Differentiating Tardive Dyskinesia: Early Identification and Treatment

Leslie Citrome, MD, MPH
Clinical Professor of Psychiatry and Behavioral Sciences
New York Medical College
Valhalla, New York

1

Disclosures

- Consultant: AbbVie/Allergan, Acadia, Adamas, Adheretech, Alkermes, Alumis, Angelini, Astellas, Autobahn, Avanir, Axsome, Biogen, BioXcel, Bristol-Myers Squibb, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Delpor, Draig Therapeutics, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, INmune Bio, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Luye, Lyndra, MapLight, Marvin, Medavante-ProPhase, Merck, Mitsubishi-Tanabe Pharma, Neumora, Neurocrine, Neurelis, Noema, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sumitomo/Sunovion, Supernus, Teva, University of Arizona, Vanda, Wells Fargo, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research
-
- Speaker: Acadia, Alkermes, Angelini, Axsome, BioXcel, Bristol-Myers Squibb, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Neopharm, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, Teva, Vanda, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies
- Stocks (small number of shares of common stock): Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased > 10 years ago, stock options: Reviva
-
- Royalties/Publishing Income: Taylor & Francis (Editor-in-Chief, Current Medical Research and Opinion, 2022-date), Wiley (Editor-in-Chief, International Journal of Clinical Practice, through end 2019), UpToDate (reviewer), Springer Healthcare (book), Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics, through Spring 2025)

2

Drug-Induced Movement Disorders Commonly Seen in Psychiatric Practice

- Drug-induced Parkinsonism (DIP) [and Acute Dystonia]
- Acute Akathisia
- Tardive Dyskinesia (TD)

They are managed differently with very different pharmacological agents

3

Drug-Induced Parkinsonism

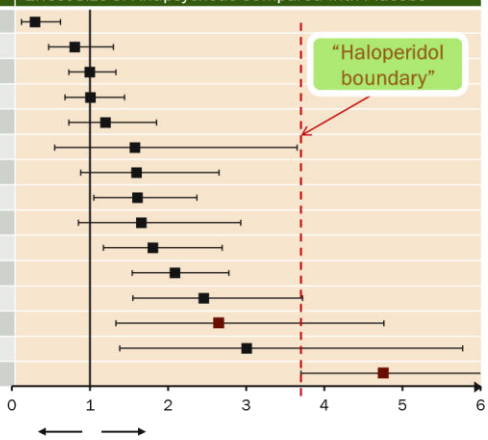
- Caused by dopamine blockade in the dorsal striatum, “collateral damage” when using antipsychotics
- Prevalence rates 20 to 35% and occurs at higher rates in elderly patients
- Less common with SGAs than FGAs, but dependent on dose
- Four SGAs have rates of DIP similar to that with placebo in RCTs: lumateperone, iloperidone, quetiapine, and clozapine
- Absent with Xanomeline-Trospium Combination
- DIP presents acutely and sub-acutely with approximately 50–75% of cases appearing within the first month, and 90% of cases within the first 3 months

Ward L, Citrome L. Neurol Ther. 2018;7(2):233-48; Citrome L et al. Neuropsychiatr Dis Treat. 2015;11:3095-104; Brannan SK, et al. N Engl J Med. 2021;384(8):717-726; Kaul I, et al. Lancet. 2024;403(10422):160-170; Kaul I, et al. JAMA Psychiatry. 2024; 81(8):749-756; Citrome L, et al. J Clin Psychiatry. 2023;84:22r14631.

4

Antipsychotics and Drug-Induced Parkinsonism

Drug	Odds Ratio (95% CrI)
Clozapine	0.30 (0.12 to 0.62)
Sertindole	0.81 (0.47 to 1.30)
Olanzapine	1.00 (0.73 to 1.33)
Quetiapine	1.01 (0.68 to 1.44)
Aripiprazole	1.20 (0.73 to 1.85)
Iloperidone	1.58 (0.55 to 3.65)
Amisulpride	1.60 (0.88 to 2.65)
Ziprasidone	1.61 (1.05 to 2.37)
Asenapine	1.66 (0.85 to 2.93)
Paliperidone	1.81 (1.17 to 2.69)
Risperidone	2.09 (1.54 to 2.78)
Lurasidone	2.46 (1.55 to 3.72)
Chlorpromazine	2.65 (1.33 to 4.76)
Zotepine	3.01 (1.38 to 5.77)
Haloperidol	4.76 (3.70 to 6.04)



DIP assessed through use of anti-Parkinson medication.
Leucht S, et al. Lancet. 2013;382(9896):951-962.

5

Management of Drug-Induced Parkinsonism

- APA recommends monitoring for acute onset extrapyramidal side effects weekly during initial treatment and until stable for 2 weeks, then at every follow-up visit
- Switching to an antipsychotic with less propensity to cause DIP is often a workable strategy, but improvement can take days to months and in some cases, DIP can persist longer
- Additional strategies include:
- Gradually lowering the antipsychotic dose if clinically possible
- Adding an anticholinergic medication, such as benztropine or trihexyphenidyl
- Adding a non-anticholinergic agent such as amantadine

Ward L, Citrome L. Neurol Ther. 2018;7(2):233-48.

6

The Anticholinergic Controversy

- Used extensively, and often prophylactically, upon the initiation of antipsychotic medication to manage DIP
- However, anticholinergics can increase the risk of developing TD, can worsen comorbid TD, and negatively impact cognition
- Avoid in the elderly due to an increased risk of delirium
- Peripheral side effects such as blurred vision, dry mouth, constipation, and urinary retention can also be encountered
- If prescribed, a typical duration of anticholinergic use is 3 months, and they should be periodically stopped to assess the need for continued use
- Consider amantadine as an alternative to anticholinergic medication to manage DIP

Ward L, Citrome L. Neurol Ther. 2018;7(2):233-48.

7

Acute Dystonia is Related to DIP

- Sustained muscle action (maximal contraction)
- More common in young adults and children
- The muscles of the head and neck are most commonly affected, and involvement of the laryngeal and pharyngeal muscles may lead to respiratory distress and asphyxia, and dysphagia and choking
- Occurs sooner than DIP
- Pathophysiology similar as DIP
- Anticholinergics work well with acute dystonia
- Resolves when offending drug is stopped
- Strategy is to change the antipsychotic

Gervin M and Barnes TRE. Advances in Psychiatric Treatment. 2000;6:332-43; Ward L, Citrome L. Neurol Ther. 2018;7(2):233-48.

