



38TH ANNUAL MEETING

Today and Tomorrow in Pain
Medicine: Innovations and
Practical Applications



IDDS for Spasticity

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3/20/22

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- Disclosures

- Funded research from Avanos, NIH, FUS Foundation, FUS Mobile
- Steering committee/honoraria from Avanos

- The presentation does not include off label use of drugs.

Objectives

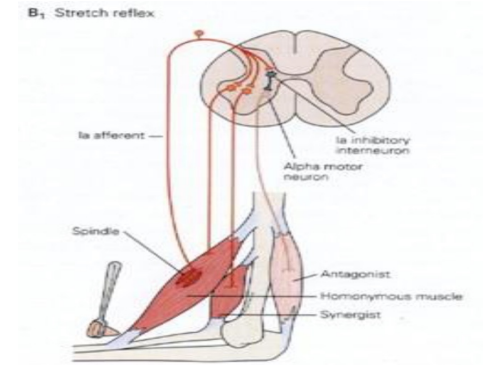
- Briefly describe the basic pathophysiology of spasticity
- Demonstrate understanding of the clinical presentation of spasticity and its assessment tools
- Identify when to use intrathecal baclofen
- Describe basic methods for trialing intrathecal baclofen

Spasticity Definition

2005 SPASM Consortium

Disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as **intermittent or sustained involuntary activation of muscles**

- Focuses more on abnormal muscle activity
- Clonus, co-contraction, associated reaction, dystonia, and spasms can all be included



Pathophysiology

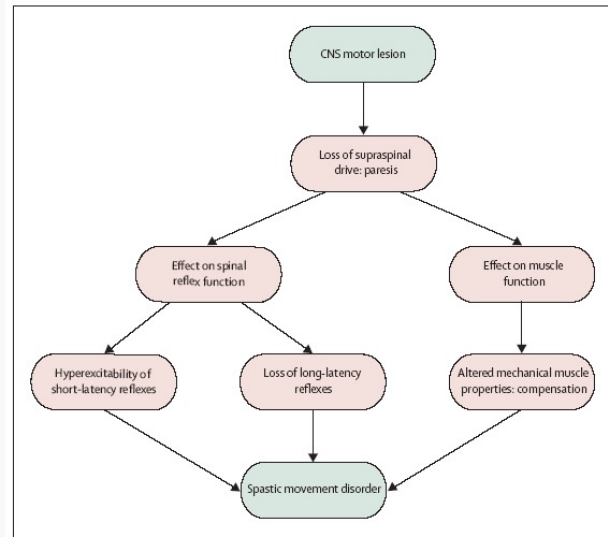
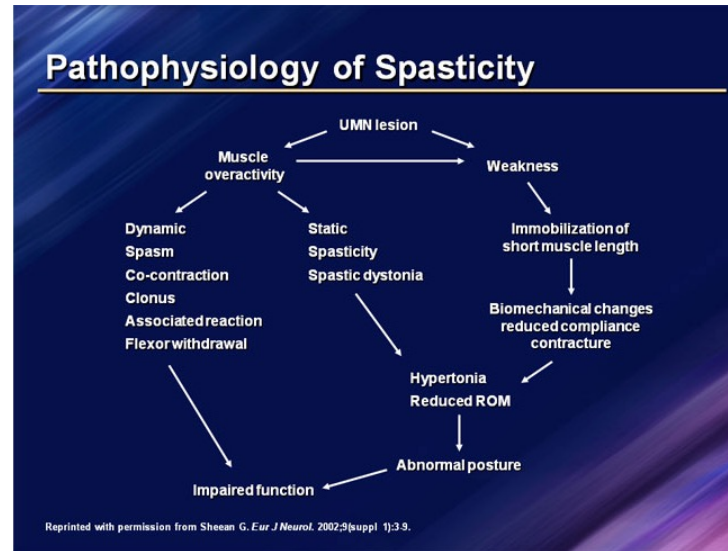


Table 2
Pathophysiology of spasticity

Supraspinal pathways

Release of brain stem reflexes from cortical inhibition

Overactivity of non-adrenergic pathways from locus coeruleus

Overactivity of serotonergic pathways from raphe nucleus

Spinal cord

Loss of recurrent inhibition, mediated by motor axon collaterals and Renshaw cells

Loss of reciprocal inhibition, mediated by antagonistic muscle spindle afferents

Reduced inverse stretch reflex, mediated by Golgi tendon organs

Reduced presynaptic inhibition of muscle spindle afferents

Spinal motor neurone

Denervation supersensitivity

Collateral sprouting

Muscles and joints

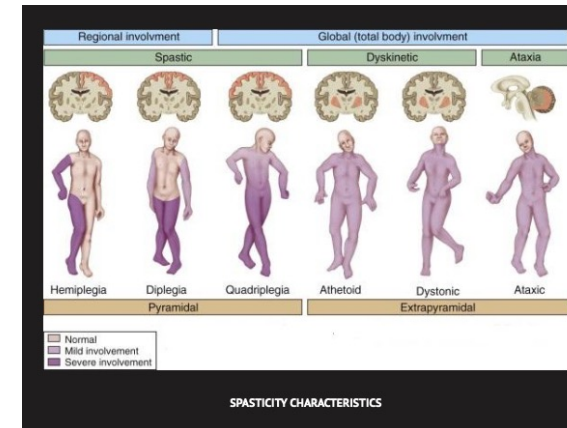
Shortening of sarcomeres

Loss of elastic tissue

Fibro-fatty deposits in muscles and tendons

Clinical presentation

- Diverse
- Distinction based on number of muscle groups involved
 - Quadriplegic
 - Paraplegic
 - Hemiplegic
 - Combination
 - Axial musculature
- Focal
 - Just a few muscles or muscle groups involved



<https://mobilephysiotherapyclinic.in/techniques-to-inhibit-spasticity-with-physiotherapy-treatments/>

Box 1 Clinical features of spasticity

Clonus

Involuntary rhythmic contractions triggered by stretch; these can interfere with walking, transfers, sitting, and care

Spasms

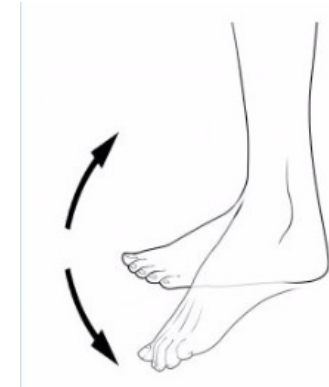
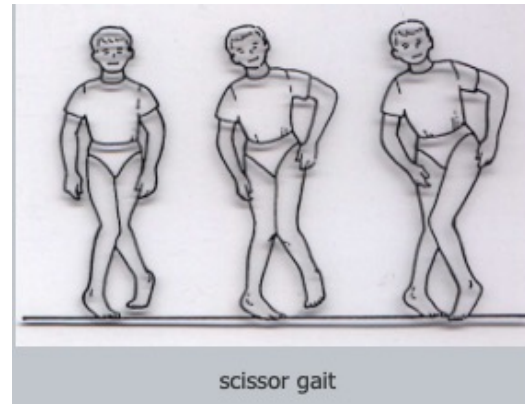
Sudden involuntary movements that often involve multiple muscle groups and joints in response to somatic or visceral stimuli

Spastic dystonia

Tonic muscle overactivity without any triggers owing to the inability of motor units to cease firing after a voluntary or reflex activity⁶; results in characteristic limb postures and contractures

Spastic co-contraction

Inappropriate activation of antagonistic muscles during voluntary activity due to lack of reciprocal inhibition causing a loss of dexterity and slowness in movements⁶



