Disorders of tone: why do they matter and what to do about them?

Nathan Rosenberg, MD
Physical Medicine and Rehabilitation
Nationwide Children's Hospital
The Ohio State University

Laurie Glader, MD, FAAP
Section Chief, Division of Complex Care
Medical Director, Comprehensive Cerebral Palsy Program
Nationwide Children's Hospital
Professor, The Ohio State University

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Northwestern Medicine
Feinberg School of Medicine

C6 Seminar Series

Presenter Disclosure

- **Presenter:** Laurie Glader
- **Relationships with commercial interests:**

  Royalties: MacKeith Press, UpToDate

  Advisory Boards: Cerebral Palsy Foundation, Cerebral Palsy Research Network

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Accreditation

Accreditation Statement

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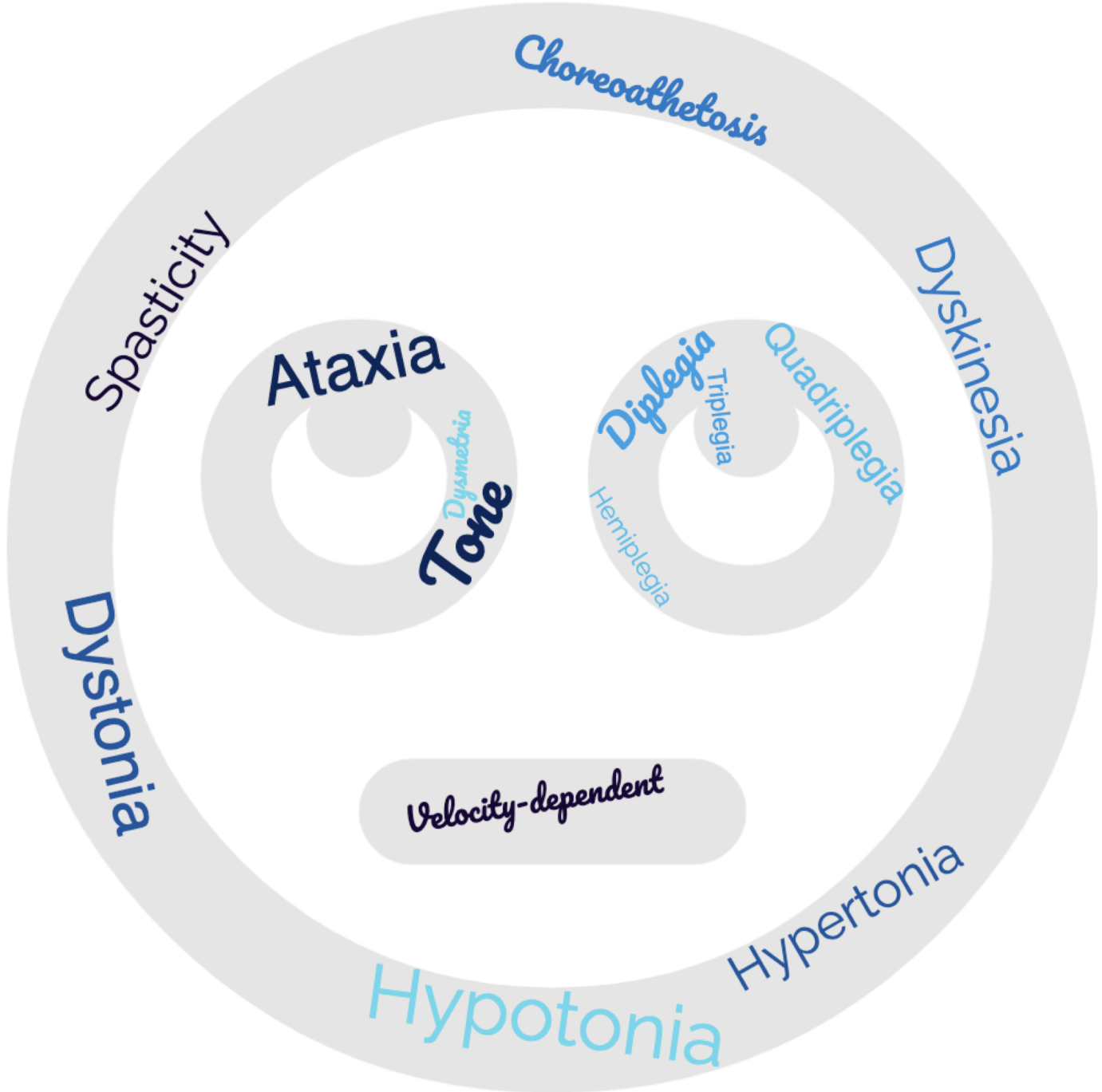
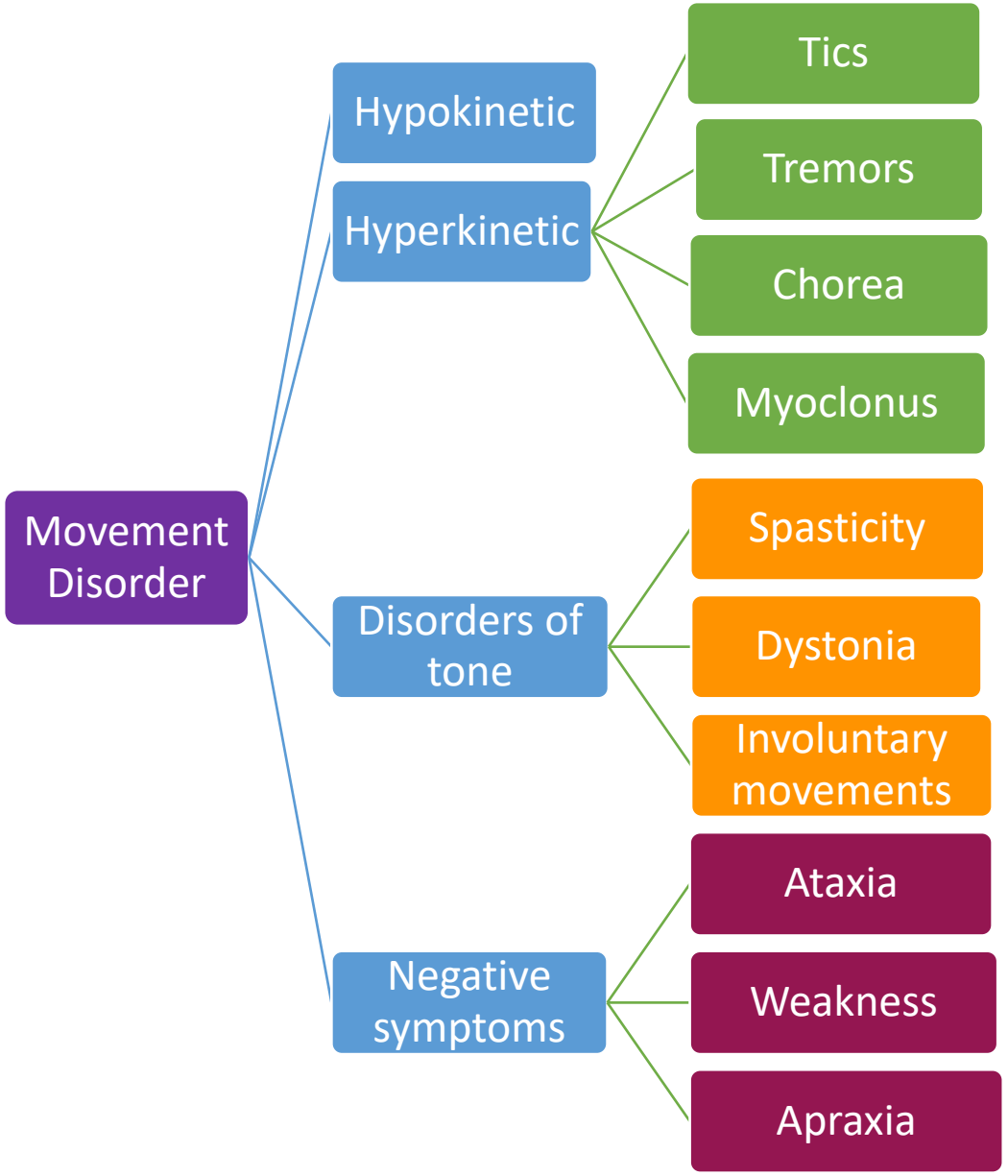
Disorders of tone: agenda

