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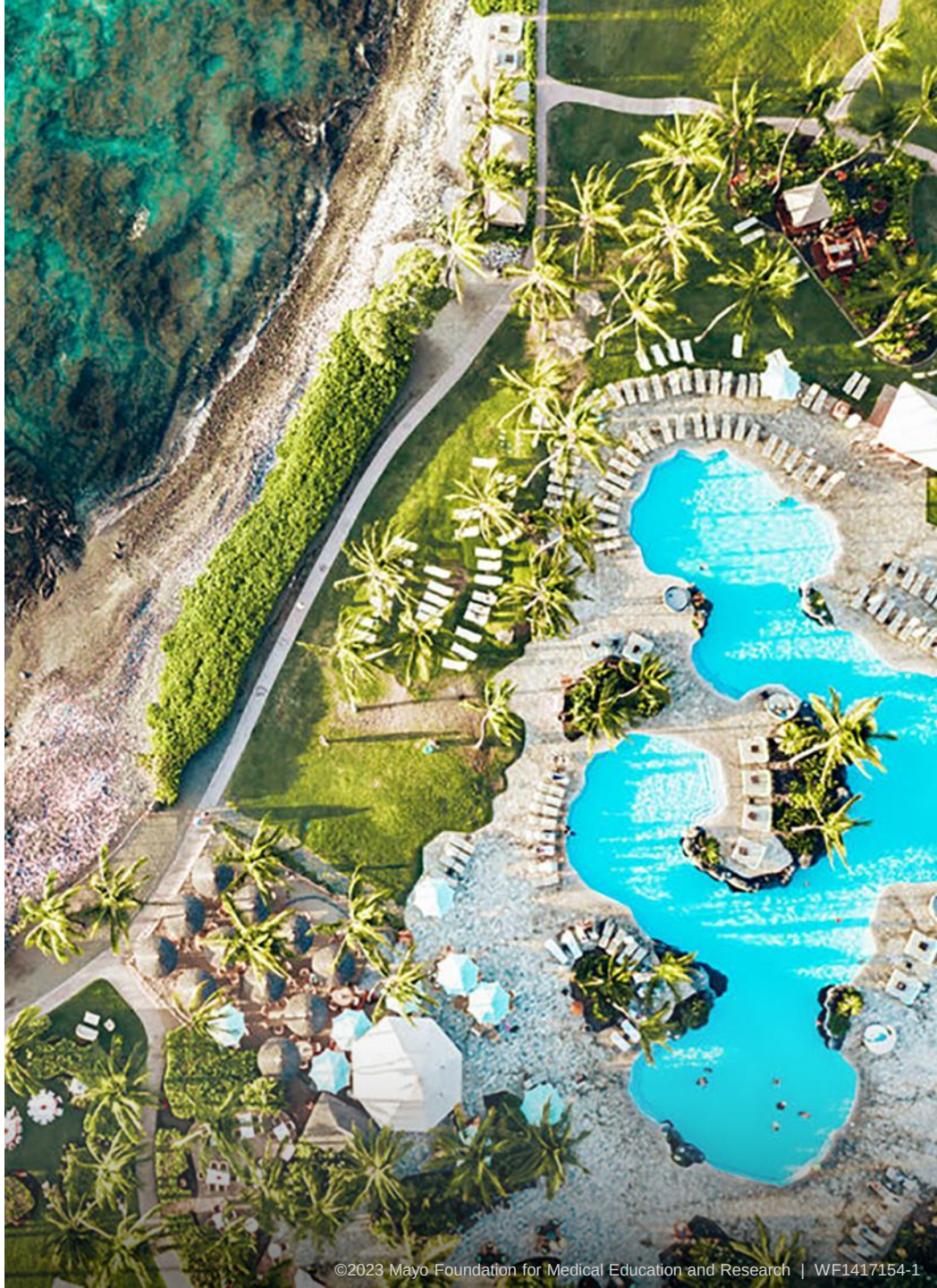
PSYCHIATRY CLINICAL UPDATES 2023

