Medication Management for Tics and Tourette Syndrome

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Disclosures
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History

- 1498: Jakob Sprenger and Heinrich Kraemer
  - Described motor and vocal tics in a priest

- 1825: Jean Marc Gaspard Itard
  - Described involuntary movements and coprolalia in Marquise de Dampierre

- 1884: Hughlings Jackson
  - Reported a single case of what would be known as Tourette Disorder

- 1885: Georges Albert Édouard Brutus Gilles de la Tourette
  - Described a condition referred to as ‘maladie des tics’ of childhood onset:
    - Stereotyped, abnormal movements and vocalizations (tics)
    - Coprolalia
    - Echolalia
    - Waxing and waning of symptoms
    - Premorbid sensation
    - Hereditability
History

- 1921: Psychosocial/Psychoanalytic treatments
- 1968: Pharmacological therapy with haloperidol
- 1970: Surgical interventions (thalamotomy)
- 1972: Establishment of Tourette Syndrome Association
- 1974: Habit Reversal therapy
- 1984: FDA approves pimozide (Orap®)
- 2005: Gene and brain changes described
- 2006: Deep Brain Stimulation shows benefit
- 2009: Additional gene mutations reported
- 2010: Comprehensive Behavioral Intervention for Tics (CBIT)

Overview

- Tourette Syndrome affects up to 1% of children
- Additional numbers with various Tic Disorders
- Many adults afflicted
- Neurobiological Disorder
  - Brain circuits: frontal and striatal (limbic?) regions
    - “Movement Disorder”
    - Neurochemical changes: dopamine, serotonin, noradrenaline, neuropeptides
  - Genetic Susceptibilities
  - Possible Acquired Forms

Tourette Syndrome: Diagnosis

- “Mental Health” Diagnosis
  - Four tic disorders are included in the DSM-IV-TR:
    - Tourette Disorder (also called Tourette Syndrome [TS])
    - Chronic motor or vocal tic disorder
    - Transient tic disorder
    - Tic disorder not otherwise specified
  - Diagnosis:
    - Multiple complex motor tics
      - At least one vocal tic
    - Onset prior to 18 years of age
    - Symptoms and signs for at least one year from onset
      - Symptom free intervals of less than three months
      - Not the result of medications or other disorders/illnesses
  - Clinical Presentation:
    - Solely as a movement disorder
    - Complex array of involuntary movements and behavioral/psychiatric issues
Motor and Vocal Tics

- Sudden, rapid, recurrent, non-rhythmic movements or sounds
- Simple involve one group of muscles
  - Rapid: Blinking, shrugging, head jerk, throat clearing, grunting, “sounds/noises” and more
  - Dystonic/tonic: such as shoulder rotation, blepharospasm
- Complex involve several muscles, coordinated movements
  - Bending, gyrate, echolalia, palilalia, coprolalia
- Premonitory sensations

Associated Neurological & Neuropsychiatric Disorders

- 50-90%
  - Attention Deficit Hyperactivity Disorder (ADHD)
  - Obsessive Compulsive Disorder
  - Anxiety
  - Depression
  - Personality disorders
  - Learning disability
  - Executive dysfunction
  - Impulse Control Disorder
  - Anger management
  - Sleep Disorders
  - Mimickers:
    - Seizures
    - Other Movement Disorders
    - Chorea
    - Dystonia, Spasms
    - Benign motor stereotypes
    - Conversion Disorders
    - Allergies
    - Sleep Phenomena

Treatment

- Education and Demystification
  - Patient and Peers
  - Health Optimization
  - Adequate Sleep; Reduce Stress; Healthy Diet; Sufficient Exercise
  - Target causes and mimickers
- Behavioral
  - Comprehensive Behavioral Intervention for Tics (CBIT)
  - Cognitive Behavior Therapy (CBT)
  - Habit Reversal Training (HRT)
  - Exposure-Response Therapy
- Pharmacological
  - Brain Stimulation
  - Deep Brain Stimulation
  - Transcranial Magnetic Stimulation
  - Direct Current Stimulation: anecdotal
  - Neurosurgical: disruption of brain networks
  - Variable results; not well studied; not recommended
Why Use Medications?

