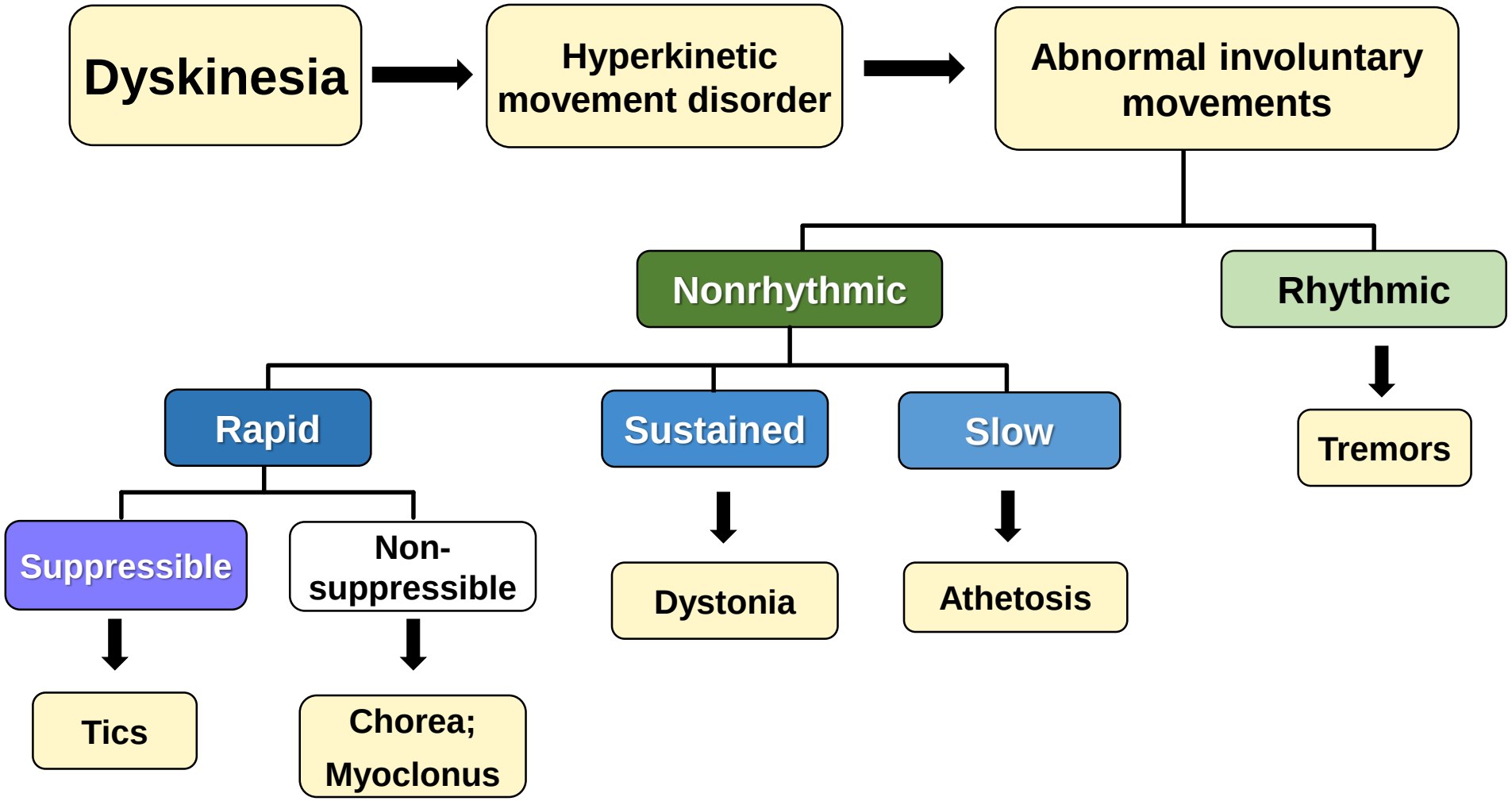
Handout for the Neuroscience Education Institute (NEI) online activity:

MOVING TOWARD THE FUTURE: NEW DEVELOPMENTS IN THE MANAGEMENT OF TARDIVE DYSKINESIA

Learning Objectives

- Apply a systematic approach to assessing suspected drug-induced movement disorders
- Discuss the diagnosis and management of TD and comorbid disorders in psychiatric patients
- Individualize treatment choices, giving consideration to efficacy, safety, long-term data, and unique patient characteristics
- Formulate appropriate treatment regimens considering the emergence of new treatment options

What is Dyskinesia?



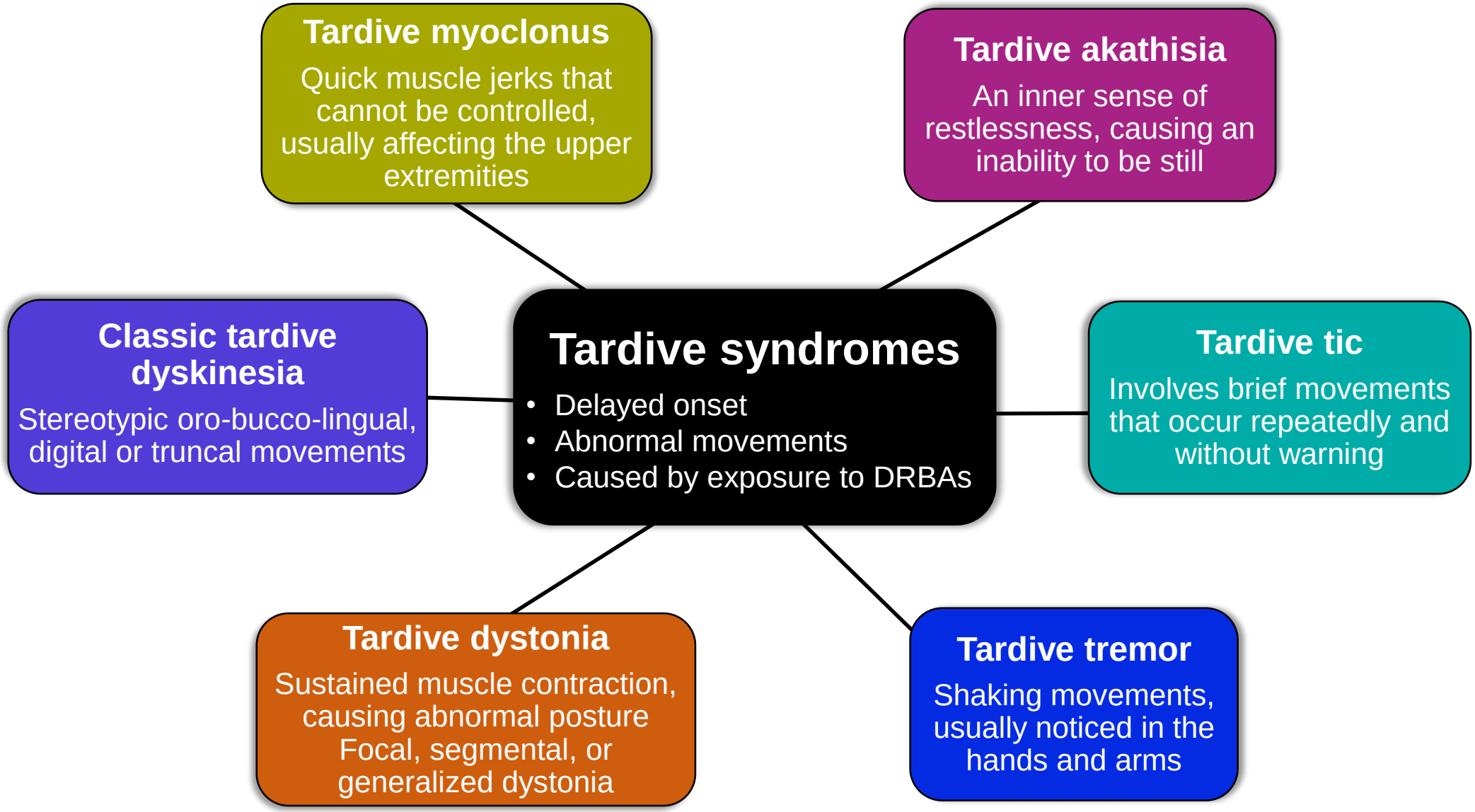
Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87;
Aquino CC, Lang AE. Parkinsonism Related Disord 2014;20(suppl 1):S113-7.

Types of Dyskinesia

Drug-induced

- Levodopa-induced dyskinesia
- Antipsychotic-induced dyskinesia
- Dopamine receptor blocking agents (DRBAs)

Vijayakumar D, Jankovic J. Drugs 2016;76(7):759-77; Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.



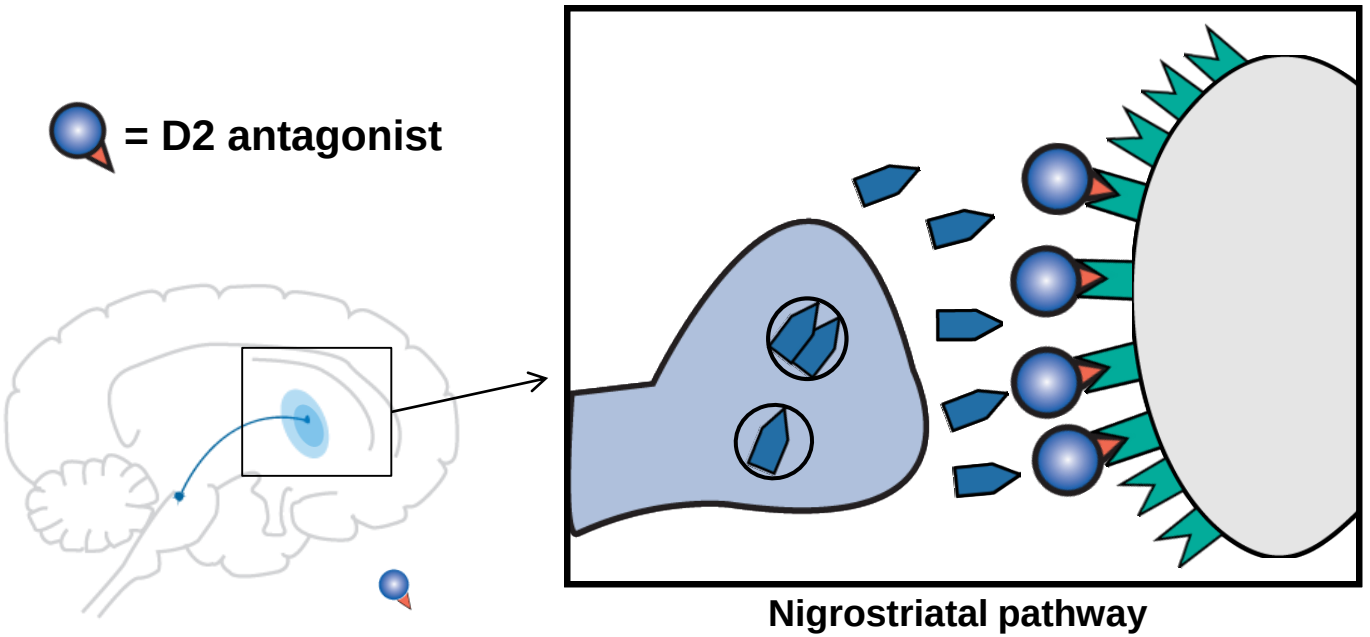
Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87;
Aquino C, Lang A. Parkinsonism Related Disord 2014;20(suppl 1):S113-7;
Waln O, Jankovic J. Tremor Other Hyperkinetic Movements 2013;3. doi:10.7916/D88P5Z71.