Spasticity

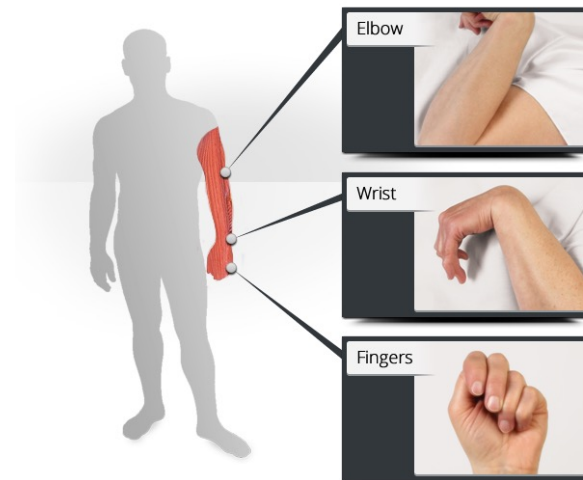
Good

Stiffness-Can help with transfers
Muscle strengthening



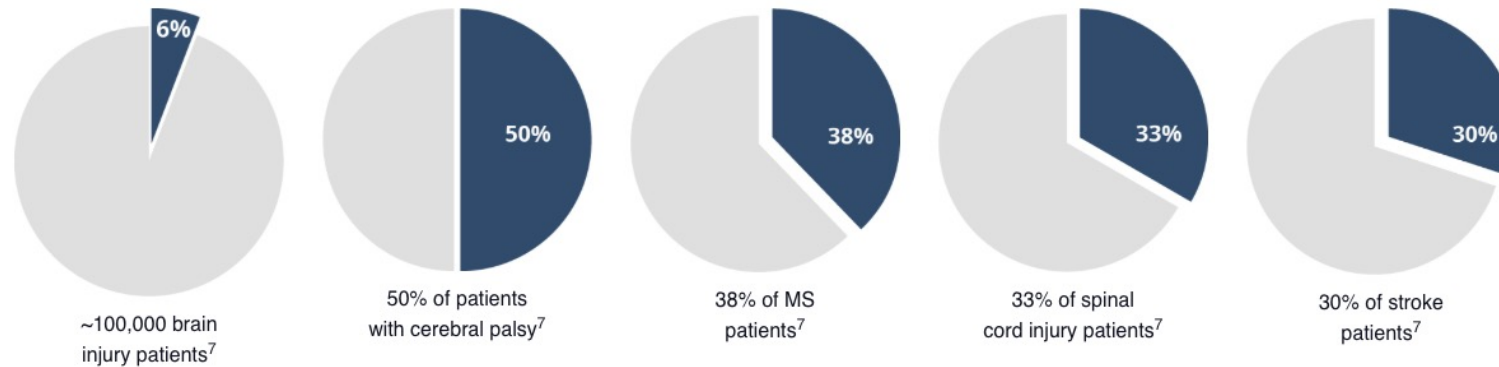
Bad

Pain
Reduced mobility
Contractures
Wounds



Impact

Who may be affected by Severe Spasticity?



Approximately 2.7 million people in the U.S. have spasticity, and 1.1 million people are affected by severe spasticity.⁶

Assessment: Subjective

Action

Does spasticity (muscle tightness/muscle stiffness):	
A ctivities limited	Limit functional activities that you were able to do previously?
C are tasks difficult	Limit your or others' ability to carry out your personal care tasks?
T ight muscles	Reduce your ability to stretch or position your joints?
I ntegrity of skin	Lead to pressure sores on your skin?
O ngoing pain	Cause you pain or discomfort?
N ails digging in	Cause your nails to dig into the palm of your hand?

Penn Spasm Frequency Score (PSFS)

Score	Spasm frequency score
0	No spasms
1	One or fewer spasms per day
2	Between 1 and 5 spasms per day
3	Five to less than 10 spasms per day
4	Ten or more spasms per day, or continuous contraction

Christofi G. Et al. Improving the management of post stroke spasticity: time for action. J of Rehab Med. 2017; 1:1-7. JRM-CC 2018; 1: 1000004

Adapted from Reference 2: Walker HW, Hon AJ, Kirschblum S. Chapter 23: Spasticity due to disease of the spinal cord: pathophysiology, epidemiology, and treatment. In: Brashear A, Elovic E, eds. *Spasticity: Diagnosis and Management*. 2nd ed. New York, NY: Demos Medical Publishing, LLC, 2016.

Objective/physiologic

MODIFIED ASHWORTH SCALE

Score	Ashworth Scale (1964)	Modified Ashworth Scale Bohannon & Smith (1987)
0 (0)	No increase in tone	No increase in muscle tone
1 (1)	Slight increase in tone catch when limb moved	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension.
1+(2)		Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM (range of movement).
2 (3)	marked increase in tone limb easily flexed	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved.
3 (4)	passive movement difficult	Considerable increase in muscle tone passive, movement difficult.
4 (5)	Limb rigid	Affected part(s) rigid in flexion or extension.

Tardieu scale

A

Tardieu scale

Quality of muscle reaction is measured as:

0	No resistance throughout the course of the passive movement
1	Slight resistance throughout the course of the passive movement
2	Clear catch at precise angle, interrupting the passive movement, followed by release
3	Unsustained clonus (less than 10 sec when maintaining the pressure) occurring at a precise angle, followed by release
4	Sustained clonus (more than 10 sec when maintaining the pressure) occurring at a precise angle

Angle of muscle action is measured relative to the position of minimal stretch of the muscle (corresponding to angle zero) for all joints except the hip where it is relative to the resting anatomical position.

TREATMENT

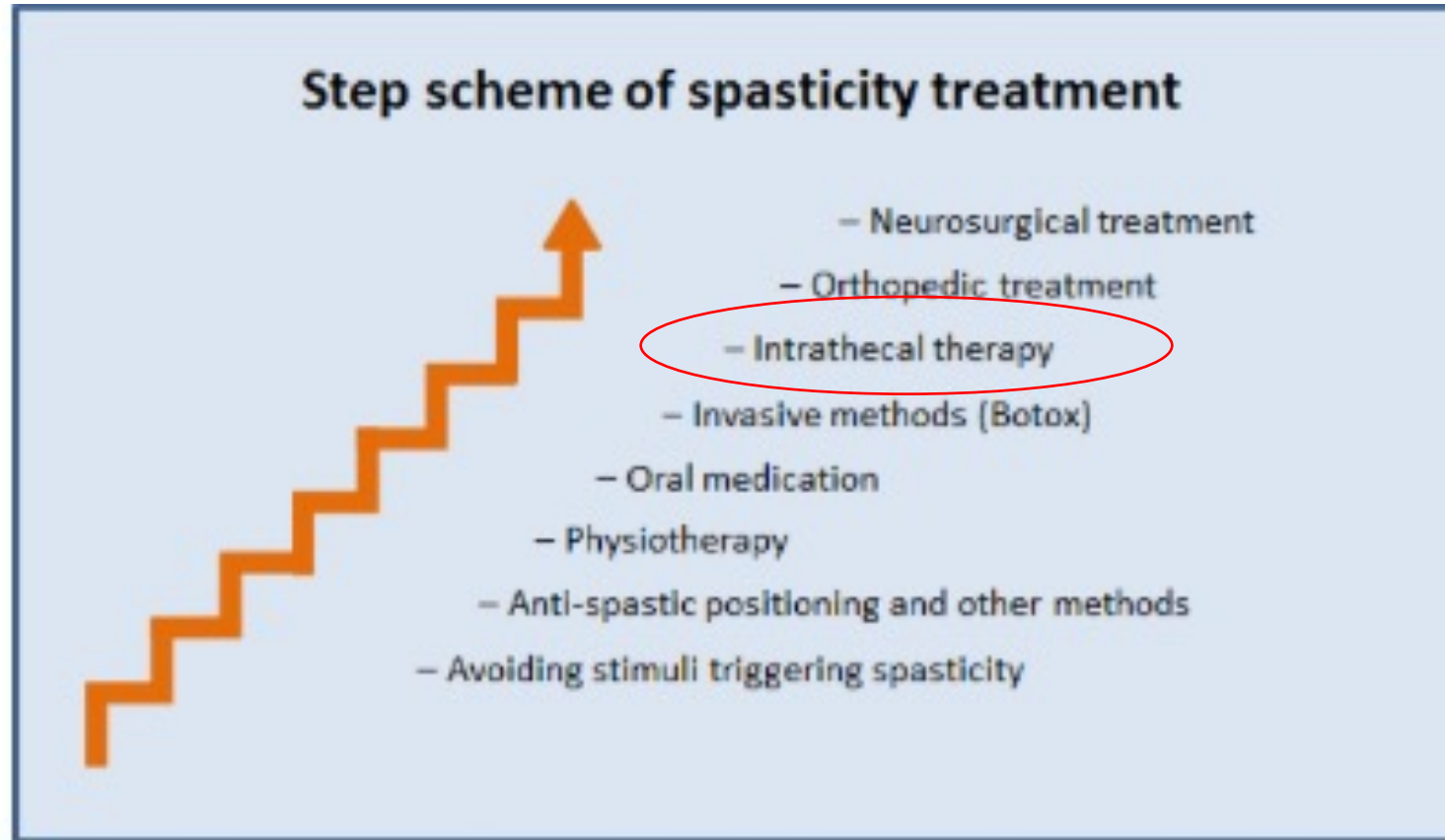
Synergistic Model of Spasticity Management



