

# Tardive Dyskinesia

**Chris Aiken, MD**

Sub-Investigator, High Point Clinical Trials

Director, Mood Treatment Center

President, Forsyth County Psychiatric Association

Instructor, Wake Forest University School of Medicine

November, 2015

# Disclosures

- Sub-Investigator, High Point Clinical Trials
- All treatments for Tardive Dyskinesia that will be discussed are off label

# Objectives

To understand...

1. Risk factors for Tardive Dyskinesia (TD)
2. Diagnosis and presentation of Tardive Dyskinesia
3. Treatment options for Tardive Dyskinesia

# History

# History

- **1900:** TD described by Kraepelin and Bleuler
- **1952:** first antipsychotic chlorpromazine introduced
- **1964:** drug-induced tardive dyskinesia recognized
- **1968:** first high-potency antipsychotic (haloperidol)
- **1970s:** high-dose, high-potency antipsychotics common
- **1982:** tardive dystonia recognized
- **1990:** first atypical, clozapine, released in US  
followed by risperidone in 1994
- **2009:** black-box warning of TD on metoclopramide  
(Reglan)

# Diagnosis



# DSM Criteria for TD

- Involuntary movements of the:  
tongue (e.g., twisting, protrusion),  
jaw (e.g., chewing),  
lips (e.g., smacking, puckering),  
trunk or extremities.
- *Athetoid*: slow, continuous and sinuous
- *Choreiform*: rapid, jerky and non-repetitive
- *Rhythmic*

# DSM Criteria: Timing

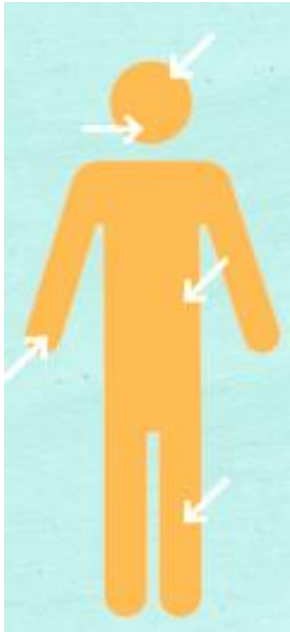
- Onset > 2 month after starting antipsychotic  
*(or 1 mth if over 60)*
- Can also occur within 1 mth of discontinuation  
*(2 mth if d/c of depot)*
- Duration > 1 month



# Characteristics

- Gradual onset, waxing/waning course
- Resolves during sleep
- Worsens with finger-tapping, walking, excitement or anxiety
- Improves during eating, talking, finger to lips

# Location



- **Oral-buccal-lingual:** most common (80%): chewing, lip smacking, lip pursing, sucking, puckering, writhing and coiling of tongue
- **Face:** eye-blinking, head nodding
- **Fingers/toes:** repetitive flex/extend, “piano playing”
- **Trunk:** rhythmic rocking, pelvic thrusting, “belly dancer”
- **Legs:** resembles akathisia
- **Respiratory:** rapid irregular breathing

# Differential Diagnosis

- **Akathisia:** associated with urge to move, but may have tardive onset (which may be permanent)
- **Tics:** preceded by urges, semi-volitional
- **Dystonia:** involuntary, sustained muscle contraction, causing *twisting* or repetitive movements, or abnormal postures. Usually acute but may be tardive.
- **Stereotypies:** purposeless, *complex* actions
- **Denture or dental problems:** volitional
- **Psychogenic:** onset after traumatic event

# Differential Diagnosis

- **Antipsychotic withdrawal dyskinesia:** self-resolving, lasts hours to days
- **Neurologic:** These involve other somatic or cognitive symptoms., e.g. Wilson's, Huntington's, Sydenham's chorea, neuroacanthocytosis, Fahr's syndrome, Hallervorden-Spatz disease
- **Amphetamine or Cocaine abuse/WD:** chorea, dystonia, and stereotyped behavior
- **Rare drug causes of dyskinesia:** dopamine agonists, anticholinergics, antihistaminic, oral contraceptives, chloroquine-antimalarials, tricyclics/SSRIs