March 7-10, 2023
Fairmont Orchid
Kohala Coast, Big Island, Hawaii



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TARDIVE DYSKINESIA

MONITORING AND TREATMENT OPTIONS

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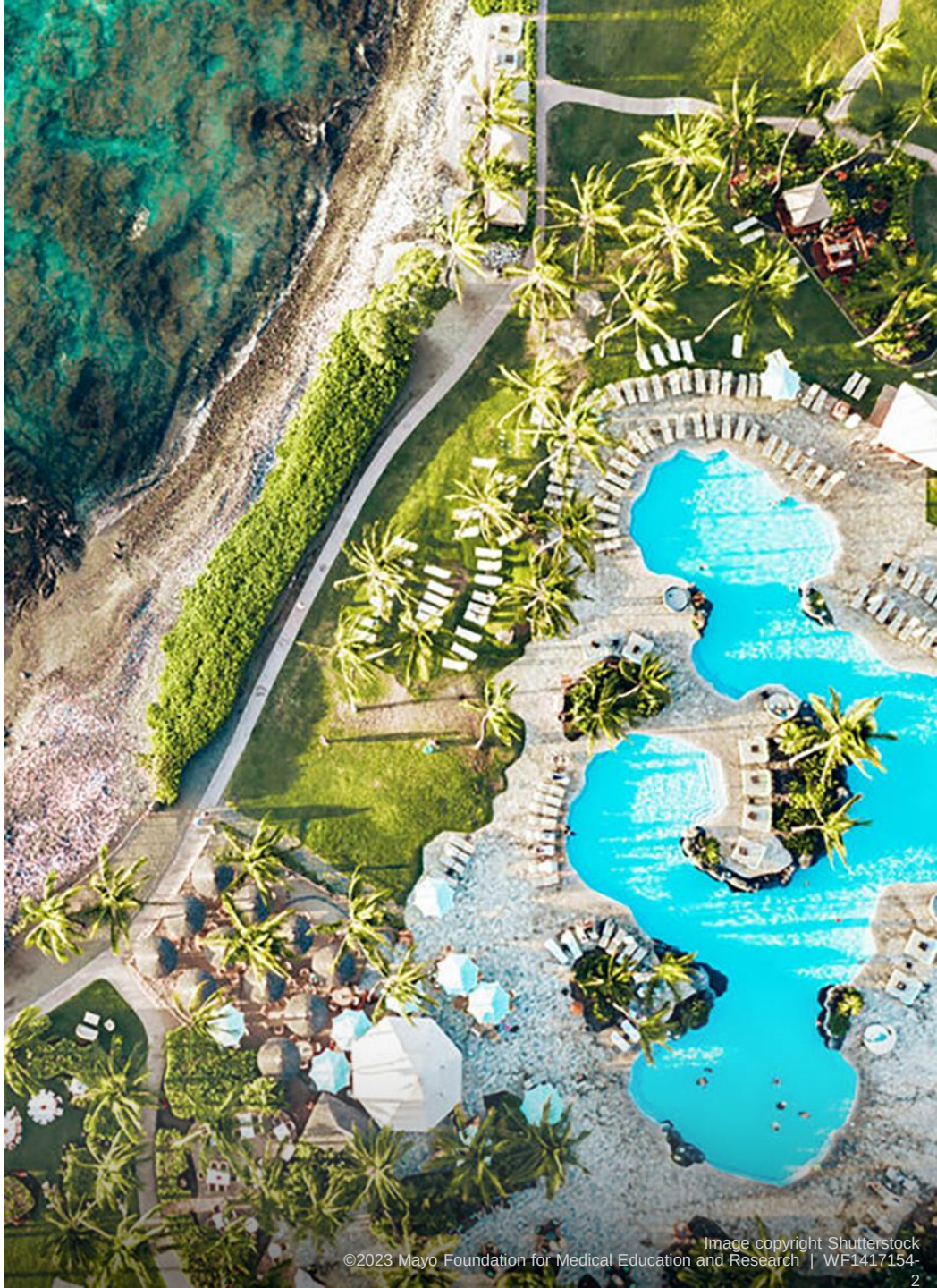
Pharmacotherapy Specialist - Psychiatry



DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

All relevant financial relationships have been mitigated.

LEARNING OBJECTIVES

- Review risk factors associated with tardive dyskinesia
- Describe monitoring parameters for tardive dyskinesia
- Develop a pharmacotherapy plan for a patient who has developed tardive dyskinesia

TARDIVE DYSKINESIA

HISTORICAL VIEW

1950 — Chlorpromazine

First synthesized

- Rhone-Poulenc scientists sought to create a promethazine like agent with "anesthetic-potentiating" effects

1952 — Expanding Use

A "Large CNS Effect"

- Largactil use in
- France during surgeries, nausea/ vomiting

Serendipity

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EPS for effect

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1960s+ — Tardive Dyskinesia

1966:

- Drug companies refute
- *"…one can no longer deny the occasional persistence of drug-induced dyskinesias"*

1970s:

- Permanent
- Dopamine receptor hypersensitivity theory
- Reserpine, tetrabenazine, antipsychotics, hypnotics, amantadine, B6
- Avoid anticholinergics
- AIMS published

Guy W. 1976: 534.7.
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TARDIVE DYSKINESIA

EARLY DESCRIPTIONS AND SUSPECTED RISK FACTORS

- Tardive dyskinesia, terminal extrapyramidal insufficiency syndrome, terminal extrapyramidal hyperkinesia
  - Involuntary movements, predominantly oral region but impacts others
  - More noticeable under observation vs. examination
  - Often persistent and disabling manifestations for months to years
- Prevalence from studies 1964-1971 ranging 0.5%-41.3%
  - Limitations based on definitions, design, accounting for prior treatment, etc.
- Risks described in the 1960s-1970s
  - Women>Men, 50-70 years of age, prior CNS insult, dose

Crane GE. 1968; 124: 40-8. Kazamatsuri, et al. 1972; 27: 491-9.

