Tone management in MND

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Overview

Definitions

Presentations in MND

Assessment

Goal setting

Management

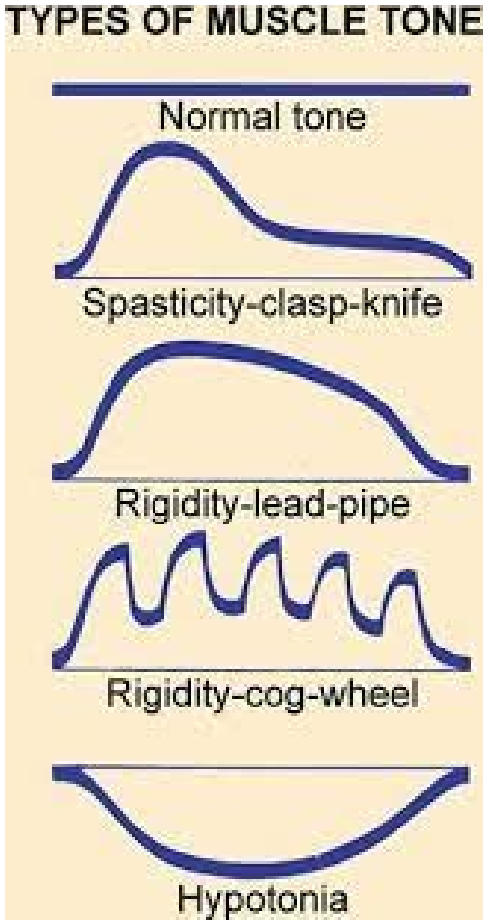
- Non-pharmacological
- Pharmacological

Definitions

- Tone
  - resting state of activity /amount of tension or resistance in muscles
  - posture, position, movement
- Hypertonia – stiff, resistance, spasms
  - Rigidity
  - Spasticity
  - Paratonia
- Hypotonia – floppy, loose
- Dystonia – uncontrolled muscle movements/contraction, sustained & repeated

Hypertonia presentations in MND

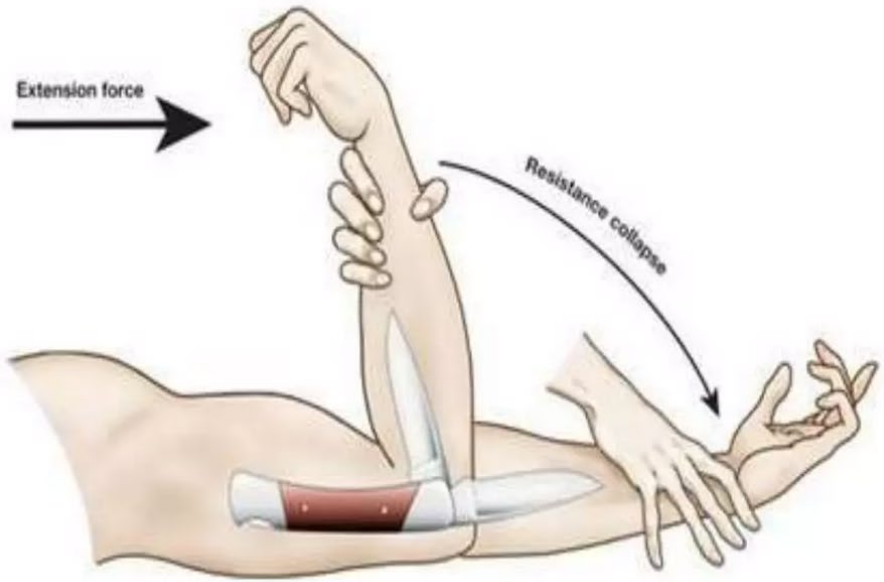
- Spasticity
- Rigidity
- Muscle cramps
- Clasp knife



Hypertonia

- RIGIDITY
  - “Lead pipe” i.e. not velocity dependent
  - Balanced flexor and extensor tone
- MUSCLE CRAMPS
  - > 90% of patients with ALS
  - Painful, involuntary contractions
  - Due to instability/dysfunction of motor unit (= a single motor neurone and all the muscle fibres it innervates)

Clasp knife



Spasticity

- Velocity dependent increase in muscle tone (Lance 1980)
- Unopposed contraction (spastic dystonia) leads to abnormal limb posture resulting in soft tissue change & biomechanical changes …in turn prevents muscle lengthening & perpetuates further stiffness (Burke , Wissel et 2013)
- UMN lesion presenting as intermittent or sustained involuntary activation of muscles (SPASM group, Burridge, Wood et al 2005)
- Imbalance between flexors and extensors

Spasticity in MND

- Spasticity due to UMN lesion
- All MND – 36% presented with spasticity[2]

- Primary Lateral Sclerosis > Amyotrophic Lateral Sclerosis [1]

  (and ? not in Progressive Muscular Atrophy = LMN form, <3-5%)

  - Those presenting with spasticity (27/ 661) had significantly better survival rates to those presenting with other signs & symptoms (p = 0.009)
  - No significant difference disease duration; tending to be younger at disease onset
  - Spasticity "ubiquitous" in PLS, but only 4.1% (27 patients) presented with it in ALS (and of those who developed it, had a long disease duration, consistent with UMN dominant variant)