Table 1
Various options for spasticity management

Category	Intervention	Description/Example	Advantages	Disadvantage
Nonpharmacologic	Removal/avoidance of noxious stimuli	• Treatment of neurogenic bladder • Treatment of neurogenic bowel • Pressure sore management	• Returns patient to baseline hypertonia • May eliminate ongoing stimuli • Low cost • Minimal adverse events	• May not easily be reversible • Modulation may not be predictable
	Manual stretching	Physical movement of limbs	• Low cost • Minimal risk	• Short duration of action
	Passive stretching	• Bracing • Splinting • Serial casting	• Low cost • Minimal risk	• Potential for skin breakdown • Restricts patient movement • Requires some expertise in prescribing
Oral Medications	GABAergic agents	Benzodiazepines	• Noninvasive	• Poor patient tolerability
		Baclofen	• Low cost	• Weakness
	α -adrenergic agonists	Clonidine	• Allows patient control	• Sedation
		Tizanidine	• Global effectiveness	• Hepatotoxicity
	Serotonin antagonists	Cyproheptadine	• Secondary indications (eg, sleep aide, pain, etc.)	
	Peripheral acting agents	Dantrolene		
	GABA analogues	Pregabalin		
		Gabapentin		

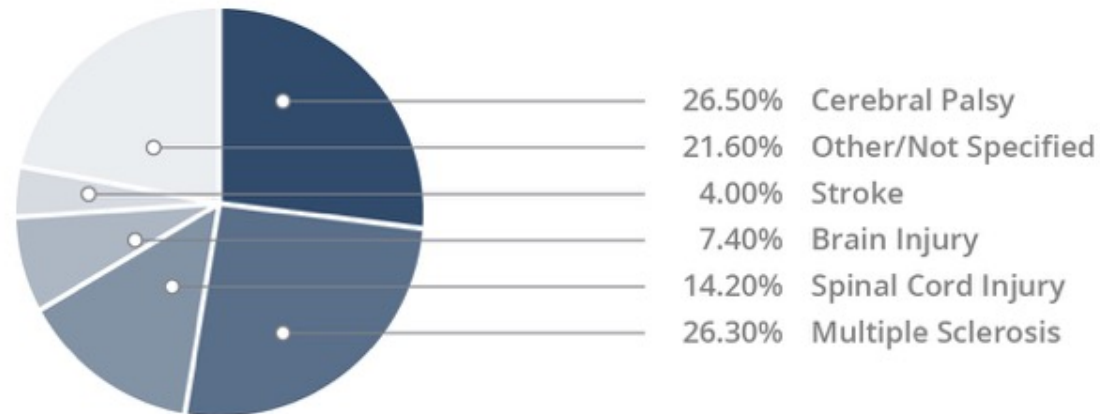
Spasticity Treatment



Indications

- FDA approved for spasticity of spinal (traumatic spinal cord injury and MS) and cerebral origin (brain injury, cerebral palsy, stroke).

Use of Medtronic Infusion Systems for Spasticity (2003-2006)⁵



- Formal labeling:
 - Requires waiting 1 year after traumatic brain injury before ITB tx

Both 2016 ITB Therapy Best Practices Expert Consensus Panel and German Consensus Panel Group in agreement

- Spasticity that is poorly controlled despite maximal therapy
- “Any patient who demonstrates spasticity that interferes with comfort, active or passive function, activities of daily living, mobility, positioning, or caregiver assistance should be considered”
- A need for adjustable spasticity reduction, which is afforded by the programmable variable flow pump
- “Therapy primarily aims at the functional level to reduce spasticity and at the activity level to improve general well being, reduce pain, and facilitate patient care and everyday activities, acknowledged as important aspects for quality of life”

Paradigm shifting?