TARDIVE DYSKINESIA

PATIENT CASE

- 56-year-old woman with a history of PTSD, borderline personality disorder, MDD, AUD
- At an outpatient appointment akathisia with new hyperkinetic oral and neck movements were noted
- Current medications: acamprosate 666 mg TID, bupropion ER 450 mg daily, buspirone 10 mg TID, gabapentin 800 mg TID, lurasidone 120 mg daily (4-year history), desvenlafaxine 50 mg daily, trazodone 200 mg HS, prazosin 10 mg HS
  - Past intermittent exposures: aripiprazole, risperidone, quetiapine
- Movements were persistent, worsened by anxiety, and bothersome
- Lurasidone was tapered

VEVOX QUESTION – NEEDS FORMATTING

PATIENT CASE

- In addition to prolonged antipsychotic exposure, age, and gender which of the following best describes a risk factor associated with TD for this patient?

A. History of PTSD
B. Buspirone exposure
C. Trazodone exposure
D. Intermittent antipsychotic use

TARDIVE DYSKINESIA

A MODERN VIEW

- Oral–buccal–lingual dyskinesias most common
  - 80% of cases involve the lower 1/3 of the face; 20% predominantly trunk/limbs
  - Impact on internal muscles rare: speech changes, hiccups, vocalizations, dyspnea
- TD risk with SGAs lower but not absent, prevalence estimates: 13.1%-20%
  - Meta-analysis of 41 studies:
    - Current SGA vs FGA treatment, 20.7% vs. 30.0%, $p = 0.002$
    - SGA (FGA-naïve) vs SGA (likely prior FGA). 7.2% vs 23.4%, $p < 0.001$
- Patient factors: older age, women, history of acute EPS, mood disorders, diabetes, substance use disorders
- Medication factors: potency, cumulative exposure, drug-holidays, dopamine blocking antiemetics, amoxapine

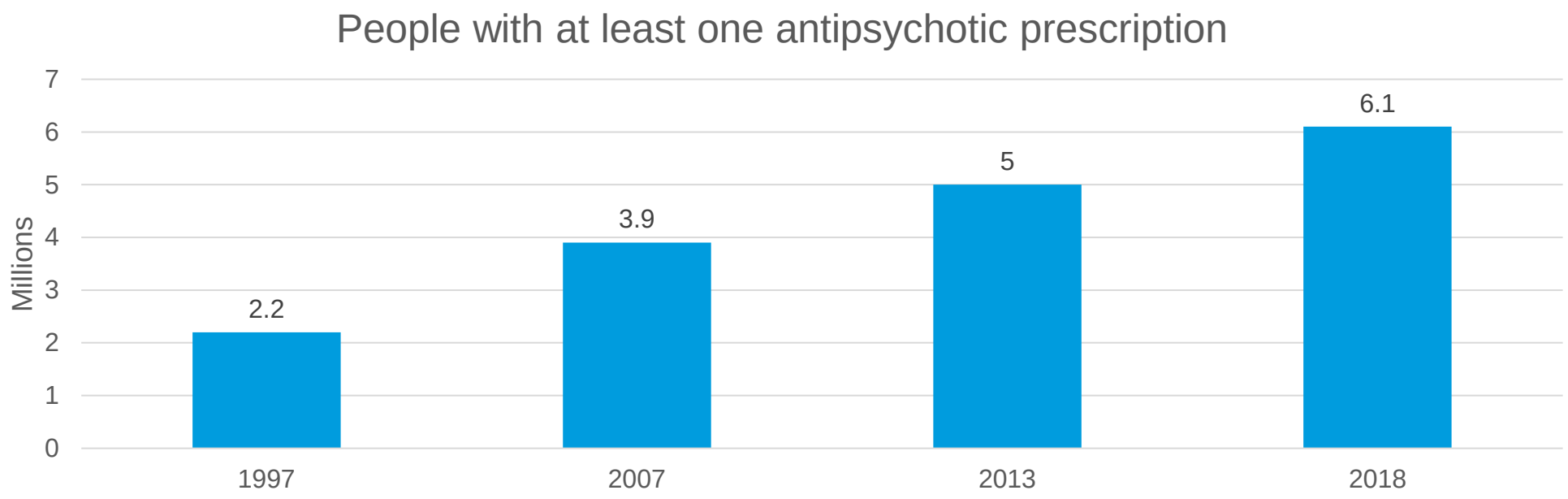
Correll CU. 2017;78:1136-47. Carbon M. 2017;78:e264-e278. Owens D. 2019; 25: 57-69

TARDIVE DYSKINESIA

A MODERN VIEW

- Impact on quality of life and as a barrier to treatment adherence

- 6.1 million people obtained at least one antipsychotic prescription in 2018
  - Expanding use due to both FDA approved and off-label indications



