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CNNHSM
The Center for Neurological and
Neurodevelopmental Health

Medication Management for Tics and Tourette Syndrome

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President, CEO & Founder

Sponsored by: New Jersey Center for Tourette Syndrome and Associated Disorders

May 8, 2013

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Disclosures April 2012-May 2013

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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
 - Premonitory sensation
 - Heritability


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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)


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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



IT'S HARD TO BELIEVE,
BUT HE'S FATHERED
THREE HYPERACTIVE
CHILDREN.


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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


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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

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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
 - Rage
- Sleep Disorders
- Mimickers:
 - Seizures
 - Other Movement Disorders
 - Chorea
 - Dystonia, Spasms
 - Benign motor stereotypies
 - Conversion Disorders
 - Allergies
 - Sleep Phenomena
 - Movement Disorders resolve with sleep


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Treatments


- 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


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 **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

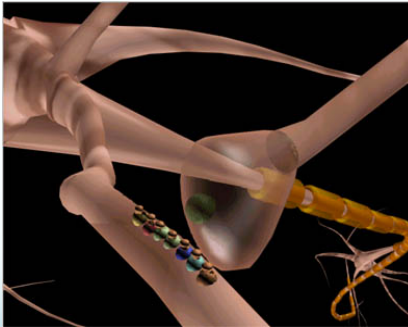



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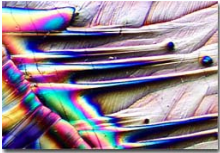
 **Neurochemistry 101**

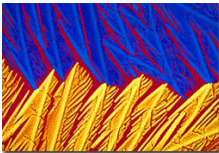
- Synapse
 - Presynaptic Axons
 - Postsynaptic Dendrites
- Neurotransmitters
 - Amino Acids
 - Aspartate
 - Glutamate
 - GABA
 - Glycine
 - Monoamines
 - Dopamine
 - Norepinephrine
 - Serotonin (5-HT)
 - Histamine
 - Other
 - Acetylcholine
 - Nitric Oxide
 - Carbon Monoxide
 - Substance P

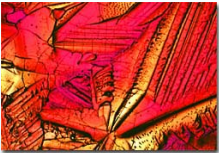


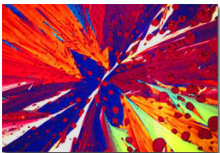
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norepinephrine



acetylcholine


serotonin


dopamine


Crystallization and polarized light: photomicrography


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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




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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”


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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
 - 2-8 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


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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


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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"




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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
 - Atypical 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




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Baseline Testing

- Clinical Phenotyping/Profiling
 - Neurological/Neuropsychiatric Assessment
 - Clinical Examination
 - Neurodiagnostic 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


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Which Drug to Choose?

- Sources of evidence
 - Clinical Trials
 - Phase III/IV
 - 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


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Which Drug to Choose?

- 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


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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


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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/D₁): Haloperidol, pimozide, fluphenazine, trifluoperazine
 - Atypical
 - Selective D₂ and 5-HT_{2A} (serotonin) Receptor Antagonists: risperidone, ziprasidone, olanzapine
 - Aripiprazole
 - Partial D₂ and 5HT_{2A} receptor agonist, 5HT_{2A} antagonist, Alpha blocking
 - Multiple neurotransmitter antagonism: quetiapine, paliperidone
 - Weak D₂/D₁, Strong D₄: clozapine


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Medications: Tics

- 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


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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**


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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


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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


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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


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Dopamine Depletors

- **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


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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


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Medications for Associated Disorders

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


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Atomoxetine

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


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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

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 **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”

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 **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