- Types of abnormal tone
- The International Classification of Functioning, Disability and Health
- Management options
- Putting it all together

Introduction to tone


Choreoathetosis
Dyskinesia
Hypertonia
Hypotonia
Dystonia
Spasticity
Velocity-dependent
Ataxia
Tone
Dysmetria
Diplegia
Triplegia
Quadriplegia
Hemiplegia

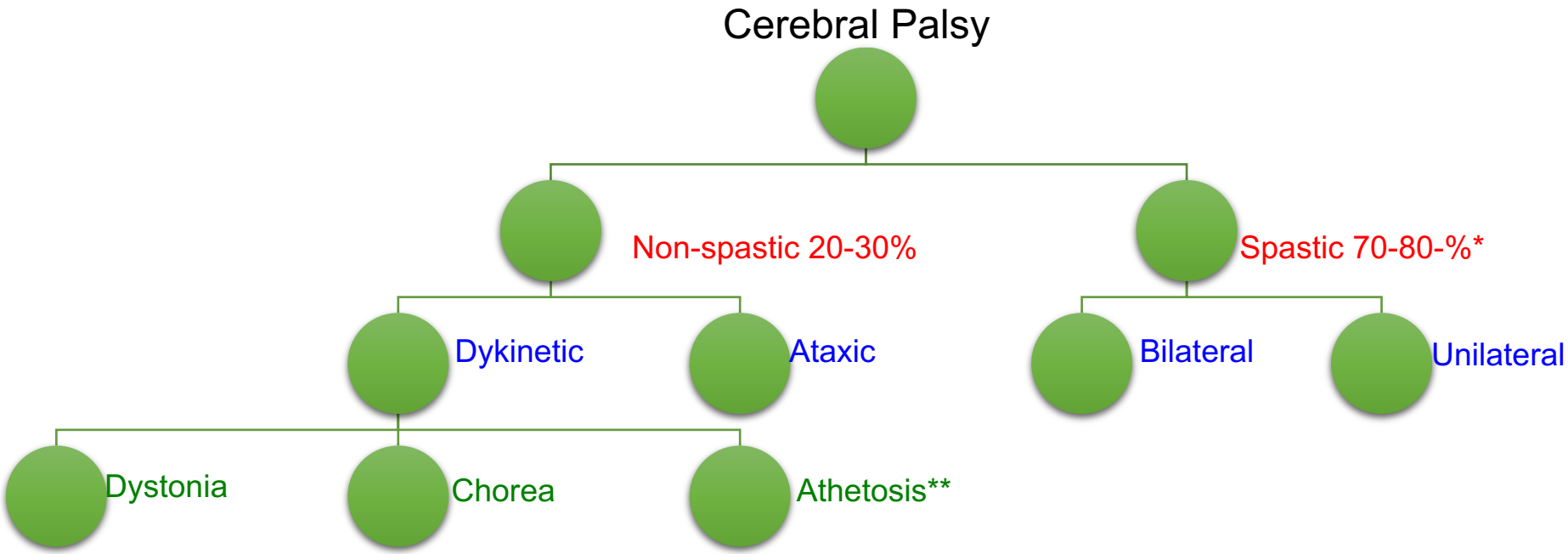


Other important considerations:

- Genetic v. structural etiology
- Static v. progressive
- Grey v. white matter

Adapted from Tilton, 2020

Cerebral palsy by motor type



*Topographic description: diplegia, hemiplegia, quadriplegia…

**There are mixed types of CP: spastic athetoid, choeroathetotic, etc.

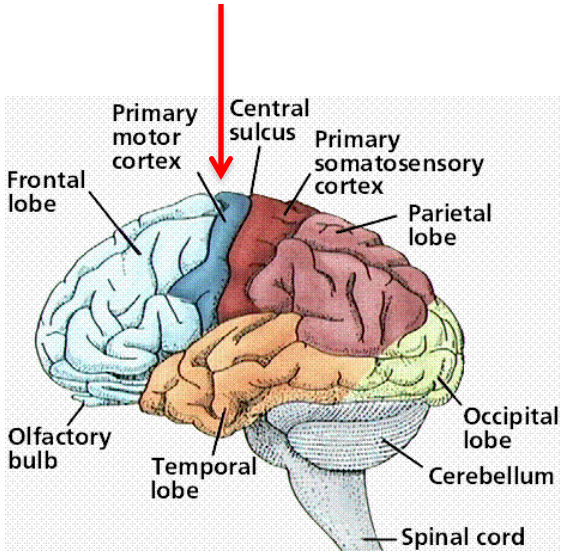
Spasticity

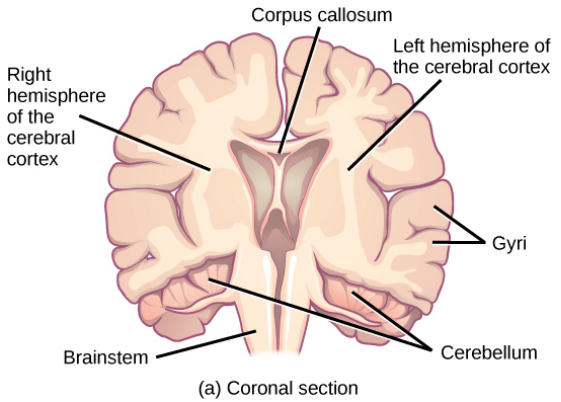
- Injury to the motor cortex
  - Imbalance between excitatory and inhibitory reflexes resulting in hypertonia
  - Velocity dependent resistance to stretch
  - Topographic distribution (bilateral, unilateral)
  - Affects flexors, adductors, internal rotators

- Upper motor neuron "classic triad" in the setting of spasticity
  - Brisk deep tendon reflexes
  - Clonus
  - Persistent primitive reflexes
    - Up-going toes (positive Babinski)

