MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

New treatments for schizophrenia

Oliver Freudenreich, MD, FACLP
Co-Director
MGH Schizophrenia Clinical and Research Program

Disclosures

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

- Alkermes – Consultant honoraria (Advisory Board)
- Avanir – Research grant (to institution)
- Janssen – Research grant (to institution), consultant honoraria (Advisory Board)
- Neurocrine – Consultant honoraria (Advisory Board)
- Novartis – Consultant honoraria
- Otsuka – Research grant (to institution)
- Roche – Consultant honoraria
- Saladax – Research grant (to institution)
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- UpToDate – Royalties, honoraria (content developer and editor)
- American Psychiatric Association – Consultant honoraria (SMI Adviser)

New words we learned this year

Merriam-Webster

- COVID-19, coronavirus, nCoV, SARS-CoV-2
- SARS-CoV, MERS-CoV
- Index case, super-spreader, patient zero, contact tracing
- Social distancing, self-quarantine

Other

- PHE, PPE, N-95
- R0 (basic reproductive number)
- Hydroxychloroquine, remdesivir, convalescent serum therapy
- Cordon sanitaire

https://www.merriam-webster.com/words-at-play/new-dictionary-words-coronavirus-covid-19

Outline

1. Unmet needs
   A. Schizophrenia is a syndrome with dimensions
      - Refractory positive symptoms
      - Prominent negative symptoms*
      - Neurocognitive impairment*

   *Contributor to functional impairment

   B. Long-term tolerability of antipsychotics
      - Extrapyramidal symptoms
      - Weight gain

   C. Adherence
2. Thinking outside the box
3. Why is drug development so hard?

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

A. SYMPTOMS

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.
Kane JM et al. J Clin Psychiatry. 2019 Mar 5;80(2). pii: 18com12123. [Clinical Guidance]

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/**

Lu AF35700

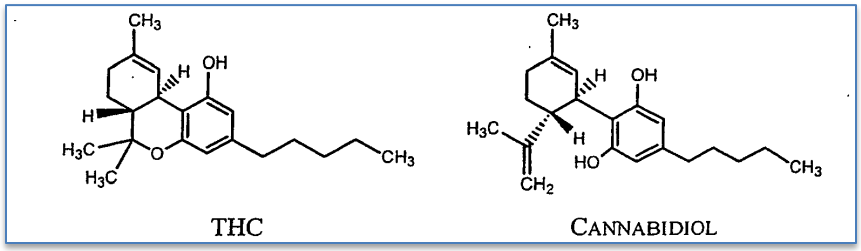
- Mechanism of action
  - Predominant D1 vs. D2 receptor antagonist
    - Profile comparable to clozapine
  - High occupancy 5-HT2A and 5-HT6 serotonin receptors
- Phase III development program initiated by Lundbeck ("DayBreak" and "Debut")
  - Target population: treatment-refractory schizophrenia patients
  - FDA fast-track designation for TRS
  - 6 weeks prospective treatment with olanzapine or risperidone, then 10 weeks 10 mg/20 mg or olanzapine/risperidone
  - Nightfall for DayBreak: no difference in PANSS total score[1]
  - Waiting for 52-week Debut extension data

ClinicalTrials.gov Identifier: NCT02717195 [DayBreak]
ClinicalTrials.gov Identifier: NCT02892422 [Debut]

[1]https://investor.lundbeck.com/news-releases/news-release-details/lundbeck-updates-clinical-phase-iii-study-lu-af35700-treatment

Cannabidiol (CBD)

- Cannabis sativa
  - THC
  - CBD



- Endocannabinoids
  - Anandamine* (“bliss”)
  - CB receptors
  - Biomarker development[1]

*N-arachidonoylethanolamine or AEA

Non-dopamine antipsychotic?

- First case report[2]
- Positive add-on RTC[3]
  - 1000 mg/d CBD
  - Positive symptoms
    - PANSS -1.4, [95% CI=-2.5, -0.2]
  - Cognition negative
- Negative add-on RCT[4]
  - PANSS total score; MCCB
- Effects on fMRI in CHR[5]

[1]Minichino A et al. JAMA Psychiatry. 2019; 76(9):914-923.

[2]Zuardi AW et al. J Clin Psychiatry. 1995;56:485-6.
[3]McGuire P et al. Am J Psychiatry. 2018;175(3):225-31.
[4]Boggs DL et al. Psychopharmacology. 2018;235(7):1923-32.
[5]Bhattacharyya D et al. JAMA Psychiatry. 2018; 5(11):1107-17.
Kopelli E et al. Psychiatry Res. 2020;291:113246. [meta-analysis]

Pimavanserin

5-HT2A inverse agonist

- Mechanism[1]

SSIA = Selective Serotonin Inverse Agonist

  - 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
- Phase III (Acadia's HARMONY study) for dementia-related psychosis[6]

[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. [6]ClinicalTrials.gov Identifier: NCT03325556.

