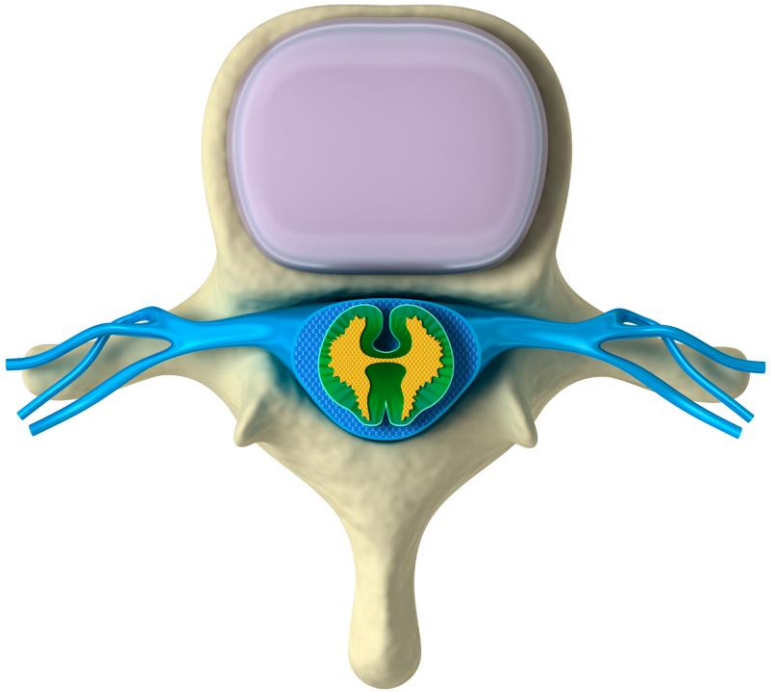
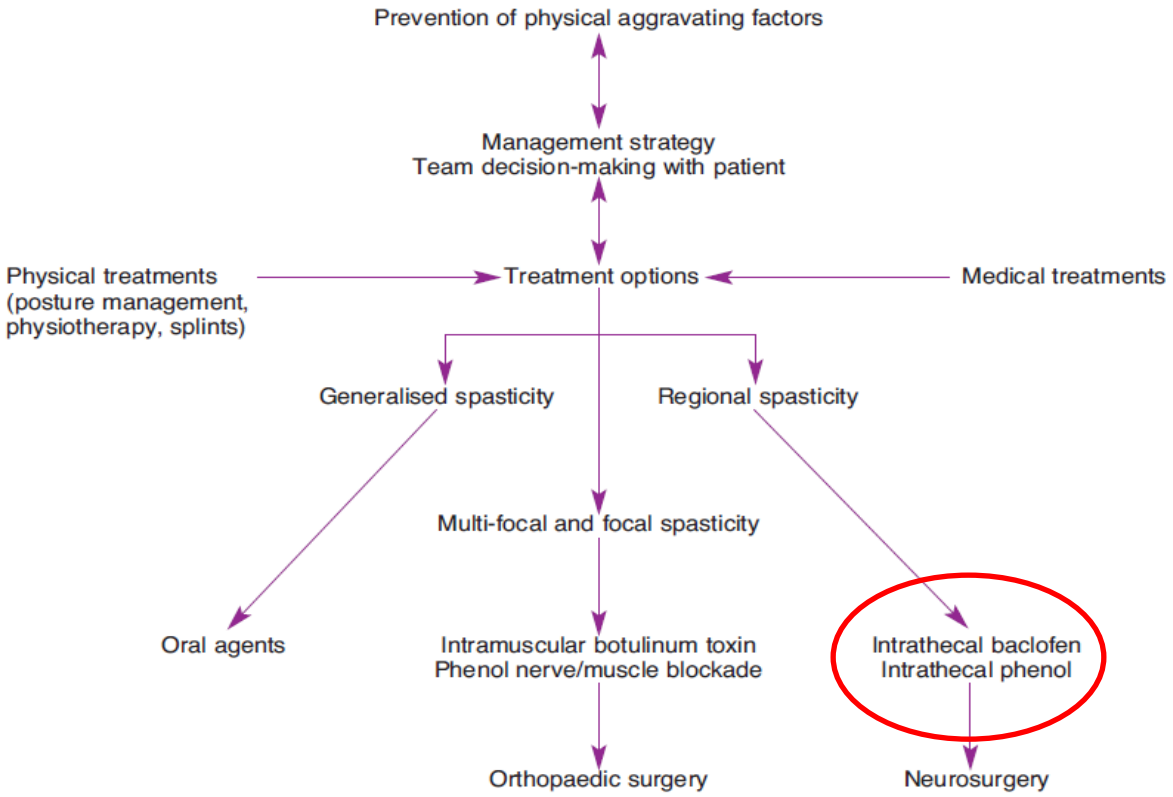
ADVANCES & CONSIDERATIONS IN THE USE OF INTRATHECAL TREATMENTS FOR MANAGING SPASTICITY



HAYDEN KIRK
DOC Conference
14th Sept 2016

SPASTICITY INTERVENTIONS

Particularly challenging in prolonged disorders of consciousness



+ psychology, psychiatry, pain management….. *or nothing*

- Thibaut et al., Spasticity in disorders of consciousness: A behavioral study *Europ Jnl of Phys & Rehab Med*. Volume 51, Issue 4, 1 August 2015, Pages 389-397
- Spasticity in adults: management using botulinum toxin RCP 2009

INTRATHECAL PHENOL

- First used in 1950's
- Neurolytic chemical – protein coagulation causes nonselective tissue destruction and initiates Wallerian degeneration in motor and sensory nerves
- Aim: Reduce hip flexor, extensor and adductor spasms
- Treatment surpassed by new oral antispasmodics, ITB and botulinum toxins.

- Jarrett, L; Nandi, P; Thompson, AJ. Managing severe lower limb spasticity in multiple sclerosis: does intrathecal phenol have a role? *Journal of neurology neurosurgery and psychiatry*; DEC, 2002; 73; 6; p705-p709
- Pinder, Colin; Bhakta, Bipin; Kodavali, Krishna, Intrathecal phenol: an old treatment revisited *Disability & Rehabilitation* 2008, Vol. 30 Issue 5, p381

PATIENT SELECTION

- Indications
  - Intractable lower limb spasticity unresponsive or unsuitable to other management options and causing pain, or day to day care problems (e.g. difficulties with seating, perineal hygiene, dressing, hoisted transfers)

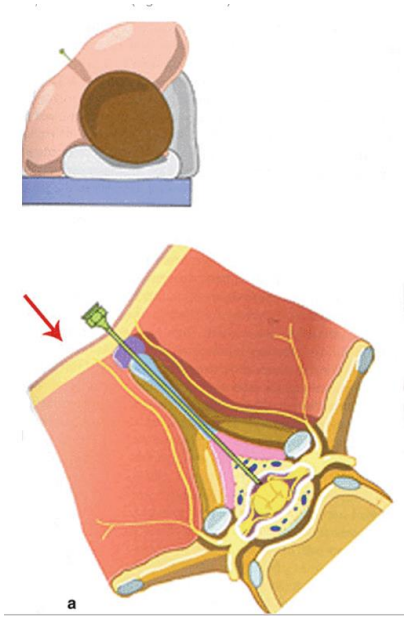
- Relative contraindications
  - Being sexually active. Patient able to pass urine but incontinent, bladder managed with convene/pads.
  - Patient incontinent of faeces but some sensation of need to pass faeces still present

- Absolute contraindications
  - Intact bowel and bladder function, intact sensation, functionally useful lower limb movement, *potential for spontaneous recovery of underlying neurological condition*

- Pinder, Colin; Bhakta, Bipin; Kodavali, Krishna, Intrathecal phenol: an old treatment revisited *Disability & Rehabilitation* 2008, Vol. 30 Issue 5, p381

IP PROCEDURE

- Patient position with lumbar spine horizontal and 30˚ anterior rotation
- Trial of local anaesthetic (bupivacaine) injected L2/3 or L3/4
- If successful proceed to IP injection
- 5% Phenol in glycerol injected and position maintained for 20mins – 6 hours
- Repeat on alternate side if required >24hrs
- Monitor BP for at least 1 hour



Stevenson VL, Jarrett L Spasticity Management; A practicle multidisciplinary Guide. 1st ed. 2006 Informa Oxon.

