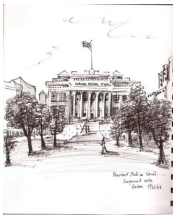
Treatment of Schizophrenia, Cognition, Prodrome, First Episode, Relapse, Highlighting New Drugs and Dosing



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Harvard Medical School, Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center

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Disclosures:
Alkermes, takeda, Natalia Foundation

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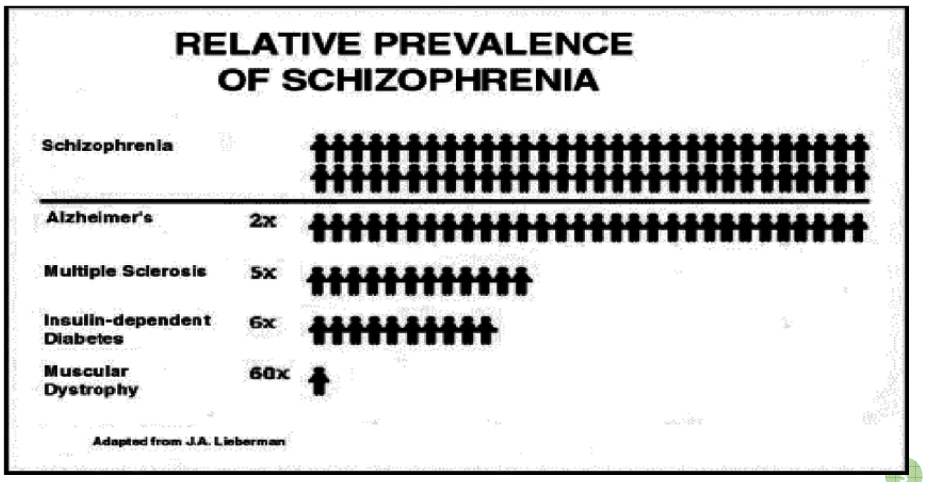
Issues We'll Touch Upon

- Current understanding on schizophrenia and its unmet therapeutic needs
- What we know about the neurobiology of schizophrenia and what that means for treatment
- Review safety and efficacy of available antipsychotics
- Early intervention and the prodrome
- Relapse prevention: Role of LAIs
- Cognitive impairments and recovery
- Treatment resistance: Focus on clozapine
- Future trends in schizophrenia treatment

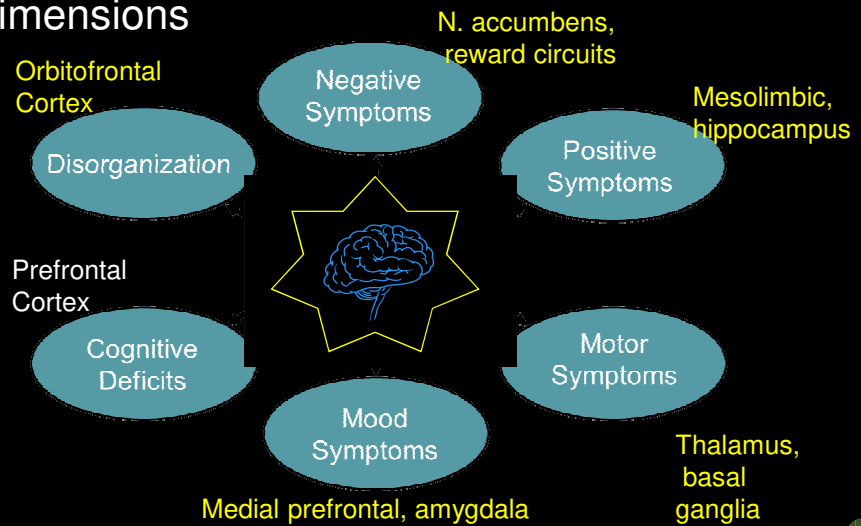
Schizophrenia	Neuro-biology	Anti-psychotics	Early intervantion	Relapse prevention	Cogntion & recovery	Treatment resistance	Future

Schizophrenia is common



Tandon R, et al. *Schizophr Res.* 2008;102(1-3):1-18.

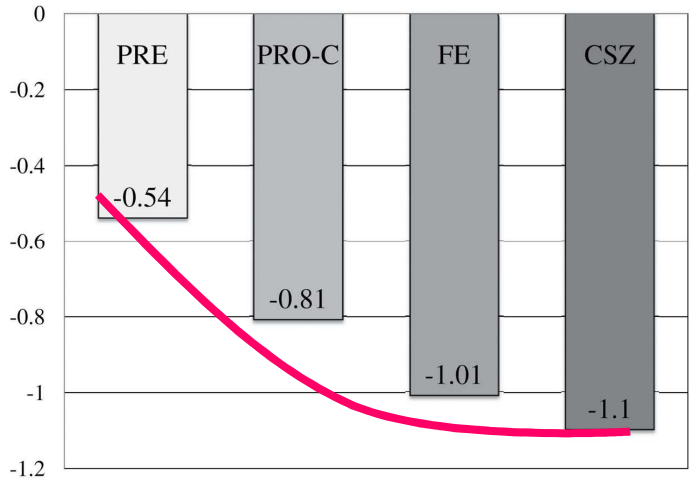
Schizophrenia is heterogeneous with many Dimensions



Tandon Nasrallah and Keshavan. *Schizophr Res*. 2009;110(1-3):1-23.

Cognitive Deficits are a core aspect

Effect sizes from 4 meta-analyses on cross-sectional IQ impairment in individuals with psychosis or at risk for psychosis compared to controls (Cohen's d).



PRE=premorbid; PRO-C=prodrome converter; FE=first episode; CSZ=chronic schizophrenia.
Liu, Keshavan and seidman. *Schizophr Bull.* 2015;41(4):801-816.

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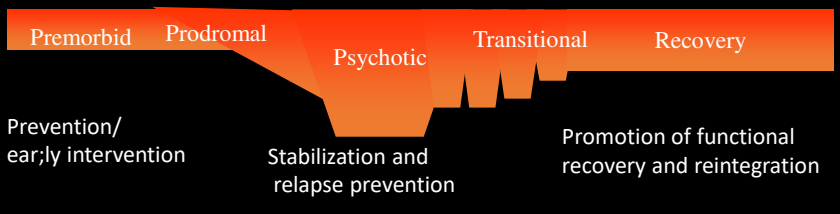
Schizophrenia evolves in phases

- ***Jeffrey is a 26-year-old single unemployed man living with his parents. His early milestones were slightly delayed. He had been evaluated by a psychologist for a possible attention deficit disorder.***
- ***His grades began to decline during high school and his grades were mostly Cs by his junior year. He had increasing anxiety and feelings that he had more important missions in life than just getting a college degree.. He withdrew socially, and began to post garbled political messages. on twitter***
- ***During his second year of college, Jeffrey began believing that he is destined to become the President of the United States and that FBI and the CIA were"vetting him" to be groomed to the highest office. He was briefly hospitalized.***
- ***Over the past 4 years, intermittently relapses because of poor adherence as well as forgetfulness. he has few significant friendships and has no steady job.***