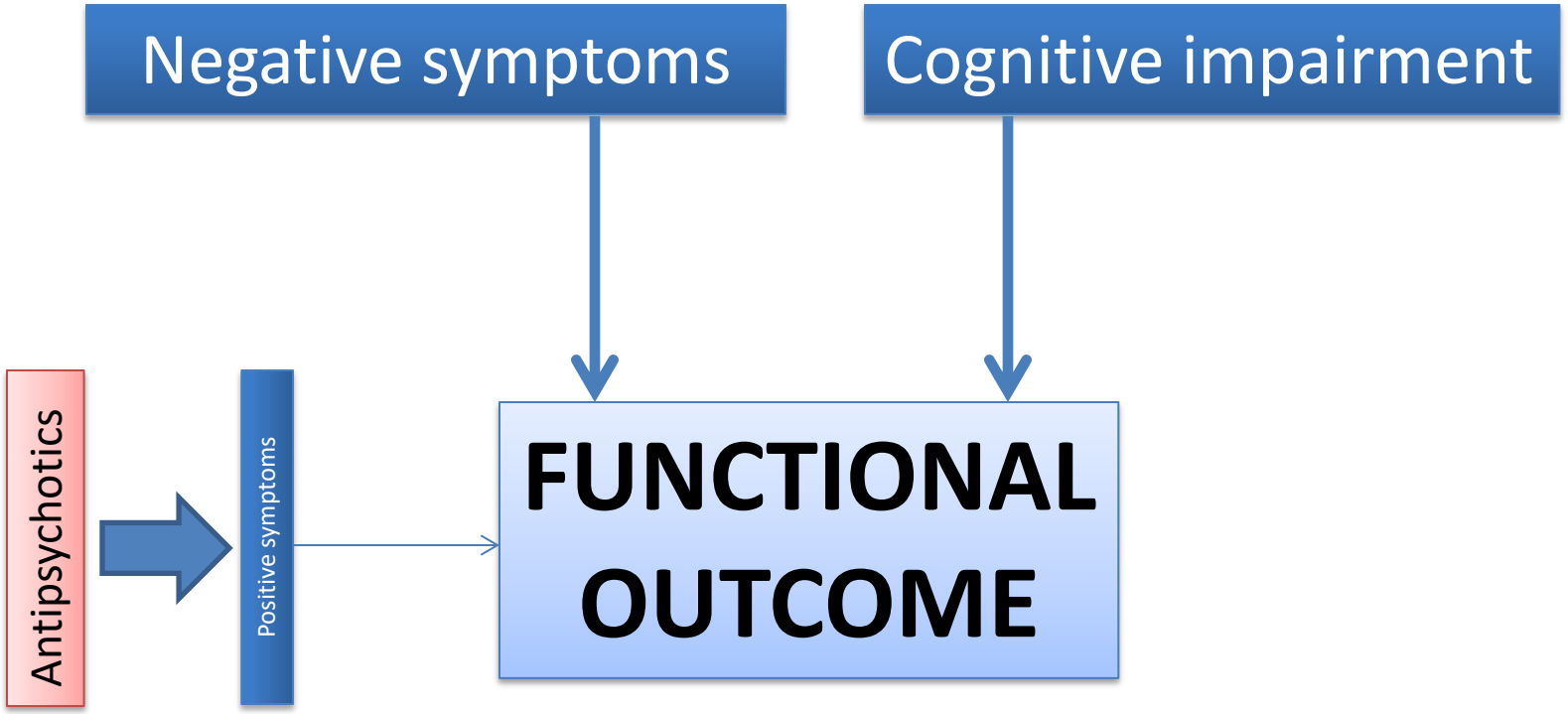
Treatment-resistant schizophrenia

- Non-dopaminergic drugs
  - Phase III by Sunovion (SEP-363856)
  - Mechanism of action: TAAR-1 agonism[1]
- Sodium benzoate augmentation
  - 2 positive trials
    - 1g/d added to antipsychotics[2]
    - 2g/d added to clozapine[3]
  - Mechanism of action: DAAO inhibitor

TAAR-1 = Trace amine-associated receptor 1
DAAO = D-amino acid oxidase

[1]Rutigliano G et al. Front Pharmacol. 10 January 2018.
[2]Lane HY et al. JAMA Psychiatry. 2013;70(12):1267-1275.
[3]Lin CH et al. Biol Psychiatry. 2018;84(6):422-432.

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.