IP OUTCOMES – Jarrett 2002

- 25 patients with MS with EDSS ≥ 8 (non-ambulatory)
- Mean 3.2 injections (11 repeat)
- 16 improved ease with PADL
- Pain reduced from 11 with pre-existing pain to 4 no pain, 7 reduced pain
- Ashworth Scores reduced by median1.5 – 2
- All experienced a reduction in spasms (10 complete)

ADVERSE EFFECTS

- No AE's with bladder or sexual function
- Five reported changes in bowel function
- Short term moderate drop in BP

- Jarrett, L; Nandi, P; Thompson, AJ. Managing severe lower limb spasticity in multiple sclerosis: does intrathecal phenol have a role? *Journal of neurology neurosurgery and psychiatry*; DEC, 2002; 73; 6; p705-p709

IP OUTCOMES – Pinder 2008

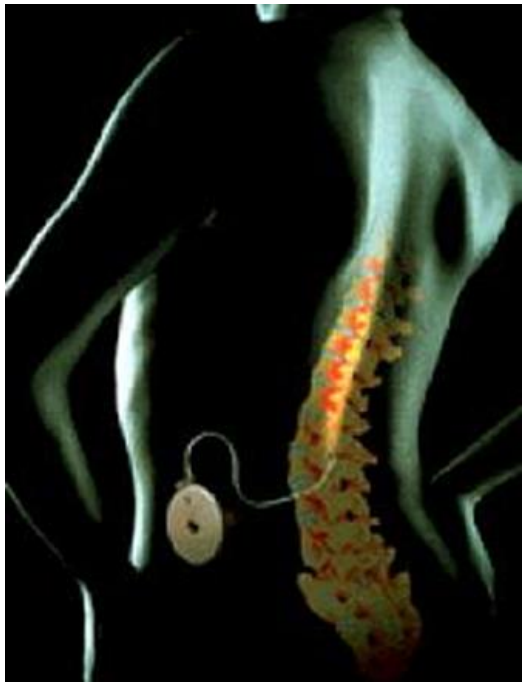
- Forty patients: 34 with MS, 3 had multiple strokes affecting both legs,1 had traumatic brain injury, 1 had hypoxic brain injury and 1 CP
- Spasticity: 6 slight improvement, 28 substantial improvement, 6 excellent improvement
- Goals: 56% substantial improvement or excellent improvement
- ROM: 38 had increased passive ROM
- No change in upper limb function
- Duration of action 2 -23months (mean 8.3)

ADVERSE EFFECTS

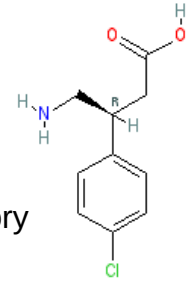
- 3 patients acute urinary retention requiring temporary catheterisation
- 1 mild chemical meningitis

- Pinder, Colin; Bhakta, Bipin; Kodavali, Krishna, Intrathecal phenol: an old treatment revisited *Disability & Rehabilitation* 2008, Vol. 30 Issue 5, p381

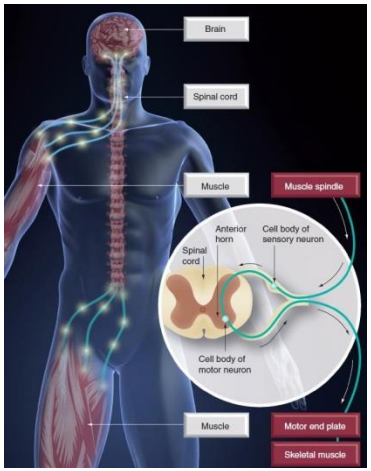
INTRATHECAL BACLOFEN

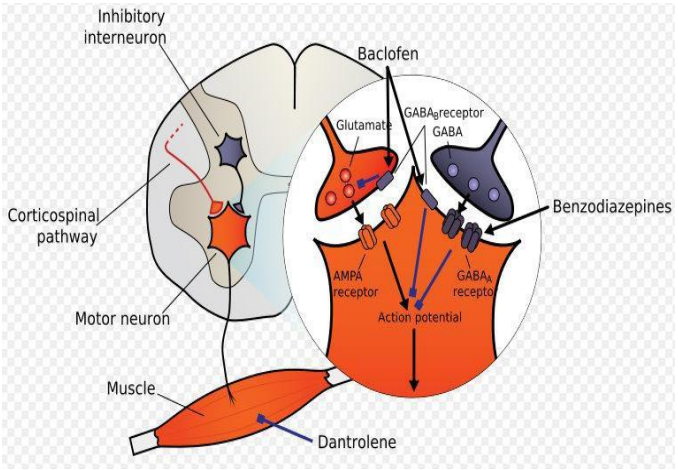


PHARMACODYNAMICS



- **BACLOFEN**:
  - β-(4-chlorophenyl)-γ-aminobutyric acid (β-(4-chlorophenyl): a chemical analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).
  - is a selective $GABA_B$ agonist and lipophilic so crosses the blood brain barrier whereas GABA cannot cross.
  - binds to $GABA_B$ receptors, which are found predominantly pre-synaptically in the 1a sensory afferent neurones, the interneurones and also post-synaptically in the dorsal horn motor neurones. The pre-synaptic agonistic action on $GABA_B$ receptors reduces calcium influx and suppresses the release of excitatory neurotransmitters, including glutamate – PRESYNAPTIC INHIBITION. In addition, there is a postsynaptic increase in potassium conductance - POSTSYNAPTIC HYPERPOLERAISATION, the net result being *inhibition of both monosynaptic and polysynaptic reflexes*