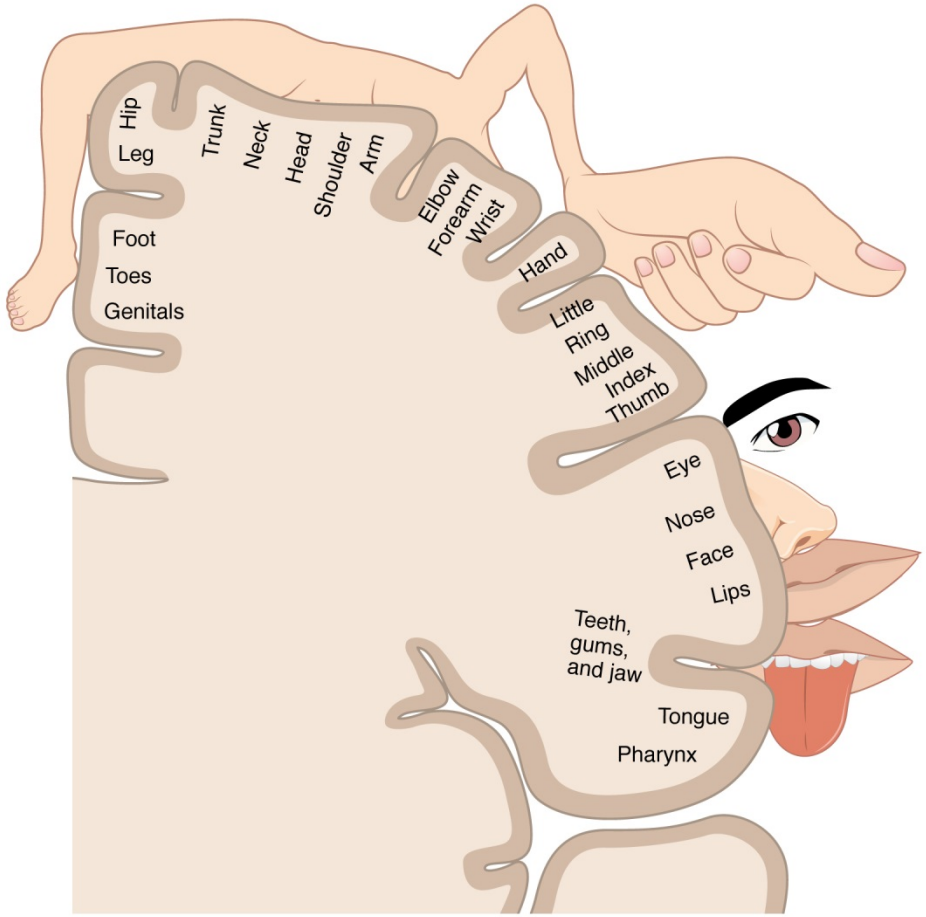
- Other exam features
  - Pathologic reflexes
  - Absent/abnormal protective reflexes
  - Delay in motor development

The Motor Cortex

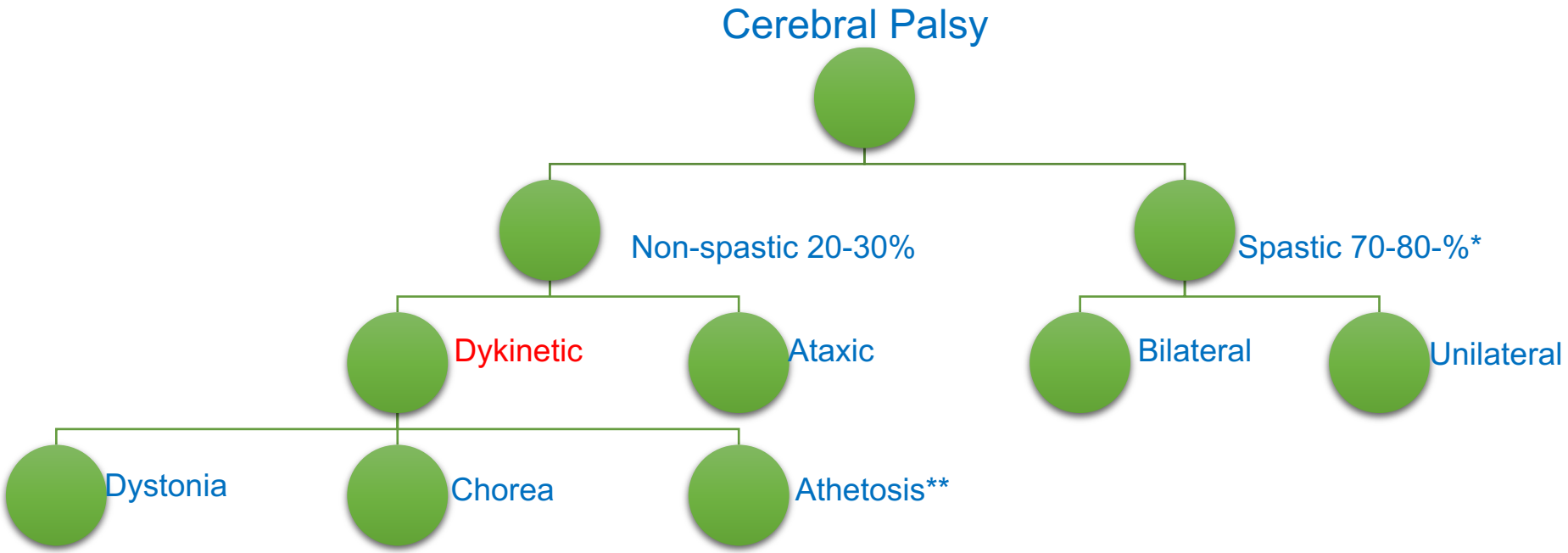




(a) Coronal section



Cerebral palsy by motor type



*Topographic description: diplegia, hemiplegia, quadriplegia…

**There are mixed types of CP: spastic athetoid, choeroathetotic, etc.

Dyskinesias

- Involuntary movement
- Injury to the basal ganglia
- No topographic distribution