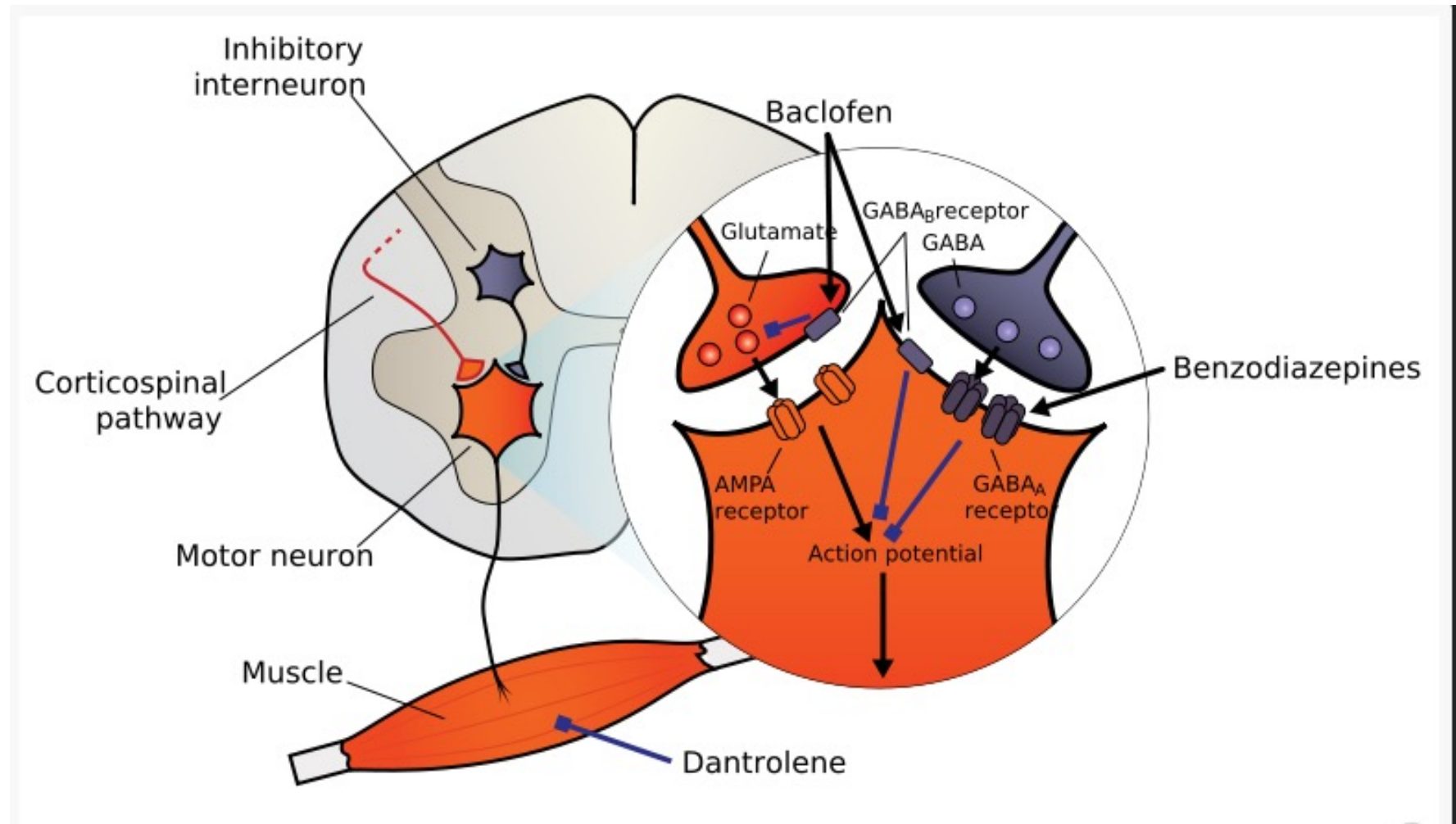
- Studies have shown that it is safe to utilize earlier in the course of disease/injury.
- Earlier tx may help to prevent contractures, skin breakdown, ankylosis.

Francisco G et al. Efficacy of early use of intrathecal baclofen therapy for treating spastic hypertonia due to acquired brain injury. *Brain Inj* 2005;19:359–364.

Francois B, Vacher P, Roustan J et al. Intrathecal baclofen after traumatic brain injury: early treatment using a new technique to prevent spasticity. *J Trauma* 2001;50:158–161.

Meythaler JM, Guin-Renfroe S, Grabb P, Hadley MN. Long-term continuously infused intrathecal baclofen for spastic-dystonic hypertonia in traumatic brain injury: 1-year experience. *Arch Phys Med Rehabil* 1999;80:13–19.

What is baclofen?



Oral vs IT

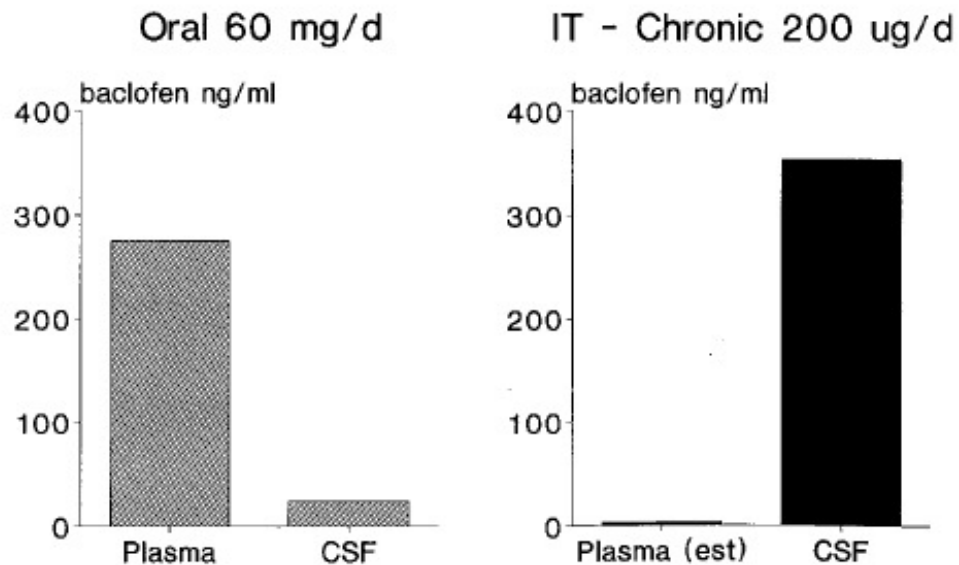


Figure 5.1. A comparison of plasma and CSF drug levels after oral and intrathecal baclofen administration. (Reprinted with permission from Penn R. and Kroin J. Intrathecal baclofen in the long-term management of severe spasticity. *Neurosurgery*. 1989; 4(2):325-332.

Table III. Relationship between baclofen dosage and severity or cause of spasticity

		Baclofen dosage, mg/day	
		Median (min–max)	Range (min–max)
Severity of spasticity			
Mild to moderate	1	15–20	15–20
Moderate	5	15–60	5–120
Moderate to severe	7	10–80	5–90
Severe	3	15–50	30–100
Indication			
Multiple sclerosis	15	15–60	5–120
Cerebral palsy	3	20–60	10–60
Brain injury	2	12.5–65	5–80
Stroke	1	10–50	10–50
Spinal cord injury	3	17.5–80	5–200

Ertzgaard P, et al. Efficacy and safety of oral baclofen in the management of spasticity: A rationale for intrathecal baclofen. *J Rehabil Med* 2017;49:193-203.

Adverse effects

Oral

- Confusion
- Nausea
- Weakness
- Tiredness

Intrathecal

- Urinary retention
- Hypotonia
- Mechanical failures of pump
- Movement of pump
- Spinal infection
- Spinal leak from surgery
- Withdrawal
- Overdose
- Ongoing need to follow and adjustments