Ahrnsbrak R. Available from: https://www.ncbi.nlm.nih.gov/books/NBK581170/
Correll CU. 2017;78:1136-47. Carbon M. 2017;78:e264-e278. Dhir A. 2017; 32 (suppl 2). /

TARDIVE DYSKINESIA

SCREENING – APA GUIDELINE FOR PATIENTS WITH SCHIZOPHRENIA

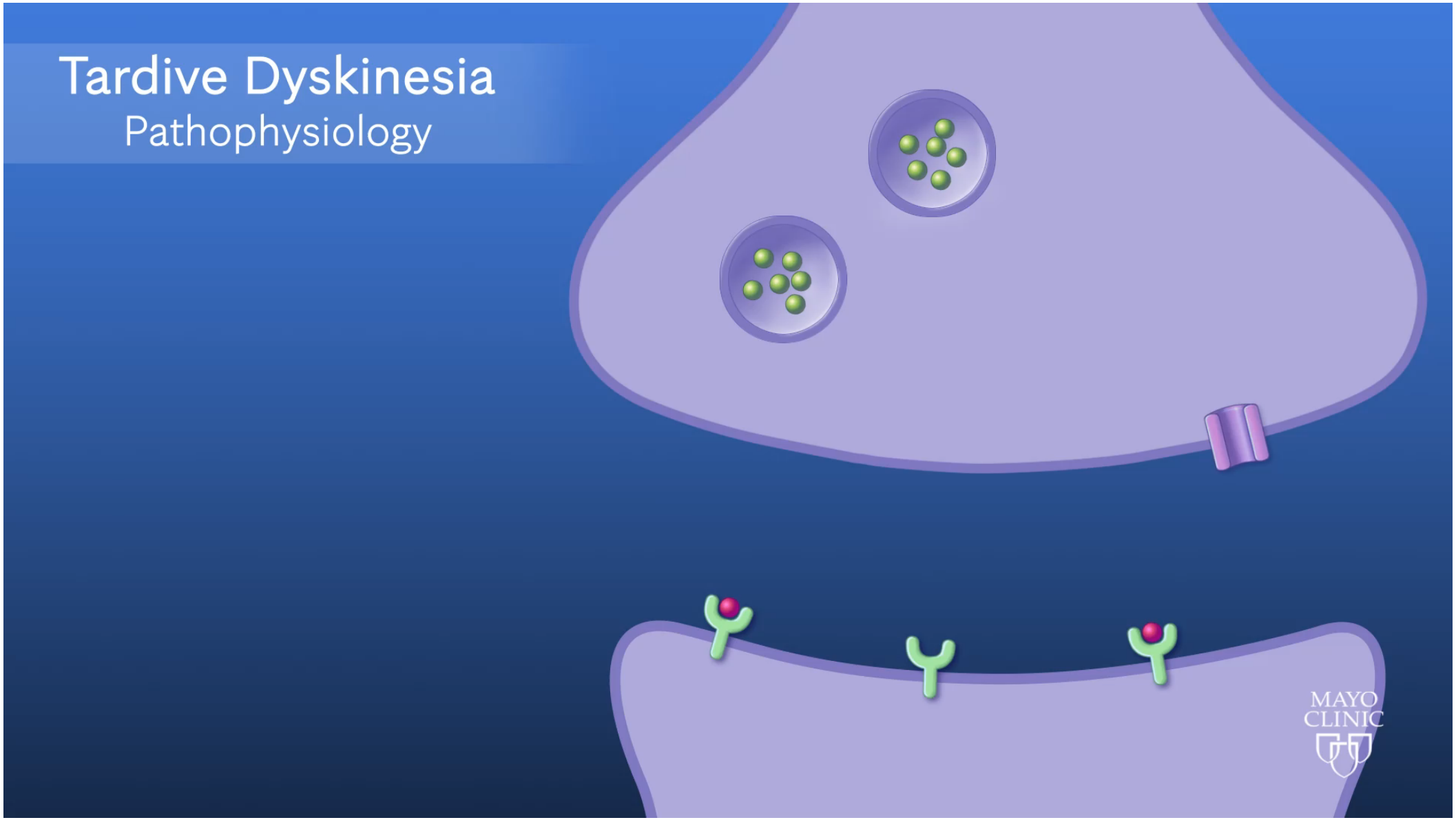
Time	Recommendation
Baseline	• Clinical assessment –and– • Assessment with a structured instrument
Follow-up	• Clinical assessment at each visit –and– • Assessment with a structured instrument at least every 12 months (6 months if high risk*) or there is new onset or exacerbation of preexisting movements
**High Risk:*	• *Age >55 years, women* • *Mood disorder, SUD, intellectual disability, CNS injury* • *History of acute drug-induced movement DO* • *"high cumulative exposure to antipsychotic medications, particularly high-potency dopamine D2 receptor antagonists"*