    Dystonia

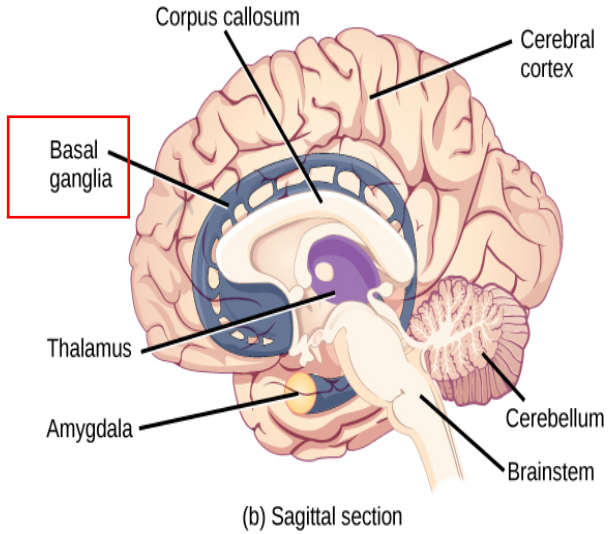
        Slow, repetitive movements and/or abnormal postures

    Chorea

        Brief, irregular contractions, not rhythmic or smooth

    Athetosis

        Twisting, writhing



(b) Sagittal section

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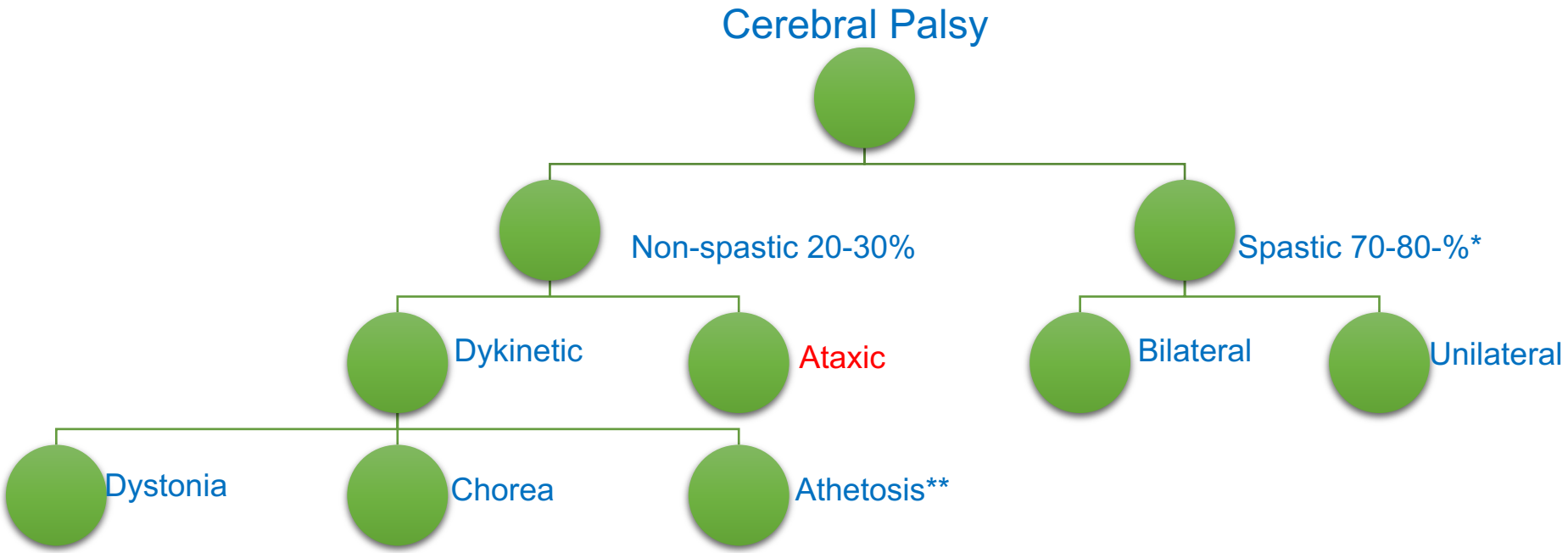

