Neuroscience Education Institute

MOVE IT ON OVER: DIAGNOSING AND TREATING TARDIVE DYSKINESIA

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Learning Objectives

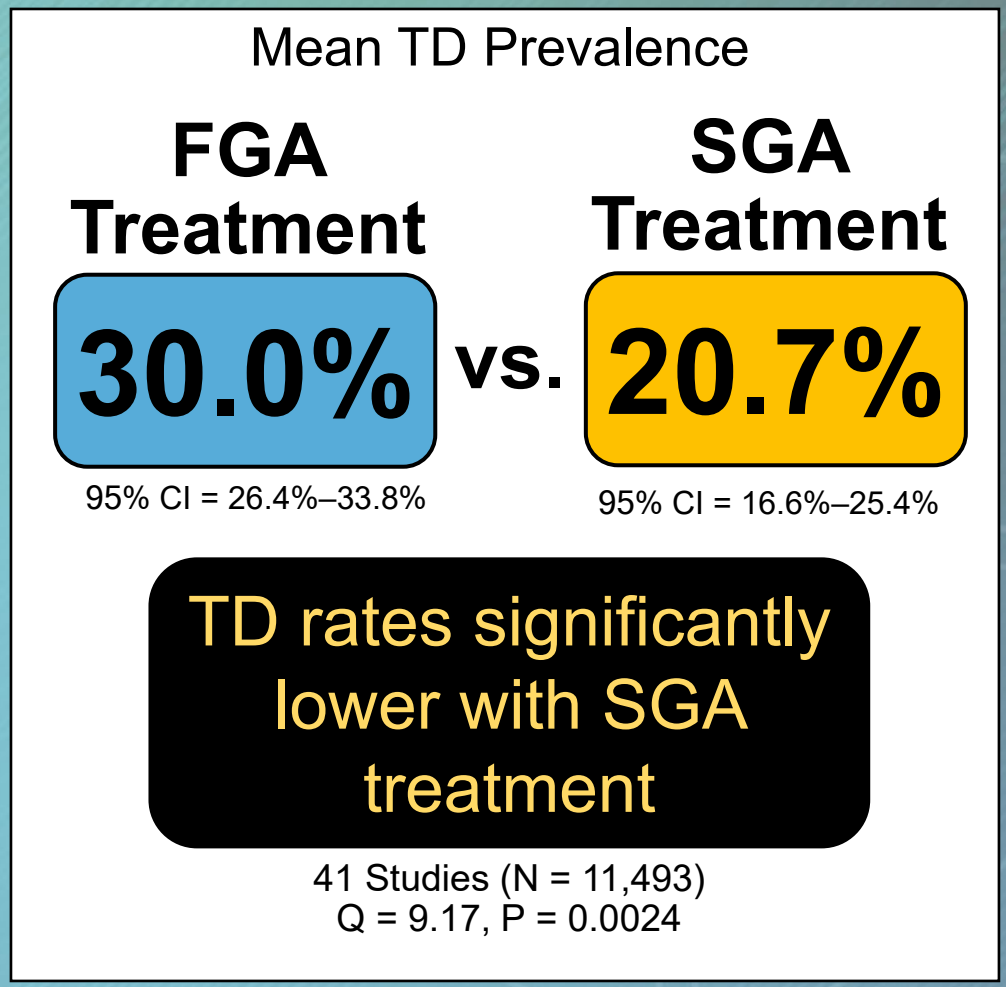
- Describe the neurological bases of tardive dyskinesia
- Identify the risk factors for tardive dyskinesia in patients being treated with antipsychotics
- Recognize the early signs of tardive dyskinesia through regular screening and patient/family education about symptoms
- Differentiate FDA-approved treatment options for tardive dyskinesia based on efficacy and safety

What Is Tardive Dyskinesia?

- Involuntary **choreoathetoid** movements usually associated with lower facial and distal extremity musculature (truncal movements also possible)
  - **Chorea**: Quick, irregular, non-stereotyped movements
  - **Athetosis**: Slow, writhing, serpentine movements
- Not associated with direct sensory problems
- Of considerable clinical, medical, and legal concern because of potential persistence despite drug discontinuation

Tardive Dyskinesia (TD) Prevalence in Second-Generation Antipsychotic Use

- TD prevalence is higher in patients treated with first-generation antipsychotics (FGAs)
- Recent meta-analysis compared TD prevalence in FGA vs. second-generation antipsychotic (SGA) users
- **SGAs still show risk of TD**



Carbon M et al. J Clin Psychiatry 2017;78(3):e264-78.

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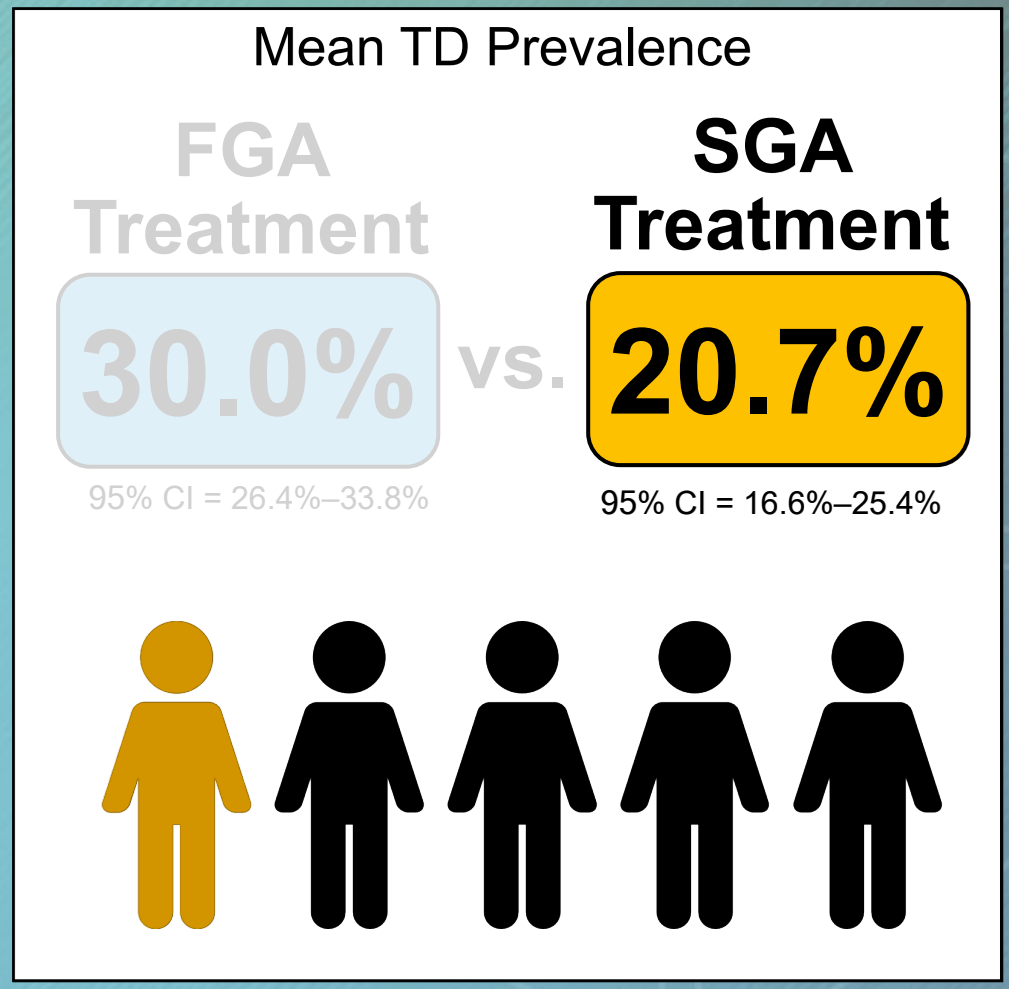
  - 1/5 of patients treated with SGAs showed this “rare” side effect
- In four studies, **7.2%** prevalence with SGA was reported in patients *without prior FGA treatment*



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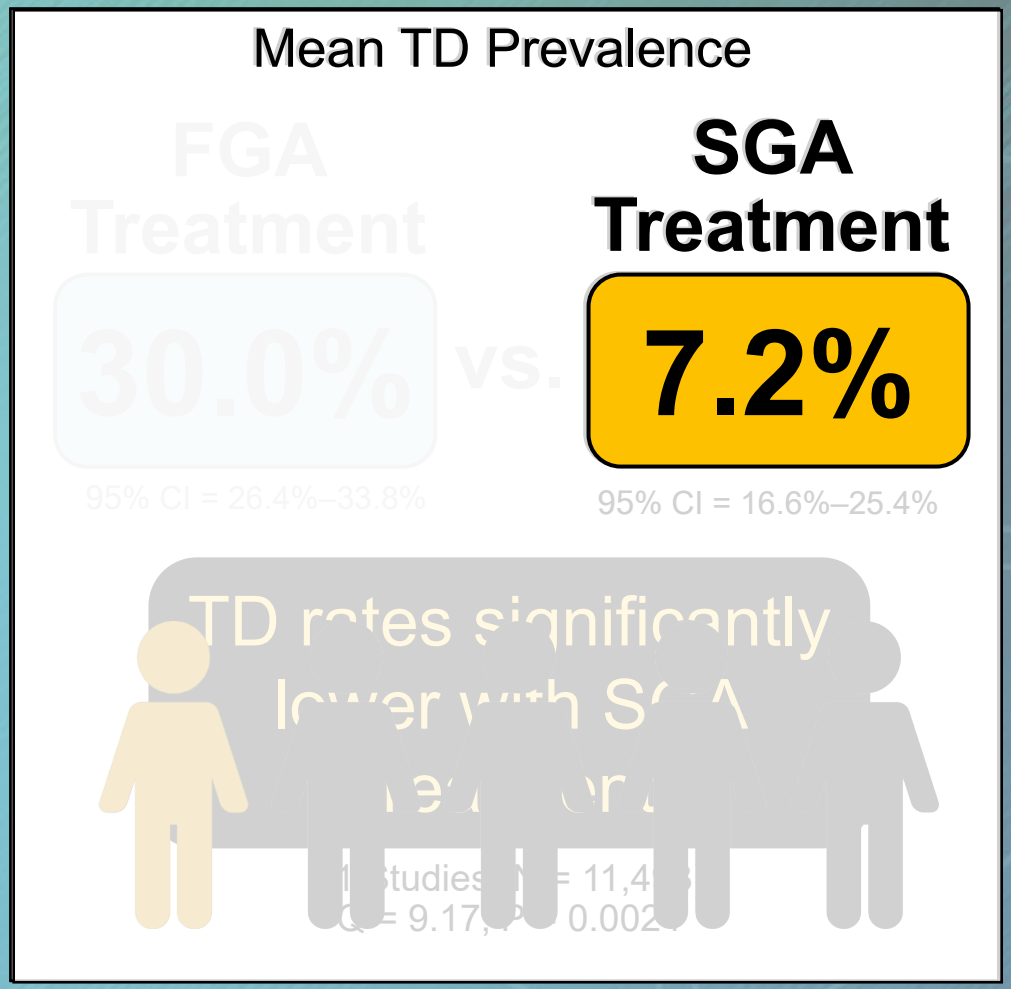

