CRPS AND NEUROMODULATION

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OBJECTIVES

- Brief Overview of CRPS
- Brief Overview of Treatment Options
- Use of Neuromodulation (SCS) in CRPS – Past & Current Practices – Examination of current evidence.

CRPS: THE CHALLENGE

"Of all the chronic neuropathic pain syndromes, none has perplexed patient, clinician, and scientist more than the complex regional pain syndromes (CRPS), heretofore known as reflex sympathetic dystrophy (RSD) and causalgia."

Galer BS CRPS Chapter 20 Bonica's Management of Pain 3rd Ed. Lippincott Williams &Wilkins 2001

CHALLENGES

1. NATURAL COURSE AND PATHOPHYSIOLOGY REMAINS POORLY UNDERSTOOD – hence CRPS I & II based on inciting event

2. INFLAMMATION, VASODYSREGULATION / AUTONOMIC DYSTONIA AND AXONAL INJURY ARE IMPLICATED IN THE PATHOGENESIS

3. THERAPEUTIC INTERVENTIONS REMAIN CONTROVERSIAL DUE TO THE LACK OF RCT's

4. DIAGNOSIS IS USUALLY MADE BY HIGH INDEX OF SUSPICISION, EXAMINATION AND CAREFUL HISTORY AND EXCLUSION

5. THERE IS ASSOCAITED SIGNIFICANT MORBIDITY AND LODD OF QOL INDICATORS

1. Jänig W. In: Harden, Baron, Jänig. *Complex Regional Pain Syndrome*. 2001:3-15.
2. Oaklander AL. *Pain*. 2009;139;239-240.
3. Bogduk N. *Curr Opin Anaesthesiol*. 2001;14:541-546.
4. Raja SN et al. *Anesthesiology*. 2002;96:1254-1260.

EPIDEMIOLOGY

- INCIDENCE – 26.2 PER 100,000 PERSON YEARS (Crps I > CrpsII)
- AGE – COMMON IN YOUNGER ADULTS --- MEAN 41.8 , AGE AT INJURY 37.7 (CHILDREN 12.5)
- MEAN DURATION OF SYMPTOMS BEFORE SEEING A PAIN SPECIALIST 30MO
- 3.4 MORE FREQUENT IN FEMALES THAN MALES
- EARLY STAGE USUALLY INVOLVES SINGLE LIMB

1. De Mos M. *Pain.* 2007;129;12-20.
2. Galer BS, et al. In: Loeser. Ed. *Bonica's Management of Pain.* 2001;388-411.

CRPS (I & II)-----NEUROPATHIC PAIN CONDITION ----(CRPS-NOS)

- A clinical diagnosis of CRPS can be made when the following criteria are met:

1. * Continuing pain that is disproportionate to any inciting event
2. * At least 1 symptom reported in at least 3 of the following categories:
   - o Sensory: Hyperesthesia or allodynia
   - o Vasomotor: Temperature asymmetry, skin color changes, skin color asymmetry
   - o Sudomotor/edema: Edema, sweating changes, or sweating asymmetry
   - o Motor/trophic: Decreased range of motion, motor dysfunction (eg, weakness, tremor, dystonia), or trophic changes (eg, hair, nail, skin)
3. * At least 1 sign at time of evaluation in at least 2 of the following categories:
   - o Sensory: Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure, or joint movement)
   - o Vasomotor: Evidence of temperature asymmetry (>1°C), skin color changes or asymmetry
   - o Sudomotor/edema: Evidence of edema, sweating changes, or sweating asymmetry
   - o Motor/trophic: Evidence of decreased range of motion, motor dysfunction (eg, weakness, tremor, dystonia), or trophic changes (eg, hair, nail, skin)
4. * No other diagnosis better explaining the signs and symptoms

IASP Modified Criteria

IF 2 OUT OF 4 SIGNS ARE PRESENT AND 3 OUT 4 SYMPTOMS ARE PRESENT THEN

Sensitivity was 0.85 and the specificity was 0.69 for a clinical diagnosis of CRPS (2007-Budapest Group Meeting of 2003)

This has been fairly accurate clinically in diagnosing CRPS and reducing the high false positive rates associated with the original 1994 criteria (over diagnosis)

Higher specificity is required to meet research criteria, so the recommendation that 2 of the 4 sign categories and all 4 symptom categories must be positive for the diagnosis to be made in a research setting, results in a sensitivity of 0.70 and specificity of 0.94.

Due to this 15% of patient previously diagnosed with CRPS will be excluded even if they fulfill the original 2003, 1997 criteria – Hence a new category of CRPS - NOS

PATHOPHYSIOLOGY

- **Peripheral and Central Sensitization**: involves algogenic substances, SP and CGRP instigate antero and retrograde actions with recuritment of other cell types as well as involvement of WDR's and second order neurones

- SMP – defined as an underlying mechanism in a subset of patients with neuropathic pain. SMP is not a clinical entity per se. Nor is it a sine qua non for CRPS as was previously believed. (Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain*. Oct 1995;63(1):127-33)

