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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

SCHIZOPHRENIA:
TREATMENTS AND GENETIC RISK FACTORS

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

DISCLOSURES

No significant financial conflicts of interest.

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SCHIZOPHRENIA: TREATMENTS AND GENETICS

1. Approaches for treatment resistant schizophrenia
   - Clozapine
   - Dual long-acting injectable (LAI) antipsychotic use
   - Cobenfy

2. Family-based genetic research
   - Recruiting families with schizophrenia
   - iPSC to characterize rare genetic mutations in schizophrenia

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TREATMENT RESISTANT SCHIZOPHRENIA

- Treatment resistance is common: 36.7% (Diniz, 2023)
- Clozapine is effective for TRS: 40% response rate (Siskind, 2017)
  - ~22% of people with schizophrenia will not respond to current treatments.
- Combining antipsychotic medications may be helpful (APA guidelines, 2020)
- Switching or augmenting with novel treatments: Cobenfy
- ECT

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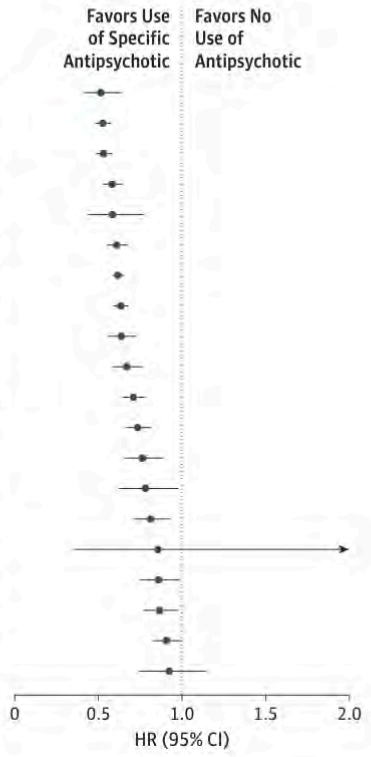
CLOZAPINE IS THE BEST TREATMENT FOR TRS

- Clozapine continues to show improved outcomes in RTC and naturalistic studies. (Dong, 2024; Siskind, 2016)
- Outcomes include hospitalization rates and symptoms reduction.
- Olanzapine is probably a close runner up and clozapine is not always superior to olanzapine.

Figure 2. Adjusted Hazard Ratios (HRs) and 95% CIs for Psychiatric Rehospitalization During Monotherapy Compared With No Use of Antipsychotic in Within-Individual Analyses in the Prevalent Population

Treatment	HR (95% CI)
LAI paliperidone	0.51 (0.41-0.64)
LAI zuclopenthixol	0.53 (0.48-0.57)
Oral clozapine	0.53 (0.48-0.58)
LAI perphenazine	0.58 (0.52-0.65)
LAI olanzapine	0.58 (0.44-0.77)
LAI risperidone	0.61 (0.55-0.68)
Polytherapy	0.62 (0.58-0.65)
Oral olanzapine	0.63 (0.59-0.68)
LAI haloperidol	0.64 (0.56-0.73)
Oral zuclopenthixol	0.67 (0.59-0.76)
Oral risperidone	0.71 (0.64-0.78)
Oral aripiprazole	0.73 (0.66-0.81)
Oral levomepromazine	0.76 (0.66-0.89)
LAI flupentixol	0.78 (0.62-0.98)
Oral haloperidol	0.81 (0.71-0.93)
LAI fluphenazine	0.86 (0.35-2.08)
Other oral formulations	0.86 (0.75-0.98)
Oral perphenazine	0.86 (0.77-0.97)
Oral quetiapine	0.91 (0.83-1.00)
Oral flupentixol	0.92 (0.74-1.14)



(Tilhonen, 2017)

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CLOZAPINE: REMS AND UNDER-UTILIZATION

- Clozapine is likely underutilized

- This likely due to its side effects, monthly lab monitoring and titration requirements
  - Titration: approx 2 weeks to therapeutic dose of 200-400mg daily increasing by 25mg daily
  - Missed doses > 2 days require retitration
  - Monitoring CBC: weekly x 6 months, EO-week x 6 months, monthly thereafter (REMS)
  - SE: neutropenia, seizures, myocarditis, constipation, drooling, sedation, weight gain, fever, nocturia, tachycardia, hypotension
  - 1-2% have a serious neutropenia leading to cessation (Northwood, 2024)

(APA guidelines, 2020)

CLOZAPINE REMS IS NOW RETIRED

- FDA discontinued the clozapine REMS in 2/2025
- FDA recs: as previously required by REMS
- Recent studies have suggested that less frequent monitoring could be supported

(Siskind, 2026)

(Northwood, 2024)

(Jen Jepsen; Clayton English)

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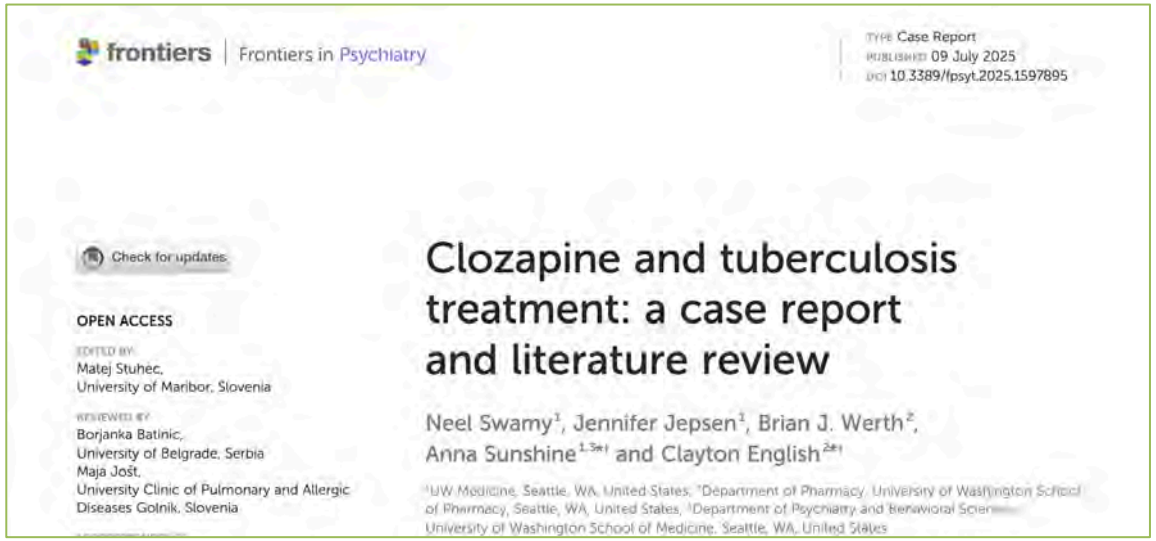
CLOZAPINE – CASE REPORT

