

Update on Spasticity Management

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BOTOX[®] (onabotulinumtoxinA)

Licensed indications in post stroke spasticity

- UK licence for focal spasticity, including the treatment of:
 - wrist & hand disability due to upper limb spasticity associated with stroke in adults
 - ankle disability due to lower limb spasticity associated with stroke in adults

Programme

- Functional improvements with BoNT-A
- Realisation of importance of pain in muscle activation problems
- Picking up patients with post-stroke spasticity

The BOTOX[®] Economic Spasticity Trial

Ward AB, Wissel J, Borg J, Ertzgaard P, Hermann C, Kulkarni J, Lindgren K,
Reuter I, Sakel M, Satero P, Sharma S, Wein T, Wright N, Fulford-Smith A.
on behalf BEST Study Group

B.E.S.T.

- Multi-centre, double-blind, prospective, randomised study to evaluate patient outcomes & costs of managing adults with focal spasticity
- 300 patients - equal distribution between treatment arms - stratified by spasticity location
- 33 sites – 10 United Kingdom, 10 Germany, 10 Sweden & 3 Canada
- BoNT-A (BOTOX®) + standard of care (SC) versus placebo +SC
- Real life study over 52 week period (1 year)
 - 24/52 double-blind treatment followed by up to 30/52 open-label phase

Study Objective & Endpoints

Study objective

- Evaluate the effectiveness of BOTOX® + standard of care (SC) versus placebo + SC for treatment of adult post-stroke focal spasticity

Primary endpoint

- No. of patients who achieved 1^o active functional goal*

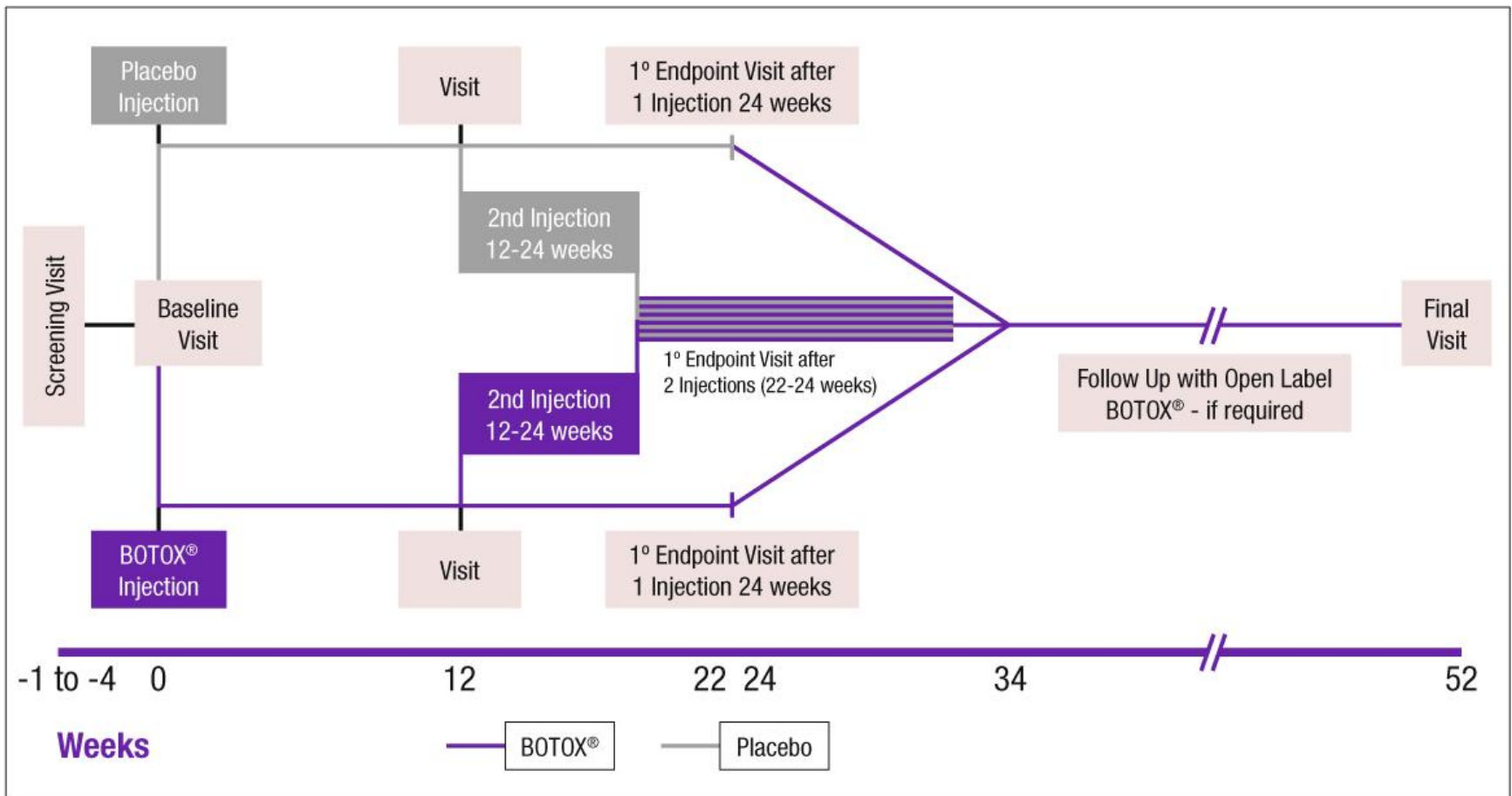
Secondary endpoints

- No. of patients who achieved their 2^o goal (either active functional or passive)*
- Level of primary active functional goal score*
- Level of 2^o active functional or passive goal score*
- Change in health-related quality of life scores

All evaluated at the Week 24 (if only one injection) or 10 weeks after the second injection.

