novel positive allosteric modulator of cholinergic M4 receptors, for the treatment of schizophrenia: a two-part, randomised, double-blind, placebo-controlled, phase 1b trial. *Lancet*. 2023;400(10369):2210-2220.

Another Interesting Mechanism

A Non–D2-Receptor-Binding Drug for the Treatment of Schizophrenia

Kenneth S. Koblan, Ph.D., Justine Kent, M.D., Seth C. Hopkins, Ph.D., John H. Krystal, M.D., Hailong Cheng, Ph.D., Robert Goldman, Ph.D., and Antony Loebel, M.D.

Ulotaront / SEP-363856

New Mechanism with a Strong Basic Science Rationale

- Preclinical data suggest that agonism at trace amine–associated receptor1 (TAAR1) inhibits firing of a subset of neurons in the ventral tegmental area of the midbrain,
- This inhibitory effect is consistent with a report of inhibition of dopaminergic neurons through activation of TAAR1.
- Several studies have suggested that the G-protein–coupled TAAR1 receptor has a role in modulating dopaminergic circuitry and has potential as a therapeutic target in patients with schizophrenia

Similar Roche Compound

- Ralmitaront, also developed with PsychoGenics smart-cube technology
- TAAR 1 partial agonist
- Failed for partial treatment response
- In trials for negative symptoms

Is a mechanism alone enough?

- We have heard this story before:
  - 3rd Generation Antipsychotic (Aripiprazole), D2 partial agonism
- The way the payment system is arranged, different is not good enough
- Also, side effects may not be a selling point for many payers

Conclusions

- There are several promising new developments that seem likely to be approved for schizophrenia
  - KARxT is closest, followed by Ulotaront
- Several others have to jump the phase 3 hurdle
  - Iclepertin and Pimavanserin
- Some, like Roluperidone, seem stalled

Conclusions, 2

- Although we have been here before, some previous drug failures actually were failures in trial conduct or patient selection
- It seems like at least a couple of potentially game-changing treatments will be available soon