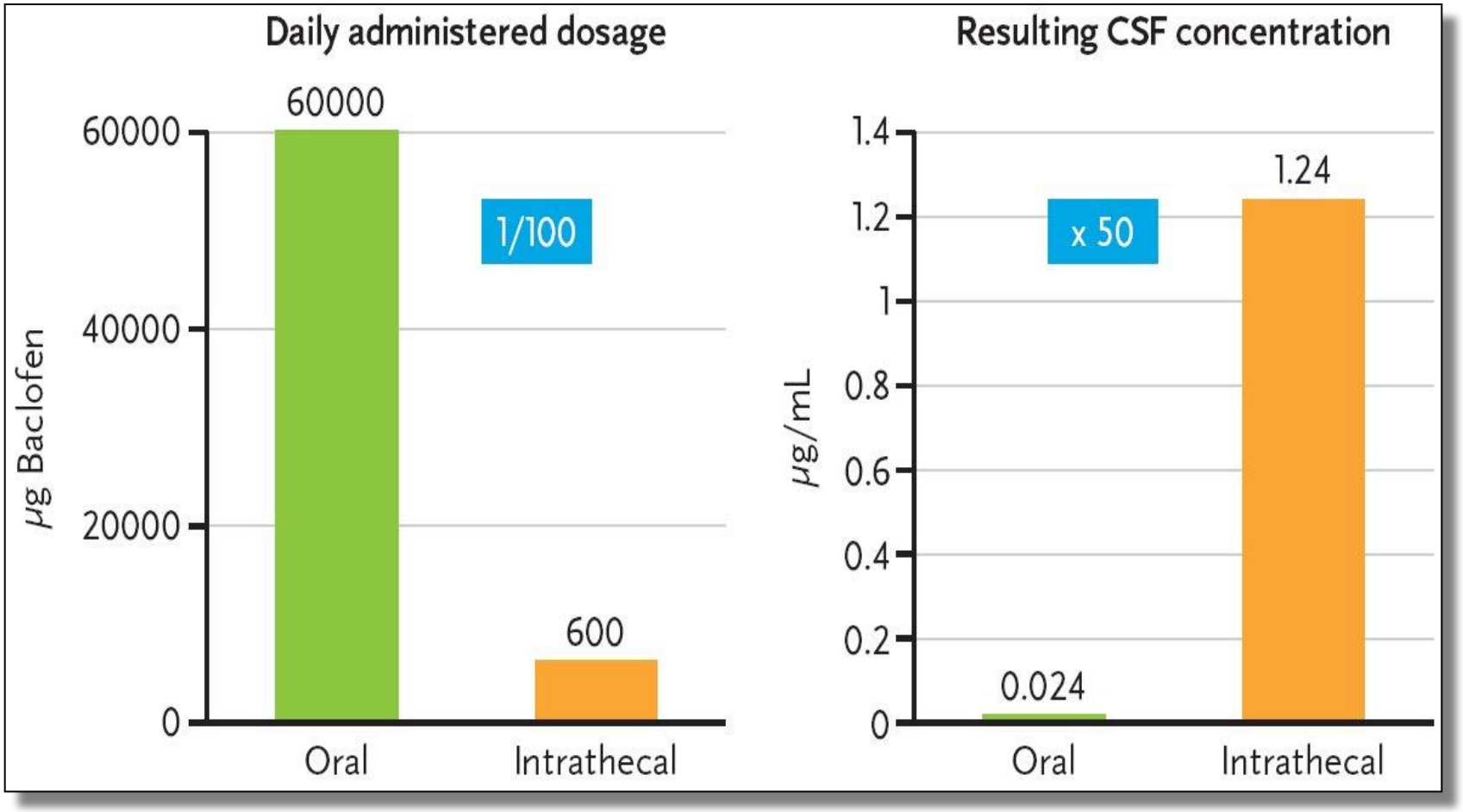




Yang et al., Distribution & depression of the GABA(B) receptor in the spinal dorsal horn of adult rat. Brain Res Bull 2001;55:579-85

DOSAGE: ITB VS. ORAL BACLOFEN

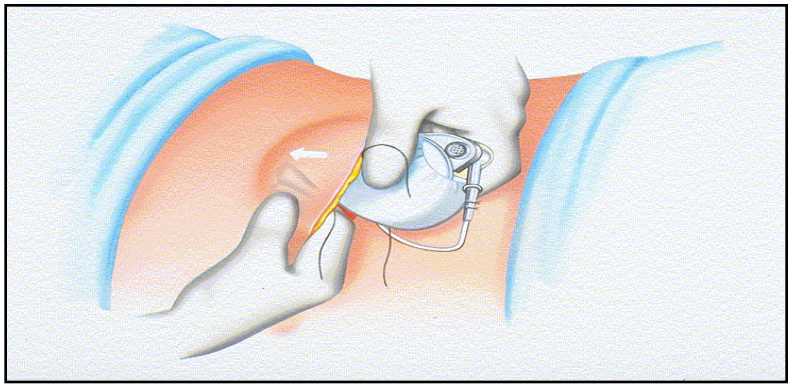
ITB Therapy: higher CSF concentrations (↑50 times) with lower baclofen dose (↓100 times)1

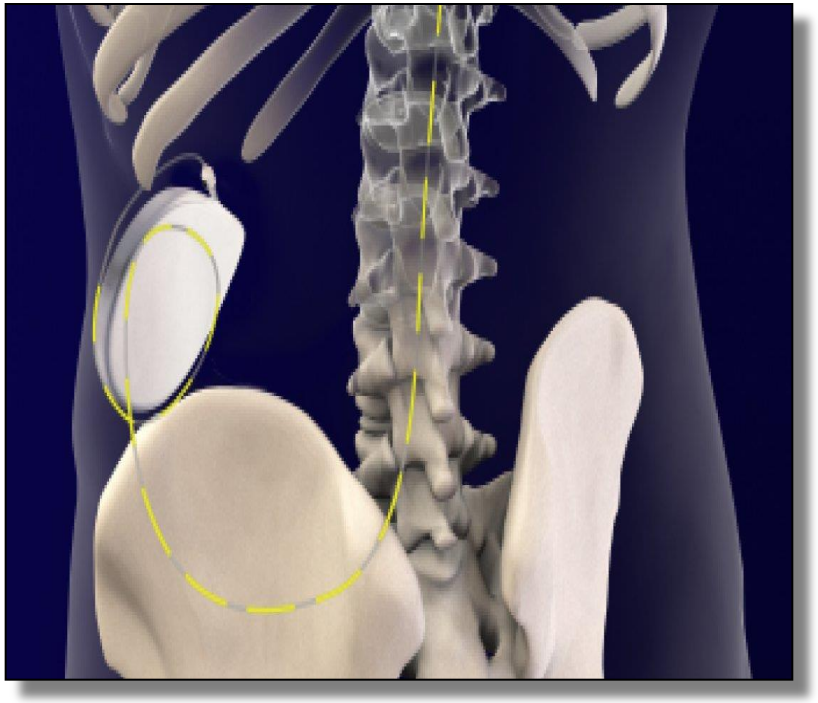


WHAT IS ITB THERAPY?

- Implantable, programmable pump delivers baclofen directly into the intrathecal space. Trialed 1985

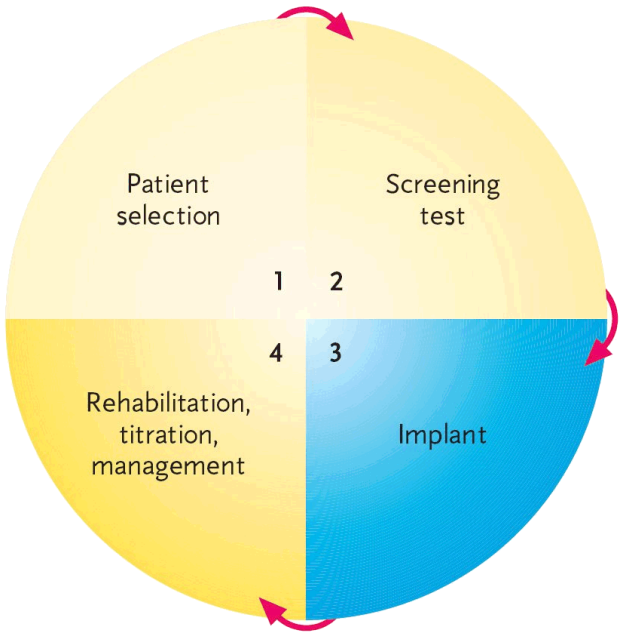
- Commissioned when a patient has chronic, severe, diffuse spasticity and/or dystonia of spinal or cerebral origin which renders them a full time wheelchair user or bed bound. Defined as having an Ashworth score of ≥4 in at least two muscle groups which is uncontrolled by oral medication or conventional means





- Penn RD, Kroin JS. Continuous intrathecal baclofen for severe spasticity. Lancet 1985;ii:125–7
- ITB Policy – Neurosciences CRG NHSCB/D04/P/c 2013

STAGES OF ITB THERAPY



Patient Selection Algorithm: Intrathecal Baclofen (ITB™) Therapy for Spasticity of Cerebral and Spinal Origin

See the intrathecal baclofen (baclofen injection) drug package insert for full prescribing information, including indications and precautions in patients with impaired renal function, autonomic dysreflexia, psychotic disorders, schizophrenia, or confusion states; and in women who are pregnant or during lactation.

Step 1: INCLUSION CRITERIA FOR ITB THERAPY

1. Spasticity due to spinal cord injury, multiple sclerosis, cerebral palsy, brain injury (1 year post trauma), of any etiology, i.e. trauma, stroke and anoxia.

Yes

2. Spasticity is severe – Ashworth Scale score ≥3.
   Patient presents with increase in tone that significantly interferes with movement and/or care, which may be accompanied by spasms.
   These conditions may place the patient at risk for complications associated with immobility:
   – contractures
   – hip dislocations
   – bony deformity
   – decubitus ulcer
   – urinary tract infections

Yes

3. Patient has sufficient body mass to support a pump.

Yes

4. Patient/family/caregivers and providers agree on treatment goals that are both explicit and suitable for the patient. Appropriate goals range from facilitating transfer and hygiene among dependent patients to improving ambulation among patients who are less severely disabled.

Yes

5. Patient/family/caregivers are motivated to achieve the treatment goals, and they are committed to meeting the follow-up care requirements.