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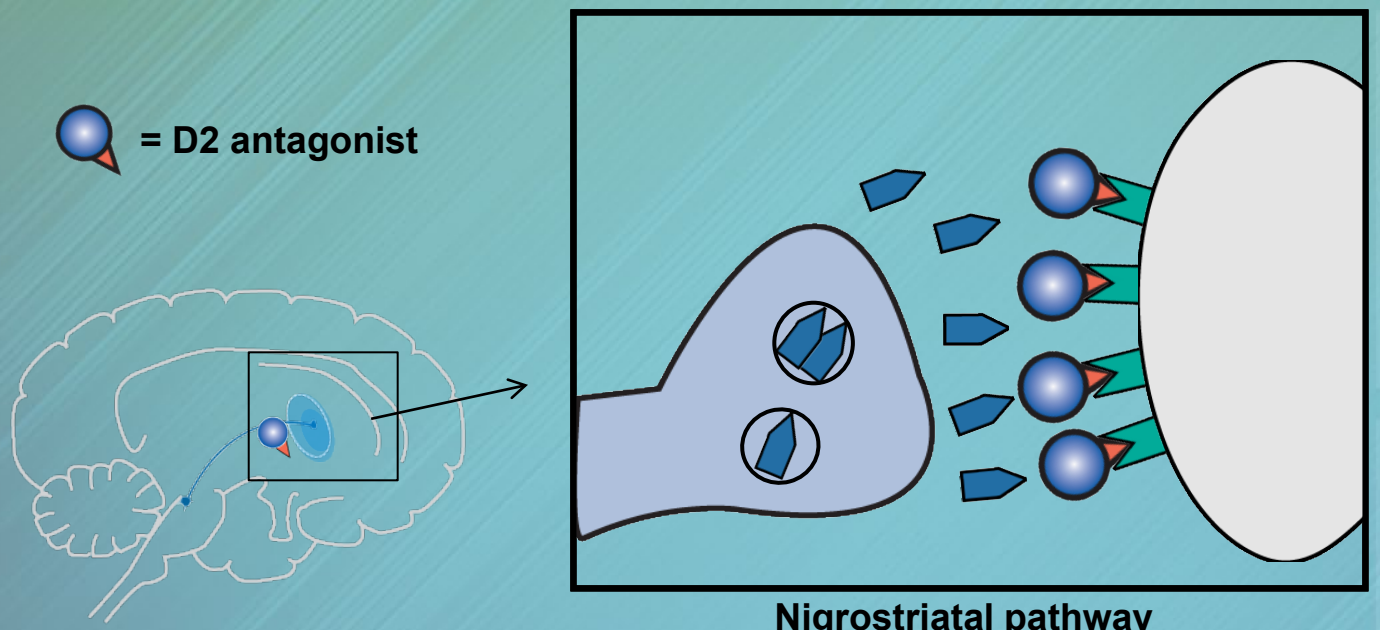
Dopamine Supersensitivity?

Blockade of D2 receptors in the nigrostriatal dopamine pathway causes them to upregulate

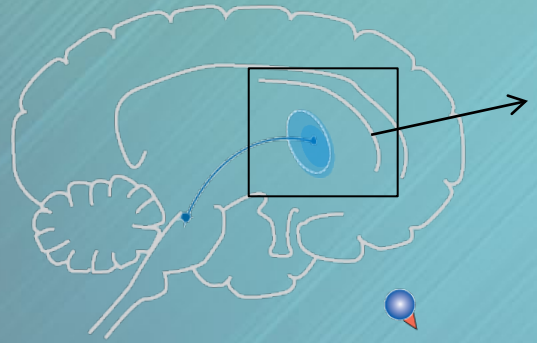


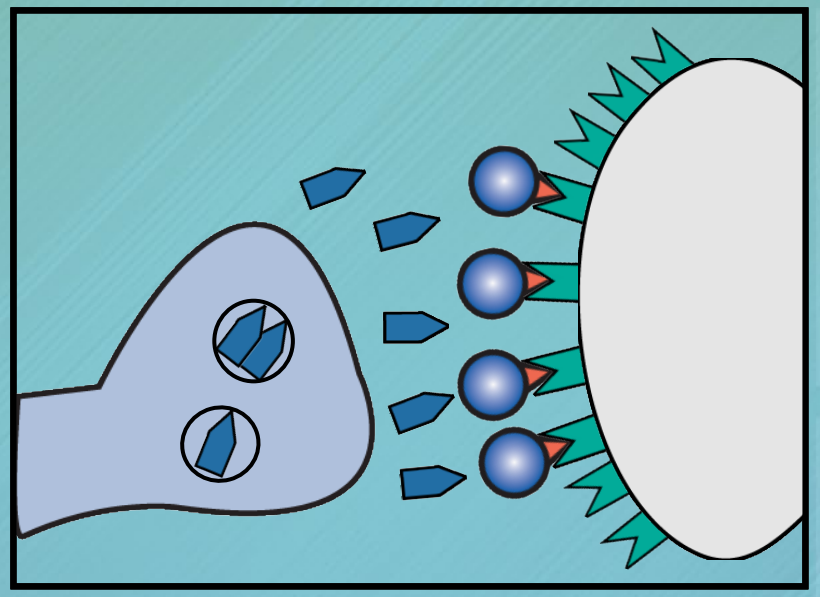
Stahl SM. Stahl's essential psychopharmacology. 4th ed. 2013.

Dopamine Supersensitivity?

This upregulation may lead to tardive dyskinesia

= D2 antagonist





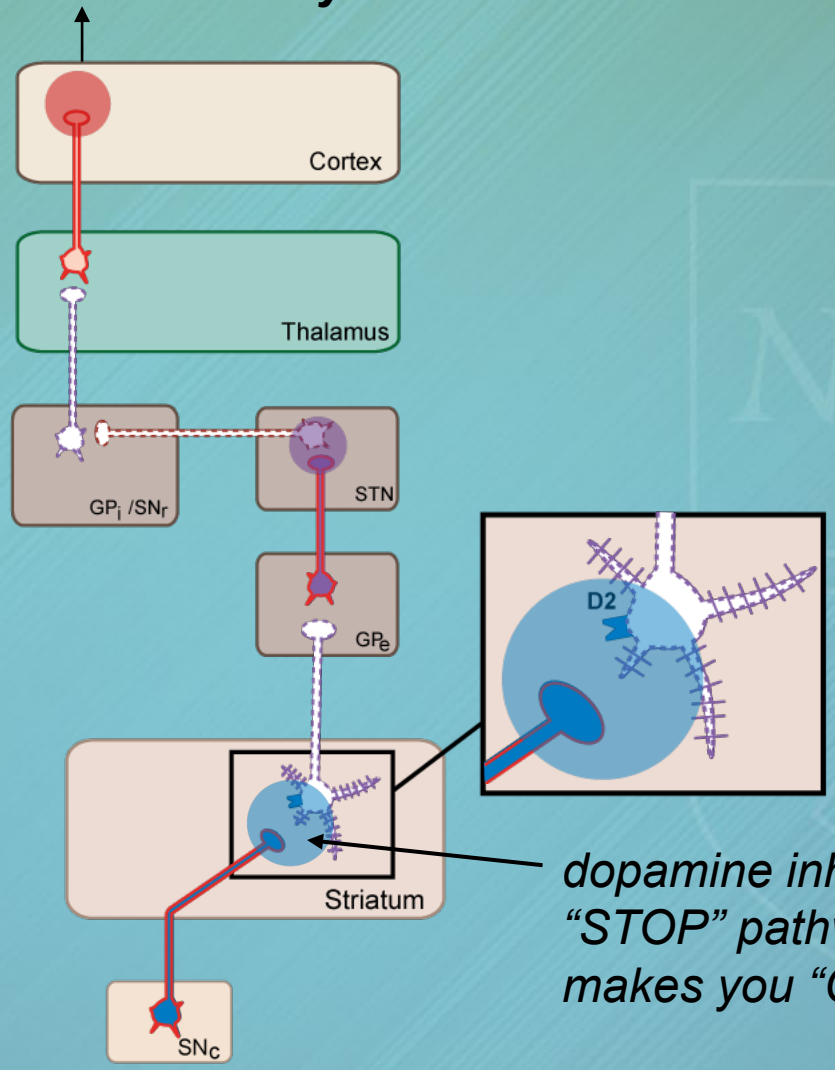
Nigrostriatal pathway

Tardive dyskinesia

Stahl SM. Stahl's essential psychopharmacology. 4th ed. 2013.