- Spasticity (and pain?) may result in faster functional deterioration[2]

[1] *Tartaglia et al. Arch Neurol. 2007;64(2):232-236. https://doi:10.1001/archneur.64.2.232*

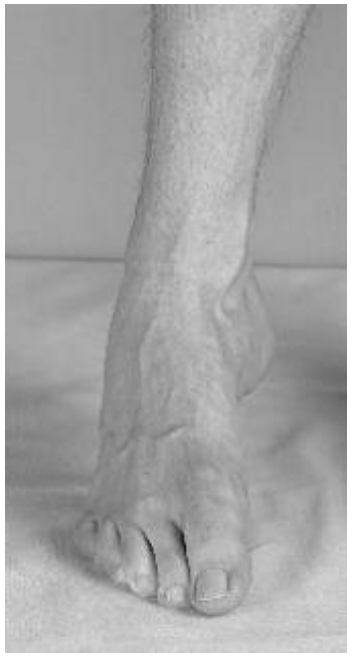
[2] *Verscheuren at al. Revue Neurologique. 2021; 177 (6);694-698. https://doi.org/10.1016/j.neurol.2020.08.009*

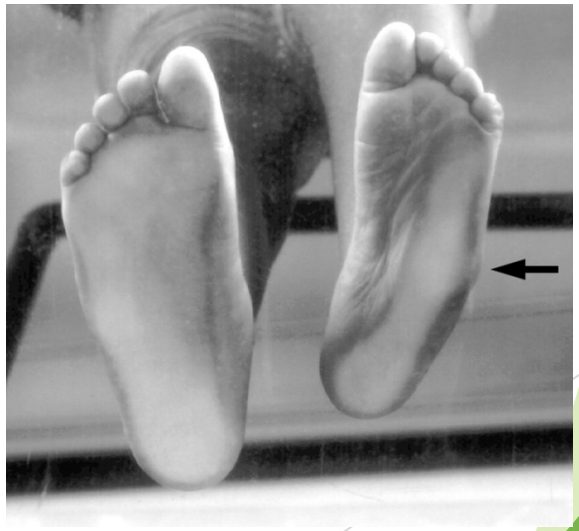
Why treat?

ICF	Problem	Effect
Impairment	Muscle spasms	Pain
		Difficulty with seating & posture
		Fatigue
	Abnormal trunk & limb posture	Contractures
		Pressure sores
		Deformity
	Pain	Distress & low mood
		Poor sleep
Activity	Active function loss	Reduced mobility
		Inability to use a limb in function
		Difficulty with sexual intercourse
	Passive function loss	Difficulty with care & hygiene
		Increased carer burden
Participation	Impact of any / all of above	Poor self esteem / self image
		Reduced social interaction
		Impact on family relationships
		Impact on work / societal role

Adapted from RCP / BSRM National Guidelines Spasticity in adult management


Medscape





Clinical assessment

- Aims:
  - To diagnose and identify pattern
  - Identify problems & set goals for intervention
  - Baseline measurement against which to measure

What else could it be?

- Contracture
- Pain

Key measurement methods

Method	Examples
Physical (generally at level of impairment)	**Range of movement** e.g. goniometry Anatomical distance e.g. inter-knee distance **Spasm frequency**
Rating scales (for symptoms or tasks)	**Graphic rating scales e.g. numeric or VAS for pain** **Verbal rating scales e.g. Likert scale**
Goal attainment	**Simple recording of treatment goals achieved** Goal attainment scaling
Formal standardised scales	**Impairment scales e.g. Ashworth, Tardieu** Passive function e.g. carer burden scales, timed care tasks **Active function e.g. motor function test**

