APPROACHES TO THE MANAGEMENT OF SPASTICITY:
ORAL MEDICATIONS, INTRATHECAL BACLOFEN AND BOTULINUM TOXIN
Spasticity: 
*Traditional Treatment Options*

- Pharmacological
  - Oral
  - Nerve Blocks
- Rehabilitation
- Surgical
Oral medications have traditionally included:

- benzodiazipines (diazepam/Valium®, clonazepam/Klonopin®)
- baclofen (Lioresal®)
- dantrolene sodium (Dantrium®)

Other oral medications include:

- clonidine (Catapres®)
- cyproheptadine (Periactin®)
Benzodiazepines

- Long-acting and short-acting formulations
- Mechanism of Action (CNS):
  - binds in brain stem and spinal cord
  - post-synaptic site of action
  - potentiates presynaptic effect of GABA
Benzodiazepines

- Clinical Indications: SCI, MS
- Possible Applications: TBI, CP, CVA
- Clinical Effects:
  - decreased resistance to passive ROM
  - decrease in hyperreflexia
  - reduction in painful spasms
  - sedation and reduced anxiety
Diazepam

- **Recommended Dose:**
  - initial = 2 mg. bid
  
  *(consider starting with single dose at night if nocturnal spasticity is the presenting problem)*
  
  - maximum = 60 mg. daily (20 mg. tid)

  **NB:** long half-life; active metabolite

- **Side Effects:** weakness, sedation, hypotension, GI symptoms, memory impairment, uncoordination, confusion, depression, ataxia

- **Controlled substance with potential for dependency**
Oral Baclofen

- **Mechanism of Action (CNS):**
  - GABA$_b$ selective agonist
  - pre- and post-synaptic actions
  - acts on mono and polysynaptic pathways
Oral Baclofen

- Clinical Indications: spasticity of spinal origin
  
  NB: Intrathecal Baclofen approved for cerebral and spinal spasticity

- Clinical Effects:
  - decreased hyperreflexia and resistance to passive ROM
  - reduction in painful spasms and clonus
Oral Baclofen

- **Recommended Dose:**
  - initial = 5 mg. tid
  - maximum = 80 mg. Daily (20 mg. qid)
- **Side Effects:** weakness, sedation, hypotonia, ataxia, confusion, fatigue, nausea, dizziness, lower seizure threshold
- Sudden withdrawal may cause seizures, hallucinations, and rebound spasticity
- May potentiate effects of antihypertensive agents
Dantrolene Sodium

- **Mechanism of Action = peripheral**
  - interferes with calcium release
  - uncouples muscle contraction from excitation
  - effects both intrafusal and extrafusal fibers
Dantrolene Sodium

- Clinical Indications: CVA, CP
- Possible Applications: TBI, SCI, MS
- Clinical Effects:
  - decreased resistance to ROM
  - decrease in hyperreflexia and tone
  - reduction in painful spasms and clonus
  - problems with weakness
New for Spasticity: Tizanidine (Zanaflex®)

- Tizanidine effectively decreases tone and spasm frequency *preferentially* in spastic muscles.
- It has been reported to eliminate the unwanted side effect of muscle weakness.
Tizanidine

- Appropriate as first line oral monotherapy; may have utility in polypharmacy program

- No evidence of dependency, withdrawal, or tolerance effects
Tizanidine:
Pharmacology and Mechanism of Action

- Mechanism of Action (spinal and supraspinal):
  - decreases facilitory inputs by acting primarily on spinal polysynaptic pathways

- Alpha-2, noradrenergic receptor agonist

- Peak effect occurs 1-2 hours following administration
Tizanidine: *Clinical Effects*

- Reduces muscle tone
- Reduces spasm frequency
- Reduces hyperreflexia
- Does not decrease muscle strength
Tizanidine: Dosage