D2 Inhibition of "STOP" Pathway

Inhibition of stop or "GO" normally

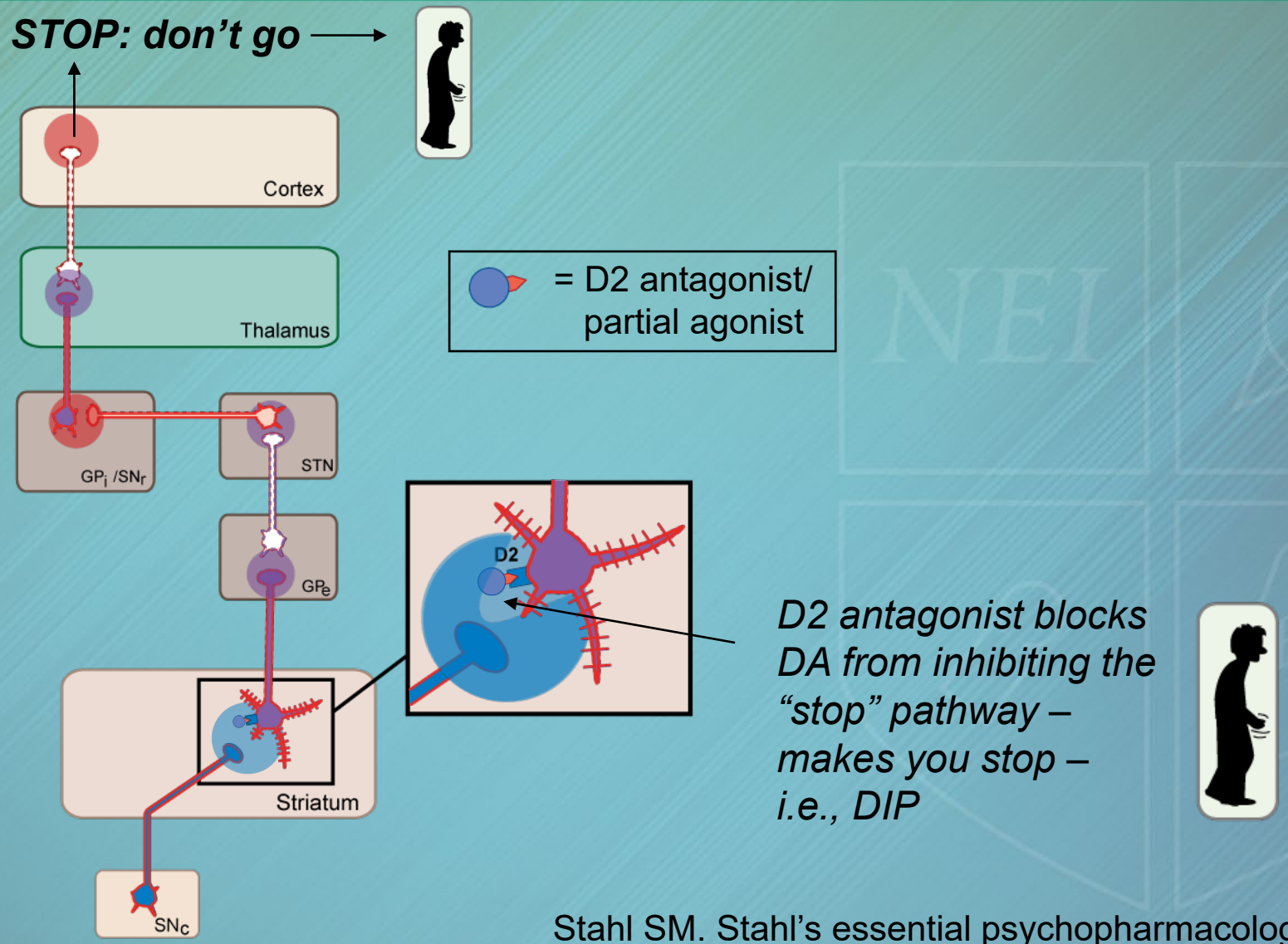


STN= subthalamic nucleus
SN_r = substantia nigra reticulata
SN_C= substantia nigra compacta
GP_e = globus pallidus externa
GP_i = globus pallidus interna
SN = substantia nigra
Glu = glutamate
GABA = γamino butyric acid
DA = dopamine
D1 = dopamine 1 receptor
D2 = dopamine 2 receptor

dopamine inhibiting the "STOP" pathway makes you "GO" normally

Stahl SM. Stahl's essential psychopharmacology. 5th ed. 2020.

D2 Blocker Activates "STOP" Pathway and Causes Drug-Induced Parkinsonism (DIP)



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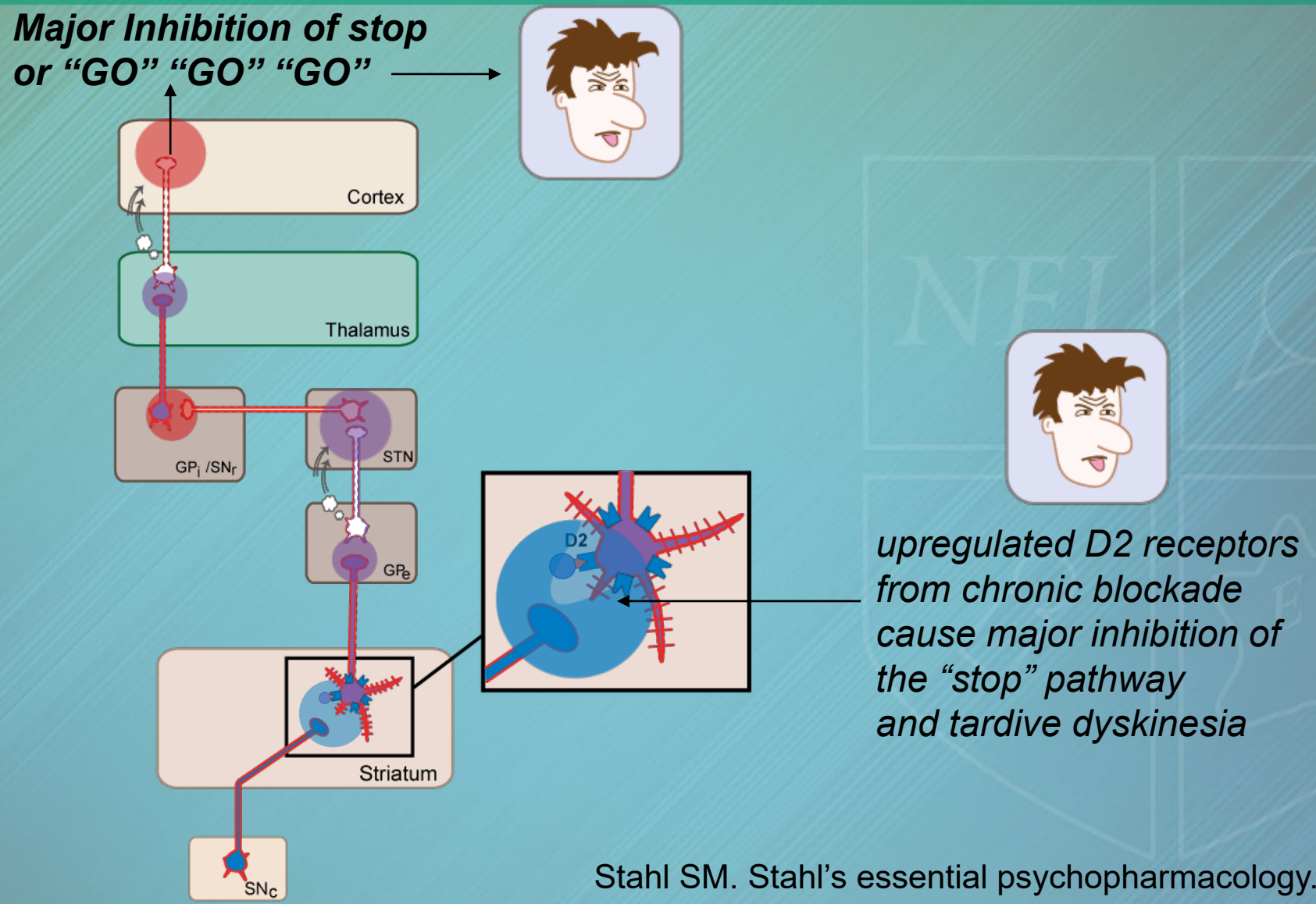
Chronic D2 Blockade Causes Upregulation of D2 Receptors, Enhanced Inhibition of "STOP" Pathway, and Tardive Dyskinesia



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Other Mechanisms of Drug-Induced TD

- **Abnormal synaptic plasticity**
  - Chronic blockade of D2 receptors provokes maladaptive plasticity in corticostriatal transmission
- **Aberrant spine formation**
  - D2 receptors on necks; glutamate receptors on heads
- **Neuronal degeneration hypothesis**
  - Oxidative and/or excitotoxic damage from free radicals
  - Considerable basic scientific evidence
  - May offer avenues for clinical treatment

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87; Teo JT et al. Mov Disord 2012;27(10):1205-15; Aquino CC, Lang AE. Parkinsonism Relat Disord 2014;20(Suppl 1):S113-7; Stahl SM. CNS Spectr 2017;22(6):427-34.

