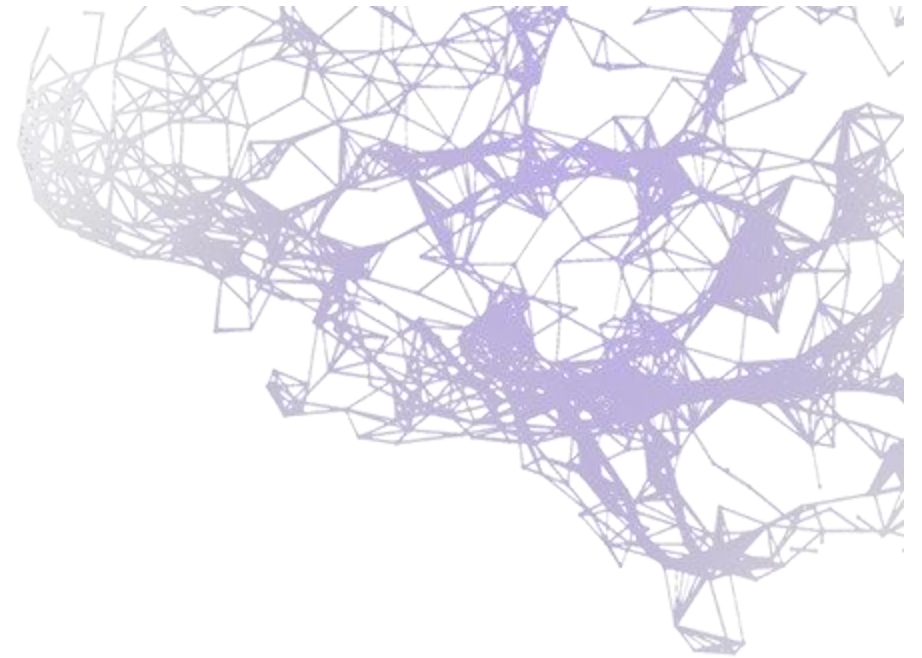


Tardive Syndromes

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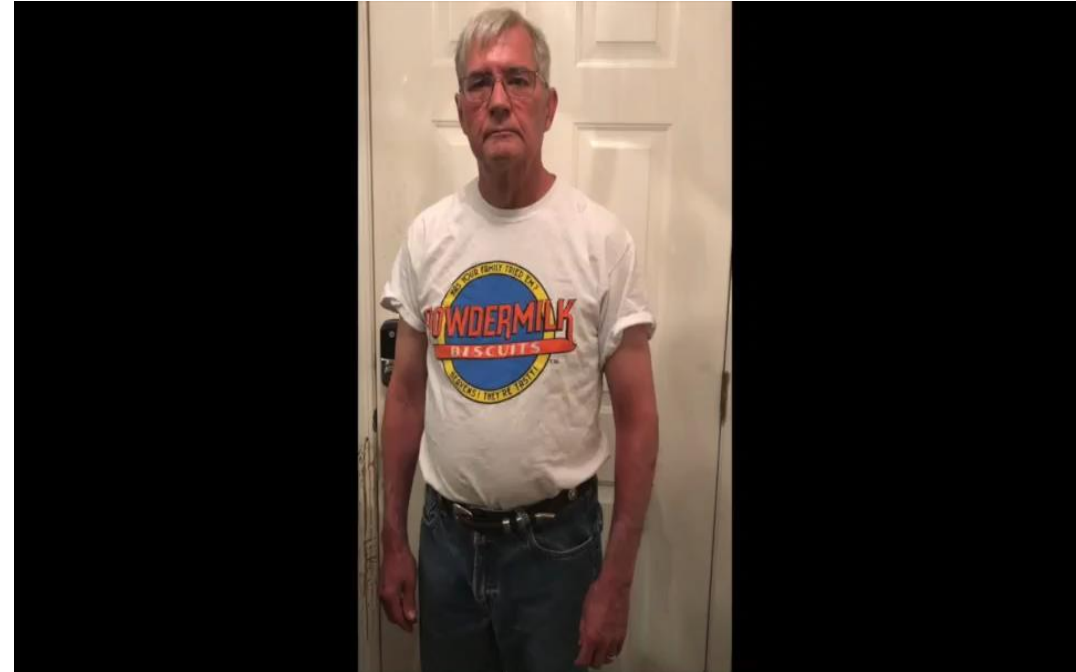
- No relevant disclosure

