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ANNUAL CONGRESS OF PHYSICAL AND REHABILITATION MEDICINE

REGION

New developments in CRPS management

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MPRC

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Disclosure

Bo Biering-Sørensen

Has received honoraria for lectures from

- IPSEN, Merz, Desitin, Allergan, Abbvie, UCB Pharma, Medtronic, Nordic Infucare, Berlin-Chemie AG, Orion Pharma, Bial, Ambu, Britannia

Received honoraria for participating in Advisory Boards from

- IPSEN, Medtronic, Allergan, Merz, Almirall Nordic, Innoventa Medica, Abbvie and TEVA

Received unconditional grants and funding for Investigator initiated clinical trials from

- Allergan, Abbvie, Nordic Infucare, Merz, Desitin, Toyota Foundation, Innoventa Medica, Danish Parkinson Association, Ortbit Health, Britannia

Agenda

- Traditional management/ treatments for CRPS
- Emerging therapies to enhance pain control, functional recovery, and quality of life for individuals affected by this complex condition

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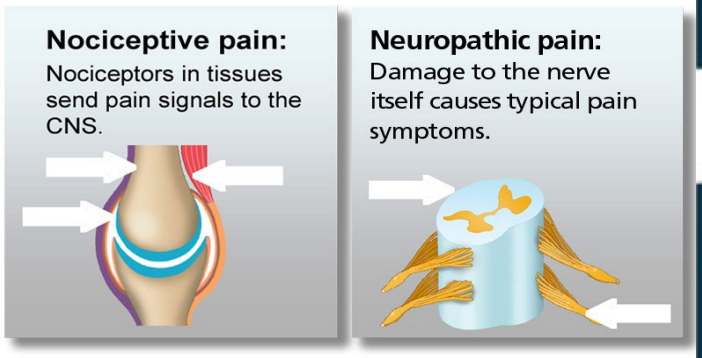
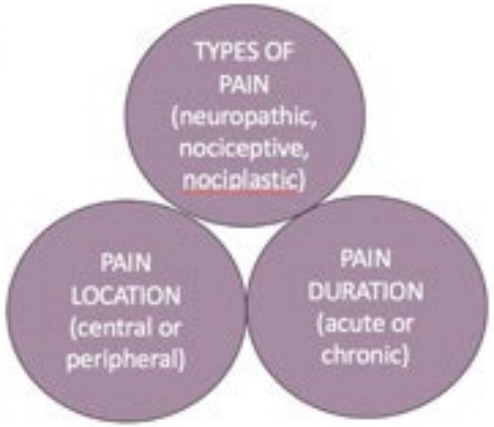
Types of Pain:



Reference: Google Picture

NOCICEPTIVE / INFLAMMATORY	NOCIPLASTIC	NEUROPATHIC	MIXED TYPES (NOCICEPTIVE / NEUROPATHIC)
Pain in response to an injury or stimuli; *typically* acute	Pain that arises from altered nociceptive function; *typically* chronic	Pain that develops when the nervous system is damaged; *typically* chronic	Primary injury and secondary effects
Postoperative pain, sports injuries, arthritis, sickle cell disease, mechanical low back pain	Fibromyalgia, irritable bowel syndrome, non-specific low back pain	Post-herpetic neuralgia, trigeminal neuralgia, distal polyneuropathy, CRPS neuropathic low back pain	

Possible development of chronic pain after an acute injury.