- ZZ was admitted to the hospital with cough, vomiting and malaise.
- Clozapine dose was decreased to 650mg daily
- Diagnosed with active pulmonary tuberculosis and started on RIPE therapy
- Clozapine dose was increased to 950mg daily
- Clozapine level fluctuated during treatment from 134-1280ng/ml throughout RIPE therapy



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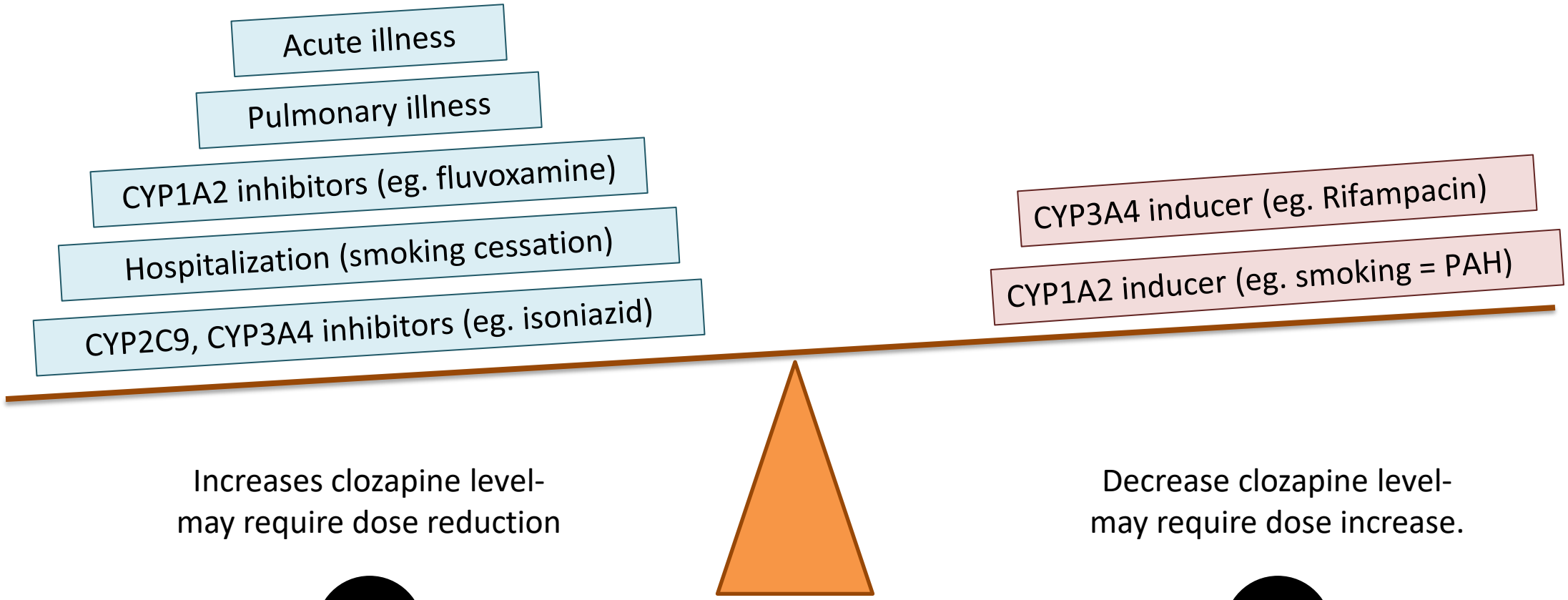
CLOZAPINE DOSE ADJUSTMENTS



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Combination antipsychotics for TRS

- APA guidelines suggests that for TRS, where a trial of clozapine is not feasible, then a combination of antipsychotic medications may help reduce hospitalizations and that there is not evidence that such an approach is harmful.
    - APA Practice Guideline for Treatment of Schizophrenia, 2020
- Adding an additional antipsychotic can reduce hospitalizations
    - Cohort, N = 62,250 (Tiihonen, 2019)
- Stopping a second antipsychotic can lead to worsening symptoms
    - RTC, N= 104 (Constantine, 2015)

Dual LAI therapy for TRS

- Patient 1: Aristada 882mg, monthly + Haldol decanoate 50mg monthly
- Patient 2: Aristada 882mg, monthly + Invega sustenna 234mg monthly

- Systematic review: all patients did well without significant new side effects
  - N = 123 patients
  - 4 patients had AE: EPS, bradykinesia, polyuria/polydipsia

- Two larger observational studies found reductions in hospitalizations following addition of a second LAI
  - N= 13 (Calvin, 2023) and N = 83 (Kenar, 2023)

	Haldol dec	Fluphenazine dec	Aripiprazole maintena	Olanzapine
Haldol				
Fluphenazine				
Aripiprazole	2			
Olanzapine	1		3	
Risperidone	2	1		1
Paliperidone (monthly)	6		32	1
Paliperidone (3 month)			2	

(Cipolla, 2024)