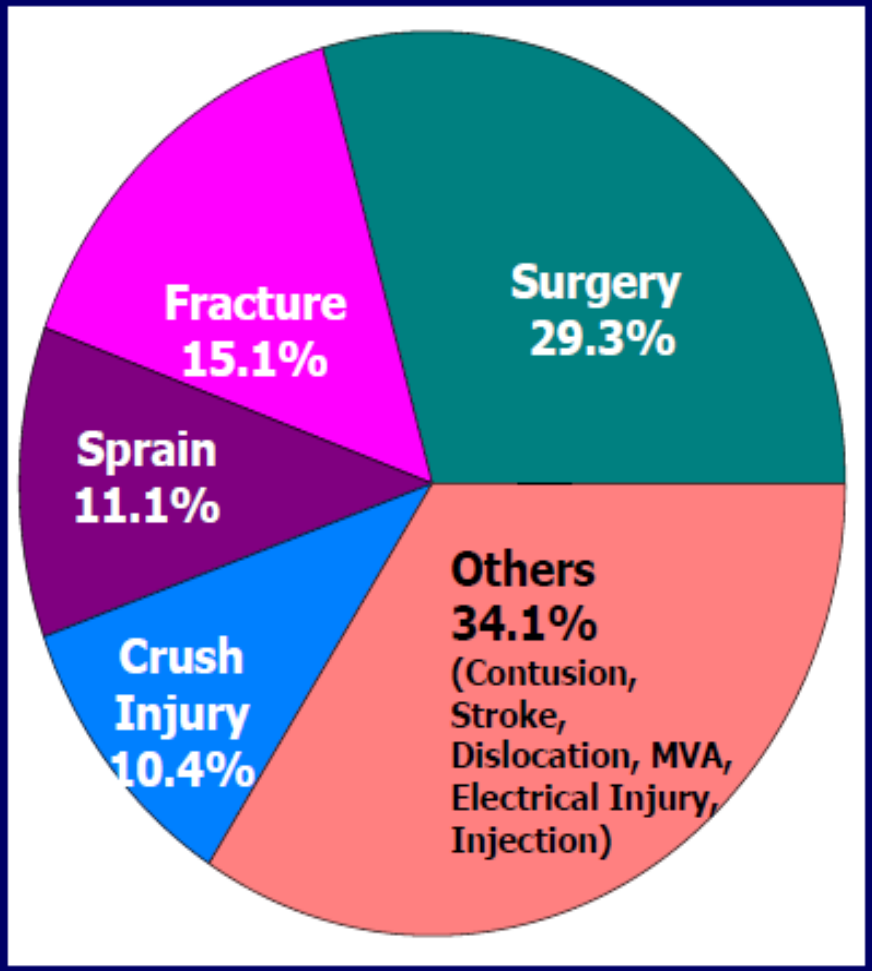
- **Sensory and Motor Dysfunction** - peripheral and central sensitization explains the pathophysiology of spontaneous pain and hyperalgesia. Similar mechanisms involving abnormalities of CNS motor processing of muscles and abnormalities of visual and sensory integration resulting in tremors (>50%) (Deuschl, Blumberg S, Jensen M. Tremor in reflex sympathetic dystrophy. *Arch Neurol*. 1999;48:1247-1252)

- **Aberrant healing and exaggerated inflammation** – SP, CGRP & Pronociceptor mediators in tissue

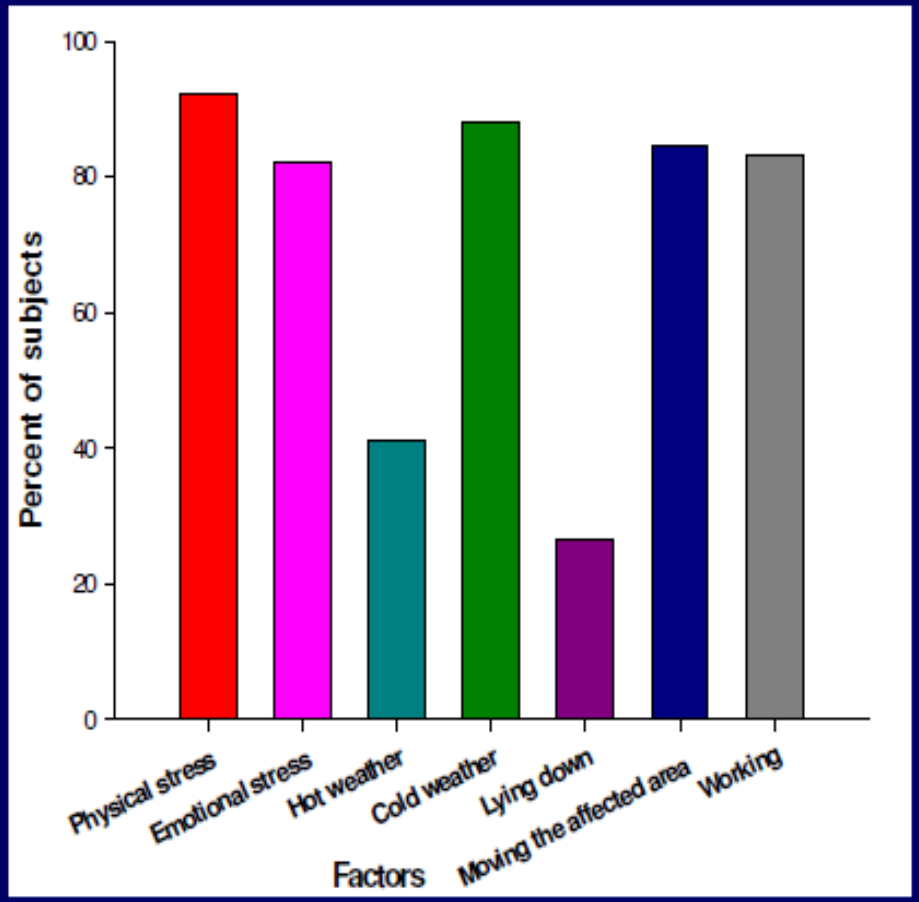
- **Protective disuse** - postulated as a cause in some patients with CRPS (Deuschl, Blumberg S, Jensen M. Tremor in reflex sympathetic dystrophy. *Arch Neurol*. 1999;48:1247-1252) .. An unused dependent limb eventually develops swelling (dependent edema), coolness (decreased blood flow), and trophic changes (decreased blood flow). (Galer BS, Butler S, Jensen MP. Case reports and hypothesis: a neglect-like syndrome may be responsible for the motor disturbance in reflex sympathetic dystrophy (Complex Regional Pain Syndrome-1). *J Pain Symptom Manage*. Jul 1995;10(5):385-91)