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]

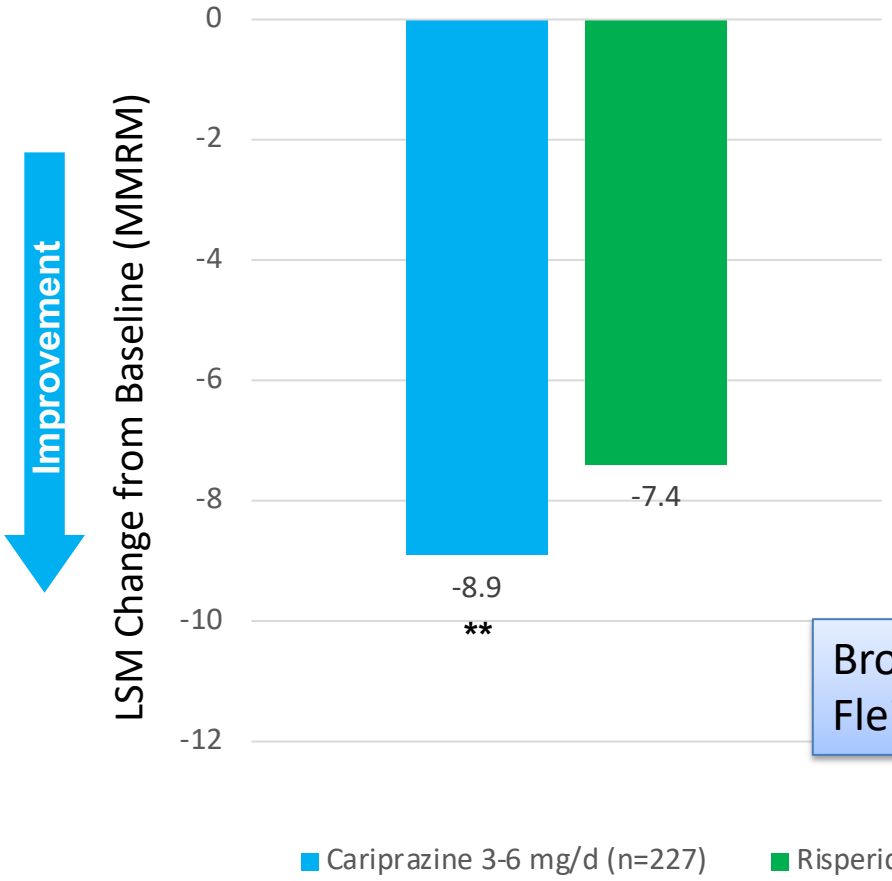
[1]Marder SR and Galderisi S. World Psychiatry. 2017;16(1):14-24.
[2]Mucci A et al. Schizophr Res. 2017;196:19-28. [3]Harvey PD et al. Schizophr Res. 2020;215:352-356.
[4]Straus GP et al. Schizophr Bull. 2020;46(4):964-970.

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.

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

- Mechanism[1]

SSIA = Selective Serotonin Inverse Agonist

  - 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 2 26-week add-on trial in schizophrenia (Acadia's ADVANCE)[4]
  - Primary endpoint Negative Symptom Assessment-16 (NSA-16) total score
  - ES = 0.34 for 34 mg dose
- Safety of pimavanserin[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]ClinicalTrials.gov Identifier: NCT02970305.
[5]Tampi RR et al. World J Psychiatry. 2019;9(3):47-54.

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.