Reference: Medscape Education

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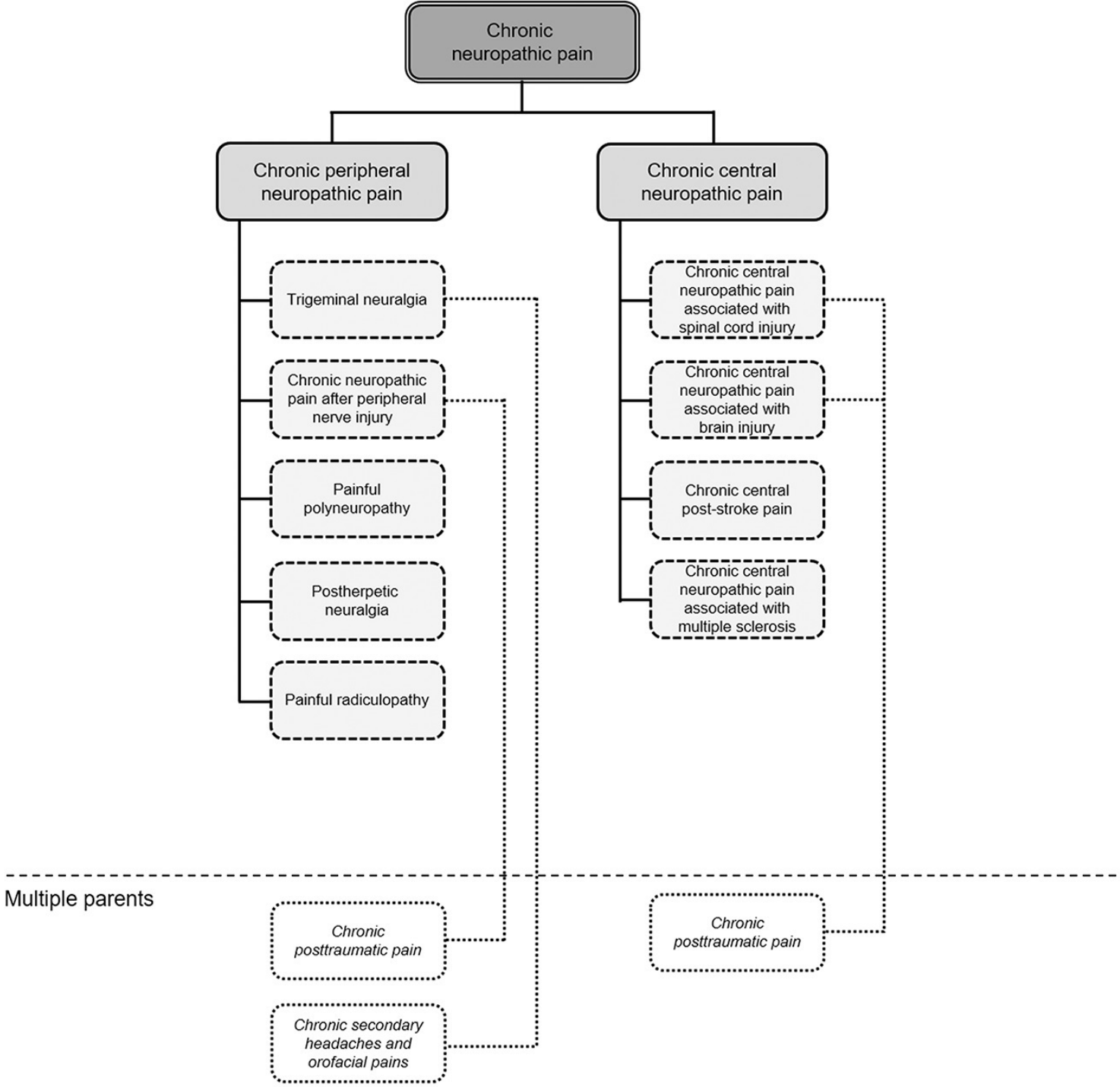
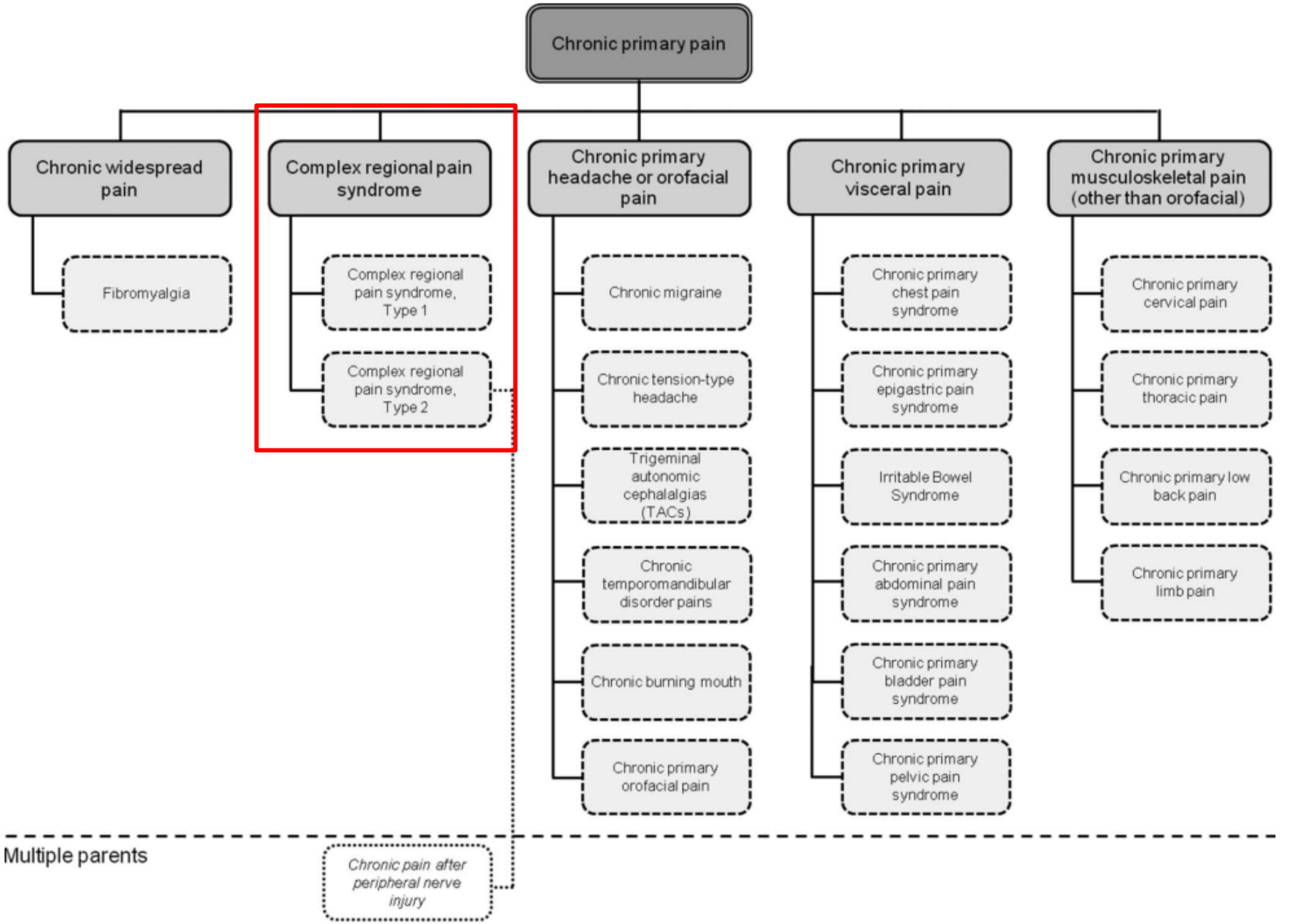
ICD-11



The IASP classification of chronic pain for *ICD-11*: chronic neuropathic pain **PAIN160(1):53-59, January 2019.**



The IASP classification of chronic pain for ICD-11: chronic primary pain. M. Nicholas et al. Paii· (2019) 28–37

Acute CRPS (6-12 months)

Acute CRPS (6-12 months)

Acute CRPS (6-12 months)

Chronic CRPS

Chronic CRPS

Definitive pathophysiological mechanisms behind CRPS are not known

- **Regional and Neurogenic inflammation** – Increase of proinflammatory cytokines (IL-1beta, IL-2, IL-6 and TNF-alpha) and reduction of anti-inflammatory cytokines (IL-4 and IL-10)
- **Oxidative stress** as a result of inflammation
- **Autoantibodies** against antigens in the autonomic nervous system
- **Peripheral sensitization** (inflammation -> repetitive activation of the "dorsal root ganglion" -> neuronal sprouting and sensitization)
- **Central sensitization** (increased excitability and reduced inhibition in the ventroposterolateral nucleus of the thalamus)
- **Cortical reorganization** – contralateral primary and secondary somatosensory cortex to non-painful tactile stimuli (fMRI studies)

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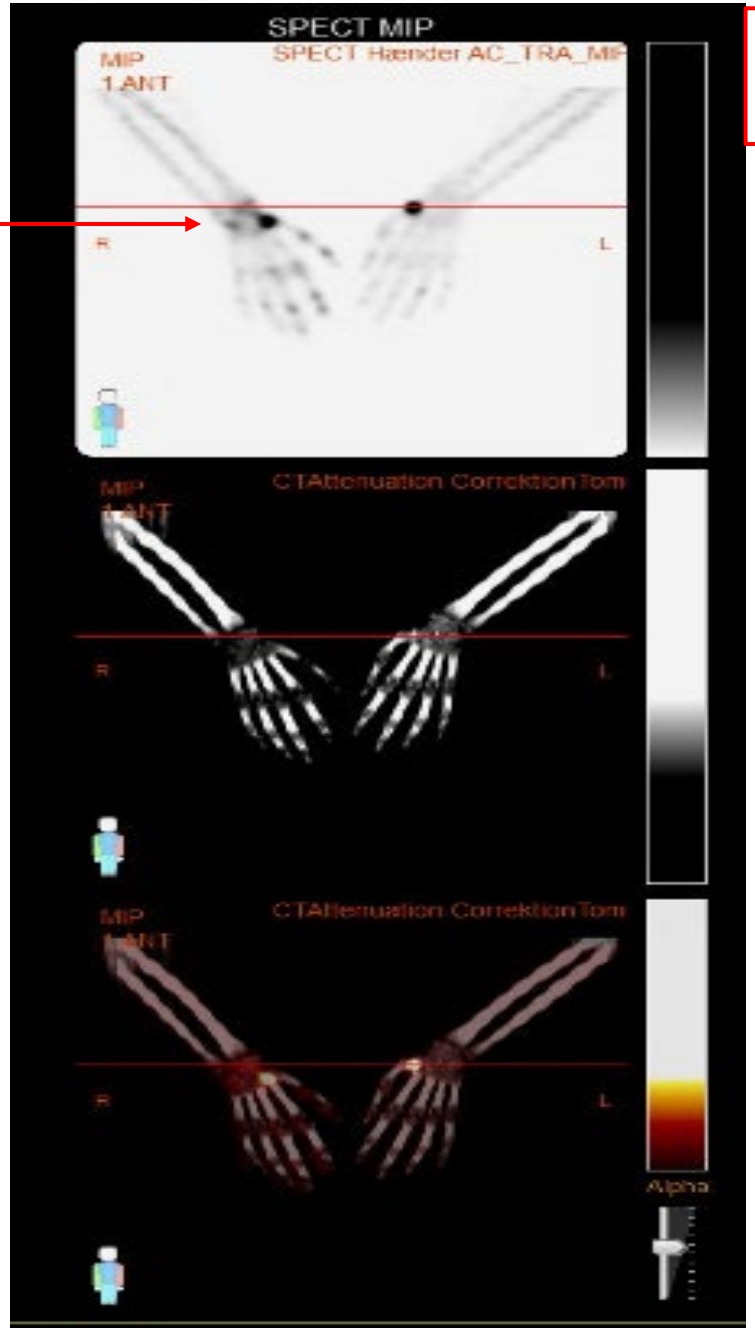