CRPS: A web-based survey

Inciting event



Factors associated with increased pain



Sharma A, Agarwal S, Broatch J, Raja SN. *Reg Anesth Pain Med.* 2009;34:110-115.

SPREAD OF SYMPTOMS

- 77% reported spread of symptoms to site other than the initial location
- Exact spread of CRPS not known in Literature
- Independent spread known to occur in 6.7% of CRPS I cases
- Investigators agree that spread id not uncommon

1. Sharma A, Agarwal S, Broatch J, Raja SN. *Reg Anesth Pain Med.* 2009;34:110-115.
2. Maleki J, LeBel AA, Bennett GJ, Schwartzman RJ. *Pain.* 2000 Dec 1;88(3):259-266.

Diagnostic considerations CNS

- Brain (stroke, neoplasm, encephalitis)
- Spinal cord (trauma, transverse myelitis, either structural or tumor-related syringomyelia)
- Tabies dorsalis
- Multiple sclerosis
- Poliomyelitis

Radiculopathy

- Structural (eg, due to structural impingement of a diskal, osteophyte-, or tumor-related nature)
- Metabolic (eg, diabetes, vasculitis infectious)
- Neoplastic

Neuropathy

- Focal
  - Diabetes
  - Inflammatory or infectious (Lyme), sarcoid
  - Posttraumatic
  - Entrapment (eg, carpal tunnel, cubital tunnel)
  - Toxic
  - Neoplastic (neuroma)
- Multifocal (mononeuritis multiplex)
  - Diabetes
  - Vasculitis
  - Infectious
  - Toxic
- Bilateral or diffuse
  - Diabetes
  - Alcohol
  - Nutritional
  - Guillain Barre syndrome or chronic inflammatory demyelinating polyneuropathy
  - Porphyria

- Plexopathy
  - Infectious
  - Autoimmune/idiopathic
  - Tumor (primary or secondary neoplasm), especially Pancoast syndrome
  - Trauma (macro or cumulative)
  - Entrapment (thoracic outlet syndrome)
- Vascular disorders
  - Raynaud phenomena
  - Peripheral atherosclerotic disease
  - Arterial insufficiency
  - Phlebothrombosis
- Monomelic amyotrophy
- Psychological
  - Hysteria
  - Somatoform disorder, including malingering
- Movement disorders
- Metabolic or systemic (eg, renal failure, amyloidosis)
- Autoimmune or rheumatological disorder
- Infectious (eg, viral, fungal, Lyme) Iatrogenic (eg, prescribed medication)
- Demyelinating (CIDP, paresis or sensory deficiency due to multiple sclerosis)
- Toxic exposure (eg, vinca alkaloids, heavy metals)

WORKUP---NO SPECIFIC TEST/S CONFIRM THE DIAGNOSIS

- LAB Studies: Blood work – CBC, ESR, CRP, ANA, RA, CFP, Immune studies, Bone Scan, Hb A1C

  EMG / sensory NCV – to define nerve issues , c fiber function

  Vascular Studies

- Imaging studies: Radiography: In the chronic stages of CRPS, plain radiographs may reveal endosteal and intracortical excavation, resorption of subperiosteal and trabecular bone, localized bone demineralization, and/or osteoporosis

  Bone scintigraphy: Higher specificity and sensitivity than X-Ray in early post fracture (Todorovic-Tirnanic M, Obradovic V, Han R, Goldner B, Stankovic D, Sekulic D. Diagnostic approach to reflex sympathetic dystrophy after fracture: radiography or bone scintigraphy?. *Eur J Nucl Med*. Oct 1995;22(10):1187-93)

  Only helpful in the first year (Zyluk A. The usefulness of quantitative evaluation of three-phase scintigraphy in the diagnosis of post-traumatic reflex sympathetic dystrophy. *J Hand Surg (Br)*. 1999;24:16-21.)

  MRI : Sensitive less specific – joint effusion, swelling soft tissue

- Other studies: Quantitive Sensory Testing – removes subjectivity

  Autonomic Function Testing – thermography, QSART, TST, laser Doppler flow

  Neurogenic Inflammation – proinflmmatory mediators and vasoactive elements – interleukin 6, tryptase, TNF alpha, endothelin 1