Objectives

- Review Tardive syndromes.
- Discuss phenomenology and clinical features.
- Brief overview of pathophysiology.
- Management of TS

Case

- A 71-year-old man referred for Parkinsonism.
- PMH: Depression
- Rx: Aripiprazole for 9 mo → developed slow gait, hypomimia and reduced speech volume.
- Switched to Brexpiprazole due to concern for Drug-induced Parkinsonism.
- Brexpiprazole was later discontinued by psychiatrist.
- Initial evaluation – mild Parkinsonism and no dyskinesia
- Within weeks of stopping brexpiprazole, developed involuntary movements in his body which were very disabling.



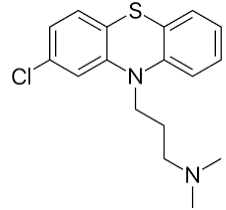
Sharma et al., 2020

Tardive Syndromes (TS)

- Spectrum of iatrogenic neurological disorders characterized by ***delayed onset, persistent movement disorder*** (hyper or hypokinetic) or sensory phenomenon resulting from exposure to neuroleptics or dopamine-receptor blocking agents (DRBAs).
- Prevalence of TS – 30% with FGA and 20% with SGA

Factor et al, 2019

History of Tardive syndromes



First Dopamine blocking agent introduced – Chlorpromazine

Schonecker described development of lip-smacking after treatment with Chlorpromazine

Sigwald et al. described ***delayed-onset*** orofacial movements after treatment with antipsychotics

Faurbye et al. published first collective description and coined Tardive dyskinesia

1952

1957

1959

1964

M Schonecker, 1957; Caroff et. Al JNS 2018

Relevance in Clinical Practice

- Often underrecognized, inappropriately managed
- Treatable movement disorders

- Increase trend to prescribe antipsychotics
- ~ 5 million in USA are exposed to antipsychotics/year
- ~ 20% of nursing home residents are on antipsychotics

Mulroy et al, 2020; Chouksey et al, 2020

Diagnosis of Tardive Syndromes

Important points to consider

- Symptoms should be associated with use of DRBAs for few months or less.
- Onset of symptoms during treatment or after discontinuation of treatment.
- Get worse after offending drug (DRBAs) is withdrawn.
- Persist > 4 weeks after medication is stopped.

Medications associated with TS

Antipsychotics

Typical or FGA

- Haloperidol
- Loxapine
- Droperidol
- Fluphenazine
- Chlorpromazine
- Thioridazone

Atypical /SGA/TGA

- Quetiapine
- Olanzapine
- Risperidone
- Paliperidone
- Clozapine
- Ziprasidone
- Aripiprazole
- Brexpiprazole

Anti-emetics

- Metoclopramide
- Prochlorperazine
- Promethazine

Antidepressants – Amoxapine

Mood stabilizers – Lithium

Calcium channel blockers – Flunarizine and Cinnarizine

Tardive syndromes - classification

- Classic tardive dyskinesia/Tardive stereotypies
- Tardive dystonia
- Tardive akathisia
- Tardive tremor & parkinsonism
- Tardive tics
- Tardive pain and other sensory phenomenon
- Tardive myoclonus
- Tardive ocular deviations

Video

- 67 y/o man with involuntary tongue and oral movements from prochlorperazine for chronic nausea.