Three phase bone scan in Acute CRPS

X-rays in Chronic CRPS

How to treat this complex disease?

Reference: Google Picture

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Multimodal therapy and management of CRPS patients

Health Care Professionals involved in the assessment and multimodal treatment of CRPS patients at the CRPS clinic Rigshospitalet Denmark

Team Conferences every week to discuss progress for the patients and how to proceed with the treatment

The primary aims of treatment

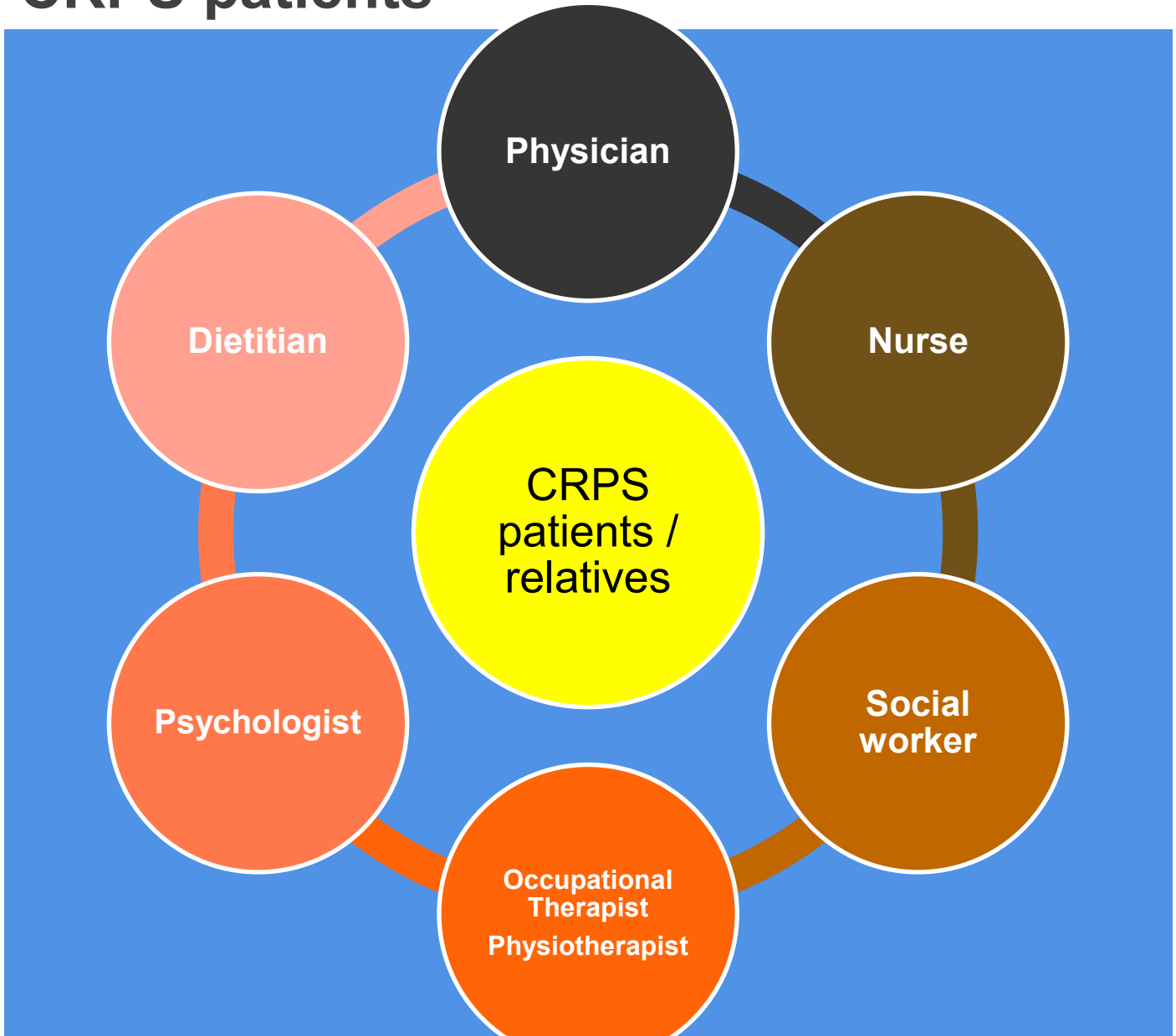
- Reduce pain
- Preserve or restore function
- Enable patients to manage their condition
- Improve their quality of life
  - Harden RN. Complex regional pain syndrome. Br J Anaesth 2001;87(1):99–106

- *The four 'pillars' of care* Complex regional pain syndrome in adults
- UK guidelines for diagnosis, referral and management in primary and secondary care
- Education → 7 weeks CRPS school for patients and relatives
- Pain relief
- Physical rehabilitation
- Psychological intervention

Education program for CRPS patients

All 7 sessions focus on:

- Knowledge about CRPS symptoms
  - Pain
  - Fatigue
  - Consequences for activities and participation
- Patient empowerment
- Self-management skills
- Networking



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The patients participates in seven sessions – Relatives participates in Introduction, Dietitian and a session just for Relatives (Relative session is not shown):

