MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

New treatments for schizophrenia

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose (recipient SELF; content area SCHIZOPHRENIA):

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Outline

1. Treatment-resistant schizophrenia
2. Unmet needs
   - **A. Symptom** clusters
     - Refractory positive symptoms
     - Prominent negative symptoms*
     - Neurocognitive impairment*
   - B. Long-term **tolerability** of antipsychotics
     - Extrapyramidal symptoms
     - Weight gain
   - **C. Adherence**
3. Thinking outside the box
4. Why is drug development so hard?

*Contributor to functional impairment

Fellner C. Pharmacy and Therapeutics. 2017;42(2):130-134.

Scope of the problem

20-30% of patients with schizophrenia have limited response to first-line antipsychotics.

At least 10% of patients with schizophrenia have no response to clozapine.

The tragedy of life is what dies inside a man while he lives – the death of genuine feeling, the death of inspired response, the death of the awareness that makes it possible to feel the pain or the glory of other men in oneself.

-Albert Schweitzer, 1875-1965

Siskind D et al. Can J Psychiatry. 2017;62(11):772-777.

Treatment-resistant schizophrenia (TRS)

- Consensus guidelines on diagnosis and terminology developed by TRRIP Working Group
  - Clinical sub-specifiers for positive, negative, cognitive symptom domains
  - Time-course (i.e., early, medium, late onset)
  - Ultra-treatment resistant (i.e., clozapine)
- Minimum requirements for TRS:
  - Current symptoms
    - Symptom threshold at least moderate severity (rating scale!)
    - Symptom duration at least 12 weeks
    - Functional impairment at least moderate (rating scale!)
  - Adequate treatment
    - At least two trials of at least 6 weeks of at least 600 CPZ-EQ
    - At least 80% adherence

TRRIP = Treatment Response and Resistance in Psychosis

Howes OD et al. Am J Psychiatry. 2017;174(3):216-229. Campana M et al. Schizophr Res. 2021;228:218-226. Kane JM et al. J Clin Psychiatry. 2019 Mar 5;80(2). pii: 18com12123. [Clinical Guidance]

Establishing TRS – clinical approach

Assumption: correct diagnosis of schizophrenia

Persistent symptoms …

- ✓ Characterize cross-sectional symptom cluster profile
- ✓ Characterize disability

… despite adequate treatment

- ✓ Rule-out pseudo-resistance: substance use and poor adherence
- ✓ Establish adequacy of prior treatment with first-line antipsychotics (history review)
- ✓ Consider your own prospective LAI trial

Common reasons for non-response

"Pseudo-resistance"

- Diagnosis incorrect
- ***Substance use***
- Insufficient dose
- Insufficient duration
- Unusual genetic metabolism
- Drug interactions
- ***Insufficient adherence***

True biological non-response

- Treatment-resistance to usual treatments
- Target symptom not responsive to selected intervention

***1 in 3 TRS patients have subtherapeutic drug levels.**

Based on: Freudenreich O et al. Facing Serious Mental Illness. MGH Psychiatry Academy, 2021.
***McCutcheon R et al. Acta Psychiatr Scand. 2018;137(1): 39–46.**

Stepped care for TRS

Treatment-resistant schizophrenia

- Two failed antipsychotic trials

Clozapine trial

- Timely and optimal clozapine trial

Clozapine augmentation

- Judicious use of add-on treatments

https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

A. SYMPTOMS

Biology of treatment-resistance

- Heterogeneous pathophysiology and biotypes
  - "The group of treatment-resistant schizophrenias"[1]
- Time course[2]
  - Resistance from the "get-go"
  - Evolving over time and related to relapse
- Mechanism[3]
  - Dopamine supersensitivity[4]
  - Neurotransmitters other than dopamine
  - Inflammation

[1]Kinon BJ. Front Psychiatry. 2019;9:757.
[2]Howes OD et al. Am J Psychiatry. 2017;174(3):216-229.
[3]Potkin SG et al. npj Schizophrenia (2020) 6:1.
[4]Chouinard G et al. Psychother Psychosom 2017;86:189–219.

Pimavanserin

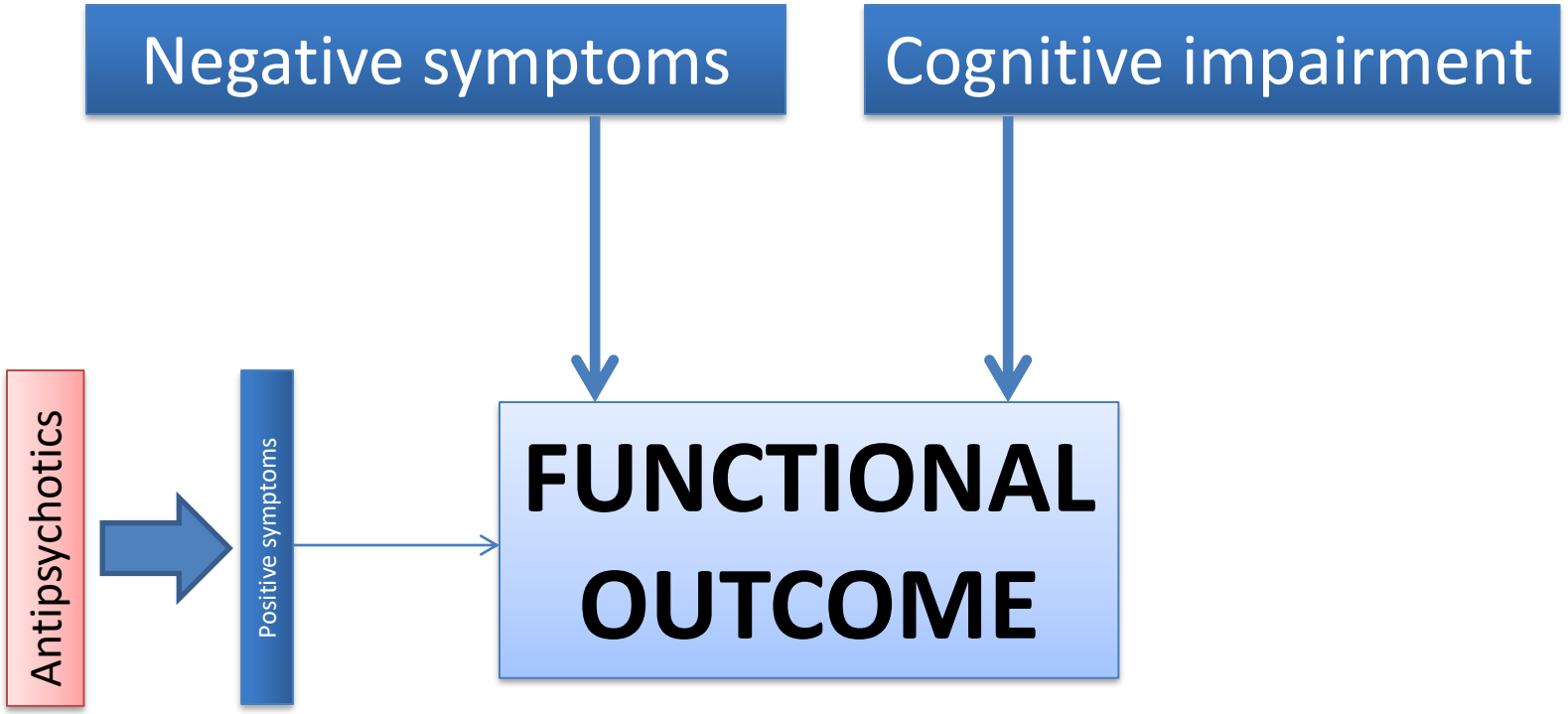
SSIA = Selective Serotonin Inverse Agonist