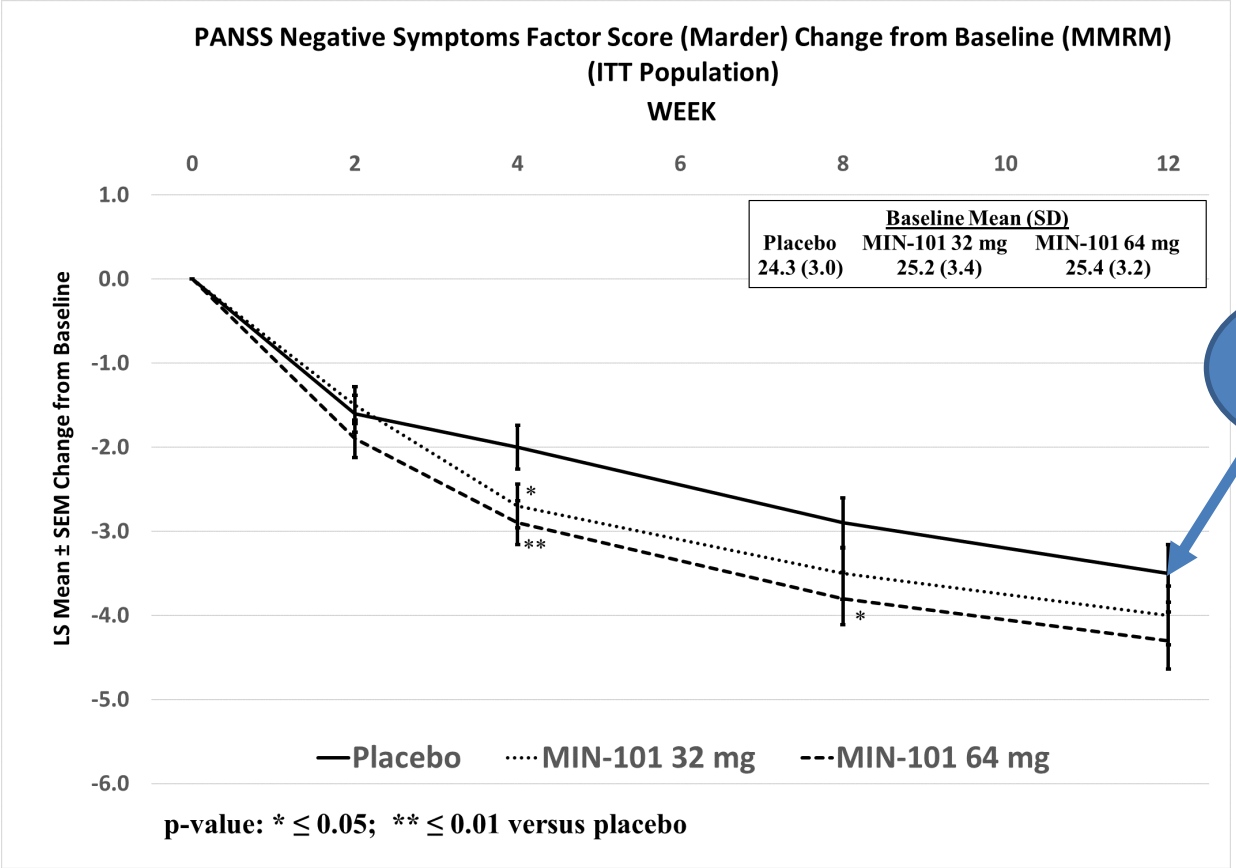
Roluperidone (MIN-101)

- 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

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/

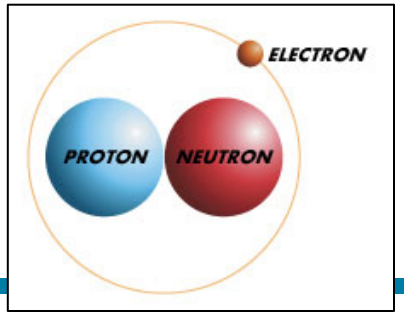
Roluperidone (MIN-101) for negative symptoms



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

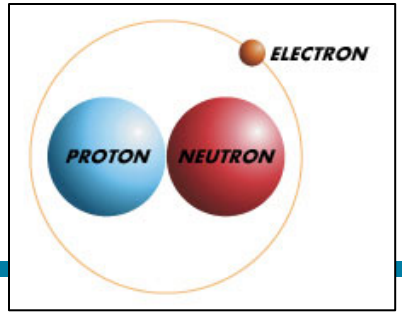
Deuterated medicines



- 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	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]
- Consider cognitive training if available[3]
- Psychopharmacology add-on strategies
  - Numerous pharmacological strategies including enhancing glutamatergic activity, cholinesterase inhibitors, cannabidiol, alpha-7 nicotinic agonists have failed
  - Missing: dopaminergic strategies (COMT inhibitors)[4]

[1]Coupland CAC et al. JAMA Intern Med. 2019 [Epub ahead of print].
[2]Vermeulen JM et al. Am J Psychiatry. 2018;175(11):1121-8.
[3]Keshavan MS et al. Am J Psychiatry. 2014;171(5):510-22. Review
[4]Sinkeviciute I et al. NPJ Schizophr. 2018;4:22.

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	Recruiting
Cannabidiol		Partial cannabinoid$_1$ receptor antagonist Add-on trials	2 negative studies
BIIB-104	Biogen Phase II NCT03745820	Glutamate receptor modulator Primary outcome: MCBB (working memory domain)	Recruiting

B. TOLERABILITY

FDA approval December 23, 2019

Lumateperone (ITI-007)