8

Acute Akathisia is Different from DIP

- Akathisia = “inability to sit” in greek
- Subjective and objective psychomotor restlessness
- Can be seen with antipsychotics, SSRIs, and buspirone
- Occurs sooner than DIP
- Pathophysiology not the same as DIP
- Anticholinergics do not work for acute akathisia
- Resolves when offending drug is stopped
- Can be managed by dose reduction, switching drug, or beta blockers (propranolol 20 to 40 mg BID)
- Benzodiazepines and low dose mirtazapine can also be used
- If left untreated can be associated with suicidality and agitation

Forcen FE. Current Psychiatry. 2015;14(1):14-8.

9

Tardive Dyskinesia: Overview

- Tardive dyskinesia (TD) can be observed with long-term treatment with dopamine receptor blocking agents such as antipsychotic agents
- First described in 1957 by Schonecker, about five years after the commencement of neuroleptic treatment in psychiatry
- Lower TD risk for second-generation antipsychotics (SGA) than for first-generation antipsychotics (FGA), but rates are not zero
- Can be associated with significant functional impairment and can be socially stigmatizing - TD remains a significant treatment issue
- New treatment approaches to persistent TD are available, as approved by the US FDA for this purpose

Jankelowitz SK. Neuropsychiatric Disease and Treatment. 2013;9:1371-80; Schonecker M. Nervenarzt.1957;28:550–3; Citrome L. J Neurol Sci. 2017;383:199-204.

10

Tardive Dyskinesia (ICD-10 Code G24.0)

- TD consists of involuntary movements of the tongue, lips, face, trunk, and extremities that occur in patients treated long-term with dopamine antagonist medications
  - Can see grimacing, tongue movements, lip smacking, lip puckering, pursing of the lips, excessive eye blinking
  - Rapid, involuntary movements of the limbs, torso, and fingers (“piano-playing”) may also occur
  - Respiratory system (diaphragmatic) involvement can sometimes occur
  - TD can be irreversible, even after stopping the antipsychotic
- Variants of TD include tardive dystonia and tardive akathisia
- Can also be seen after use of antitussive agents such as promethazine and antiemetic medications such as metoclopramide used for gastroesophageal reflux and for diabetic gastroparesis

Citrome L et al. American Journal of Managed Care. 2007;13(Suppl):1-12.
Lerner V, Miodownik C. Curr Psychiatry Rep. 2011;13(4):295-304.
Brasic JR. Medscape. Aug 8, 2015. http://emedicine.medscape.com/article/1151826.
Jeste DV & Wyatt RJ. Am J Psychiatry. 1981;138:297-309.
Citrome L. J Neurol Sci. 2017;383:199-204.

11

Tardive Dyskinesia: Awareness

- Six hundred seven patients in a state mental hospital in Singapore were assessed using the Abnormal Involuntary Movement Scale (AIMS)
- Of the 607 patients, 242 (39.9%) met criteria for TD
- 163 of those 242 patients with TD (67.4%) were not aware of the presence of TD
- The majority of patients with SMI who have TD will not seek treatment themselves – relatives will ask for help with them, or clinicians will intervene

Chong SA et al. J Clin Psychopharmacol. 2001 Apr;21(2):235-7.

12

Tardive Dyskinesia: Continued Concern

- Thousands of patients are left with TD as a legacy of past treatment
- TD, once established, can be irreversible
- The "indications" for dopamine antagonist antipsychotic medications have expanded, and large numbers of persons are receiving these medications

Caroff SN et al. Current Psychiatry. 2011;10(10): 23-32.

13

Tardive Dyskinesia Prevalence Rates

Meta-analysis of 41 studies

- N = 11,493, mean age = 42.8 years, male = 66.4%, schizophrenia spectrum = 77.1% Findings
- Overall TD prevalence = 25.3%
- Prevalence with current SGAs = 20.7%
- Prevalence with current FGAs = 30.0%
- TD prevalence with SGAs was especially low in the 4 studies reporting on patients without prior FGA treatment: 7.2%
- Risk factors: older age, longer illness duration, early EPS, AfricanAmerican ethnicity

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

14

Tardive Dyskinesia: What We Can Expect

In a prospective study of 352 initially TD-free outpatients, compared with subjects treated with FGAs alone since the previous visit, the adjusted TD incidence rate-ratio for subjects treated with SGAs alone was 0.68 (95% CI, 0.29–1.64, hence not statistically significantly different)

- The incidence and prevalence TD was similar to previous findings at this site in the 1980s
- TD rating scale scores were only slightly lower among incident cases of TD appearing after recent SGA exposure vs. recent FGA exposure

Woods SW et al. J Clin Psychiatry. 2010;71:463-74.

15

Tardive Dyskinesia: What We Can Expect

In a prospective study of 352 initially TD-free outpatients, compared with subjects treated with FGAs alone since the previous visit, the adjusted TD incidence rate-ratio for subjects treated with SGAs alone was 0.68 (95% CI, 0.29–1.64, hence not statistically significantly different)

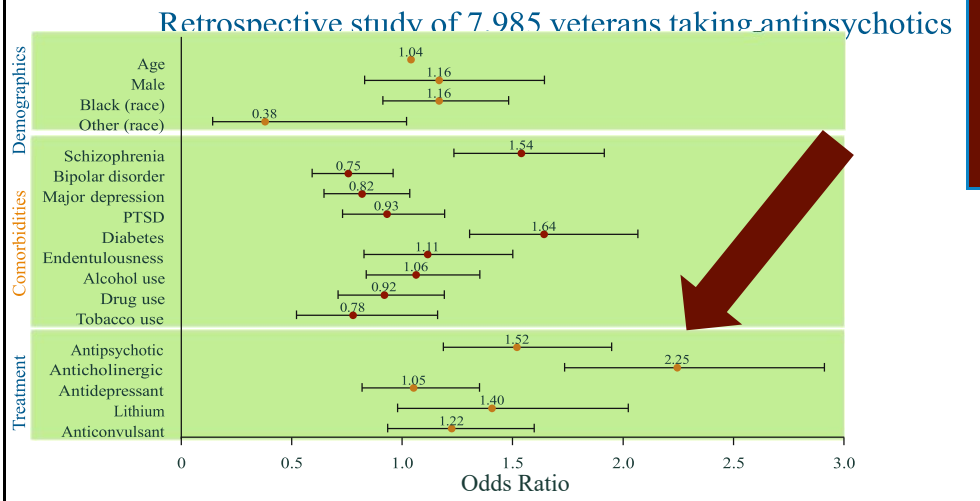
- The incidence and prevalence TD was similar to previous findings at this site in the 1980s
- TD rating scale scores were only slightly lower among incident cases of TD appearing after recent SGA exposure vs. recent FGA exposure

Of note, staff involved in this study were well trained to identify TD, and systematically looked for it. What would the yield be in your practice if you were to screen your own patients for TD on a regular basis?