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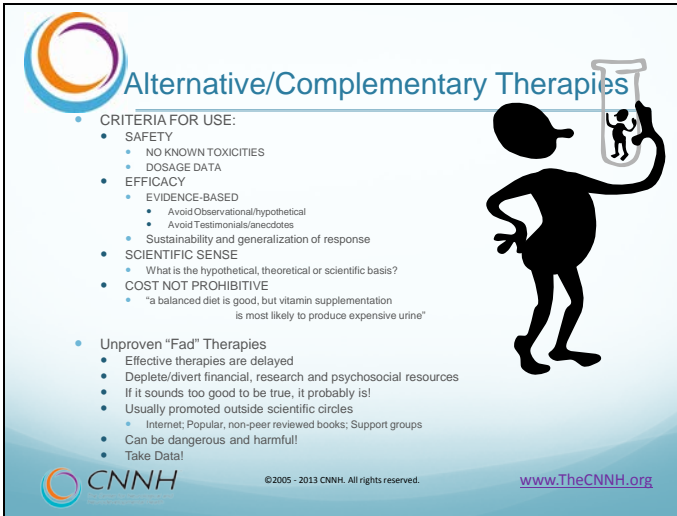
 **“NATURAL” THERAPIES**

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



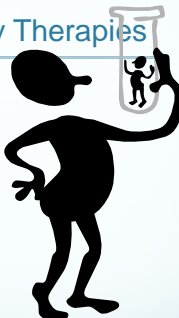
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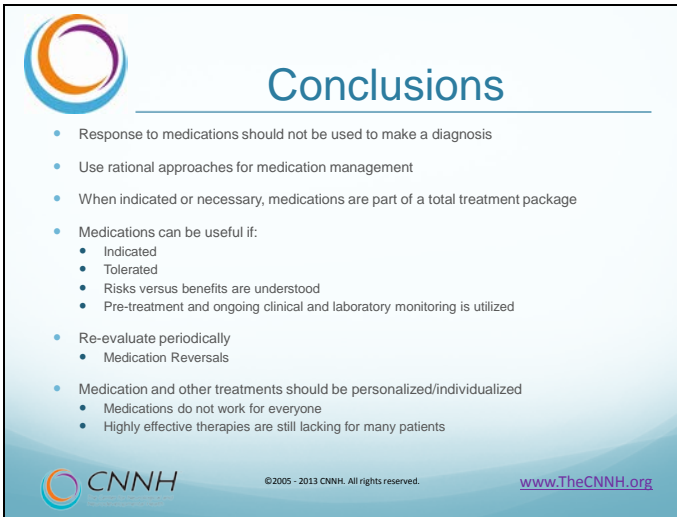
Alternative/Complementary Therapies

- CRITERIA FOR USE:
 - SAFETY
 - NO KNOWN TOXICITIES
 - DOSAGE DATA
 - EFFICACY
 - EVIDENCE-BASED
 - Avoid Observational/hypothetical
 - Avoid Testimonials/anecdotes
 - Sustainability and generalization of response
 - SCIENTIFIC SENSE
 - What is the hypothetical, theoretical or scientific basis?
 - COST NOT PROHIBITIVE
 - "a balanced diet is good, but vitamin supplementation is most likely to produce expensive urine"
- Unproven "Fad" Therapies
 - Effective therapies are delayed
 - Deplete/divert financial, research and psychosocial resources
 - If it 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!




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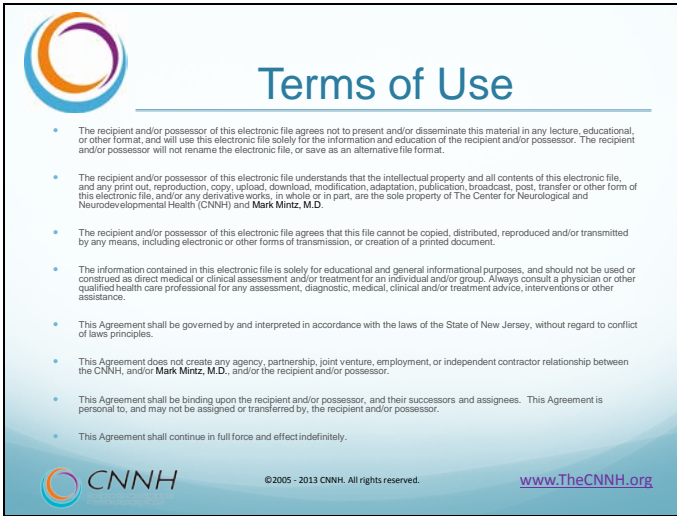


Conclusions

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


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