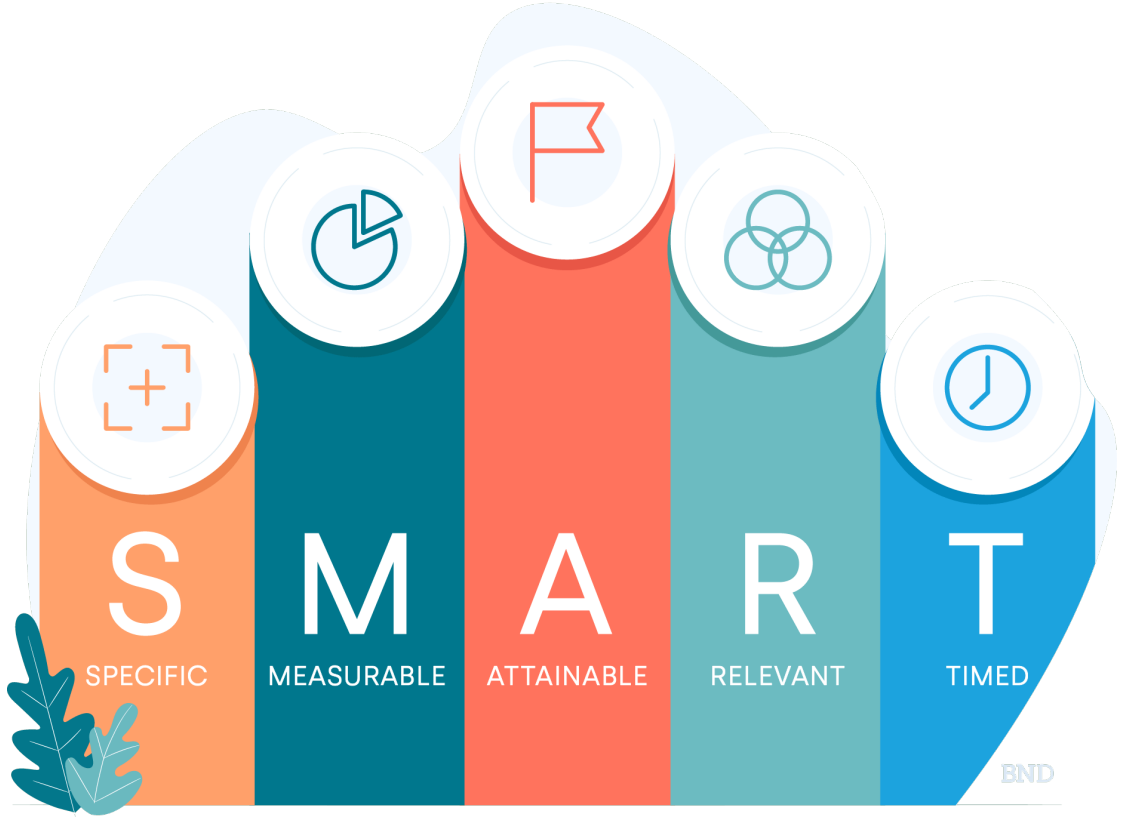
Modified Ashworth Scale

0	• No increase in tone
1	• Slight increase in tone • Catch/release at end ROM
1+	• Slight increase in tone • Catch/release and resistance through rest ROM (1/2 ROM)
2	• More marked increase in tone through ROM, but affected part moved easily
3	• Considerable increase in tone, passive movement difficult
4	• Affected part in rigid flexion and extension

Goal setting

- Prioritise what is important to the patient / is important for their care & wellbeing
- Motivation
- Efficiency (co-operative working)
- Effectiveness
- Enables progression of management

SMART goals



Management

- Goal orientated
- MDT
- No one single treatment will be effective in isolation

- Physical
- Pharmacological

Evidence for spasticity management in MND

- Limited
- Cochrane review 2012[1] – one study on exercise, too small
- De Visser 2018
- Principles are broadly same as for spasticity / increased tone management of other conditions

[1]Ashworth NL, Satkunam LE, Deforge D. Cochrane Review 2012. Treatment for spasticity (muscle tightness and spasm) in people with amyotrophic lateral sclerosis/motor neuron disease

[2]De Visser M. Lancet Neurology. 2018 Evidence for treatment of spasticity in motor neurone disease. https://doi.org/10.1016/S1474-4422(18)30493-9

NICE guideline NG42 – MND: Assessment and management

- Muscle cramps (all below unlicensed indications)
  - Quinine 1st line
  - Baclofen 2nd line
  - Tizanidine, dantrolene, gabapentin
- Muscle stiffness, spasticity or increased tone
  - Baclofen, tizanidine, dantrolene, gabapentin
  - Referral to specialist spasticity service – Sussex Rehabilitation Centre, Brighton General Hospital
- Review via MDT assessments
- Exercise programmes

Physical

Management of aggravating factors = NOCICEPTIVE STIMULI

- Pain / discomfort
- Constipation
- Infection (UTI, RTI, pressure sores)
- Ingrown toenail
- Tight clothing
- Poor postural management

Physical therapy interventions

- Education
- Self management
- 24 hour postural management – lying, seated, mobilising – changes in position
- Stretching – manual / exercises, standing, positioning, orthoses /splints
- Training – task training and strength training
- Electrical stimulation (TENS, FES)

Pharmacological agents for muscle cramps

- NB Cochrane review 2012 – no evidence for any particular treatment
- Quinine 200-300mg before bed (restricted use in USA due to adverse events)
- Magnesium (Mg citrate 200-400mg 1-2 hours before bedtime)
- Clonzepam 250mcg before bed
- Levetiracetam (20 patients, small open label pilot study) – reduced cramp frequency & severity

Mexiletine for muscle cramps

- Sodium channel blocker (cramps may be due to persistent sodium ion increase of LMNs) with muscle relaxant properties (by reducing persistent sodium currents)
- Used in myotonia. Now also trialled in SCA type 3 and ALS [1,2]
- 2 randomised double blind placebo controlled trials
  - Effective – reduction in cramp frequency (P 0.04 / P<0.05) and intensity (P 0.08 / 0.01)
    - Average reduction 1.8 cramps per day (from 5.3 with placebo to 3.5 with mexiletine)
  - Safe – in each study, one episode of imbalace
  - Well tolerated at lower doses of 150mg twice daily (SEs occurred at 450mg bd doses – dizziness, falls, tremor, nausea)