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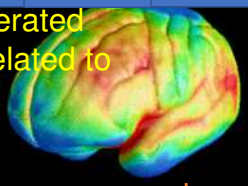
Schizophrenia | Neuro-biology | Anti-psychotics | Early intervantion | Relapse prevention | Cogntion & recovery | Treatment resistance | Future

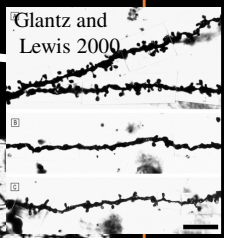
Unmet Needs in Schizophrenia

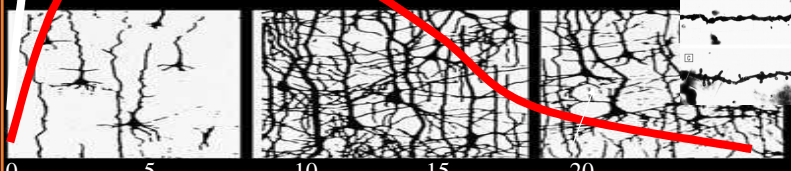
- Cognitive impairments
- Negative symptoms
- Treatment-resistant positive symptoms
- Side effects
- Treatment nonadherence

Schizophrenia | Neuro-biology | Anti-psychotics | Early intervantion | Relapse prevention | Cogntion & recovery | Treatment resistance | Future

Schizophrenia is thought to be related to exaggerated synaptic pruning during adolescence, perhaps related to genetic factors







Feinberg 1982,
Keshavan 1994;
Sekar et al 2016

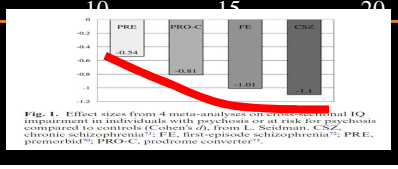
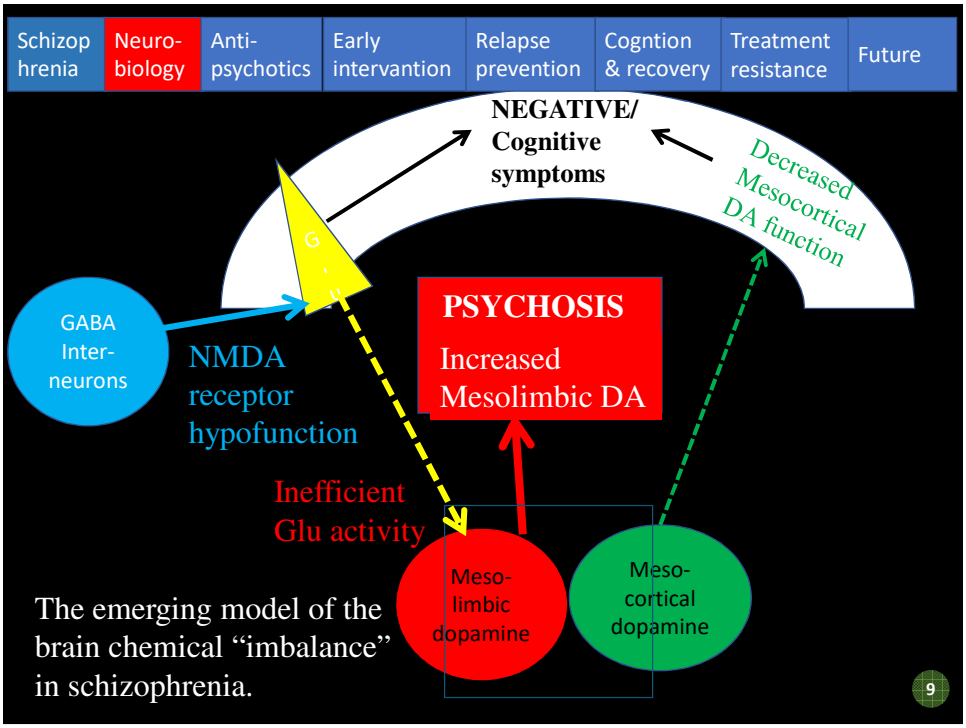


Fig. 1. Effect sizes from 4 meta-analyses on cross-sectional IQ impairment in individuals with psychosis or at risk for psychosis compared to controls (Cohen's *d*), from L. Seidman. CSZ, chronic schizophrenia[75]; FE, first-episode schizophrenia[76]; PRE, premorbid[76]; PRO-C, prodrome converter[77].

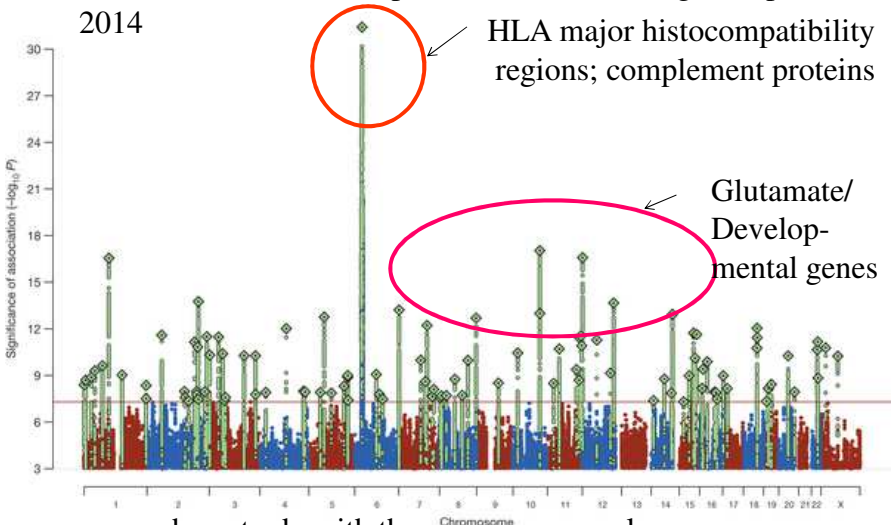
Cognitive decline in parallel to synapse loss

Liu, Keshavan, Tronick and Seidman Schiz Bulletin 2015

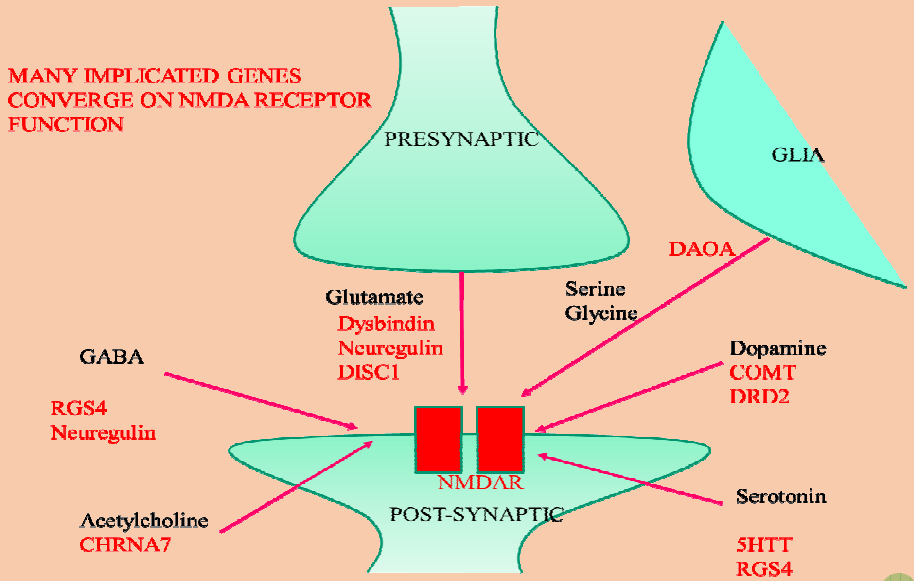


The emerging model of the brain chemical "imbalance" in schizophrenia.