- Neurobiological syndrome
- If Tics and/or Co-Morbidities
  - Impair Daily Function
  - Fail to Respond to Non-pharmacological therapies
  - Cause Pain
  - Create Impairments of Social Development/Interaction

Medications Can:
- Facilitate multimodal therapies
- Maximize cognitive potential
- Maximize functional potential
- Improve quality of life

Medication Treatments are:
- Adjunctive
- Not curative

Neurochemistry 101

- Synapse
  - Presynaptic Axons
  - Postsynaptic Dendrites
- Neurotransmitters
  - Amino Acids
    - Aspartate
    - Glutamate
    - GABA
    - Glycine
  - Monoamines
    - Dopamine
    - Norepinephrine
    - Serotonin (5-HT)
    - Histamine
  - Other
    - Acetylcholine
    - Nitric Oxide
    - Carbon Monoxide
    - Substance P

Crystallization and polarized light: photomicrography
How Do Central Nervous System (CNS) Drugs Work?

- Neurotransmitters
  - Change neurotransmitter “balance”
  - Enhance availability
  - Reuptake inhibitors
  - Stimulate release
  - Mimic transmitter
  - Stimulate postsynaptic receptor
  - Decrease availability
  - Receptor blockade
  - Depleting agents

How Do CNS Drugs Work?

- Modulate Neuronal Communication/Circuits
  - Decrease Neuronal Excitability
    - Modulate electrolyte channels
    - sodium, chloride, calcium, potassium
    - Antagonism of excitatory neurotransmitters
    - Potentiate inhibitory neurotransmitters
  - “Neuroprotection”

Rational Drug Therapy

- Baseline Testing/Evaluation
  - Use proper titration rate
  - Start low, go slow
  - Direct titration vs. cross taper vs. re-establish new baseline
  - Ensure adequate dose
  - Target: minimum effective dose
  - Rational dosing
  - Ensure adequate duration of medication trial
  - 2-4 weeks for neuroleptics, AEDs, SNRIs/SSRIs
  - If partial response, allow for longer duration of observation
  - Evaluate for compliance/side effects
  - Utilize blood levels if applicable
  - Assess for atypical responses
  - Monitor for side effects
  - Physical/neurological examination
  - Laboratory testing
  - Ensure proper diagnosis
  - Determine if there are co-morbid diagnoses
  - Evaluate whether proper therapeutic targets have been chosen

- Evaluate for underlying systemic triggers
  - Pain
  - Allergies
  - Underlying medical condition
  - Maximize non-pharmacological interventions
  - Secure objective or quantitative outcome measures
  - Avoid polypharmacy
  - If necessary, utilize it rationally with compatible drugs
  - Periodic review of regimen
  - Consider medication reversals
  - Tapering/discontinuing medication to see if it is still exerting a benefit, while monitoring behavior for stability or worsening
  - Drug Holidays
  - In select situations
  - Ensure experienced/qualified prescriber
Rational Drug Therapy

- Use Objective Assessment and Outcome Measures
- Treating the Patient versus the Parent/Caretaker/Staff/Teacher
- Need for Clinical/Biological Profiling
- Need to look at the brain
- Tourette Syndrome, ADHD, OCD
  - Not medication deficiency syndromes
  - Many performance enhancing drugs
- Avoid blunting creativity
- Enhance function/productivity

Concerns About Medications

- Side effects
  - Short-term
  - Long-term
- Little data in children
  - “off label”
- Fear
  - “Addictions”
  - Dependence
- Aura of “natural” approaches
- Lack of “cure”

Medications: Usual Suspects

- Metabolic changes
  - Weight gain/loss
- Risk of movement disorders
- Organ toxicities
  - Allergic reactions
  - Idiosyncratic
  - Dose related
    - Cardiac
    - Liver/Spleen
    - Bone Marrow
- Adverse behavioral reactions
  - Abnormal responses
  - Induction of mania
  - “Suicidality”
- Cognitive effects
  - Sedation
- Sleep Disruption
- Narrow therapeutic window
- Lack of friendly dosage forms
- May not target comorbid disorders
- Monitoring needs
- Paucity of controlled trials
- Lack of pediatric safety data/indications
- Pediatric pharmacokinetics
  - Faster absorption
  - Lower protein binding
  - Higher metabolic rates
  - Higher clearance
Baseline Testing

- Clinical Phenotyping/Profiling
  - Neurological/Neuropsychiatric Assessment
  - Clinical Examination
  - Neuropsychological Testing
  - Medical Testing
  - Neuropsychological evaluation
  - Functional Behavioral Analysis

- Cardiology Testing
  - Electrocardiogram

- Laboratory parameters
  - Routine
  - Diagnostic
  - Pharmacogenomic Profiling
    - Presently 14 relevant genes for psychotropics
    - Code for Drug Metabolism, Transport and Receptors
    - Pharmacokinetic availability
    - Pharmacodynamic effects
    - Avoid or minimize side effects

Which Drug to Choose?