Woods SW et al. J Clin Psychiatry. 2010;71:463-74.

16

Anticholinergic Agents May Be a Risk Factor in TD



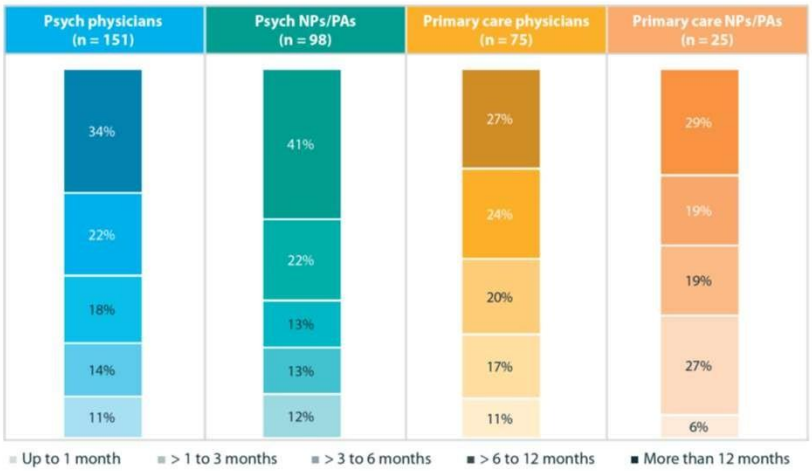
Anticholinergic use was associated with the highest risk of TD:
OR: 2.25
95% CI, 1.73-2.91;
P<.0001

Dots and error bars give the ORs and 95% CIs for all variables.
CI = confidence interval; OR = odds ratio; PTSD = post-traumatic stress disorder.
Caroff SN, et al. J Clin Psychopharmacol. 2020;40(1):38-45.

17

Benztropine is Used Chronically

Health Care Provider Survey: Duration of Benztropine Treatment, Mean % of Patients Treated[a]



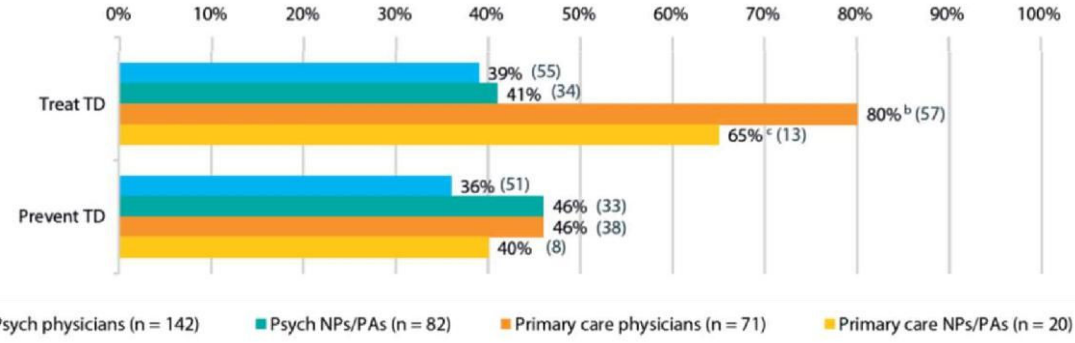
[a]The shading indicates the duration (ie, darkest shading indicates > 12 months and lightest shading indicates ≤ 1 month).
Abbreviations: NP = nurse practitioner, PA = physician assistant, psych = psychiatric.

Chepke C, et al. Prim Care Companion CNS Disord. 2023;25(4):22m03472.

18

Benztropine is Used to Treat or Prevent TD

Health Care Provider Survey: Reasons Health Care Providers Initiate Benztropine, % (n) of HCPs

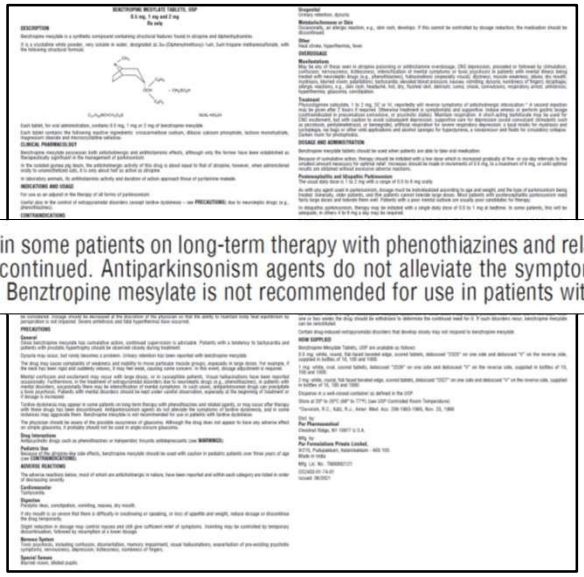


[a]$P < .05$ vs primary care physicians.
[b]$P < .05$ vs psych physicians and psych NPs/PAs.
[c]$P < .05$ vs psych physicians.
Abbreviations: DIMD = drug-induced movement disorder, HCP = health care provider, NP = nurse practitioner, PA = physician assistant, psych = psychiatric, TD = tardive dyskinesia.

Chepke C, et al. Prim Care Companion CNS Disord. 2023;25(4):22m03472.

19

Benztropine is Not Recommended for TD



Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued. Antiparkinsonism agents do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate them. Benztropine mesylate is not recommended for use in patients with tardive dyskinesia.

https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=959363b8-6847-4f6e-9957-6254febb085c&type=display

20

Anticholinergic Medications in Older Individuals

- Common anticholinergic adverse effects include dry mouth, urinary retention, constipation, cognitive decline and loss of the functional capacity to perform activities of daily living
- Adverse anticholinergic effects are particularly problematic in older adults due to agerelated changes in pharmacokinetic and pharmacodynamic processes, and the presence of multi-morbidity, polypharmacy and geriatric syndromes such as frailty
- In older adults, the anticholinergic burden is linked with serious adverse effects including falls, functional decline, delirium and death
- A recent Cochrane review suggests that older adults without cognitive impairment who are exposed to drugs with anticholinergic effects may be at an increased risk of cognitive decline and dementia; many drugs with anticholinergic effects may cause significant deterioration in the oral health of older adults

Hilmer SN, Gnjidic D. Aust Prescr. 2022;45(4):118-120.

21

2023 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

- Anticholinergics are called out for delirium, ataxia, impaired psychomotor function, syncope, falls, urinary retention
- Use of more than one medication with anticholinergic properties increases the risk of cognitive decline, delirium, and falls or fractures

TABLE 7 Drugs with strong anticholinergic properties.