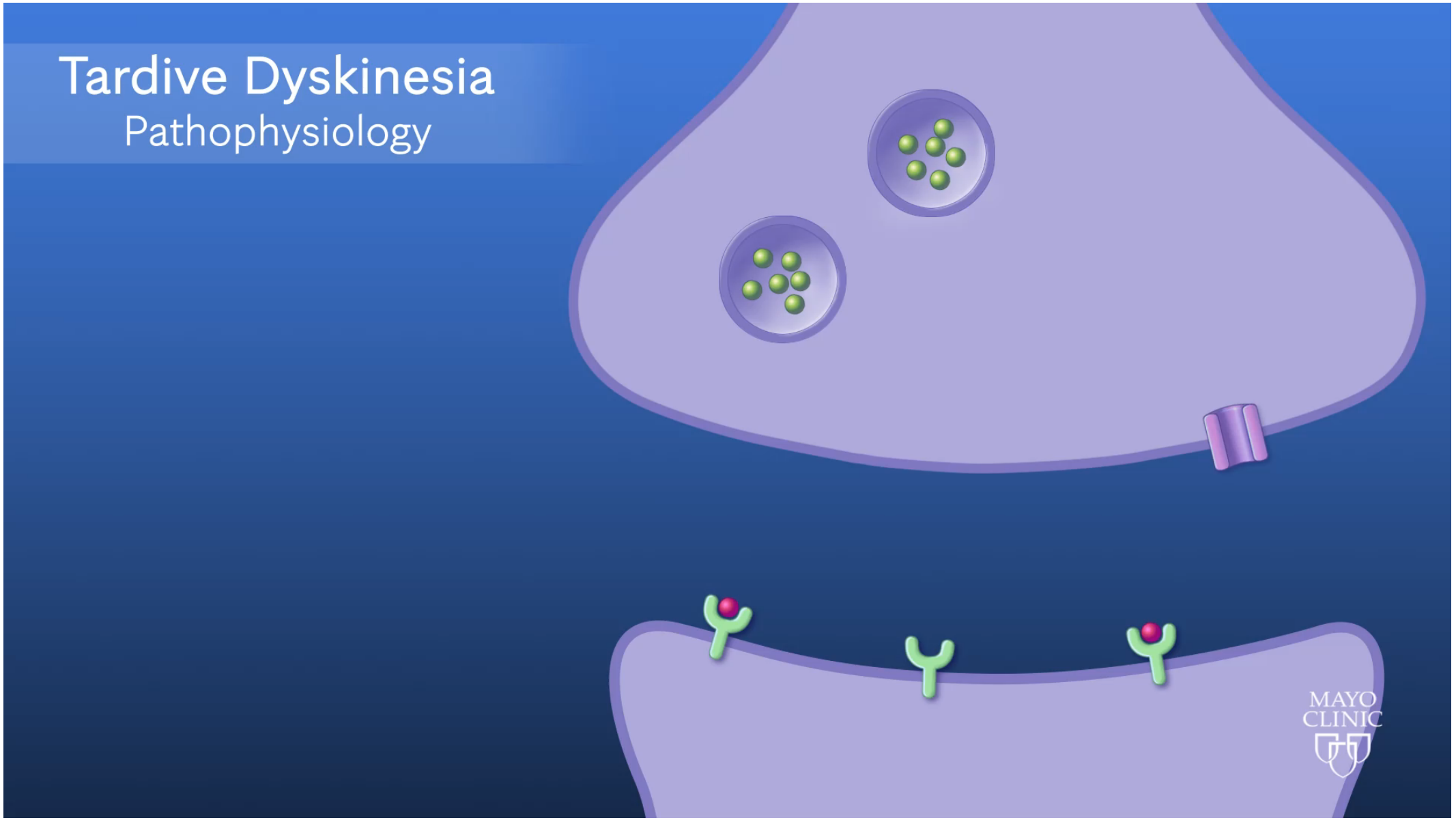
Keepers GA. 2020; 177(9):868-872

TARDIVE DYSKINESIA

SCREENING TOOLS

- Example tools
  - AIMS = Abnormal Involuntary Movement Scale
  - DISCUS = Dyskinesia Identification System: Condensed User Scale
- Barriers:
  - (Perceived) time of screening
  - Lack of formal AIMS training
  - Who should/can screen
- Opportunities:
  - EHR tools
  - EHR identification of at-risk patients
  - Training across disciplines





TREATMENT APPROACHES

PRACTICAL STEPS

- Is it bothersome? What is the severity?

- Is non-adherence or rapid tapering/cross tapering contributing?
  - Reintroducing the antipsychotic will likely alleviate movements, but an underlying pathology should be recognized
  - Cross taper more gradually
  - Withdrawal emergent dyskinesias may take months to resolve

Schooler NR, Kane JM. 1982; 39:486-7. Niemann, et al. 2018; 75: 525-541.