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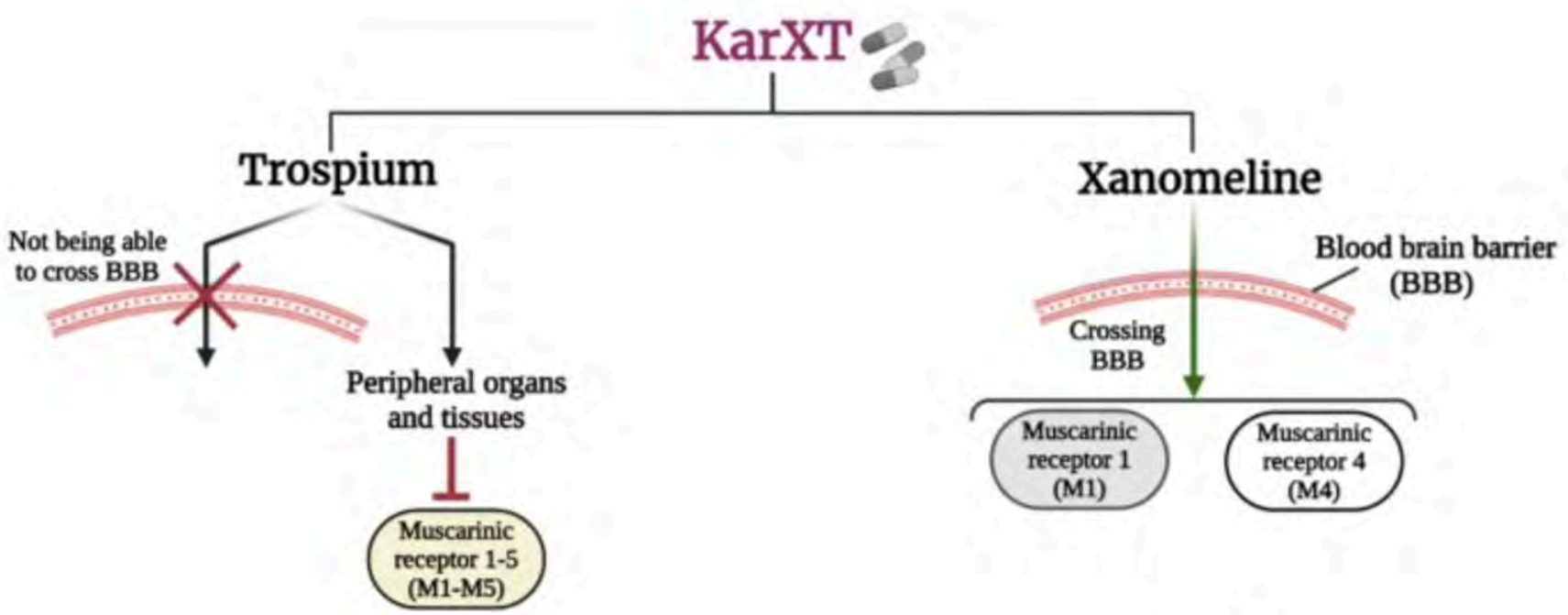
COBENFY - MOA

- Xanolmeline-tropsium
- KarXT



(Azargoonjahromi, 2024)

COBENFY - MOA

FIGURE 5. Activation of M_4 receptors modulates cholinergic tone within midbrain dopamine (DA) centers to regulate terminal DA release[a]

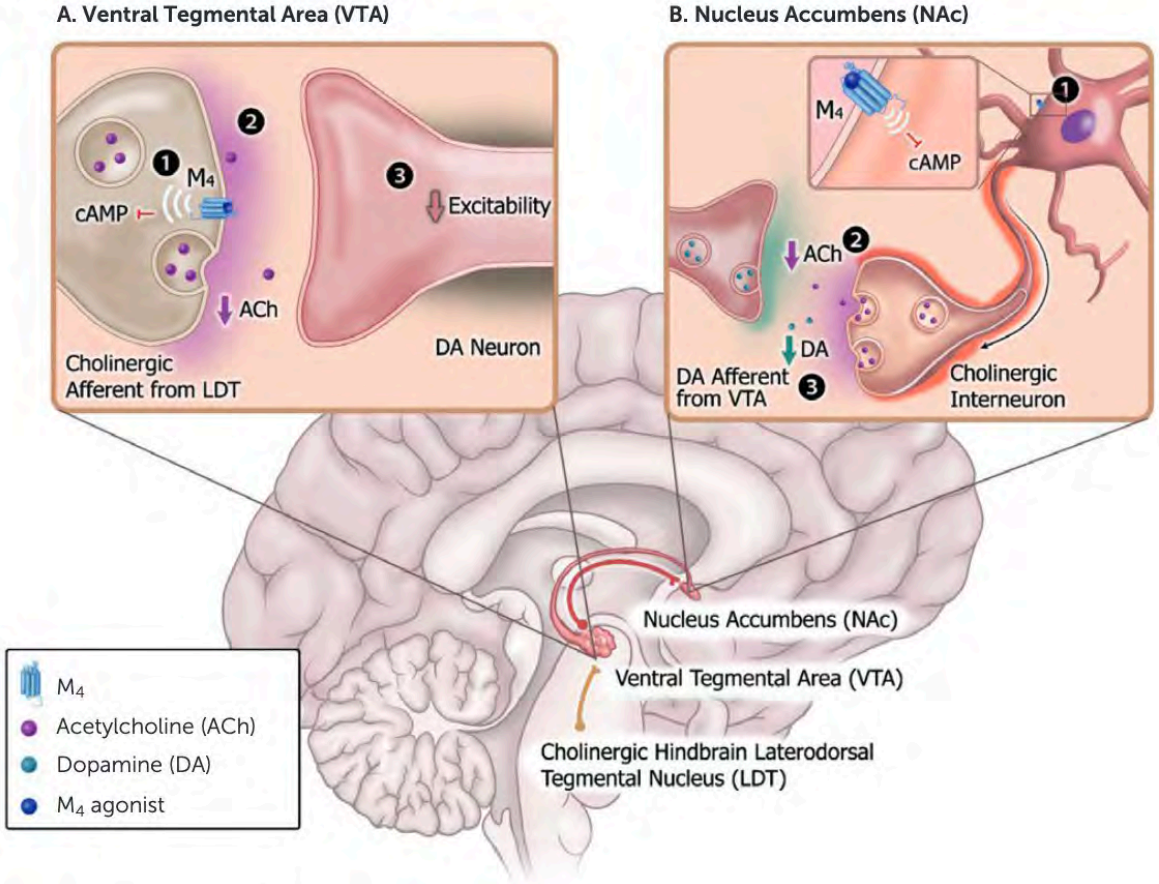
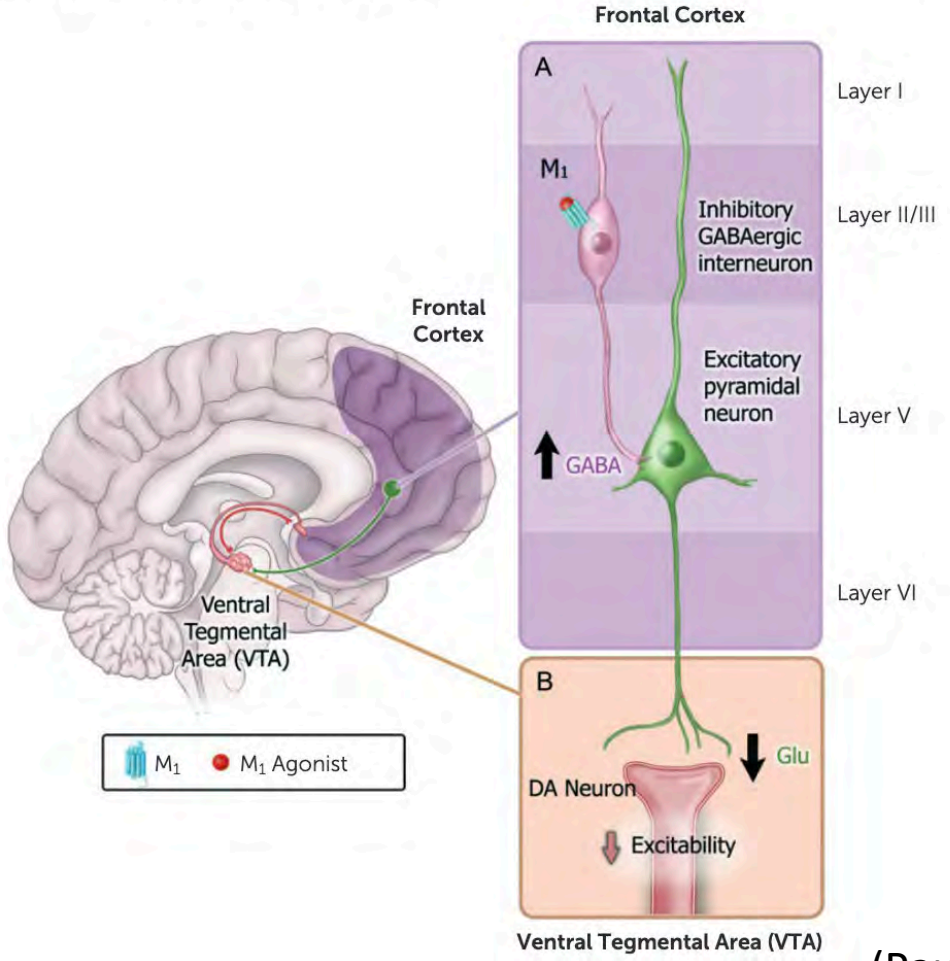