# Formal Assessment

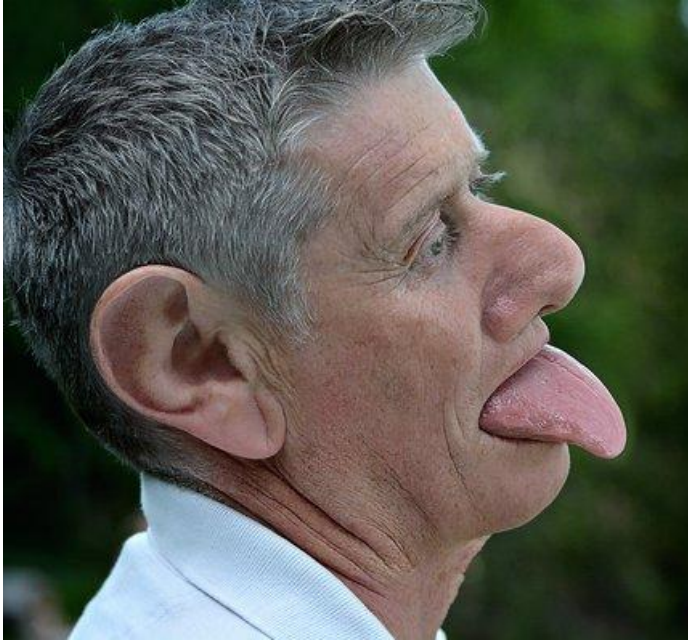
- Recommended every 6 months
- Abnormal Involuntary Movement Scale (AIMS)

# Patient Education

- Helps to identify the syndrome early
- Does not impede adherence

*(Chaplin and Kent, 1998; Chaplin and Timehin, 2002)*

# Impairments



- Shame
- Social stigma
- Gait, handwriting, speech impairment
- Falls
- Dyspnea
- Pain and dental problems
- Awareness is greater in non-schizophrenic patients