Brand name CAPLYTA, from Intra-Cellular Therapies

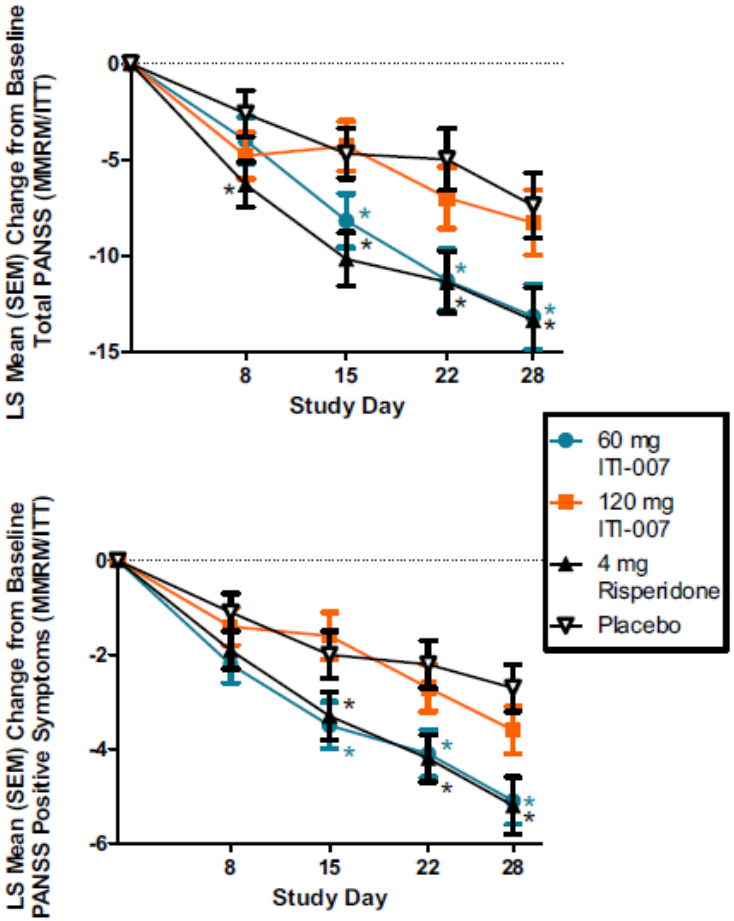
***Very high affinity. 60-fold higher than for D_2**
Lower dose (10 mg) preferentially 5-HT2A

- 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
- Other clinical trials
  - Bipolar depression

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

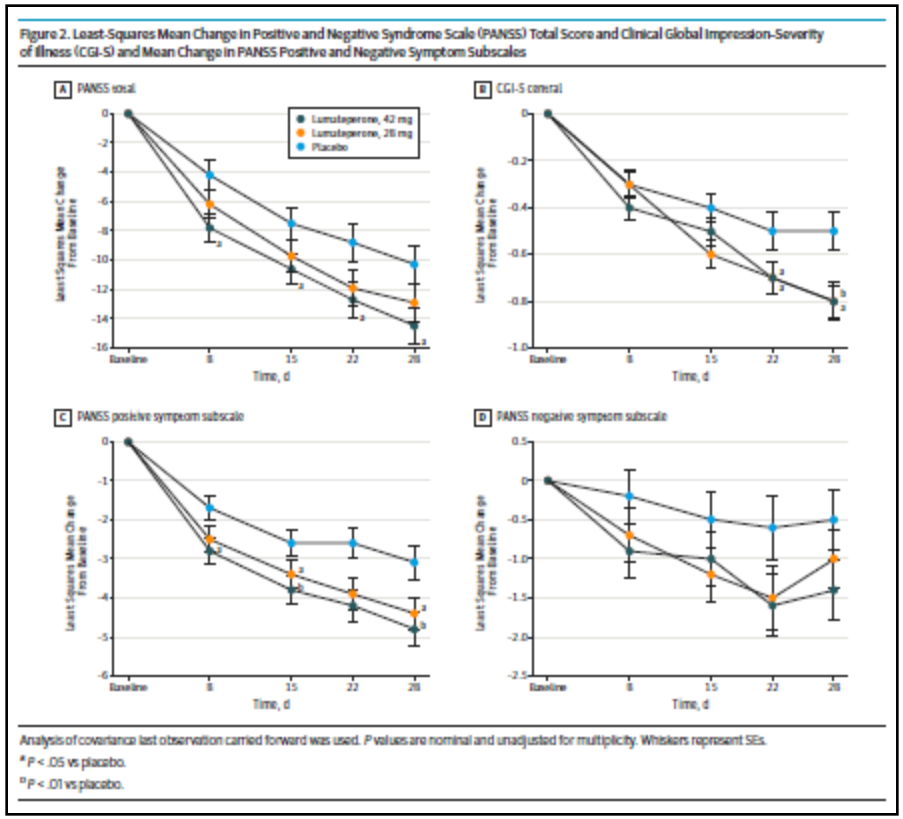
Lumateperone (ITI-007)

- Intra-Cellular-Therapies program
  - Positive phase II (‘005)[1]
    - Positive for 60 mg dose and 4 mg risperidone
    - Effect size 0.40 for 60 mg dose
    - Negative for 120 mg dose
  - Positive phase III (‘301)[2]
    - Effect size 0.30 for 60 mg dose
    - Negative for 40 mg dose
  - Negative phase III (‘302)[3]
    - Positive for comparator drug (risperidone)
    - High placebo response rate