Antidepressants	***Antiparkinsonian agents***
Amitriptyline	Benztropine
Amoxapine	Trihexyphenidyl
Clomipramine	***Antipsychotics***
Desipramine	Chlorpromazine
Doxepin (>6 mg/day)	Clozapine
Imipramine	Olanzapine
Nortriptyline	Perphenazine
Paroxetine	***Antispasmodics***
Antiemetics	Atropine
Prochlorperazine	Clidinium-chlordiazepoxide
Promethazine	Dicyclomine
Antihistamines (first-generation)	Homatropine
Brompheniramine	Hyoscyamine
Chlorpheniramine	Scopolamine
Cyproheptadine	***Skeletal muscle relaxants***
Dimenhydrinate	Cyclobenzaprine
Diphenhydramine	Orphenadrine
Doxylamine	
Hydroxyzine	
Meclizine	
Promethazine	
Triprolidine	
Antimuscarinics (urinary incontinence)[a]	
Darifenacin	
Fesoterodine	
Flavoxate	
Oxybutynin	
Solifenacin	
Tolterodine	
Trospium	

Note: This table is not a comprehensive list of all medications with anticholinergic properties.
[a]Data on whether certain bladder antimuscarinics confer greater adverse cognitive effects than others lack consistent quality. Oxybutynin has the best evidence for adverse cognitive effects. However, caution is warranted for all bladder antimuscarinics given their potential anticholinergic effects.[20]

By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023;71(7):2052-2081.

22

Anticholinergic Drug Scale (ADS) and the Anticholinergic Risk Scale (ARS)

Both the ADS and ARS are calculated the same way. Ratings on the ADS are defined as follows: level 0 = no known anticholinergic properties; level 1 = potentially anticholinergic as evidenced by receptor binding studies; level 2 = anticholinergic adverse events sometimes noted, usually at excessive doses; and level 3 = markedly anticholinergic. The ARS ranks medications for anticholinergic potential also on a 3-point scale (0, no or low risk; 3, high anticholinergic potential). ADS and ARS total scores are determined by summing the ratings of all drugs received by a patient.

APPENDIX
THE ANTICHOLINERGIC DRUG SCALE: LEVEL 1, 2, AND 3 DRUGS (AS OF JUNE 2006)

Level 3 Drugs

amitriptyline	dicyclomine	oxybutynin
atropine	dimenhydrinate	procyclidine
benztropine	diphenhydramine	promethazine
brompheniramine	doxepin	propantheline
carbinoxamine	flavoxate	protriptyline
chlorpheniramine	hydroxyzine	pyrilamine
chlorpromazine	hyoscyamine	scopolamine
clemastine	imipramine	thioridazine
clomipramine	meclizine	tolterodine
clozapine	nortriptyline	trihexyphenidyl
darifenacin	orphenadrine	trimipramine
desipramine		

Level 2 Drugs

carbamazepine	disopyramide	molindone
cimetidine	loxapine	oxcarbazepine
cyclobenzaprine	meperidine	pimozide
cyproheptadine	methotrimeprazine	ranitidine

Vanegas-Arroyave N, et al. CNS Drugs. 2024;38(4):239-254; Carnahan RM, et al. J Clin Pharmacol. 2006;46(12):1481-1486; Rudolph JL, et al. Arch Intern Med. 2008;168(5):508-13.
https://accp1.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1177%2F0091270006292126&file=jcph_1481_sm_Online_Appendix.pdf

23

Deprescribing Anticholinergics: Use a Gentle Hand

Studies in patients with schizophrenia/schizoaffective disorder on long-term anticholinergics

Study of 20 patients in Canada	Study of 34 patients in Japan
Weekly taper: 100%→75%→50%→25%→12.5%→0%	Tapered by 1mg of benztropine-equivalents every 2-4 weeks
90% successfully tapered	96% successfully tapered
20% with TD at baseline no longer met criteria	Mean length of taper 4.5 (±1.6) weeks
Improvement in cognitive measures ($p<0.001$, ES=0.34)	Improvement in cognitive measures ($p=0.002$, ES=0.42)

Desmarais, JE, et al. Therapeutic advances in psychopharmacology 4.6 (2014): 257-267. Ogino, S, et al. Progress in Neuro-Psychopharmacology and Biological Psychiatry 35.1 (2011): 78-83. De Leon, J, et al. Psychiatric Services 45.6 (1994): 606-607.

24

Is it Tardive Dyskinesia or Drug-Induced Parkinsonism?

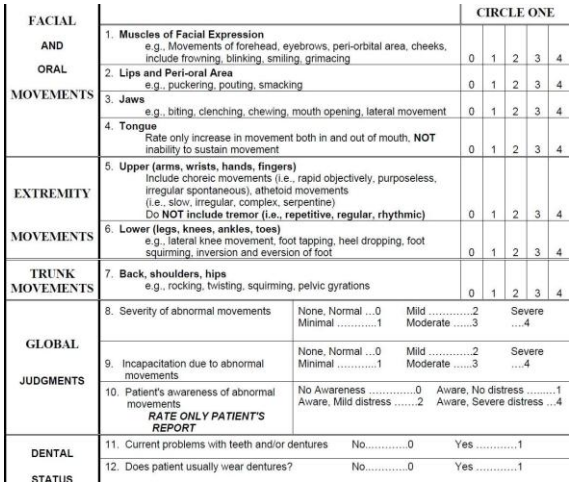
Characteristic	Tardive Dyskinesia	Drug-Induced Parkinsonism
Onset	Delayed (months-years) after initiation of an antipsychotic	Immediate (hours-days-weeks) after initiation of an antipsychotic or after dose is increased
Motor symptoms observed	Arrhythmic movements (generally choreoathetoid) of the face, trunk and extremities	Rhythmic tremor (3-6 Hz), rigidity, shuffling gait; akathisia may be present
Immediate (hours-days-weeks) effects of increasing antipsychotic dose	Improves	Worsens
Immediate (hours-days-weeks) effects of decreasing antipsychotic dose	Worsens	Improves
Effects of anticholinergic medications (e.g., benztropine)	Can worsen	Improves
Pharmacotherapeutic treatment options	VMAT2 inhibitors (tetrabenazine, valbenazine, deutetrabenazine), Ginkgo biloba, clonazepam, amantadine	Anticholinergics (for example, benztropine), amantadine

Ward L, Citrome L. Neurol Ther. 2018.