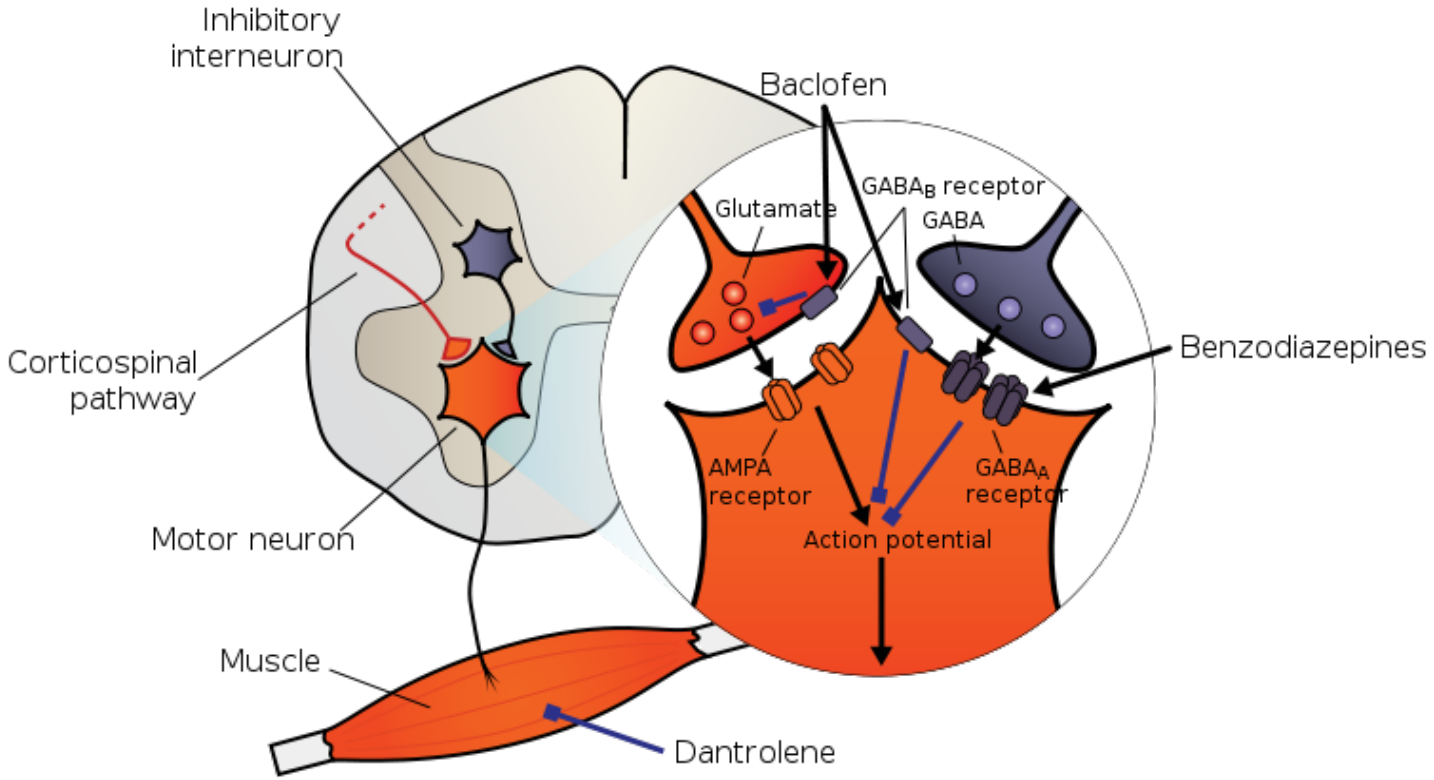
[1]*Weiss et al. Neurology. 2016 Apr 19; 86(16): 1474–1481. doi: 10.1212/WNL.0000000000002507*

[2]*Oskarsson et al. Muscle Nerve. 2018 Mar 6:10.1002/mus.26117. doi: 10.1002/mus.26117*

Pharmacological agents for spasticity

- Oral agents (generalised)
  - Baclofen
  - Tizanidine (clonidine – transdermal)
  - Dantrolene
  - Benzodiazepines
  - Gabapentin / pregabalin
  - Cannabis based
- IM BTX / phenol (focal or multifocal)
- Nerve blocks (LA / phenol)
- IT baclofen / phenol (regional)

Treatment targets



General principles

- Most useful for generalised / multifocal spasticity but can be used in any pattern +/- other interventions
- Use early if physical interventions insufficient
- Titrate dose up for an effective trial
- Side effects may occur – but can settle if persisted with for >2 weeks
- Multiple agents can be used – but try to introduce one at a time
- Consider if any contraindications / interactions – but these may be relative cautions & could still be used

- Target pain management

Baclofen

- Starting dose 5-10mg twice a day – aiming to titrate up in 5-10mg increments every 3- 7days
- Maximum dose 100mg total daily dose in 3-4 divided doses
- Main limiting side effect is sedation. Watch for exacerbating existing weakness
- No monitoring requirements
- If withdrawn, needs to be done gradually to avoid rebound/withdrawal symptoms

Tizanidine

- Can be used as 2nd line (if baclofen not effective or tolerated)
- Or as add on therapy to baclofen (but watch for excessive sedation)

- 2mg once daily to start, building up to 2mg three times a day, and further increases every 3 days – aiming for 24mg total in 3-4 doses (max 36mg)