Yes

CONTINUE TO STEP 2

Step 2: EXCLUSION CRITERIA FOR ITB THERAPY

1. Infection is present at time of screening or implant.

No

2. Patient has a history of allergy (hypersensitivity) to oral baclofen.

No

CONTINUE TO STEP 3

Step 3: GENERAL CLINICAL CONSIDERATIONS

Please see reverse side of chart to review General Clinical Considerations.

Case-related considerations support decision to proceed with screening test.

Case-related considerations do not support decision to proceed with screening test.

STOP

Step 4: TEST SCREENING FLOW CHART

Day 1 (optional) Bolus: 25mcg
+ response → Implant
No response

Day 2 (24 hrs. after previous screening bolus, if any). Bolus: 50mcg
+ response → Implant
No response

Day 3 (24 hrs. after previous screening bolus). Bolus: 75mcg
+ response → Implant
No response

Day 4 (24 hrs. after previous screening bolus). Bolus: 100mcg
+ response → Implant
No response → Discontinue screening: not an Intrathecal Baclofen Therapy candidate.

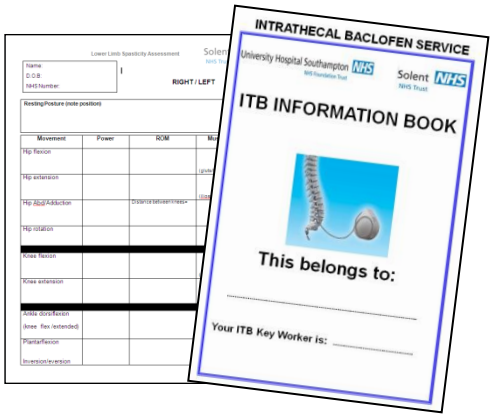
ITB REVIEWS & REFILLS

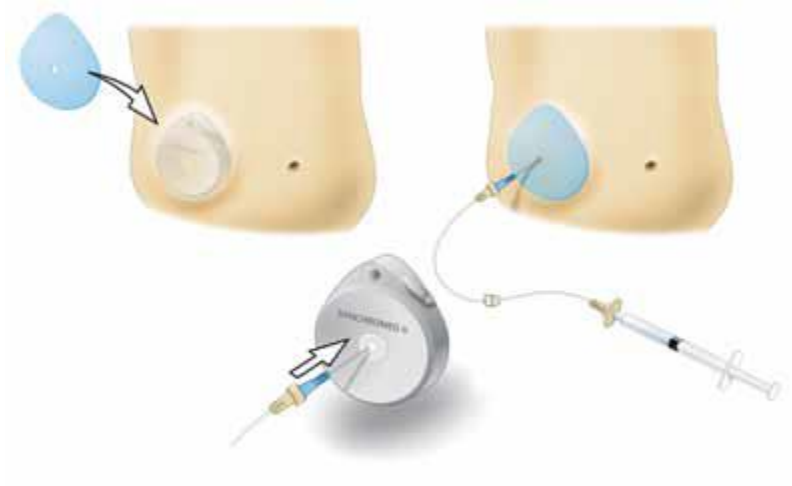
REVIEWS:

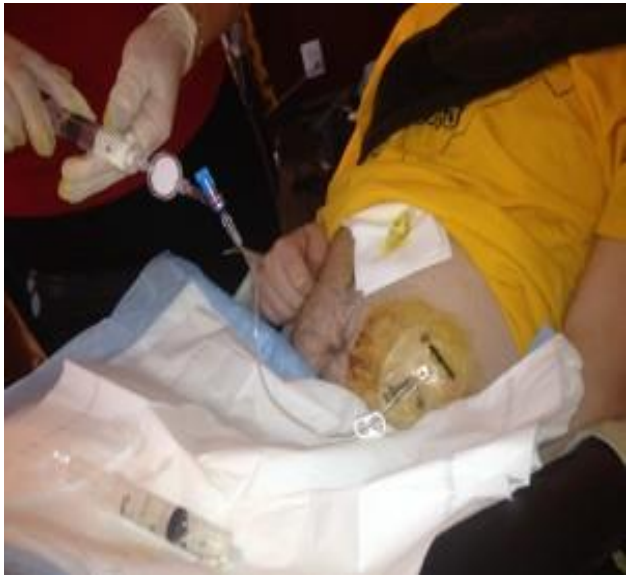
- life style, medication & medical changes, spasticity aggravating factors & symptoms

REFILLS & DOSE CHANGES:

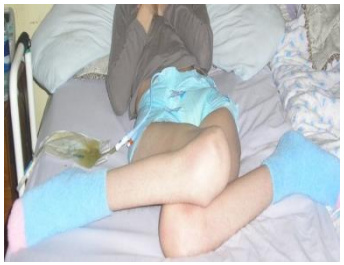
- aseptic technique
- programming







2014/5 AUDIT: PATIENT PROFILE



DIAGNOSIS: 6 MS, 3 TBI, 2 CP, 1 Anoxia, MND, Metachromatic, Spinal tumour.

AGE: 40 (18 – 60)

SEX: 9 Female, 6 Male*

AMBULANT: 2 walkers, 2 standing transfers, 11 hoist

DOSE: 455mcg/24 hrs (37 – 1500mcg)

DELIVERY: 10 SC, 5 BOLUS (2 night, 1 day, 2 periodic)

MEDICATION: 6 (antispasmodics)

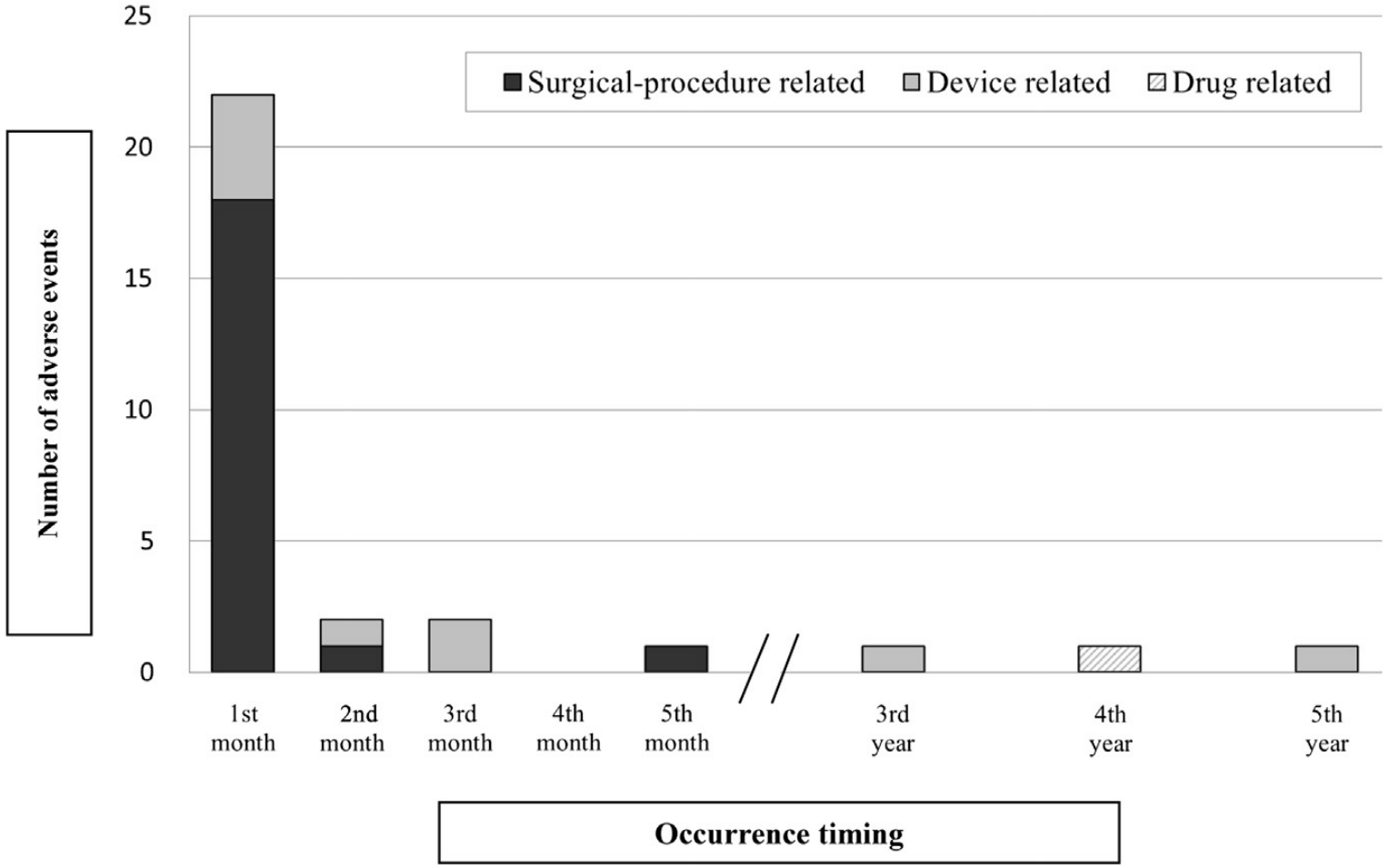
COMPLICATIONS: 0 (1 battery alarm, 1 revised catheter)