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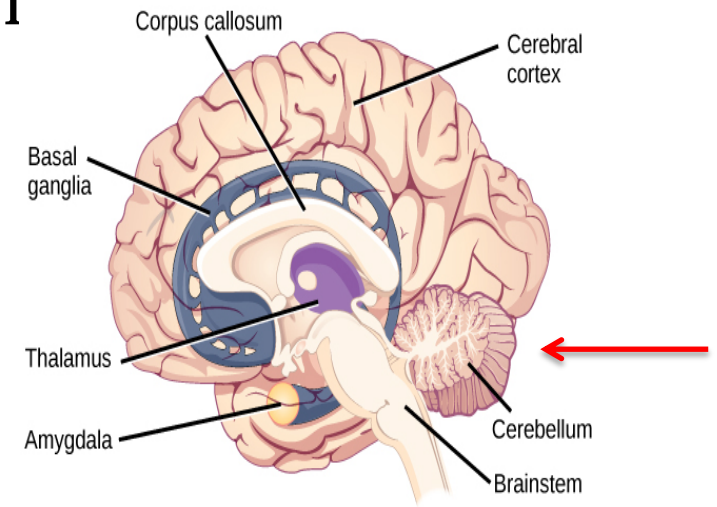
Ataxia

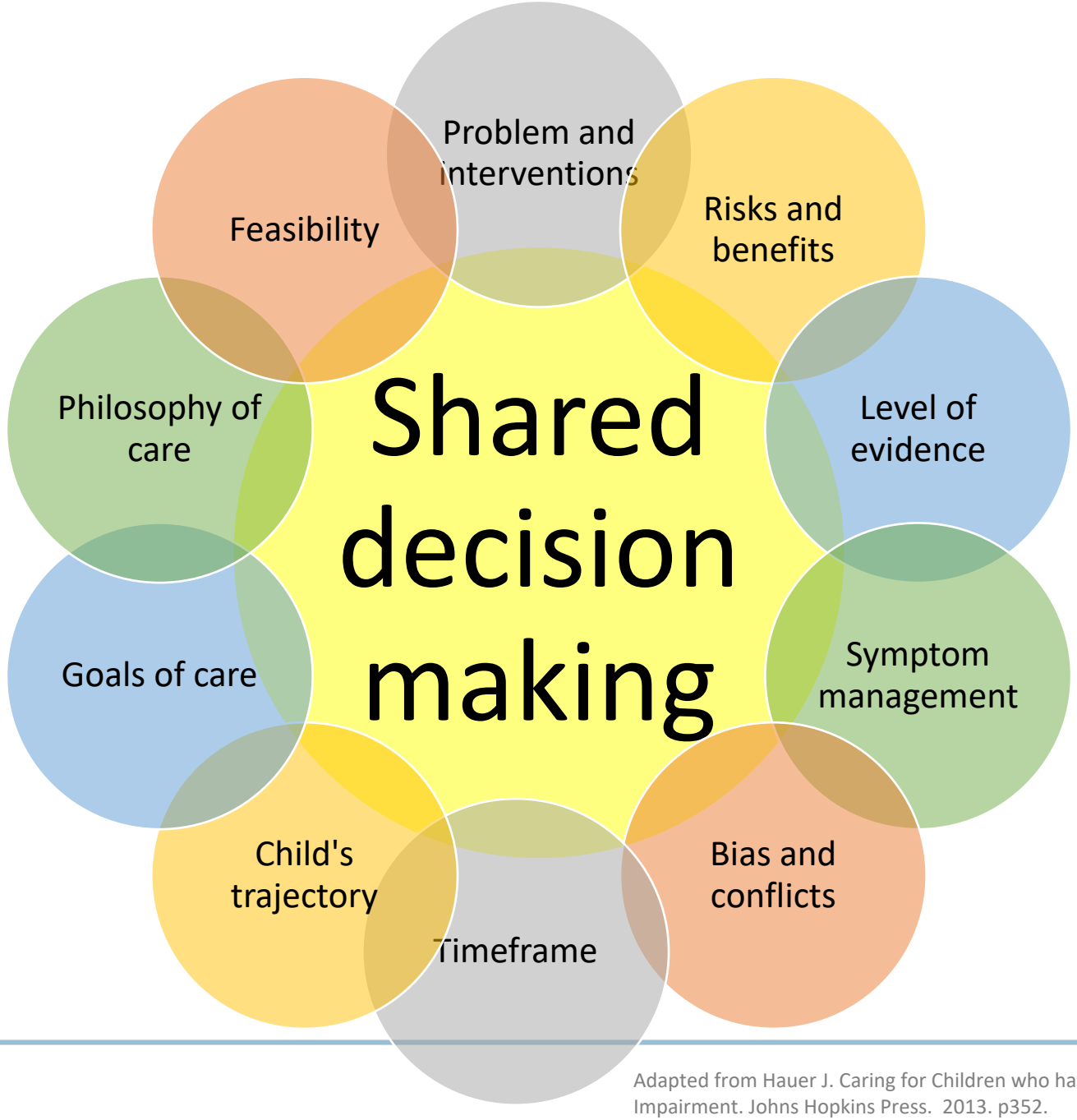
- Impacts coordination and balance
- May be associated with cerebellar abnormalities
- Often associated with h[illegible] and dysmetria