5-HT2A inverse agonist

- Mechanism of action[1]
  - Antagonist/inverse agonist at serotonin 5HT2A receptors
  - Less potent antagonist/inverse agonist at 5HT2C receptors
- 2016 FDA-approval for psychosis in Parkinson's disease (Nuplazid)[2,3]
- Clinical case series (N=10) for TRS[4]
- Phase III 6-week add-on trial in (somewhat) TRS (Acadia's ENHANCE-1)[5]
  - Negative results for psychosis (PANSS total score)

[1]Stahl SM. CNS Spectr. 2016;21:271-5. [2]Cummings J et al. Lancet. 2014;383(9916):533-40.
[3]Mathis MV et al. J Clin Psychiatry. 2017; 78(6):e668-e673. [4]Nasrallah HA et al. Schizophr Res. 2019;208:217-220.
[5]ClinicalTrials.gov Identifier: NCT02970292.

Symptom domains and functional outcome



Fervaha G et al. Acta Psychiatr Scand. 2014;130(4):290-9.
Rabinowitz J et al. Schizophr Res. 2012;137(1-3):147-50.
Galderisi S et al. World Psychiatry. 2014;13(3):275-87.
Mucci A et al. JAMA Psychiatry. 2021;78(5):550-559.

Negative symptoms in clinical trials

- Terminology and conceptualization[1]
  - Primary versus secondary
  - Categorical versus dimensional
  - **Persistent negative symptoms[2]**
- Clinical trials methodology
  - Which study design should we use?
  - Which scale should we use?
  - Which dimensions are treatment-responsive?
    - Expressive and experiential deficits[3]
  - Which dimensions are functionally relevant?
    - Avolition (motivational processes)[4]

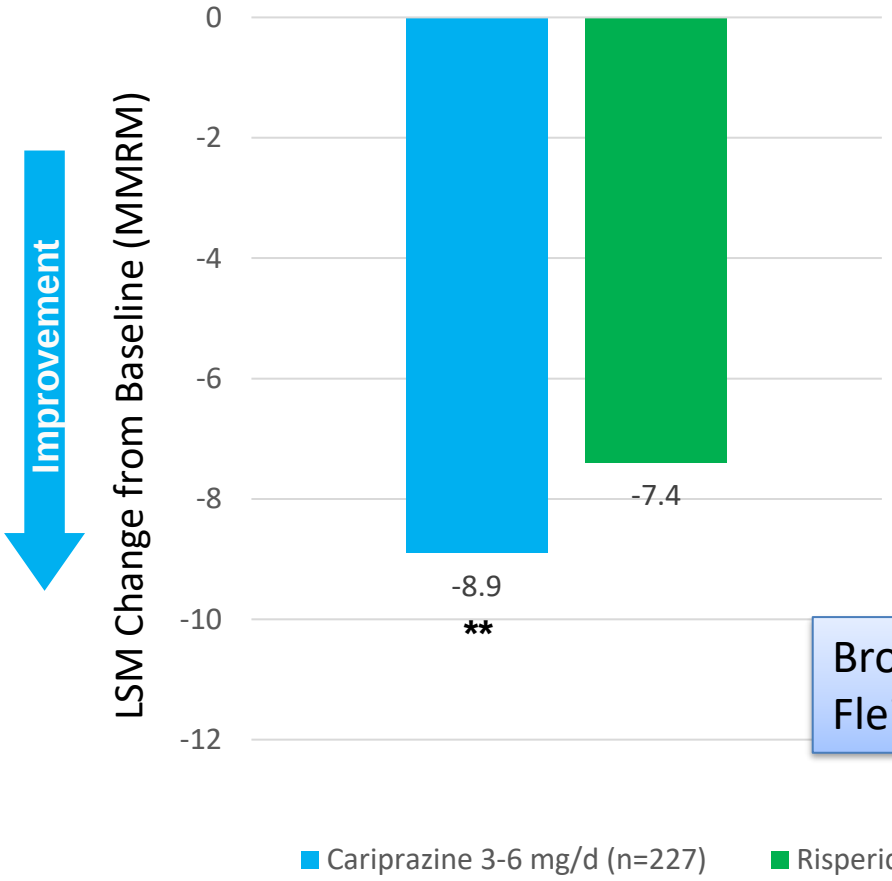
[1]Marder SR and Galderisi S. World Psychiatry. 2017;16(1):14-24.
[2]Mucci A et al. Schizophr Res. 2017;196:19-28. [3]Harvey PD et al. Schizophr Res. 2020;215:352-356.
[4]Straus GP et al. Schizophr Bull. 2020;46(4):964-970.

Cariprazine for negative symptoms

- Cariprazine is high-affinity D3 preferring D3/D2 partial agonist
- 26-week double-blind phase III RCT
  - Cariprazine 3 to 6 mg/d (N=227) versus risperidone 4 mg/d (N=229) as active reference antipsychotic
  - Stable schizophrenia patients with prominent negative symptoms but no prominent psychosis or depression
  - Minimum score of 24 on the PANSS-negative factor score (NFS)
- Outcome variables
  - Primary endpoint: PANSS-NFS
  - Secondary endpoint: Personal and Social Performance Scale (PSP)

Nemeth G et al. Lancet. 2017;389(10074):1103-13.

PANSS-NFS change from baseline to week 26* in cariprazine for negative symptoms trial



*Primary efficacy endpoint
** p < 0.01 vs. risperidone

LSM = least squares mean; MMRM = Mixed-Effects Model for Repeated Measures
Based on ITT population

Broad-spectrum efficacy
Fleischhacker W. Eur Psychiatry. 2019;58:1-9.

Nemeth G et al. Lancet. 2017;389(10074):1103-13.

The D3 story[1]

- D3 has interesting brain distribution
  - Limbic system (ventral striatum) and thalamus
- D3 is of interest for several areas of psychiatry
  - Negative symptoms
  - Drug addiction
  - Mood disorders
  - Cognition
- Interesting observation that a pure D2/3 antagonist [amisulpride] does not cause EPS
  - Full D3 antagonists: antipsychotic without causing EPS?
  - D3-preferring antipsychotic candidate F17464 under development[2,3]
- D3 agonist drugs [pramipexole, ropinirole; signal for aripiprazole] increased risk for pathological gambling, hypersexuality, compulsive shopping[4,5]

[1]Sokoloff P and Le Foll B. Eur J Neurosci. 2017;45:2-19.
[2]Slifstein M et al. Psychopharmacology. 2020;237(2):519-527.
[3]Bitter I et al. Neuropsychopharmacology. 2019;44(11):1917-1924
[4]Seeman P. Synapse. 2015;69:183-9. [5]Moore TJ et al. JAMA Intern Med. 2014;174:1930-3.