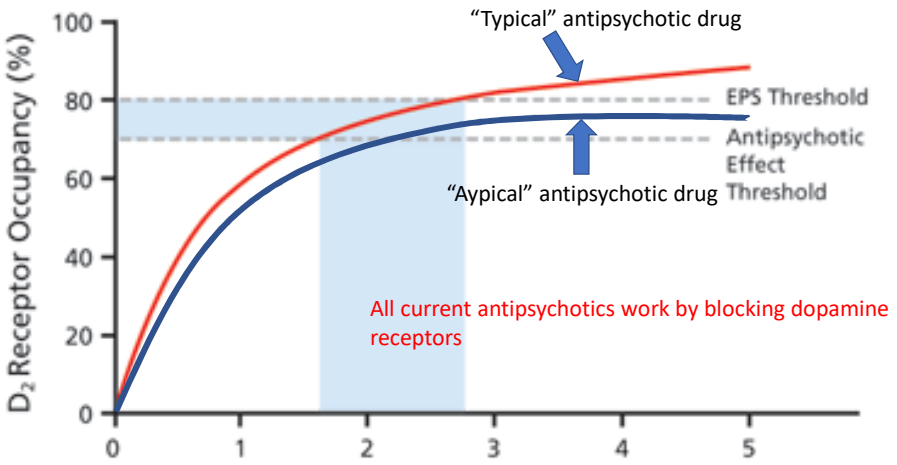
108 Gene Loci in schizophrenia Schiz Working Group, Nature 2014



genes may have to do with the excess synapse loss



Keshavan et al prog Neurobiol 2015



Adapted from Farde et al Arch Gen Psychiatry 1992

First-Generation or typical Antipsychotics(FGAs)

Drug	Dose Range	Side Effects
HIGH-POTENCY		High selectivity for D_2
Haloperidol	6-20 mg/day	EPS
Fluphenazine	6-20 mg/day	EPS
MID-POTENCY		Medium selectivity for D_2
Perphenazine	8-64 mg/day	Moderate-high EPS, mild sedation
Loxapine	30-100 mg/day	Moderate EPS, moderate sedation
LOW-POTENCY		Low selectivity for D_2; H1, AChR, AR antagonism
Chlorpromazine	100-1000 mg/day	Sedation, anticholinergic side effects, hypotension

AChR=acetylcholine; AR=adrenergic; EPS=extrapyramidal symptoms; H1=histamine.

Buchanan RW, et al. *Schizophr Bull*. 2010;36(1):71-93.

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Schizophrenia | Neuro-biology | Anti-psychotics | Early intervantion | Relapse prevention | Cogntion & recovery | Treatment resistance | Future

Second-Generation Antipsychotics (SGAs)

Drug	Dose Range	Side Effects
Clozapine	25-900 mg/day	Sedation, weight gain, agranulocytosis
Olanzapine	5-20 mg/day	Sedation, weight gain, dyslipidemia
Risperidone	0.5-8 mg/day	Sedation, weight gain, hyperprolactinemia
Paliperidone	3-6 mg/day	Sedation, weight gain, hyperprolactinemia
Quetiapine	25-750 mg/day	Sedation, weight gain, postural hypotension
Asenapine	10-20 mg/day	Sedation, weight gain, EPS
Iloperidone	12-24 mg/day	Sedation, moderate weight gain
Ziprasidone	40-160 mg/day, with food	Akathisia, QTc prolongation, minimal weight gain
Lurasidone	40-160 mg/day, with food	Akathisia, EPS, minimal weight gain Procognitive?
Amisulpiride	**400- 800 mg/ day**	**Sedation, hyperprolactinemia**

Freudenreich O, et al. *Antipsychotic Drugs.* In: Stern TA, et al (eds). *Massachusetts General Hospital Clinical Psychiatry (2nd edition).* Elsevier, 2016:475-488.

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Partial Agonist/Antagonist Antipsychotics

Drug	Dose Range	Side effects
Aripiprazole partial agonist at presynaptic and post-synaptic D_2 receptors	10-30 mg/day	Akathisia, activation, some weight gain, tremor **Can reverse prolactin increases**
Brexpiprazole partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2	2-4 mg/day	Akathisia, insomnia, minimal weight gain; **Has antidepressant effects**
Cariprazine partial agonist at the dopamine D3 and D2, 5HT2a and b-antagonist	3-6 mg/day	Akathisia, EPS, insomnia, tremor, minimal weight gain; **Good for Negative symptoms?**
Lumateperone serotonin, dopamine and glutamate	42 mg single daily dose	Akathisia, EPS, insomnia, tremor, minimal weight gain **Good for Negative symptoms?**

Kane JM, et al. *J Clin Psychiatry*. 2002;63:763-771; Kane JM, et al. *Schizophr Res*. 2016; 174:93-98; Citrome L. *Clin Schizophr Relat Psychoses*. 2016; 10:109-119; Corponi et al Europian Neuropsychopharmacology 2019

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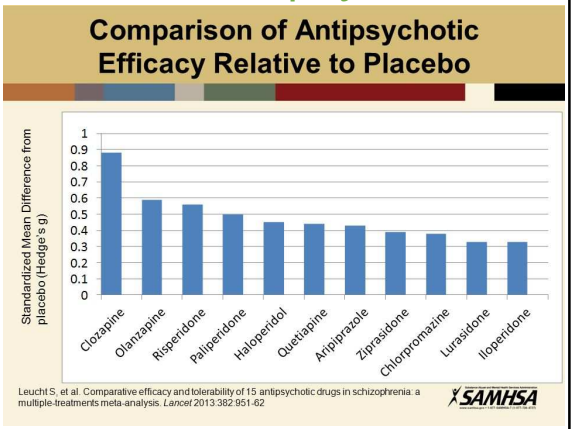
Treatment Selection with Antipsychotics

- All antipsychotics are effective against psychotic symptoms
- Clozapine more effective than other agents in otherwise treatment-refractory patients
- SGAs have lower risk of EPS and TD than FGAs
- Some SGAs (clozapine, olanzapine, Quetiapine have significant metabolic side effects
- Individual patients may respond preferentially to different medications



SGA=second-generation antipsychotic; FGA=first-generation antipsychotic; EPS=extrapyramidal symptoms; TD=tardive dyskinesia.

Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

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Antipsychotic side effects

	EPS/TD	Dyslipidemia	Weight gain/T2DM	Elevated prolactin	Anticholinergic effects	Orthostatic hypotension	QTC prolongation
*First generation**							
chlorpromazine	+	+++	+++	++	+++	+++	+++
haloperidol	+++	+	+	+++	+/-	-	++ (+++ if IV)
fluphenazine	+++	+	+	+++	+/-	-	+/-
*Second generation**							
aripiprazole	+	-	+	-	-	-	+/-
asenapine	++	-	++	++	-	+	++
brexpiprazole	+	+	+	+/-	+/-	+/-	+/-
lurasidone	++	+/-	+/-	+/-	-	+	+/-
olanzapine	+	++++	++++	+	++	+	++
paliperidone	+++	+	+++	+++	-	++	++
pimavanserin	+/-	-	+	-	+	++	+
quetiapine	+/-	+++	+++	+/-	++	++	+++
risperidone	+++	+	+++	+++	+	+	++
ziprasidone	+	+/-	+/-	+	-	+	+++ (BBW!)
clozapine	+/-	++++	++++	+/-	+++	+++	++

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Stopping and switching antipsychotics

Stopping

Beware withdrawal syndromes
anticholinergic syndrome
Withdrawal dyskinesia
Dopamine supersensitivity
(esp. clozapine)

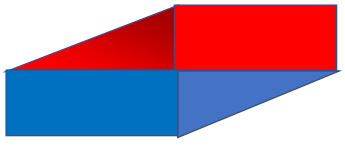
Direct switch

Simple, but Risk of discontinuation
Symptoms Can be done as inpatient
Avoid with clozapine

Cross-titration

balance between minimising risk of relapse and minimising risk of adverse effects' Keep in mind differing pharmacokinetics and possibility of drug interactions

Continuation with slower titration and subsequent discontinuation:



Useful for patients with a high risk of relapse
Risk for additive side effects

Bagnall A-M, Jones L, Ginnelly L, Lewis R, Glanville J, Gilbody S, *et al*. A systematic review of atypical antipsychotic drugs in schizophrenia. *Health Technol Assess* 2003;7(13). [PubMed]

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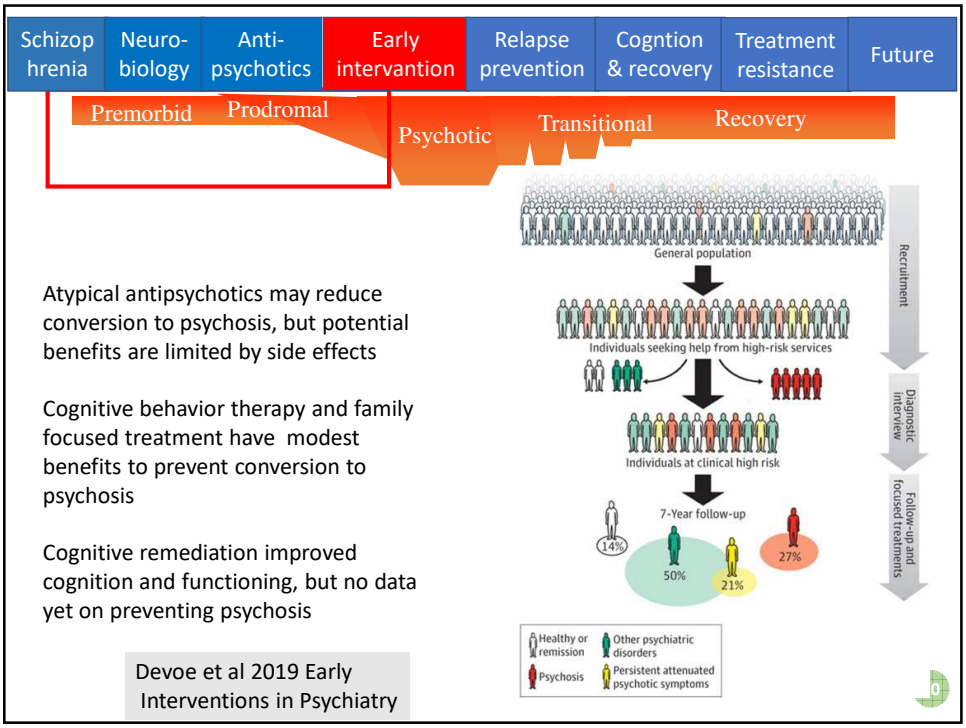
Limitations of Antipsychotic Therapies

- Incomplete efficacy
- Significant adverse effects

- Poor treatment adherence
  - Leads to recurrent relapses with adverse consequences
  - Higher mortality
  - Worse functional ability
  - Worse quality of life

Keshavan MS, et al. *Prog Neurobiol*. 2017;152:3-20.



Atypical antipsychotics may reduce conversion to psychosis, but potential benefits are limited by side effects

Cognitive behavior therapy and family focused treatment have modest benefits to prevent conversion to psychosis

Cognitive remediation improved cognition and functioning, but no data yet on preventing psychosis

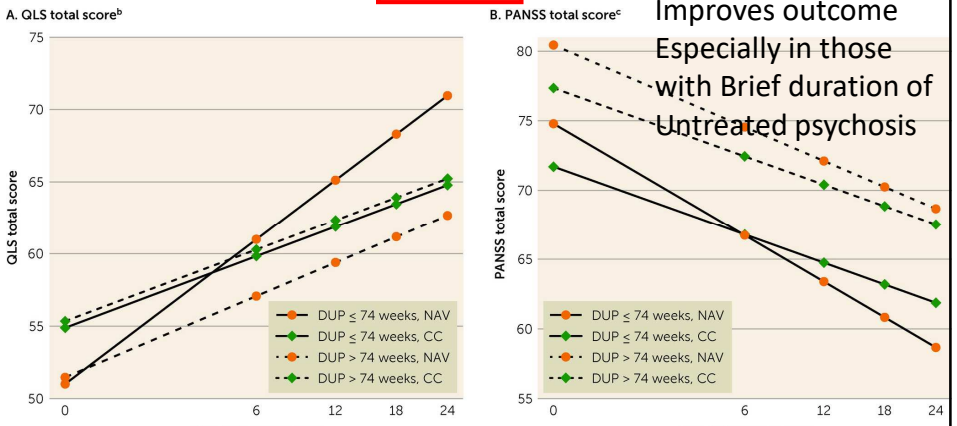
Devoe et al 2019 Early Interventions in Psychiatry

Schizophrenia | Neuro-biology | Anti-psychotics | Early intervantion | Relapse prevention | Cogntion & recovery | Treatment resistance | Future

Premorbid | Prodromal | Psychotic | Transitional | Recovery

Kane et al Am J Psychiatry

Early intervention
Improves outcome
Especially in those
with Brief duration of
Untreated psychosis