(b) Sagittal section

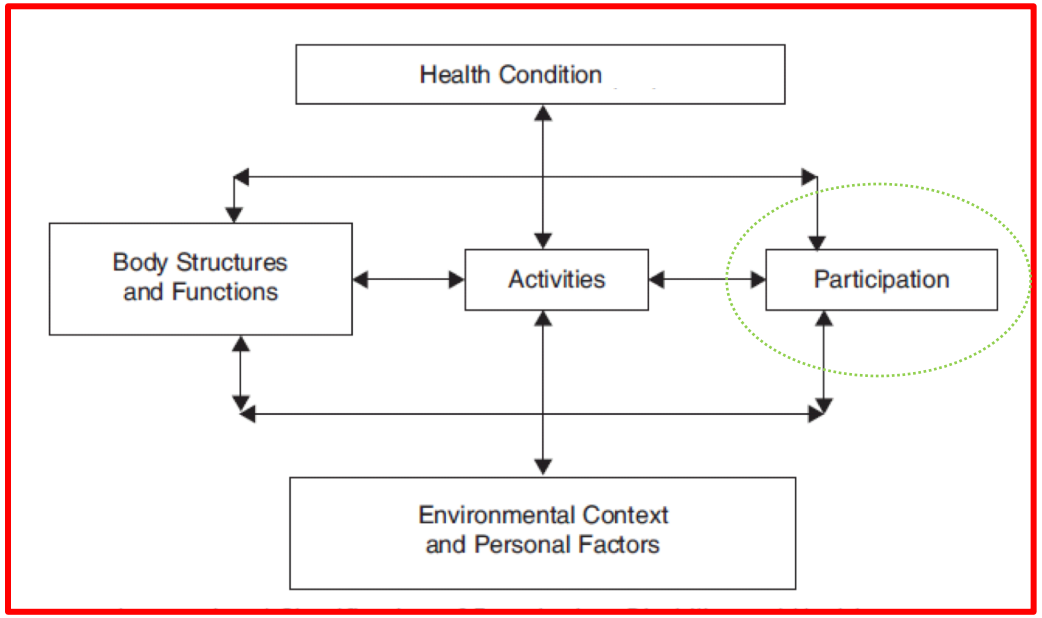
Treatment goals

Functional improvement



Adapted from Hauer J. Caring for Children who have Severe Neurologic Impairment. Johns Hopkins Press. 2013. p352.

International Classification of Function, Disability and Health (ICF)



World Health Organization 2001. The International Classification of Functioning, Disability and Health (ICF). Geneva: WHO. http://www.who.int/classifications/icf/en/

“Through participation we acquire skills and competencies, connect with others and our communities, and find purpose and meaning in life.”

Law, Am J Occup Ther (2002)

Seminar Series

Tools in the toolbox

- Stretching
- Medications to be given by mouth or tube
- Injections
- Implantable devices and surgeries

Before we talk about the tools

- <u>Efficacy is variable and unpredictable</u>
- It's important to say that to patients and families
- Malnutrition, infection, GI distress and sleep deprivation frequently worsen tone. If these problems are chronic, consider treating them first

Stretching

- More than just for range of motion maintenance
- Could reduce spasticity for a period of time -- 30-60 minutes?
- Useful prior to activities such as bathing or dressing

Baclofen – Spasticity, dystonia

- FDA approved for 12 and older
- Dosing is quite variable (details on next slide)
- Half-life 3-4 hours (three times daily dosing)
- Side effects: sedation, constipation
- Risks: withdrawal, severe
- Cost: low

PM R 10 (2018) 235-244

www.pmrjournal.org

Original Research—CME

Pharmacogenomic Variability of Oral Baclofen Clearance and Clinical Response in Children With Cerebral Palsy

Matthew J. McLaughlin, MD, MS, Yang He, PhD, Janice Brunstrom-Hernandez, MD, Liu Lin Thio, MD, PhD, Bruce C. Carleton, PharmD, Colin J.D. Ross, PhD, MS, Andrea Gaedigk, PhD, Andrew Lewandowski, PhD, Hongying Dai, PhD, William J. Jusko, PhD, J. Steven Leeder, PharmD, PhD

"After univariate analysis of the data, the **SNP of ABCC9** (rs11046232, heterozygous AT versus the reference TT genotype) was associated with a **2-fold increase in oral baclofen clearance** (mean 0.51standard deviation 0.05 L/h/kg for the AT genotypeversus 0.250.07 L/h/kg for the TT genotype, adjustedP<.001). Clinical responses were associated with **decreased spasticity** by Modified Tardieu Scale in allelic variants with SNPs **ABCC12, SLC28A1, and PPARD.**"

TAKE HOME: Not only is the impact of baclofen variable, it's REALLY variable and has many factors involved.

Diazepam – spasticity, dystonia

- FDA approved for 6 months and older
- 0.12mg/kg/day dosing, generally twice daily
- Half life 18-50 hours
- Side effects: sedation, cognitive slowing
- Risks: withdrawal, tolerance
- Cost: low

Dantrolene – spasticity

- FDA approved 5 years and older
- 0.5mg/kg daily, titrate to 2mg/kg three times daily
- Half life 8 hours
- Side effects: swallowing difficulty, sedation
- Risks: Liver injury (can be severe) F > M
- Cost: low - medium

Gabapentin – spasticity, dystonia?