25

Abnormal Involuntary Movement Scale (AIMS): The Standard of Care

- Observer-rated 12-item anchored scale that takes only 5-10 minutes
- Adopted by many agencies for routine clinical use – baseline and periodically
- With FGAs, examine for TD at least every 6 months
- With SGAs and no concomitant FGAs, examine for TD annually
- With patients at high risk for EPS (e.g., older age, history of dystonic reactions, akathisia, clinically significant parkinsonism), examine every 3 months with FGAs or 6 months with SGAs
- Is the primary outcome measure in research of drugs for TD



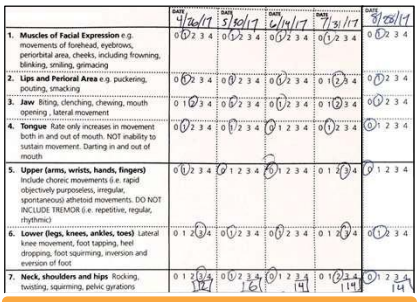
		CIRCLE ONE
FACIAL AND ORAL MOVEMENTS	1. **Muscles of Facial Expression** e.g., Movements of forehead, eyebrows, peri-orbital area, cheeks, include frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. **Lips and Peri-oral Area** e.g., puckering, pouting, smacking	0 1 2 3 4
	3. **Jaws** e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. **Tongue** Rate only increase in movement both in and out of mouth, **NOT** inability to sustain movement	0 1 2 3 4
EXTREMITY MOVEMENTS	5. **Upper (arms, wrists, hands, fingers)** Include choreic movements (i.e., rapid objectively, purposeless, irregular spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine) Do **NOT include tremor (i.e., repetitive, regular, rhythmic)**	0 1 2 3 4
	6. **Lower (legs, knees, ankles, toes)** e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
TRUNK MOVEMENTS	7. **Back, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
GLOBAL JUDGMENTS	8. Severity of abnormal movements	None, Normal ...0 Mild .....2 Severe Minimal .....1 Moderate 3 4
	9. Incapacitation due to abnormal movements	None, Normal ...0 Mild .....2 Severe Minimal .....1 Moderate 3 4
	10. Patient's awareness of abnormal movements ***RATE ONLY PATIENT'S REPORT***	No Awareness .....0 Aware, No distress .....1 Aware, Mild distress .....2 Aware, Severe distress ...4
DENTAL STATUS	11. Current problems with teeth and/or dentures	No.....0 Yes 1
	12. Does patient usually wear dentures?	No.....0 Yes 1

Guy W (ed): ECDEU Assessment Manual for Psychopharmacology, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. J Neurol Sci. 2017;383:199-204.

26

Yes, AIMS Takes Time, But…Three More Reasons To Do This

Some payers require it for VMAT2 inhibitor coverage



	DATE 4/26/17	DATE 5/30/17	DATE 6/19/17	DATE 7/31/17	DATE 8/28/17
1. **Muscles of Facial Expression** e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 0 2 3 4	0 0 2 3 4	0 0 2 3 4	0 1 2 3 4	0 0 2 3 4
2. **Lips and Perioral Area** e.g. puckering, pouting, smacking	0 0 2 3 4	0 0 2 3 4	0 0 2 3 4	0 1 2 3 4	0 0 2 3 4
3. **Jaw** Biting, clenching, chewing, mouth opening , lateral movement	0 1 2 3 4	0 0 2 3 4	0 0 2 3 4	0 1 2 3 4	0 0 2 3 4
4. **Tongue** Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth	0 0 2 3 4	0 0 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
5. **Upper (arms, wrists, hands, fingers)** Include choreic movements (i.e. rapid objectively purposeless, irregular, spontaneous) athetoid movements. DO NOT INCLUDE TREMOR (i.e. repetitive, regular, rhythmic)	0 0 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
6. **Lower (legs, knees, ankles, toes)** Lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4	0 0 2 3 4	0 0 2 3 4	0 1 2 3 4	0 1 2 3 4
7. **Neck, shoulders and hips** Rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4 14?	0 0 2 3 4 16?	0 1 2 3 4 14	0 1 2 3 4 14?	0 1 2 3 4 14

Enables measurement-based care

Helps us slow down and use a systematic thought process

VMAT = vesicular monoamine transporter.

McEvoy JP. J Clin Psychiatry. 2020;81(6):NU19047BR4C. Munetz MR, et al. Hosp Community Psychiatry. 1988;39(11):1172-1177. Chepke C. Personal communication. February 17, 2022.

27

Abnormal Involuntary Movement Scale (AIMS): The Standard of Care

- Observer-rated 12-item anchored scale that takes 5-10 minutes
- Adopted by many agencies for routine clinical use – baseline and periodically

Items 1 to 7: Four items dedicated to face, lips, jaws, tongue. Only one item each for the upper extremities, lower extremities, and trunk. The sum of the score of these 7 items is the clinically significant parkinsonism), examine primary

- With FGAs, examine for TD at least every 6 months
- With SGAs and no concomitant FGAs, examine for TD annually
- With patients at high risk for EPS (e.g., older age, history of dystonic reactions, akathisia, dyskinesia score and is used as the

		CIRCLE ONE
FACIAL AND ORAL MOVEMENTS	1. **Muscles of Facial Expression** e.g., Movements of forehead, eyebrows, peri-orbital area, cheeks, include frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. **Lips and Peri-oral Area** e.g., puckering, pouting, smacking	0 1 2 3 4
	3. **Jaws** e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. **Tongue** Rate only increase in movement both in and out of mouth, **NOT** inability to sustain movement	0 1 2 3 4
EXTREMITY MOVEMENTS	5. **Upper (arms, wrists, hands, fingers)** Include choreic movements (i.e., rapid objectively, purposeless, irregular spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine) Do **NOT include tremor (i.e., repetitive, regular, rhythmic)**	0 1 2 3 4
	6. **Lower (legs, knees, ankles, toes)** e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
TRUNK MOVEMENTS	7. **Back, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
GLOBAL JUDGMENTS	8. Severity of abnormal movements	None, Normal ...0 Minimal .....1 Mild .....2 Moderate .....3 Severe 4
	9. Incapacitation due to abnormal movements	None, Normal ...0 Minimal .....1 Mild .....2 Moderate .....3 Severe 4
	10. Patient's awareness of abnormal movements ***RATE ONLY PATIENT'S REPORT***	No Awareness .....0 Aware, Mild distress .....2 Aware, No distress .....1 Aware, Severe distress ...4
DENTAL STATUS	11. Current problems with teeth and/or dentures	No.....0 Yes 1
	12. Does patient usually wear dentures?	No.....0 Yes 1

outcome measureevery 3 months with FGAs or 6 months with for TD studies SGAs

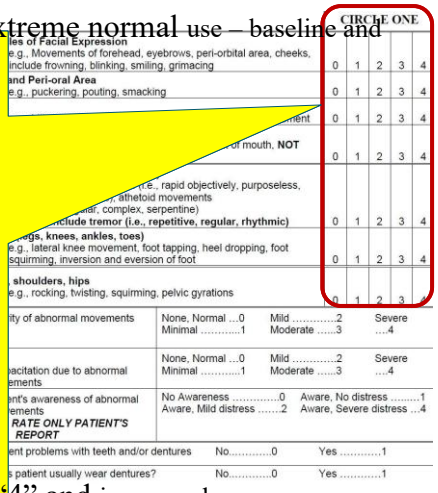
- Is the primary outcome measure in research of drugs for TD

Guy W (ed): ECDEU Assessment Manual for Psychopharmacology, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. J Neurol Sci. 2017;383:199-204.