* Endpoints evaluated by physician and patient

Study Design

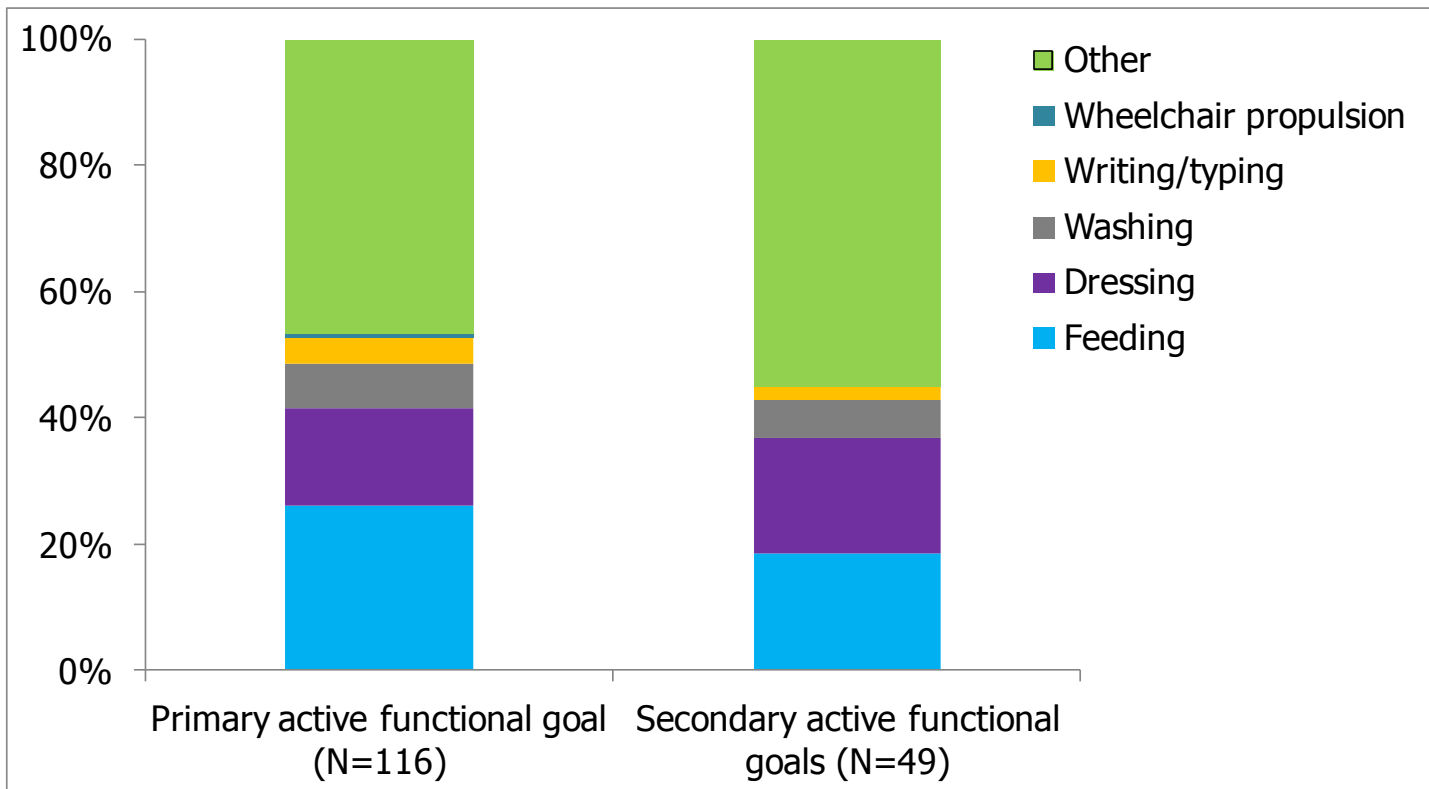


Goal Attainment Scaling (GAS)