- FDA approved seizures and pain in adults
- We're not sure how it works or if it works or why it works
- Half life: 5-7 hours
- Side effects: sedation, balance issues
- Risks: Possible seizures if stopped abruptly
- Cost: low

Clobazam - spasticity

- FDA approval: 2 years and older for seizures
- Works in a similar place as baclofen, diazepam. Not much experience using it for spasticity
- Dosing: For seizure control
- Half life:36-42 hours
- Side effects: sedation
- Cost: high

Carbidopa / Levadopa - chorea / athetosis

- FDA approval: adults, Parkinson disease
- Dosing: 0.5mg/kg daily, titrate to 2mg/kg TID
- Half life: 90 minutes
- Side effects: low blood pressure, vomiting
- Cost: low-medium

Tetrabenazine – Dyskinesias

- FDA approval: orphan drug for Huntington disease
- Dosing: Start at 12.5mg daily for adolescents
- Half life: 10-12 hours
- Side effects: Sedation
- Cost: high, difficult to get authorized

Trihexyphenidyl – Dyskinesias

- FDA approval: Adults for Parkinsonian symptoms
- Dosing: 0.02mg/kg/day three times daily to start
- Half life: 6-12 hours
- Side effects: constipation, dry mouth, urinatry retention
- Cost: low

Brief notes on other drugs

- Alpha-2 agonists: tizanidine, clonidine
  - Likely will sedate young children, thus decreasing their degree of movement disorder
  - Tizanidine is approved for muscle spasticity in adults. Recommend caution with these drugs in children.
- Cannabinoids
  - Weak evidence overall
  - Caution with unknown effect profile in developing brain
  - Future evidence for spasticity may come from secondary studies from epilepsy trials

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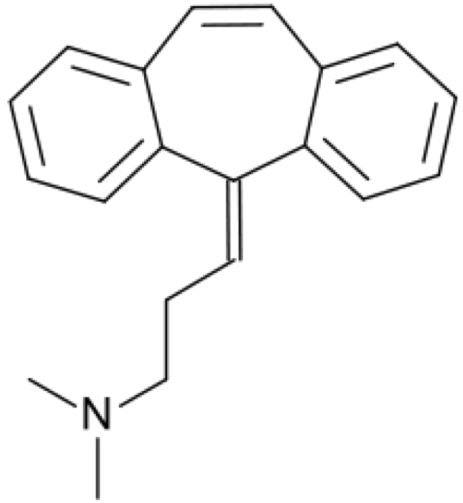
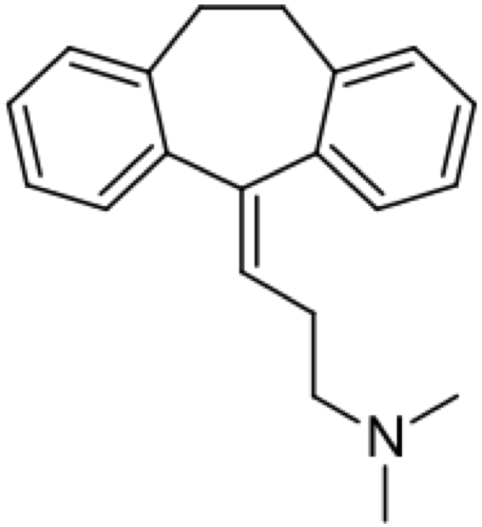
Brief notes on other drugs

- Cyclobenzaprine
  - Nice name – suggestive
  - Structure very close to TCA – may have an impact on nerve pain

Cyclobenzaprine



Amitriptyline



Botulinum Toxins

- FDA approval: abobotulinum toxin A for spasticity in children 2 years and older
- Dosing: Variable (surprise!)
- Time to onset: 1-2 weeks
- Lasts 3-4 months (maybe, sometimes)
- Side effects: Weakness
- Risk: Botulism
- Cost: High

Surgeries

- Intrathecal baclofen pump
- Selective dorsal rhizotomy
- Deep brain stimulation
- Multiple level orthopedic surgery (for spasticity?)

Time limits prevent the in-depth discussion necessary

Bottom line

- We have tools -- some are sharp and some are dull, depending on the person
- LISTEN FIRST! Identify functional, measurable goals and make sure those goals were achieved
- Stay humble about the potential for “treatment failure” and differentiate that from “patient failure”

Future Directions and Innovations

Answer the questions we already have

- Dose and choose medications based on genetics as opposed to age and weight
- Determine why different neurotoxins have different impacts
- Predict neurotoxin dosing impact better

Innovations

- Drug development – many different receptors left to chase. How do we incentivize this chase?
- Ventral rhizotomy for people who have “mixed tone”
- Deep brain stimulation for dystonia

nathan.rosenberg@nationwidechildrens.org

laurie.glader@nationwidechildrens.org

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