TREATMENT APPROACHES

PRACTICAL STEPS

- Guidelines and systematic reviews conclude there is insufficient evidence to recommend dose reduction as a treatment for TD
  - This may be a practice in real-world settings, especially if a specific agent is effective and TD is mild/not bothersome
- Switching from a high potency agent to a low potency agent may improve TD, specifically switching to clozapine or quetiapine
  - No RCTs comparing SGAs switching and impact on TD
  - Improvement may take months to years

Bhidayasiri R. 2013; 81: 463-9.. Correll et al. *J Clin Psychiatry* 2017 Citrome. *J Neurological Sciences* 2017 Schooler NR, Kane JM. 1982; 39:486-7. Niemann, et al. 2018; 75: 525-541.

TREATMENT APPROACHES

CLOZAPINE

- Individual studies have been small
- Multiple systematic reviews and meta-analyses indicate the benefits of switching to clozapine for patients with TD
  - May have the greatest impact on moderate to severe TD
- Barriers not excluded (i.e., monitoring, REMS, ADRs)

Wong. 2022; 239: 3393-420. Pardis P, et al. 2019; 33: 1187-98. Ricciardi L. et al, 2019; 64: 388-399. Mentzel TQ, et al. 2018;79(6):17r11852.

TARDIVE DYSKINESIA

PATIENT CASE

- 56-year-old female with a history of PTSD, borderline personality disorder, MDD with psychotic features, AUD
- 8 months since stopping lurasidone, oral and neck movements have persisted
  - No subsequent antipsychotic started
- Movements are distressing and socially impairing
- Treatment options for tardive dyskinesia are suggested, and the patient is open to options

VEVOX QUESTION – NEEDS FORMATTING

PATIENT CASE

- For this patient, which of the following would you recommend starting to manage tardive dyskinesia?

A. Valbenazine 40 mg daily
B. Haloperidol 2.5 mg BID
C. Benztropine 1 mg BID
D. Clonazepam 0.5 mg BID
E. Other

TREATMENT APPROACHES

DOPAMINE ANTAGONISM

- Using a dopamine antagonist (i.e., haloperidol) to improve TD symptoms is not recommended
  - Masking underlying pathology
  - Short-lived benefits and theoretical need for ongoing dose escalation
  - May cause other ADRs/movement disorders

Ricciardi L, et al. 2019; 64: 388-99 Niemann, et al. 2018; 75: 525-541. Bhidayasiri R 2018;389:67-75.
Bhidayasiri R. 2013; 81: 463-9..

TREATMENT APPROACHES

MINIMIZE ANTICHOLINERGIC AGENTS

- Anticholinergic agent discontinuation may improve TD symptoms

- The prescribing information of benztropine notes:
  - *“agents do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate them. Benztropine is not recommended for use in patients with tardive dyskinesia.”*

- VA study found patients with TD were more likely to be prescribed benztropine, (OR 2.25: 95% CI 1.73-2.91, p <0.0001)

- Monitor for worsening of parkinsonism, if tapering

Ricciardi L, et al. 2019; 64: 388-99
Caroff SN, et al. 2020; 40:38-45.

TREATMENT APPROACHES

PHARMACOLOGIC TARGETS FOR TARDIVE DYSKINESIA

- Mechanisms targeted
  - Dopamine depletion
  - Gamma aminobutyric acid modulation
  - Antioxidants
  - Cholinergic agents
  - Others
  - (Dopamine antagonism)

TARDIVE DYSKINESIA

HISTORICAL VIEW

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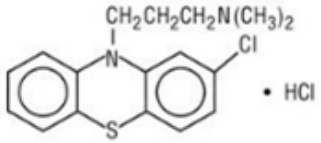
First synthesized
- Rhone-Poulenc scientists sought to create similar promethazine like agent with "anesthetic-potentiating" effects
- *4560 RP*



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Bower. 1954; 251:689-692. Schmidt, et al. 1966; 14: 369-77. Kazamatsuri, et al. 1972; 27: 491-9. Shen WW. 1999; 40: 407-14

TREATMENT APPROACHES

SELECT OPTIONS LIKELY INEFFECTIVE OR WITH INSUFFICIENT EVIDENCE

Baclofen	Diltiazem, nifedipine
Botulinum toxin	Galantamine, donepezil, physostigmine
Bromocriptine	Levetiracetam, zonisamide
Buspirone, isocarboxazid, selegiline	Vitamin E, B6, phenylalanine, melatonin

Bhidayasiri R 2018;389:67-75.
Miller ER 3rd, 2005;142(1):37-46.