Risk Factors for Tardive Dyskinesia

- The following patient or treatment attributes contribute to high risk of TD development:
  - Current or recent treatment with a first-generation antipsychotic
  - Older age
  - Longer cumulative exposure to antipsychotics
  - Acute extrapyramidal symptoms (e.g., parkinsonism) and acute akathisia
  - Female sex

Caroff SN et al. J Clin Psychiatry 2020;81(2):19cs12983.

Early Identification

All patients currently taking any drug with dopamine receptor blocking properties (e.g., antipsychotics, metoclopramide) should be screened for TD at every clinical encounter

Caroff SN et al. J Clin Psychiatry 2020;81(2):19cs12983.

Clinical Screening

- Clinical screening includes asking about and looking for TD
- Clinical screening should include routine semi-structured assessment (at every clinical encounter) and less frequent structured assessment
  - Annually in patients taking SGAs
  - Every 6 months in patients taking FGAs
  - Every 3 months in high-risk patients
- The Abnormal Involuntary Movement Scale (AIMS) is the standard structured assessment for screening and monitoring for severity of abnormal movements

Caroff SN et al. J Clin Psychiatry 2020;81(2):19cs12983;
Citrome L. J Neurol Sci 2017;383:199-204.

Semi-Structured Assessment

- A semi-structured assessment, which should be done at every clinical encounter with a patient taking an antipsychotic, should include:
  - Patient recognition of current/recent abnormal movements as part of a review of side effects at time of assessment
  - Visual observation of psychomotor abnormalities on mental status examination
  - Caregiver report of recent/current abnormal movements
  - Patient report of history of movement/psychomotor changes
  - Patient complaints about changes in movement being distressful or interfering with functioning or quality of life

Caroff SN et al. J Clin Psychiatry 2020;81(2):19cs12983.

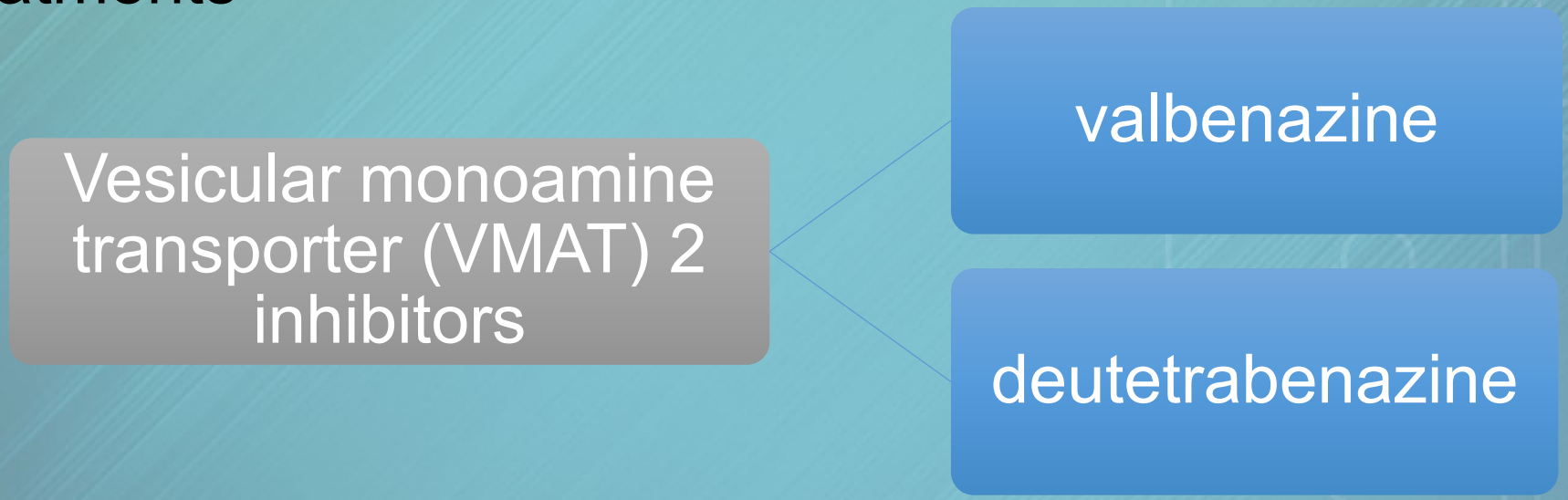
Patient and Family Education

- Recognize the early signs of TD through patient/family education about symptoms
- Clinicians should discuss diagnosis, prognosis, and treatment options of TD with patients and caregivers
- Psychoeducation that emphasizes immediately reporting side effects like TD improves outcomes (number of days in hospital) in schizophrenia and schizoaffective disorder without an increase of side effects at 7-year follow-up

Caroff SN et al. J Clin Psychiatry 2020;81(2):19cs12983;
Chaplin R, Timehin C. Aust N Z J Psychiatry 2002;36(1):99-103;
Bäuml J et al. Schizophr Bull 2016;42(Suppl 1):S62-70.

Treatment Options for Tardive Dyskinesia

- If TD is mild and of recent onset
  - Slowly taper off an offending dopamine receptor blocking agent **if possible**
- Food and Drug Administration (FDA)-approved treatments



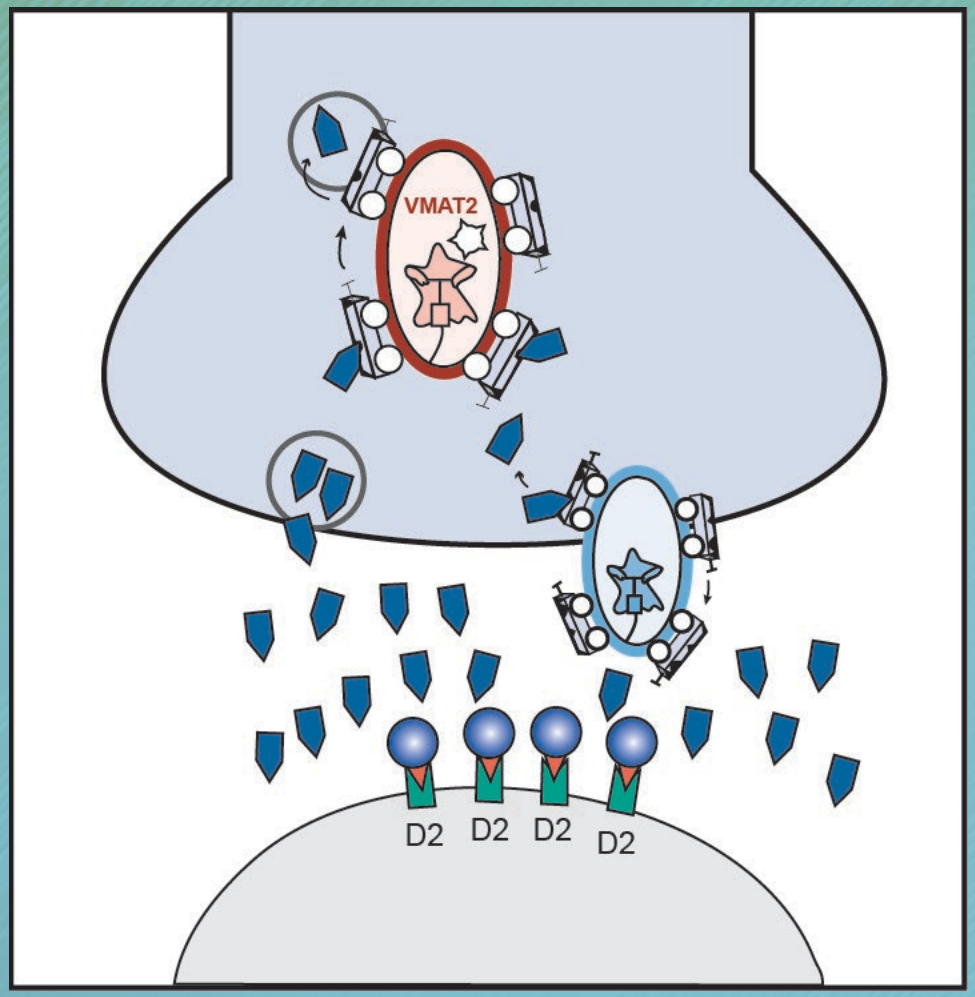
Bhidayasiri R et al. J Neurol Sci 2018;389:67-75.

Vesicular Monoamine Transporter (VMAT)

- Protein integrated into the membrane of synaptic vesicles of presynaptic neurons
- Transports monoamine neurotransmitters (DA, 5HT, NE, epinephrine, histamine) into vesicles
- Two forms: VMAT1 and VMAT2
  - VMAT1: expressed mainly in peripheral nervous system
  - VMAT2: expressed mainly in monoaminergic cells of the central nervous system

Kenney C, Jankovic J. Expert Rev Neurother 2006;6(1):7-17;
Shen V et al. Tremor Other Hyperkinet Mov (N Y) 2013;3:tre-03-191-4337-1;
Waln O, Jankovic J. Tremor Other Hyperkinet Mov (N Y) 2013;3:tre-03-161-4138-1.

VMAT2 Inhibition in Tardive Dyskinesia



Psychosis

Stahl SM. Stahl's essential psychopharmacology. 4th ed. 2013.