Amisulpride

- Pure, high-affinity D2/3 antagonist
  - Not available in US for schizophrenia (but for PONV as injection)
  - Low EPS and weight gain risk; prolactin elevation
- Excellent efficacy and effectiveness in clinical trials
  - EUFEST: first-episode patients
  - CUtLASS 1: quality of life
  - OPTiMiSE: first-episode patients
  - BeSt InTro: amisulpride vs. olanzapine vs. aripiprazole*
- Best efficacy for positive symptoms after clozapine
- Effective clozapine augmentation
- Drug development
  - Methylated amisulpride (LB-102)

***Johnsen E et a al. Lancet Psychiatry. 2020;7(11):945-954. NCT01446328.**

https://psychnews.psychiatryonline.org/doi/10.1176/appi.pn.2021.4.11

[Psychiatric News July 2021]

D2/3 Partial Agonist Antipsychotics

	Indications	Typical dose range	Binding affinities (Ki)	Comments
Aripiprazole	Schizophrenia Bipolar disorder Adjunct depression Tourette Autism	10 to 30 mg/d	D2/3 0.21/0.93 **D2/D3 = 0.22** 5-HT1a 1.7 5-HT 2a 3.4	Half-life 94 h** CYP3A4 CYP2D6 High affinity for 5-HT 2c
Brexpiprazole	Schizophrenia Adjunct depression	2 to 4 mg/d 0.5 to 2mg/d	D2/3 0.30/1.1 **D2/D3 = 0.27** 5-HT1a 0.12 5-HT 2a 0.47	Half-life 91 h CYP3A4 CYP2D6
Cariprazine***	Schizophrenia Acute mania/mixed *Negative symptoms**	1.5 to 6 mg/d 3 to 6 mg/d	D2/3 0.49/0.09 **D2/D3 = 5.76** 5-HT 1a 2.6 5-HT 2a 18.8	Longest half-life (1-3 weeks)** CYP3A4

***Not** FDA-approved **Half-life including active metabolite

***Cariprazine metabolite has very high D3 selectivity D2/D3 = 24.87

Frankel JS and Schwartz TL. Ther Adv Psychopharmacol. 2017;7:29–41.
Kiss B et al. J Pharmacol Exp Ther. 2010;333:328-40.

Pimavanserin

5-HT2A inverse agonist

SSIA = Selective Serotonin Inverse Agonist

- Mechanism[1]
  - Antagonist/inverse agonist at serotonin 5HT2A receptors
  - Less potent antagonist/inverse agonist at 5HT2C receptors
- 2016 FDA-approval for psychosis in Parkinson's disease (Nuplazid)[2,3]
- Phase 3 ENHANCE-1 for refractory positive symptoms negative*
- Phase 2 ADVANCE (NCT02970305)**
  - Primary endpoint Negative Symptom Assessment-16 (NSA-16) total score
  - ES = 0.34 for 34 mg dose
- Phase 3 ADVANCE-2 (NCT04531982) enrolling
- Safety of pimavanserin[4,5]

[1]Stahl SM. CNS Spectr. 2016;21:271-5. [2]Cummings J et al. Lancet. 2014;383(9916):533-40.
[3]Mathis MV et al. J Clin Psychiatry. 2017; 78(6):e668-e673.
[4]Tampi RR et al. World J Psychiatry. 2019;9(3):47-54. [5]Tariot PM et al. N Engl J Med 2021; 385:309-319.
*https://ir.acadia-pharm.com/news-releases/news-release-details/acadia-pharmaceuticals-announces-top-line-results-phase-3
**https://ir.acadia-pharm.com/news-releases/news-release-details/acadia-pharmaceuticals-announces-positive-top-line-results

L-methylfolate for negative symptoms

- Folate metabolism
  - MTHFR gene polymorphism
    - MTHFR C677 T
  - L-methylfolate
    - Fully reduced, active form of folate
- 12-week RTC
  - 15 mg L-methylfolate (N=29; 26 placebo)
  - Improved PANSS total (d=0.61, p=0.03)
  - Increased thickness of mPFC and reduced limbic connectivity

Roffman JL et al. Mol Psychiatry. 2018;23(2):316-322.
Review: Brown HE and Roffman JL. Harv Rev Psychiatry. 2016;24(2):e1-7.

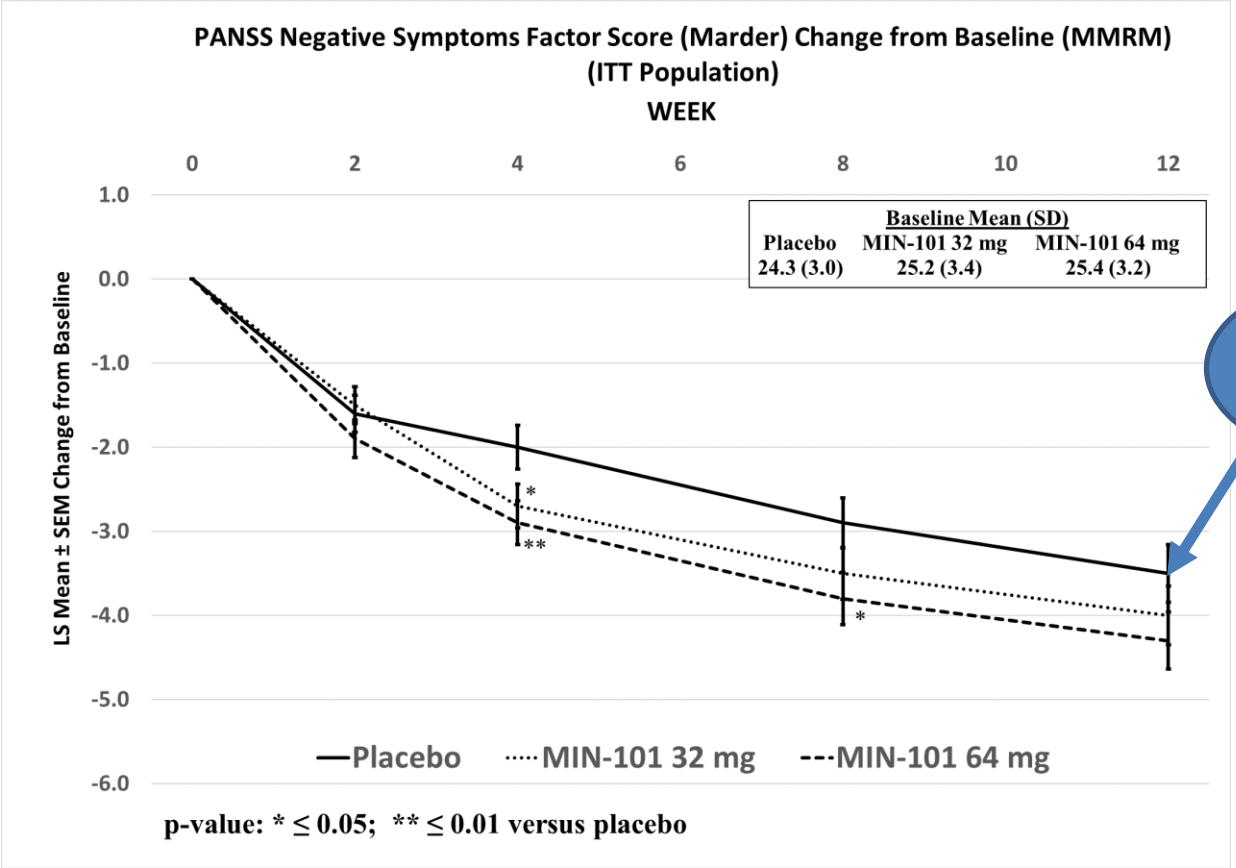
Roluperidone (MIN-101)