What is Tardive Dyskinesia?

- Involuntary **choreoathetoid** movements usually associated with lower facial and distal extremity musculature (truncal movements also possible)
  - **Chorea**: Quick, irregular, non-stereotype 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

Dopamine supersensitivity?

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

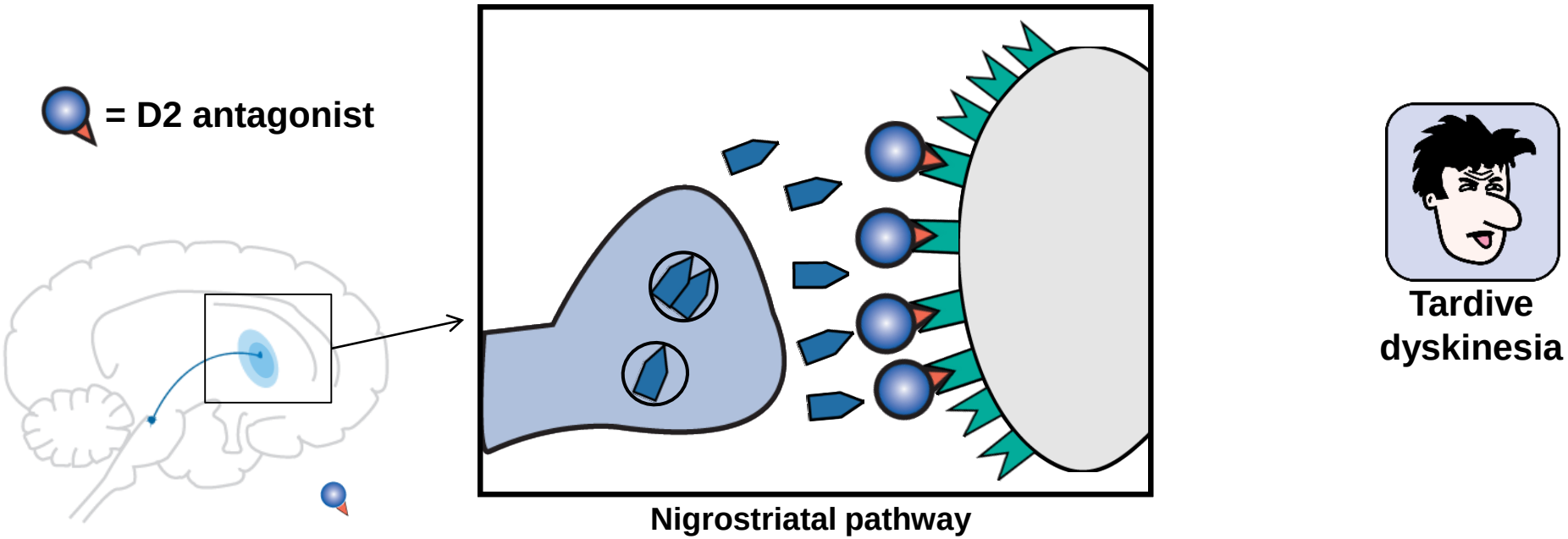


Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. 2013; Lohr JB et al. CNS Drugs 2003;17:47-62.

Dopamine supersensitivity?

This upregulation may lead to tardive dyskinesia

= D2 antagonist



Nigrostriatal pathway

Tardive dyskinesia

May contribute, but lots of problems

Probably better model for withdrawal-emergent dyskinesia

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. 2013; Lohr JB et al. CNS Drugs 2003;17:47-62.

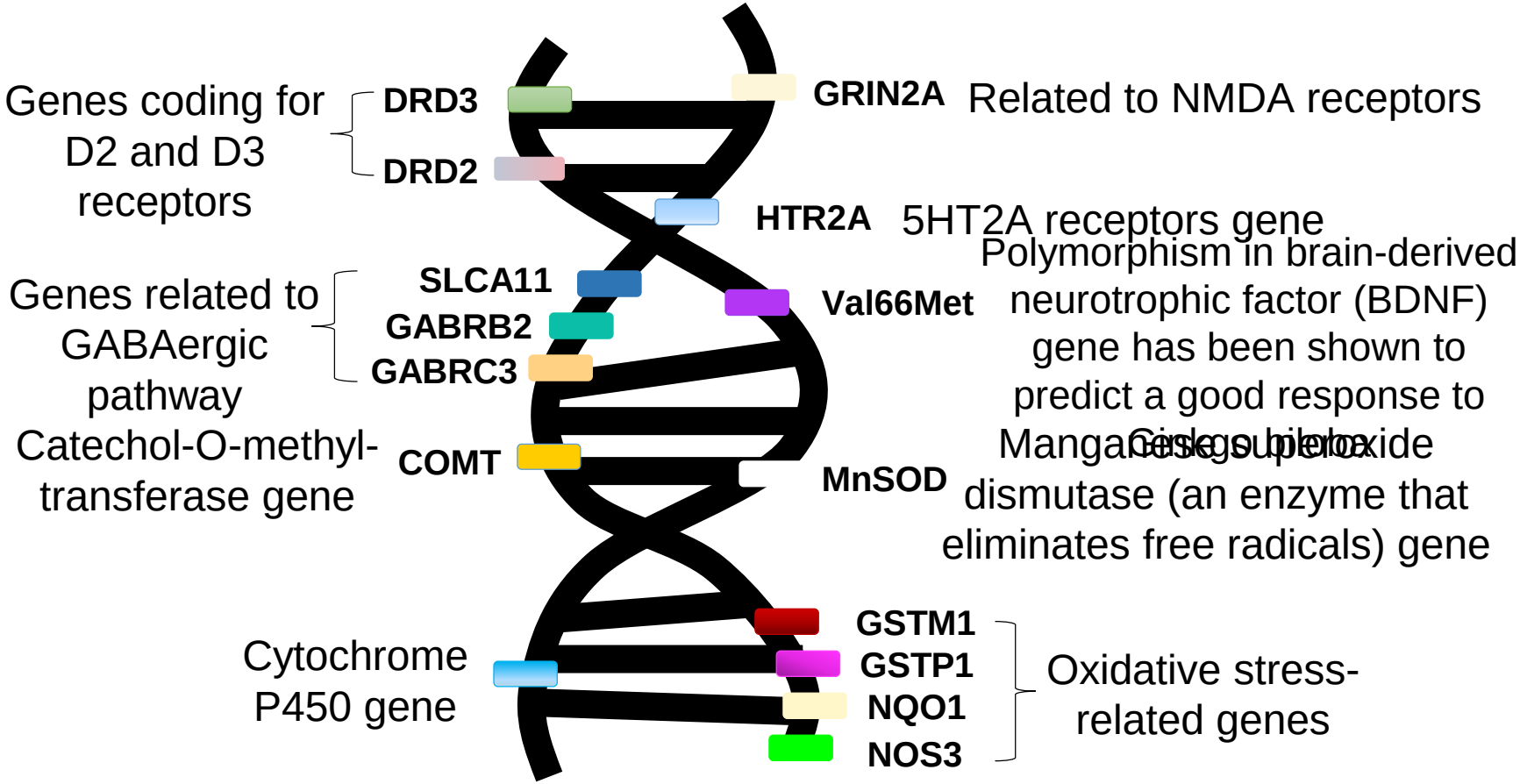
Other Mechanism(s) of Drug-Induced TD

- **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 science evidence
  - May offer avenues for clinical treatment

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87; Teo JT et al. Movement Disord 2012;27(10):1205-15; Aquino CC, Lang AE. Parkinsonism Related Disord 2014;20(suppl 1):S113-7; Stahl SM. CNS Spectr. 2017;22(6):427-434.

What Do We Know About the Genetics of Tardive Dyskinesia?

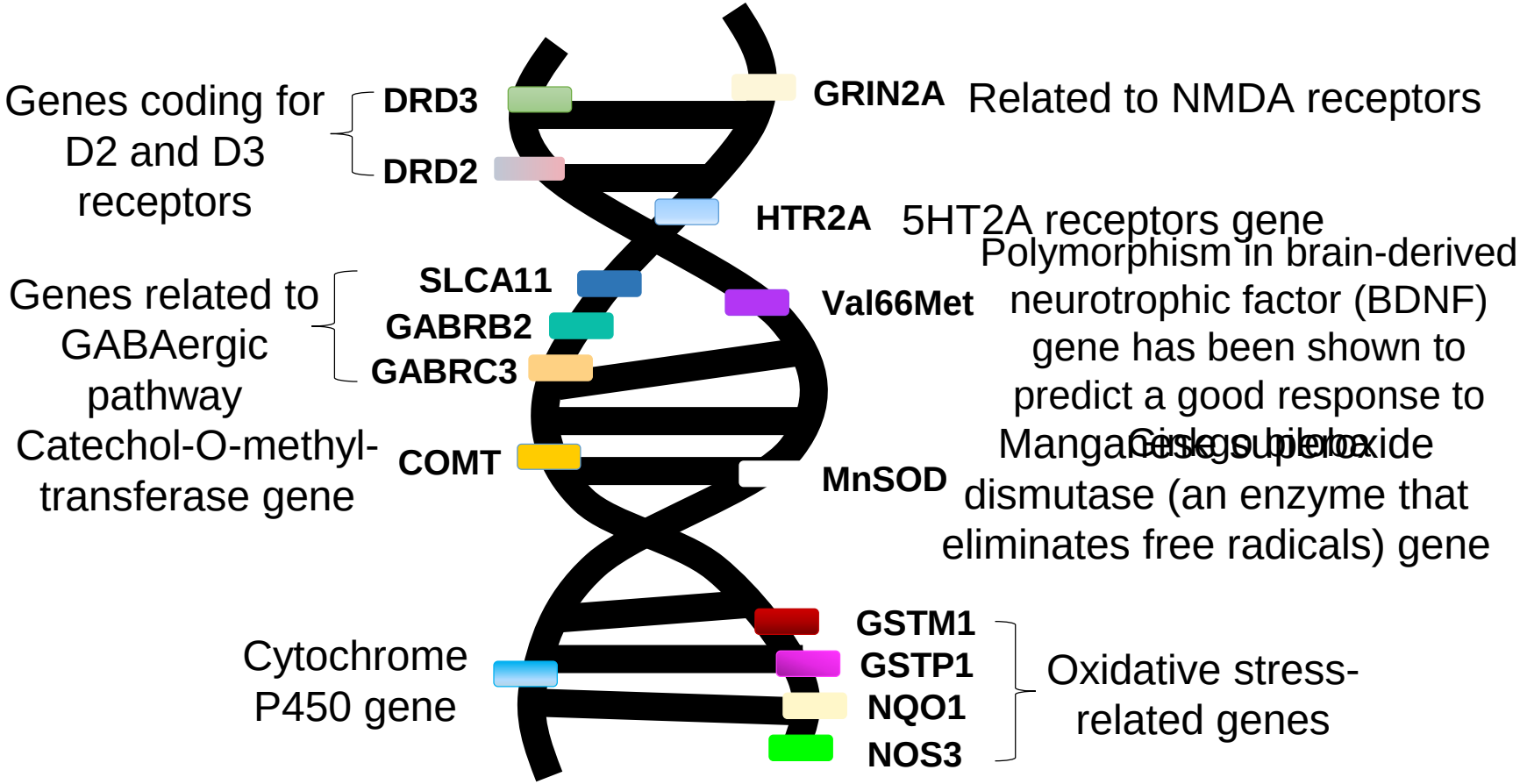
Polymorphisms in genes have been shown to influence the risk for TD



Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87;
Aquino CC, Lang AE. Parkinsonism Related Disord 2014;20(suppl 1):S113-7.