General introduction for patients and relatives

Introduction to pathophysiology and treatment of CRPS

Pain and anti-inflammatory medicine and sleep

Rehabilitation activities

Work-life and socioeconomic matters

Psychological interventions - Bio-Psycho-Social chronic pain model

Nutrition and medication

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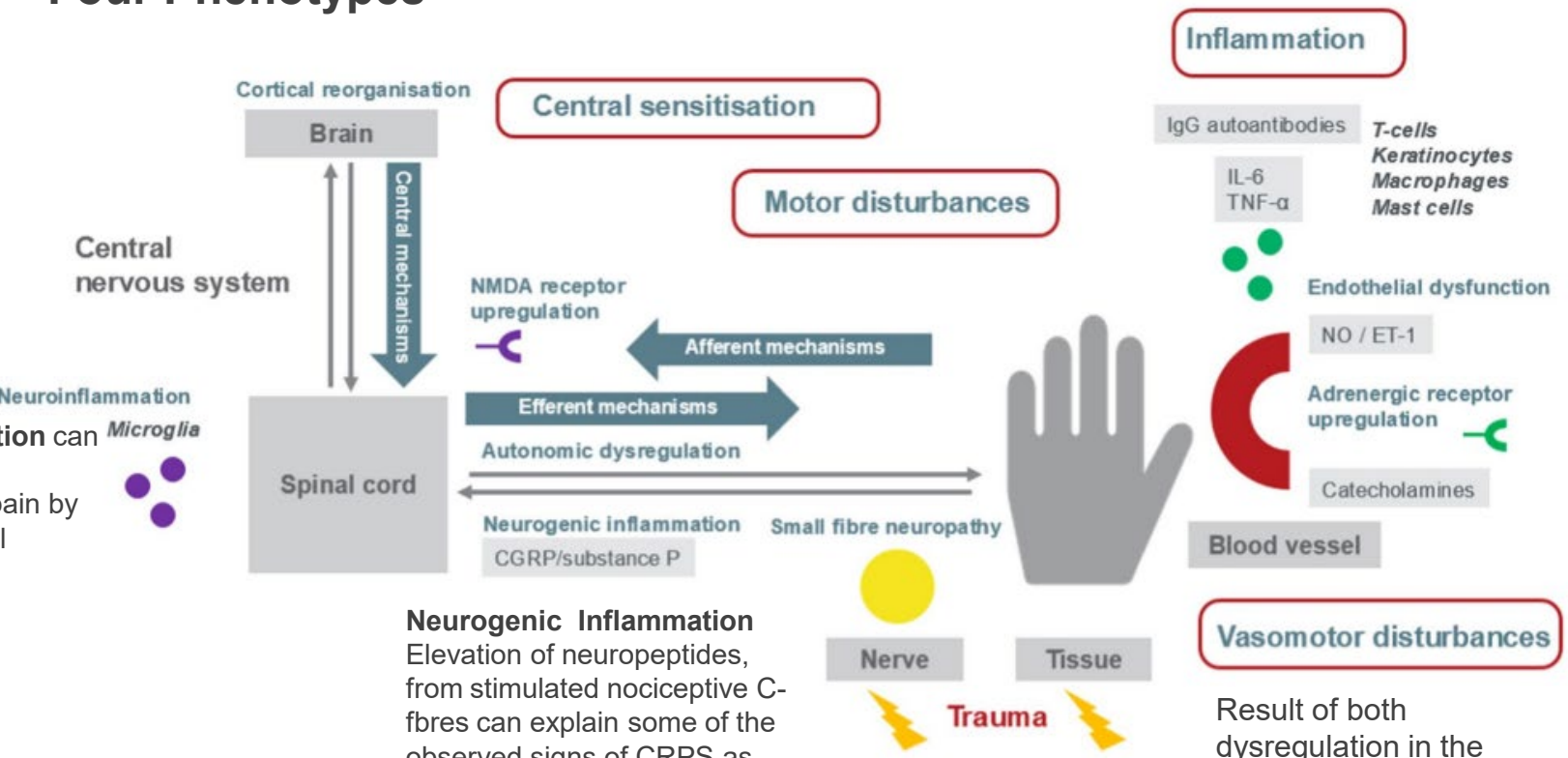
From a Symptom-Based to a Mechanism-Based Pharmacotherapeutic Treatment in Complex Regional Pain Syndrome

Four Phenotypes



Inflammation as a result of dysregulation of the immune system cytokines are linked to peripheral nociceptor activation and sensitisation, which can lead to hyperalgesia and pain

Neuroinflammation can contribute to the chronifcation of pain by facilitating central sensitisation

Neurogenic Inflammation Elevation of neuropeptides, from stimulated nociceptive C-fbres can explain some of the observed signs of CRPS as these neuropeptides cause vasodilation, protein extravasation and sweating

Result of both dysregulation in the autonomic nervous system and endothelial dysfunction