- 5-HT2A and σ2 receptor antagonist
- Positive phase II trial
  - Primary end point: negative symptoms[1]
  - Secondary end point: cognition[2]
- Negative phase III trial
  - Primary end point: NSFS
  - Secondary end point: PSP
- Positive (?) long-term open-label extension trial
  - Continuous improvement of negative symptoms
  - Few relapses

NSFA =PANSS Marder Negative Symptoms Factor Score
PSP =Personal and Social Performance Scale Total Score

[1]Davidson M et al. Am J Psychiatry. 2017;174:1195-1202.
[2]Keefe RSE et al. J Clin Psychiatry. 2018;79:e1-e6.
http://www.minervaneurosciences.com/innovation-pipeline/min-101/
http://ir.minervaneurosciences.com/news-releases/news-release-details/minerva-neurosciences-announces-results-phase-3-trial-0

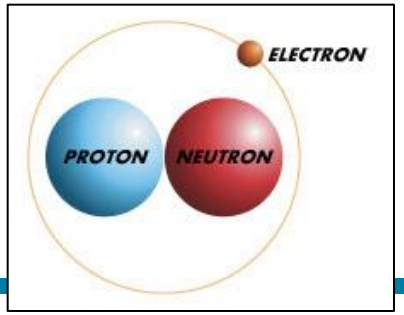
Roluperidone (MIN-101) for negative symptoms



Placebo response

https://www.globenewswire.com/news-release/2020/05/29/2040974/0/en/Minerva-Neurosciences-Announces-Results-From-Phase-3-Trial-of-Roluperidone-MIN-101-for-Treatment-of-Negative-Symptoms-in-Schizophrenia.html

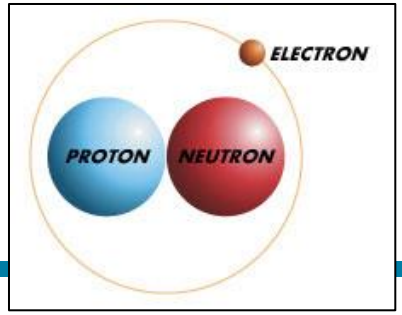
Deuterated medicines



- Hydrogen isotopes
  - Hydrogen (H); "heavy" H = deuterium (D); tritium (T)
  - D is stable (not radioactive!) and not toxic (1-2 gm)
  - (Remember "heavy water")
- Deuteration of a molecule
  - Same 3-D structure!
    - Preserves pharmacodynamic properties
  - C-D bond 10x stronger than C-H bond
    - Changes pharmacokinetics: slows metabolism = longer half-life
- First FDA-approved deuterated product: Austedo

http://www.concertpharma.com/news/documents/IPT32ConcertPharma.pdf

AVP-786



- "Broad-spectrum psychotropic"
- AVP-786 = deuterated (d6)-dextromethorphan + ultra-low dose quinidine
  - Dextromethorphan is uncompetitive NMDA receptor antagonist, sigma-1 receptor agonist, and inhibitor of serotonin and norepinephrine transporters
  - Increase half-life
    - Deuterated dextromethrophan molecule
    - Added (low-dose) quinidine which is inhibitor of CYP 2D6
- Avanir clinical development programs
  - Phase III: Agitation in Alzheimer's disease
  - Phase II: Residual (negative) symptoms of schizophrenia*
  - Phase III: Negative symptoms of schizophrenia

*ClinicalTrials.gov Identifier: NCT02477670

**ClinicalTrials.gov Identifier: NCT03896945

Treatment for negative symptoms

Treatment	Clinical trial	Mechanism of action	Results
Cariprazine		D3-preferring D3/D2 partial agonist Active comparator Primary endpoint: PANSS-NFS	Better than risperidone
Pimavanserin (Acadia)	Phase II; NCT02970305 Phase III; NCT04531982	5-HT2 inverse agonist Add-on Primary endpoint: NSA-16	Positive phase II
AVP-786 (Avanir)	Phase II; NCT02477670 Phase III; NCT03896945	NMDA antagonist, sigma-1 agonist, SER and NOR transporter inhibitor Add-on Primary endpoint: PANSS NSFS	Positive phase II
Lu AF11167 (Lundbeck)	Phase II; NCT03793712	PDE-10 inhibitor Monotherapy Primary endpoint: BNSS	
Roluperidone [MIN-101] (Minerva)	Phase III; NCT03397134	5-HT2A and σ2 antagonist Add-on Primary endpoint: PANSS NSFS	Positive phase II Negative phase III
TAK-831 (Takeda)	Phase II	D-amino acid oxidase (DAAO) inhibitor Monotherapy	

Treatment for CIAS

CIAS = Cognitive Impairment Associated with Schizophrenia

- Avoid adding insult to injury
  - Reduce anticholinergic burden
    - Short-term and long-term risks (10% of dementia cases)[1]
  - Quit smoking![2]
  - Treat cardiovascular risk factors[3]
- Consider cognitive remediation, if available[4]
  - Active therapist, structured, integrated with rehab
- Psychopharmacology add-on strategies
  - Graveyard of drug development
  - BUT: CONNEX trial program for BI 425809 promising[5]
    - Medication combined with computerized cognitive training[6]

By age 66, 28% of patients with schizophrenia have dementia diagnosis (compared to 1.3%)!
- Stroup TS et al. JAMA Psychiatry. 2021;78(6):632-41.

[1]Coupland CAC et al. JAMA Intern Med. 2019179(8):1084-1093. [2]Vermeulen JM et al. Am J Psychiatry. 2018;175(11):1121-8.
[3]Hagi K et al. JAMA Psychiatry. 2021;78(5):510-518 [Cardiovascular riks factors and cognitive impairment]
[4]Vita A et al. JAMA Psychiatry. 2021.78(8):848-858. Review and meta-analysis
[5]Fleischhacker WW et al. Lancet Psychiatry. 2021;8(3):191-201. [6]Harvey PD et al. Clin Drug Invest. 2020:40:377-85.

Exercise for CIAS

- The challenge
  - Cardiovascular morbidity and mortality in SMI patients
  - Sedentary life-style associated with poor cognition[1]
- The simple solution
  - Exercise is "neuroprotective"
  - Exercise has broad effects on well-being[2]
    - Improves global cognition[3]
    - Key pathways: inflammatory pathways, BDNF (hippocampus)[4]
- Challenges
  - Implementation: supported exercise
  - Maintaining gains: sustaining exercise
    - Need clinical trial with physical activity as end-point
    - Improving Cognition Via Exercise (ICE) in Schizophrenia[5]

COVID-19 adjustments

[1]Hamer M et al. Psychol Med. 2009;39:3-11.[2]Noordsy DL et al. Am J Psychiatry. 2018;175(3):209-214.
[3]Firth J et al. Schizophr Bull. 2017;43:546-556. [4]Kimhy D et al. Schizophr Bull. 2015;41(4):859-68.
[5]ClinicalTrials.gov Identifier: NCT03270098. [PI David Kimhy]

Treatment for CIAS

CIAS = Cognitive Impairment Associated with Schizophrenia

Treatment	Company	Mechanism of action	Results
BI-425809	Boehringer-Ingelheim Phase II (PoC) NCT03859973	Glycine-transporter-1 (GLYT-1) inhibitor Add-on trial Plus computerized cognitive training Primary outcome: MCBB	Positive results FDA fast tracked
Cannabidiol		Partial cannabinoid$_1$ receptor antagonist Add-on trials	2 negative studies
BIIB-104	Biogen Phase II NCT03745820	AMPA positive allosteric modulator Primary outcome: MCBB (working memory domain)	Recruiting [TALLY]