[1]Lieberman JA et al. Biol Psychiatry. 2016;79(12):952-61.
[2]Correll CU et al. JAMA Psychiatry. 2020;77(4):349-358.
[3]https://globenewswire.com/news-release/2016/09/28/875435/0/en/Intra-Cellular-Therapies-Announces-Top-Line-Results-from-the-Second-Phase-3-Trial-of-ITI-007-in-Patients-with-Schizophrenia-Study-302.html

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

Samidorphan/olanzapine (ALKS 3831)

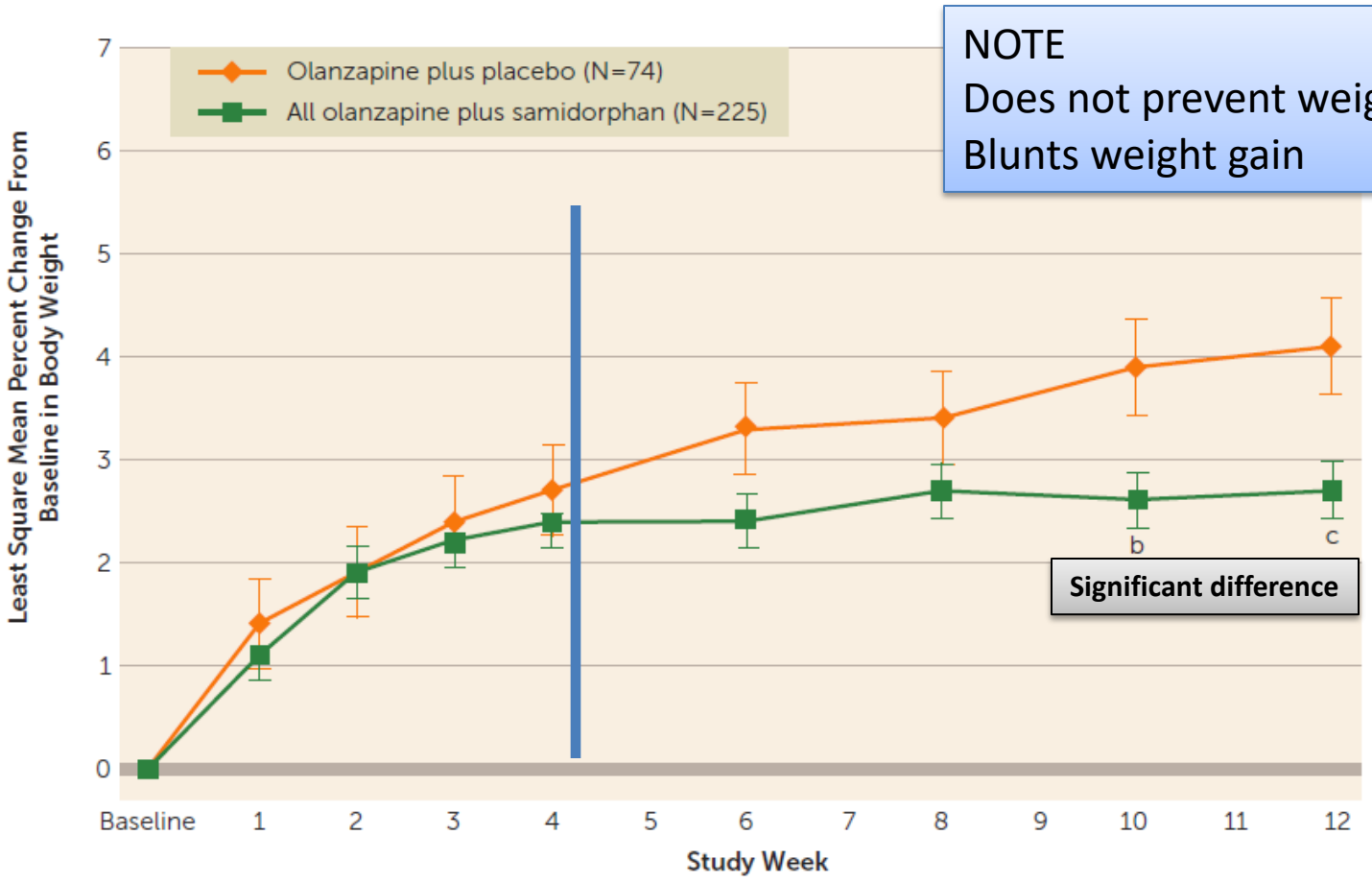
PDUFA date November 15, 2020

- 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.

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

C. ADHERENCE

Initiation of aripiprazole lauroxil

What is a non-Newtonian fluid?