Mangnus TJP. Et al. Drugs. 2022

Acute CRPS Pharmacotherapy

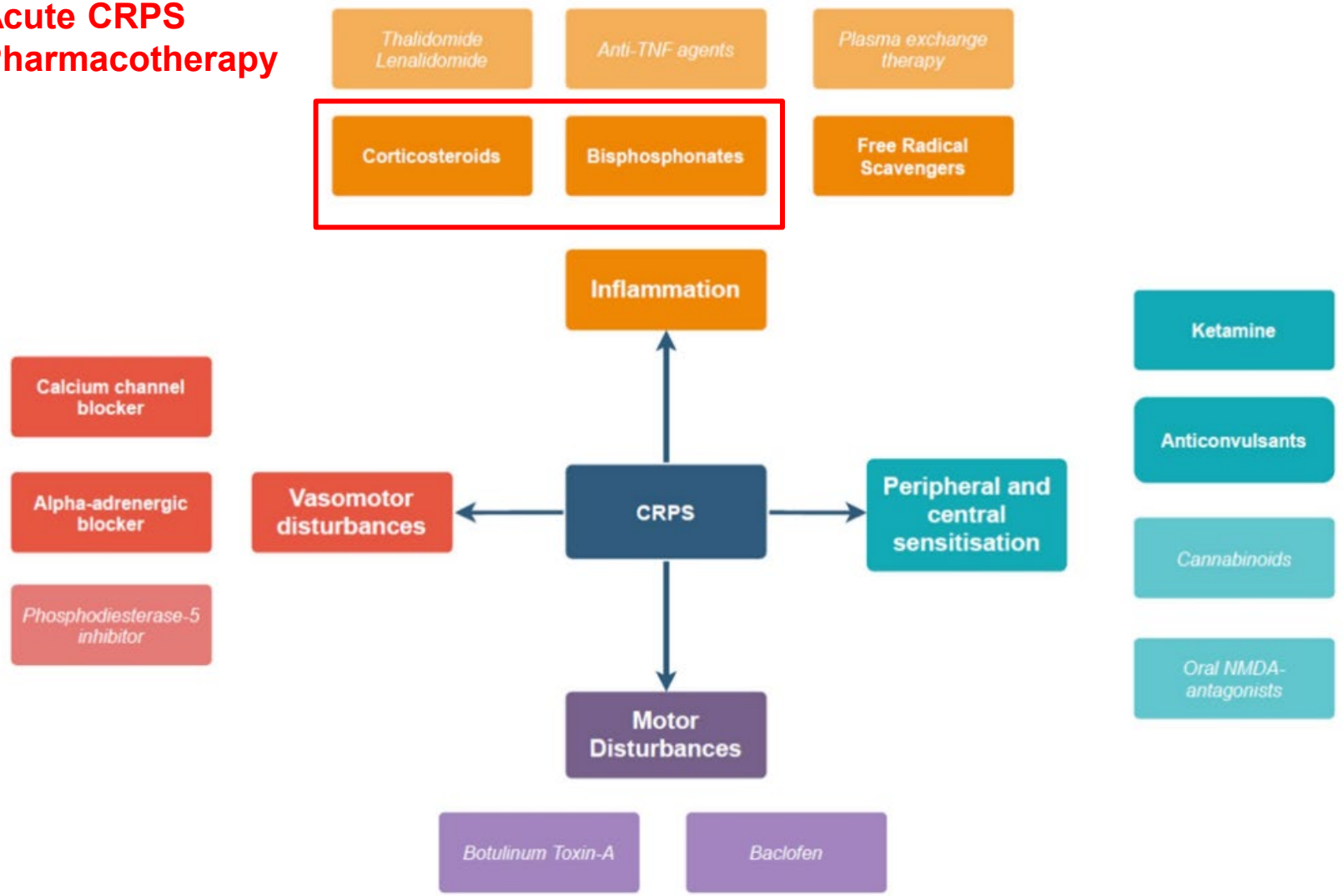


Fig. 1 Overview of mechanism-based pharmacotherapeutic options in complex regional pain syndrome. Experimental therapies are light-coloured and italicised. *CRPS* complex regional pain syndrome, *NMDA* *N*-methyl-D-aspartate, *TNF* tumour necrosis factor

Mangnus TJP, et al. Drugs. 2022

From a Symptom-Based to a Mechanism-Based Pharmacotherapeutic Treatment in Complex Regional Pain Syndrome

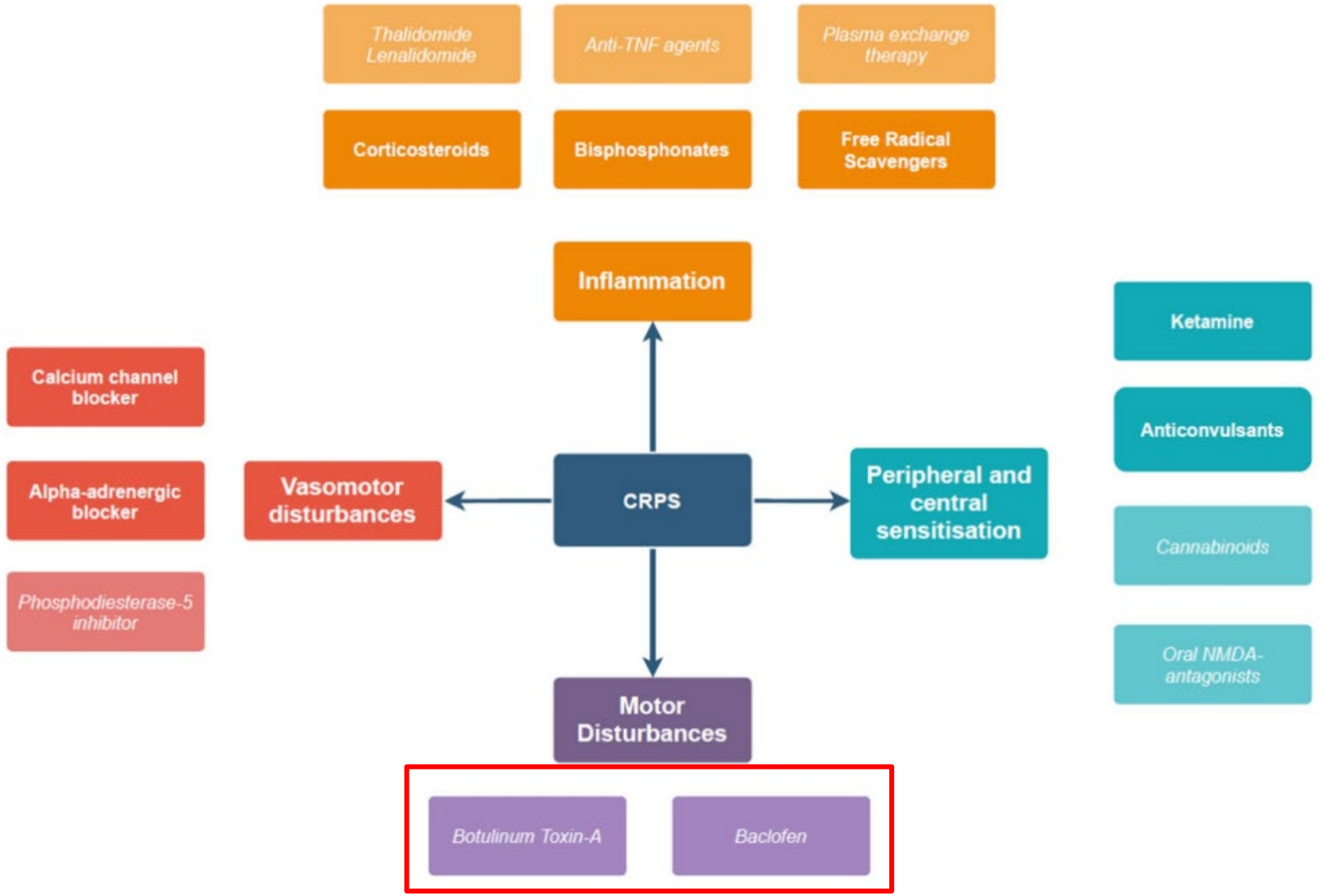


Fig. 1 Overview of mechanism-based pharmacotherapeutic options in complex regional pain syndrome. Experimental therapies are light-coloured and italicised. *CRPS* complex regional pain syndrome, *NMDA* *N*-methyl-D-aspartate, *TNF* tumour necrosis factor

Mangnus TJP, et al. Drugs. 2022

From a Symptom-Based to a Mechanism-Based Pharmacotherapeutic Treatment in Complex Regional Pain Syndrome

Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. Cochrane Database Syst Rev. 2023 Jun 12. Ferraro MC et al.

- 17 systematic reviews and synthesised the results reported for 127 RCTs
- **There are very few well-designed, wellreported, and large RCTs of the many interventions proposed for the treatment of CRPS**
- The *critical lack of high-quality evidence prevents us from drawing any firm conclusions* regarding the efficacy or effectiveness of any intervention for treating pain and disability in adults with CRPS

Treatment	Description / Mechanism	Indication	Level of Evidence	Grade of Rec.	Notable Findings / RCTs
Corticosteroids (oral prednisone)	Potent anti-inflammatory; dampens neurogenic inflammation in CRPS[3].	**Acute** CRPS (within ~6 months of onset), especially "warm" (inflammatory) stage with edema.	Level II (2 good RCTs in acute CRPS).	**B** (moderate)	Short prednisone courses (e.g. 30–40 mg taper over 2–12 weeks) significantly improved pain in early CRPS[4].
Bisphosphonates (e.g. alendronate, pamidronate)	Inhibit osteoclast-mediated bone resorption; reduce bone loss and possibly pain by modulating inflammation.	**Subacute or chronic** CRPS, especially with osteopenia ("cold" dystrophic phase) or persistent pain.	Level I (multiple RCTs; meta-analysis)[4].	**B** (moderate)	Several RCTs show bisphosphonates significantly reduce CRPS pain[4] and even improve joint motion[5]. Recommended in guidelines for analgesia in CRPS[4].
Calcitonin (intranasal)	Thyroid hormone that reduces bone turnover and may have central analgesic effects[6].	**CRPS (acute or chronic)** – historically used especially in post-traumatic CRPS to alleviate pain and improve bone density.	Level I (meta-analysis showed benefit)[7], but conflicting Level II trials[8].	**C** (limited)	Early trials and a meta-analysis found intranasal calcitonin (100–300 IU daily) improved CRPS symptoms[7], but two high-quality RCTs gave mixed results (one positive, one negative)[8]. Rarely used now due to availability and variable efficacy[8].
NSAIDs / COX-2 inhibitors	Anti-inflammatory analgesics; reduce prostaglandin-mediated inflammation and pain.	**Acute or subacute CRPS** with inflammatory signs (pain, swelling). Often trialed empirically.	Level III (poor-quality or extrapolated evidence)[9].	**C** (weak)	No high-quality CRPS-specific trials; overall **no clear benefit** shown in CRPS[9]. (Some