AAN 2013 GUIDELINES AND 2018 UPDATE

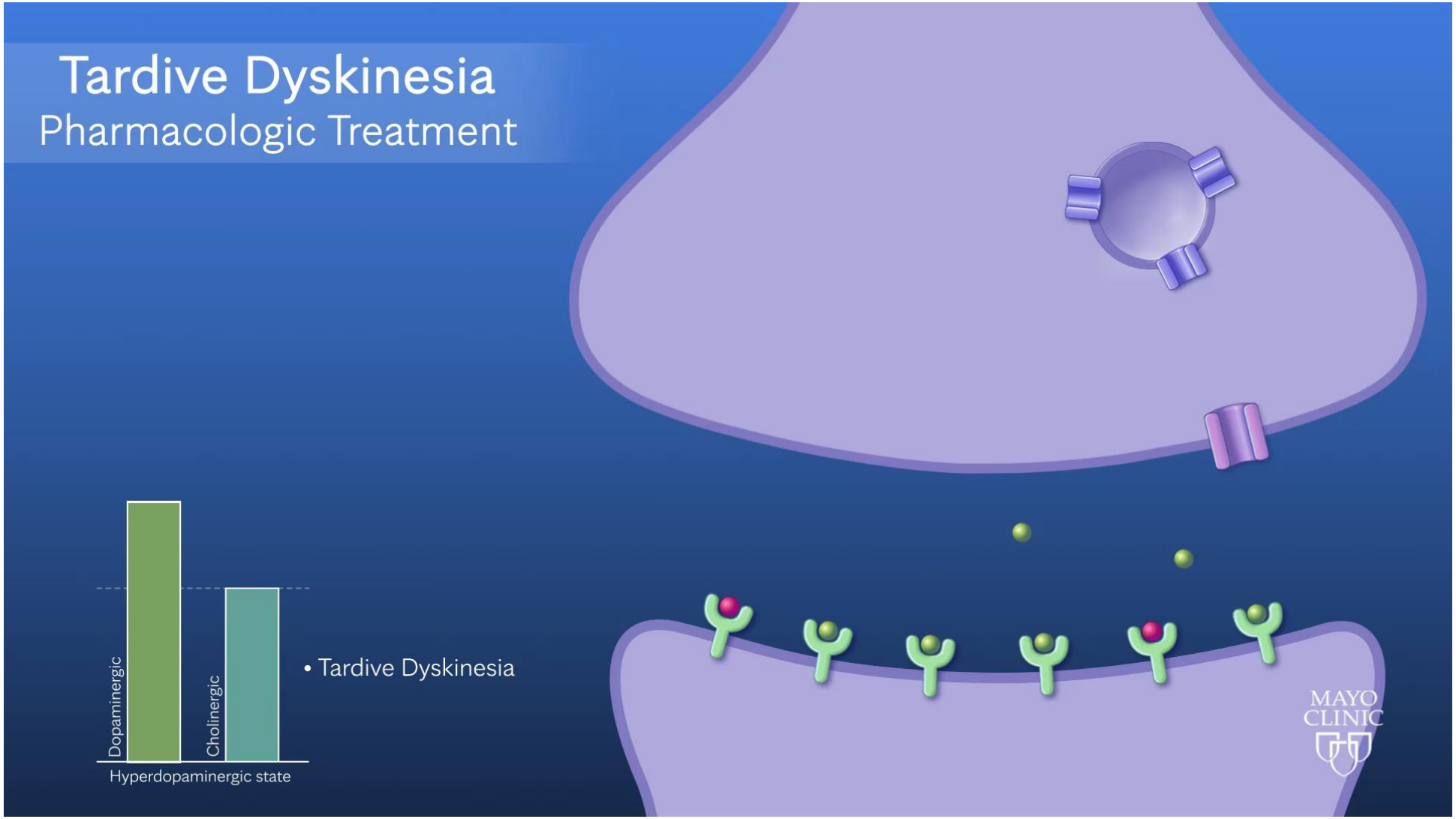
Agent (Evidence)	Description
Clonazepam (Probable benefit, Level B)	• Indirect GABA agonist • One RCT/crossover; (n=19); great improvement with dystonic predominance (41.5% decrease) vs. choreoathetoid symptoms (26.5%) • Benefits with dosing 2 mg to 3.5 mg • Limited clinic improvement with mild symptoms
Ginkgo biloba (Probable benefit, Level B)	• One RCT (n = 157); benefit at 240 mg (generally available as 60-120 mg supplement) • Bleed risks via antiplatelet action
Tetrabenazine (Probable benefit, Level C)	• Reversible vesicular monoamine transporter 2 (VMAT2) inhibitor • Side effect burden, suicidality warning
Amantadine (Probable benefit, Level C)	• Blocks N-methyl-D-aspartate receptors • Average 15-22% reduction in AIMS score compared to placebo in two small trials • Pro-dopaminergic, potential psychosis

→ 2018

Agent (Evidence)	Description
Valbenazine or deutetrabenazine (Established benefit, Level A)	• Vesicular monoamine transporter 2 (VMAT2) inhibitor • FDA approved • Better tolerated as compared to tetrabenazine

2013 American Academic of Neurology. Treatment of Tardive Dyskinesia Guidelines
Correll et al. *J Clin Psychiatry* 2017
Citrome. *J Neurological Sciences* 2017