B. TOLERABILITY

FDA approval December 23, 2019

Lumateperone (ITI-007)

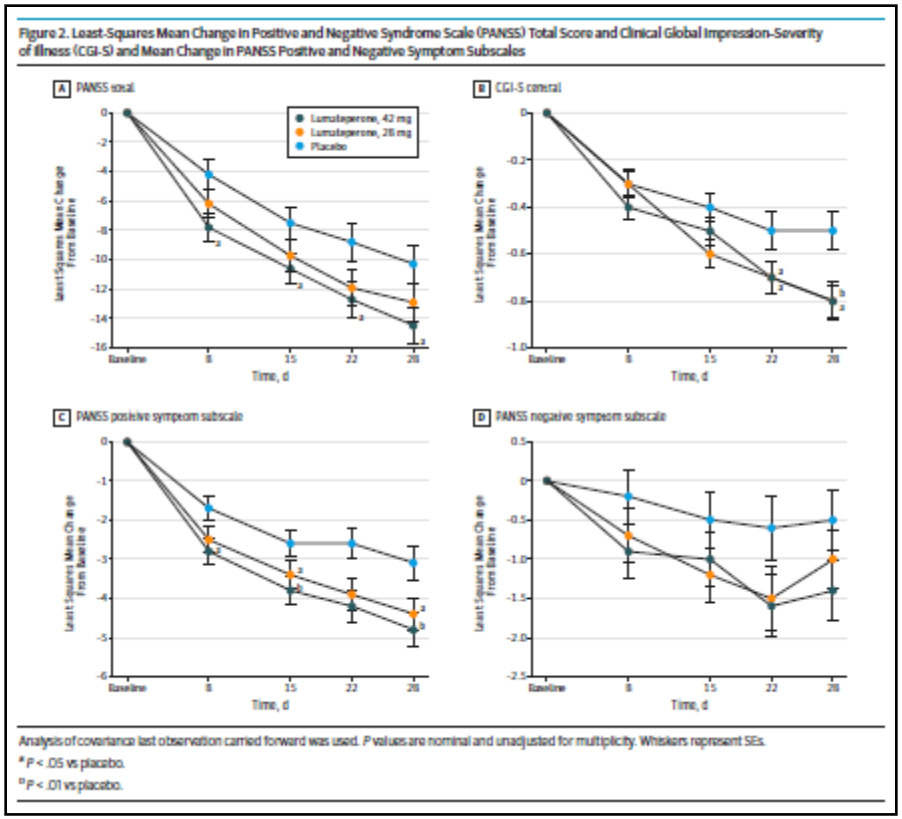
Brand name CAPLYTA, from Intra-Cellular Therapies

- Mechanism of Action
  - 5-HT2A antagonist (K_i=0.54 nM)*
    - Antagonism for 5-HT2A >>> (post-synaptic) D2 receptors[1]
  - D2 antagonism
    - Only 40% D2 occupancy in PET study
    - Pre-synaptic partial agonist and post-synaptic antagonist at D_1/D_2
  - Also binds to serotonin transporter; D1; others; low muscarinic and histaminergic[2]
- Schizophrenia clinical trials program
  - NCT03817528, TRS (Lieberman); 40 to 60 mg/d; terminated
- Other clinical trials
  - Bipolar depression

*Very high affinity. 60-fold higher than for D_2
Lower dose (10 mg) preferentially 5-HT2A

[1]Vanover KE et al. Neuropsychopharmacology. 2019;44(3):598-605.
[2]Kumar B et al. Drugs Today. 2018;54(12):713-9.

Lumateperone (ITI-007) – phase III



42 mg lumateperone (active moiety)
=
60 mg lumateperone tosylate

Effect size (42 mg) = 0.3

Good tolerability
- **Low EPS risk**
- **Low metabolic risk**

Correll CU et al. JAMA Psychiatry. 2020;77(4):349-358. [NCT02282761]
Kantrowitz JT. JAMA Psychiatry. 2020;77(4):343-344. [Editorial]

The day the music died

MELT trial

MELT = MEtformin and Lorcaserin for WeighT Loss in Schizophrenia

- Phase IV trial
- 52-week RTC comparing
  - lorcaserin/metformin combination treatment
    - Lorcaserin 10 bid
    - Metformin 1000 bid
  - lorcaserin monotherapy
  - Placebo
- Target population
  - Chronic, treated [illegible] overweight, no diabetes)
- Lorcaserin (B[illegible]c agonist anorectic
  - Sched[illegible]
  - S[illegible]me unlikely[1]
  - [illegible]y less likely than with fenfluramine[2]

February 13, 2020 – Lorcaserin (brand name Belviq) withdrawn from market[3]

ClinicalTrials.gov Identifier: NCT02796144 [1]**Nguyen CT et al. Clin Ther. 2016;38(6):1498-509.**
[2]**Halpern B and Halpern A. Expert Opin Drug Saf. 2015;14(2):305-15.**
[3]https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market

Samidorphan/olanzapine (ALKS 3831)