FIGURE 6. Activation of M_1 receptors in the frontal cortex exerts top-down control onto midbrain dopamine (DA) circuits[a]



(Paul, 2022)

COBENFY – REAL WORLD USE

- Limited use at HMC: 2 unsuccessful trials
- 3 typical cases summarized recently (Price, 2025):
  1. Aripiprazole → Cobenfy
     - Decreased akathisia attributed to trospium
     - Nausea treated with ondansetron
  2. Olanzapine → Cobenfy
     - Constipation/GERD (excessive GI anticholinergic effects): took Cobenfy w/food.
     - Improved cognition after cross taper
  3. Clozapine + fluoxetine → Cobenfy + fluoxetine
     - Significant nausea, perhaps due to fluoxetine CYP2D6 inhibition and ↑ xanolmeline

COBENFY – AUGMENTATION

PANSS, PSP and CGI-S Change from Baseline by Treatment Group					
	Endpoint	*Cobenfy* + APD	Placebo + APD	LSMD (95% CI)	p-value
mITT Population, N		190	196		
Primary Endpoint	Change in PANSS Total Score LS Mean (SE)	-14.3 (1.01)	-12.2 (0.98)	-2.0 (-4.5, 0.5)	0.11
Key Secondary Endpoint	Change in PSP Score LS Mean (SE)	5.3 (0.75)	5.9 (0.73)	-0.6 (-2.4, 1.2)	0.52*
Secondary Endpoint	Change in CGI-S LS Mean (SE)	-0.6 (0.06)	-0.5 (0.06)	-0.1 (-0.3, 0.04)	0.14*
Post-Hoc Subgroup Analysis					
Risperidone	Change in PANSS Total Score LS Mean (SE)	(N=60) -11.3 (2.13)	(N=69) -12.3 (2.10)	1.1 (-3.7, 5.9)	0.66*
Non-Risperidone	Change in PANSS Total Score LS Mean (SE)	(N=130) -15.1 (1.18)	(N=127) -11.7 (1.17)	-3.4 (-6.3, -0.5)	0.03*

https://news.bms.com/, ARISE trial

- Trial excluded people already taking anticholinergic meds: clozapine, quetiapine, olanzapine
- Post-hoc analysis showed benefit of Cobenfy in combination with most other APD when risperidone was removed
- Possible reason: risperidone is a CYP2D6 inhibitor. Increased SE from xanolmeline?
- 70% discontinuation in state hospital case series (Vadiei, 2025)