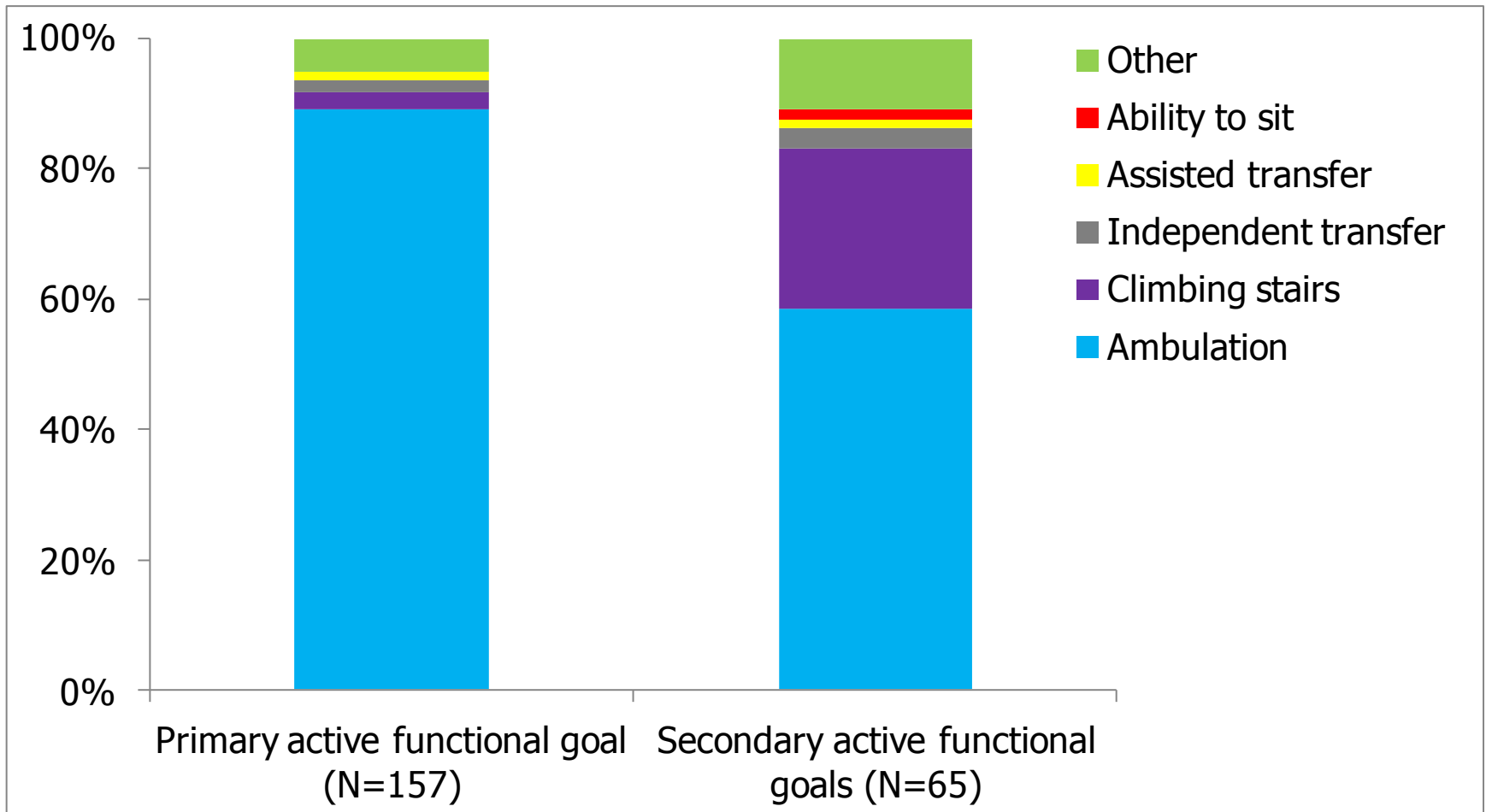
-3	Worse than at start
-2	Equal to start: patient's initial condition; no change
-1	Less than expected: slight improvement, but below defined therapeutic goal
0	Expected goal: attains defined therapeutic goal
+1	Somewhat more than expected: improvement slightly exceeds defined therapeutic goal
+2	Much more than expected: improvements clearly exceed defined therapeutic goal

- Active functional goals: required an improvement in the active function of the primary assessment limb¹
- Passive goals: included relief of symptoms or facilitation of services¹

Upper Limb Functional Goals



Lower Limb Functional Goals



Lower Leg Subgroup Analysis

Primary endpoint

- 78 patients injected into
 - Gastrocnemius + soleus + tibialis posterior (GSTP)
 - Predominantly Caucasian (94.9%)
 - Mean age = 60
- Analysis of 1^o active functional goal and 2^o goal achievement (GAS)
- Analysis of ankle Ashworth scores (as part of REPAS)

Investigator-Assessed Goal Attainment GSTP Subgroup Analysis

Primary endpoint

	BoNT-A + SC	Placebo + SC
Primary active functional goals		
Number assessed	N=34	N=30
Goal attainment	16 (47.1%)	10 (33.3%)
P-value	p=0.265	
All secondary goals		
Number assessed	N=29	N=32
Goal attainment	20 (69.0%)	11 (34.4%)
P-value	p=0.007	

Level of Goal Attainment: GSTP Subgroup Analysis

Primary endpoint

	BoNT-A + SC	Placebo + SC
Primary active functional goals		
Number assessed	N=34	N=30
Mean level of goal attainment	-0.5	-1.1
P-value		p=0.003
All secondary goals		
Number assessed	N=29	N=32
Mean level of goal attainment	0.0	-1.0
P-value		p=0.001