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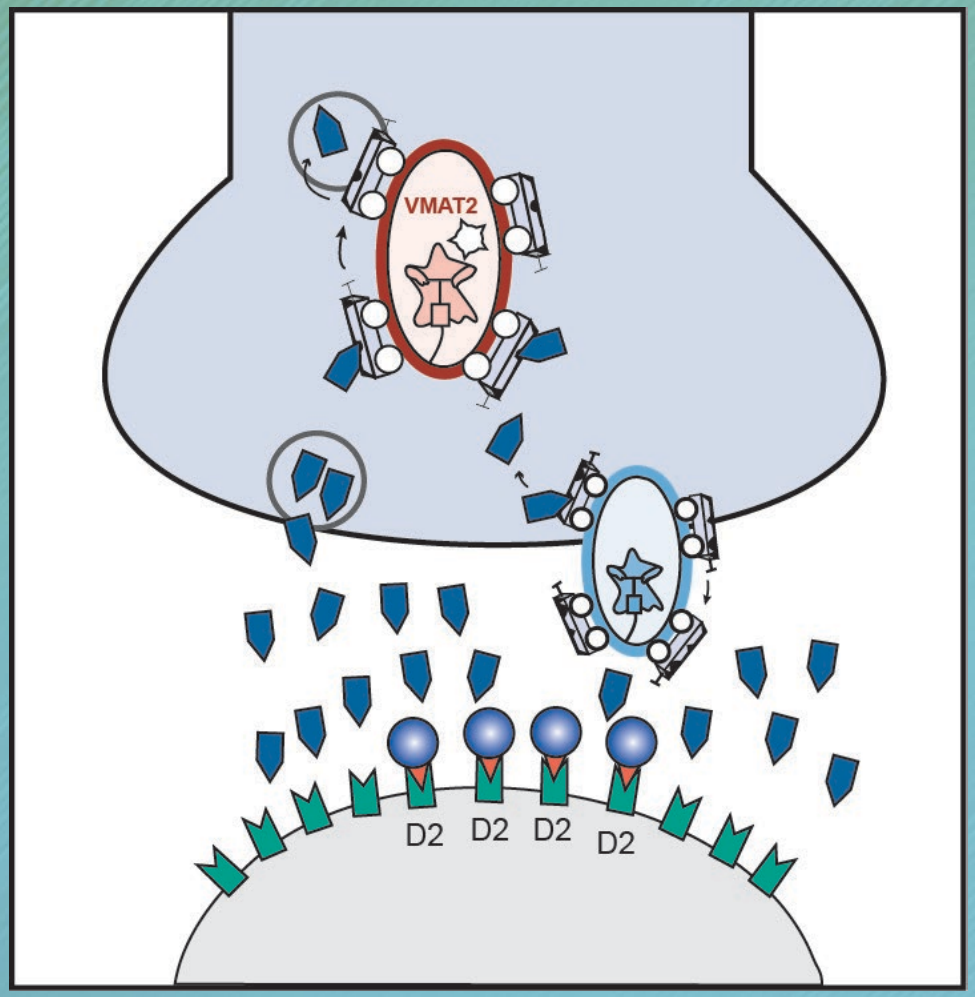

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Tardive dyskinesia

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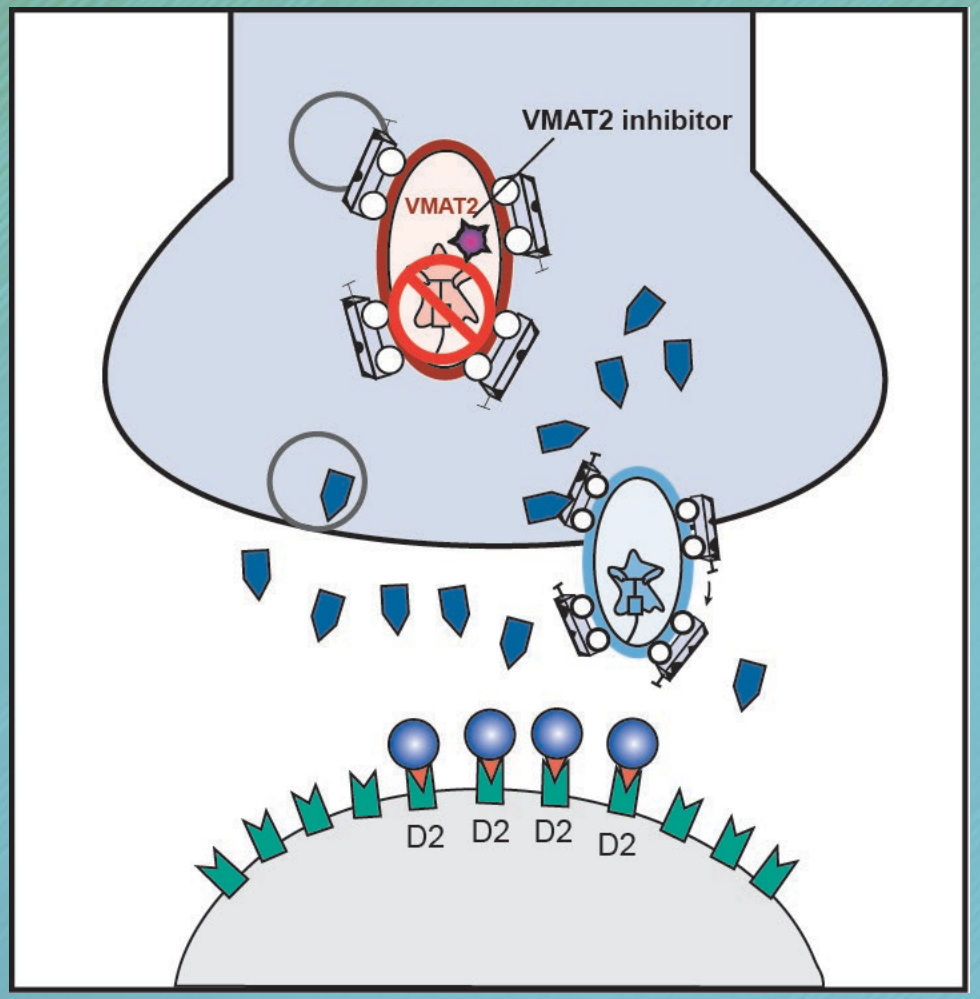

Psychosis

Tardive dyskinesia

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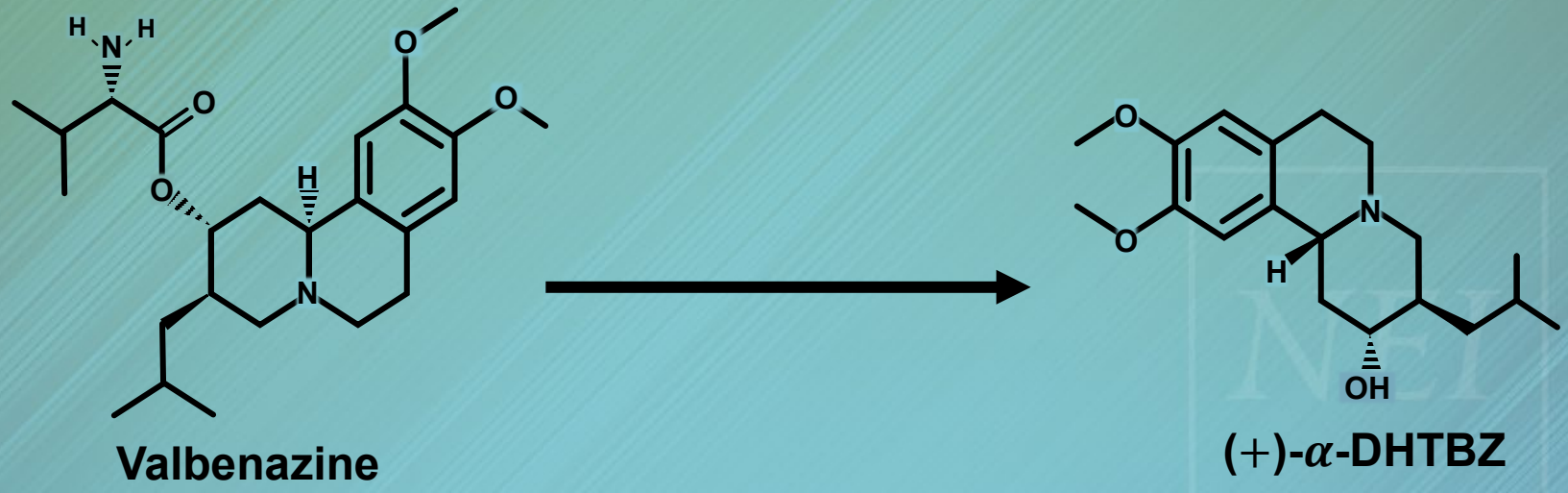
Valbenazine