28

Abnormal Involuntary Movement Scale (AIMS): The Standard of Care

- Observer-rated 12-item anchored scale that takes 5-10 minutes0 = no movements
- Adopted by ~~many agencies for routine clinical~~ 1 = minimal or extreme normal use – baseline and periodically2 = mild
- With FGAs, examine for TD at least every 6 3 = moderate (and usually quite months obvious)
- With SGAs and no concomitant FGAs, examine for TD annually4 = severe
- With patients at high risk for EPS (e.g., older age, history of dystonic reactions, akathisia, Sum can equal 7 but would be clinically significant parkinsonism), examine irrelevant if all items scored as a "1" every 3 months with FGAs or 6 months with SGAs
- Is the primary outcome measureSum of 7 when one item is a "4" and in research of drugs for TDanother item is a "3" would indicate a severe case



Guy W (ed): ECDEU Assessment Manual for Psychopharmacology, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. J Neurol Sci. 2017;383:199-204.

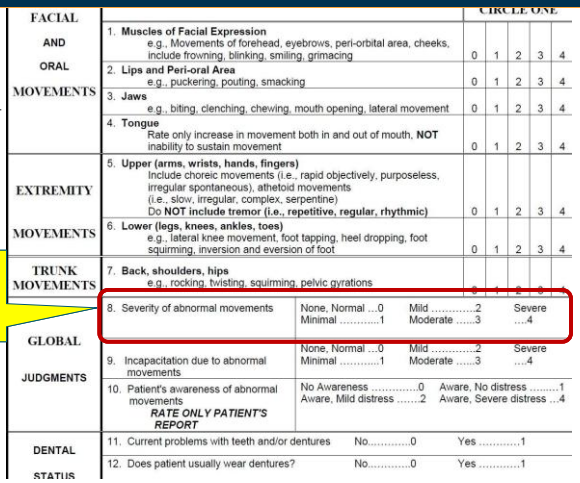
29

Abnormal Involuntary Movement Scale (AIMS): The Standard of Care

- Observer-rated 12-item anchored scale that takes 5-10 minutes
- Adopted by many agencies for routine clinical use – baseline and periodically
- With FGAs, examine for TD at least every 6 months
- With SGAs and no concomitant FGAs, examine for TD annually

Global severity: based on the highest• With patients at high risk for EPS (e.g., older single score in the first 7 items age, history of dystonic reactions, akathisia, clinically significant parkinsonism), examine every 3 months with FGAs or 6 months with SGAs

- Is the primary outcome measure in research of drugs for TD



		CIRCLE ONE
FACIAL AND ORAL MOVEMENTS	1. **Muscles of Facial Expression** e.g., Movements of forehead, eyebrows, peri-orbital area, cheeks, include frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. **Lips and Peri-oral Area** e.g., puckering, pouting, smacking	0 1 2 3 4
	3. **Jaws** e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. **Tongue** Rate only increase in movement both in and out of mouth, **NOT** inability to sustain movement	0 1 2 3 4
EXTREMITY MOVEMENTS	5. **Upper (arms, wrists, hands, fingers)** Include choreic movements (i.e., rapid objectively, purposeless, irregular spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine) Do **NOT include tremor (i.e., repetitive, regular, rhythmic)**	0 1 2 3 4
	6. **Lower (legs, knees, ankles, toes)** e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
TRUNK MOVEMENTS	7. **Back, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
GLOBAL JUDGMENTS	8. Severity of abnormal movements	None, Normal ...0 Minimal .....1 Mild .....2 Moderate .....3 Severe 4
	9. Incapacitation due to abnormal movements	None, Normal ...0 Minimal .....1 Mild .....2 Moderate .....3 Severe 4
	10. Patient's awareness of abnormal movements ***RATE ONLY PATIENT'S REPORT***	No Awareness .....0 Aware, Mild distress .....2 Aware, No distress .....1 Aware, Severe distress ...4
DENTAL STATUS	11. Current problems with teeth and/or dentures	No.....0 Yes 1
	12. Does patient usually wear dentures?	No.....0 Yes 1

Guy W (ed): ECDEU Assessment Manual for Psychopharmacology, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. J Neurol Sci. 2017;383:199-204.

30

•Degree of incapacitation due toObserver-rated 12-item anchored scale that

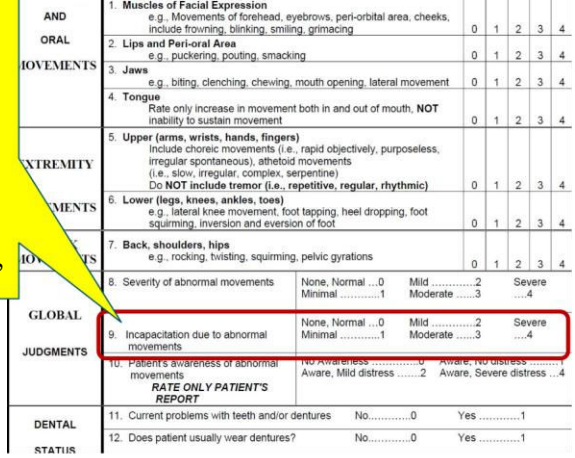
abnormal movements - the patient will takes 5-10 minutes

- Adopted by many agencies for routine clinical need to be asked to what extent any use – baseline and periodically

•movements interfere with activities With FGAs, examine for TD at least every 6 such as eating, drinking, speaking, months

•breathing, dressing oneself, writing, With SGAs and no concomitant FGAs, working, leisure activities, being with examine for TD annually

- With patients at high risk for EPS (e.g., older others, etc.
  age, history of dystonic reactions, akathisia, clinically significant parkinsonism), examine every 3 months with FGAs or 6 months with SGAs
- Is the primary outcome measure in research of drugs for TD