Personalized medication management Family psychoeducation; Resilience-focused individual therapy; Supported employment and education, Team based approach

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Schizophrenia | Neuro-biology | Anti-psychotics | Early intervantion | Relapse prevention | Cogntion & recovery | Treatment resistance | Future

	Early intervention Is superior	Treatment as usual is superior
All cause discontinuation Psych hospitalization / Relapse	✓	
Remission Recovery School/ work	✓	
Positive symptoms Negative symptoms General symptoms Depressive symptoms	✓	
Global functioning Quality of life	✓	

Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: Meta-analysis Of 10 RCTs
Correll C et al JAMA Psychiatry

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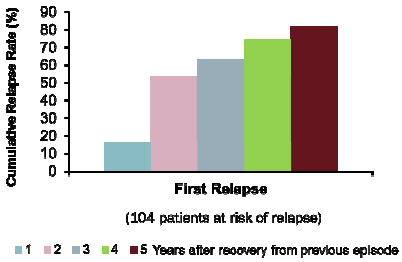
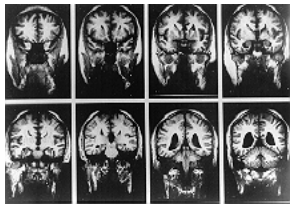
Cumulative relapse rates in patients with schizophrenia, by year following recovery from the first episode



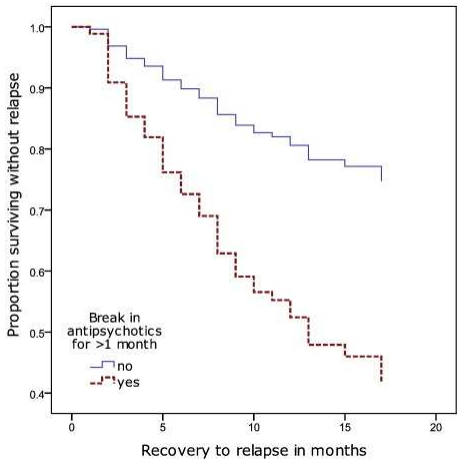


- About 82% of patients with schizophrenia or schizoaffective disorder experienced ≥1 relapse over 5 years
- Relapse can cause:
  - Rehospitalization
  - Slow and incomplete recovery
  - Treatment-resistant illness
  - Persistent symptoms
  - Progressive cognitive decline and possibly brain changes
  - Increasing difficulty to regain previous level of functioning
  - Reduced quality of life

Relapse is Common

Robinson D, et al. *Arch Gen Psychiatry*. 1999;56(3):241-247; Csernansky JG, et al. *CNS Drugs*. 2002;16(7):473-484; Kane JM. *J Clin Psychiatry*. 2007;68 Suppl 14:27-30; Lewis DA, et al. *Neuron*. 2000;28(2):325-334; Levander S, et al. *Acta Psychiatr Scand Suppl*. 2001;104(408):65-74; Briggs A, et al. *Health Qual Life Outcomes*. 2008;6:105.

Antipsychotics Reduce Relapse Rates (five-fold)



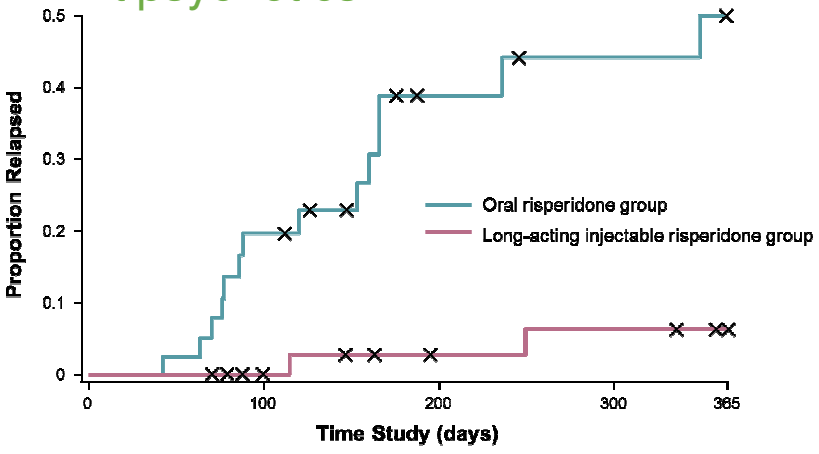
Winton-Brown et al 2017

Methods to Improve Adherence

- Adherence training (eg, motivational interviewing, CBT)
- Reminder cues
- Simplify treatment regimens
- Patient/family psychoeducation
- Long-acting antipsychotic formulations

Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

LAIs Have Less Relapses Than Oral Antipsychotics



Time to first psychotic exacerbation and/or relapse as a function of form of medication administration in 83 patients.
Subotnik KL, et al. *JAMA Psychiatry*. 2015;72(8):822-829.

Schizophrenia | Neuro-biology | Anti-psychotics | Early intervantion | **Relapse prevention** | Cogntion & recovery | Treatment resistance | Future

Drug	Dose (IM) & Frequency	Notes
Haloperidol decanoate	**50-300 mg Q4wks**	**Overlap with PO**
Fluphenazine decanoate	**12.5-100 mg Q2-3wks**	**Overlap with PO**
Risperidone LA (Consta) **Risperidone (Perseris)**	**25-50 mg Q2wks** **90-120 mg monthly**	**3 week overlap with PO** **No overlap with PO**
Paliperidone palmitate **(Invega Sustenna)** **Paliperidone palmitate** **(Invega Trinza)**	**39-234 mg Q4wks** **273-819 mg Q12wks**	**No overlap with PO** **Q12wks can be used after 4 months on Q4wks**
Olanzapine pamoate	**150 or 300 mg Q2wks** **405 mg Q4wks**	**No overlap with PO** **Monitor for 3 hours post injection**
Aripiprazole monohydrate (Maintena)	**300, 400 mg Q4wks**	**2 week overlap with PO**
Aripiprazole lauroxil Available LAIs	**441, 662, 882 mg Q4wks** **882 mg Q6wks** **1064 mg Q8wks**	**3 week overlap with PO** (One day alternative with Aripiprazole initio inj+ single oral dose)

Schizophrenia | Neuro-biology | Anti-psychotics | Early intervantion | **Relapse prevention** | Cogntion & recovery | Treatment resistance | Future

Advantages

- Better adherence
- Lower relapse rates
- Minimal GI absorption problems, circumventing first-pass metabolism
- Improved patients' and physicians' satisfaction, and better outcomes
- Regular contact between the patient and mental healthcare team