2014/5 AUDIT: OUTCOMES

SPASTICITY CLINIC RECOMMENDATIONS PRE ITB TRIAL	
Oral antispasmodics	7 (6 gabapentin, 4 baclofen, 2 pregablin, 1 diazepam)
Physio/exercise/posture	6
FES	2
Continence	2
BTX	1
Other	1 orthotics, 1 environmental controls, 1 OT, Intrathecal Phenol
N/A	2 (no spasticity)

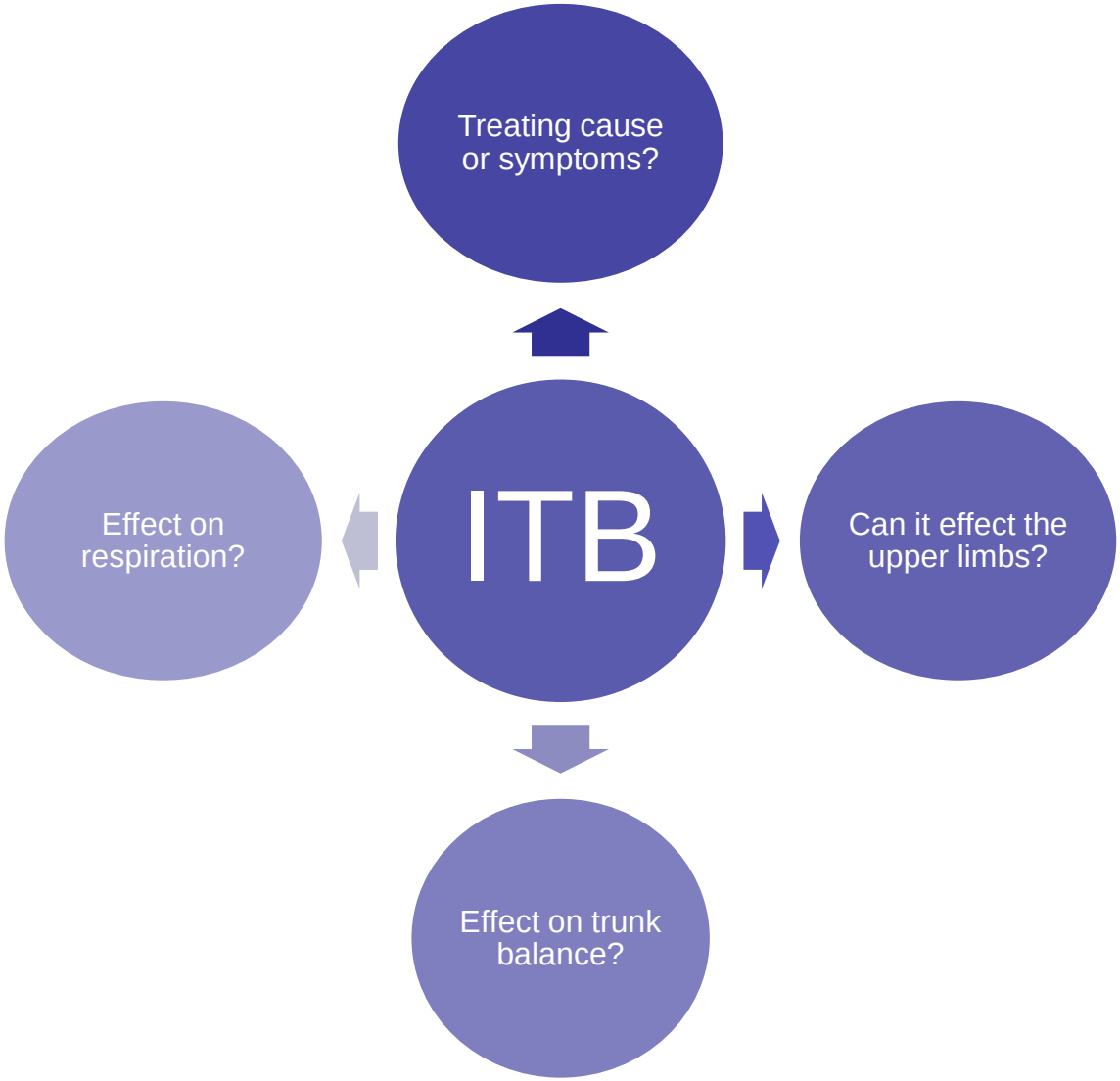
Code	EFFECTIVENESS OF ITB:	ITB GOALS (/9)
1	Cease / control spasms	**7**
2	Improve seating comfort	**6**
3	Improve transfers	**3**
4	Improve ease of care including dressing	**2**
5	Improve maintaining personal hygiene	**3**
6	Reduce pain	**4**
7	Reduce risk of pressure sores	**4**
8	Allow withdrawal of oral anti-spasmodics	**9**
9	Reduce risk of other complications (specify)	**1**
10	Other	