Physical Therapy and Rehabilitation

Treatment	Description / Mechanism	Indication	Level of Evidence	Grade of Rec.	Notable Findings / RCTs
Physical Therapy (PT) (exercise & mobilization)	**Gradual exercise therapy** to restore range of motion, strength, and function in the affected limb. Emphasizes **"reanimation"** of the limb through active movement, weight-bearing, and normalization of use[36][37]. Also includes edema management, posture training, and pacing of activity.	**All CRPS patients** – first-line cornerstone of treatment[38]. PT is started as early as possible, tailored to tolerance (pain-limited at first). Indicated in both acute and chronic CRPS to prevent disuse and improve function.	Level I–II (strong consensus and moderate clinical evidence)[39][40].	**A** (strong)	PT is universally recommended as the **foundation of CRPS therapy**[38]. Clinical trials show that structured PT can significantly improve pain and mobility: e.g. Oerlemans et al. found upper-limb CRPS patients getting PT (and OT) had better pain relief and active range of motion than controls receiving only counseling (Level 2 evidence)[39]. A meta-analysis also supports that pain-focused PT combined with medical management yields meaningful improvements[41]. *Early, appropriate graded exercise may*

Treatment	Description / Mechanism	Indication	Level of Evidence	Grade of Rec.	Notable Findings / RCTs
					preserve limb function and even shorten disease duration[42].
Occupational Therapy (OT)	Therapy focused on **functional use** of the affected limb in daily activities. Involves task-specific training, adaptive techniques, and **desensitization** exercises to help patients perform self-care, work tasks, and hobbies. Often addresses fine motor skills (for upper limb CRPS) and coping strategies for one-handed techniques if needed.	**All CRPS, especially upper extremity** – to regain independence in daily activities and hand function. OT complements PT (while PT works on gross movement and strength, OT works on practical skill retraining).	Level II (used in trials alongside PT)[39].	**A** (strong)	Integrated OT/PT approaches improve outcomes. In CRPS-I of the hand, adding OT (e.g. functional training, desensitization) to PT helps restore ability to perform ADLs and reduces disability (supported by clinical experience and subset analyses in trials)[39]. Guidelines include OT as a standard part of multidisciplinary CRPS care[37].

Treatment	Description / Mechanism	Indication	Level of Evidence	Grade of Rec.	Notable Findings / RCTs
					mood and sleep, indirectly aiding pain coping.
Multidisciplinary Pain Management Program	A comprehensive program combining medical management, physiotherapy, occupational therapy, and psychological therapy in an integrated fashion. Often involves a team (physician, PT, OT, psychologist) coordinating a structured rehab schedule (sometimes day-program or inpatient).	**Moderate to severe CRPS, especially chronic cases** that have not responded to single-modality outpatient treatments. The team approach is beneficial for complex cases addressing all aspects (biomedical and psychosocial).	Level II (clinical studies show better outcomes with interdisciplinary approach)[61][62].	**A** (strong)	**Interdisciplinary programs** are considered the most effective strategy for chronic CRPS[61]. For example, programs following the "Malibu protocol" (functional restoration emphasis) have been validated by clinical use, leading to improved pain and function in many patients (though formal RCTs of entire programs are scarce)[62]. One evidence review found that programs including medical, physical, and psychological components were more likely to succeed than single therapies[63]. Consequently, a graded functional restoration algorithm with timely incorporation of meds, blocks, and psych therapy as needed is recommended for