BEST Conclusions

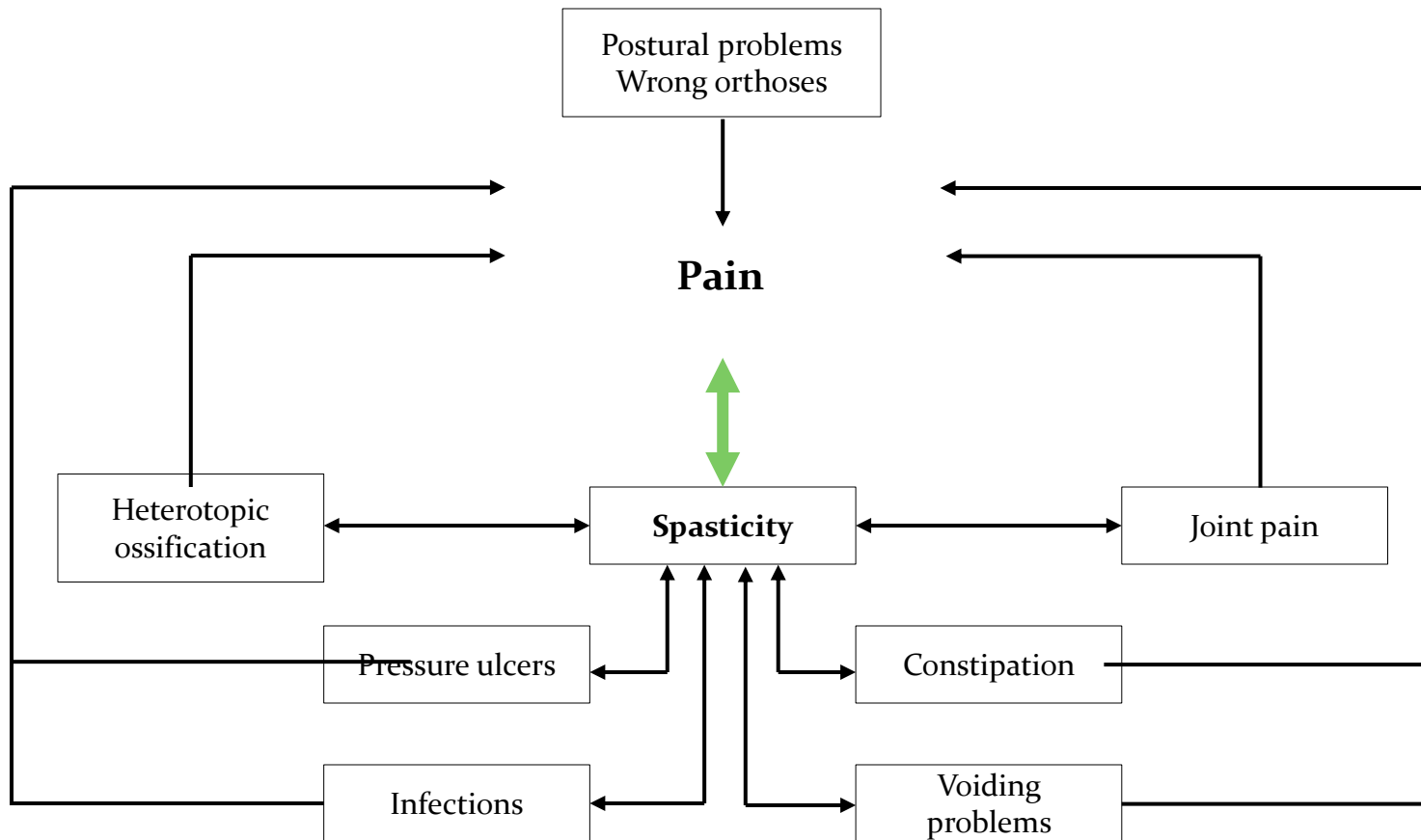
- Clinically meaningful outcomes can still be achieved by rehabilitation methods even 4 years post-stroke
 - Clear achievable goals for treatment should be established
- Standard of care is an important & effective intervention for PSS patients
- BOTOX[®] is an important adjunctive treatment to standard of care
 - Confirms improvement of passive function
 - First study to demonstrate that addition of BOTOX[®] to SC improves active function scores in both the upper limb & ankle flexor muscles
 - Following 24 weeks of SC the addition of BOTOX[®] can significantly improve patients goal achievement

Is Spasticity Painful?

- Pain from spasticity itself
 - Aetiology unclear
 - Possible mechanisms
- Pain from underlying conditions
 - Hemiplegic shoulder pain
 - Back pain in multiple sclerosis
 - Limb pain in cerebral palsy
 - Acquired brain injury¹
 - Headaches, dysautonomia, neuropathic pain, heterotopic ossification

1. Ivanhoe C, Hartman. J Head Trauma Rehabil 2004; 19: 29-39.

Pain and Spasticity



Correlation of Pain and Spasticity

- Reduction in pain coincides with a reduction in spasticity
 - Suggests a causal relationship
- Assumption that spasticity causes pain^{1,2}
- Pain helped by antispastic treatments
 - Baclofen, tizanidine and BoNT all act on central pain systems to reduce pain²
 - Effective pain reduction with baclofen or tizanidine is doubtful, but BoNT is effective³
- Stroke-related pain is associated with paresis, sensory disturbance and depression, but not independently with spasticity¹