Tardive dyskinesia

- Oral-buccal-lingual stereotypy.
- Other body regions can also be affected.
- Clinical features
 - Complex repetitive, lip smacking, chewing movements, grimacing , puckering, pouting, tongue protrusion.
 - Slow and repetitive tongue retraction or sweeping tongue movement in the mouth producing bulge in cheek “ Bon-bon sign”
 - Difficulty chewing, swallowing, tongue or lip biting
 - Choreiform movements in limbs distally “Piano playing movements”

Other Tardive stereotypies

- Purposeless, coordinated but involuntary, repetitive, ritualistic movements.
 - Truncal rocking, pelvic thrusting
 - to and fro leg movements, crossing/uncrossing of the legs.
- Can resembles akathisia

Tardive Akathisia

- Inner sense of restlessness with difficulty to stay still.
- Body rocking movement, shifting weight from one foot to another
- Crossing/uncrossing legs, body rocking.
- Associated with moaning or repetitive touching.

Savitt et al. 2018

Video

47 y/o man with hx of PTSD, MDD

- Hx of treatment with quetiapine, aripiprazole, risperidone
- Switched to Chlorpromazine after which he developed tongue movements
- Chlorpromazine dose reduction caused to development of head movements



before and after treatment with propranolol

Video

- 51 y/o woman with history of schizophrenia, treated with haloperidol for several years.
- Developed writhing movements in hands.
- Switched to Abilify
- Developed stooped posture, jaw opening, episodes of truncal twisting and turning, difficulty speaking.
- Has active delusions and spells of abnormal vocalizations and taking off her clothes.



Shared by Dr. Varghese

Tardive dystonia

- Common in men, younger age of onset
- Focal, segmental or generalized dystonia.
- Involves cranio-cervical region – blepharospasm, OMD, retrocollis, truncal hyperextension - opisthotonic posturing, extension of arms at the elbow
- Partial improvement with sensory trick

Videos



Respiratory dyskinesia

- Involvement of respiratory muscles
 - Irregular breathing, tachypnea
 - Huffing, grunting or gasping and take shorter breath
- Often difficult to recognize
- Mimic other respiratory and cardiac disorders
- ABG - may develop uncompensated respiratory alkalosis

Video

- 74 y/o man with breathing issues, speech difficulty and slight involuntary movements in limbs
- Detail work up by cardiology and pulmonology – negative