- Designed to deliver metabolite in a controlled fashion

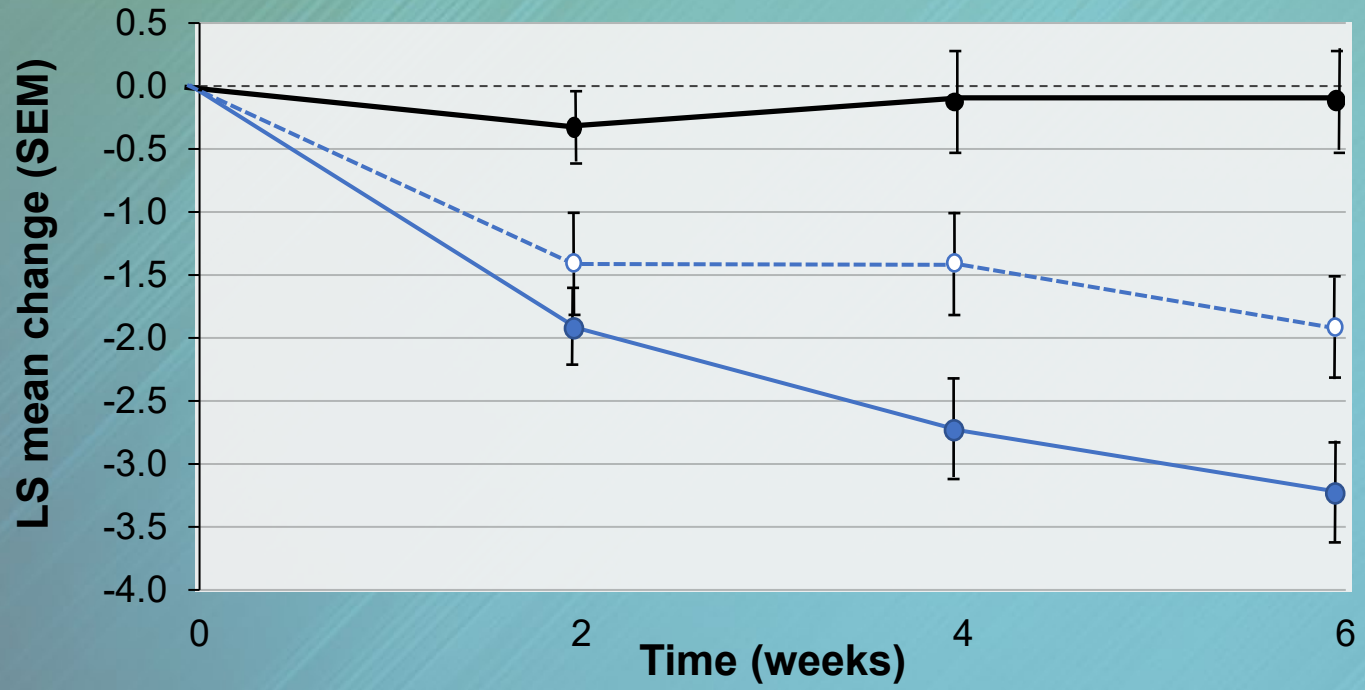


- Limited off-target receptor binding
- FDA-approved for the treatment of TD in April 2017
  - Initial dose 40 mg/day, after 1 week increase dose to 80 mg/day
  - **No need for CYP2D6 genotyping**

Müller T. Expert Opin Investig Drugs 2015;24(6):737-42; O'Brien CF et al. Mov Disord 2015;30(12):1681-7; Skor H et al. Drugs R D 2017;17(3):449-59.

Valbenazine Efficacy: KINECT 3 AIMS Outcomes at Week 6

Change from baseline in the severity of TD symptoms assessed by the Abnormal Involuntary Movement Scale (AIMS) through week 6



Placebo

AIMS score (least squares [LS] ± standard error of the mean [SEM]) mean change from baseline to week 6:

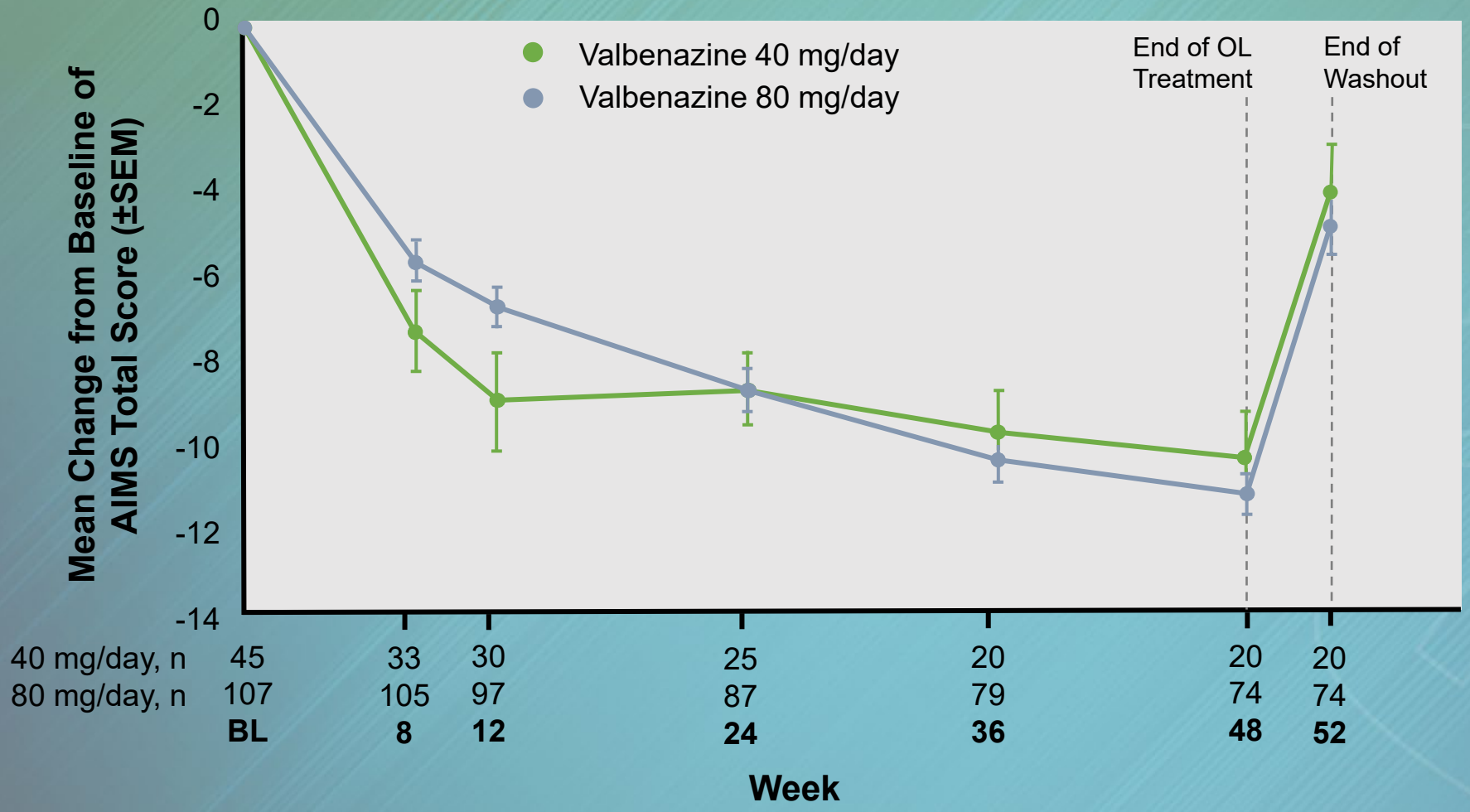
Valbenazine 40 mg
-1.9 vs. -0.1 placebo;
p<0.05; effect size, d=0.52

Valbenazine 80 mg
-3.2 vs. -0.1 placebo;
p<0.001; effect size, d=0.90

AIMS at week 6 for the valbenazine 80 mg dose was reduced 3.1 points more than placebo (*p*<0.001), which is clinically meaningful

Hauser RA et al. Am J Psychiatry 2017;174(5):476-84; Stacy M et al. Mov Disord 2019;34(8):1203-9.

Valbenazine Efficacy and Safety: 1-Year Open-Label Trial (KINECT 4)



Weeks 4–48

Any TEAEs: 64.7%

Most common TEAEs:

- Urinary tract infection (8.5%)
- Headache (5.2%)

BL: baseline; OL: open-label; SEM: standard error of the mean; TEAE: treatment-emergent adverse event.

Marder SR et al. J Clin Psychopharmacol 2019;39(6):620-7.

Valbenazine Safety and Tolerability

- Pharmacokinetic profile permits once-daily dosing
- Psychiatric status remained stable
- Improved TD regardless of the use or type of concomitant antipsychotic
- Somnolence is the most common treatment-related adverse effect
  - Valbenazine (all doses), 10.9%; placebo, 4.2%
  - May be due to depletion of monoamines in people with higher plasma levels of valbenazine

O'Brien CF et al. Mov Disord 2015;30(12):1681-7; Hauser RA et al. Am J Psychiatry 2017;174(5):476-84; Citrome L. Int J Clin Pract 2017;71(7):10.1111/ijcp.12964.

Valbenazine Appears Safe and Well-Tolerated Long Term

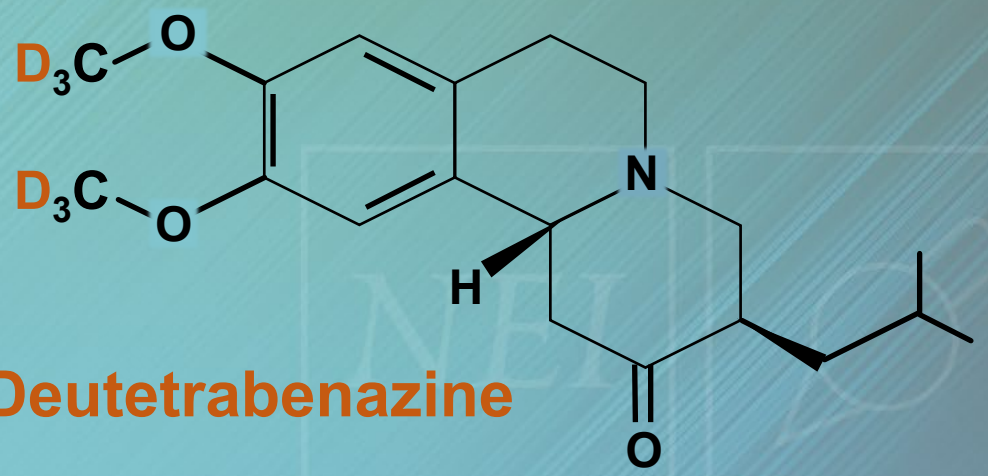
- Data pooled from three studies with valbenazine (up to 48 weeks) in adults with TD (N=430)
- 66.5% of patients experienced treatment-emergent adverse events (TEAEs), but only 14.7% discontinued the drug due to adverse events

- Patients with schizophrenia or schizoaffective disorder (71.7%):
  - urinary tract infection (6.1%)
  - headache (5.8%)
  - somnolence (5.2%)
- Patients with mood disorders (28.3%):
  - headache (12.4%)
  - urinary tract infection (10.7%)
  - somnolence (9.1%)

Josiassen RC et al. Psychopharmacol Bull 2017;47(3):61-8.