- Side effects – sedation, hypotension, rarely – liver dysfunction

- Requires monitoring of LFTs whilst establishing
- Gradual reduction of dose if weaning off

Dantrolene

- 3rd line or can be used if sedation is biggest limiting factor as works at muscle rather than CNS level
- Starting 25mg once daily, build up to 25mg three times daily (increase every 3-5 days). Aiming for 75mg three times a day (max total dose 100mg four times a day)
- Side effects – nausea, abdo pain, bowel change, liver dysfunction
- Requires monitoring of LFTs whilst establishing
- Gradual reduction of dose if weaning off

Benzodiazepines

- Diazepam
- Clonazepam

- Can be used regularly or as prn
- Especially useful for spasms or cramps, particularly in evening / night

- Side effects - sedation

- Clonazepam 250 - 500mcg at night (can use daytime doses also)

GABAergic agents

- Gabapentin
  - 100 – 300mg three times a day starting dose
  - Maximum 1200mg three times a day
- Pregabalin
  - 75-150mg twice a day
  - Maximum 300mg twice a day

- 1st or 2nd line for spasticity in MS – NICE guideline
- Useful if concomitant neuropathic or chronic pain

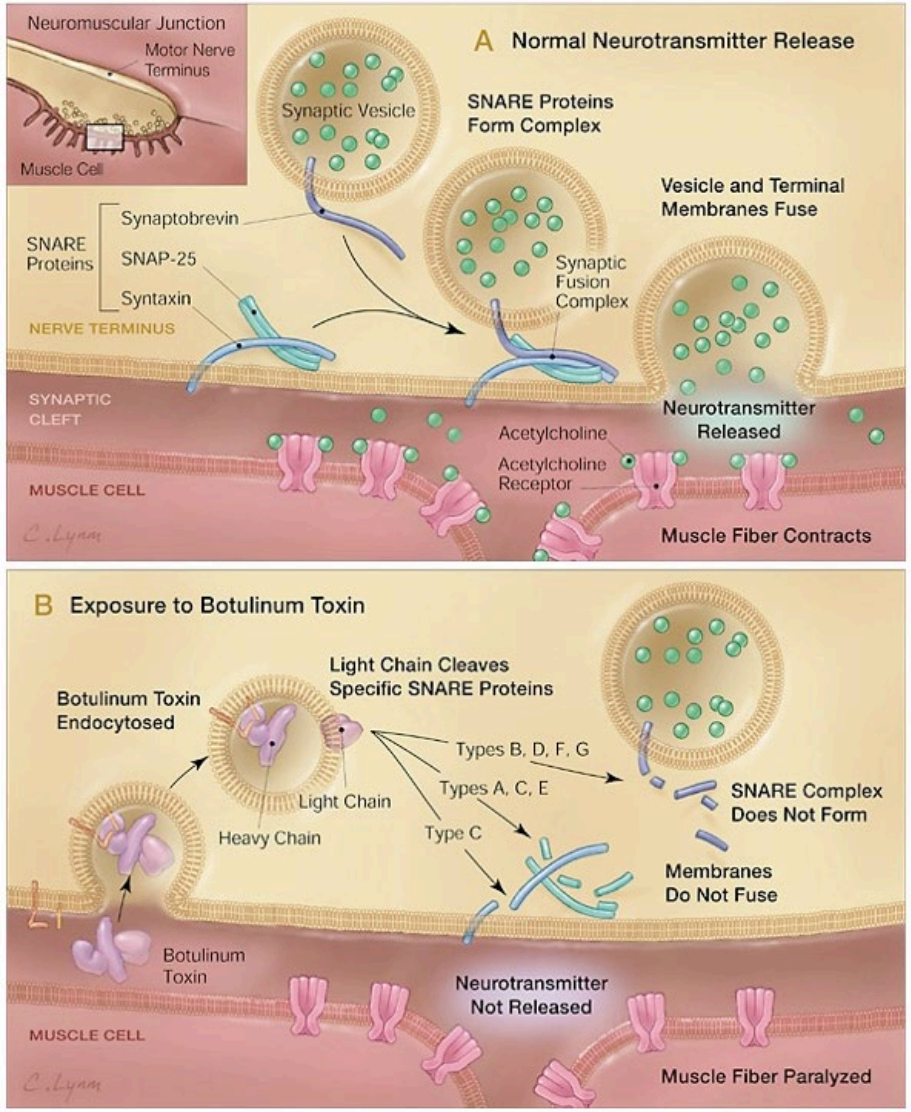
- Side effects – sedation, oedema

Cannabis based medicines

- Nabiximols (THC and cannabidiol, 1:1, Sativex)
- CANALS[1] (Cannabis Sativa Extract in Amyotrophic Lateral Sclerosis and other Motor Neuron Disease) – 60 patients, 4 Italian Centres. Randomised, double blind, placebo controlled proof of concept study.
- Improvement in MAS on nabiximol, deterioration on placebo over 6 weeks
- Well tolerated, no serious adverse effects

[1]*Riva et al. Lancet Neurology 2019; 18(2): 155-164. doi.org/10.1016/S1474-4422(18)30406-X*