Was on metoclopramide around the time movements started

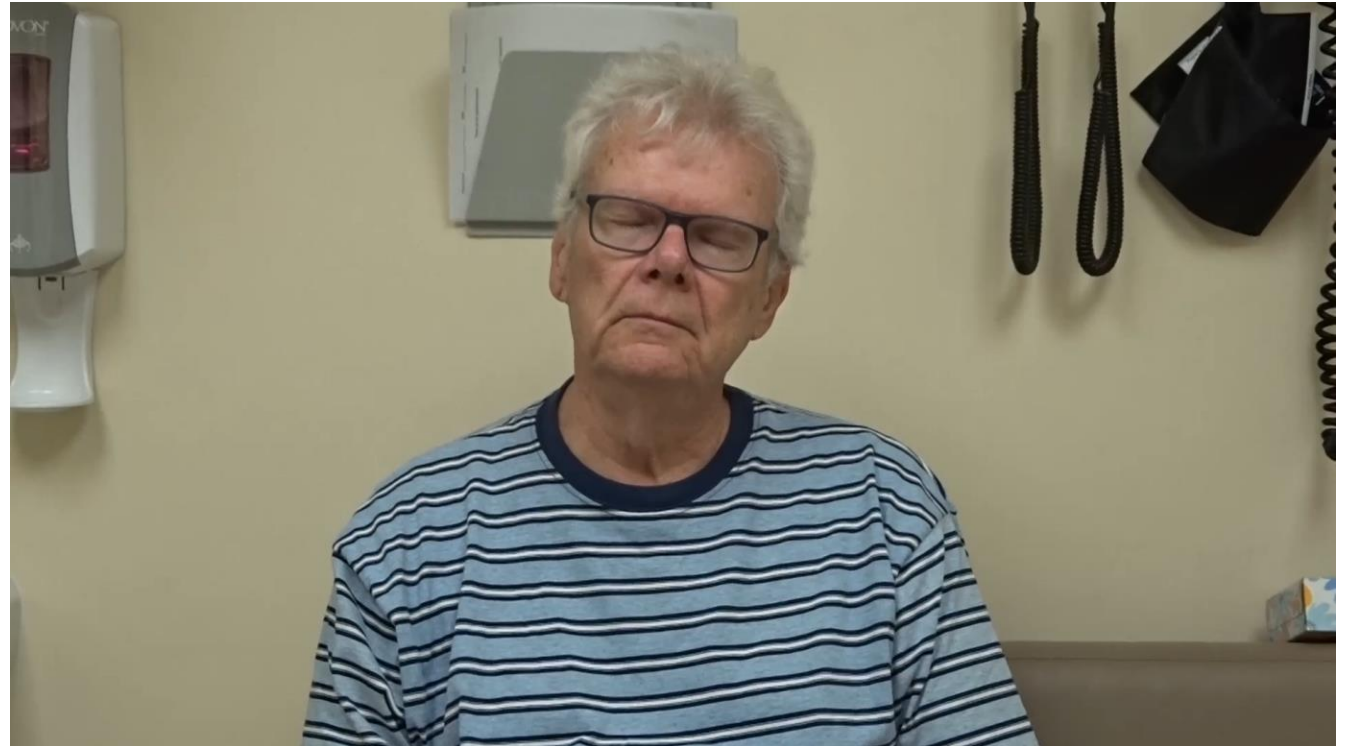


Tardive pain syndrome

- Oral pain syndrome – uncomfortable, burning sensation in the mouth, tongue and lips
- Painful genital syndrome
- Disabling and impairs quality of life
- Associated with other tardive syndromes

Video

- 68 y/o man with orofacial dyskinesia and constant burning sensation in mouth all the time “*like ate hot pizza*”



TD and Oral pain syndrome after treatment with Aripiprazole

Tardive tremor & Parkinsonism

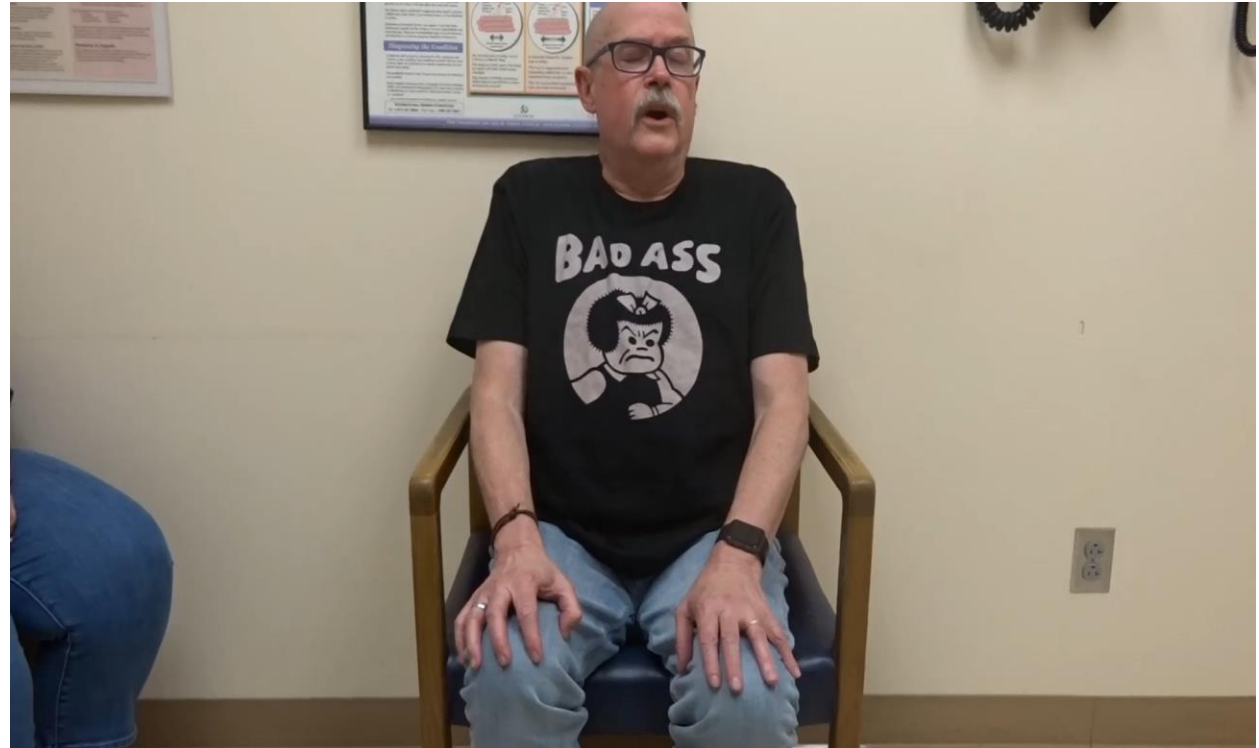
- Few case reports
- Postural and kinetic tremor > rest tremor, no signs of parkinsonism
- Poor response to levodopa
- May improve with dopaminergic blockade or VMAT2 inhibitors