- Starting dose: 4 mg. At HS
- Optimum dose:
  12-36 mg./day in 3 or 4 divided doses
- Daily maximum dose = 36 mg.
- Requires gradual titration to optimal dose in 2-4 mg. steps
- Check liver function tests at baseline and during treatment
Tizanidine: *Side Effects*

- Most frequent side effects include: drowsiness, dry mouth, tiredness, dizziness
  (as with other anti-spasticity agents, side effects are dose related and may be mitigated by dosage titration)
- Literature suggests that tizanidine may be better tolerated than other anti-spasticity agents, as measured by “global tolerance rating scale”*

* Lataste et al., 1994
Regional Treatments
Intrathecal Baclofen Infusion System

- Implanted in subcutaneous fat (RLQ)
- Drug reservoir (10 mL or 18 mL) and pump connected to catheter
- Battery
- External radio-telemetry wand to control pump

Albright AL. *JAMA*. 1993;270:2475-2479.
Intrathecal Baclofen: Implantation

- Tip placed intrathecally between T10 and L1
- Pump is implanted into a subcutaneous pocket in the abdomen

Intrathecal Baclofen: Selection Criteria

- Severe multifocal and regional muscle overactivity
- Failed adequate trial of oral agents
- Minimum age 4 years (body-size dependent) and clinically stable
- Patient/caregiver goals for treatment are realistic
- Family committed to intrathecal baclofen as a treatment option
- Exclusion criteria
  - Infection, history of allergy, or hypersensitivity to baclofen
  - Potential for pregnancy or active breast-feeding

Intrathecal Baclofen: Screening

50-100 μg intrathecal bolus

Peak response
2-4 hours
Improvement of function
or no deterioration
Candidate

No response
Select other treatment

Intrathecal Baclofen: Follow-up

- Postimplantation
  - Titrate dose to ensure balance, stability, and postural control
  - Instruct patient and caregiver about refill schedule, management of complications, and potential adverse effects
  - Refills, assessments, and possible dose adjustments are at ITB therapy center at 4- to 12-week intervals
  - Replace pump after 5-7 years

Intrathecal Baclofen: Complications

- Local
  - Seroma
  - Hematoma
  - Erosion
  - Infection
- Systemic
  - Withdrawal
  - Drug toxicity
- Catheter
  - Migration
  - Breakage
  - Puncture/rupture
  - Dislodgment
  - Disconnection
  - CSF leaks

Current Treatment Options: Neurosurgical Interventions

- Selective dorsal rhizotomy
- Peripheral neurectomy
- Myelotomy
- Dorsal column electrical stimulation
Selective Dorsal Rhizotomy
Spasticity: Injection

- Regional and local
- Motor point and nerve blocks; phenol, alcohol

NB: Limitations - painful; time-consuming; dysesthesia; variable duration of effect
Alcohol

- Indications
- Cost
- Outcome
Phenol

- Indications
- Cost
- Outcome
Botulinum Toxin and Spasticity

- Local injections of botulinum toxin are well accepted as treatment for:
  - focal dystonias
  - spasticity
  - other neurological disorders characterized by inappropriate muscle spasms
- Not approved for use in CP by the FDA
Botulinum Toxin A

- Botulinum toxin produced by the bacteria: *Clostridium botulinum*

- Seven serotypes of toxin (A-G)
  - Trade names of botulinum toxin type A are: BOTOX® (Allergan, Inc.)
  - DYSPORT® (Speywood Pharmaceuticals Ltd.)
Botulinum Toxin Type B

- Approved for use for cervical dystonia
- Manufactured as Myobloc (Elan Pharmaceuticals)
- Studies on the use of Myobloc in children with spasticity have not been published
Botulinum Toxin A: Mechanism of Action