Disadvantages

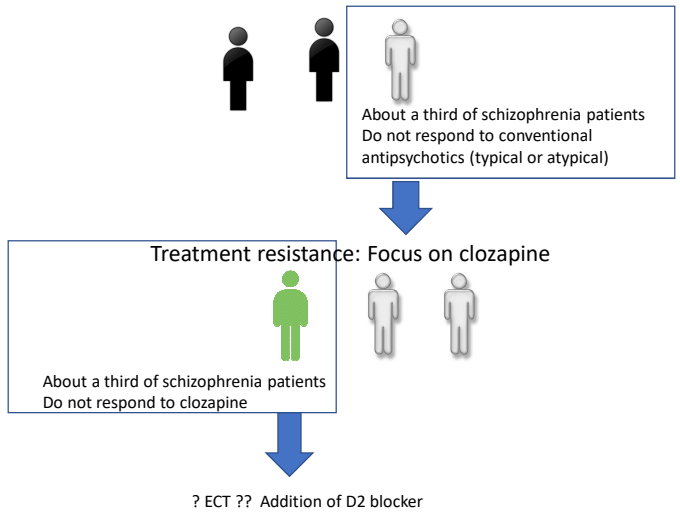
- Slow dose titration
- Longer time to achieve steady state levels
- Less flexibility of dose adjustment
- Delayed disappearance of side effects
- Pain at the injection site (especially for oily LAI)
- Perception of stigma

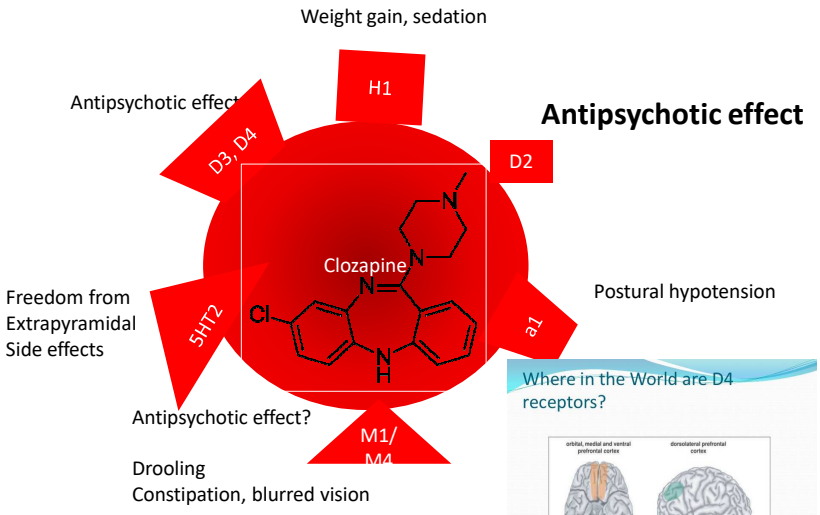
Brissos S, et al. *Ther Adv Psychopharmacol*. 2014;4(5):198-219; Salquerio M, et al. *Int Clin Psychopharmacol*. 2019;34(2):51-56.

Current Recommendations: LAIs

- LAIs should not be restricted to patients with adherence problems, but instead should be more widely prescribed
- LAIs should systematically be offered to all patients through shared decision-making
- Any patient for whom long-term treatment is indicated should be considered a candidate for an LAI
- Even if patients initially refuse an LAI, it would be helpful to discuss it further to better understand the potential advantages
- A common reason for non-acceptance of LAI therapy may be that psychiatrists are ambivalent or unenthusiastic about this option even as they recommend it
- Recent evidence suggests that LAIs are effective for treating first-episode psychosis and for early initiation of treatment for schizophrenia

Kane JM, et al. *Br J Psychiatry Suppl*. 2009;52:S63-S67
.Stevens et al *Early Intervention in Psychiatry, 10*(5), 365–37





CLOZAPINE MECHANISM

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Before concluding that patient has Treatment resistance , verify:

- Correct diagnosis (of a psychotic disorder)?
- Continuing psychosocial stressors?
- Comorbid condition (such as depression or substance abuse)?.
- Compliance (Is patient is taking the meds?)
- Concentration (Is level within therapeutic limits?)

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Managing treatment resistance

- The evidence is limited that adding a second antipsychotic to improve symptom response helps patients who are already taking one antipsychotic (Lin, 2020) •
- Evidence is also limited for augmenting antipsychotics with mood stabilizers (Lin, 2020)
- Adding dopamine partial agonists such as aripiprazole may help treat negative symptoms but this might be achieved by a simple switch to a dopamine partial agonist
- Consider early introduction of clozapine
- Augmentation with ECT may be effective in clzapine resistant schizophrenia (Petrides et al 2019)
- Consider augmentation with psychotherapy

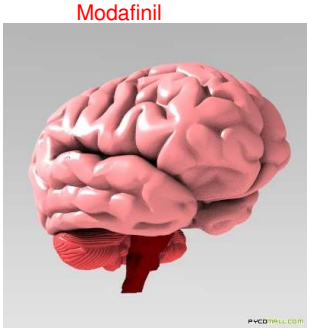
Lin SK. Antipsychotic Polypharmacy: A Dirty Little Secret or a Fashion? Int J Neuropsychopharmacol. 2020 Feb 1;23(2):125-131.

Schizophrenia	Neuro-biology	Anti-psychotics	Early intervantion	Relapse prevention	Treatment resistance	Cognition & recovery	Futurei