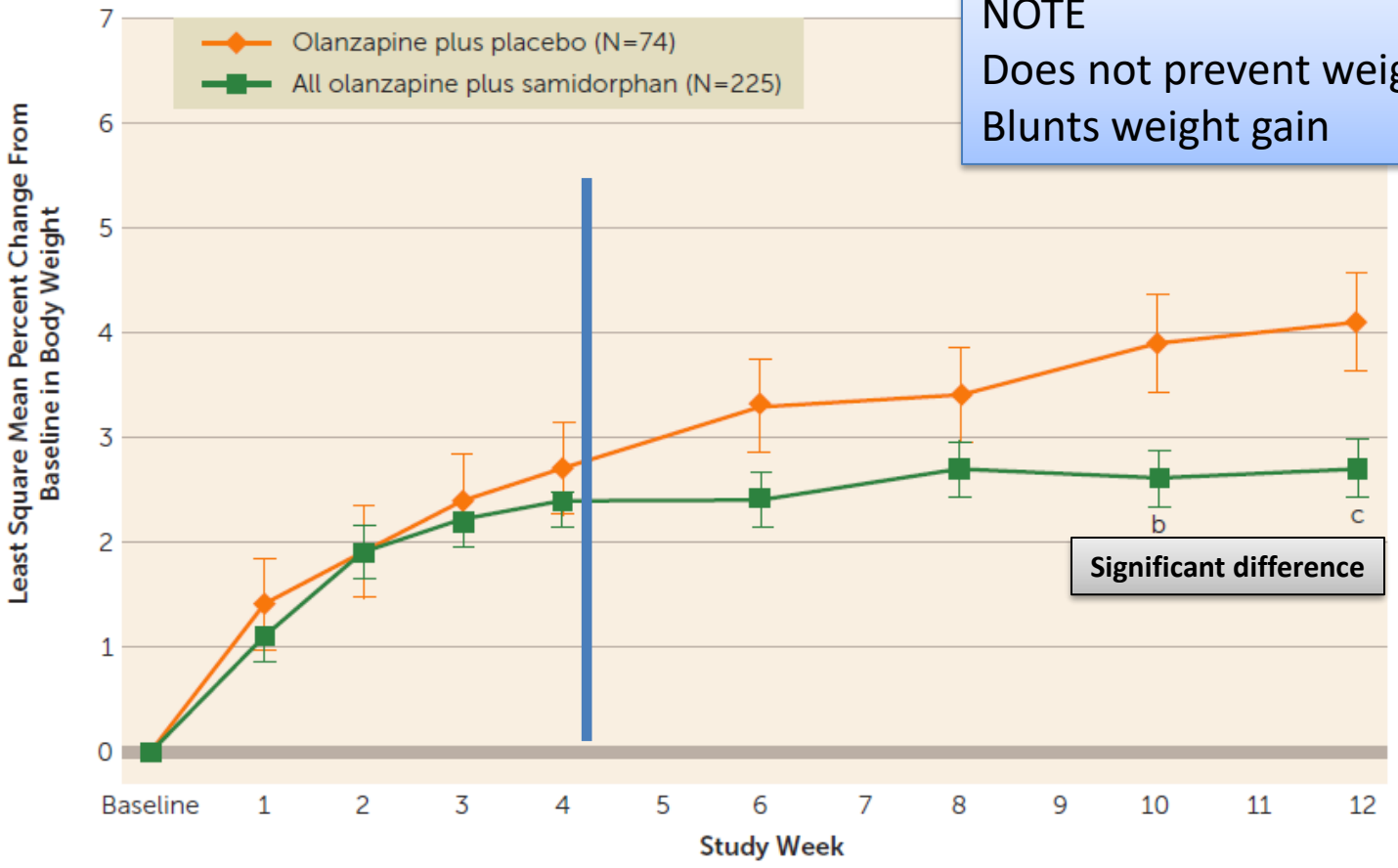
FDA approval Jun 1, 2021

- ALKS 3831 = samidorphan + olanzapine
  - Samidorphan[1]
    - 3-carboxamido-4-hydroxynaltrexone
    - Potent mu-opioid receptor antagonist
- Alkermes development program
  - ENLIGHTEN phase III development program
    - Short-term (4 weeks) ENLIGHTEN-1 established efficacy[2]
    - Long-tem (6 months) ENLIGHTEN-2 (completed)[3]
      - Lower percent weight gain and lower proportion 10% or more
  - No benefit for schizophrenia and alcohol use disorder[4]
    - Post-hoc analysis of CATIE trial[5]

[1]Turncliff R et al. Clin Ther. 2015;37(2):338-48. Silverman BL et al. Schizophr Res. 2018;195:245-251. [Phase I, PoC]
[2]Potkin SG et al. J Clin Psychiatry. 2020;81(2):61-9.
[3]ClinicalTrials.gov Identifier: NCT02694328. [4]Brunette MF et al. J Clin Psychiatry. 2020;81(2):22-9.
[5]Pathak S et al. J Clin Psychiatry. 2020;81(2):19m12731.

Samidorphan/olanzapine (ALKS 3831)

Phase II (PoC); NCT01903837



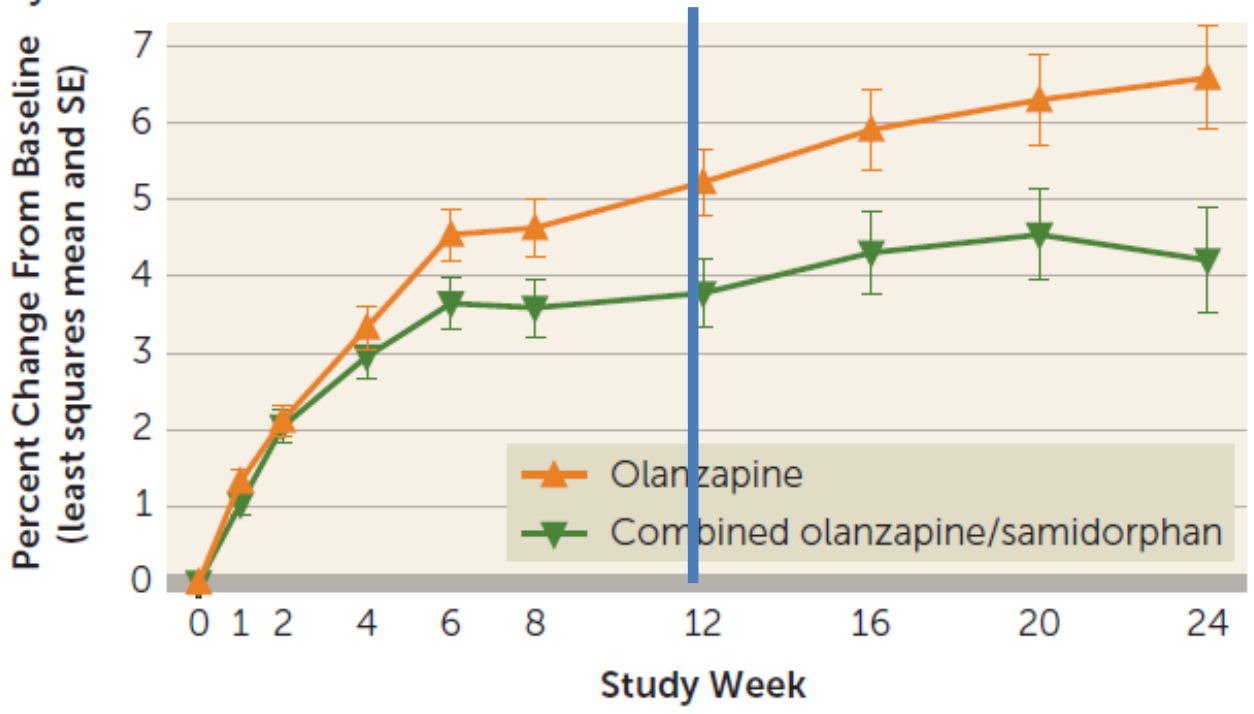
NOTE
Does not prevent weight gain
Blunts weight gain

Martin WF et al. Am J Psychiatry. 2019;176(6):457-67.

Samidorphan/olanzapine (ALKS 3831)

Phase III; NCT02873208

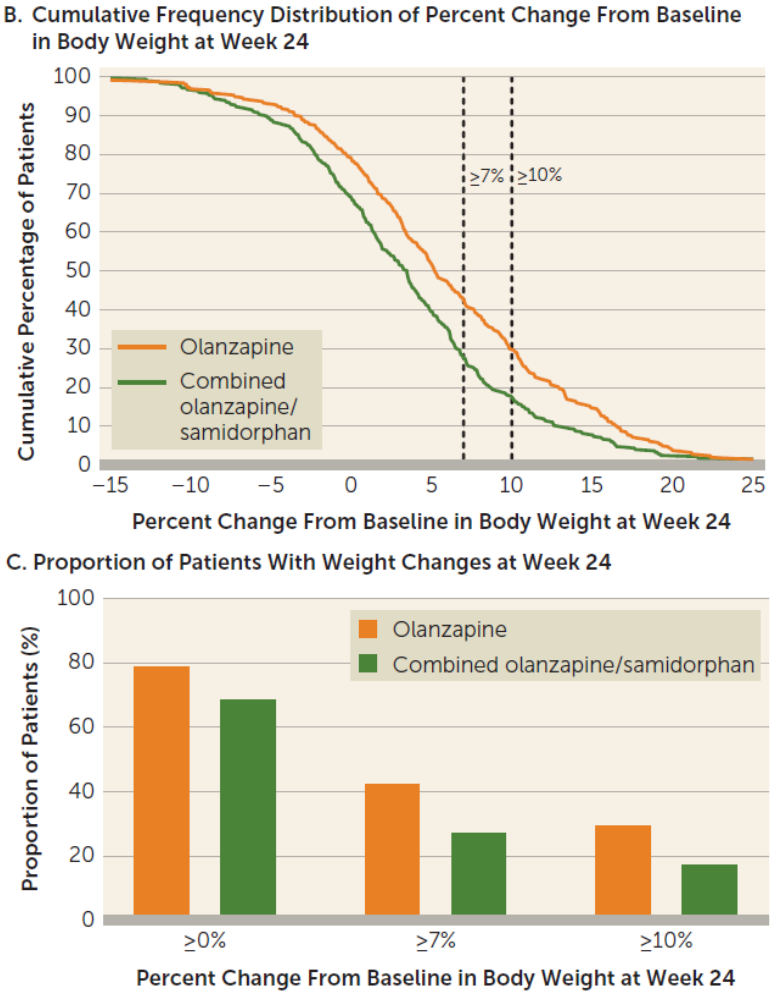
A. Least Squares Mean of Percent Change From Baseline in Body Weight by Visit



Correll CU et al. Am J Psychiatry. 2020;177:1168-1178.