1. Lundström P, et al. Eur J Neurol 2009; 16: 88–93.

2. Sheean G. Eur J Neurol 2009; 16: 157–8.

3. Beard L, Hunn , Wight . HTA Winchester 2003; 7: iii, ix–x, i–iii.

Possible Associations of Pain & Spasticity

- Pain from intermittent muscle contraction
 - Flexor and extensor spasms
 - Pain in contracting muscles
 - Stretched muscle and soft tissue
 - Stiff joints
 - Striatal toe deformity
- Secondary tissue damage from abnormal postures
 - Skin breakdown in flexion creases, intertrigo, palmar nail pressure
 - Decubitus ulcers

Possible Associations of Spasticity Pain

- Musculoskeletal consequences of abnormal postures (spasticity/spastic dystonia)
 - Soft tissue stiffness in shortened mm – painful during active and passive stretch
 - Joint stiffness from immobilisation (e.g. frozen shoulder)
 - Joint subluxation
 - Weight bearing on deformed (upper and) lower limb
 - Equinovarus
 - Hyper-extended knee
 - Flexed toes
 - Adducted hip
 - Poor seating posture
 - Strain on spine and pelvis

Epidemiology

- 4–42% develop spasticity post-stroke¹⁻⁵
- 21–24.5% of stroke survivors have hypertonia 1 week after stroke^{2,3}
 - Prevalence: any spasticity 17%; disabling spasticity 4%³
- Estimated prevalence of stroke-related pain is 21%⁶
- Spasticity present in⁷
 - 4% of patients at days 2–10
 - 27% of patients at 1 month
 - 23% of patients at 6 months
 - Severe arm paresis at 2–10/7 associated with higher risk for spasticity at 1/12
 - (Odds Ratio: 10; 95% CI: 2.1–48.4)
 - Disabling spasticity present in 2% at 1 month and 13% at 6 months

1. Verplancke et al. Clin Rehabil 2005; 19: 117–25.

3. Lundström et al. Eur J Neurol 2008; 15: 533–9.

5. Dobkin. N Engl J Med. 2005; 21: 1677–1684.

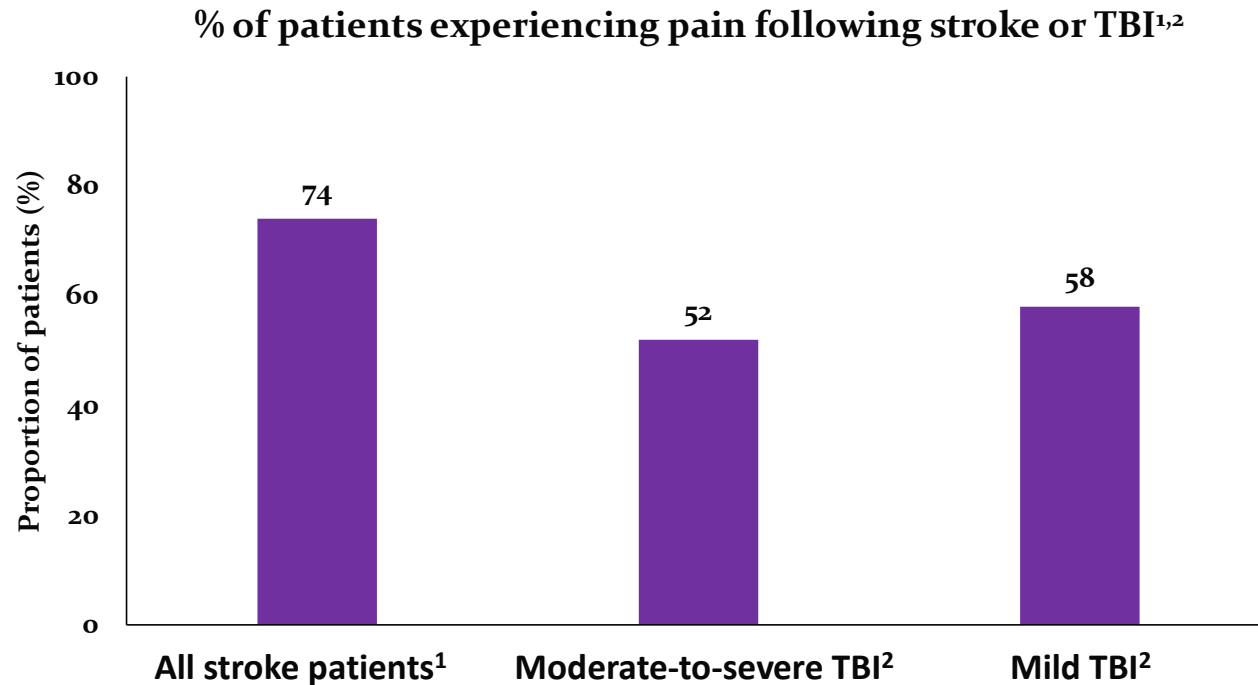
7. Lundstrom et al. J Rehabil Med 2010; 42: 296–301.

2. Paul et al. Curr. Drug Targets 2007; 8: 786–93.

4. Wissel et al. J Neurol 2010; 257: 1067–1072.

6. Lundström et al. Eur J Neurol 2009; 16: 188–93.

Pain is Common Post-CNS Injury



- Daily pain reported by >80% of patients following traumatic brain injury (TBI)²

TBI = traumatic brain injury.