- Sources of evidence
  - Clinical Trials
    - Phase II/III
    - Double Blind/Placebo Controlled
    - Comparator Studies
    - Open Label
    - Single Subject
  - Medical Literature
    - Published Studies
      - Retrospective
      - Population studies
      - Prospective: open label and controlled
    - Case Reports
    - Clinical Experience
      - Peer Experience
    - “Off Label” reports
    - Parental Impressions
    - Testimonials
    - Anecdotal
    - Media and Internet Influences

- Safety
  - Low Toxicity
  - Pediatric Data
  - Monitoring Considerations
  - Paradoxical Considerations
  - Idiosyncratic vs. Dose Dependent Side Effects

- Efficacy
  - Treatment Targets
  - Evidence-basis

- Compatibility
  - Polypharmacy regimens

- Generics versus Brand
  - Contents/Formulations
  - Switching
FDA and TS

- FDA Approved Medications for TS:
  - Pimozide (Orap®)
  - Haloperidol (Haldol®)

- Clinical Trials for Pediatric Neurobehavioral/Neuropsychiatric Disorders
  - Poorly designed studies
  - Heterogeneous cohorts
  - Lack of functional behavior analysis
  - Subjective outcome endpoints
  - Lack of biomarkers
  - Lack of head-to-head studies

Medications: Tics

First Tier
- Alpha-2 adrenergic agonists (guanfacine, clonidine)
  - Activate inhibitory neurons
  - Reduce sympathetic outflow

Second Tier
- Neuroleptics (Post-Synaptic Dopamine and Serotonin Receptor Blockers)
  - Typical (Non-selective D2/D3): Haloperidol, pimozide, fluphenazine, trifluoperazine
  - Atypical
    - Selective D2 and 5-HT1 Receptor Antagonists: risperidone, ziprasidone, olanzapine
    - Aripiprazole
      - Partial D2 and 5HT2A receptor agonist, 5HT2A antagonist, Alpha blocking
      - Multiple neurotransmitter antagonism: quetiapine, paliperidone
    - Weak D2/D3, Strong D4: clozapine

Other Considerations for Second or Third Tier
- Antiepileptic Drugs (levetiracetam, topiramate)
- Dopamine Depleters (tetrabenazine)
- Benzodiazepines (clonazepam, others)
  - Facilitate GABA and other inhibitory neurotransmitters
- Chemodenervation: botulinum toxin
- Dopamine Agonists (ropinirole)
  - Hypothesized to reduce dopamine receptor supersensitivity
**Alpha-2 Adrenergic Agonists**

- **Catapres®**, Kapvay®, Tenex®, Intuniv®
- **Mode of action**: alpha-2 adrenergic receptor agonists
- **Indication**: Tics (mild to moderate), ADHD
- **Adverse effects**: Sedation, dizziness, fatigue, hypotension, irritability, rebound hypertension
- **Extended Release Forms Available**

**Typical Neuroleptics**

- Haldol®, Orap®, Prolixin®, Stelazine®
- **Mode of Action**: Dopamine D₂ receptor antagonists
- **Indication**: Tics (moderate to severe)
- **Usage**: Second-line treatment in patients who do not respond to alpha-2-adrenergic agonists; haloperidol and pimozide are both FDA-approved for Tourette Syndrome
- **Adverse Effects**: Sedation, weight gain, muscle stiffness, dystonia, tremor, akathisia, tardive dyskinesia, parkinsonism, cognitive impairment, school phobia, cardiac conduction problems (most likely with pimozide), hyperprolactinemia, diabetes

**Atypical Neuroleptics**

- Abilify®, Risperdal®, Geodon®, Zyprexa®, Seroquel®, Clozaril®, Invega®
- **Indication**: Tics (moderate to severe)
- **Usage**: Second-line treatment in patients who do not respond to alpha-adrenergic agonists: preferred over typical antipsychotics owing to a reduced risk of neurological and systemic adverse effects
- **Adverse Effects**: Sedation, weight gain, akathisia, tardive dyskinesia, school phobia, hyperprolactinemia, diabetes
Antiepileptic Drugs