  Skin, Muscel, Nerve biopsies

PHARMACOTHERAPY

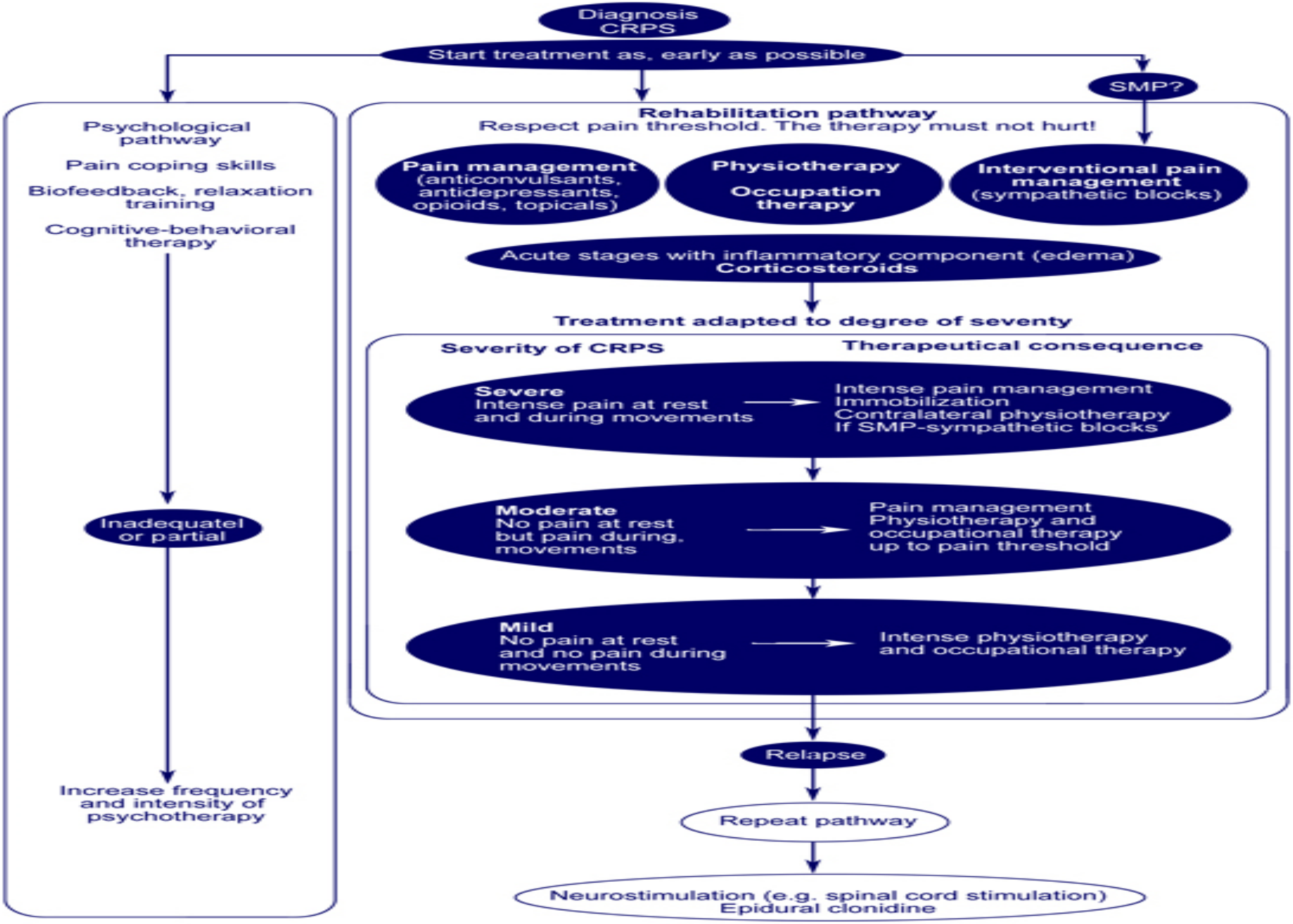
- Steroids – used early effective 60-80mg/day instituted within 2mo of the inciting event
- Calcium Regulating agents – intranasal calcitonin reduces pain, Intravenous (IV) clodronate (300 mg daily) and alendronate (either 7.5 mg/d IV or 40 mg/d orally) have been shown to significantly improve pain, swelling, and range of movement in patients with acute CRPS ---- mechanisms unkown
- Opioids & NASID's – No studies done , used as part of treating pain
- TCA's & SSRI's/SNRI's – has been beneficial in DPN & PHN – no studies in CRPS
- IV Lidocaine - no controlled studies some efficacy reported – Mexilitene, Patch
- GABA Agonists – no studies on effects on pain, Intrathecal Baclofen useful in dystonia
- Calcium Channel Modulators – Gabapentin, Pregabalin – mildly beneficial in CRPS
- Beta Blockers – some reports state benefit – no studies.
- Oral Sympatholytics – in theorpy would be effective – side effect profiles too high.
- Clonidine – no controlled long term trials, case reports show benefit, new gel may show promise

INTERVENTIONAL PROCEDURES

- Sympathetic Blocks – Specific/IV – 70% of patients report some form of response – no studies on long term benefits, techniques have been studied.
- IV Regional sympathetic Block – Guanethidine (7 controlled studies no benefit), Bretyllium, --- ?effects of Tourniquet on A-β and A-δ fiber conduction.
- IV Phentolamine – may have benefit superior to stellate block – not fully studied
- IV Ketamine – Most promising to date - 66-80% patients showed an overall improvement as measured by increased function, reduced medication requirements, or both (Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Med*. Sep 2004;5(3):263-75)
- IV Immunoglobulin – postulated thru effects of astrocystes and microglia production of cytokines
- Epidural Clonidine – effective but side effect profile very high
- Surgical Sympathectomy – not suggested routinely, seems to have benefit if done within the first 12 mo, most symptoms reappear after successful sympathectomy
- Physiotherapy –essential for eventual successful outcome
- Psychotherapy

DIAGNOSIS AND MANAGEMENT OF COMPLEX REGIONAL PAIN SYNDROMES

Treatment algorithm for complex regional pain syndromes.