Tardive Parkinsonism

- Parkinsonism features exist after stopping DRBAs

Video case

- 58 y/o man with hx of bipolar dx with bilateral rest and action tremor after treatment with aripiprazole
- DaT scan – negative
- No improvement with levodopa



TD tremor vs drug-induced. Exam on quetiapine 300 mg per day.

Video

- 72 y/o woman with tardive oromandibular dystonia, tardive dyskinesia and tardive tremor from brexpiprazole and aripiprazole
- OSH neurology - HD and paraneoplastic panel negative



Pathophysiology of TS

- Dopamine receptor hypersensitivity
 - Disorder does not resolve after stopping DRBA
 - Post-mortem studies – no significant difference in D2 receptors in TS vs no TS
 - No correlation with in vivo striatal D2 receptor ligand binding on PET scan and severity of TS
- Oxidative stress theory
- Altered NMDA mediated synaptic plasticity leading to abnormal potentiation of neurotransmission
- Dysfunction of GABAergic neurons
- Genetic factors

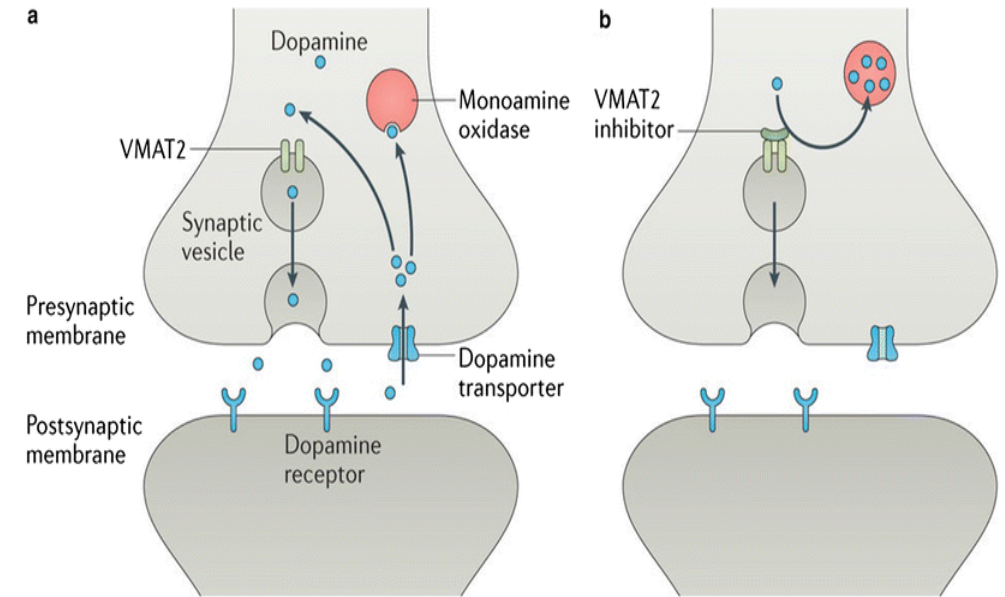
Teo et al, 2012; Mulroy et al 2020

Risk factors

- Older age
- Female > male
- Neuroleptic load and duration of exposure
- Typical Neuroleptics > atypical neuroleptics
- Pre-existing mood disorders
- Cognitive impairment
- Alcohol and substance abuse
- Diabetes
- HIV