# Causes and Risk Factors

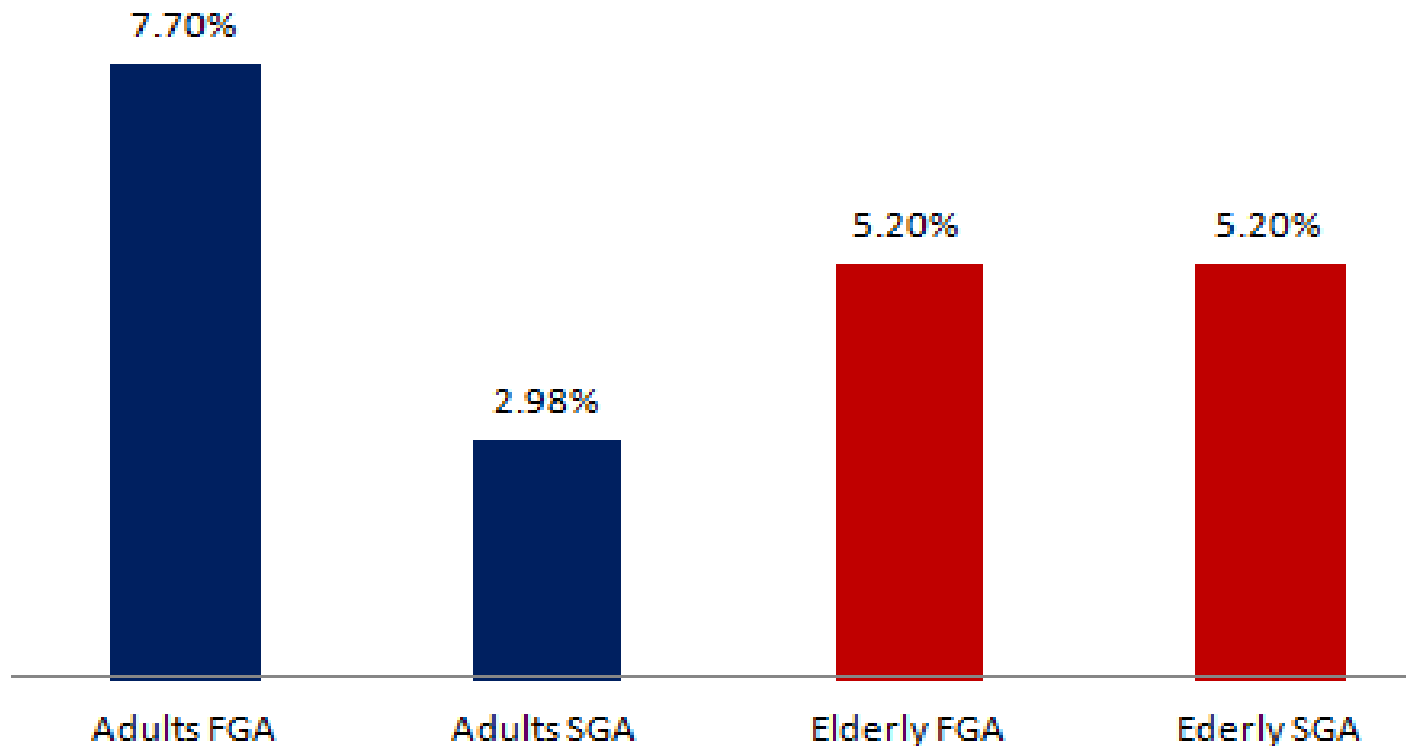


# Risk Factors

- Older age (>50)
- Dementia
- Female gender
- Duration, intensity of antipsychotic treatment
- High potency > low potency > atypical
- Early extrapyramidal symptoms (not hypokinesia)
- Affective disorder
- African descent
- Genetic pre-disposition

# Can Atypicals cause TD?

- Typicals > Atypicals > No antipsychotic in bipolar *Van Russom 2008*
- Annualized rate of TD from 12 trials, n = 28,051:

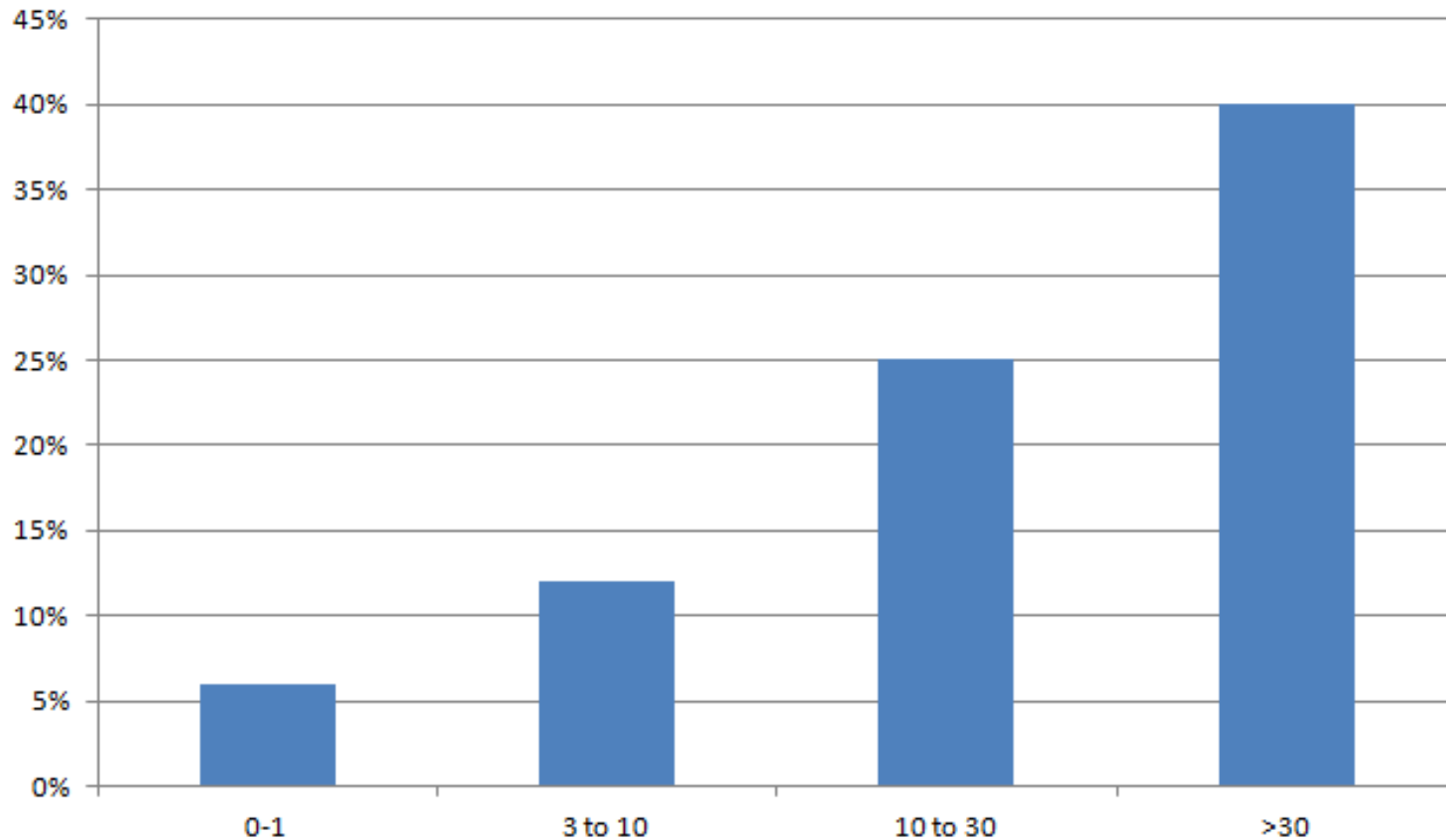


*Correll, 2008*

# Spontaneous Dyskinesias

- Rates from 4-40% in antipsychotic naïve schizophrenia
- Higher rates in first-degree relatives of schizophrenia (2-3x) and in schizotypal disorder
- Worsens with chronicity of illness and intensity of positive symptoms
- Spontaneous dyskinesia *improves* on antipsychotic
- Spontaneous dyskinesias not observed in other disorders

Prevalence of spontaneous dyskinesias increases with duration of illness - towards 40% - in schizophrenia



# Treatment

# Antipsychotic Discontinuation

- Reasonable if diagnosis is not schizophrenia
- May worsen TD initially, but 30-50% improvement over time (uncontrolled data)
- Improvement greatest in those younger than 50 or with short-duration TD
- Dose reduction: 50% improvement (small study)

# Clozapine

- Likely does not cause TD
- Appears to improve TD in open-label data and 12-mth comparison to haloperidol

# Switch to Atypical

- Atypicals have approx ½ the risk of TD vs. typicals
- Switch was beneficial (1 open-label, 2 RCTs)
- Outside of clozapine, no atypical is superior for TD  
*(Caroff 2011, Chan 2010, Woerner 2011)*



# Antioxidants

- Vitamin E 1,200 IU daily: preventative only
- Melatonin 20mg/d (RCT, 12wk, n=7, Castro 2011)
- Vitamin B6 1,200mg daily (small study)
- Ginkgo extract EGb-761 240mg/d, brand = Tebonin (RCT, 12wk, n=157, Zhang 2011)

# N-methyl-D-aspartate antagonist

- NMDA subunits in basal ganglia are altered in TD, NMDA-antagonists reduce neuronal hypersynchrony there and have helped Parkinson's disease
- Amantadine 100mg/d (RCT, n=22, 2wks, Pappa, 2010)
- Levetiracetam 500-2,000mg/d (RCT, n=50, 12wks)

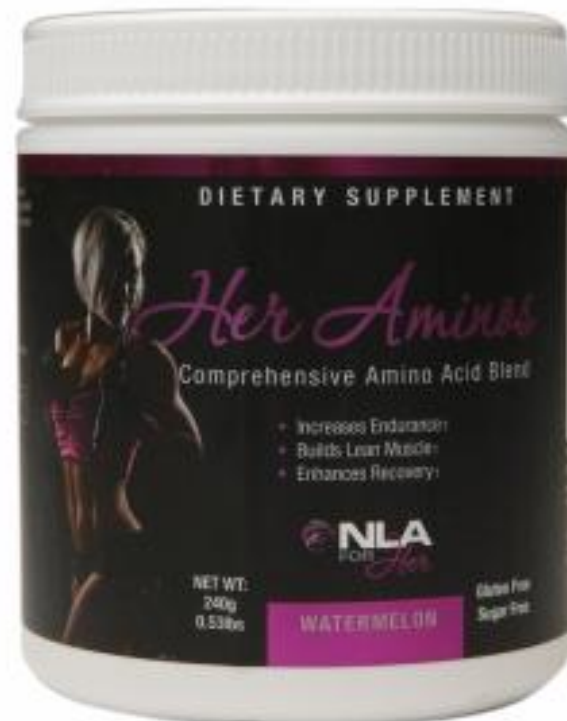
# Tarvil

- Deficient clearance of the large neutral amino acid phenylalanine was associated with tardive dyskinesia
- Treatment with branched-chain amino acids improved TD in men (RCT, n=18, 3wk, Richardson 2003) and children (open label, n=6, 2wk, Richardson 2004)