- **Botulinum toxin molecule** = light and heavy chain linked by a disulfide bond
- **Inhibits release of acetylcholine**
  - toxin binds to presynaptic axon terminal
  - internalization of toxin (endocytosis)
  - inhibition of neurotransmitter release
- **Storage and synthesis of acetylcholine is normal**
- **Toxin is a zinc-dependent enzyme, substrates identified**
Botulinum Toxin Type A Mechanism
Current Hypothesis

1. [Image]
2. [Image]
3. [Image]
4. [Image]
5. [Image]

Data published: dePaiva et al. PNAS 1999, 96:3200
Botulinum Toxin Type A: 
Mechanism of Action

◆ Binding:

Botulinum toxin type A first binds to cholinergic nerve ending.
Botulinum Toxin Type A: 
Mechanism of Action

- **Internalization:**
  
  Botulinum toxin type A is internalized via receptor-mediated endocytosis.
Botulinum Toxin Type A: 
**Mechanism of Action**

- **Blocking:**

  Once inside cell, botulinum toxin type A blocks release of acetylcholine transmitter. This produces functional muscle denervation.
Botulinum Toxin Type A: 
*Mechanism of Action*

- **Sprouting:**
  In muscles treated with botulinum toxin type A, chemical denervation of neuromuscular junction stimulates nerve sprouting.
Botulinum Toxin Type A: 
Mechanism of Action

- Establishing Sprout connection:
  Single nerve sprout establishes new neuromuscular junction. Muscle tone is restored and spasms return, making it necessary to repeat injections approx. every 3-6 months, depending on individual patient response.
Reestablishment of Neuromuscular Junction

- The sprouted nerve retracts and the original neuromuscular junction is reestablished
BOTOX®: Commercial Preparation

- Cultures of C. botulinum are established in fermenter, grown, and harvested
- Diluted with human serum albumin
- Freeze-dried in vials of 100 Units
In clinical use, dose range = 60-400 Units

No anaphylactic reactions have been reported

Not indicated during pregnancy or lactation
Botulinum Toxin Type A: Possible Adverse Effects

Side effects are a result of the pharmacology and are temporary

- Resulting symptoms are site specific, e.g. weakness in injected and neighboring muscles
- Patient may have temporary change in posturing or pain due to re-alignment of nerve-muscle-bone relationships
- Patient may report subjective symptoms of weakness and fatigue (‘flu-like’ syndrome) that usually last less than four days
Botulinum Toxin Type A: 
**BTX for Spasticity: Patient Selection**

- Pre-injection muscle imbalance is present with identifiable and relatively stronger spastic agonist muscle(s)

- Antagonist muscle(s) must be:
  - sufficiently powerful for functional control if “agonists” are weakened, or
  - capable of hypertrophy and strengthening, if allowed to perform through the appropriate range of motion, or
  - acceptable in a flaccid state
Injection of Botulinum Toxin: Patient Selection

- No fixed joint deformity present
- Weakening spastic limb will not further compromise residual function (including gait).
Treating Spasticity with Botulinum Toxin

- Effects are local and dose dependent with minimal distal effect
- Selected, graded weakness in injected and adjacent muscles
- If too much weakness, strength gradually returns
- Can be used in conjunction with other therapies, e.g. systemic medications, intrathecal baclofen pump
Day of Injections

- Administer Versed (Midazolam)
  - dose = 0.25 - 1.0 mg/kg PO
  - injectable
  - Versed orally or intranasally
  - new Versed syrup

- Effects of Versed
Day of Injections

- Order BOTOX®
  - dose = 8-12 units/kg
  - diluted in normal saline ≈ 1cc per injection site
  - may also dilute 1-2 cc/100 Unit vial
Day of Injections

- Patient to Treatment Room
- Obtain BOTOX® from Pharmacy
- Confirm dosage and sites with MD
- Attach 25g; 1-1.5” needle
- Position patient and prep sites
- Injections given by MD
Post injection serial casting
Spasticity can be treated by:

- Oral Medications
- Nerve Blockade by alcohol or toxin
- Neurosurgical techniques
Thank You