- **Topamax®, Keppra®**
- **Mode of Action**: Not Known for Tics
- **Indication**: Tics (moderate)
- **Usage**: Favorable side effect profiles; Not well-studied for tics, but available data are promising
- **Adverse Effects**: Cognitive and/or language problems, sedation, allergic reactions

Dopamine Depleters

- **Xenazine®**
- **Mode of Action**: Dopamine-depleting agent
- **Indication**: Tics (moderate to severe)
- **Usage**: Third-line treatment; Not well-studied in Tourette Syndrome
- **Adverse Effects**: Sedation, depression, parkinsonism and akathisia

Botulinum Toxin

- **Botox®**
- **Mode of Action**: Blocks acetylcholine release at neuromuscular junctions: muscle paralyzation
- **Indication**: Tics (disabling and/or bothersome motor or vocal tics, especially of the eyelids and neck)
- **Usage**: Localized injections into muscles
- **Adverse Effects**: Weakness, motor restlessness, blurry vision, hypophonia, hoarseness, dysphagia and aspiration
Medications for Associated Disorders

- Psychostimulants
- Alpha-2 Adrenergic Agonists
- Benzodiazepines
- Selective Norepinephrine Reuptake Inhibitors (SNRI)
- Selective Serotonin Reuptake Inhibitors (SSRI)

Atomoxetine

- **Strattera®**
- **Mode of Action:** SNRI
- **Indication:** Tics and ADHD; does not exacerbate tics
- **Usage:** ADHD
- **Adverse Effects:** Sedation, irritability, abdominal discomfort, suicidality

Benzodiazepines

- **Klonopin®, Tranxene®, Valium®**
- **Mode of Action:** GABA_A receptor modulators
- **Indication:** Anxiety; muscle relaxation
- **Usage:** Co-existing anxiety; muscle relaxation
- **Adverse Effects:** Fatigue, irritability, dizziness: abrupt withdrawal can lead to increased anxiety
Psychostimulant Drugs

- Methylphenidates: Ritalin/SR®, Concerta®, Focalin/XR®, Metadate CD/ER®, Methylin/ER®, Quillivant XR®, Daytrana®
- Mixed Amphetamine Salts: Adderall/XR®, Vyvanse®
- Mode of Action: Dopamine and norepinephrine reuptake inhibitors
- Indication: ADHD
- Usage: Effective for ADHD; Methylphenidate has been studied in combination with either clonidine or guanfacine
- Adverse Effects: Decreased appetite, insomnia, irritability and increased tics, “Performance Enhancing Drugs”

SSRI

- Prozac®, Zoloft®, Celexa®, Lexapro®, Luvox®, Paxil®
- Mode of Action: Selective serotonin reuptake inhibitors
- Indication: OCD, anxiety and depression
- Usage: Varying levels of positive effects
- Adverse Effects: Behavioral activation (hypomania), insomnia, suicidality, risk of interactions with other drugs

“NATURAL” THERAPIES

- Quality Control
- Purity
- Active Ingredient
- Many Toxins Are “Natural”
- High Doses Can Become Toxic
- “Aura” Of Food Supplements
- Seduction
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**Responses to Medications**

- Effective therapies are delayed
- Deplete/divert financial, research and psychosocial resources
- It’s sounds too good to be true, it probably is!
- Usually promoted outside scientific circles
- Internet; Popular, non-peer reviewed books; Support groups
- Can be dangerous and harmful!
- Take Data!

**Unproven “Fad” Therapies**

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**Criteria for Use**

- Safety
- No known toxicities
- Dosage data
- Efficacy
- Evidence-based
- Avoid anecdotal/hypothetical
- Avoid testimonials
- Sustainability and generalization of response
- Scientific sense
- What is the hypothetical, theoretical or scientific basis?
- Cost not prohibitive
- “Is balanced diet good, but elective supplementation is most likely to produce expansion ultra”

**Response to medications should not be used to make a diagnosis**

**Avoid Testimonials/Anecdotal Data**

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**Use rational approaches for medication management**

- When indicated or necessary, medications are part of a total treatment package
- Medications can be useful if:
  - Indicated
  - Tolerated
  - Risks versus benefits are understood
  - Pre-treatment and ongoing clinical and laboratory monitoring is utilized
- Re-evaluate periodically
- Medication Reversals
- Medication and other treatments should be personalized/individualized
- Medications do not work for everyone
- Highly effective therapies are still lacking for many patients

**Conclusions**

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