PM R 8 (2016) 553-562

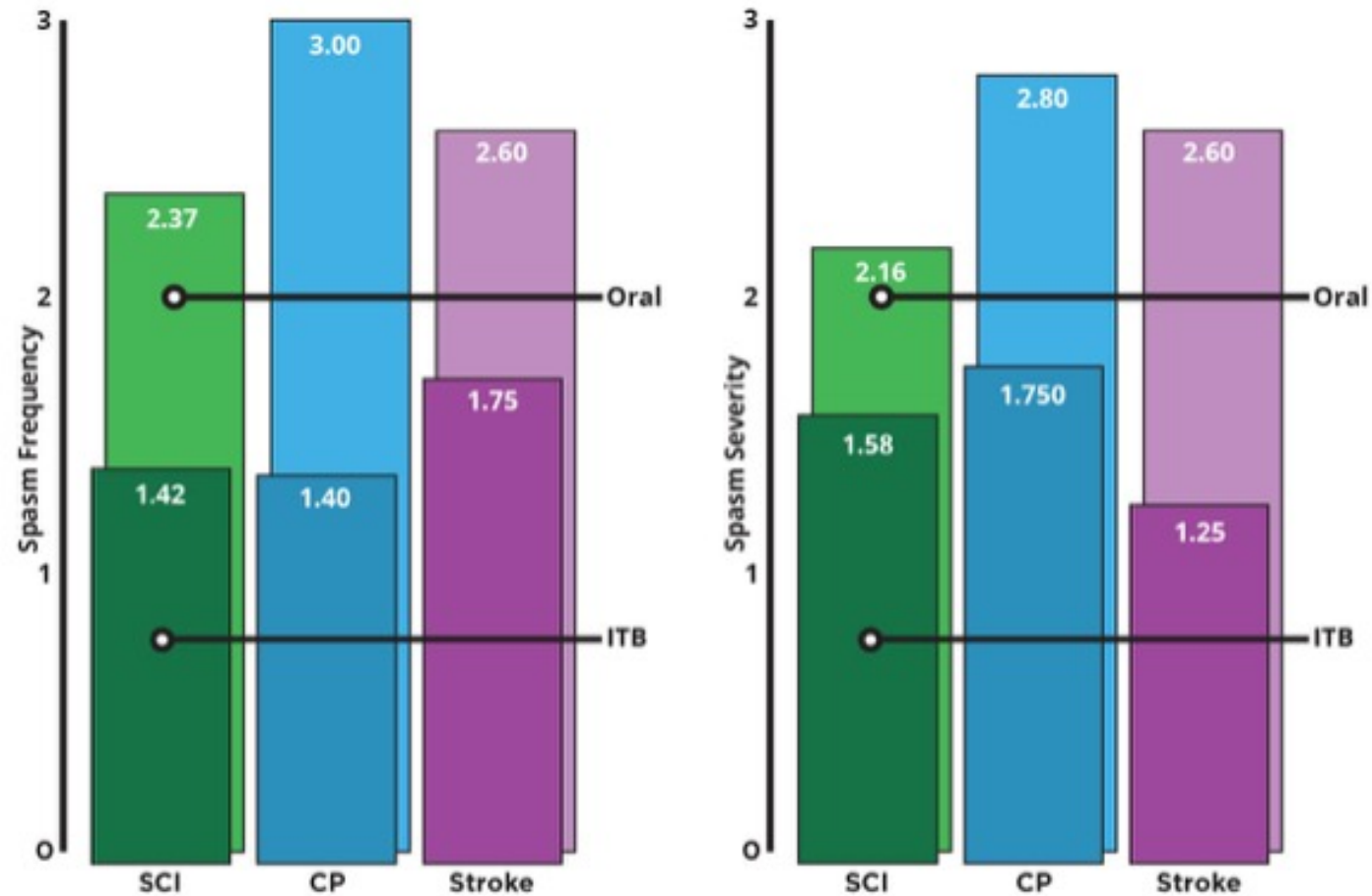
www.pmrjournal.org

Original Research

Intrathecal Versus Oral Baclofen: A Matched Cohort Study of Spasticity, Pain, Sleep, Fatigue, and Quality of Life

Zachary L. McCormick, MD, Samuel K. Chu, MD, Danielle Binler, MS,
Daniel Neudorf, DO, Sunjay N. Mathur, MD, Jungwha Lee, PhD, MPH,
Christina Marciniak, MD

Efficacy oral vs IT



McCormick ZL, Chu SK, Binler D, et al. Intrathecal versus oral baclofen: a matched cohort study of spasticity, pain, sleep, fatigue, and quality of life. *PM R*. 2016;8(6):553-562

Pt selection

- Impact of spasticity on pt and course of disease
- Multimodal therapies/review of previous and current therapies
- Reliability/adequate infrastructure/access to care
- Mental health/cognitive function
- Education
- Goal setting

Table 1. Goal Setting for ITB Therapy.

Examples of Goals Potentially Achieved With Intrathecal Baclofen Therapy

ACTIVE GOALS

Improved mobility: speed, safety, and quality in the home and the community

Increased ability and independence for ADLs: dressing, eating, hygiene

Decreased time for ADLs
Reduced stretching time during home exercise

PASSIVE GOALS

Improved positioning
Improved wheelchair tolerance

Prevention of complications such as contractures

Decreased caregiver burden and time
Improved quality of sleep

Reduced spasticity-related pain
Discontinuation of oral antispasmodics

ADLs = activities of daily living.

Contraindications

- Hypersensitivity reaction to baclofen or implant materials
- Relative contraindications
 - Unrealistic goals
 - Unmanageable mental health or psychosocial factors
- Special consideration
 - Prior abdominal surgeries

To trial or not to trial?

Pro

- Considered best practice
- Assess improvements in spasticity and function
- Tolerability
- Pt and caregiver acceptance

Con

- Does not always provide reliable prediction of long-term tx outcome
- Risk of infection
- Time delay between testing and implantation

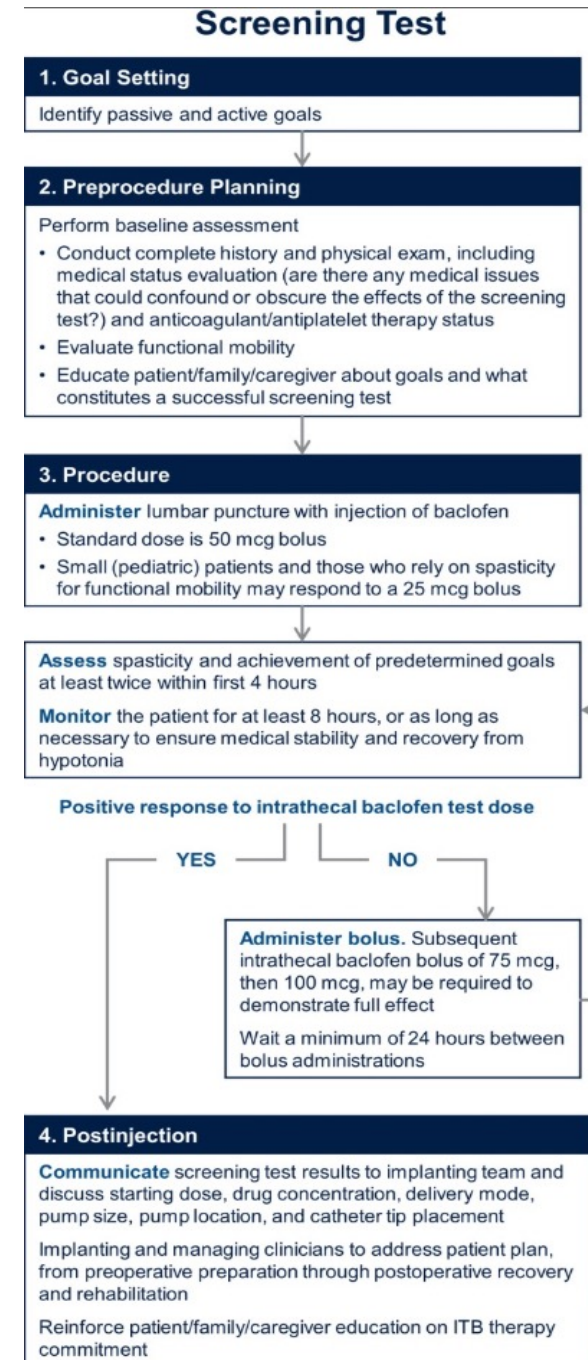
Trialing: Single Bolus vs Continuous



Trialing: Single Bolus

Single Bolus

- Onset 1-3 hours
- Peak usually about 4-6 hrs after injection
- Duration of action 6-8 hours
- Typical starting dose is 50 mcg
- Can repeat after a least 24 hrs if dose is inadequate



Continuous trial

- Performed in OR setting
- Pre evaluation of spasticity in pre-op area
- Can use Spirol epidural catheter connected to external pump
- Can have PT/OT work with during hospitalization

Pretrial parameters

- External pump flow rate 0.2–5 mL per hour
- Desired starting dose: 0.5 μg per hour (24 μg per day)
- Desired length of trial: 5 days

Concentration calculation

$$\begin{aligned} &= \text{starting dose} / \text{minimum flow rate} \\ &= (0.5 \mu\text{g/h}) / (0.2 \text{ mL/h}) \\ &= 2.5 \mu\text{g/mL} \end{aligned}$$

Volume

$$\begin{aligned} &= \text{duration of trial} \times \text{maximum flow rate} \\ &= 5 \text{ days} \times (24 \text{ h/day}) \times (5 \text{ mL/h}) \\ &= 600 \text{ mL} \end{aligned}$$

Solution prescription: 600 mL at 2.5 $\mu\text{g/mL}$ of sterile liquid baclofen.