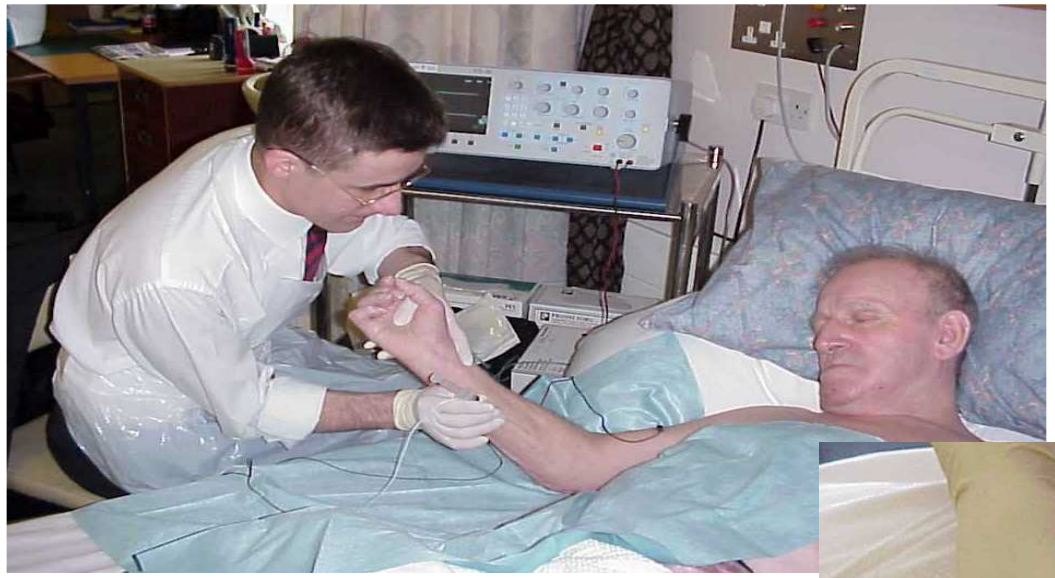
Mechanism of action of BTX

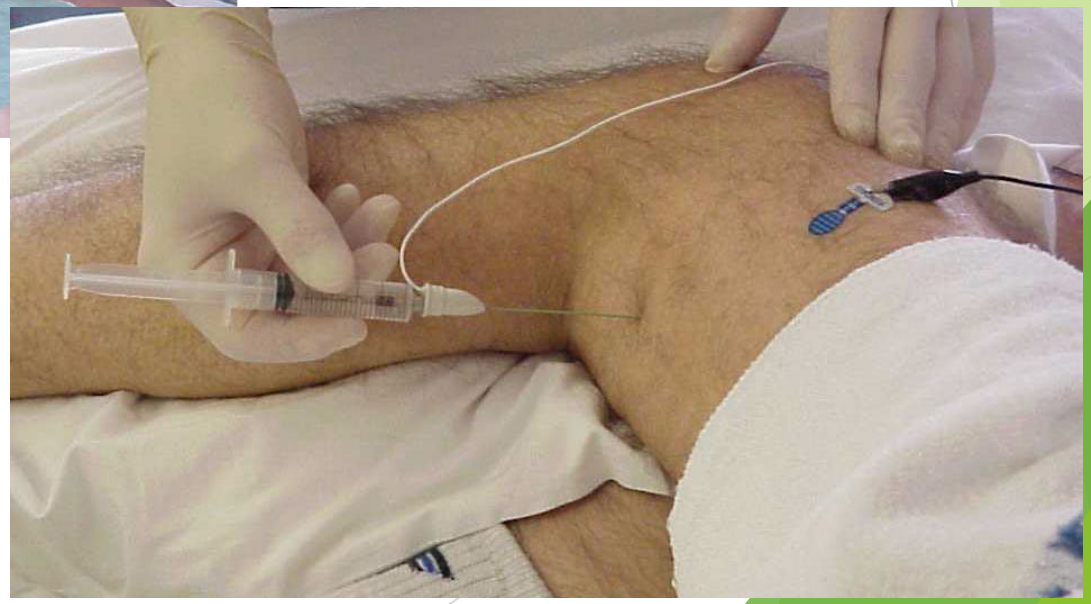


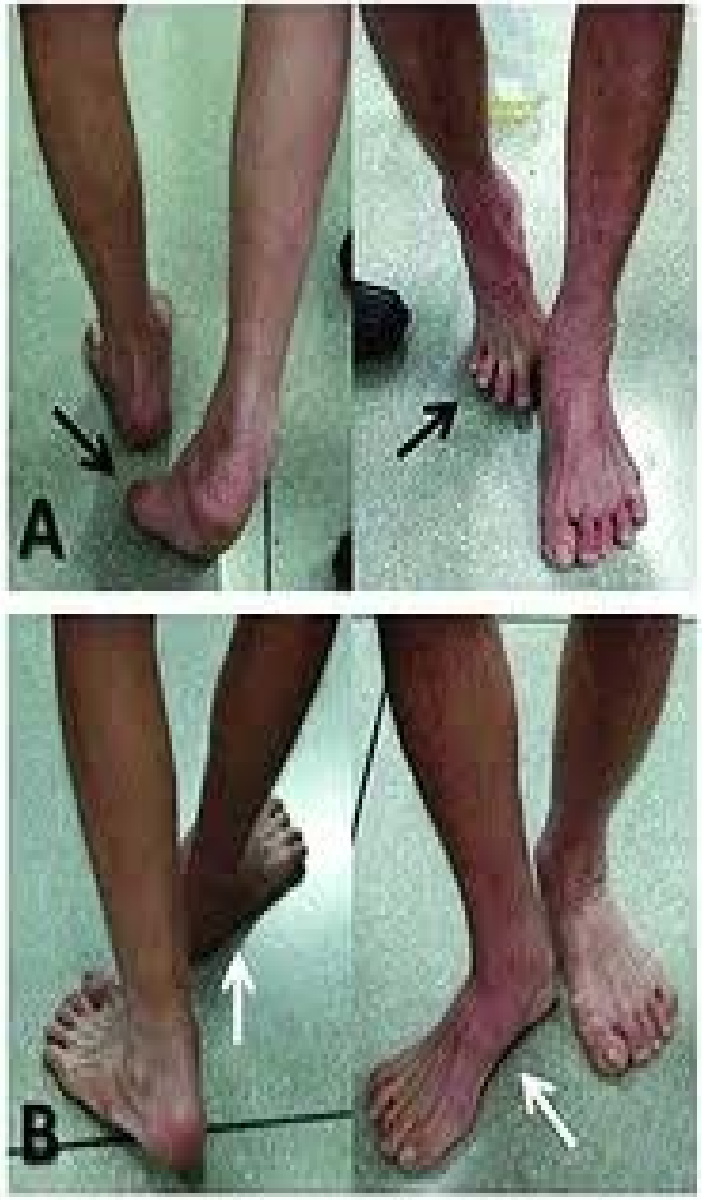
Injection technique

- Muscle selection
  - Common patterns
  - e.g. “thumb in palm” – opponens pollicis, adductor pollicis, FPB, lumbricals, interossei
  - e.g. plantar flexed & inverted (equinovarus) – gastrocnemius, soleus, posterior tibialis
- Larger muscles – surface anatomy
- Smaller muscles – EMG, nerve/muscle stimulation, USS (occasionally CT/MRI)
- Post injection management
  - Stretches, posture, position, FES
  - Orthotics / splints / Lycra

BTX injection



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Points re BTX use

- Maximum doses
- It wears off
  - Not permanent
  - May need repetition
- Will not recover lost function
  - Unless due to antagonist muscle over-activity
- Diffusion may result in unwanted weakness
- Follow up to assess outcome & plan