NEUROMODULATION -- (SCS)

1962 – Mazars (France) used SCS for severe neuropathic pain – based on theory of Head & Holmes - “epicritic and protopathic afference” of chronic pain

1965 (Science) -- Melzack & Wall – Gating Theory at first spinal relay--Selective activation of large fibers

1967 -- Shealy - First report of electrical stimulation of spinal cord. 80 % benefit – Sweet – worst results (back pain)-- Focus was on psychological selection not type of pain

1969 – Reynolds - Descending pathways from PAG -

1973 -- Bonica – First meeting

1975 – IASP – SCS Selective action on neuropathic pain not nociceptive pain

1977 – Richardson & Akil PAG stimulation

1980's – Not effective in nociceptive forms of pain

1985's – awareness that SCS is effctive for neuropathic pain, PVD, Angina

1990-93—Tsubokawa Motor Cortex Stimulation – based on concpet of attenuation of Brain Stem

NEUROMODULATION – (SCS) CONTD

Improvements in technology, techniques, electrical selectivitiy have increased the use of SCS – further understanding of SCS

Accepted mode of Action:

- Activation of low threshold, large fibers
- Decrease in excitatory amino acid release (Glutamate)
- Enhancement of GABA inhibitory system ($GABA_{\beta}$)
- Increase release of Adenosine, Serotonin and Norepinephrine

SCS – Indications and Expected outcomes

Success >Failure	Success>Failure	Variable Success	Failure>Success	Failure>Success
Angina Pectoris	CRPS 1 & 2	Amputation-Phantom Limb	Perianal/Genital	Central post-stroke
PVD:Vasospastic	Peripheral nerve damage	Intercostal Neuralgia	Partial cord lesion	COMPLETE CORD LESION
PVD: Occlusive	Diabetic neuropathy	Postherpetic neuralgia		Complete root avulsion
	Brachial plexus damage	Low Back Pain		
	Lumbosacral/Cervical Rhizopathy			
	Cauda Equina			
	Amputation-Stump Pain			

CRITERIA FOR SUCCESS

Neuropathic Pain:

1995 – Lazorthes --- 152/132 (90%) 2-20 yrs outcomes positive – peripheral nerve injury

1989 – Barolat – 18/9 CRPS -1 – good relief

2004 – Kemler -54/36 CRPS-1 – good benefit

1982 – Broseta – 70% - CPRS – 2 – excellent outcomes

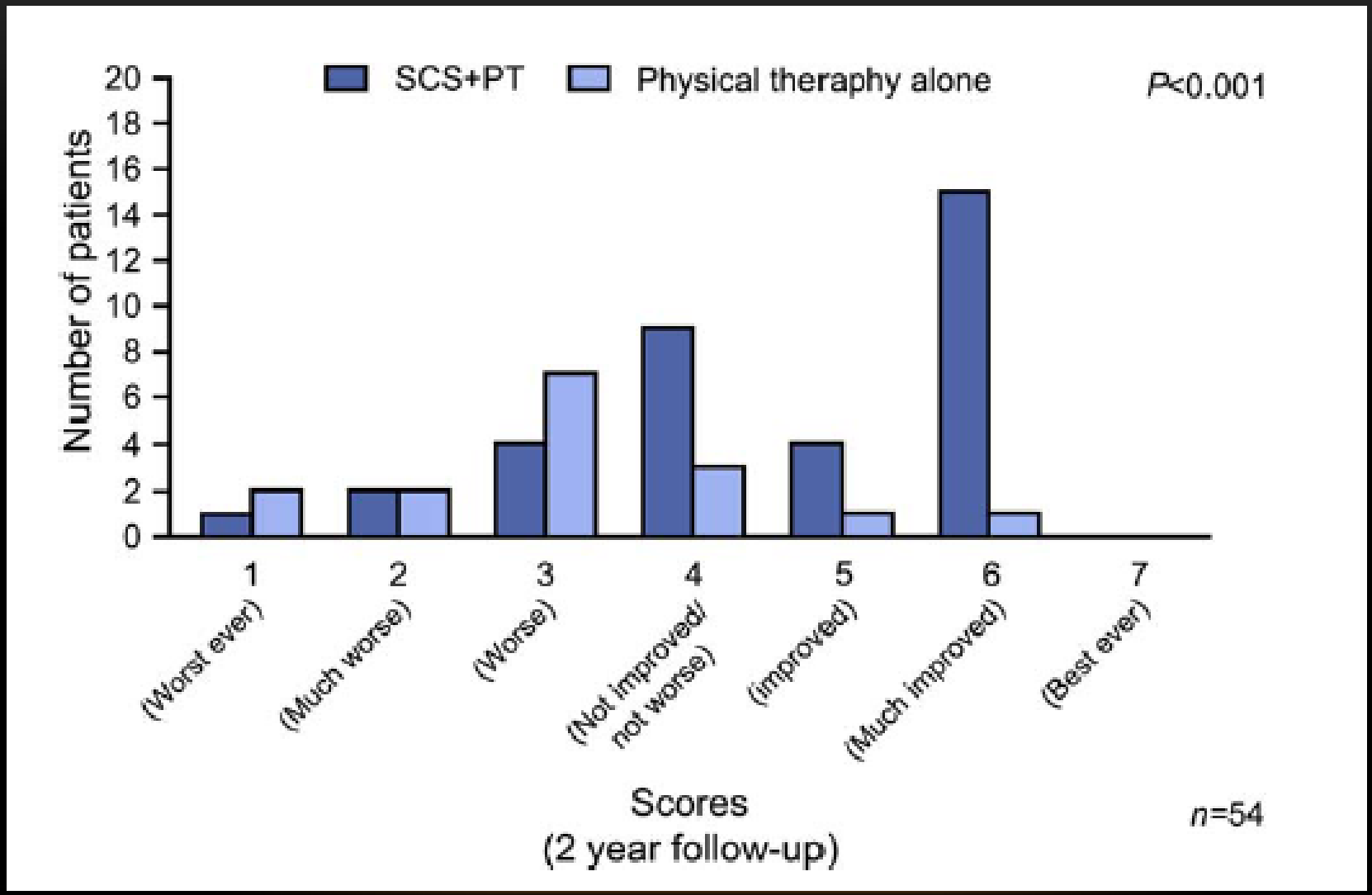
Factors:

- Time between symptoms – diagnosis – SCS
- Severity of symptoms at time of SCS
- Stage of pathology at time of SCS
- Patient expectations of SCS

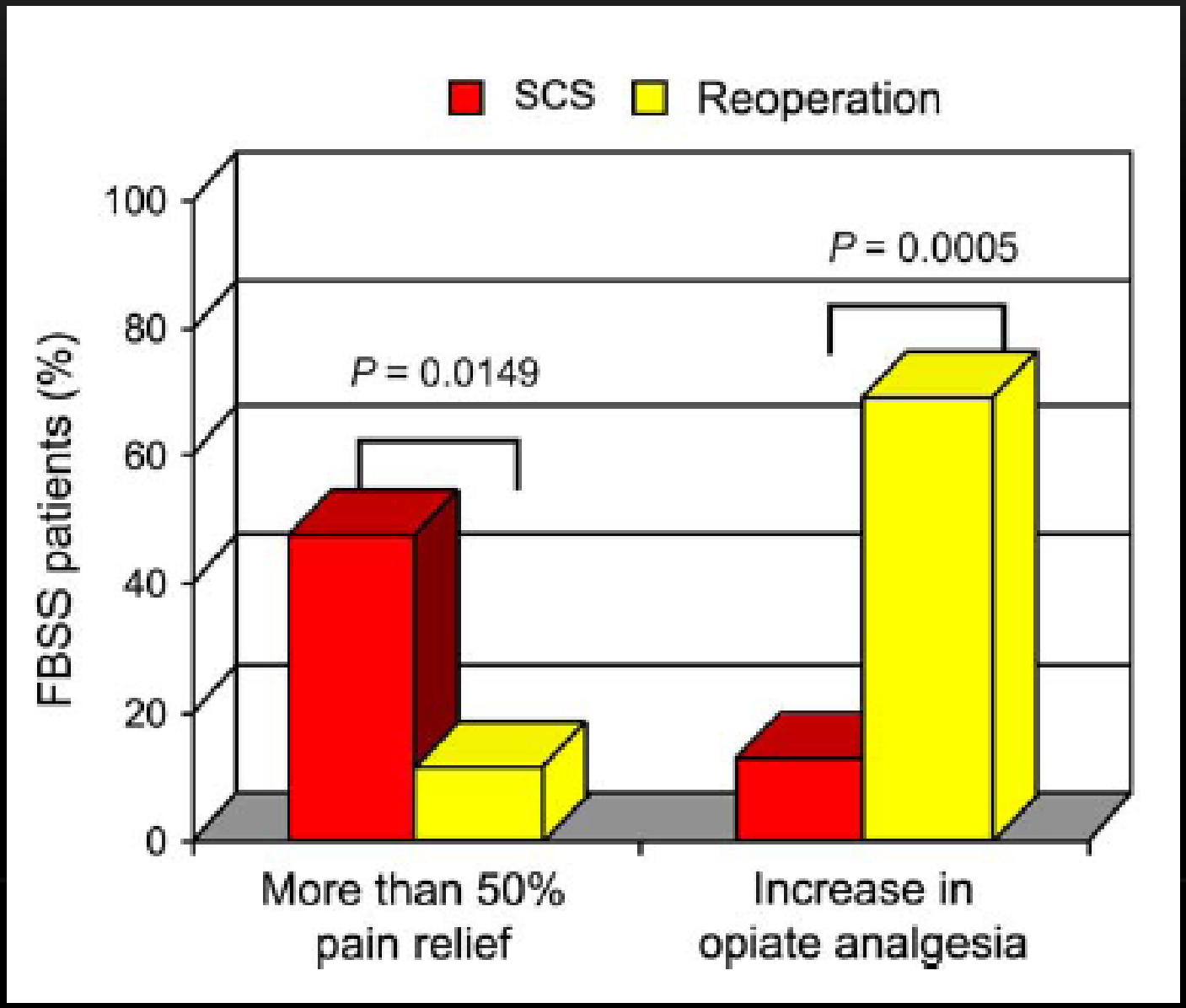
NEUROMODULATION

- Both SCS and PNS have been used in CRPS ---). SCS may be considered for CRPS type I, while PNS is considered a treatment for CRPS type II, providing relief from pain that is limited to the distribution of a major nerve (Ghai and Dureja, 2004). A review of the literature indicates that there is some evidence that these procedures can reduce pain in patients with CRPS.
- SCS for CRPS type I, based on the evidence, this treatment appears to be effective ((Cruccu, et al., 2007)—Grade A (Grade D for CRPS II)
- SCS for CRPS II , the available evidence is positive but l requires confirmatory comparative trials before the use of SCS can be unreservedly recommended in these conditions ((Cruccu, et al., 2007)
- Cochrane Review on 2 studies done (Mailis-Gagnon, et al., 2004),-- , there is limited evidence that spinal cord stimulators are effective for some types of chronic pain (i.e., failed back syndrome and CRPS type I) and that patient selection should be thorough and indications for SCS need to be clear before treatment is provided.
- Clinical and cost-effectiveness and predictors of SCS outcome (Taylor, et al., 2006)- concluded that SCS appears to be an effective therapy in the management of patients with CRPS type I and type II