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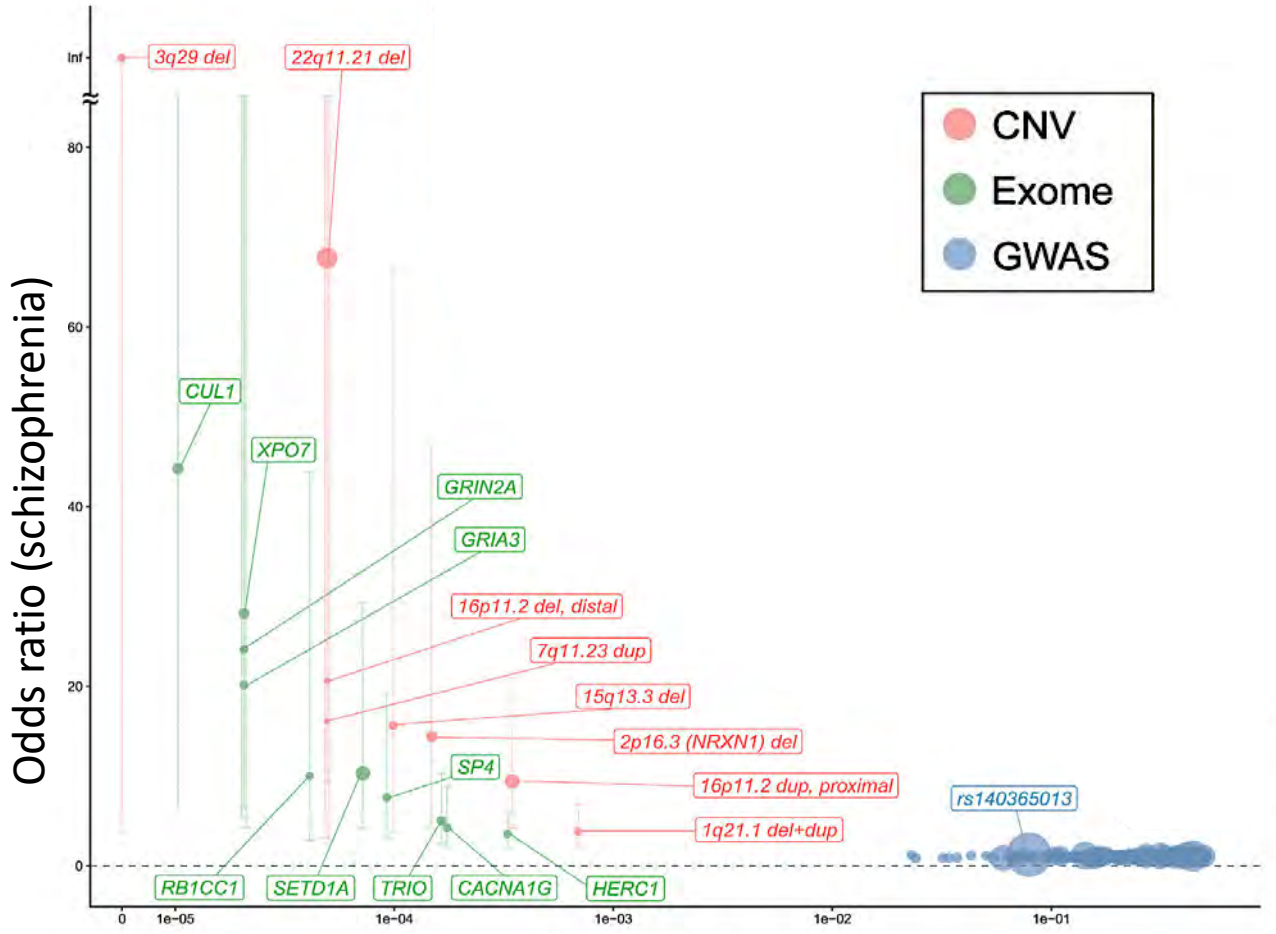
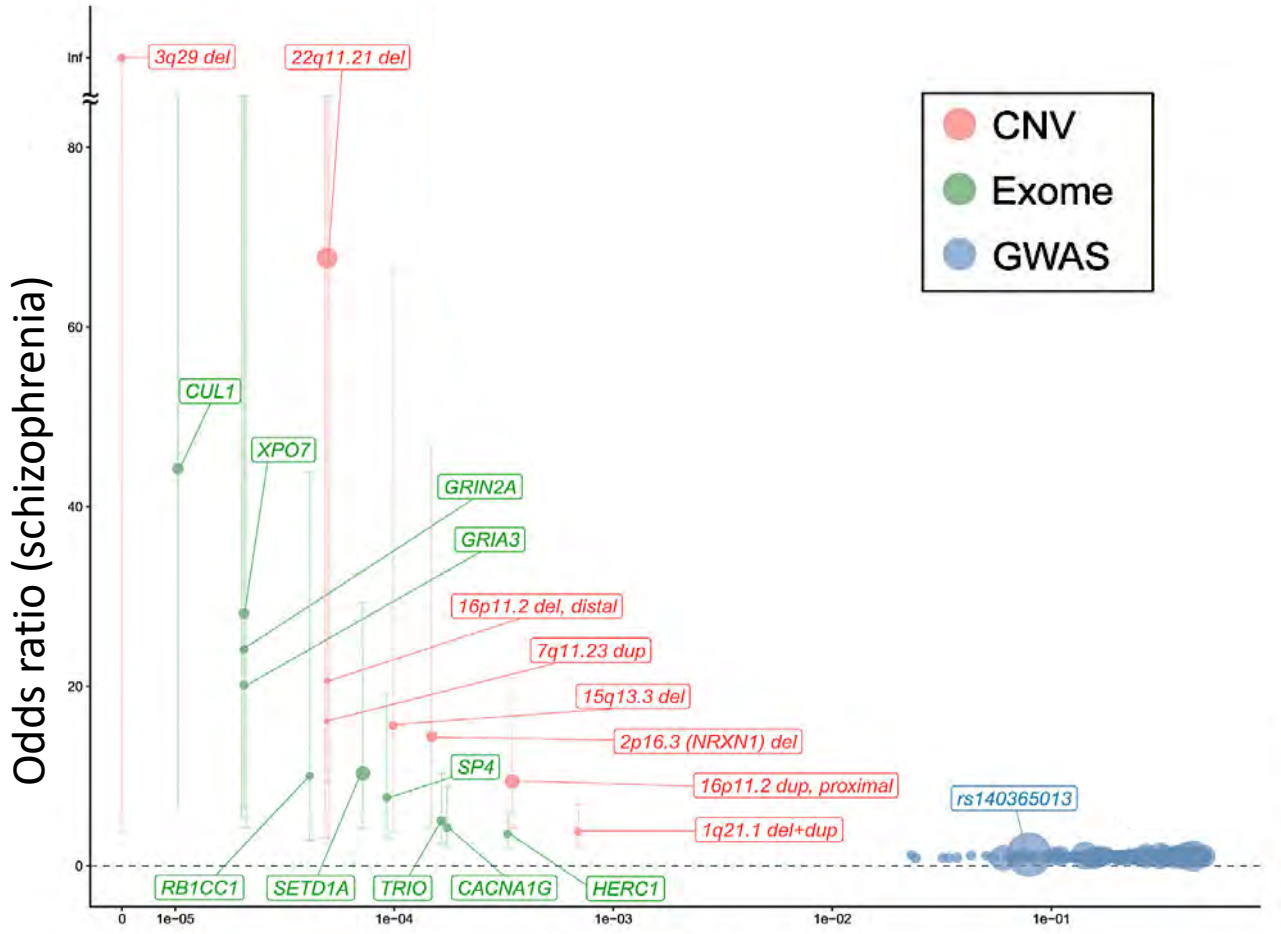
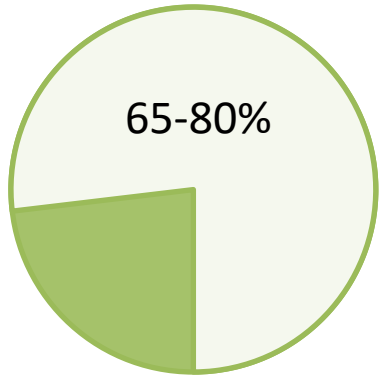
Schizophrenia is a neurodevelopmental disorder

