Tardive Dyskinesia

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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
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-antimalarial, 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
- Annualized rate of TD from 12 trials, n = 28,051:

Van Russom 2008

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)
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).
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) as a "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