What Do We Know About the Genetics of Tardive Dyskinesia?

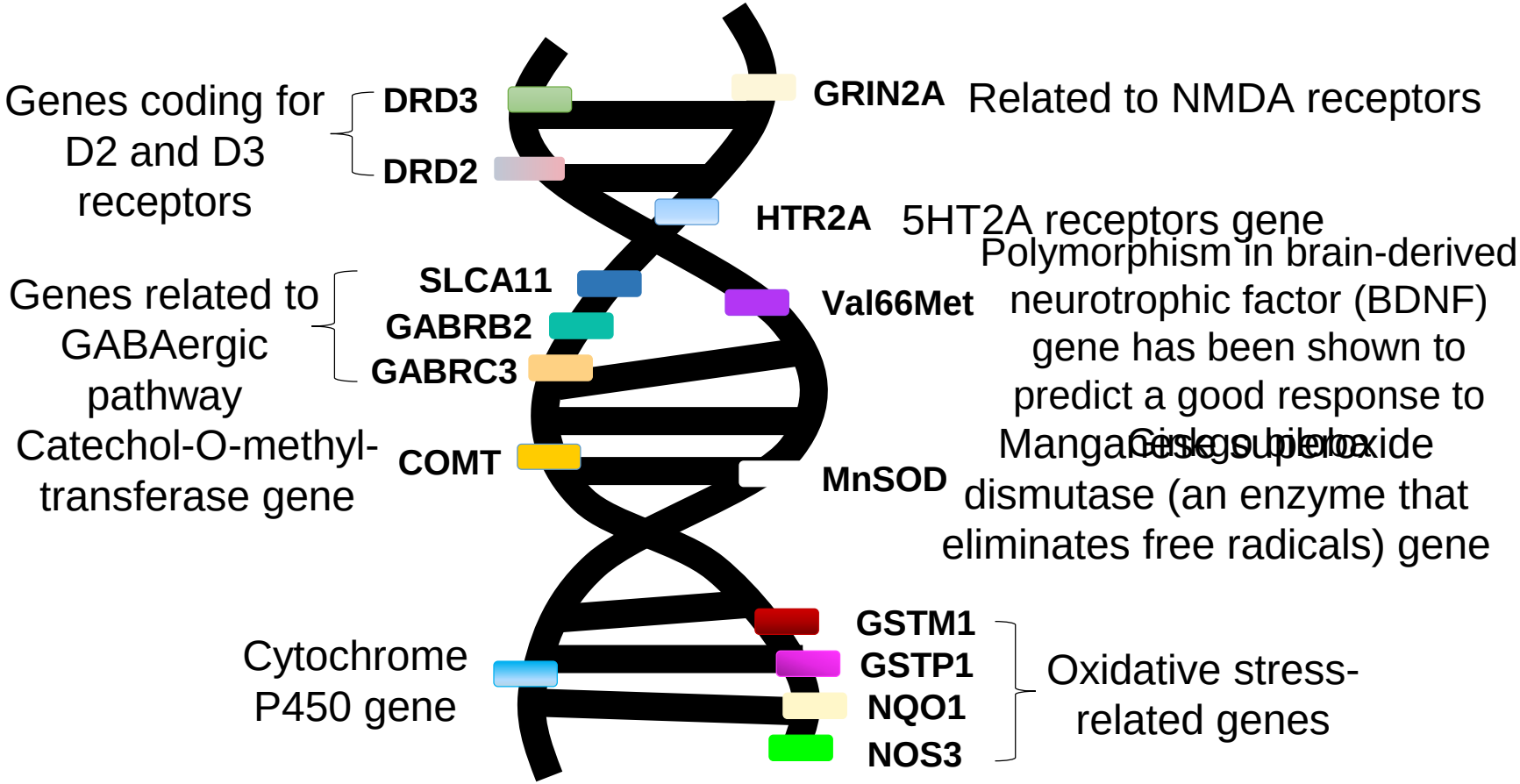
Variances in other genes have also been linked to TD



Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87;
Aquino CC, Lang AE. Parkinsonism Related Disord 2014;20(suppl 1):S113-7.

What Do We Know About the Genetics of Tardive Dyskinesia?

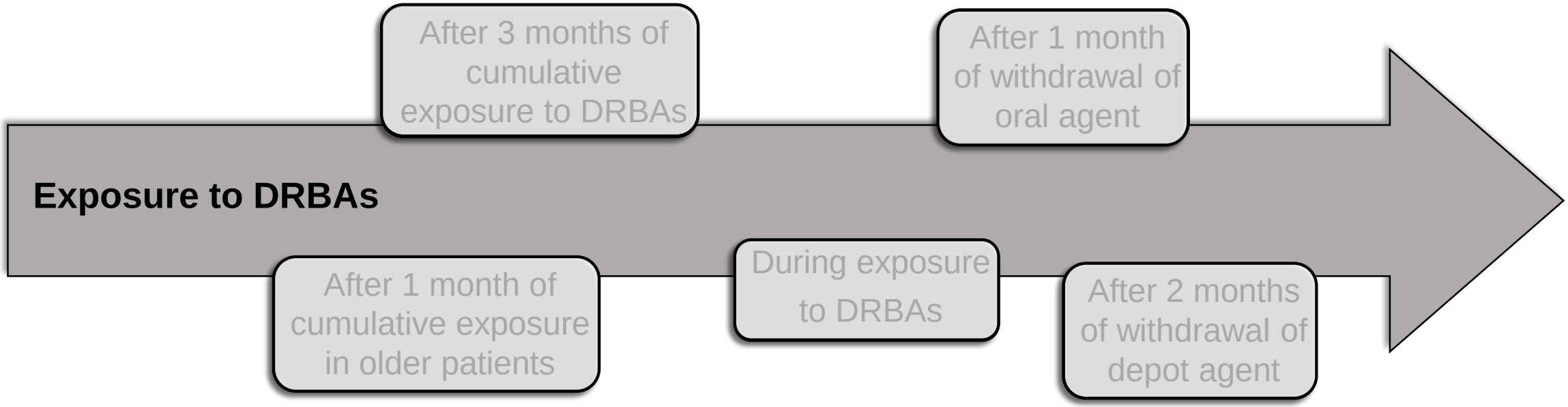
Genes have also been linked to response to treatment



Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87;
Aquino CC, Lang AE. Parkinsonism Related Disord 2014;20(suppl 1):S113-7.

Tardive Dyskinesia: Delayed Onset

Tardive dyskinesia can occur in patients...



Symptoms should persist for longer than a month

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.

Diagnostic Criteria for TD

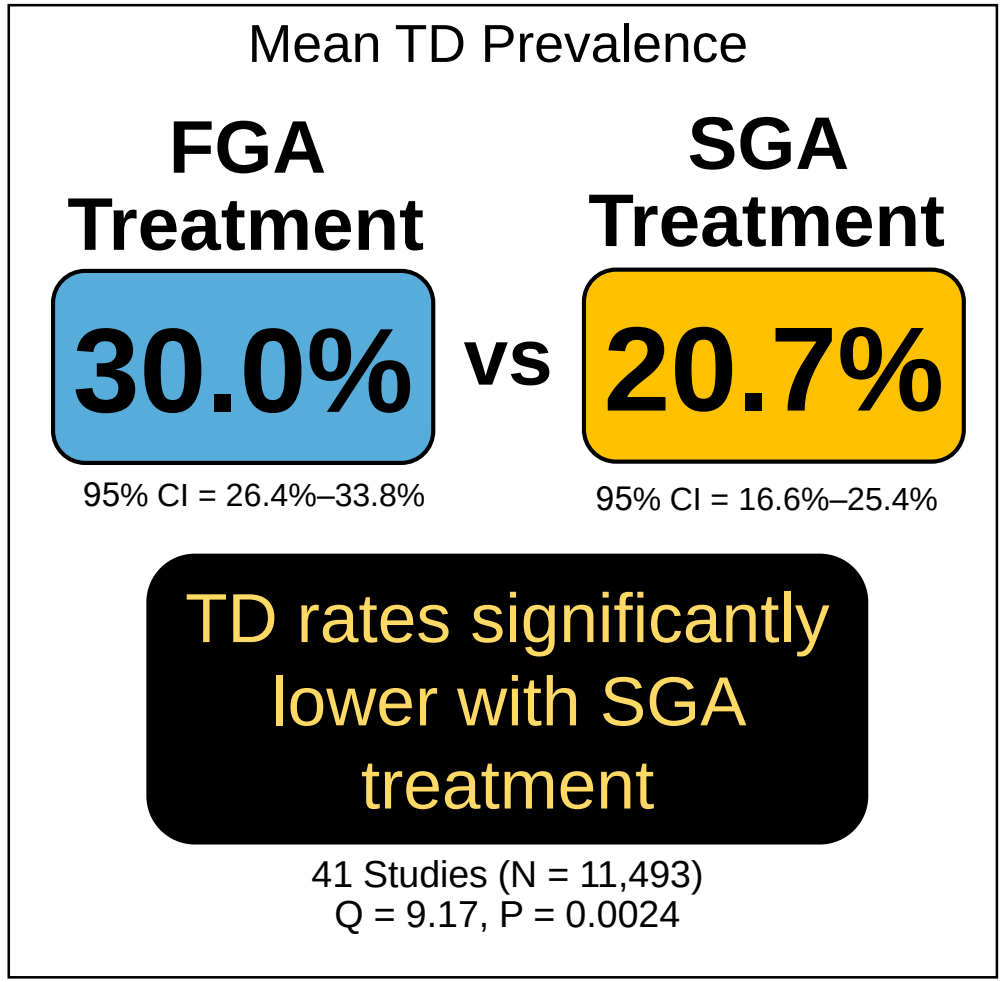
Source	Exposure	Severity threshold	Duration	Miscellaneous
Schooler-Kane (1982)	≥3 months	AIMS items: ≥3 in one area or ≥2 in 2 areas	Persistent ≥3 months	Dx of exclusion
Glazer et al. (1993)	≥3 months	AIMS items: ≥3 total with at least one ≥2 in 1 area	Persistent ≥2 exams	Dx of exclusion
DSM-IV (1994) 333.82	≥3 months ≥1 month if ≥60 years	Involuntary movements	≥4 weeks	Dx of exclusion
DSM-5 (2013) 333.85 (G24.01)	At least few months	Involuntary movements	≥8 weeks	

DSM = *Diagnostic and Statistical Manual of Mental Disorders*; Dx = diagnosis; APA = American Psychiatric Association

Schooler NR, Kane JM. *Arch Gen Psychiatry.* 1982;39:486-487. Glazer WM et al. *J Clin Psychiatry.* 1993;54:133-139. APA. DSM-IV. Washington DC: APA; 1994. APA. DSM-V. Washington DC: APA; 2013.