		CIRCLE ONE
AND ORAL MOVEMENTS	1. Muscles of Facial Expression e.g., Movements of forehead, eyebrows, peri-orbital area, cheeks, include frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. Lips and Peri-oral Area e.g., puckering, pouting, smacking	0 1 2 3 4
	3. Jaws e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. Tongue Rate only increase in movement both in and out of mouth, NOT inability to sustain movement	0 1 2 3 4
XTREMITY MENTS	5. Upper (arms, wrists, hands, fingers) Include choreic movements (i.e., rapid objectively, purposeless, irregular spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine) Do NOT include tremor (i.e., repetitive, regular, rhythmic)	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
	7. Back, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
GLOBAL JUDGMENTS	8. Severity of abnormal movements	None, Normal ...0 Minimal .....1 Mild .....2 Moderate .....3 Severe 4
	9. Incapacitation due to abnormal movements	None, Normal ...0 Minimal .....1 Mild .....2 Moderate .....3 Severe 4
	10. Patient's awareness of abnormal movements RATE ONLY PATIENT'S REPORT	No Awareness .....0 Aware, Mild distress .....2 Aware, No distress .....1 Aware, Severe distress ...4
DENTAL STATUS	11. Current problems with teeth and/or dentures	No.....0 Yes 1
	12. Does patient usually wear dentures?	No.....0 Yes 1

Guy W (ed): ECDEU Assessment Manual for Psychopharmacology, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. J Neurol Sci. 2017;383:199-204.

31

Patient's awareness (and distress level) of the abnormal movements (0–4, with 0 noting no awareness, 1 noting being aware with no distress, and 2–4 noting awareness and distress rating from mild to moderate to severe) • With SGAs and no concomitant FGAs, examine for TD annually

It is not unusual for persons with schizophrenia to have little insight into their dyskinetic movements; however, patients with mood disorders may be better able to articulate their distress

- Observer-rated 12-item anchored scale that takes 5-10 minutes
- Adopted by many agencies for routine clinical use – baseline and periodically
- With FGAs, examine for TD at least every 6 months
- With patients at high risk for EPS (e.g., older age, history of dystonic reactions, akathisia, clinically significant parkinsonism), examine every 3 months with FGAs or 6 months with SGAs
- Is the primary outcome measure in research of drugs for TD

		CIRCLE ONE
	1. Muscles of Facial Expression e.g., Movements of forehead, eyebrows, peri-orbital area, cheeks, include frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. Lips and Peri-oral Area e.g., puckering, pouting, smacking	0 1 2 3 4
	3. Jaws e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. Tongue Rate only increase in movement both in and out of mouth, NOT inability to sustain movement	0 1 2 3 4
	5. Upper (arms, wrists, hands, fingers) Include choreic movements (i.e., rapid objectively, purposeless, irregular spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine) Do NOT include tremor (i.e., repetitive, regular, rhythmic)	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
	7. Back, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
	8. Severity of abnormal movements	None, Normal ...0 Minimal .....1 Mild .....2 Moderate .....3 Severe 4
	9. Incapacitation due to abnormal movements	None, Normal ...0 Minimal .....1 Mild .....2 Moderate .....3 Severe 4
	10. Patient's awareness of abnormal movements RATE ONLY PATIENT'S REPORT	No Awareness .....0 Aware, Mild distress .....2 Aware, No distress .....1 Aware, Severe distress ...4
	11. Current problems with teeth and/or dentures	No.....0 Yes 1
	12. Does patient usually wear dentures?	No.....0 Yes 1

Guy W (ed): ECDEU Assessment Manual for Psychopharmacology, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. J Neurol Sci. 2017;383:199-204.

32

Tips on Scoring

- Thumb-finger tapping, arm extension and walking are “activation” maneuvers used to elicit abnormal movements in other body areas
  - Score activated movements the same way; do not lower those numbers as was proposed at one time
  - An additional activation maneuver that can be used is a cognitive task such as asking the patient to count backwards from 100 or to recite the months of the year in reverse order
- Score the highest amplitude or frequency in a movement on the 0-4 scale, not the average
- The instructions for the AIMS also include an assessment of upper extremity rigidity by flexing and extending the patient's left and right arms, as well as observation of gait, but these are not rated
  - Nevertheless, findings from these actions may be helpful when determining if the patient has drug-induced parkinsonian side effects

Guy W (ed): ECDEU Assessment Manual for Psychopharmacology, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. J Neurol Sci. 2017;383:199-204.

33

Deutetrabenazine vs. Valbenazine: NNT in Fixed-Dose Trials

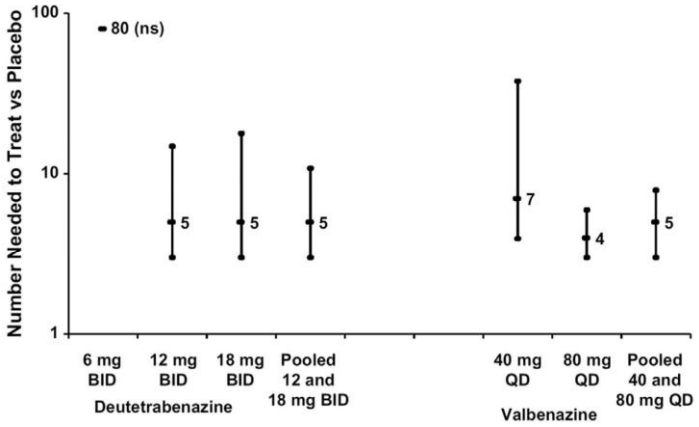


Fig. 1. ≥ 50% reduction in AIMS dyskinesia score from baseline to endpoint, NNT vs. placebo and 95% CIs, for the Phase III fixed-dose studies of deutetrabenazine (12 weeks) and valbenazine (6 weeks); reproduced with permission from [11].

Citrome L. J Neurol Sci. 2017;383:199-204.

34

Deutetrabenazine vs. Valbenazine: NNT in Fixed-Dose Trials

Citrome L. J Neurol Sci. 2017;383:199-204.