1. Kim JS. *Exp Rev Neurother*. 2009;9(5):711-721.
2. Lahz S, et al. *Arch Phys Med Rehabil* 1996;77:889-891

Effect on Patients' Lives

- Function
 - Impaired ability to perform everyday tasks (e.g. household tasks, self-care)¹⁻⁴
 - Decreased mobility^{1,4}
- Reduced HRQoL⁵
 - Negative impact on family/carer
 - e.g. impaired caregiver wellbeing, depression, anxiety and relationships⁴⁻⁶
 - Negative association after spinal cord injury⁷

HRQoL, health-related quality of life.

1. Sommerfeld et al. Stroke 2004;35:134-9.
2. Brashear et al. N Engl J Med 2002;347:395-400.
3. Bhakta. Br Med Bull 2000;56:476-85.

4. Anderson et al. Stroke 1995;26:843-49.
5. Welmer et al. Cerebrovasc Dis 2006;21:247-53.
6. Carnwath et al. BMJ 1987;294:409-11.
7. Westerkam et al. Spinal Cord 2011;49:990-4.

Treatment Considerations in Focal Spasticity

- Motor impairments (body structures & function)
 - Muscle tone
 - Spasms
 - Other features of the upper motor neurone syndrome
- Loss of activity
 - Mobility
 - Dexterity
- Limitation of participation
 - Care
 - Driving
 - Employment/leisure activities

Conventional Pharmacological Treatments

- Analgesia
 - Opiates
 - Non-opiates
- NSAIDs*
- Pain modifiers
 - Antidepressants
 - Anticonvulsants
- Neuromuscular blockade
 - Local anaesthesia
 - Chemical neurolysis
 - Botulinum toxin
- Sympathetic blockade
 - Generalised (ganglion blocks)
 - Regional (guanethidine)
 - Local

*NSAIDs, non-steroidal anti-inflammatory drugs

Treatment

- Limited analgesic effectiveness of
 - Selective serotonin reuptake inhibitors
 - Sodium channel blockers (lidocaine, etc.)
 - GABA-B agonists (baclofen)
 - N-methyl-d-aspartate (NMDA) receptor antagonists (ketamine)
- More likely to be effective with
 - Carbamazepine
 - Gabapentin
 - Intrathecal opiates (now controversial)
 - Alpha 2 agonists (clonidine)
- Neuro-stimulation, only if it produces paraesthesiae
- Cognitive behavioural rehabilitation techniques
- Destructive procedures (to be avoided)

Conclusions

- PSS is associated with sensory (pain) symptoms in addition to motor symptoms
 - Chronic pain is common following CNS injury
 - Can be caused by spasticity
- The symptoms of upper motor neuron lesions result from afferent and efferent pathways
- The sensorimotor symptoms of PSS have a significant impact on the HRQoL of patients and should be considered when planning treatment

Post-Stroke Checklist UK Pilot

- To assess PSC's value in clinical practice & usefulness to stroke survivors within a UK healthcare setting
- To evaluate PSC's content & face validity

Based upon the 'Development of a Poststroke Checklist to Standardize Follow-up Care for Stroke Survivors' - I Philp et al.

Consent

Post-stroke Review

Informed consent given

- Follow-up 6 months (Xa7Om)
- Stroke annual review (XaIzF)

New Recall

1. Secondary Prevention

Since your stroke or last assessment, have you seen anyone regarding advice on changes to lifestyle or medications for preventing another stroke?

- Secondary prevention (Yes)
- Lifestyle counselling (Yes)
- Medication Discussed (Yes)

If not, refer to Primary Care Team for risk factor assessment and treatment if appropriate.

Refer to member of Primary Health Care Team (GP)

2. Activities of Daily Living (ADL)

Since your stroke or last assessment, are you finding it **more** difficult to take care of yourself?

Difficulties in ADL (Yes)

Difficulties in Activities of Daily Living

- Difficulty bathing self (Xa2ud)
- Difficulty dressing (Xa2xl)
- Difficulty preparing drink (Xa3U6)
- Difficulty preparing food for eating (Xa3TK)
- Difficulty mobilising outside (Xa80c)

If yes to any, refer to the Community Stroke Team or an appropriate therapist (i.e. OT or PT) for further assessment.

- Referral to stroke service
- Referral to physiotherapist
- Referral to occupational therapist

Please remember to complete 'Observations of Progress' at the end of the template

Informed consent given

Date ▾ Checked ...

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3. Mobility

Since your stroke or last assessment, are you finding it **more** difficult to walk or move safely from bed to chair?

Difficulty mobilising (Yes)

Are you continuing to receive rehabilitation therapy?

Stroke rehabilitation (Yes)

If not, refer to Community Stroke Team for further assessment.

Referral to stroke service Community Stroke Team (Yes)

4. Spasticity

Since your stroke or last assessment, do you have **increasing** stiffness in your arms, hands and/ or legs?

Spasticity (Yes)

Is this interfering with activities of daily living?

Difficulties in ADL - Spasticity (Yes)

If yes, refer to a physician with an interest in post-stroke spasticity for further assessment.