Tardive Dyskinesia Prevalence in Second-Generation Antipsychotic Use

- TD prevalence higher in patients treated with first-generation antipsychotics (FGAs)
- Recent meta-analysis comparison of TD prevalence in FGAs versus second-generation antipsychotics (SGAs) users
- **However, SGAs still show risk of TD**
  - 1/5 of patients treated with SGAs showed this “rare” side effect
- In four studies, **7.2%** prevalence with SGA reported in patients *without prior FGA treatment*



Carbon M et al. J Clin Psychiatry. 2017;78(3):e264-e278.

Epidemiology of Tardive Dyskinesia

Approximately 20–50% of patients receiving antipsychotics develop TD

Risk Factors

- Duration or cumulative antipsychotic exposure
- Potency of antipsychotic
- Older age is consistently found to be a risk factor for TD
  - Geriatric patients: increased movement disorders, even in neuroleptic-naïve patients
    - TD rates of 26–31% after 1 year of exposure to FGA
    - TD rates of 2.5% after 1 year of exposure to atypical antipsychotic (risperidone, quetiapine)
- Children: higher TD rates in patients taking haloperidol

Woerner et al. Am J Psychiatry 1998;155(11):1521-8; Correll CU et al. J Clin Psychiatry. 2017;78(8):1136-1147; Caroff SN et al. Neurol Clin. 2011;29(1):127-48, viii; Miller et al. Schizophr Res 2005;80(1):33-43; Nasrallah. Ann Clin Psychiatry 2006;18(1):57-62. ; Jeste et al. Arch Gen Psychiatry 1995;52(9):756-65; Jeste et al. Am J Psychiatry 2000;157(7):1150-5.

Tardive Dyskinesia: Other Risk Factors

- Early onset of psychosis
- Presence of mood disorder
- Acute EPS/akathisia
- Treatment with **anticholinergics**
- Negative symptoms, cognitive symptoms
- Comorbid substance abuse
- Sex: female, especially post-menopausal
- Ethnicity?
- 5% of medication-naïve schizophrenia patients exhibit spontaneous movements

Correll CU et al. J Clin Psychiatry. 2017;78(8):1136-1147; Miller et al. Schizophr Res 2005;80(1):33-43; Nasrallah. Ann Clin Psychiatry 2006;18(1):57-62; Owens et al. Arch Gen Psychiatry 1982;39:452-61.

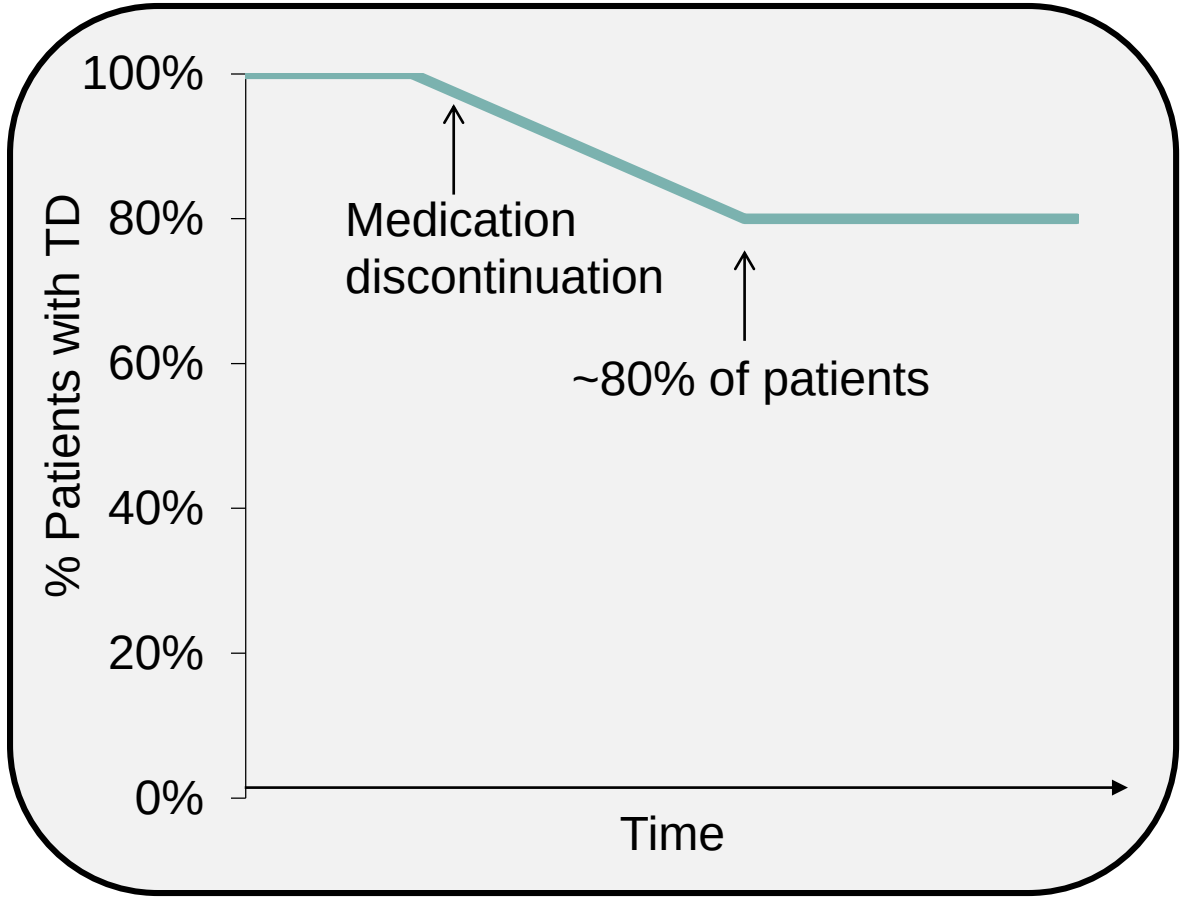
Abnormal Involuntary Movement Scale (AIMS)

12-Item Clinician-Rated Scale to Assess Severity of Dyskinesias

- Regardless of DRBA choice and symptomatic profile, regular TD screening using the AIMS should be **implemented routinely**
- With FGA, examine for TD at least every 6 months
- With second-generation antipsychotics SGA, examine for TD every 12 months
- Patients at high risk of EPS:
  - examine for TD every 3 months with FGA
  - examine for TD every 6 months with SGA

Guy W. Abnormal Involuntary Movement Scale (117-AIMS), in ECDEU Assessment Manual for Psychopharmacology.1976: 534–7; Solmi M et al. J Neurol Sci. 2018;389:21-27.

Expected Course of Tardive Dyskinesia



- Long-term studies of the course of TD provide a wide range of remission rates (0–73%)[1-4]
  - Most report remission rates below 25%
- After discontinuation of the causing DRBAs, the rate of remission is low
  - Even with atypical antipsychotics, reversibility rates remain low as only 20.5%[5]

Vinuela A et al. Tremor Other Hyperkinet Mov (N Y). 2014;4:282;
Fernandez HH et al. Neurology. 2001;56(6):805-7; Glazer WM et al. Br J Psychiatry. 1990;157:585-92;
Kang UJ et al. Mov Disord. 1986;1(3):193-208; Zutshi D et al. Other Hyperkinet Mov (N Y). 2014;4:266.

Is Tardive Dyskinesia Preventable?

- Inform patients of risk of developing TD before initiating treatment
- Use agents with less risk of TD
  - Risk increases with potency of D2 binding
- Patients should be monitored periodically for the development of TD
- Early recognition
  - Systematic evaluation including rating scales

Caroff SN et al. Current Psychiatry. 2011;10(10): 23-32; Bhidayasiri R et al. Neurology 2013;81:463-9; Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.

Switching Antipsychotics to Address Tardive Dyskinesia

- Dopamine antagonism can mask dyskinesia
- Severe TD
  - Switch to clozapine
- Mild to moderate TD on conventional antipsychotic
  - Switch to atypical antipsychotic **if possible**
- Mild to moderate TD on atypical antipsychotic
  - No clear evidence

Weiden PJ. J Psychopharmacol 2006;20(1):104-18; Bhidayasiri R et al. J Neurol Sci. 2018;389:67-75.

Treatment Options for Tardive Dyskinesia

- Slowly taper off an offending DRBA **if possible**
- VMAT2 inhibitors
  - Reserpine
  - Tetrabenazine
  - Valbenazine
  - Deutetrabenazine
- Other:
  - Gingko biloba
  - GABA agonists (e.g., Clonazepam)
  - Amantadine

Other Evidence-Based Therapies

- **Gingko biloba**
  - Positive study of gingko extract n=157 in China
- **Clonazepam**
  - Probably effective in decreasing TD symptoms short-term (approximately 3 months; efficacy wanes by 6 months)
- **Amantadine**
  - Reduced TD when used conjointly with a neuroleptic during the first 7 weeks (one positive study; short-term use only)
- **Botulinum toxin injections** for focal dystonia symptoms

Bhidayasiri et al. Neurology 2013;81(5):463-9; Aia et al. Curr Treatment Options Neurol 2011;13(3):231-41; Soares, McGrath. Cochrane Database Syst Rev 2001;(4): CD000209; Umbrich, Soares. Cochrane Database Syst Rev 2003;(2):CD000205; Zhang et al. J Clin Psychiatry 2011;72(5):615-21.