NNH vs placebo for discontinuation because of an adverse effect (AE) in the fixed dose studies for either medication was ~100; thus, LHH for response vs discontinuation because of an AE is ~20

YOU ARE TWENTY TIMES MORE LIKELY TO SEE A RFESPONDER THAN HAVE TO DISCONTINUE BECAUSE OF A SIDE EFFECT

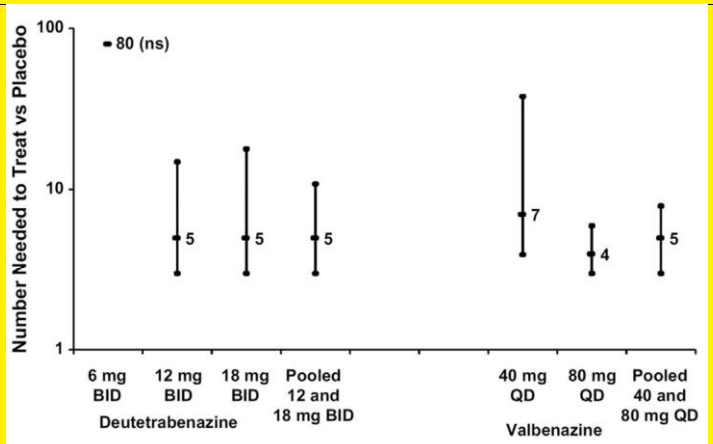


Fig. 1. ≥ 50% reduction in AIMS dyskinesia score from baseline to endpoint, NNT vs. placebo and 95% CIs, for the Phase III fixed-dose studies of deutetrabenazine (12 weeks) and valbenazine (6 weeks); reproduced with permission from [11].

35

Deutetrabenazine and Valbenazine: Adverse Events in Short-Term Studies

Adverse Reactions reported in ≥ 2% of patients treated with deutetrabenazine	Deutetrabenazine (n = 279)	Placebo (n = 131)
Headache	5%	8%
Somnolence	4%	7%
Diarrhea	4%	4%
Nasopharyngitis	4%	2%
Fatigue	4%	5%
Insomnia	4%	1%
Anxiety	4%	5%
Upper respiratory tract infection	3%	4%
Dry mouth	3%	5%
Nausea	2%	7%
Weight increased	2%	3%
Urinary tract infection	2%	2%
Depression/Dysthymic Disorder	2%	1%
Akathisia/Agitation/Restlessness	2%	1%
Arthralgia	2%	1%

Adverse Event reported at ≥ 2% for valbenazine and > placebo	Valbenazine (n = 262)	Placebo (n = 183)
Somnolence	10.9%	4.2%
Anticholinergic effects	5.4%	4.9%
Balance disorders/fall	4.1%	2.2%
Headache	3.4%	2.7%
Akathisia (akathisia, restlessness)	2.7%	0.5%
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%
Arthralgia	2.3%	0.5%

https://www.neurocrine.com/documents/26/INGREZZA-Full-Prescribing-Information_PI_Approved_7zq1xuU.pdf https://www.austedo.com/globalassets/austedo/prescribing-information.pd

36

Tardive Dyskinesia: Summary I

- Assume that TD exists in your practice
  - TD is still common, and will continue to be because of increasing use of antipsychotic medication
- Prevent if possible: harm reduction
  - Minimize drug-induced parkinsonian symptoms by selecting agents with lower risk for this problem
  - Minimize use of anticholinergic medication
- Screen
- Treat as quickly as possible after it appears
  - Reliable and effective FDA-approved treatments are available for persistent TD

Citrome L. J Neurol Sci. 2017;383:199-204.

37

Tardive Dyskinesia: Summary II

- There are now 2 FDA-approved treatments for TD: deutetrabenazine and valbenazine
- Both are efficacious and tolerable
- They differ somewhat in terms of labeled instructions
  - Titration
  - Drug-drug interactions (CYP 2D6 for both and CYP 3A4 for valbenazine) –

Contraindications

- Deutetrabenazine: hepatic impairment; taking reserpine, MAOIs, tetrabenazine, or valbenazine;
- Valbenazine: known hypersensitivity to valbenazine or any of its components) They differ somewhat in active metabolites

However, the clinical usefulness of these treatments is rendered moot if TD goes unrecognized

Citrome L. J Neurol Sci. 2017;383:199-204.

38

Let's Review the Treatments for the Drug-Induced Movement Disorders Commonly Seen in Psychiatric Practice

- Drug-induced Parkinsonism (DIP) [and Acute Dystonia]
- Acute Akathisia
- Tardive Dyskinesia (TD)

They are managed differently with very different pharmacological agents

39

Benztropine Has Been Demonstrated to Be Useful in:

A. Drug-induced parkinsonism only
B. Drug-induced parkinsonism and tardive dyskinesia
C. Tardive dyskinesia only
D. Drug-induced parkinsonism, tardive dyskinesia, and Tourette's disorder

40

Benztropine Has Been Demonstrated to Be Useful in:

A. Drug-induced parkinsonism only
B. Drug-induced parkinsonism and tardive dyskinesia
C. Tardive dyskinesia only
D. Drug-induced parkinsonism, tardive dyskinesia, and Tourette's disorder

41

Amantadine Has Been Demonstrated to Be Useful in:

A. Drug-induced parkinsonism only
B. Drug-induced parkinsonism and tardive dyskinesia
C. Tardive dyskinesia only
D. Drug-induced parkinsonism, tardive dyskinesia, and Wilson's disease

42

Amantadine Has Been Demonstrated to Be Useful in:

A. Drug-induced parkinsonism only
B. Drug-induced parkinsonism and tardive dyskinesia
C. Tardive dyskinesia only
D. Drug-induced parkinsonism, tardive dyskinesia, and Wilson's disease

43

Treatment for Acute Akathisia Includes…

A. Benztropine, lorazepam, propranolol, lowering the dose of the antipsychotic medication
B. Lorazepam, propranolol, amantadine, VMAT2 inhibitor
C. Valbenazine, lorazepam, benztropine, lowering the dose of the antipsychotic medication
D. Lorazepam, propranolol, lowering the dose of the antipsychotic medication

44

Treatment for Acute Akathisia Includes…

A. Benztropine, lorazepam, propranolol, lowering the dose of the antipsychotic medication
B. Lorazepam, propranolol, amantadine, VMAT2 inhibitor
C. Valbenazine, lorazepam, benztropine, lowering the dose of the antipsychotic medication
D. Lorazepam, propranolol, lowering the dose of the antipsychotic medication

45

Treatment for Tardive Dyskinesia Includes…

A. Benztropine, valbenazine, deutetrabenazine
B. Lorazepam, valbenazine, deutetrabenazine
C. Valbenazine, deutetrabenazine
D. Pimavanserin, Vitamin E

46

Treatment for Tardive Dyskinesia Includes…

A. Benztropine, valbenazine, deutetrabenazine
B. Lorazepam, valbenazine, deutetrabenazine
C. Valbenazine, deutetrabenazine
D. Pimavanserin, Vitamin E

47

Be sure to join the American Society of Clinical Psychopharmacology (ASCP).
Residents and other trainees are dues-exempt!
https://ascpp.org/join-ascp/

48

Questions?

nntman@gmail.com

K9NNT

49