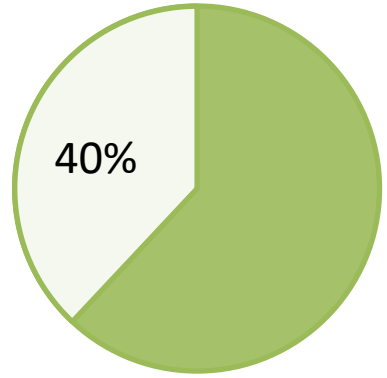


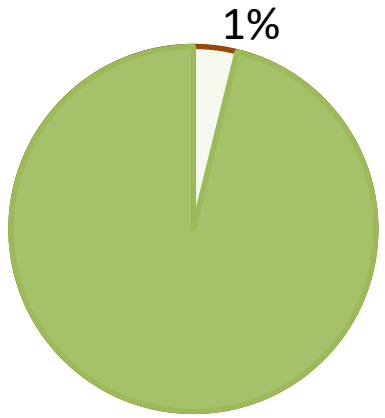
Singh, 2022

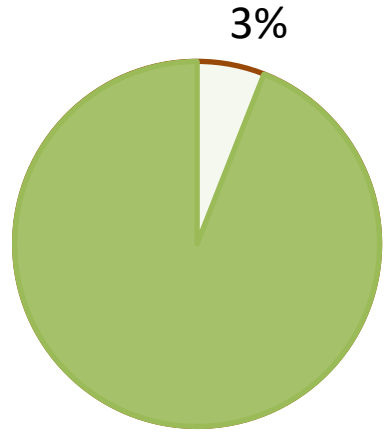
Schizophrenia genetics- what's the use?











Singh, 2022

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IS GENETIC RESEARCH IN SCHIZOPHRENIA FEASIBLE?

Specialized Treatment for Early Psychosis (STEP)

Improving Care for Youth and Young Adults with Early Psychosis

Mental Health and Addiction Services at Harborview

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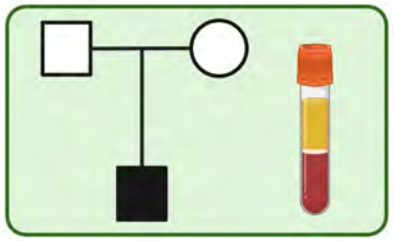
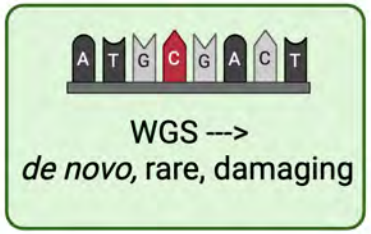
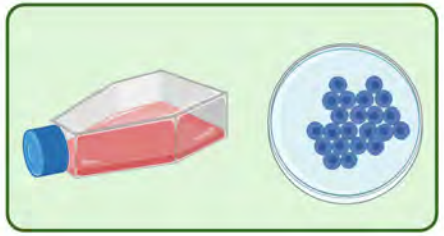
GENETICS: PATHOBIOLOGY, TREATMENTS, DIAGNOSIS







- N = 63
- 16 families and 12 individuals
- Recruitment is challenging but possible
- Successful approach to understanding how genetic mutations may lead to schizophrenia

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INO80D IS DISRUPTED BY NONSENSE MUTATION IN SCZ PROBAND

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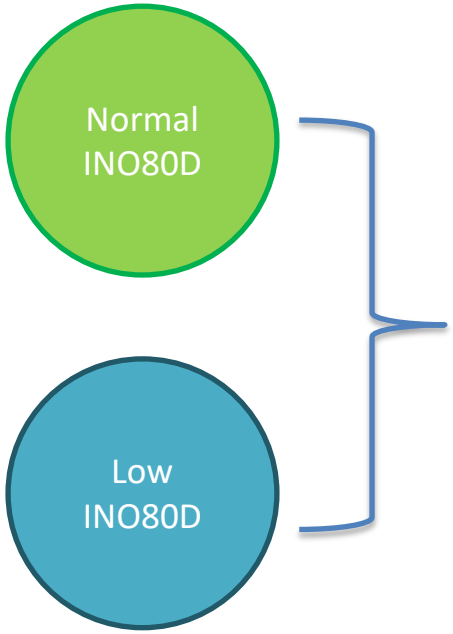
(Sunshine, 2026)

LINKING GENETIC CHANGES TO A CLINICAL PHENOTYPE



How is gene expression different?