Other Evidence-Based Therapies

Extract of Ginkgo biloba (Egb-761)

- Potent antioxidant possessing free radical-scavenging activities

Some efficacy, but data is limited to inpatients with schizophrenia

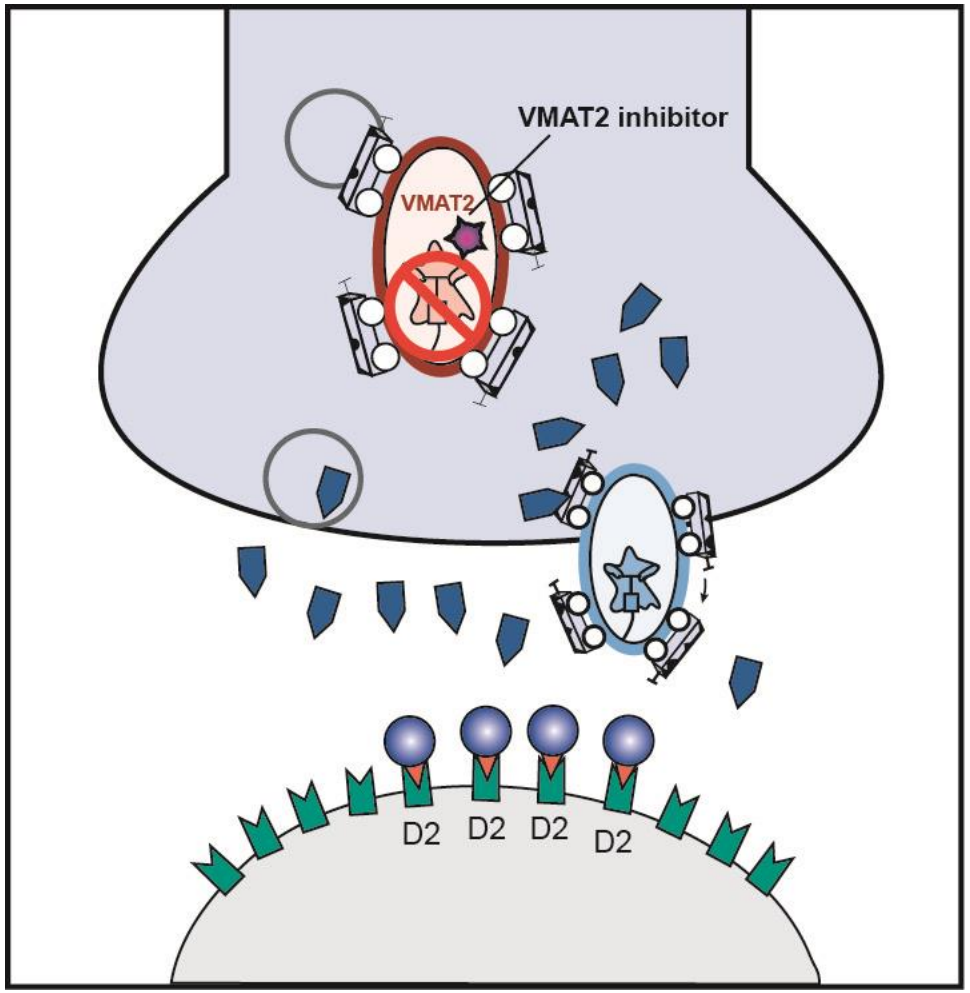
Bhidayasiri et al. Neurology 2013;81(5):463-9;
Zhang et al. J Clin Psychiatry 2011;72(5):615-21.

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 CNS

Kenney C, Jankovic J. Expert Rev Neurother 2006;6(1):7-17;
Shen V et al. Tremor Other Hyperkinetic Movements 2013;3. doi:10.7916/D8BK1B2D;
Waln O, Jankovic J. Tremor Other Hyperkinetic Movements 2013;3. doi:10.7916/D88P5Z71.

VMAT2 Inhibition in Tardive Dyskinesia



psychosis

tardive dyskinesia

Reserpine and Psychiatry

- 1954: first reported to be effective for schizophrenia
  - Adverse effects in limited use; replaced soon thereafter with chlorpromazine, which had improved efficacy and tolerability
- 1955: noted to be effective for Huntington's chorea
- 1956: Delay and Deniker reported extrapyramidal adverse effects from reserpine

López-Muñoz F et al. Actas Esp Psiquiatr 2004;32(6):387-95;
Chandler JH. Med Bull 1955;21(4):95-100;
Bourguignon A et al. Encephale 1956;45(4):1093-8.

Tetrabenazine: Efficacy and Safety

- TBZ has been shown to reduce TD symptoms by 54%[1]
  - Approved in US in 2008 for Huntington's disease
- Studies have shown improvement of symptoms in 70–71% of patients treated with TBZ [2,3]
- Level C recommendation from American Academy of Neurology (AAN)[4,6]
- Common side effects associated with TBZ include:[5]
  - Drowsiness
  - Parkinsonism
  - Akathisia
  - Depression

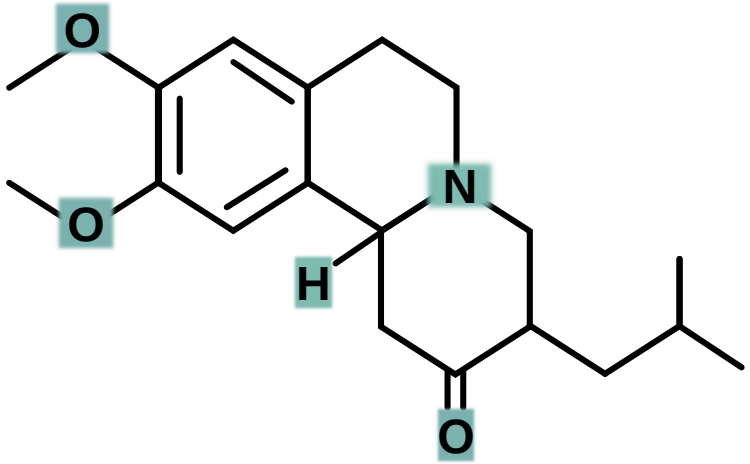
1. Ondo W et al. Am J Psychiatry 1999;156:1279-81.
2. Kenney C, Jankovic J. Expert Rev Neurother 2006;6(1):7-17.
3. Guay D. Am J Geriatr Pharmacother 2010;8(4):331-73.
4. Bhidayasiri R et al. Neurology 2013;81:463-9.
5. Kenney C et al. Movement Disord 2007;22(2):193-7.
6. Bhidayasiri R, et al. J Neurol Sci. 2018;389:67-75.

Tetrabenzine Historical Approval

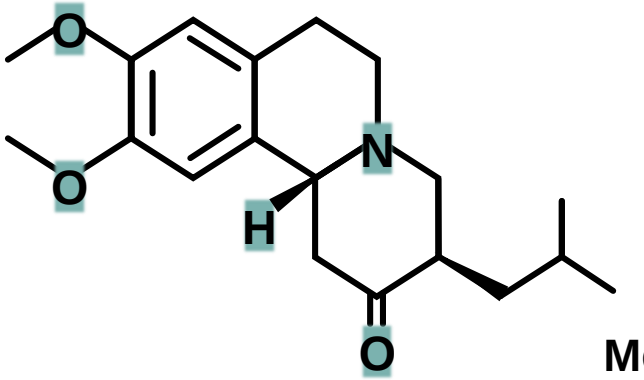
Country		
United States	Huntington’s chorea	2008
Netherlands	Huntington’s chorea	2007
Germany	Huntington’s chorea and tardive dyskinesia	2007
Italy	Organic movement disorder and tardive dyskinesia	2007
France	Huntington’s chorea and hemiballismus	2005
Israel	Organic movement disorder and tardive dyskinesia	2005
Portugal	Organic movement disorder and tardive dyskinesia	2003
Canada	Organic movement disorder and tardive dyskinesia	1995
Denmark	Hyperkinesias	1980
Australia	Organic movement disorder and tardive dyskinesia	1979
New Zealand	Organic movement disorder and tardive dyskinesia	1973
Ireland	Organic movement disorder (tardive refused)	1971
UK	Organic movement disorder and tardive dyskinesia	1971

Metabolism of Tetrabenazine

Tetrabenazine ()-1

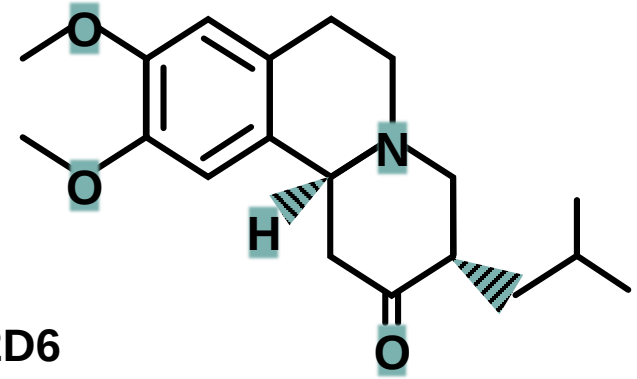


Rapidly converted to dihydrotetrabenazine α, β enantiomers in a ratio of 1:1



(+)-1
(3R,11bR)-TBZ

Metabolites are metabolized via CYP2D6

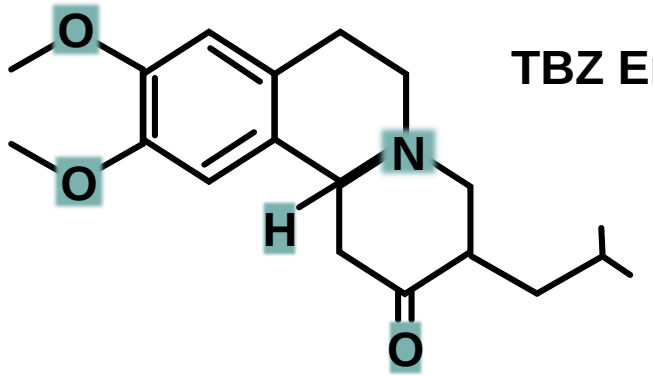


(-)-1
(3S,11bS)-TBZ

Requires mandatory CYP2D6 genotyping for doses >50 mg/day

Yao Z et al. Eur J Med Chem 2011;46(5):1841-8.