Figure 1

Sample calculations for preparing an ITB trialing solution.

Single shot: Advantages and disadvantages

Advantages

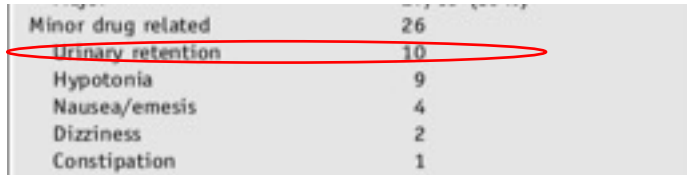
- Quick
- Easy
- Less expensive

Disadvantages

- Inability to titrate medication
- *Less accurate delivery of medication to location of choice*

Continuous Trial: Advantages and Disadvantages

- Potential advantages
 - More reliable assessment of the effect of ITB on function bc of longer evaluation period and **fine tuning** of daily ITB dose
 - More comprehensive assessment of **systemic effects** of ITB, whereas side effect might be missed in ITB bolus trials due to given time window of 4-8 hours
 - Especially to determine side effects on swallowing and GI and urinary function



Minor drug related	26
Urinary retention	10
Hypotonia	9
Nausea/emesis	4
Dizziness	2
Constipation	1

- Median duration of detection of urinary retention was 2.5 days (range 1.5-5 days)
- Higher doses

Continuous trial: Advantages and Disadvantages

- Potential Advantages
 - Continuous trial allows for placement of catheter in thoracic region vs typical lumbar injection for bolus injection
 - May not allow for accurate assessment of trunk and upper body
- Complications
 - Higher rate of complications for continuous (48%) vs bolus trials (0-10%)
 - Higher doses and longer observation time likely account for higher complications in continuous trials
- Other considerations
 - More invasive
 - Higher costs

In-patients vs out-patient

Table 1. Advantages of an Inpatient Setting for Intrathecal Baclofen Dose Titration.

- Rapid drug titration with daily pump increases and close monitoring for functional safety.
- Twenty-four-hour rehabilitation nursing to address pump-related changes in bowel and bladder function, sleep, and hygiene.
- Monitoring for postoperative complications such as spinal headache and infection.
- Reassessment of equipment needs, such as wheelchair positioning devices, spinal orthoses, etc.
- Rehabilitation-based education of patient, family and/or caregiver.
- Rapid titration for patients with barriers to clinic return.
- Titration for patients with cognitive deficits who cannot provide accurate assessment of response to therapy.

Trial adverse effects

- Spinal headache
- N/V
- Drowsiness/sedation
- Less common (<1%)
 - Hypotonia, dizziness, paresthesia, hypotension, respiratory depression

Post-implant management

- 3 available formulations of baclofen
 - 500, 1000, 2000 mcg/ml



What do you do with medications during trial?

- Consideration should be given to weaning oral antispasmodic medications prior to screening test
- Individualize the weaning plan

Weaning oral medications

- Wean 1 medication at a time
- Start with baclofen wean
- Oral baclofen can be weaned by as much as 25-50% at one time
- Oral baclofen should be made available during (during establishment of appropriate ITB dosing as well as after an established dose has been determined
- Some pt's may need prn oral baclofen

Initial Dose and Adjustments

Starting dose

- 2x the effective trial dose (for single shot bolus trial)
- Same as trial dose: If response to trial >8 hrs or pt had side effects

Drug label adjustments

Adult Patients	
Spasticity of Spinal Cord Origin	Spasticity of Cerebral Origin
Increase dose slowly by 10%-30% increments only once every 24 hours until desired clinical effect is achieved	Increase dose slowly by 5%-15% increments only once every 24 hours until desired clinical effect is achieved

At lower doses higher percentage increases are reasonable

At higher doses, generally increase <20%

Maintenance therapy dosing recommendations

Adult Patients	
Spasticity of Spinal Cord Origin	Spasticity of Cerebral Origin
• Increase dose 10%-40% (but no more than 40%) to maintain adequate symptom control • Daily dose may be reduced 10%-20% if patients experience side effects • For long-term continuous infusion: 12-2003 mcg/day • Most patients are adequately maintained on 300-800 mcg/day • There is limited experience with doses >1000 mcg/day	• Increase dose 15%-20% (but no more than 20%) to maintain adequate symptom control • Daily dose may be reduced 10%-20% if patients experience side effects • For long-term continuous infusion: 22-1400 mcg/day • Most patients are adequately maintained on 90-703 mcg/day • In clinical trials, only 3/150 patients required daily doses >1000 mcg/day

Variable opinions

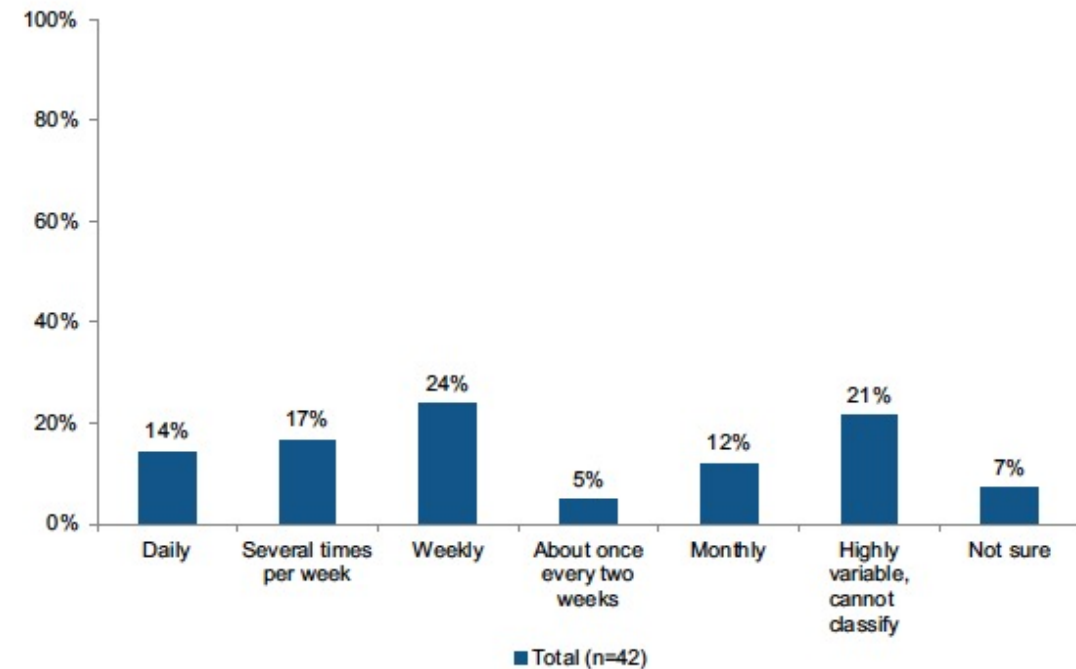


Figure 1. Frequency of changes made to dose titration schedules.