- Conventional approach
  - Give Aristada injection
  - Administer 21 days of oral aripiprazole
- New initiation path with Aristada Initio (brand name)
  - Give 675 mg IM extended release injection + single 30 mg oral aripiprazole dose
  - Give desired Aristada dose (same day OK)
  - "Size matters"[1]
- Injection technique[2]
- Phase III ALPINE study to initiate 2-month preparation[3]
  - Good harm reduction approach to avoid "falling through the cracks" when transitioning from in- to outpatient care

[1]Jain R et al. CNS Spectrums. 2019; 21:1-8.
[2]Farwich S et al. J Psychiatr Pract. 2019;25(2):82-90.
[3]Weiden PJ et al. J Clin Psychiatry. 2020;81(3):19m13207.

Technological solutions: digital medicine for adherence monitoring

- Inevitably, new and innovative technologies are applied to adherence monitoring ("digital medicine")[1,2]
- New acronyms
  - IEM = Ingestible Event Marker
  - DMS = Digital Medicine System
  - DHFS = Digital Health Feedback System
- How does a DMS work?[3]
  - Patient ingests pill with sensor embedded in that pill (i.e., IEM)
  - Wearable sensor patch on left lower ribcage detects stomach-acid activated signal from IEM
  - Signal then sent to mobile device app which sends information to cloud-based server
  - Patient (or whoever else is granted access) reviews data

[1]Elenko E et al. Nat Biotechnol. 2015;33:456-61.
[2]Kvedar JC et al. Nat Biotechnol. 2016;34:239-46.
[3]https://www.proteus.com/press-releases/otsuka-and-proteus-announce-the-first-us-fda-approval-of-a-digital-medicine-system-abilify-mycite/

Digital adherence monitoring in psychiatry

- FDA-approves first DMS in November 2017: generic aripiprazole with IEM (brand name Abilify MyCite)
- Unresolved clinical questions
  - Does digital monitoring *actually* improve adherence in *real* patients with psychosis, both in short- and long-term?
  - How palatable is it for paranoid patients to "swallow a spy?"[1]
  - Will the *average* patient with serious mental disorders be able to use this technology?[2,3]
  - Which patient group might benefit the most?[3]
    - As always in medicine, patient selection is key
    - Active substance use, memory problems, no routines
    - Monitoring for court-ordered treatment can reduce catastrophic outcomes in selected cases (non-adherence leading to violence)
    - Might increase autonomy in community-treated patients who need some medication supervision

[1]Rosenbaum, L. N Engl J Med. 2018;378:101-3.
[2]Miller BJ et al. Psychiatry Res. 2015;225:458-63.
[3]Hatch A et al. J Clin Psychiatry. 2017;78:e803-e812.

Perils of digital health

- Is a technological solutions always progress?
  - Perhaps inevitable, including hype
  - Is there a generational divide?
- Risks
  - Medical privacy and cybersecurity (COVID-19!)
  - Increasing health disparities (misuse and lack of access)
  - Digital surveillance and coercion
  - Technology could replace meaningful other interventions
    - Increasing health literacy
    - Spending time with patients to understand adherence difficulties
    - Working with patients towards accepting evidence-based treatments (clozapine, long-acting injectables)
  - AI for prediction algorithms
    - Democratic control over algorithms
    - Bias in algorithms and recourse if algorithm selects you for intervention

*90% of mental health users discontinue app within a week of installation

Kalanderian H and Nasrallah HA. Curr Psychiatry. 2019;18(8):33-37.
Wasil AR et al. World Psychiatry. 2020;19(2):252-253.
***Baumel A et al. J Med Internet Res. 2019;21:e14567.**
https://www.ama-assn.org/system/files/2020-04/cybersecurity-work-from-home-covid-19.pdf

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.

Xanomeline

- 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]https://www.medscape.com/viewarticle/921496