Evidence suggests that binding of the TBZ metabolites to VMAT2 is stereospecific



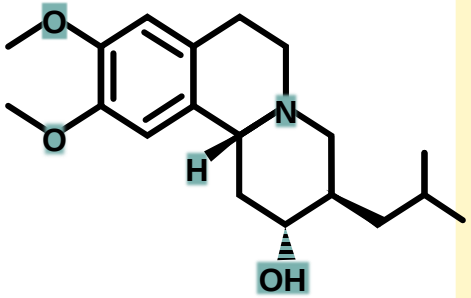
TBZ Enantiomers (±)-1

TBZ: tetrabenazine
DHTZB: dihydrotetrabenazine

Highest binding affinity for VMAT2

DHTBZ metabolites

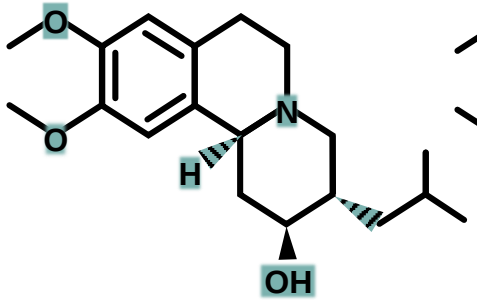
(+)-α-DHTBZ



(2R,3R,11bR)-DHTBZ (+)-2

K_i: 3.96

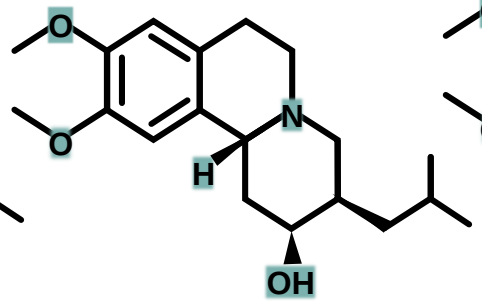
(−)-α-DHTBZ



(2S,3S,11bS)-DHTBZ (-)-2

K_i: 23,700

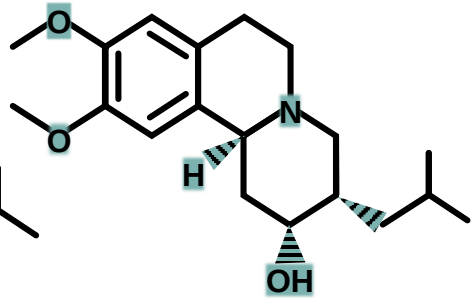
(+)-β-DHTBZ



(2S,3R,11bR)-DHTBZ (+)-3

K_i: 13.4

(−)-β-DHTBZ



(2R,3S,11bS)-DHTBZ (-)-3

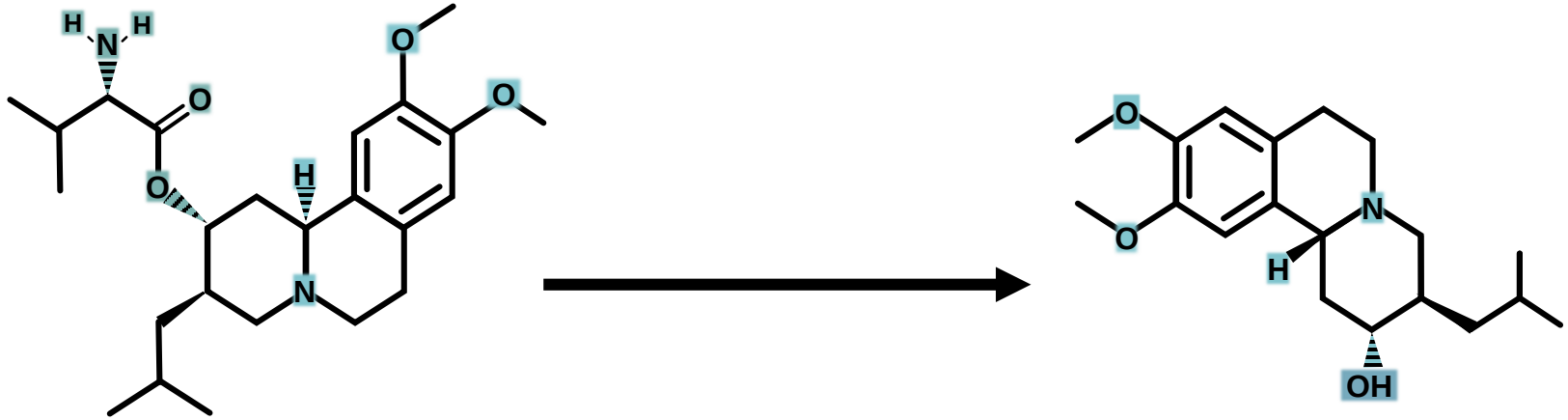
K_i: 2,460

VMAT2 binding affinity

Yao et al. Eur J Med Chem 2011;46(5):1841-8; Kilbourn et al. Chirality 1997;9(1):59-62.

Valbenazine

- Designed to deliver metabolite in a controlled fashion



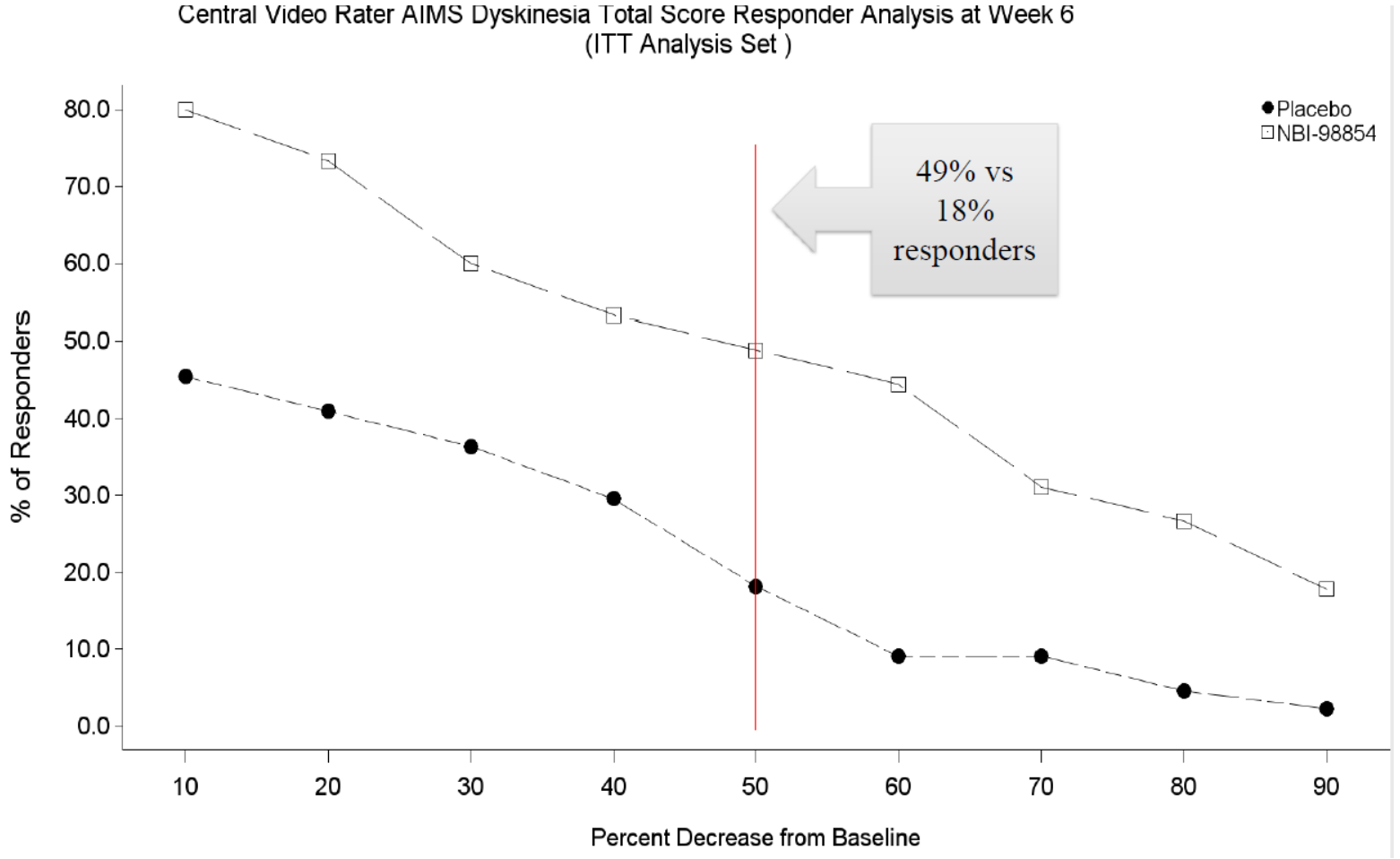
Valbenazine **(+)-α-DHTBZ**

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

Müller T. Expert Opinion Investig Drugs 2015;24(6):737-42; O'Brien et al. Movement Disord 2015;30(12):1681-7; Skor H et al. Drugs R D. 2017; 2017 Sep;17(3):449-459.

Valbenazine: Selective VMAT2 Inhibitor

Cumulative proportion of responders during 6-week, double-blind, phase II trial

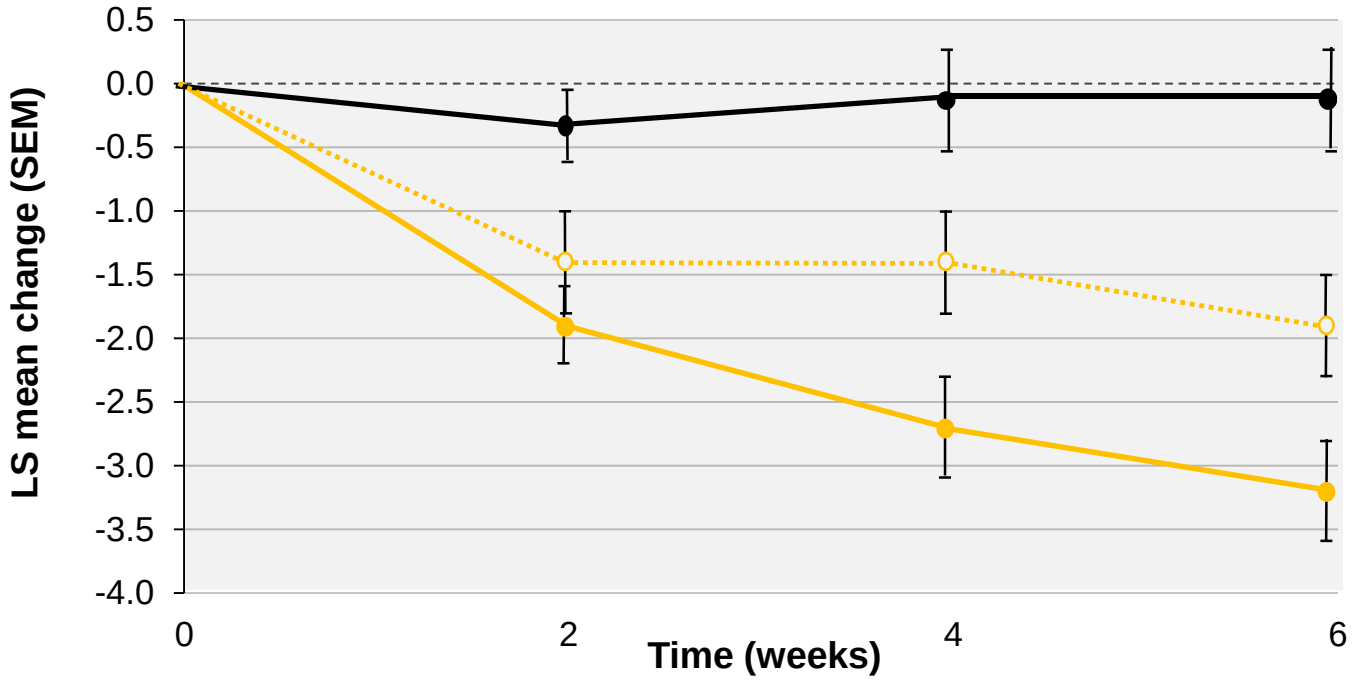


Response: at least 50% improvement in AIMS placebo n=44, NBI-98854 n=45.

O'Brien et al. Movement Disord 2015;30(12):1681-7.

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] mean change from baseline to week 6, MMRM):

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 ($p<0.001$)

Hauser RA et al. Am J Psychiatry. 2017;174(5):476-484.

Valbenazine
Safety and Tolerability

- PK profile permits once-daily dosing
- Psychiatric status remained stable
- Improved TD regardless of the use or type of concomitant AP
- Somnolence is the most common treatment-related AE
  - 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 et al. Movement Disord 2015;30:1681-7; Hauser RA et al. Neurology 2016;86(16)(suppl PL02.003); Hauser RA et al. Am J Psychiatry. 2017;174(5):476-484; Citrome L. Int J Clin Pract. 2017;e12964.