Referral to rehabilitation physician (spasticity)

5. Pain

Since your stroke or last assessment, do you have any **new** pain?

New Pain (Yes)

If yes, refer to a physician with an interest in post-stroke pain for further assessment and diagnosis.

Referral to rehabilitation physician (interest in pain)

6. Incontinence

Since your stroke or last assessment, are you having **more** of a problem controlling your bladder or bowels?

Incontinence Issues (Yes)

If yes, refer to Community Continence Adviser or equivalent for further assessment.

Referral to continence nurse

Please remember to complete 'Observations of Progress' at the end of the template

Difficulty mobilising (Yes)

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Information

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7. Communication

Since your stroke or last assessment, are you finding it **more** difficult to communicate with others?

Has difficulty with speech (Yes)

If yes, refer to Specialist Speech and Language Therapist for further assessment.

Referral to speech and language therapist

8. Mood

Since your stroke or last assessment, do you feel **more** anxious or depressed?

Variability of mood - subsequent to stroke (Yes)

If yes, refer to Primary Care Clinician with an interest in post-stroke mood change for further assessment.

Referral to physician ?? type ??

9. Cognition

Since your stroke or last assessment, are you finding it **more** difficult to think, concentrate or remember things?

Impaired cognition (Yes)

Does this interfering with activity or participation?

Difficulty participating in leisure activities (Yes)

If yes, refer to a clinician with an interest in post-stroke cognition changes for further assessment.

Referral to rehabilitation physician (cognition)

Please remember to complete 'Observations of Progress' at the end of the template

Has difficulty with speech (Yes)

Date ▾ Checked ...



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10. Life After Stroke

Since your stroke or last assessment, are you finding things important to you **more** difficult to carry out (e.g. leisure activities, hobbies, work, relationships with loved ones)?

Impact of illness on lifestyle (Yes)

If yes, refer patient to a stroke support organisation (e.g. The Stroke Association).

Referral to stroke related support groups

11. Relationship and Family

Since your stroke or last assessment, has your personal relationship with your family become **more** difficult or stressed?

Relationship difficulties (Yes)

If yes, schedule next Primary Care visit with patient and family member. Or if family member is present refer carer to a stroke support organisation (e.g. The Stroke Association).

Follow up appointment - include family member

Referral to stroke related support groups


 

Observations of Progress

Comment note - Observations of Progress



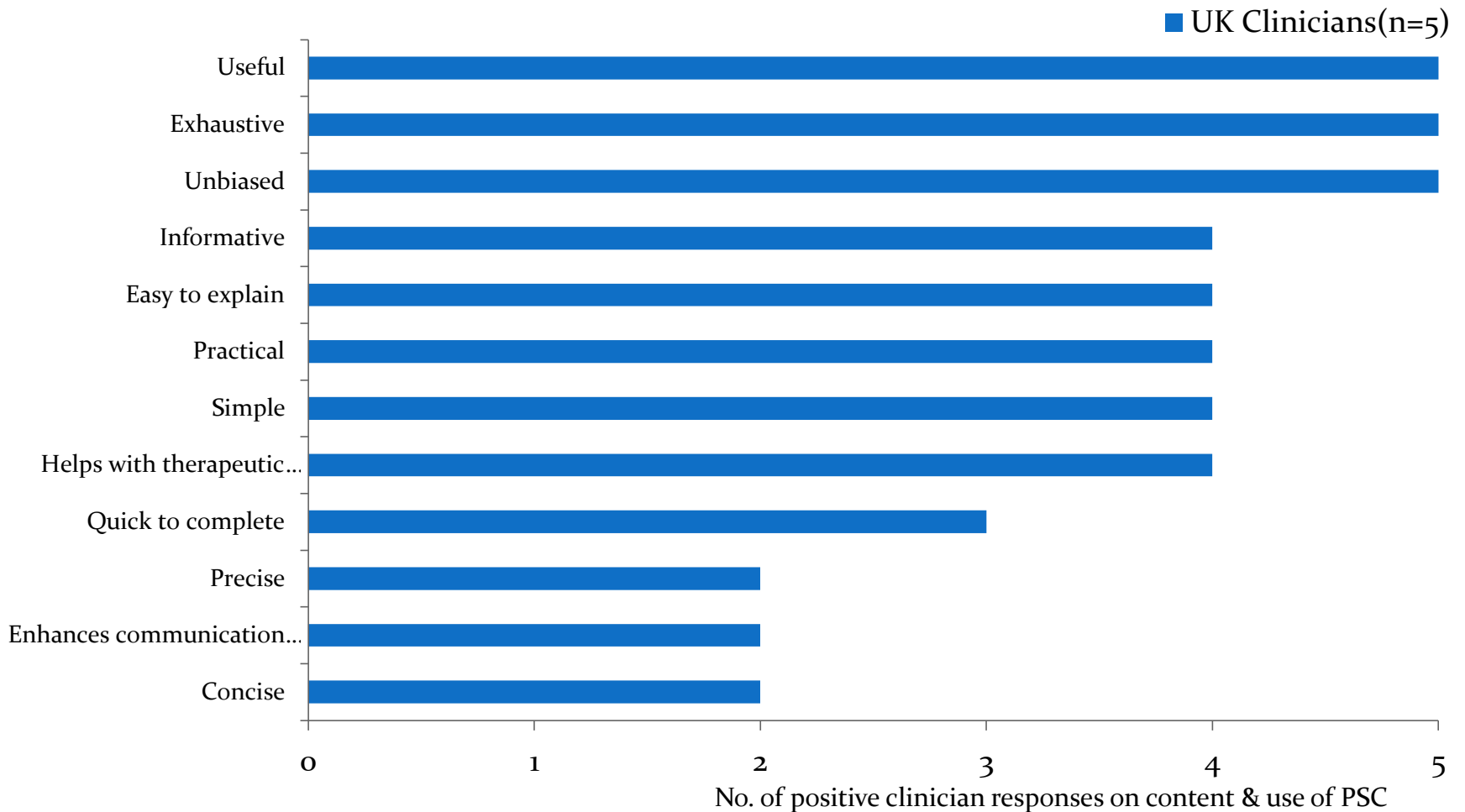
Impact of illness on lifestyle (Yes)