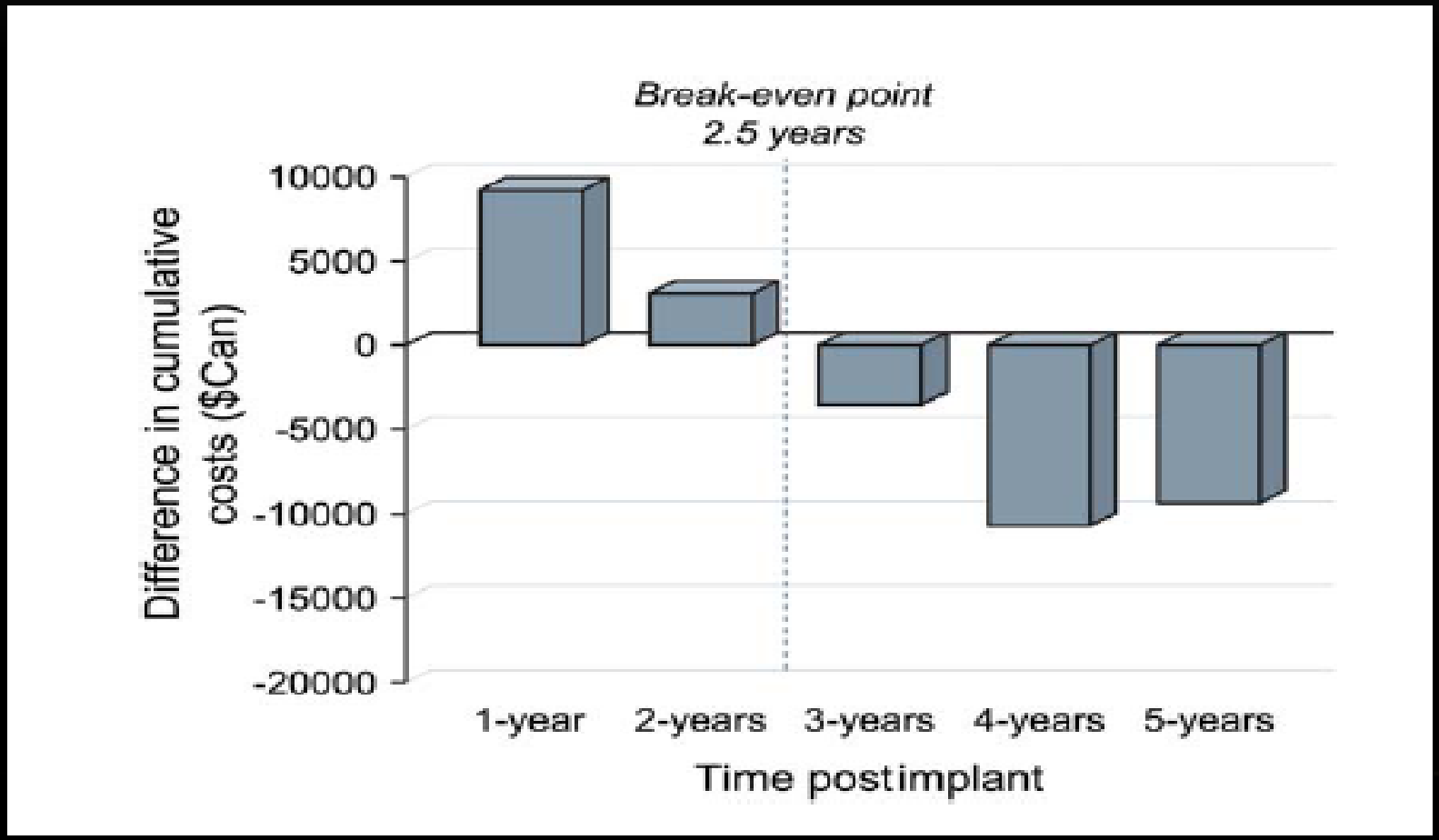
Taylor - Journal of Pain and Symptom Management Vol 31 #4S 4/06



North RB – Neurosurgery - 1994, 2005



Kumar – Neurosurgery 2002----- 4 studies in total



UK Neuromodulation Society Statement:

CRPS patients respond well to early intervention with SCS

International Guidelines for the treatment of CRPS developed under the auspices of the International Association for the Study of Pain (IASP), recommends SCS for CRPS at 12-16 weeks
((Stanton-Hicks M. et al .An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. Pain Pract. 2002;2(1):1-16)

Lack of RCTs does not equate to a lack of effectiveness and the literature on SCS should be considered as a body rather than RCTs in isolation