Valbenazine Appears Safe and Well-Tolerated Long-Term

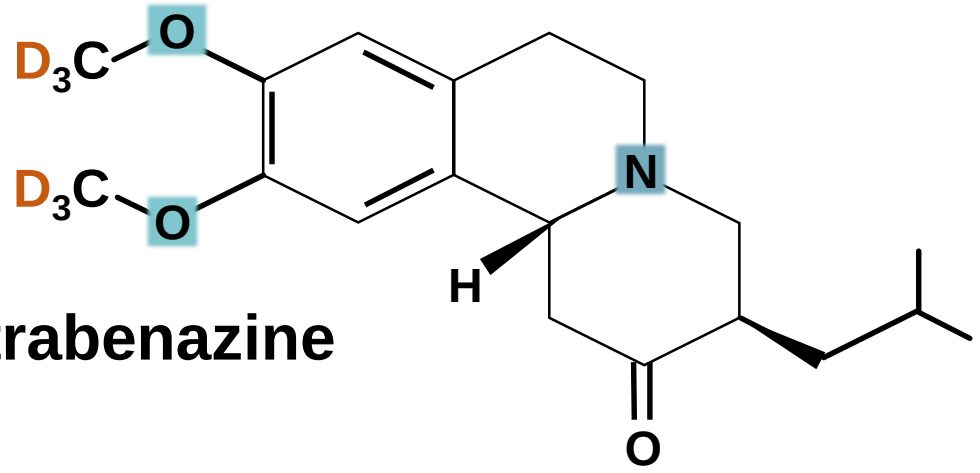
- Data pooled from three long-term studies with valbenazine (up to 48 weeks) in adults with TD
- 66.5% of patients experienced treatment-emergent adverse events (TEAEs), but only about 14.7% discontinued the drug due to AEs

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

Josiassen RC et al. Poster presented at: American Psychiatric Association (APA) 2017 Annual Meeting; May 22, 2017; San Diego, CA.

Deutetrabenazine

- Deutetrabenazine is a selective VMAT2 inhibitor
- 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 improved PK



Tetrabenazine

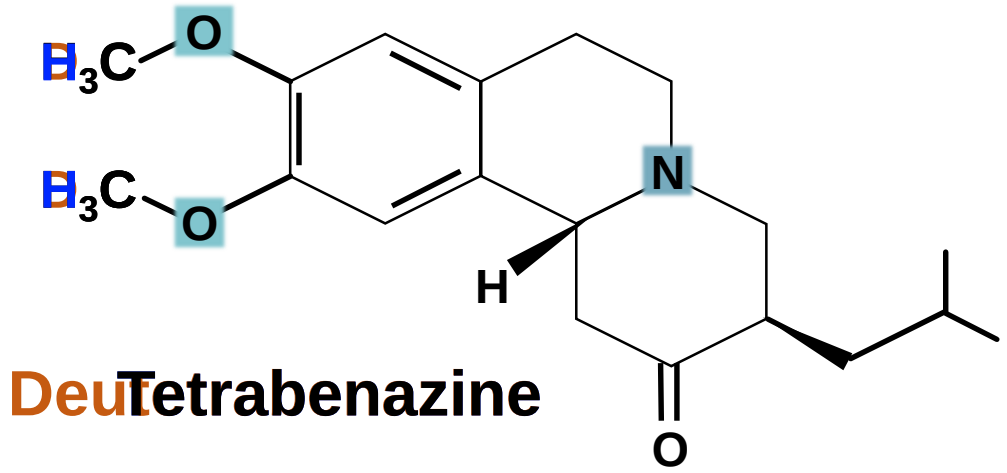
FDA Approved for Tardive Dyskinesia on August 30, 2017

- Initial dose 12 mg/day in two divided doses
- Titrate at weekly intervals by 6 mg/day based on reduction of tardive dyskinesia 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):2003-2010; Anderson et al. Poster presented at: American Psychiatric Association Annual Meeting; May 2016; Atlanta, GA; NEI Prescribe App, 2017.

Deutetrabenazine

- Deutetrabenazine is a selective VMAT2 inhibitor
- 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 improved PK



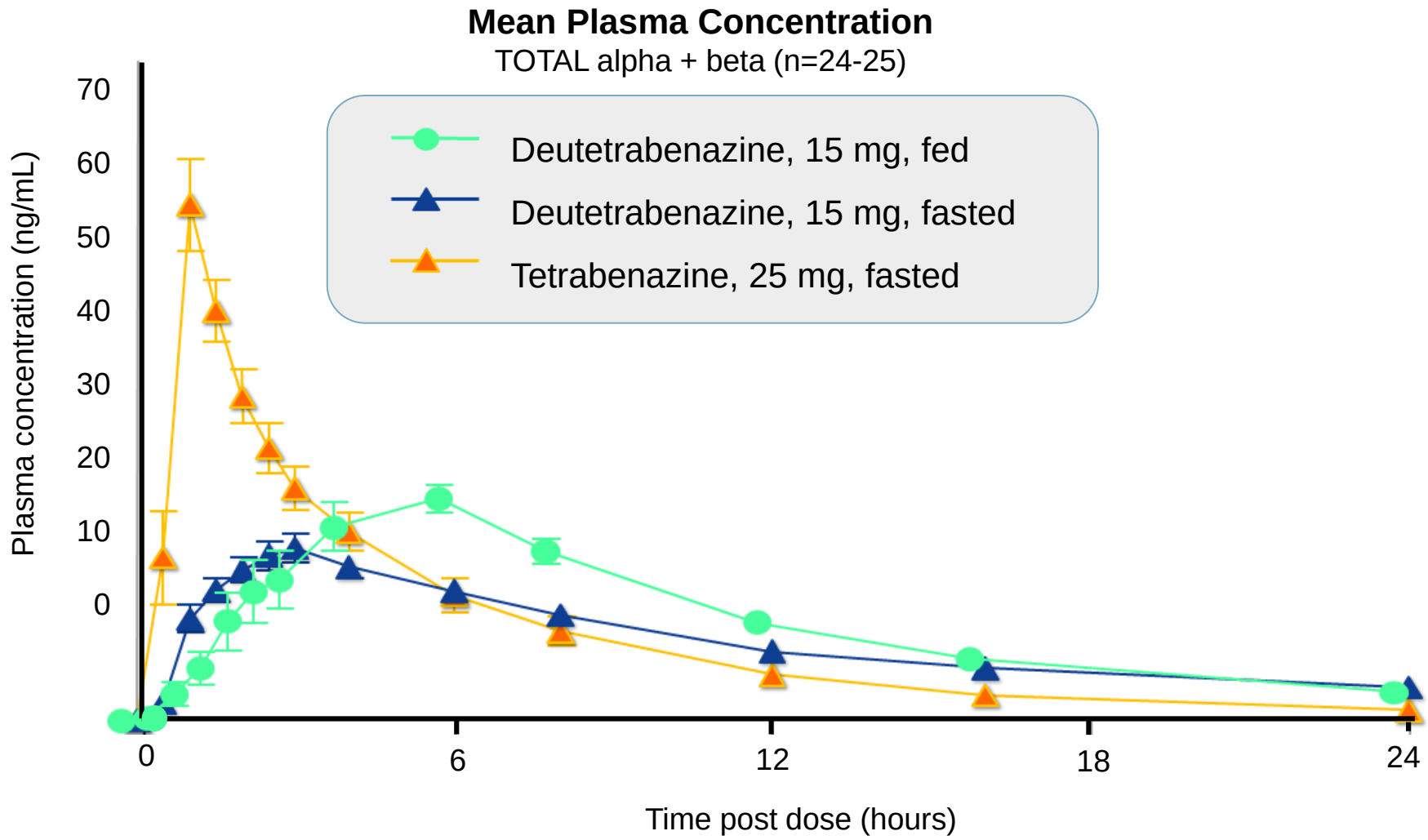
DeuTetrabenazine

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 tardive dyskinesia 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):2003-2010; Anderson et al. Poster presented at: American Psychiatric Association Annual Meeting; May 2016; Atlanta, GA; NEI Prescribe App, 2017.

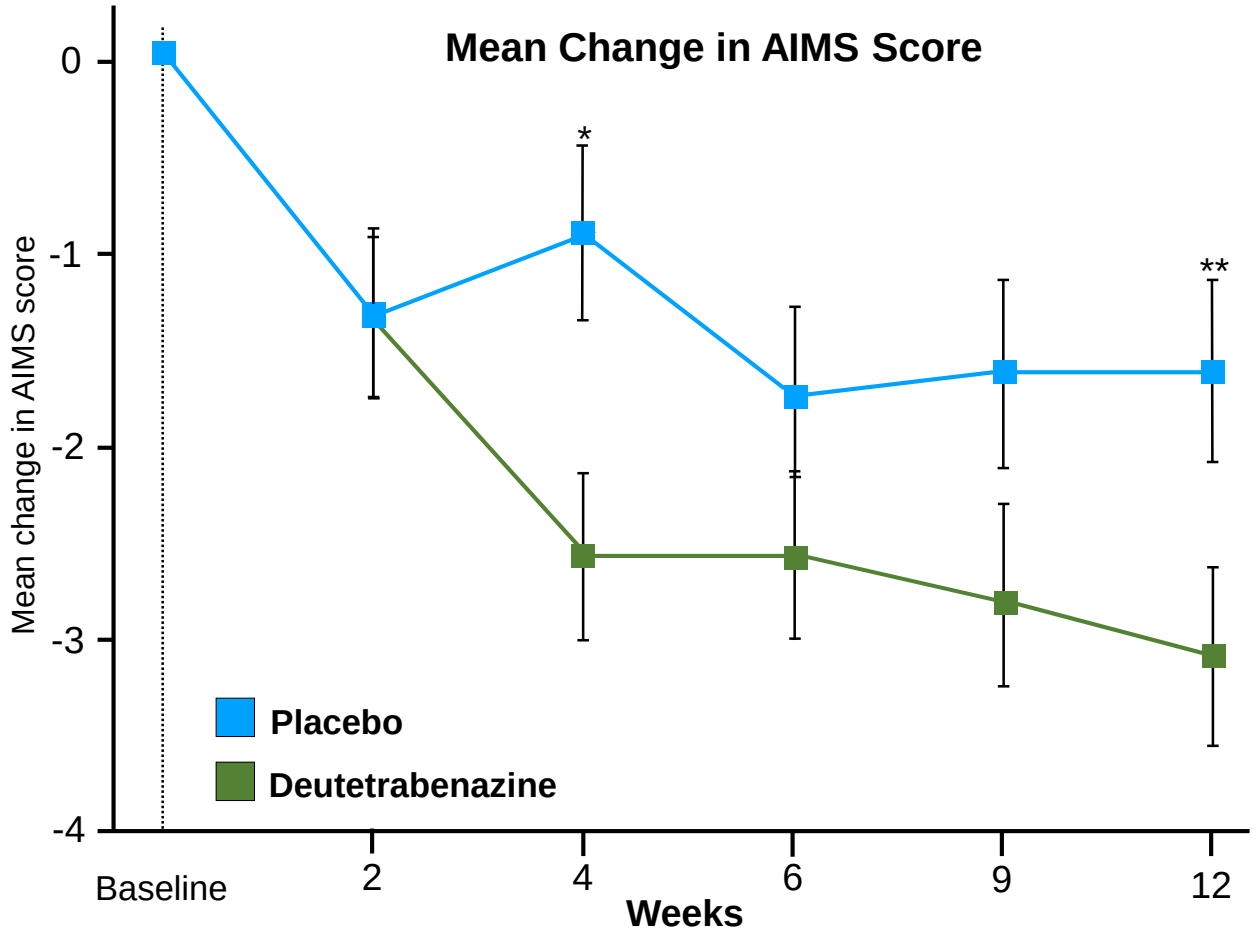
Pharmacokinetics of Deutetrabenazine



Anderson et al. Poster presented at: American Psychiatric Association Annual Meeting; May 2016; Atlanta, GA.