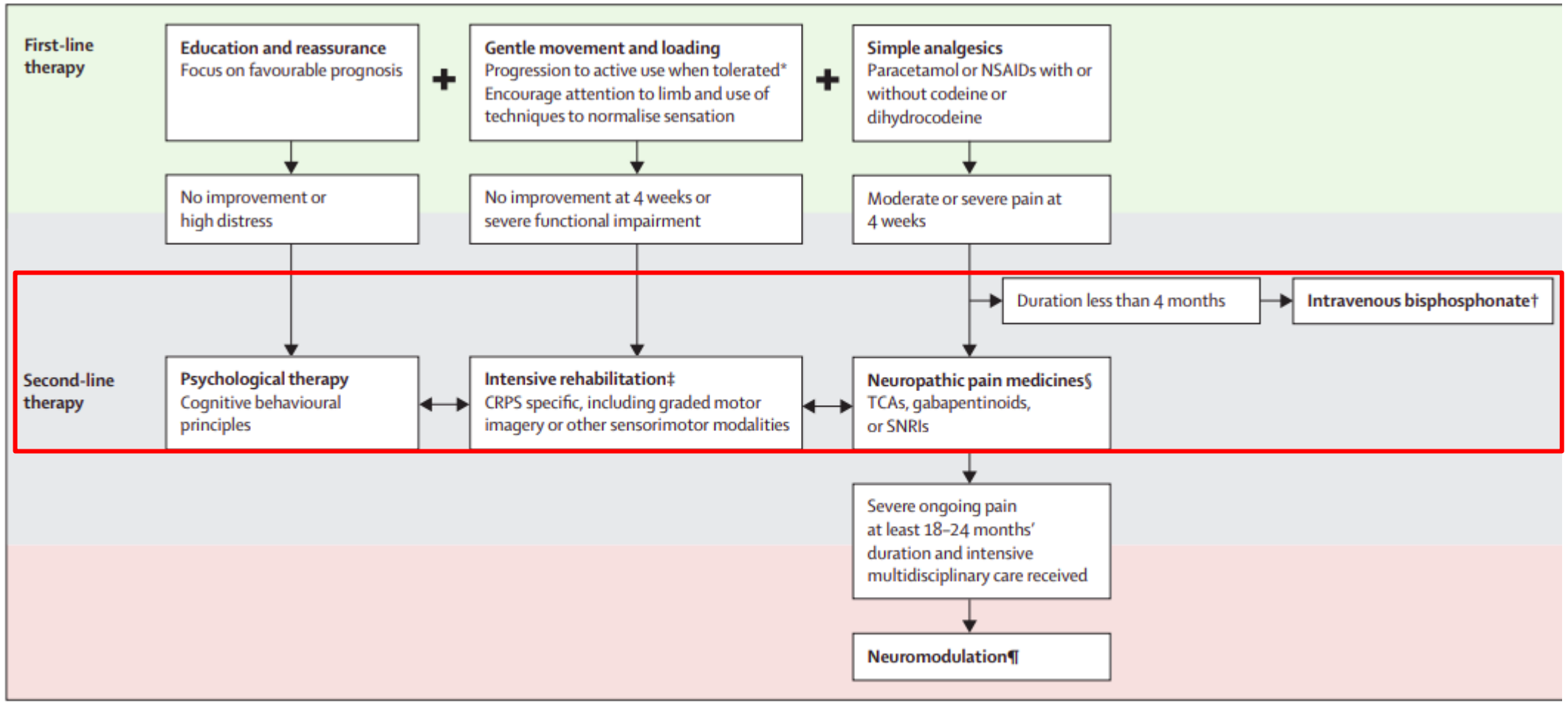
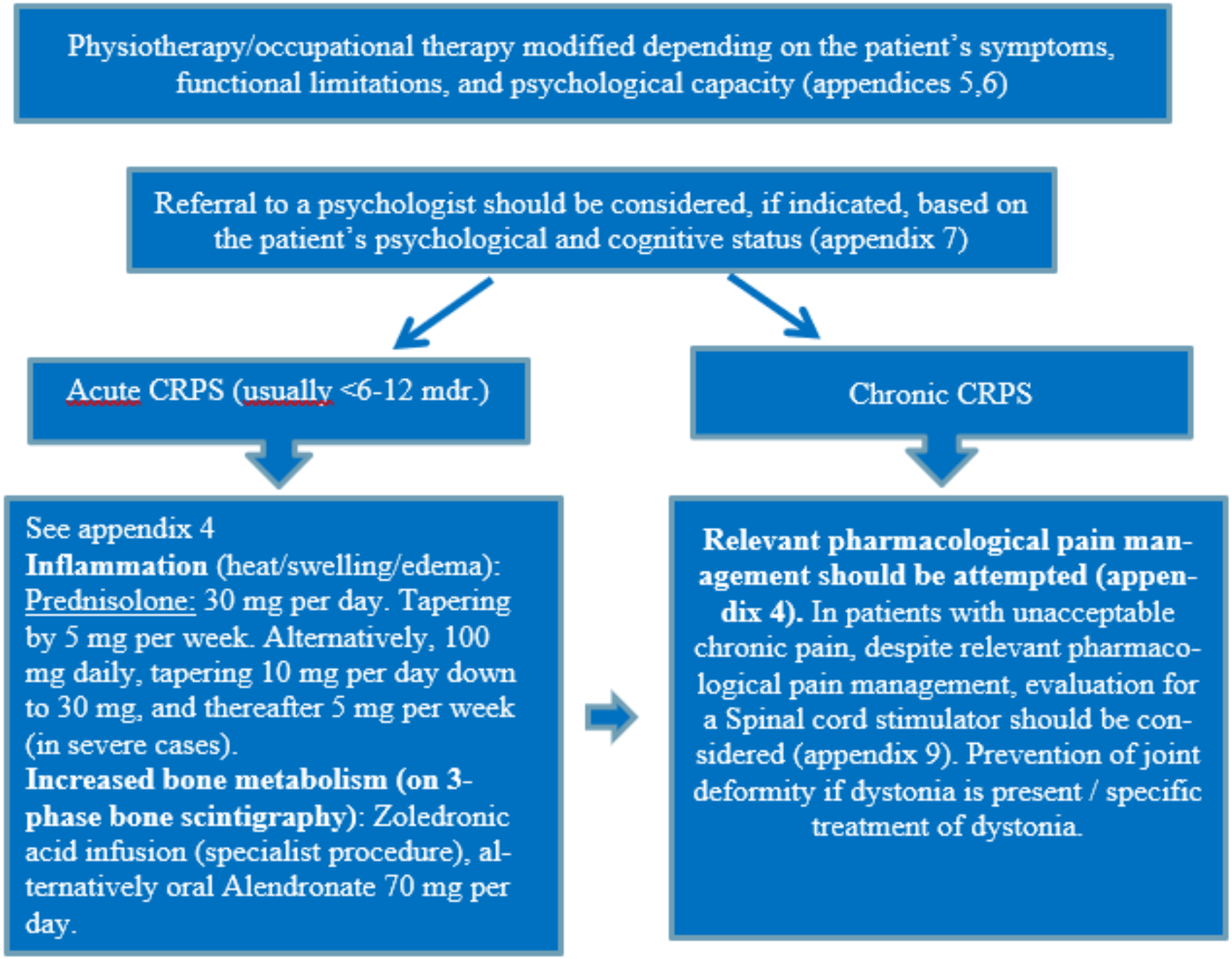


Figure 2: **Proposed algorithm for the management of complex regional pain syndrome**
Adapted from recommendations in the UK Royal College of Physicians guidelines.[64] First-line treatments are usually administered in non-specialist settings and, in most cases, irrespective of symptom duration. First-line treatments should be done together and have equal importance. Second-line treatments might be delivered individually or together within a multidisciplinary pain management

Ferraro MC, O'Connell NE, Sommer C, Goebel A, Bultitude JH, Cashin AG, Moseley GL, McAuley JH. Complex regional pain syndrome: advances in epidemiology, pathophysiology, diagnosis, and treatment. Lancet Neurol. 2024 May

National behandlingsvejledning for Complex Regional Pain Syndrome (CRPS)

Udgiver	Dansk Neurologisk Selskab (DNS), Dansk Selskab for Anæstesiologi og Intensiv Medicin (DASAIM), Danske Fysioterapeuter, Ergoterapeutforeningen, Dansk Psykologforening, Dansk Sygeplejeråd (DSR) og Dansk Ortopædisk Selskab (DOS)		
Dokumenttype	Vejledning		**Version** 29. December 2024
Forfattere	DNS: Sif Gyfaldottir, Astrid Juhl Terkelsen, Tone Heinskou, Marc Klee, Carsten Kok-Jensen og Bo Biering-Sørensen DASAIM: Thomas Enggaard Danske Fysioterapeuter og Ergoterapeutforeningen: Mette Jensen, Ditte Ulrik Rosenberg, Charlotte Baden, Helle Bjerge Nielsen, Martin Gjøl Sveistrup, Linda Nielsen og Peter Vögele Dansk Psykologforening: Karin Dons, Lone Knudsen DSR: Lotte Rasmussen, Carrinna Hansen DOS: Gert Rahbek Andersen og Tine Weis		**Godkendt:**
Fagligt ansvarlige	Astrid Juhl Terkelsen, Bo Biering-Sørensen og Thomas Enggaard		**Revisionsdato:**



Flowchart 2. Treatment of acute and chronic CRPS

Neuropathic pain management

Reference: Google picture

Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis

NB! Be aware of other symptoms when choosing treatment for neuropathic pain
NB! Go slow when up-titrating
NB! Titrate until effect or side effects