Therapeutic Dose ranges

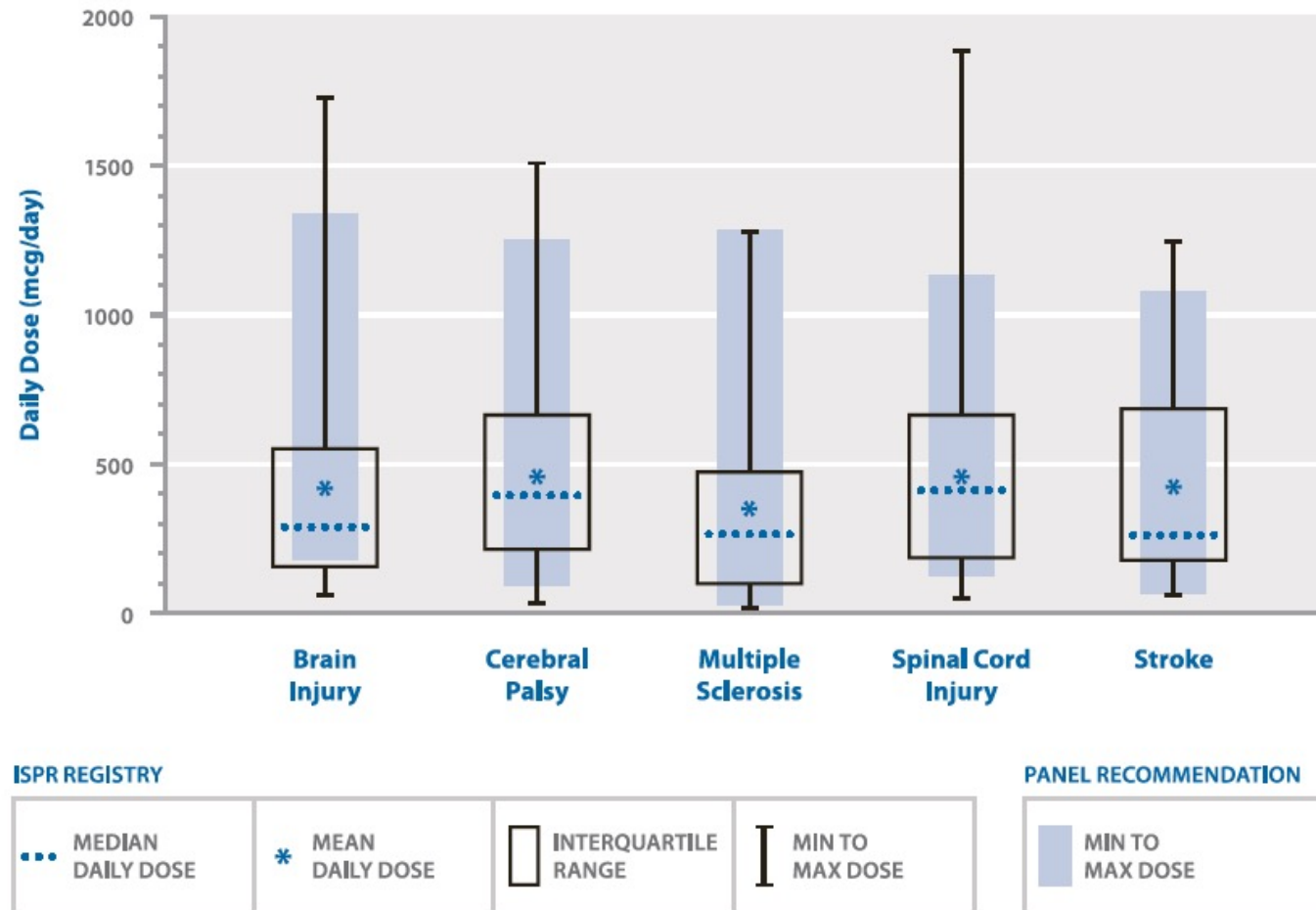


Figure 2. ITB dosing by indication (using last available daily dose for each subject): The median daily dose is the horizontal line in all boxplots. The box spans the interquartile range, with the whiskers extending to the minimum and maximum dose. The mean daily dose is denoted with a diamond.

Different modes of delivery

- Simple continuous
- Flex dosing
- Bolus dosing
- PTM

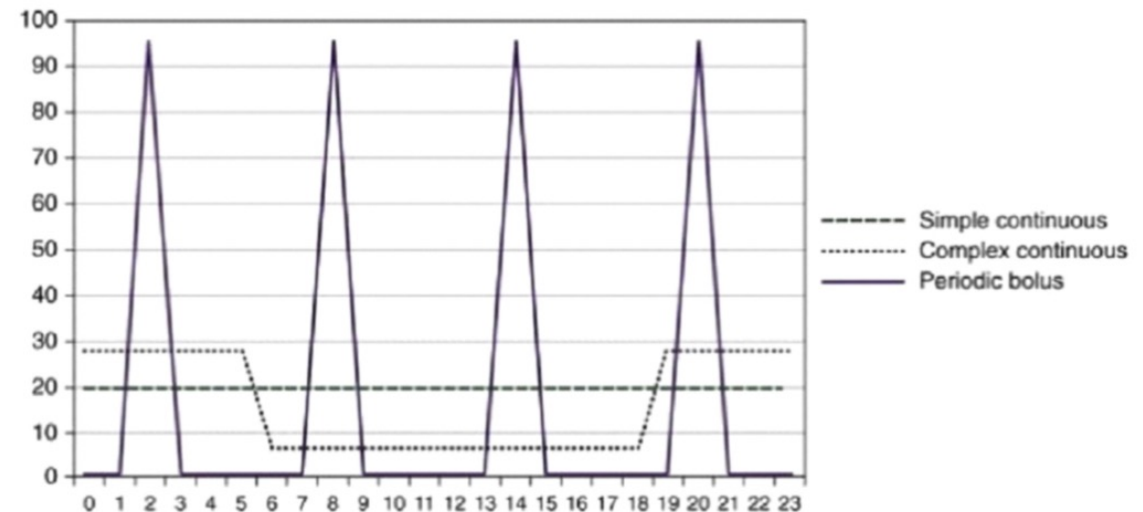


Fig. 1. Various modes of intrathecal delivery. (From Saulino M. Baclofen pump management. In: Buvanendran A, Diwan S, Deer T, editors. Intrathecal drug delivery for pain and spasticity, vol. 2. 71646th edition. Philadelphia: Elsevier; 2011. p. 167; with permission.)

Received: July 9, 2015 Revised: August 30, 2015 Accepted: September 15, 2015

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12361

Intrathecal Baclofen Dosing Regimens: A Retrospective Chart Review

Jacob S. Clearfield, MD; Mary Elizabeth S. Nelson, DNP, APNP; John McGuire, MD; Lisa E. Rein, MS; Sergey Tarima, PhD

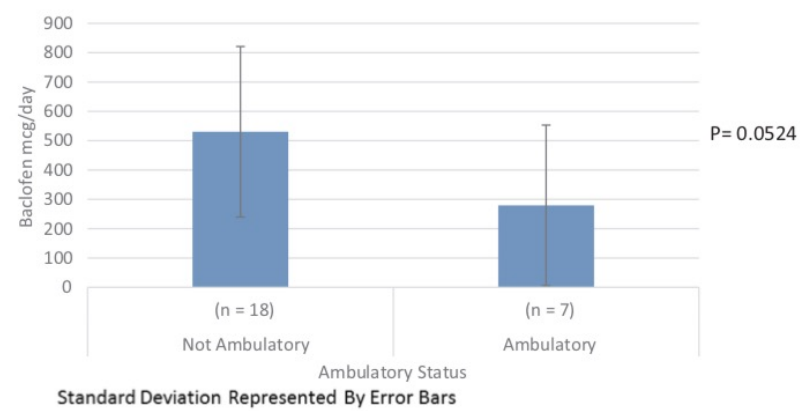


Figure 2. Mean dosages at end of study by ambulatory status.