Norepinephrine
Stimulants
Atomoxetine
Modafinil

Dopamine
COMT antagonists

Acetylcholine (nicotinergic)
Nicotinic agonists



Histamine
H3 antagonists

Acetylcholine (muscarinic)
Ach-ase antagonists
Muscarinic agonists

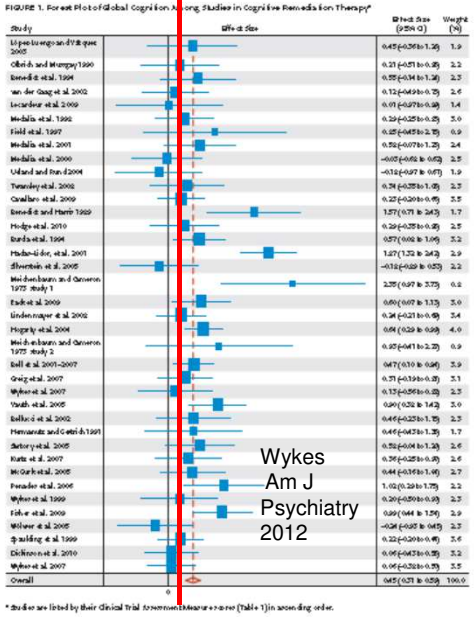
GABA
GABA agonists

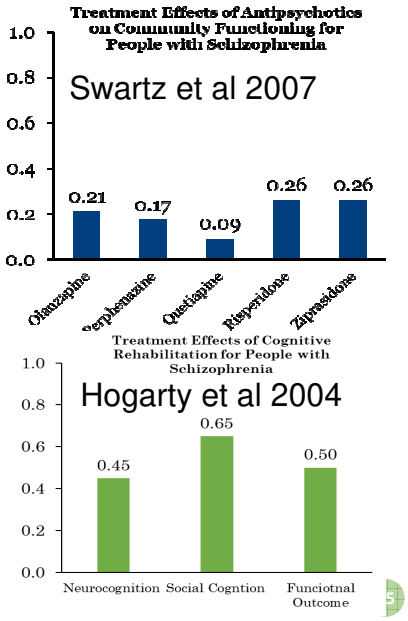
Cannabinoid receptors
CB1 antagonists

Glutamate
Glutamate modulators

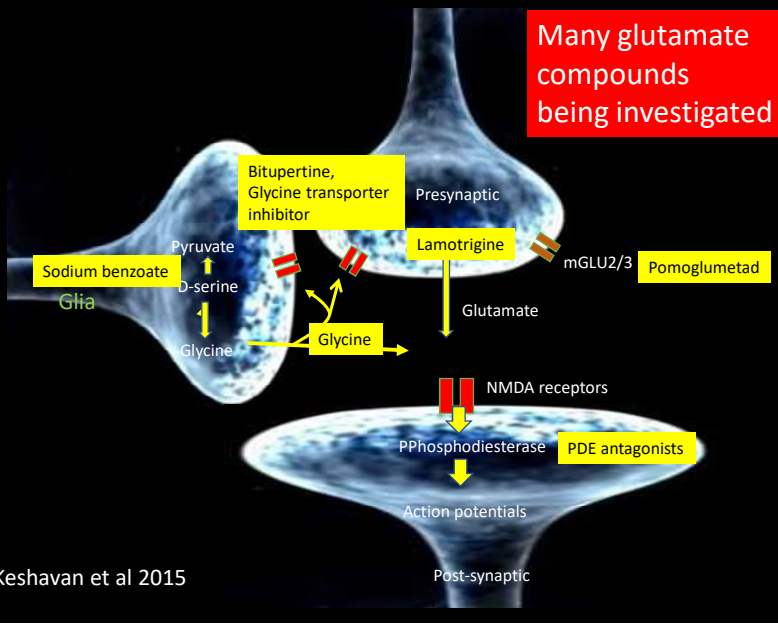
Several pharmacologic agents being tried now for cognitive deficits in schizophrenia, but have little benefit

Cognitive remediation works… better than antipsychotics for community functioning

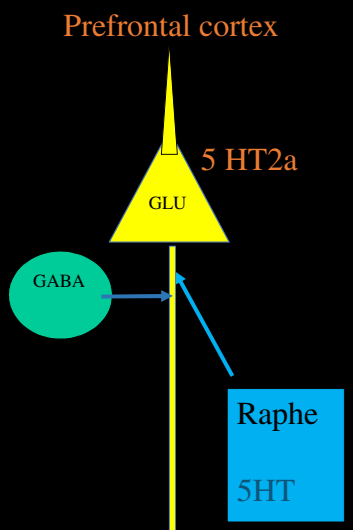




Many glutamate compounds being investigated



Keshavan et al 2015



Serotonin

Pimavanserin, (Nuplazid)
5HT2a inverse agonist

•FDA approved for Parkinsonism,

•Pending in dementia Related psychosis

•Negative trial in depression

•Not effective for Pos sx schizophrenia but may help Neg SX

Nasrallah HA, et al. *Schizophr Res*. 2019 McGuire P, et al. *Am J Psychiatry*. 2018;175(3):225-231; Solmi M, et al. *CNS Spectr*. 2017;22(5):415-426; Conus P, et al. *Schizophr Bull*. 2018;44(2):317-327.

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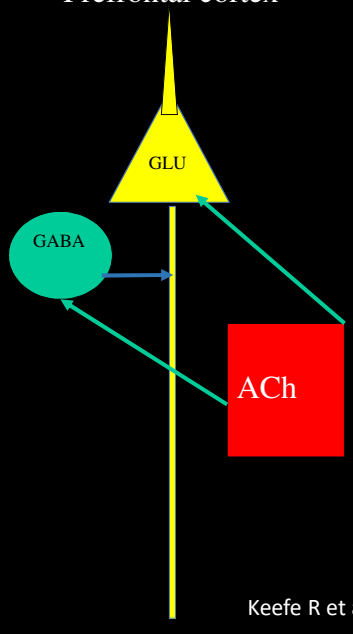

Acetylcholine

KarXT
Xanomeline (M1/M4 agonist)+
Trospium (peripheral anti-Cholinergic)

(Karuna)
Promising Phas II results for psychosis, neg sx

A7 nicotinic Encenicline, Mixed results

Keefe R et al Neuropsychopharmacology 2015

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The NEW ENGLAND JOURNAL of MEDICINE

Xanomeline–Trospium for Schizophrenia

DOUBLE-BLIND, PHASE 2 TRIAL

182 Patients with schizophrenia	Xanomeline–trospium (twice daily) (N=90)	Placebo (N=92)
Change in PANSS total score at 5 wk (range 30–210; higher score = greater symptom severity)	–17.4	–5.9
	Difference, –11.6 points; 95% CI, –16.1 to –7.1; P<0.001	
Safety and adverse events	Constipation, nausea, dry mouth, dyspepsia, and vomiting	—

Xanomeline–trospium resulted in a greater decrease in the PANSS total score at 5 wk but was associated with cholinergic and anticholinergic adverse events.

S.K. Brannan et al. 10.1056/NEJMoa2017015

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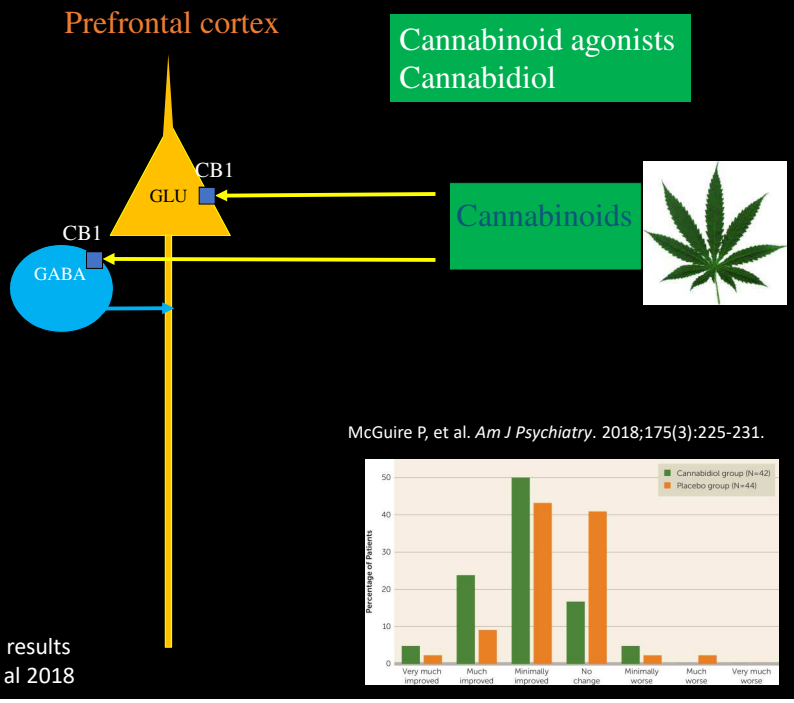

McGuire P, et al. *Am J Psychiatry*. 2018;175(3):225-231.