How is neuronal function (electrical signaling) different?

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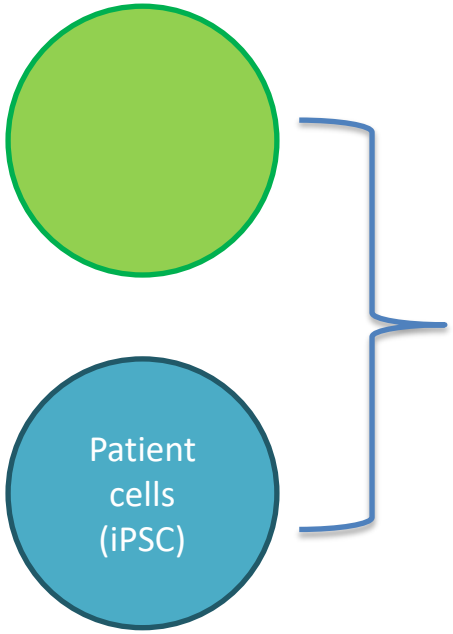

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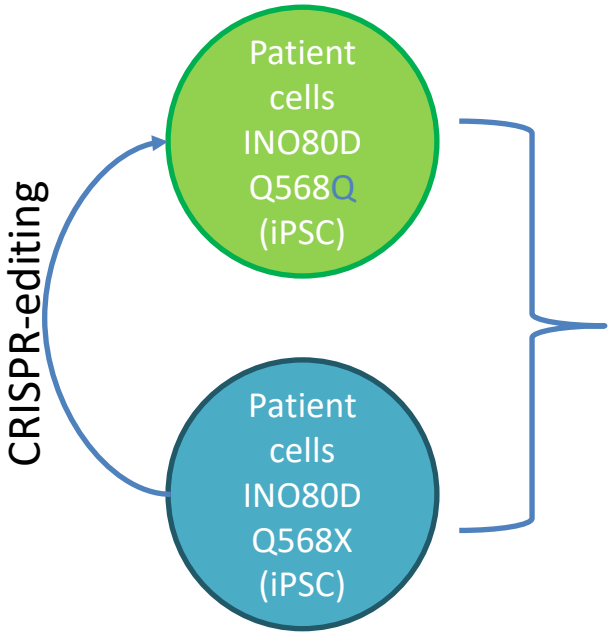

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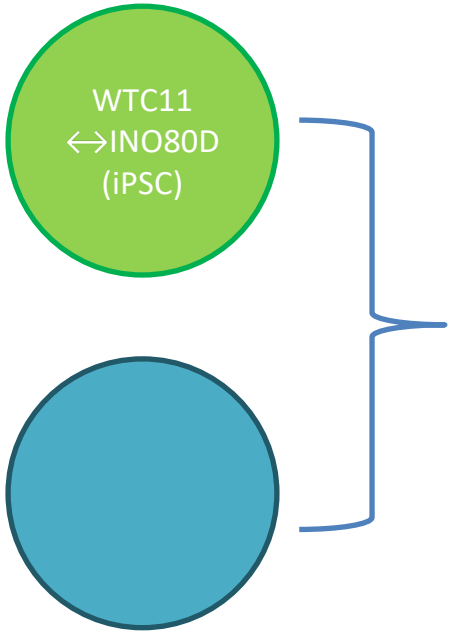

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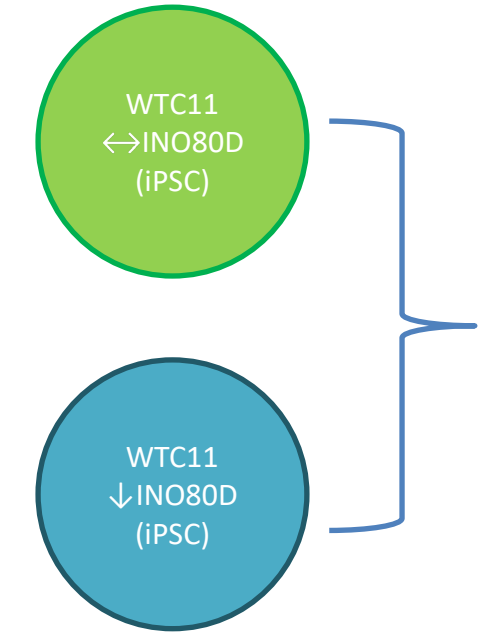

CRISPR inhibition
(CRISPRi)

How is gene expression different?

How is neuronal function (electrical signaling) different?

LINKING GENETIC CHANGES TO A CLINICAL PHENOTYPE: CELL TYPE

CRISPR inhibition (CRISPRi)

iPSC → Neural stem cells → Cortical nerons

How is gene expression different?

How is neuronal function (electrical signaling) different?