Efficacy without D2-binding

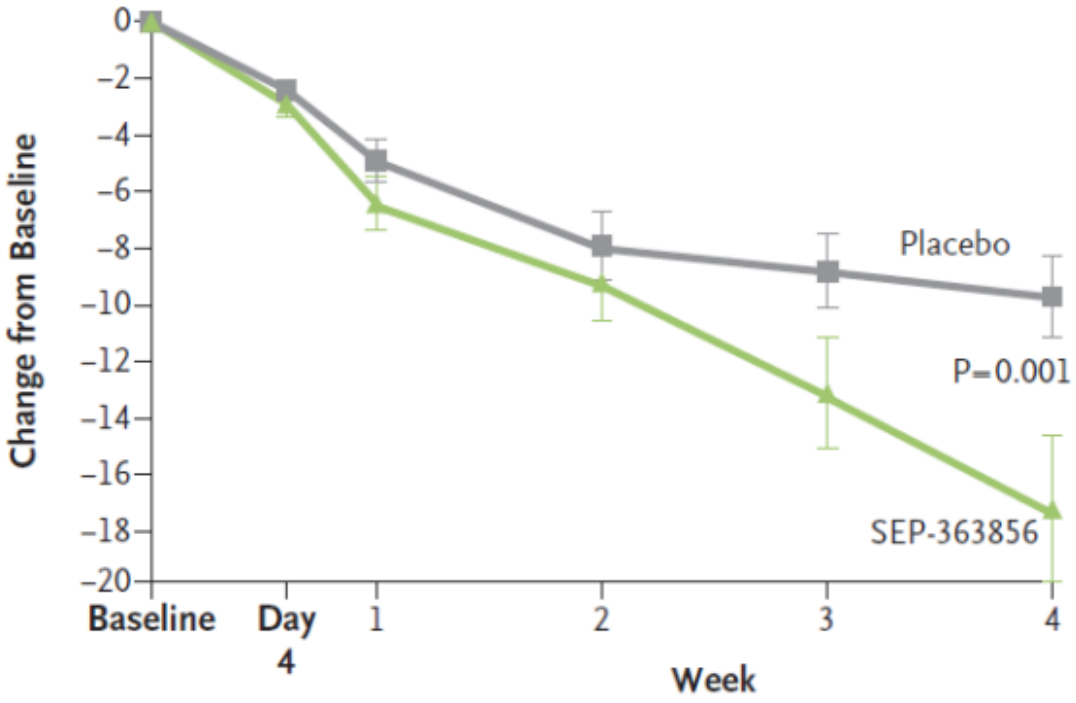
Monoamine receptor activator

- 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.

Vitamins in Psychosis Study

- Nutrient supplements for psychiatric disoders[1]
- RTC in N=120 first-episode patients[2]
- Intervention
  - Folic acid 5 mg, B_{12} 0.4 mg, B_6 50 mg
- Results
  - No improvement on co-primary outcomes
  - Personalized medicine approach
    - Elevated homocysteine, female, affective psychosis

[1]Firth J et al. World Psychiatry. 2019;18(3):308-324. [Meta analysis]
[2]Allott K et al. Biol Psychiatry. 2019;86(1):35-44.
See editorial Roffman JL. Biol Psychiatry. 2019;86(1):4-6.

Targeting the microbiome

"Psychobiotics"

Probiotic:
Live microorganism that have health benefits via restoring gut flora.

- **Microbial dysbiosis**
  - Microbiome and immune system
  - Microbiome-gut-brain axis[1]
- **Intervention trials across medicine[2]**
  - Fecal microbiota transplantation for GI disorders
  - Probiotic for Alzheimer's disease[3]
  - Antibiotics for neuropsychiatric disorders[4]
- **Probiotic intervention trials for schizophrenia[5]**
  - Characterize microbiome (metagenomic sequencing)
    - Don't forget oropharyngeal microbiome[6]
  - Assess peripheral markers of inflammation
  - Introduce probiotic to alter gut microbiota

[1]Burokas A et al. Adv Appl Microbiol. 2015;91:1-62. [2]Mangiola F et al. World J Gastroenterol. 2016;22:361-8.
[3]Akbari E et al. Front Aging Neurosci. 2016;8:256. [4]Dickerson F. Brain Behav Immun. 2017;62:46-52.
[5]Cuomo A et al. Front Pharmacol. 2018 Oct 15;9:1040. [6]Yolken R et al. Schizophr Res. 2020;S0920-9964(20)30113-4.
Dinan TG and Cryan JF. World Psychiatry. 2020;19(1):111-2.

"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)

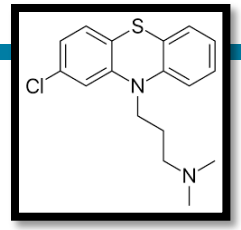
[1]Goff DC et al. Eur Neuropsychopharmacology. 2016;26(6):923-37.
[2]Leucht S et al. Am J Psychiatry. 2017;174(10):927-942.
[3]Devine EG et al. Clin Trials. 2013;10(6):935-48.

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]

Chlorpromazine and COVID-19



- First antipsychotic, Thorazine (the guy with the hammer)
- Mechanism of action
  - "A well-known clathrin-dependent endocytosis inhibitor"[1]
    - Who knew?
  - Targeting the endocytic and autophagic pathway[2]
  - Sigma receptor
- Clinical observation in France[3]
  - GHU-Paris psychiatry Hospital units (140 beds)
    - Lower prevalence of symptomatic and severe forms of COVID-19 in patients (3%) than in the health workers operating in the same facilities (19% nurses, 18% physicians)
  - Clinical CPZ add-on trial in France: reCoVery

Centre Hospitalier Sainte-Anne

https://www.nytimes.com/2020/04/30/health/coronavirus-antiviral-drugs.html

[1]Hu TY et al. Nature Nanotechnology. 2020;15:247–9. [2]Yang N and Shen H-M. Int J Biol Sci. 2020;16(10):1724–31.
[3]https://clinicaltrials.gov/ct2/show/NCT04366739