Negative results
Boggs et al 2018

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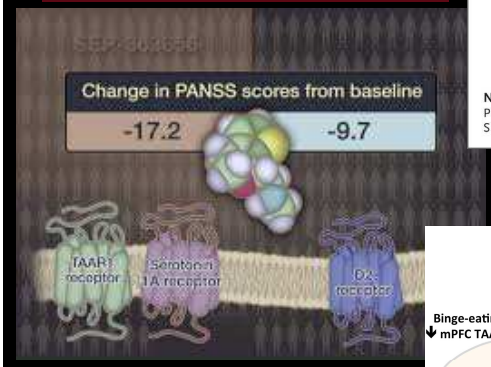
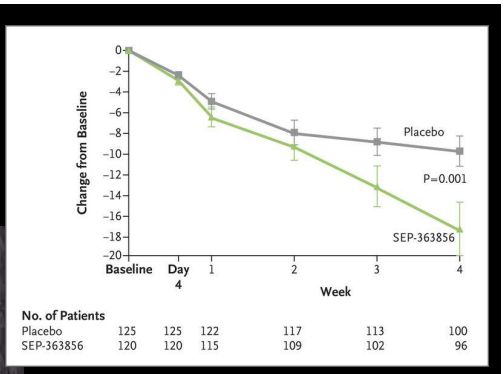
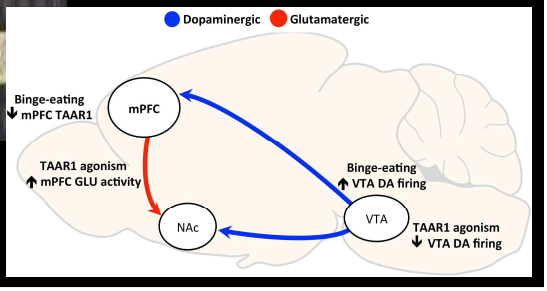
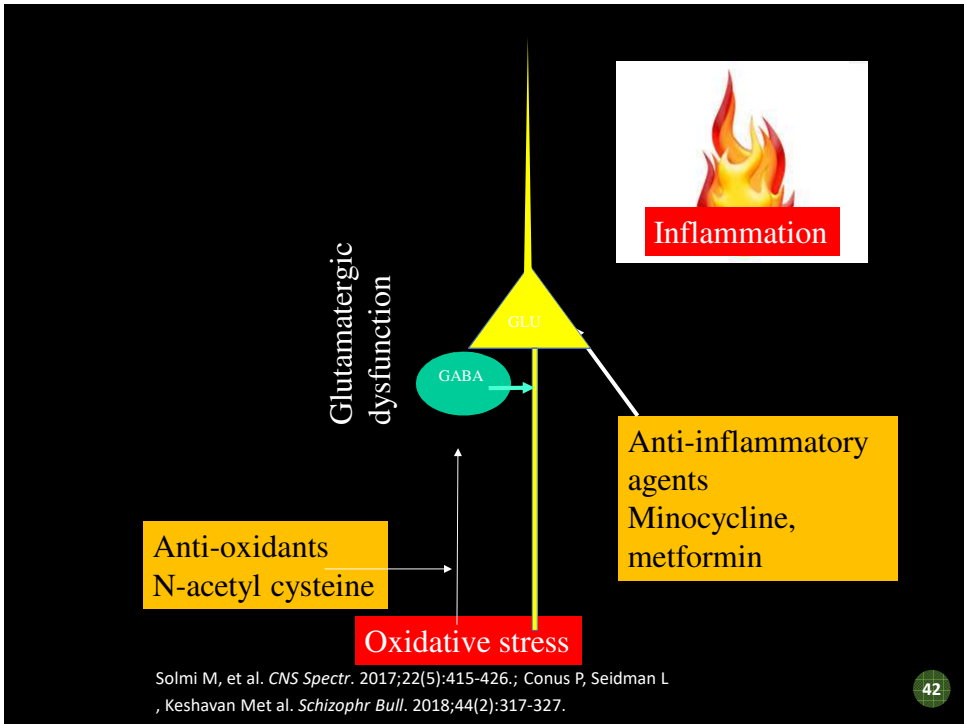
Trace amine-associated receptor 1 (TAAR1) agonist and 5HT1a agonist (Sepracor) Koblan et al NEJM 2020



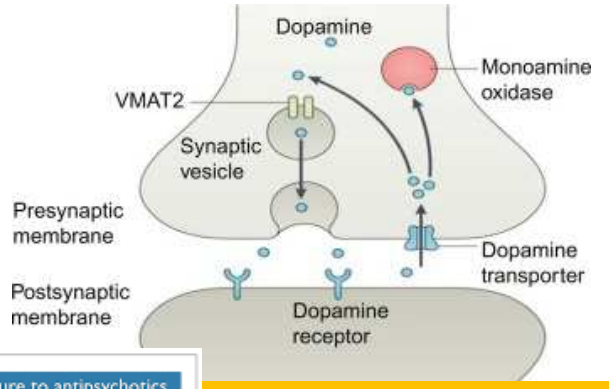


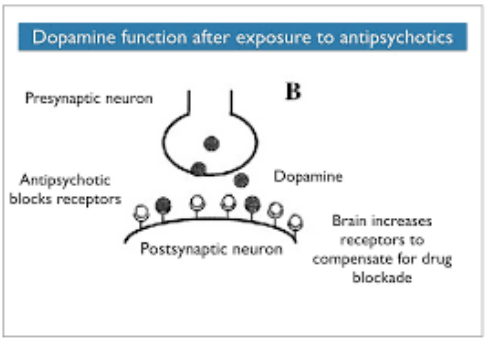




Solmi M, et al. *CNS Spectr*. 2017;22(5):415-426.; Conus P, Seidman L , Keshavan Met al. *Schizophr Bull*. 2018;44(2):317-327.

Valbenazine
for tardive dyskinesia





Valbenazine
Vesicle monoamine transporter inhibitor

40-80 mg po qd
No evidence of increased depression or suicidality (though tetrabenazine has a boxed warning)
Can prolong QT interval

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Summary

- While the neurobiology of schizophrenia is increasingly better understood, many unmet therapeutic needs remain.
- All currently used antipsychotics impact dopaminergic function, are effective in psychosis, but are limited by metabolic and/or extrapyramidal side effects, and treatment resistance in many patients.
- Early intervention of psychotic disorders in coordinated specialty care programs can improve outcome and quality of life
- Clozapine is an effective treatment for treatment-resistant schizophrenia, but is limited by substantive side effects.
- Nonadherence is a common problem; long-acting injectable antipsychotics have an important role in management of nonadherence.
- Psychosocial cognitive remediation is effective, but no clear pharmacological treatments of cognitive impairments yet available
- Novel treatments being investigated include drugs targeting non-dopaminergic mechanisms (such as glutamate, serotonin, acetylcholine, TAAR1, cannabinoid),

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Thank you!