Deutetrabenazine

- Deuteration is the replacing of **hydrogen** atoms with **deuterium** on a compound
  - No change in shape, size, charge, or target pharmacology of small molecules
  - Chemical bond C-D is 8x stronger
  - Prolongs half-life and improves PK

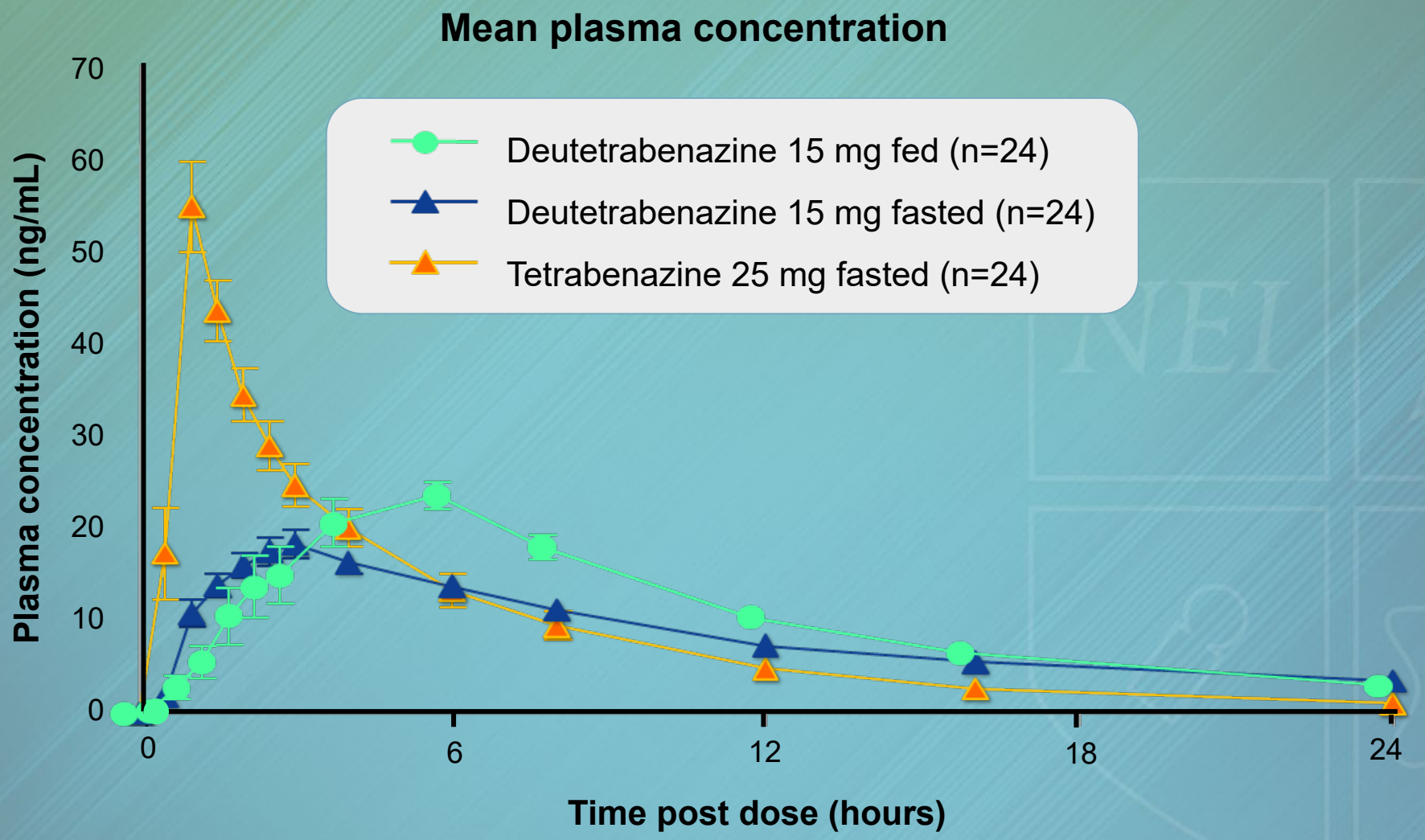


Deutetrabenazine

- FDA approved for tardive dyskinesia on August 30, 2017
  - Initial dose 12 mg/day in two divided doses
  - Titrate at weekly intervals by 6 mg/day based on reduction of TD and tolerability
  - Maximum recommended daily dosage of 48 mg (24 mg twice daily)
  - **No need to CYP2D6 genotyping**

Fernandez HH et al. Neurology 2017;88(21):2003-10; Anderson KE et al. Lancet Psychiatry 2017;4(8):595-604.

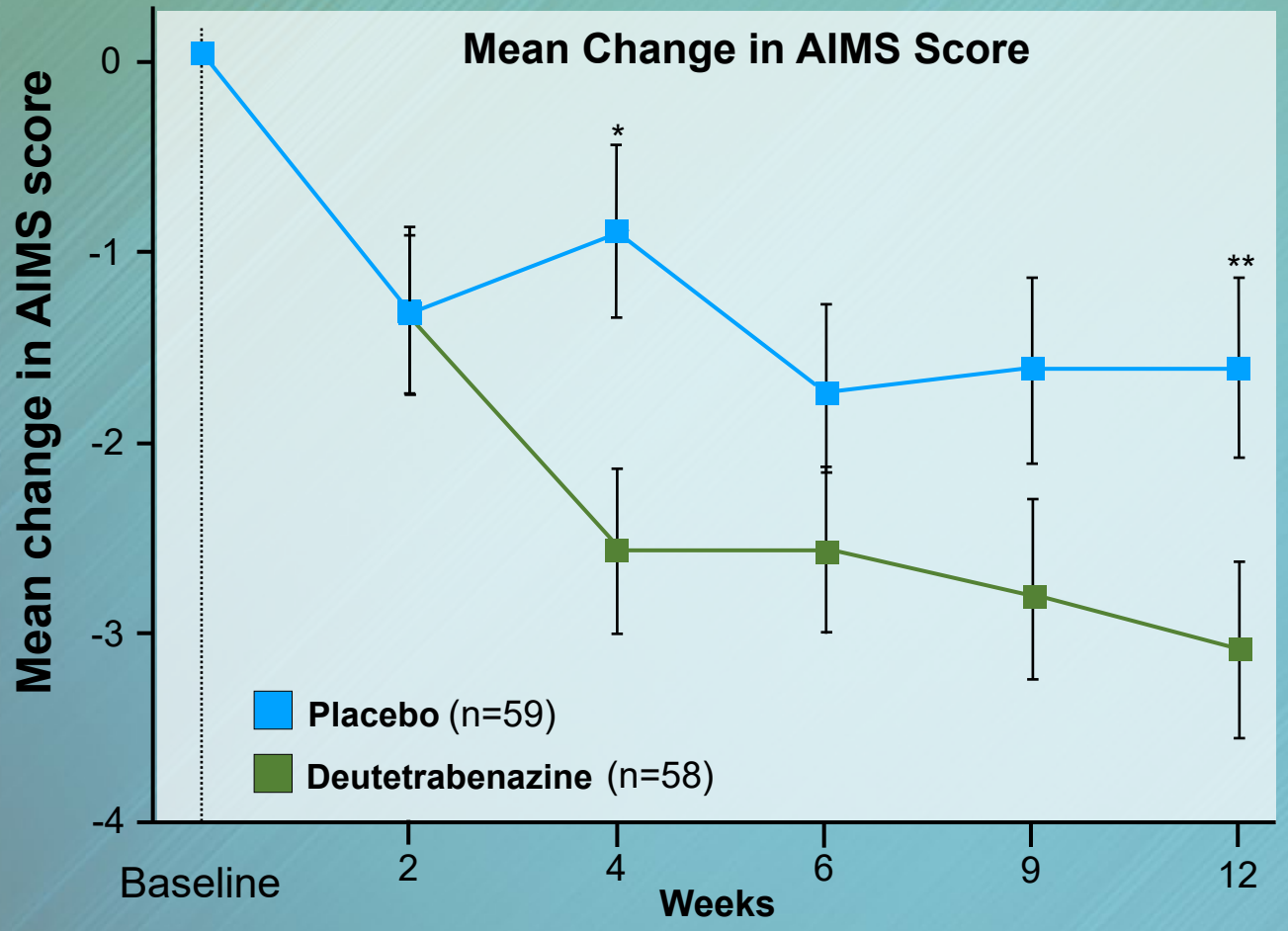
Pharmacokinetics of Deutetrabenazine



Schneider F et al. Clin Pharmacol Drug Dev 2021;10(6):647-59.