Management of TS

- Reduce and slowly discontinue the DRBAs under supervision
- Switch to atypical antipsychotics - quetiapine, clozapine
- VMAT2 inhibitors – first choice
 - **Valbenazine – FDA approved**
 - **Deutetrabenazine – FDA approved**
 - Tetrabenazine – Level C



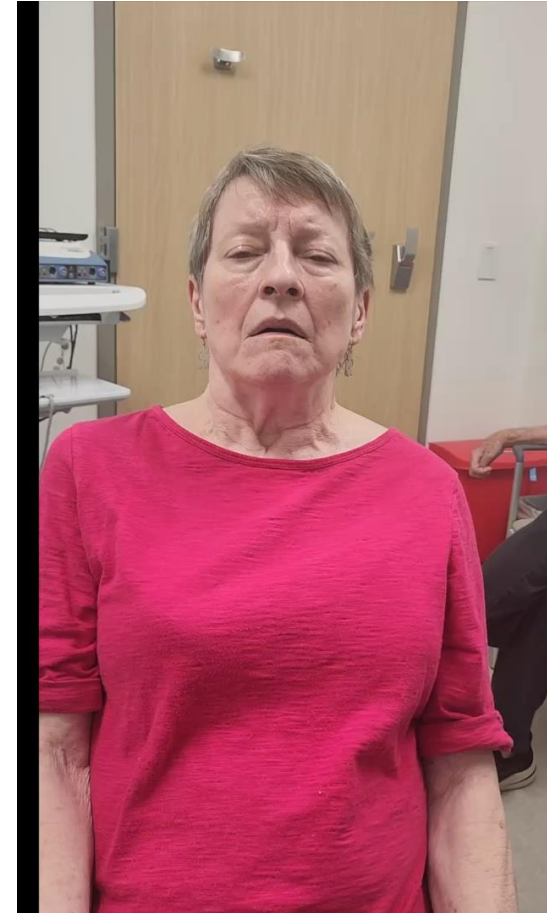
Neimann & Jankovic , Drugs 2018

	Tetrabenazine [21]	Deutetrabenazine [29]	Valbenazine [34]
Study type	Open label trial with blinded video assessments	Double blind placebo controlled trial	Double blind placebo controlled trial
Patients enrolled	20	298	234
Causative agent	Stopped	Stable ^a	Stable ^a
Trial length (weeks)	20	12	6
Dosage (mg)	57.9±22.8	36	80
Mean baseline AIMS	17.9±4.4	10.1±3.2	10.4±3.6
Mean improvement in AIMS on drug	9.7	3.3	3.2
Mean improvement in AIMS on placebo	n/a ^b	1.4	0.1
Adverse effects	Sedation (30%) Parkinsonism (25%) Akathisia (NR) Depression (NR) Suicidality (NR)	Somnolence (2%) Parkinsonism (<1%) Akathisia (<1%) Depression (2%) Suicidality (1%)	Somnolence (5.3%) Parkinsonism (NR) Akathisia (3.3%) Depression (NR) Suicidality (2.6%)

Scorr et al. Journal of Neurological Sciences 2018

Management of TS

- Other medications
 - 2nd tier: Amantadine (level C), clonazepam (level B), ginkgo biloba (Level B)
 - 3rd tier: baclofen, levetiracetam, propranolol
- Botulinum toxin injections for focal tardive dystonia



Management of TS

- Deep brain stimulation – bilateral Gpi DBS
- Good response in Tardive dystonia

Review article

Deep brain stimulation for tardive syndromes: Systematic review and meta-analysis[☆]

Antonella Macerollo^a, Günther Deuschl^{b,c,*}

Journal of Neurological Sciences, 2018

AIMS score improved by 61% and BFMDRS 75%



THANK YOU