COMPLICATIONS

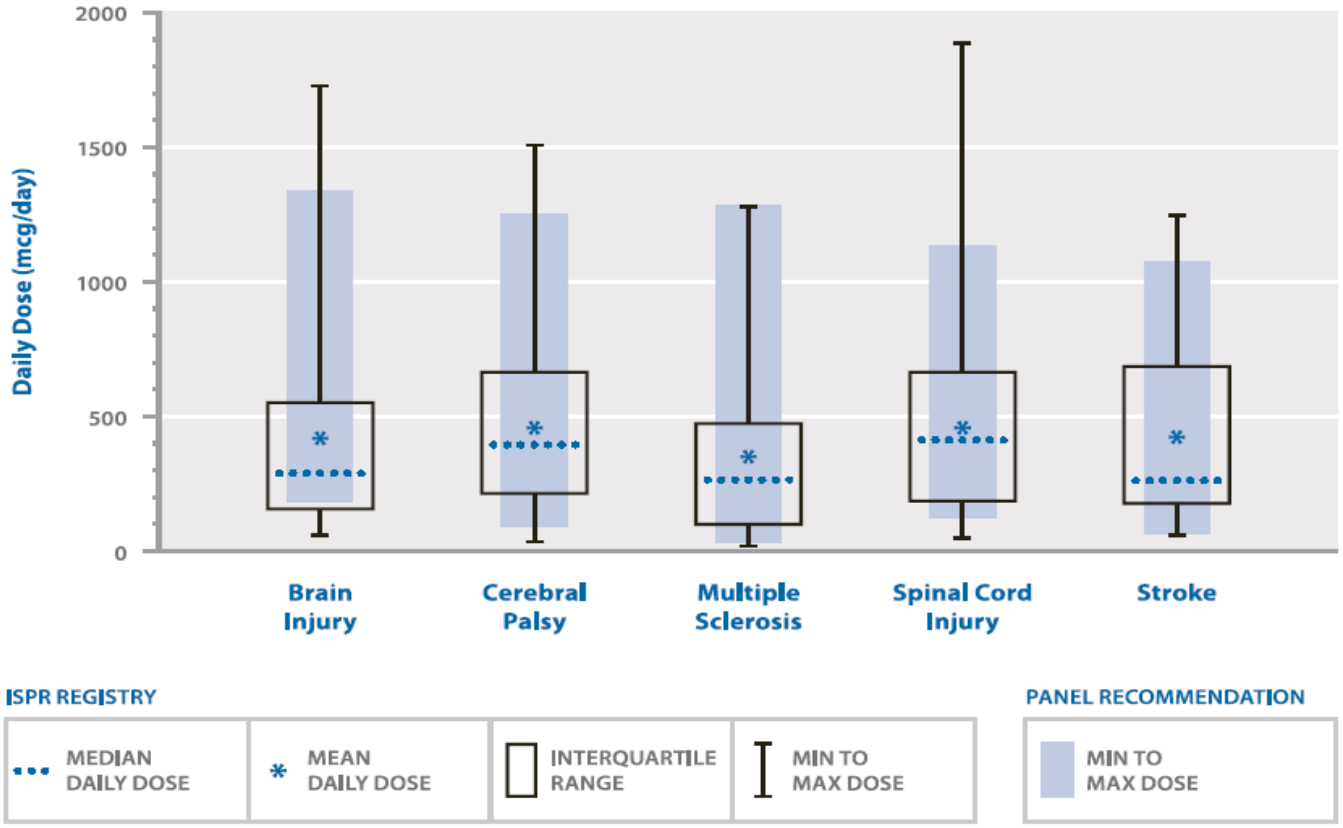


Borrini et al., Occurrence of Adverse Events in Long-Term Intrathecal Baclofen Infusion: A 1-Year Follow-Up Study of 158 Adults Archives of Physical Medicine and Rehabilitation 2014;95:1032-8

EFFECTIVE *but* UNKOWNS…



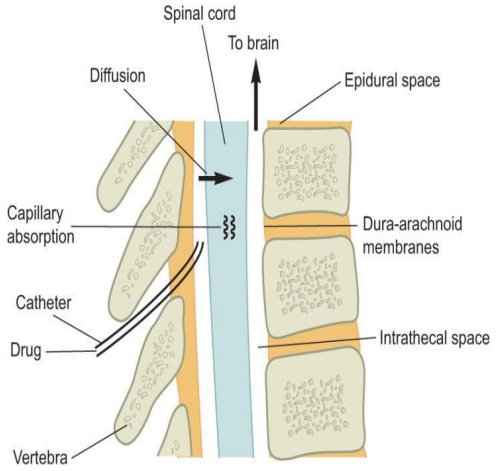
TREATING CAUSE OR SYMPTOMS?



Particularly difficult to differentiate in prolonged disorders of consciousness

- Boster A. L.,et al.,. 2016. Best Practices for Intrathecal Baclofen Therapy: Dosing and Long-Term Management. *Neuromodulation* 2016; 19: 623–631
- Thibaut et al., Spasticity in disorders of consciousness: A behavioral study *Europ Jnl of Phys & Rehab Med*. Volume 51, Issue 4, 1 August 2015, Pages 389-397
- Schnakers C et al., Assessment and Management of Pain in Patients With Disorders of Consciousness. *PM&R* 2015 7:S270-S277

PHYSIOLOGY

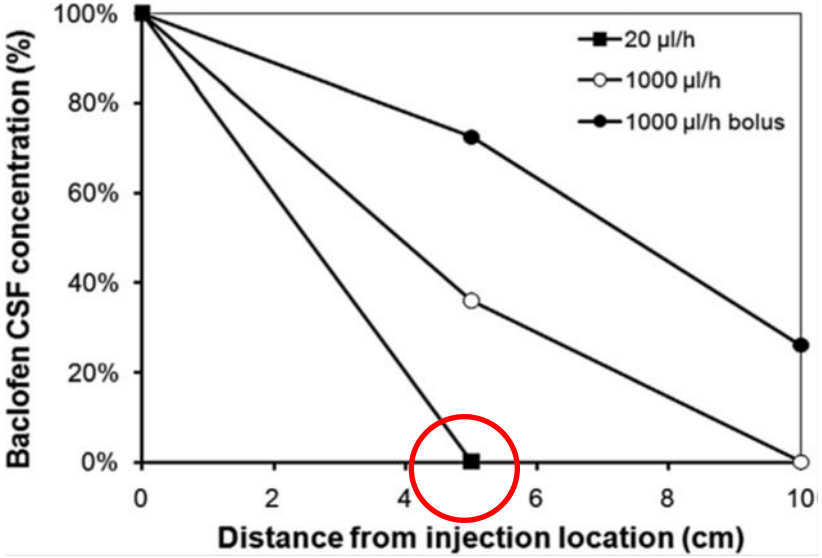


- CFS moves in pulsating manner synchronous with heart beat in caudal direction.
- Limited CFS movement at thoracic / lumbar region
- CSF Absorption via arachnoid villi at in superior sagittal sinus & spinal cord (25-50%)
- Baclofen density > CSF so distribution affected by gravity

Herre et al., Clinical Relevance of Pharmacological and Physiological Data in Intrathecal Baclofen. *Therapy Archives of Physical Medicine and Rehabilitation* 2014;95:2199-206

ABSORPTION | **DISTRIBUTION** | METABOLISM | ELIMINATION

- During intrathecal infusion the plasma concentrations do not exceed 5ng/ml, confirming that baclofen passes only slowly across the blood-brain barrier.
- According to the half-life measured in the CSF, CSF steady-state concentrations will be reached within 24hrs.
- During continuous intrathecal infusion, a baclofen concentration gradient is built up in the range between 1.8 : 1 and 8.7 : 1 (mean: 4 : 1) from lumbar to cisternal CSF.



- Herre et al., Clinical Relevance of Pharmacological and Physiological Data in Intrathecal Baclofen. *Therapy Archives of Physical Medicine and Rehabilitation* 2014;95:2199-206
- Lioresal® Intrathecal SPC emc+ 2016