Neurostimulation: Reduction in Pain

Reference	# of Patients	Mean Follow-up	Results
•North *Pain*, 1993	171	7 years	52% with ≥ 50% relief
•Turner *Neurosurgery*, 1995	39 study meta analysis	16 months	59% with ≥ 50% relief
•De La Porte *Pain*, 1993	64	4 years	55% good to excellent relief
~~•Segal *Neurol Research*, 1998~~	~~24~~	~~19 months~~	~~78% good to very good effect~~
•Kumar *Surg Neurol*, 1991	111	5.6 years	59% good to excellent results
~~•Burchiel *Spine*, 1996~~	~~70 Multi-center~~	~~1 year~~	~~55% with ≥ 50% relief~~

Reduction in analgesic consumption

Reference	# of Patients	Mean Follow-up	Results
Ohnmeiss *Spine*, 1996	40	2 years	66% decreased eliminated narcotics
North *Neurosurgery*, 1995	171	7 years	58% reduced/eliminated analgesics
De La Porte *Pain*, 1993	64	4 years	90% reduced medication
Kumar *Surg Neurol*, 1991	111	5.6 years	59% satisfactory relief
Racz *Spine,* 1989	26	1.8 years	81% reduced/eliminated narcotics
Segal	24	19 months	59% satisfactory relief

TREATMENT OUTCOMES

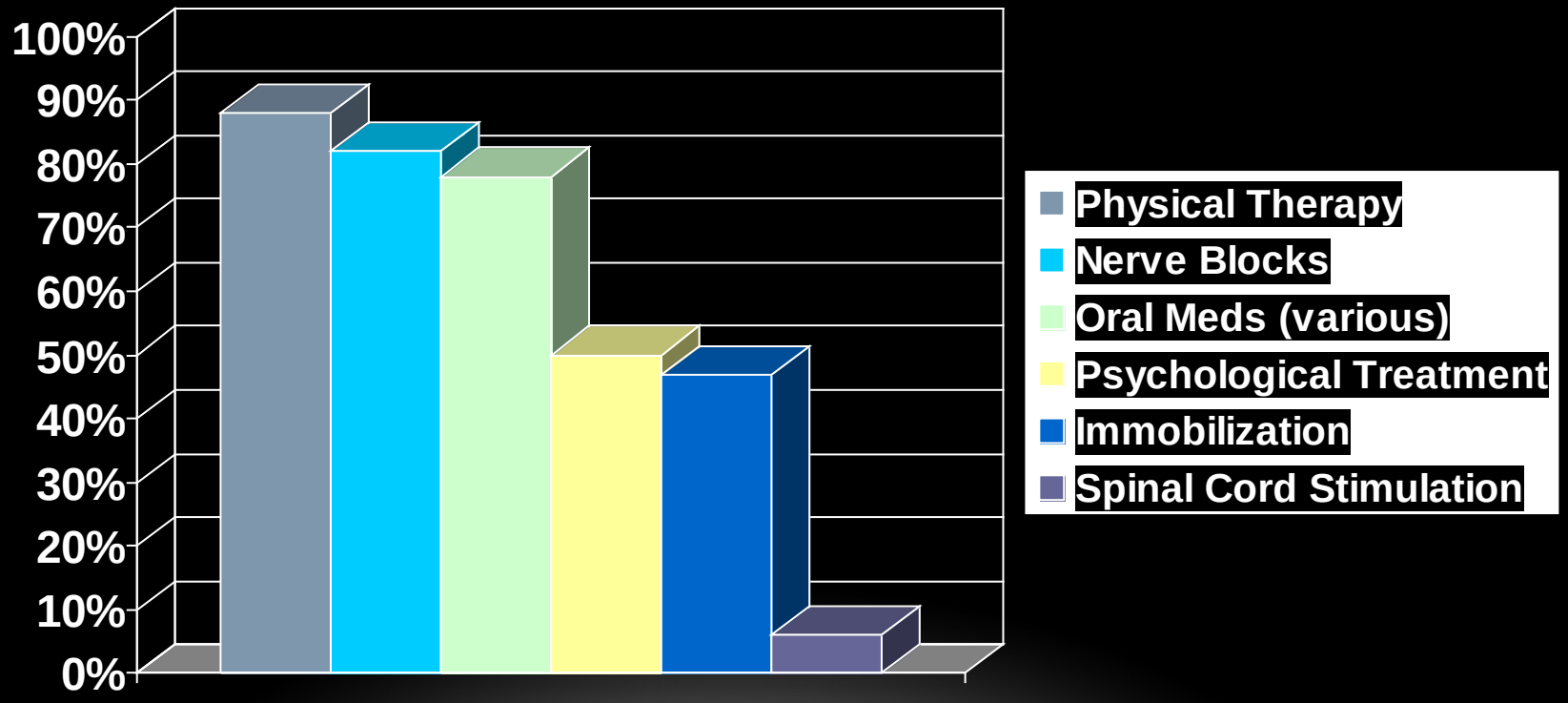
- Mode of therapy/Nature of Pathology/Patients age/Time to diagnosis

Good prognosis if onset between ages 2-22yrs, (prognosis poor if related to surgical procedure)

Delay in diagnosis results in less than adequate responses

Type of therapy introduced when diagnosis made is a strong predictor

TREATMENTS RECEIVED PRIOR TO REFERRAL TO TERTIARY CARE CENTER



Allen G et al. Pain 80 (1999) 539-544.

CLINICAL EXPERIENCE

- Post traumatic MVA Sternal Fracture Pain
- PVD with Ulcers awaiting possible amputation
- Neurogenic Claudication in patient poor surgical risk
- Post Amputation stump pain
- Occipital neuralgia
- Intercostal Neuralgia
- Interstitial Cystitis
- Pelvic endometriosis
- Ilioinguinal neuralgia
- Angina Patient died two days before trial