Samidorphan/olanzapine (ALKS 3831)

Phase III; NCT02873208



- Significant difference in primary outcome(s)
  - Weight, weight distribution
- No difference on metabolic measures
- Sample limited to BMI between 18 and 30
- Comparison to metformin needed

Correll CU et al. Am J Psychiatry. 2020;177:1168-1178.
Buchanan RW. Am J Psychiatry. 2020;177(12):1113-1114. [Editorial]

Beyond insulin

- Antipsychotics increase glucagon[1]
- Newer class (2010) of glucagon-like peptide-1 receptor agonist (GLP-1 receptor agonist)
  - Semaglutide[2]
    - 16% weight loss in 68-week trial with weekly injection
- Studied in schizophrenia
  - Liraglutide[3]
  - Loss of metabolic benefit once stopped[4]

[1]Aslanoglou D et al. Translational Psychiatry. 2021;11(1):59.
[2]Wadden TA et al. JAMA. 2021;325(14):1403-1413. [STEP-3 trial. NCT03611582]
[3]Larsen FR et al. JAMA Psychiatry. 2017;74(7):719-728.
[4]Svensson CK et al. Acta Psychiatr Scand. 2019;1139(1):26-36. [One-year follow-up]

C. ADHERENCE

Antipsychotic Therapeutic Drug Monitoring (TDM)

- Long history in psychiatry
  - Lithium
  - Tricyclic antidepressants
- Currently underutilized
- Renewed interest
  - First guideline for TDM published by TDM taskforce of AGNP in 2004 (update 2011 and 2017)
    - TDM best established for CLOZ, OLANZ, HAL, FLU, PER
  - International consensus statement 2020*
  - Development of new assays for antipsychotics**

AGNP = Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie

Hiemke C, et al. Pharmacopsychiatry. 2018 Jan;51(1-02):e1.
Horvitz-Lennon M, et al. Am J Psychiatry. 2017;174(5):421-426.
***Schoretsanitis G et al. J Clin Psychiatry. 2020;81(3):19cs13169. [Consensus Statement]**
****https://saladax.com/saladax-biomedical-launches-clozapine-test-in-the-us-after-fda-grants-market-authorization/**

Long-acting antipsychotics

- Long-acting injectable antipsychotics
  - Risperidone extended-release SC injectable
    - RISE and SHINE phase 3 studies from Teva
    - Every month or every two months
- Long-acting oral antipsychotics
  - Once-weekly risperidone capsule (LYN-005, Lyndra Therapeutics)
  - Phase 2 trial positive (NCT04567524)[1]
  - Whatever happened to penfluridol?
    - T1/2 66 hours = "oral depot antipsychotic"
    - Once-a-week dosing

[1]**Results presented at SIRS 2021 Annual Meeting, April 18, 2021**

THINKING OUTSIDE THE BOX

Transdermal delivery systems

- History
- Examples in psychiatry
  - Nicotine patch
  - Schizophrenia
    - Asenapine patch (FDA-approved)
    - Xanomeline patch
    - Aripiprazole patch once-a-week
  - Other
- Advantages
  - Avoids first-pass effect
  - Better GI tolerability
  - Easy use
  - Visual adherence

Citrome L et al. J Clin Psychiatry. 2019;80(4):18nr12554.
Stevens JR et al. Psychosomatics. Sep-Oct 2015;56(5):423-44.

BXCL501

NDA submitted to FDA

PDUFA date January 5, 2022

- Dexmedetomidine
  - Highly selective alpha-2a receptor agonist
  - Orally dissolving film formulation
  - Sublingual/buccal use for oral mucosa absorption
- Efficacy
  - SERENITY I and II phase 3 studies for acute agitation in ED (patients with schizophrenia and bipolar disorder)
  - PANSS-Excited Component scale (5 items)
  - Met endpoint after 2 hours
  - Side effects: somnolence, dizziness, dry mouth, hypotension, hypoesthesia, paresthesia

Xanomeline

Clinical trials program
EMERGENT

mAChR agonist

- Muscarinic agonist
  - *Orthosteric* muscarinic acetylcholine receptor (mAChR) agonist
    - M1/M4-preferring; M5 antagonist
  - Effective for treatment of schizophrenia[1]
  - Poor tolerability due to dose-limiting peripheral action
    - Trial with patch in DAT
  - Schizophrenia subtype: low cortical M1 receptor density[2]
- Co-formulated with trospium as KarXT
  - Karuna = Sanskrit for compassion
  - Trospium (brand name Sanctura) = FDA-approved peripheral muscarinic antagonist for overactive bladder; 20 mg bid
  - Met primary endpoint in Phase II trial, with improved tolerability[3]
- Potential treatment targets
  - Schizophrenia: psychosis, negative symptoms, cognition
  - Alzheimer's disease: psychosis, cognition
  - Analgesic

[1]Shekhar A et al. Am J Psychiary. 2008 Aug;165(8):1033-9.

[2]Dean B et al. Schizophr Bull. 2018 Apr; 44(Suppl 1): S70–S71. Hopper S et al. Int J Neuropsychopharmacol. 2019;22(10):640-650.

[3]Brannan SK et al. NEJM. 2021;384(8):717-726. Neary J et al. NEJM. 2021;384(25):e105. [Editorial]