Deutetrabenazine: Phase III
Randomized ARM-TD Dose-Finding Trial

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



At Week 12

Placebo group
(n=59)
Decrease in mean AIMS: 1.6 (SE=0.46)

Deutetrabenazine group
(n=58)
Decrease in mean AIMS: 3.0 (SE=0.45)

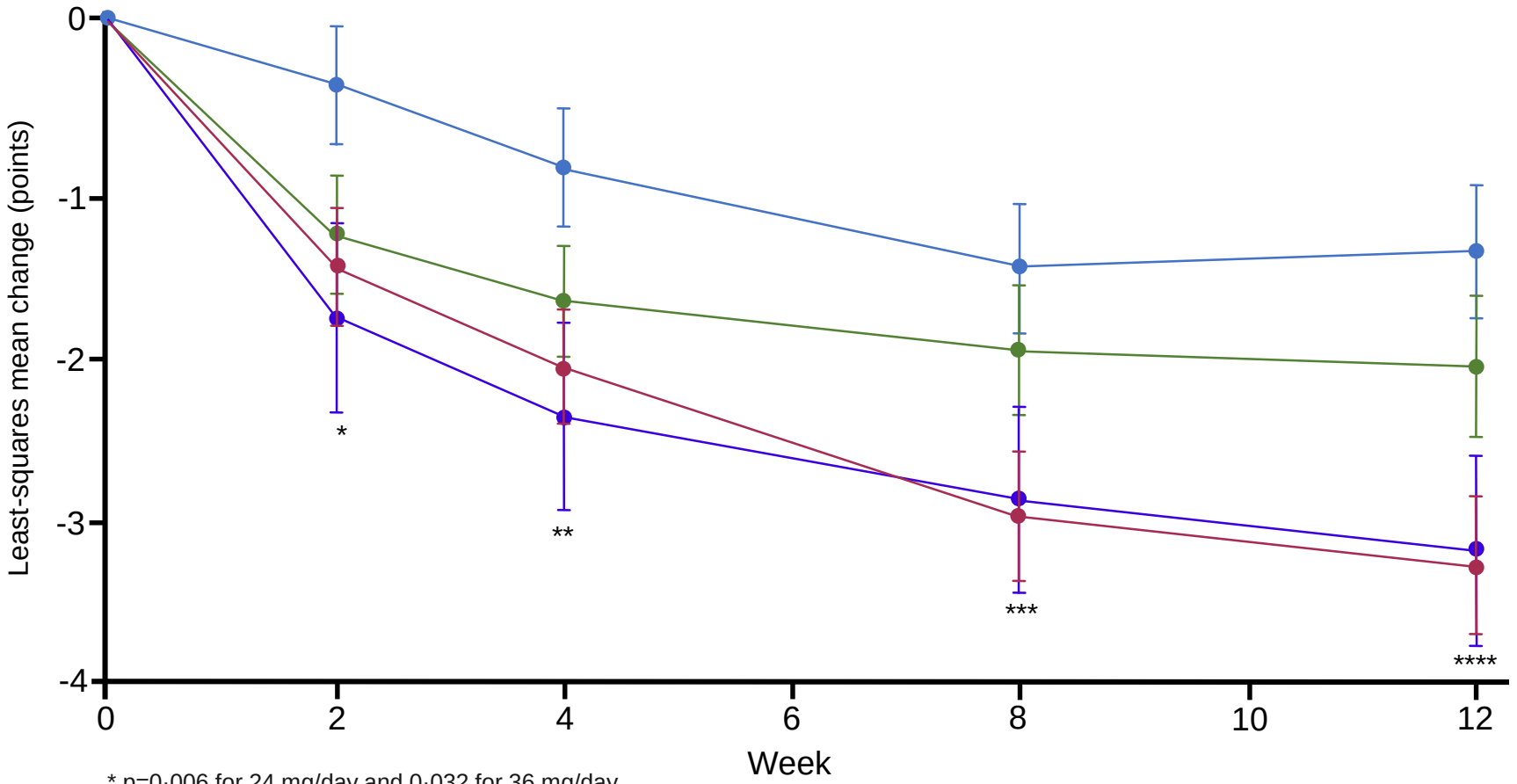
p=0.019

AEs: somnolence, headache

AIMS: Abnormal Involuntary Movement Scale.

Fernandez HH et al. Neurology. 2017;88(21):2003-2010.

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



* 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

AIMS: Abnormal Involuntary Movement Scale.

At Week 12

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

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

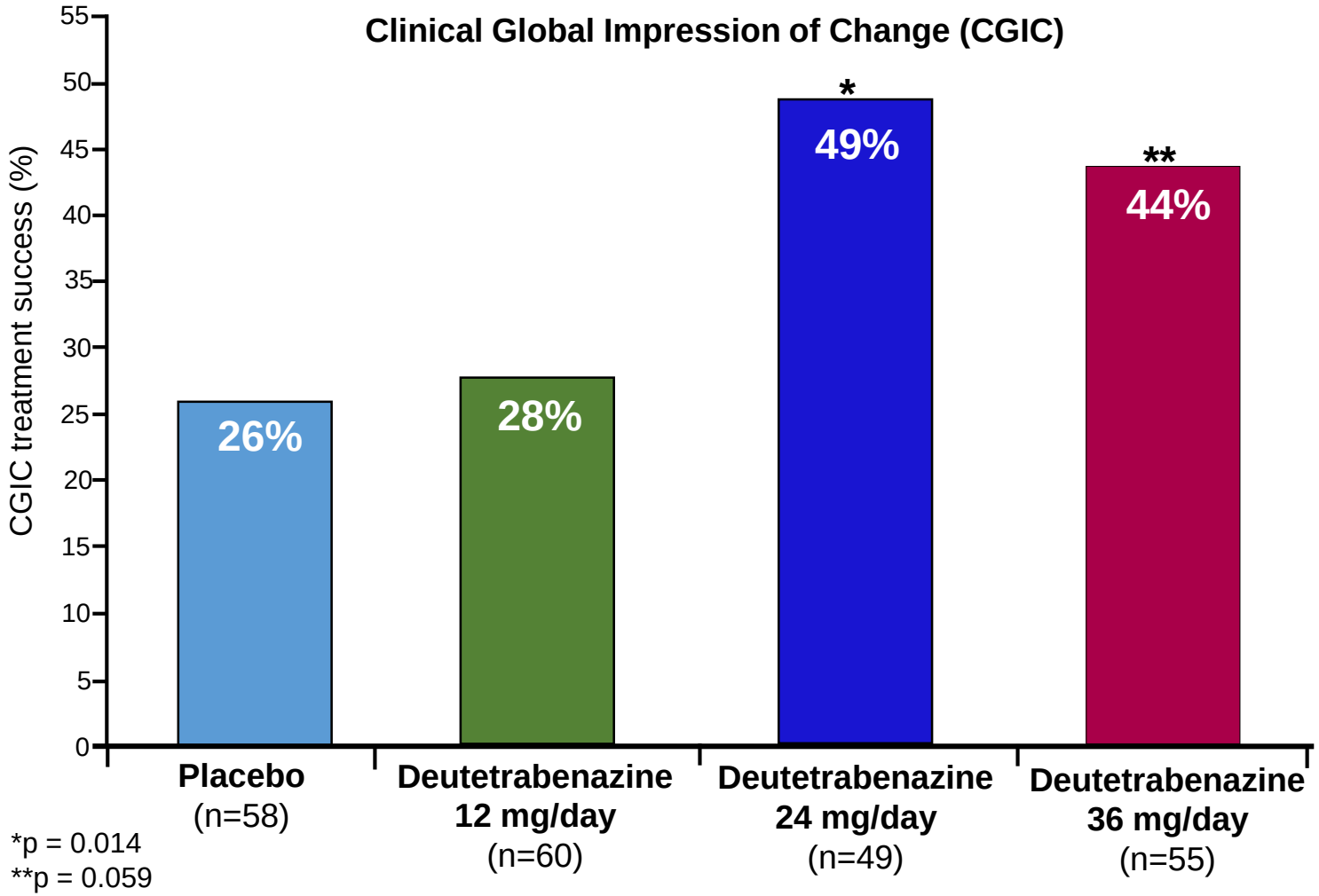
Deutetrabenazine 24 mg/d
mean AIMS: −3.2 points (SE 0.45)

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

Anderson KE et al. Lancet Psychiatry. 2017;4(8):595-604.

Deutetrabenazine: Intention-to-Treat Analysis

Significant Reductions in Abnormal Involuntary Movements



*p = 0.014
**p = 0.059

- CGIC at week 12
- Treatment success was defined as a rating of “much improved” or “very much improved” on the CGIC
- Deutetrabenazine at doses of 24 mg/day and 36 mg/day were efficacious and well tolerated

Anderson KE et al. Lancet Psychiatry. 2017;4(8):595-604.

Three Ways to Block VMAT2 With Three Benazines

1. **Tetrabenazine** – *not approved in the United States*
2. **Valbenazine** – *FDA approved for the treatment of TD, April 2017*
3. **Deutetrabenazine** – *FDA approved for the treatment of TD, August 2017*

- No head-to-head studies, all share the same fundamental mechanism
- Major differences are in pharmacokinetics, but differences in efficacy or safety not yet well established
- Deutetrabenazine and valbenazine are established as effective treatments of TD (Level A)

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

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

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	• Amantadine • Tetrabenazine • Pallidal deep brain stimulation (intractable TD)	• Withdrawing causative agents • Switching from typical to atypical DRBA

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

Summary

- Tardive dyskinesia still exists and remains a serious risk of APs and other DRBAs
  - Risk still present with SGAs
  - Rarely reversible, even after discontinuing the causing agent
- Better genetic predictors are needed
- Three ways to block VMAT2 with three benazines
- VMAT2 inhibitors have shown efficacy at reducing TD symptoms
  - **Deutetrabenazine** - *FDA approved for the treatment of TD, August 2017*
  - **Valbenazine** - *FDA approved for the treatment of TD, April 2017*