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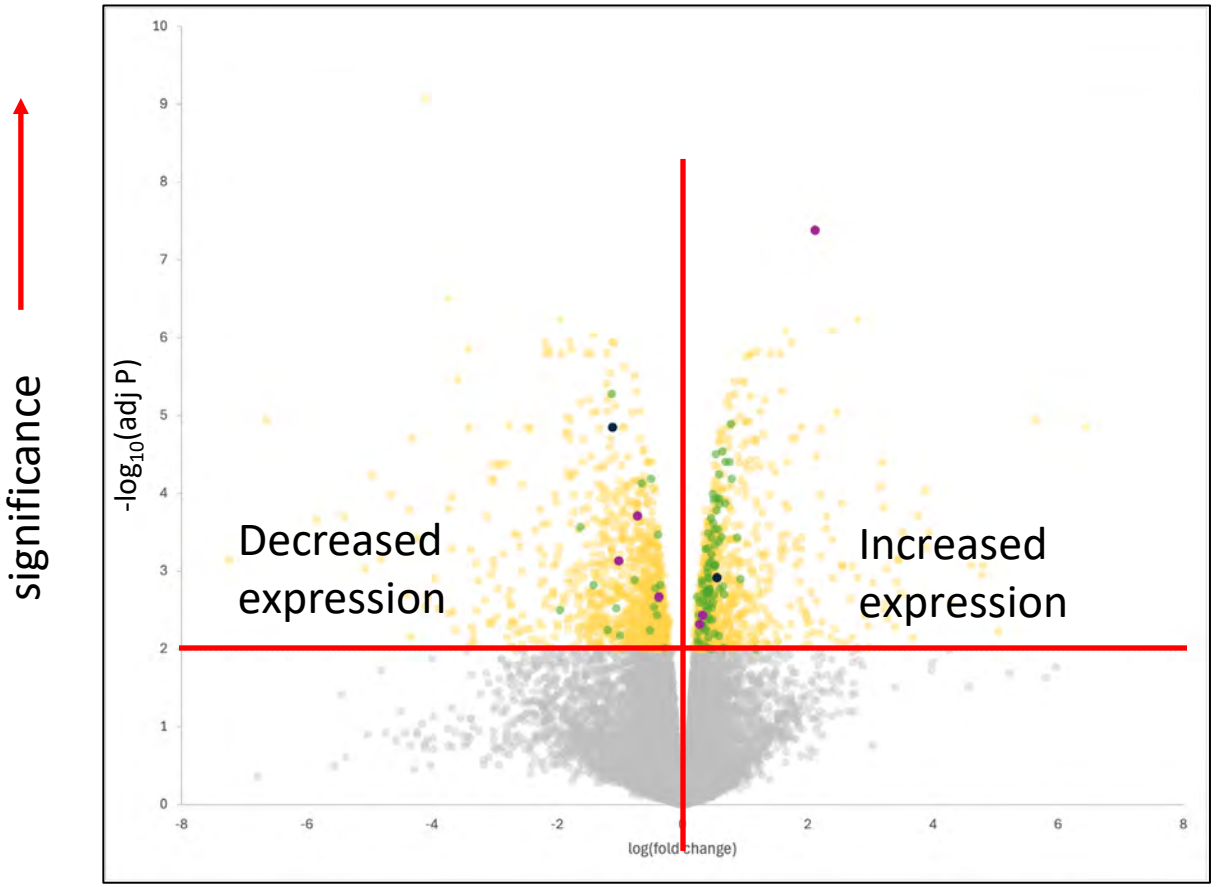
DECREASED INO80D CHANGES GENE EXPRESSION IN NEURAL STEM CELLS



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DECREASED INO80D CHANGES GENE EXPRESSION IN NEURAL STEM CELLS

(Sunshine, 2026)

Knockdown of INO80D leads to:

- downregulation of multiple gene disrupted by mutations in schizophrenia patients
- downregulation of proteins expressed at synapses

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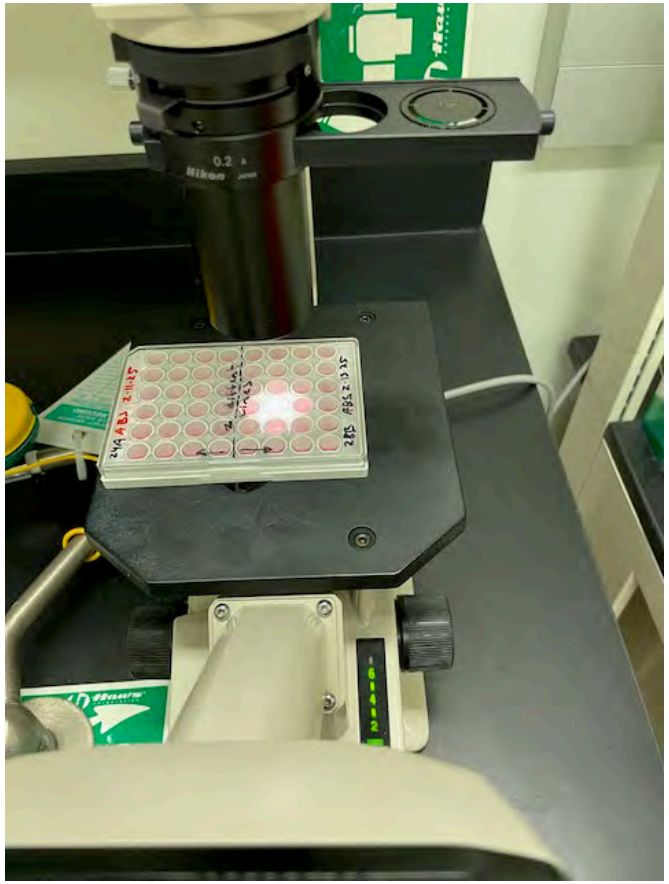
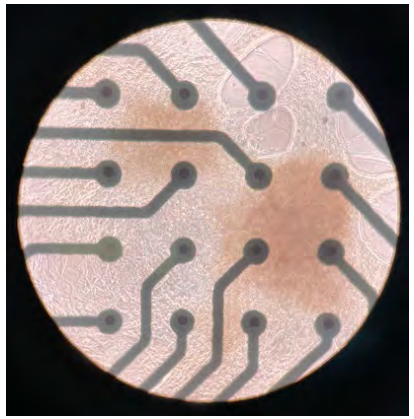
INO80D KNOCKDOWN LEADS TO INCREASED FIRING IN NEURONS





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ISCRM
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UW Medicine
DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES

ISCRM

NIH National Institute of Mental Health

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COBENFY – REAL WORLD USE

	Side effects	Mitigation strategies
Xanomeline	Nausea/vomiting/diarrhea	1. No food 1 hour before X/T and at least 2 hours after finishing a meal 2. Slower X/T titration 3. Ondansetron BID prn 4. If on X/T 100 mg/20 mg, increase to 125 mg/30 mg
	With 2D6 inhibitors	1. Lower X/T dose BID 2. Change to QD dosing
	With 3A4 substrates	Lower dose of 3A4 substrate
Trospium chloride	Gastroesophageal reflux	Famotidine
	Constipation/urinary retention	Take with food
	With central anticholinergics (clozapine, olanzapine, and quetiapine)	Take with food, titrate X/T, then taper off anticholinergic
	With peripheral anticholinergics (diphenhydramine, benztropine, and oxybutynin)	Discontinue peripheral anticholinergics

(Price, 2025)

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