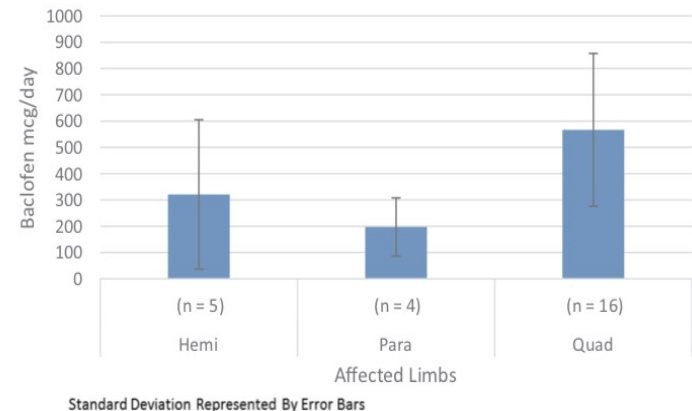


Figure 3. Mean dosages by affected limbs distribution.

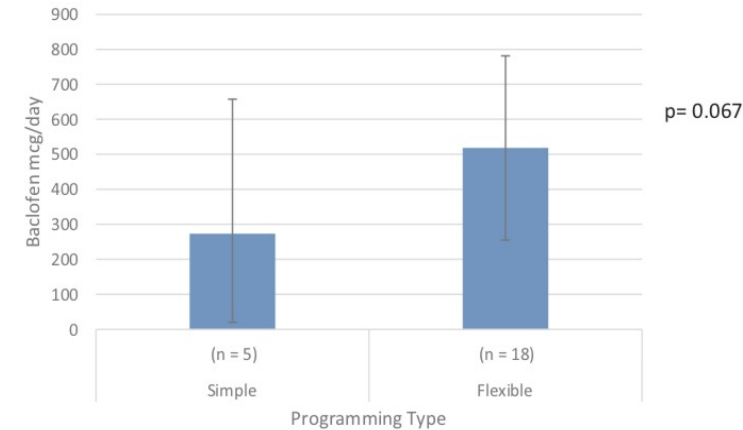


Figure 4. Mean dosages by programming type.

Long term management

PM R. 2014 Jun;6(6):506-513.e1. doi: 10.1016/j.pmrj.2013.12.005. Epub 2013 Dec 17.

Long-term intrathecal baclofen: outcomes after more than 10 years of treatment.

Mathur SN¹, Chu SK², McCormick Z³, Chang Chien GC⁴, Marciniak CM⁵.

Retrospective chart review

- Pt's with ITB for 10-24 years
- Low levels of pain
- Moderate levels of patient satisfaction
- Low to moderate levels of fatigue
- Infrequent to mild-moderate spasms
- High levels of satisfaction with ITB therapy

A Clinical Study of Intrathecal Baclofen Using a Programmable Pump for Intractable Spasticity

Daniel Guillaume, MD, PhD, Anthony Van Havenbergh, MD, PhD, Michael Vloeberghs, MD, PhD, Joan Vidal, MD, Geir Roeste, MD, PhD

- Significant decrease in muscle tone
- Pt's reported decrease pain on NRS
- 87% of physicians in one clinical study rated their overall satisfaction for patient outcomes as good or very good



Intrathecal baclofen therapy versus conventional medical management for severe poststroke spasticity: results from a multicentre, randomised, controlled, open-label trial (SISTERS)

Michael Creamer,¹ Geoffrey Cloud,^{2,3} Peter Kossmehl,⁴ Michael Yochelson,^{5,6} Gerard E Francisco,^{7,8} Anthony B Ward,⁹ Jörg Wissel,¹⁰ Mauro Zampolini,¹¹ Abdallah Abouihia,¹² Nathalie Berthuy,¹² Alessandra Calabrese,¹² Meghann Loven,¹³ Leopold Saltuari^{14,15}

Average Ashworth Scale Scores

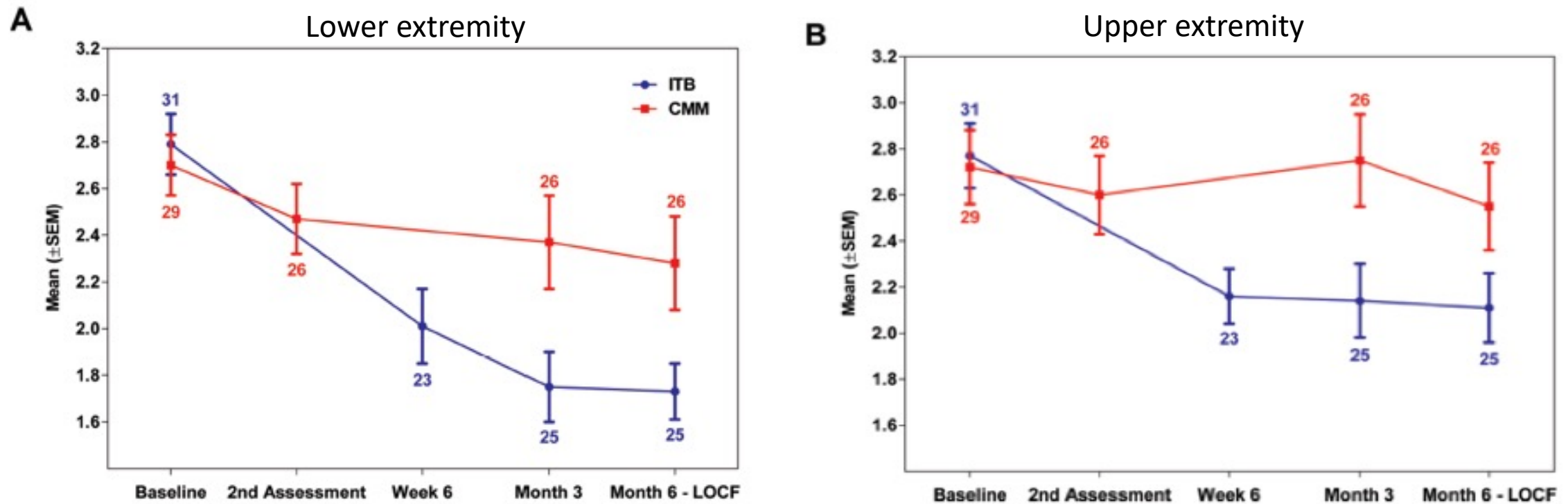


Figure 2 Average AS score for the lower and upper limbs by study visit (ITT population). Mean (SEM) values for average AS score in the LE (panel A) and UE (panel B) of the affected side across patients by treatment arm (ITB vs CMM) and study visit. LOCF imputation was performed for the month 6 assessment using month 3 data; the number of patients analysed per visit is indicated. The second assessment (CMM arm) was done on day 21. AS, Ashworth Scale; CMM, conventional medical management (arm); ITB, intrathecal baclofen (arm); ITT, intention-to-treat; LE, lower extremities; LOCF, last observation carried forward; UE, upper extremities.

Safety

- Education pt and family about baclofen withdrawal
- Low reservoir alarm should be 3 ml (instead of 2 ml)

Summary

- ITB is safe and effective in decreasing spasticity
- Pt's should be carefully selected and educated about known risks of ITB
- Dose may vary based on diagnosis and underlying functional status
- Dose should be carefully titrated within therapeutic window
- Educate all patients and family members about the risks of IT baclofen withdrawal