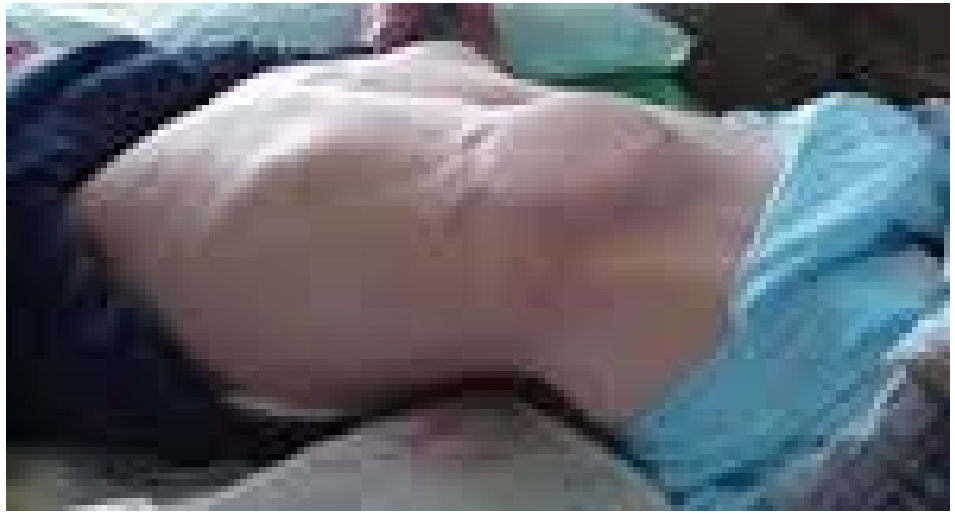
Phenol nerve and motor point blocks

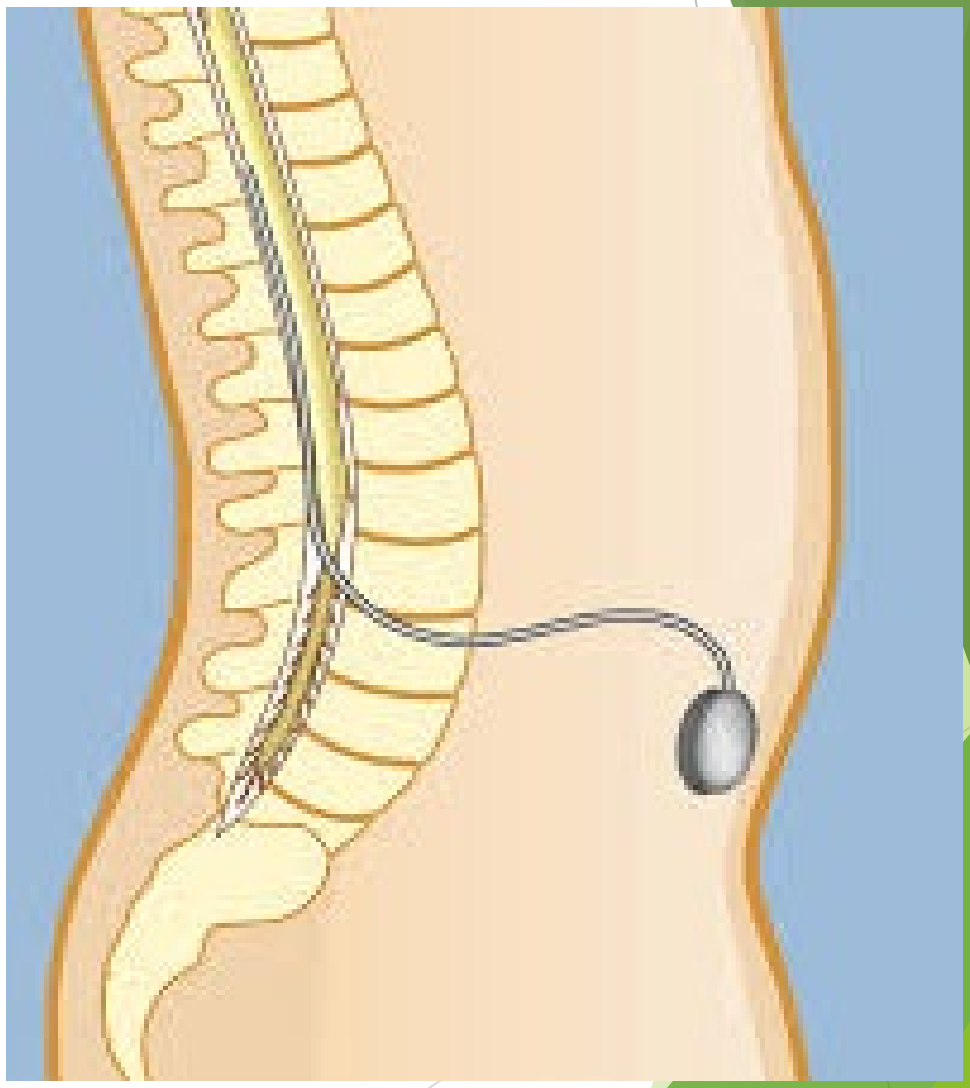
- Used for progressive or stable neurology
  - Longer duration of action than BTX
  - Cheaper
  - Useful for large muscles where max dose of BTX limits Rx
- Phenol at >3% is a neurolytic agent
- Common sites:
  - LL: obturator n., hamstring branches of sciatic n., femoral n., tibial n.
  - UL: pec major, subscapularis, lat dorsi, musculocutaneous n., biceps, brachioradialis, FCR, FCU, FDS, recurrent motor branch of median n. (thenar eminence muscles)
- Localisation:
  - ultrasound scanning, X-ray, or guided electrical stimulation
- Side effects:
  - Local redness/bruise/discomfort, skin infx/abscess, haematoma, muscle/soft tissue fibrosis, dysaesthesia, vascular injury, pelvic organ injury, systemic (arrhythmia, pulm fibrosis, confusion, renal impairment

Intrathecal baclofen (ITB)

- Suitable for regional (ie lower limb) & generalised spasticity
  - Intolerable central SEs from oral agents
  - Inadequate response to oral agents
- Test dose to assess response
- Pump implantation

ITB pump





Implications of ITB therapy

- Pros…
  - Much smaller doses of baclofen required
  - Therefore, fewer side effects esp. central
  - Dose titration & variable regimens
- Cons…
  - Requires neurosurgical procedure