Efficacy without D2-binding

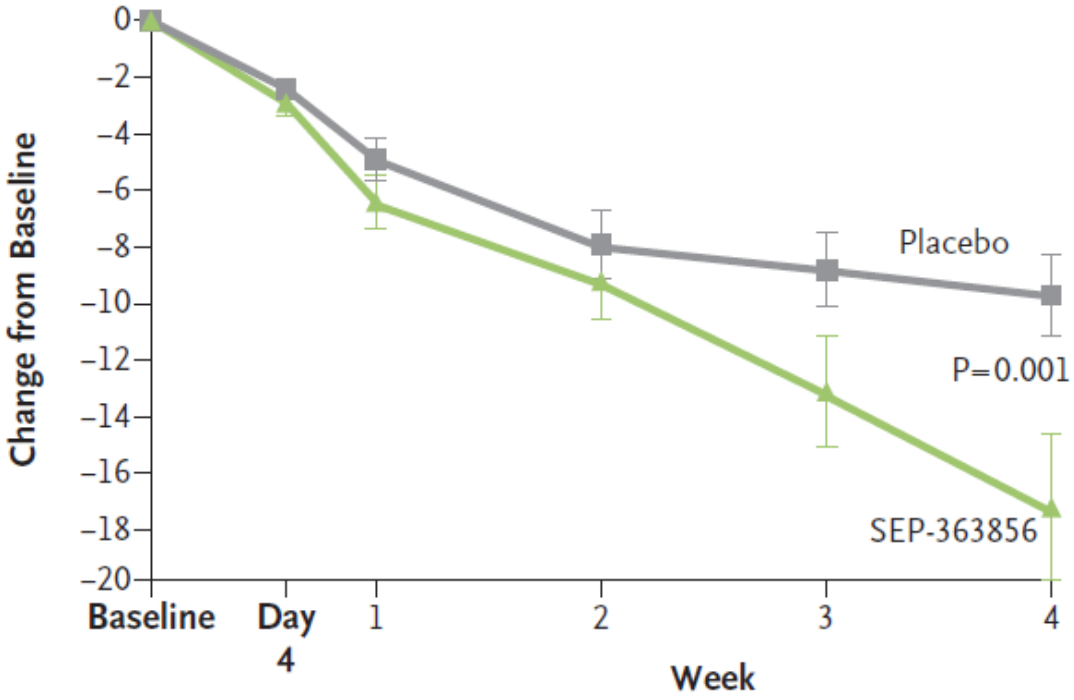
Monoamine receptor activator

- SEP-363856 [Sunovion]
- "First in class"
  - Non-D2-receptor-binding antipsychotic
  - MOA: TAAR1 + 5-HT1A
- Phase II trial [NCT02969382]
  - 4-week RCT (drug versus placebo)
  - Efficacy for PANSS total score
    - ES 0.45
  - Safety and tolerability
    - One death in treatment group (patient had heart disease)

TAAR1 = trace amine-associated receptor 1

Koblan KS et al. N Engl J Med. 2020;382(16):1497-1506.
Goff DC. N Engl J Med. 2020;382(16):1555-1556. [Editorial]

SEP-363856



No. of Patients						
Placebo	125	125	122	117	113	100
SEP-363856	120	120	115	109	102	96

Koblan KS et al. N Engl J Med. 2020;382(16):1497-1506.
Goff DC. N Engl J Med. 2020;382(16):1555-1556. [Editorial]

Targeting neurocircuits

- Lesion-based module disruption
  - Critical lesion takes out brain module
  - Classical neurology
- Distributed yet delineated circuit dysfunction
  - Alexander's parallel, segregated circuits[1]
  - Neuropsychiatry
- Large-scale network disruption
  - The search for specific cellular pathology (e.g., chandelier interneurons and GABA[2])
- TMS for schizophrenia[3,4]
- Transcranial direct current stimulation (tDCS)[5]

[1]Alexander GE et al. Annu Rev Neurosci 1986;9:357. [2]Lewis DA. Dev Neurobiol 2011;71:118.
[3]Dougall N et al. Cochrane Database Syst Rev. 2015 Aug 20;(8):CD006081.
[4]Brady RO et al. Am J Psychiatry 2019;176(7):512–520. [5]Gupta T et al. Front Behav Neurosci. 2018 May 28;12:94.

STARTS trial

Schizophrenia Treatment With Electric Transcranial Stimulation

- 2-site RTC in Sao Paulo
- N=100
- Primary outcome variable
  - PANSS **negative symptom subscale** score
- Intervention
  - **Frontotemporoparietal** transcranial direct current stimulation (**tDCS**)
  - Short, acute treatment: 10 sessions within 5 days (twice daily)
- Results
  - Superior to sham at 6 weeks; NNT = 3
    - Response rate (20% improvement) 40% tDCS versus 4% sham
  - Well tolerated
  - Treatment effects persisted at 12 weeks

Da Costa Lane Valiengo L et al. JAMA Psychiatry. 2020;77(2):121-129.
Seminal study: Bruneli J et al. Am J Psychiatry. 2012;169(7):719-24.

Diets – food and fasting as treatment

- Nutritional psychiatry[1]
- Types of dietary interventions[2]
  - Adding something (vitamins, micronutrients)
  - Removing something (toxins, allergens)
  - Combination in the form of "healthy diets"
  - Gut microbiome
  - Fasting and ketogenic diet
- Ketogenic diet[3]
  - Well-established in treatment-resistant epilepsy
  - Mechanism: restoration of normal energy metabolism

[1]Adan RAH et al. European Neuropsychopharmacology. 2019;29(12):1321-1332. [Review]
[2]Palmer CM. J Clin Psychiatry. 2020;81(1):62-63.
[3]Palmer CM et al. Schizophr Res. 2019:208:439-440.

"However beautiful the strategy*, you should occasionally look at the results."**

-Sir Winston Churchill

*** = your drug mechanism**
**** = how effective your drug is**

Haas LF. JNNP 1996;61:465.

Why is CNS drug development so hard?

- Schizophrenia as a syndrome
  - One drug does not fit all psychopathology
  - One drug does not fit all illness stages
  - Unknown pathophysiology
  - No biomarkers[1]
- Schizophrenia as a circuit disorder
  - One drug target paradigm is mostly wrong
- Clinical trials methodology
  - Placebo response[2]
  - Heterogeneity problem (subgroups)
  - Deception and professional patients[3]
  - Non-linear dosing
  - Measuring improvement and ceiling effects (function)

[1]Goff DC et al. Eur Neuropsychopharmacology. 2016;26(6):923-37.
[2]Leucht S et al. Am J Psychiatry. 2017;174(10):927-942.
[3]Devine EG et al. Clin Trials. 2013;10(6):935-48.

The way forward

- Heterogeneity as opportunity[1]
  - Focus on biology of treatment-resistance
  - Focus on other sources of treatment resistance
  - Focus on circuits underlying specific symptoms clusters
- Improve clinical trials methodology[2]
  - Increasing placebo response and decreasing treatment effect in schizophrenia trials[2]
  - Precision Clinical Trials (PCTs)[3]
    - Treatment-targeted enrichment, adaptive treatment, precision measurement
- Harness disruptive psychopharmacology[4]

[1]McCutcheon RA et al. JAMA Psychiatry. 2020;77(2):201-10.
[2]Gopalakrishnan M et al. J Clin Psychiatry. 2020;81(2):38-44. Editorial: Laughren TP. J Clin Psychiatry. 2020;81(2):19com13110.
[3]Lenze EJ et al. JAMA Psychiatry. 2020;77(7):663-664.
[4]Heifets BD and Malenka RC. JAMA Psychiatry. 2020;76(8):775-776. [Viewpoint]

Promising pipeline for CNS drugs

Compound	Mechanism of action	Target symptom	Company	Phase	NCT number Program name
CTP-692	D-serine analogue	General	Concert	2	04158687
KarXT	Muscarinic agonist	General	Karuna	2 **3**	03697252 **04659161**
BIIB-104	AMPA agonist	Cognition	Biogen	2	03745820
TAK-831	DAAO inhibitor	Negative	Takeda	2	03382639
SEP-(363)856	TAAR-1 5-HT1A agonist	General Negative	Sunovion	2 3	02969382 04072354
BI 425809	Glycine transporter-1 inhibitor	Cognition	Boeringer Ingelheim	2	03859973
Pimavanserin	5-HT2A inverse agonist	Positive Negative	Acadia	3 3	02970292 04531982
Roluperidone	Sigma-2 antagonist 5-HT2A antagonist	Negative Cognition	Minerva	3	03397134