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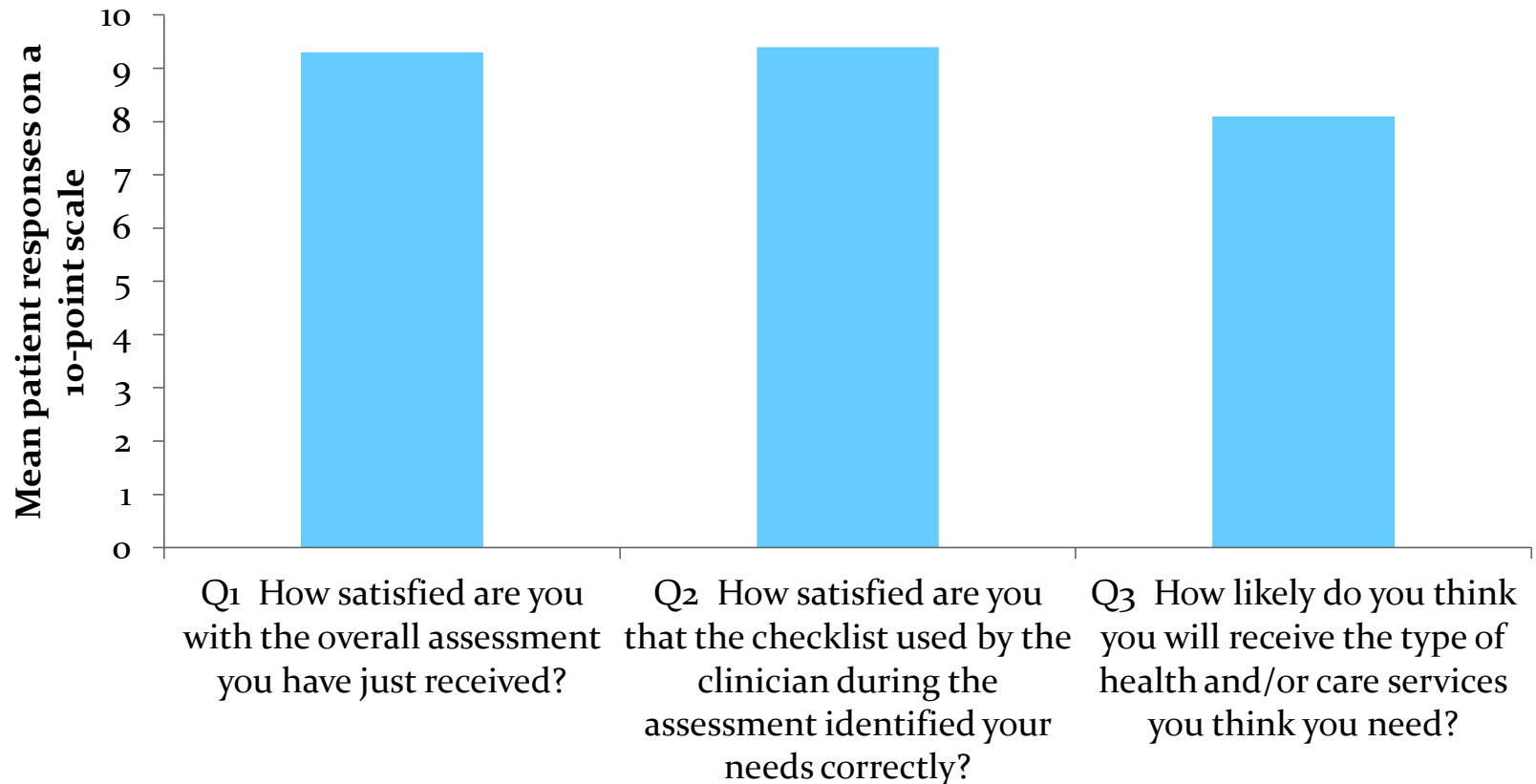
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UK Pilot

Clinician Views of the PSC



Patient Satisfaction



Post-Stroke Checklist Pilot

Overall Conclusions

- Simple and easy to use tool with strong content validity
- Able to identify wide range of unmet needs for stroke survivors
- Clinicians & patients expressed high overall satisfaction with PSC
- Generally well understood