  - Attention to system alarms & symptoms of withdrawal & overdose
  - Commitment to regular review & refills
- Adverse events….
  - Drug SE related: weakness, nausea, drowsiness, dizziness, headache
  - Device related: pump stall/failure, pump dosing errors, catheter kink/fracture, catheter/pump dislodgement, implant site infection incl meningitis
  - Interference from MRI
  - Withdrawal or overdose can be life threatening

Spasticity references

- RCP Spasticity in adults: management using botulinum toxin (2nd edition, 2018)
- Spasticity management: A Practical Multidisciplinary Guide (2nd Edition), Editors Valerie Stevenson, Louise Jarrett

- NICE guidance or Clinical Knowledge Summaries for specific conditions e.g. stroke, MS

Take home points

- Spasticity, with related pain, loss of function and complications is not uncommon in MND
- Diagnosis, assessment for baseline, patterns
- Identifying goals for treatment and MDT / holistic approach is key
- Follow up / review of effectiveness
- Cramps
  - Quinine, magnesium, clonazepam, baclofen, mexiletine, levetiracetam
- Stiffness and spasticity
  - Baclofen, tizanidine, dantrolene / GABAergic agents / Clonazepam
  - Botulinum toxin for focal spasticity
  - Intrathecal baclofen

Thank you and Questions?

- SRC referrals email: sc-tr.rehabteams@nhs.net