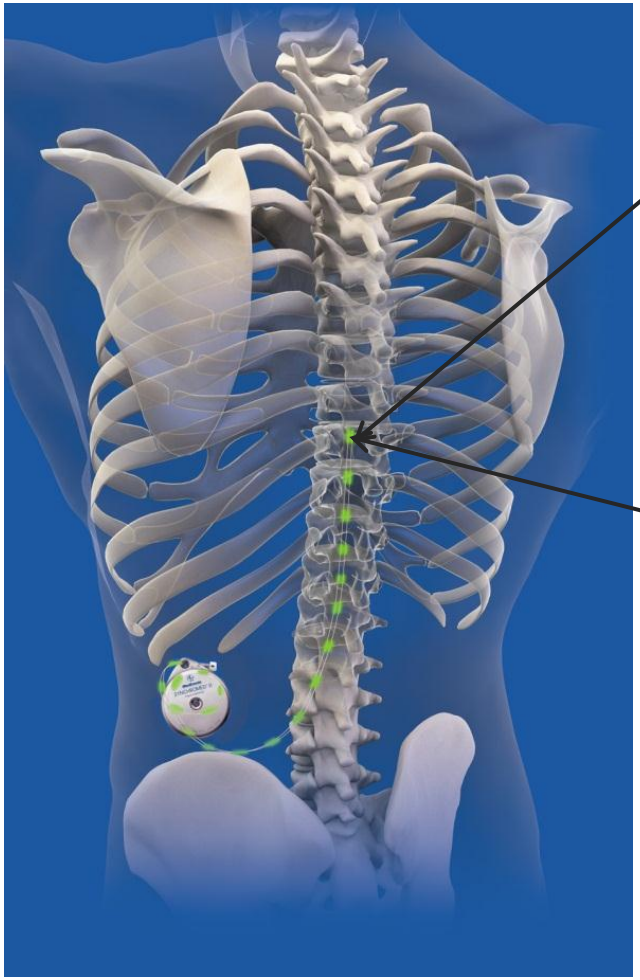
TREATMENT OPTIONS……

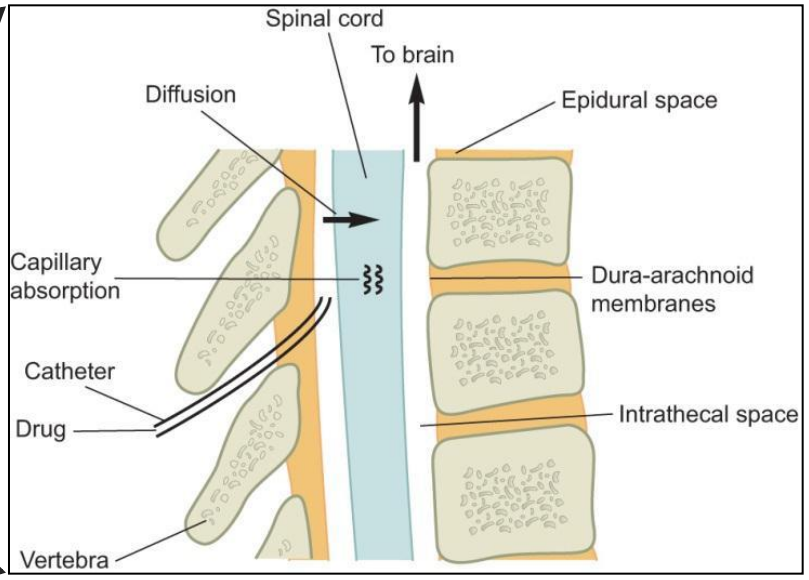
1. Increase effect on upper limbs
    - Increase dose
    - Lower concentrations and increase speed of delivery
    - Maintain concentrations but increase speed of delivery (periodic bolus)
    - Higher catheter tip placement

2. Vary effect on tone during the day/night
    - Flexi-dosing

3. Management of baclofen tolerance
    - ITB holiday
    - Periodic bolus

CATHETER PLACEMENT

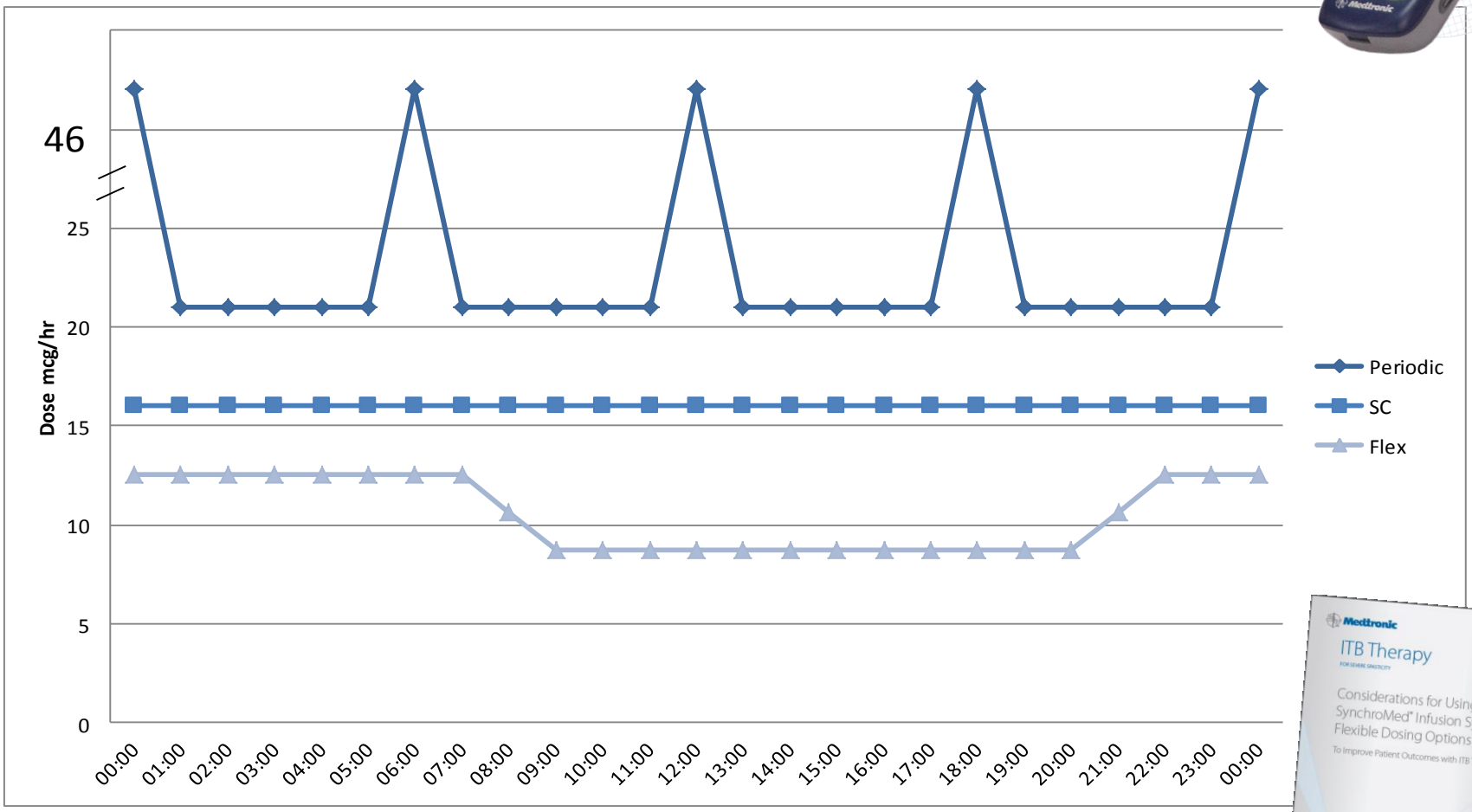


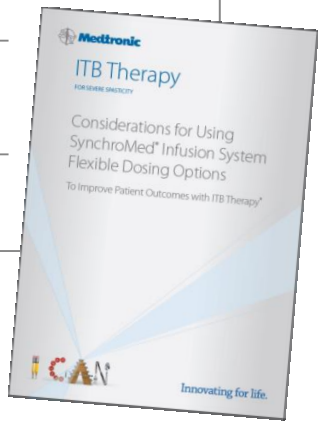


- Lower Limb spasticity:
  - Insertion at L4/5 or L3/4
  - Catheter tip *lumbar enlargement T11 – L1*
- Upper Limb spasticity:
  - Cervical enlargement C3 – T2
  - *Mid thoracic T6-7*
  - IVB

- National Intrathecal Baclofen Document Consensus Guidelines for Intrathecal Baclofen Therapy May 2010
- Grabb et al., Midthoracic catheter tip placement for intrathecal baclofen administration in children with quadriparetic spasticity. *Neurosurgery* 1999;45:833-6
- Turner M; Nguyen HS; Cohen-Gadol AA; Intrathecal baclofen as an alternative to intrathecal baclofen for intractable spasticity or dystonia: outcomes and technical considerations *Journal of Neurosurgery: Pediatrics*, 2012 Oct; 10(4): 315-319. 5p
- Albright et al., Intraventricular baclofen for dystonia: techniques and outcomes *Journal or neurosurgery: pediatrics*. January 2009 / Vol. 3 / No. 1 / Pages 11-14
- Herre et al., Clinical Relevance of Pharmacological and Physiological Data in Intrathecal Baclofen. *Therapy Archives of Physical Medicine and Rehabilitation*; 2014 ;95:2199-206