# Tarvil

- Branched-chain amino acid drink of valine, isoleucine, and leucine (222 mg/kg tid).

<b>Supplement Facts</b>	
Serving Size:	1 Scoop
Servings Per Container:	30
<b>Amino Blend *</b>	<b>5,875 mg*</b>
Taurine	
L-Lysine Mono HCl	
Beta Alanine	
BCAAs (L-Leucine, L-Isoleucine, L-Valine) Branched Chain Amino Acids	
L-Glutamine	
L-Citrulline	
* Daily Value not established.	



# Possibly Effective (case-series)

- Botulinum toxin injection (for tardive dystonia)
- Deep brain stimulation of globus pallidus
- Zonisamide 50-100mg/d (n=7, Lwata 2012)

# Tetrabenazine

- Depletes monoamines (mainly dopamine)  
*presynaptic vesicular monoamine transporter (VMAT2) inhibitor*
- Dopamine receptor blocker (low-affinity, D2)
- FDA approved for dyskinesia in Huntington's Chorea in 2008, but used since 1950s. Currently an orphaned drug.
- Improved TD within weeks (avg dose 57.9 mg/day)  
(case-series, blinded/uncontrolled, n=20, 20wks)
- Side effects: depression 10-15%
- Speculated to improve schizophrenia through action on presynaptic dopamine

# Ineffective Treatments

- Cholinergic drugs (e.g. physostigmine, galantamine)
- Withdrawal of anticholinergics (e.g. benztropine, TCAs)
- Benzodiazepines

# Possibly Harmful to TD

- Anticholinergics (e.g. benztropine / Cogentin)
- Intermittent antipsychotic treatment

(Gaebel, 1994; Goldman and Luchins, 1984; van Harten et al., 1998)



# Kinect:

A Phase-III Clinical Trial for TD

# Kinect

- Phase-III study of Valbenazine involving over 50 centers
- Up to 12-month open label treatment with study drug

# Valbenazine

- Valine ester prodrug of a tetrabenazine isomer
- More stable pharmacokinetics than tetrabenazine (given qd, avoiding on/off phenomena)
- Used in approx 400 subjects
- Most common AE: headache, fatigue

# Results from RCT phase

- 6 week placebo vs. 40mg vs. 80mg
- AIMS: Significant reduction (3.1 points) ( $p < 0.0001$ ).
- Adverse effects: similar in all groups; no safety alerts.

# Inclusion Criteria

- Schizophrenia, Schizoaffective or Mood Disorder with moderate to severe neuroleptic-induced TD
- Psychiatrically stable
- Age 18-85

# Exclusion Criteria

- Taking dopamine-agonist, stimulant, MAOI.
- Benzos and anticholinergics allowed by not PRN. Hypnotics as PRN are allowed.
- Comorbid movement disorder more prominent than TD.
- Substance-use disorder in past 3 months.
- Medical instability in past month.
- History of long QTc-syndrome or NMS.

# Protocol

- Subjects Reimbursed
- Transportation available
- Assessments every 4 weeks (video-recorded AIMS)
- CYP2D6 Profile
- AIMS, CGI-TD, Tardive Dyskinesia Impact Scale (TDIS), Assessment of Most Bothersome Movement in TD (AMBMTD) , Patient Global Impression of Change (PGIC)
- PANSS, MADRS, Calgary Depression Scale for Schizophrenia, Barnes Akathisia Rating Scale (BARS) and Simpson-Angus Scale (SAS), Columbia-Suicide Severity Rating Scale (C-SSRS), Young Mania Rating Scale (YMRS)

# Enrollment Contacts

- (855) 687-4257
- [kinect4study.com](http://kinect4study.com)