MECHANISM OF ACTION – VMAT2 INHIBITORS



TARDIVE DYSKINESIA

APA SCHIZOPHRENIA GUIDELINES - 2020

- A VMAT2 inhibitor is recommended for moderate-severe or disabling TD
- A VMAT2 inhibitor can also be considered for mild tardive dyskinesia:
  - Patient preference
  - Any related impairment from TD
  - Effect on psychosocial functioning
- Valbenazine and deutetrabenazine have the greatest evidence to support use
- Tetrabenazine may have a great side effect burden and higher incidence of associated depression and suicidal ideation in patients with Huntington's disease
- Avoid reserpine due high rates of ADRs

Keepers GA. 2020; 177(9):868-872

VESICULAR MONOAMINE TRANSPORT INHIBITORS

	Reserpine	Tetrabenazine	Deutetrabenazine	Valbenazine
MOA	VMAT1 and VMAT2	VMAT2	VMAT2	VMAT2
Site	Peripheral and CNS	CNS	CNS	CNS
Half-life	200 hours	2-8 hours (TID)	9-10 hours (BID)	15-20 hours (daily)
Metabolism	• Various pathways	• PGx testing per PI with doses >50 mg • 2D6	• Deuterium ion slows conversion to metabolites • 2D6	• Lacks metabolites that avoid off-target receptors • 2D6 and 3A4/5
Comments	• Hypotension • N/V • Depression • Itching • Congestion • EPS	• Depression: boxed warning (up to 35%) • EPS (up to 33%) • N/V, fatigue • QTc: +7.6 msec at 50 mg	• Depression: boxed warning (HD only, <4%), • Fatigue • QTc (+4.5 msec/24 mg),	• Fatigue • QTc (+6.7-11.7 msec/80 mg)

Stamler D. 2016; 86 (S16); Tarakad A, et al. 2018; 32:1131-4.

TARDIVE DYSKINESIA

PATIENT CASE

- 56-year-old female with a history of PTSD, borderline personality disorder, MDD with psychotic features, AUD, tardive dyskinesia

- The prescription for valbenazine is rejected by insurance:
  - Non-formulary: “approval requires neurology consultation, a diagnosis of tardive dyskinesia, and ongoing documentation of improvement”

- Prior authorization approved
  - As non-formulary, although approved, costs were exorbitant
  - Coverage picked up by drug company assistance plan

- Excellent improvement in TD documented, however…

TARDIVE DYSKINESIA

PATIENT CASE

- After about 1 year the patient sends a message:
  - “In 4 days, the copay will become $3,500 per month”

- Maximum annual benefit for savings program was met

VEVOX QUESTION – NEEDS FORMATTING

PATIENT CASE

- Which of the following would you subsequently recommend for this patient?

A. Deutetrabenazine
B. Tetrabenazine
C. Ginkgo biloba
D. Amantadine
E. Other

TARDIVE DYSKINESIA

PATIENT CASE

- 56-year-old female with a history of PTSD, borderline personality disorder, MDD with psychotic features, AUD in remission, tardive dyskinesia

- Deutetrabenazine prescribed after prior authorization
  - Also required neurology consultation and documentation of improvement

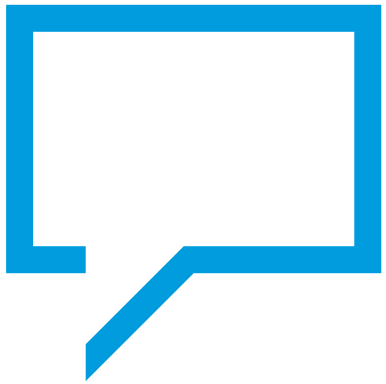
- Use of promotional card for $0.00 copay expired after 6 months
  - Maximum annual benefit $20,000

TARDIVE DYSKINESIA

TAKE HOME POINTS

- TD is still a prevalent concern
- Ongoing clinical assessment of TD and use of a screening tool is crucial
- New VMAT2 inhibitors are an evidence-based and effective approach for the treatment of tardive dyskinesia
  - Insurance and cost barriers are significant
- Other agents have less evidence and variable risks

QUESTIONS & DISCUSSION



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THANK YOU FOR JOINING US IN THIS COURSE

Rochester, Minnesota

Phoenix, Arizona

Jacksonville, Florida

TARDIVE DYSKINESIA

DEFINING

- Efforts characterize subtypes of *tardive syndromes* distinguishes TD from others (e.g., stereotypies, tics, myoclonus, dystonia)

DSM-5-TR

- Choreiform, athetoid, or semirhythmic, involuntary movements of the tongue, jaw, trunk, or extremities – present for at least 4 weeks
- Dopamine antagonist use of at least 3 months (1 month if age ≥ 60 years)
- Persists beyond 4 weeks from dopamine antagonist withdrawal or dose reduction
- No other potential causes

Schooler and Kane criteria for an initial probable TD diagnosis:

1. Standardized tool to assess for movements either as “moderate” in one body region or “mild” in two or more
2. 3 months of cumulative exposure
3. Absence of other causes

APA. DSM-5-TR.
Schooler NR, Kane JM. 1982 Apr;39(4):486-7.