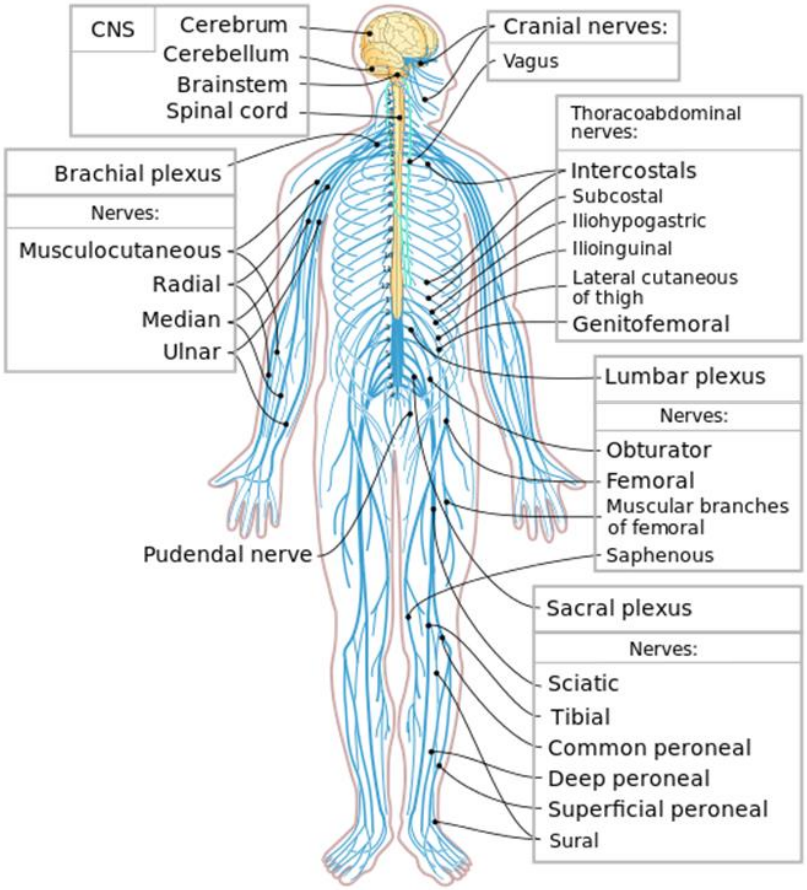
DOSING PATTERNS





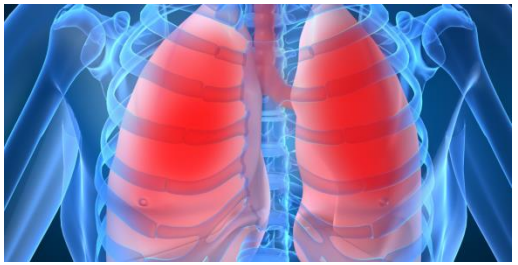
- Boster et al., Best practices for intrathecal baclofen therapy: dosing and long term management. *Neuromodulation* 2016;19:623-31
- Clearfield et al., Intrathecal Baclofen Dosing Regimens: A Retrospective Chart Review. *Neuromodulation* 2016; 19: 642–649
- Herre et al., Clinical Relevance of Pharmacological and Physiological Data in Intrathecal Baclofen. *Therapy Archives of Physical Medicine and Rehabilitation* 2014;95:2199-206

NO EFFECT ON THE TRUNK?



Gray, N.; Vloeberghs, M.. Effect of continuous intrathecal baclofen on sitting in children with severe cerebral palsy European Journal of Paediatric Neurology, January 2014, 18(1):45-49

RESPIRATORY EFFECT?



+ve:	Kishima 2016	6 pts, spirometry measures pre & post implant – increase in FVC, %FVC & FEV1.
Ln:	Bensmail 2006	20pts, polysmnography pre & post implant – improved sleep, no effect on apnoea's / LFT's
-ve:	Bensmail 2012	11pts, severely disabled patients polysmnography pre & post implant + *bolus vs SC delivery* – increased the RDI and central apnoea's with bolus

- Kishima H., et al., Respiratory Function Under Intrathecal Baclofen Therapy in Patients With Spastic Tetraplegia.*Neuromodulation* 2016 19: 650–654
- Bensmail D, et al. Effect of intrathecal baclofen on sleep and respiratory function in patients with spasticity. *Neurology* 2006 Oct;67(8): 1432–6.
- Bensmail D et al., Pilot Study Assessing the Impact of Intrathecal Baclofen Administration Mode on Sleep-Related Respiratory Parameters Arch Phys Med Rehabil 2012 Vol 93,

ITB & CONSCIOUSNESS in DOC

Drug	Type of study	Diagnosis	Patients (*n*)	Injury nature	Outcomes	Duration of clinical improvement/ recovery of consciousness
GABAergic drugs						
Zolpidem	Case series	PVS	3	TBI (2 patients), anoxia (1 patient)	Transient clinical improvement after daily therapy	4 h
Zolpidem	Case report	PVS	1	TBI	Transient clinical improvement after daily therapy	3–4 h
Zolpidem	Case report	MCS?	1	Anoxia	Transient clinical improvement after daily therapy	2–3 h
Zolpidem	Case report	MCS	1	Anoxia	Transient clinical improvement after daily therapy	3–4 h
Zolpidem	Case report	MCS?	1	Anoxia	Transient clinical improvement after daily therapy	1–6 h
Zolpidem	SPECT study case report	Aphasia post-stroke	1	–	Transient improvement of aphasia and cerebral perfusion after daily therapy	~12 h
Zolpidem	SPECT study case series	2 patients with motor deficit, 1 patient with spinocerebellar ataxia type 2, 1 patient with PVS	4	TBI, anoxia	Improvement of cerebral perfusion	–
Zolpidem	SPECT study case series	Spinocerebellar ataxia type 2	4	–	Improvement of cerebral perfusion	–
Zolpidem	SPECT study	VS	127	TBI	Improvement of cerebral perfusion	–
Zolpidem	Double-blind, placebo-controlled study	PVS, MCS	15	TBI, anoxia, stroke	Transition from PVS to MCS in 1 patient only	Permanent
Zolpidem	Prospective, double-blind, placebo-controlled, randomized study	PVS in children	3	TBI, anoxia	No significant improvement	–
Zolpidem	Case report	MCS	1	TBI	No significant improvement	–
ITB	Case report	PVS	1	Haemorrhage	Recovery of consciousness	Permanent
ITB	Case report	PVS	1	TBI	Clinical improvement	Permanent
ITB	Case series	PVS	5	TBI, anoxia, haemorrhage	Clinical improvement in all but 1 patient	Permanent

Ciurleo, R; Bramanti, P; Calabro, RS. Pharmacotherapy for Disorders of Consciousness: Are 'Awakening' Drugs Really a Possibility? *DRUGS*; NOV, 2013; 73; 17; p1849-p1862

ITB & CONSCIOUSNESS HYPOTHESES

- FDA & Medtronic - ITB not indicated in 1st Year post TBI

- GABAergic (monoaminergic)
  - Post ABI initial unfavourable conditions - inhibition dominates causes LOC
  - Prolonged O2 starvation - secondary changes to GABA receptors to provide neurodormancy protection
  - Zolpidem: modulates/stimulates abnormal /neurodormant $GABA_A$ receptors
  - ITB stimulation of $GABA_B$ receptors
    1. Spinal level modulation of ascending nociceptive and proprioceptive pathways
    2. Brain; low level baclofen may 'restore' the cortico-thalamo-cortical connections influencing wakefulness, (memory) and consciousness
    3. Stopping 'oral' anti-spasmodics…

- Clauss R.P Neurotransmitters in Coma, Vegetative and Minimally Conscious States, pharmacological interventions *Medical Hypotheses* 75 (2010) 287–290
- Sara M et al., Intrathecal Baclofen in Patients With Persistent Vegetative State: 2 Hypotheses *Arch Phys Med Rehabil* Vol 90, July 2009
- Al-Khodairy et al., Influence of intrathecal baclofen on the level of consciousness and mental functions after extremely severe traumatic brain injury: *Brain Injury*, 2015 29:4, 527-532,
- Pistoia et al., Intrathecal Baclofen: Effects on Spasticity, Pain, and Consciousness in Disorders of Consciousness and Locked-in Syndrome Curr Pain Headache Rep (2015) 19:466

CONCLUSION

- Intrathecal Phenol
  - Effective method for managing lower limb spasticity with limited follow up.
  - Potentially underutilised but irreversibility creates specific ethical considerations

- ITB spasticity
  - Limited research base but potential to *advance* therapeutic effect with more targeted treatment based on good clinical reasoning.
  - Patient status and delivery modes create many variables so careful monitoring of *all* parameters when initiating new treatments & research

- ITB consciousness & DOC
  - Case studies suggest ITB can potentially alter level of consciousness
  - Primary treatment goal should be spasticity *but* secondary monitoring and consideration of spinal and brain stimulatory effect would seem appropriate

FUTURE….?

- Less reliance on oral anti-spasmodics in cognitively vulnerable patients

- More therapeutic, pharmacological and surgical options

Ingale et al., Selective dorsal rhizotomy as an alternative to intrathecal baclofen pump replacement in GMFCS grades 4 and 5 children *Childs Nerv Syst* (2016) 32:321–325

THANK YOU FOR LISTENING