Deutetrabenazine: Phase 2/3 Randomized ARM-TD Dose-Finding Trial

Double-blind, placebo-controlled, parallel-group study



At Week 12

Placebo:

Decrease in mean AIMS: -1.6 (SE=0.46)

Deutetrabenazine:

Decrease in mean AIMS: -3.0 (SE=0.45), which is clinically meaningful

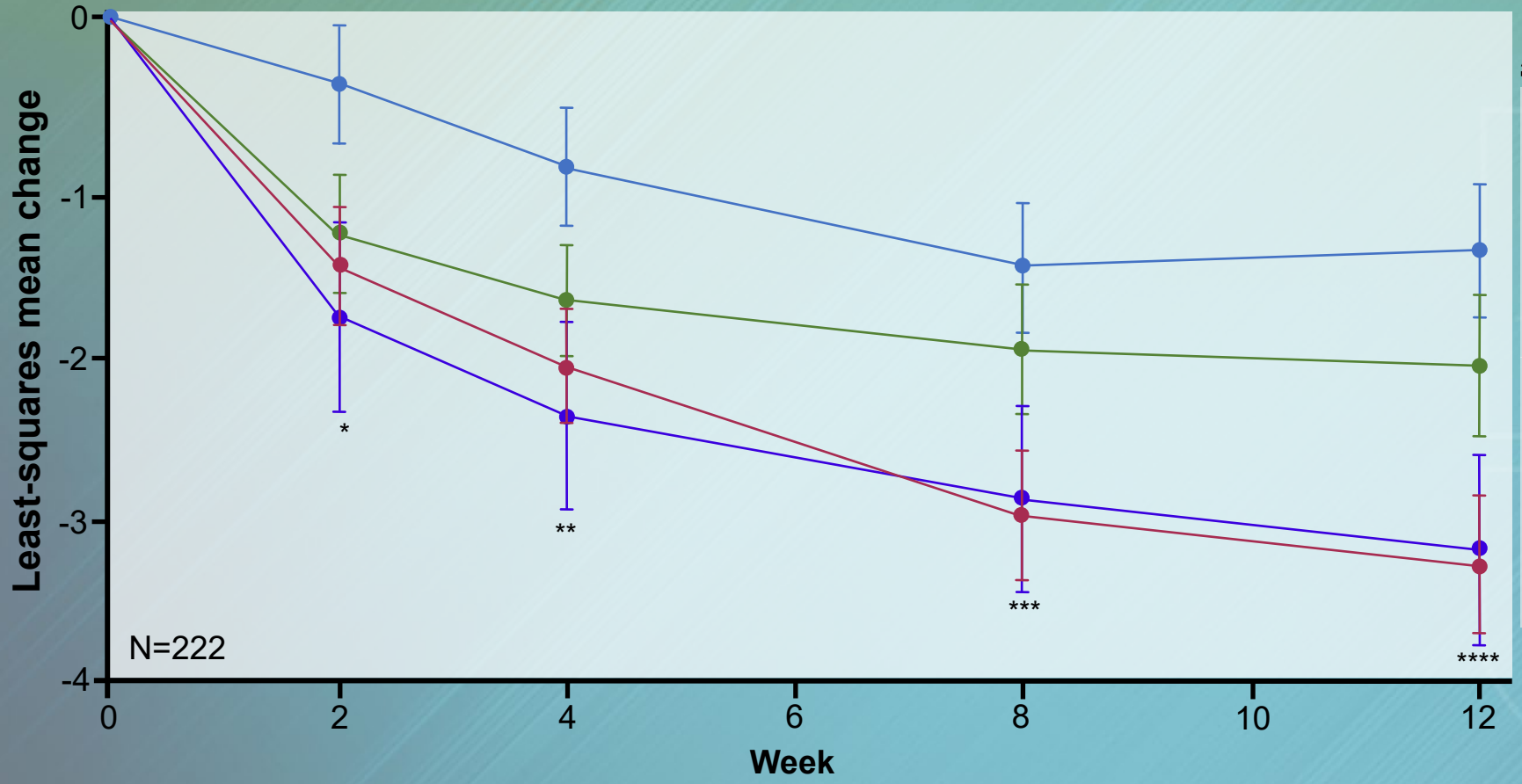
* p=0.007
**p=0.019

AIMS: Abnormal Involuntary Movement Scale;
SE: standard error.

Fernandez HH et al. Neurology 2017;88(21):2003-10; Stacy M et al. Mov Disord 2019;34(8):1203-9.

Deutetrabenazine: Phase 3 Randomized AIM-TD Fixed-Dose Trial

Double-blind, placebo-controlled study



At Week 12

Placebo
mean AIMS: -1.4 points (SE=0.41)

Deutetrabenazine 12 mg/day
mean AIMS: −2.1 points (SE 0.42)

Deutetrabenazine 24 mg/day
mean AIMS: −3.2 points (SE 0.45)

Deutetrabenazine 36 mg/day
mean AIMS: −3.3 points (SE 0.42)

AIMS: Abnormal Involuntary Movement Scale;
SE: standard error.

* p=0.006 for 24 mg/day and 0.032 for 36 mg/day
** p=0.003 for 24 mg/day and 0.018 for 36 mg/day
*** p=0.012 for 24 mg/day and 0.008 for 36 mg/day
**** p=0.003 for 24 mg/day and 0.001 for 36 mg/day

Anderson KE et al. Lancet Psychiatry 2017;4(8):595-604; Stacy M et al. Mov Disord 2019;34(8):1203-9.

Long-Term Safety and Efficacy of Deutetrabenazine

- Long-term open-label extension of placebo-controlled trials followed patients through week 145
- Improvement from baseline in AIMS were maintained through endpoint
- The most common adverse reactions were somnolence, fatigue, insomnia, headache, and diarrhea
- Suicidal ideation was reported in 5% of patients and suicidal behavior in <1%
    - Most of those participants had a history of depression or suicidal behavior

Fernandez HH et al. J Neurol Neurosurg Psychiatry 2019;90(12):1317-23;
Hauser RA et al. Presented at: Psych Congress 2020.

Comparison of Approved Drug Treatments for TD

Profile	Valbenazine	Deutetrabenazine
Dosing frequency	Once daily	Twice daily
Initial dose per day	40 mg	12 mg
Target dose per day	40–80 mg	12–48 mg (in divided doses)
Dosage forms	40, 60, and 80 mg capsules	6, 9, and 12 mg tablets
Administered with food?	With or without	With
Cytochrome P450 activity	CYP2D6, CYP3A4	CYP2D6
Warnings/precautions	Impaired driving ability due to somnolence QT prolongation Parkinsonism	Impaired driving ability due to somnolence QT prolongation Parkinsonism Neuroleptic malignant syndrome
Contraindications relevant to TD	Known hypersensitivity to valbenazine	Hepatic impairment Taking monoamine oxidase inhibitor, reserpine, tetrabenazine, or valbenazine
Common adverse events	Somnolence	Nasopharyngitis Insomnia
Number needed to treat (95% CI)	5 (3-7)	7 (4-18)

Citrome L. Expert Rev Neurother 2018;18(4):323-32; Stahl SM. Prescriber's guide. 7th ed. 2020.

Off-Label Treatments for Tardive Dyskinesia

- **Tetrabenazine** (VMAT2 inhibitor)
  - Reduces severity of TD; the potential for adverse effects and lack of large long-term treatment trials have prevented its widespread use
- **Gingko biloba**
  - Positive study of Gingko extract (n=157)
- **Clonazepam** (GABA-A receptor agonist)
  - Probably effective in decreasing TD symptoms short-term (approximately 3 months; efficacy wanes by 6 months)
- **Amantadine** (glutamate receptor antagonist)
  - Reduced TD when used conjointly with a neuroleptic during the first 7 weeks (one positive study; short-term use only)
- **Botulinum toxin A injections** for focal dystonia symptoms

Bhidayasiri R et al. Neurology 2013;81(5):463-9; Bhidayasiri R et al. J Neurol Sci 2018;389:67-75; Umbrich P, Soares KV. Cochrane Database Syst Rev 2003;(2):CD000205; Zhang WF et al. J Clin Psychiatry 2011;72(5):615-21.

American Academy of Neurology (AAN): Updated Recommendations for Treatment of Tardive Dyskinesia

Level A	Level B	Level C	Level U
must *be recommended as treatment*	***should*** *be considered as treatment*	***might*** *be considered as treatment*	*insufficient evidence to support or refute*
• Deutetrabenazine • Valbenazine	• Clonazepam • Ginkgo biloba	• Tetrabenazine ** • Amantadine • Globus pallidus interna deep brain stimulation (intractable TD)	• Withdrawing DRBA • Switching from typical to atypical DRBA • Botulinum toxin A

**Consider Level A if the new generation VMAT2 inhibitors are unavailable; DRBA: dopamine receptor blocking agent.

Bhidayasiri R et al. J Neurol Sci 2018;389:67-75.

Summary

- Tardive dyskinesia (TD) remains a serious risk of antipsychotics and other dopamine receptor blocking agents
- TD often persists even after medication is discontinued
- There are several different hypotheses as to why TD occurs
- VMAT2 inhibitors have demonstrated efficacy and two are FDA-approved for TD

Posttest Question 1

Among patients without previous exposure to first-generation antipsychotics, approximately what percentage develop tardive dyskinesia following treatment with a second-generation antipsychotic?

1. 2%
2. 7%
3. 15%
4. 20%

Posttest Question 2

John is a 25-year-old patient with schizophrenia who was recently prescribed an atypical antipsychotic. He has no history of previous antipsychotic treatment or extrapyramidal symptoms.

How often should structured clinical screening for tardive dyskinesia be documented for this patient?

1. Every 3 months
2. Every 6 months
3. Every 12 months
4. As indicated by semi-structured screening

Posttest Question 3

Which tardive dyskinesia medication(s) does/do not require CYP2D6 genotyping?

1. Valbenazine
2. Tetrabenazine
3. Deutetrabenazine
4. 1 and 3