	Daily dosages and dose regimen*	Recommendation
Strong recommendation for use		
α2δ-ligands	Gabapentin 1200–3600 mg in three divided doses Gabapentin ER 1200–3600 mg in two divided doses Pregabalin 150–600 mg in two divided doses Mirogabalin 10–30 mg in two divided doses	First line
SNRIs	Duloxetine 60–120 mg once a day Venlafaxine 150–225 mg once a day or in two divided doses	First line
Tricyclic antidepressants†	25–150 mg once a day or in two divided doses	First line
Weak recommendation for use		
Lidocaine 5% plasters‡	1–3 plasters to the painful area for up to 12 h per day	Second line for peripheral neuropathic pain
Capsaicin 8% patches‡	1–4 patches to the painful area for 30–60 min with a minimal application interval of 60 days	Second line for peripheral neuropathic pain
Capsaicin cream‡§	Usually 0·075% one to three times per day	Second line for peripheral neuropathic pain
Botulinum toxin type A‡	50–300 units to the painful area every 3 months	Third line for peripheral neuropathic pain
rTMS (10–20 Hz targeting M1)§	1200–3000 pulses per session	May be used in selected patients
Opioids§¶	Usually <120 mg morphine equivalent in two divided doses Tramadol 200–400 mg in two extended releases or three divided doses	May be used in selected patients

Soliman N. et al. Lancet Neurol 2025; 24: 413–28

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Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis

Soliman N. et al. Lancet Neurol 2025; 24: 413–28

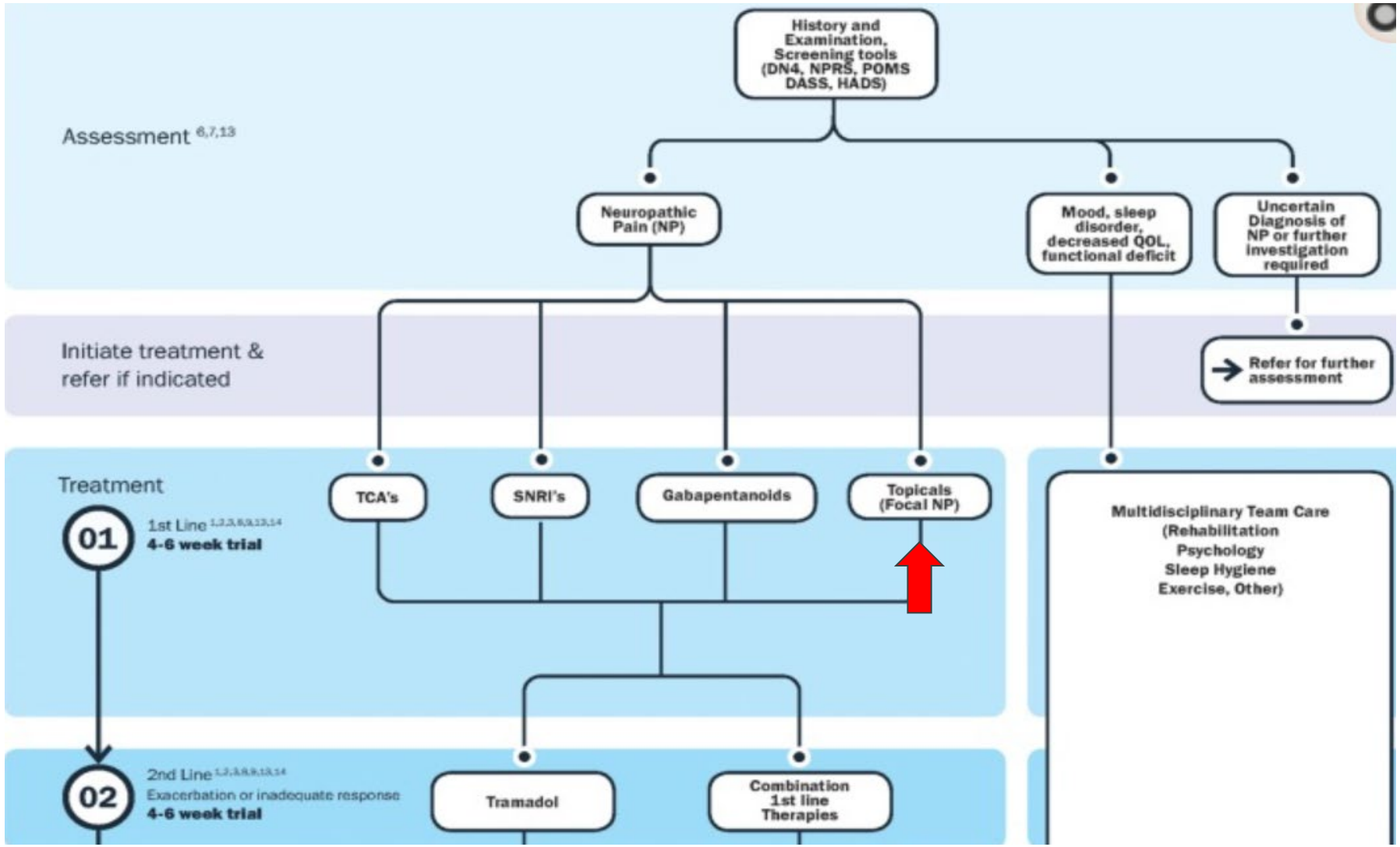
	Pain responders (n responders/N total)					Treatment withdrawals (n withdrawals/N total)			
	Active	Placebo	Total patients	Number needed to treat (95% CI)	Susceptibility to bias*	Active	Placebo	Total patients	Number needed to harm (95% CI)
Recommended first-line									
α2δ-ligands	3069/9569	1423/6617	16 186	8·9 (7·4–11·1)	1994	906/9319	332/6866	16185	26·2 (20·4–36·5)
Serotonin noradrenaline reuptake inhibitors	858/2207	364/1493	3700	7·4 (5·6–10·9)	1287	282/2363	61/1567	3930	13·9 (10·9 –19·0)
Tricyclic antidepressants	272/723	114/720	1443	4·6 (3·2–7·7)	1728	681/1352	23/671	2023	17·1 (11·4 –33·6)
Recommended second-line									
Capsaicin 8% patches	397/1242	214/868	2110	13·16 (7·6– 50·8)	NA	11/1288	5/893	2181	1129·3 (135·7–∞)
Capsaicin cream	111/249	68/223	472	6·1 (3·1–∞)	297†	53/495	15/479	974	18·6 (10·6 –77·1)
Lidocaine 5% plasters	62/249	33/238	487	14·5 (7·8–108·2)	NA	13/257	10/246	503	178·0 (23·9–∞)
Recommended third-line									
Botulinum toxin type A	102/202	18/171	373	2·7 (1·8–5·1)	1029	2/160	3/157	317	216·3 (23·5–∞)
Repetitive transcranial magnetic stimulation targeting–primary motor cortex	67/207	18/168	375	4·2 (2·3–28·3)	514	2/337	3/299	636	651·6 (34·7–∞)
Opioids	229/613	117/558	1171	5·9 (4·1–10·7)	838	84/781	22/745	1526	15·4 (10·8–24·0)

Data are n/N, unless stated otherwise. NA=not applicable. NNT=number needed to treat. *Refers to the number of patients in a trial who do not respond to treatment that would lead to an NNT>10, considered as the cutoff for reasonable clinical benefit. This calculation is not possible for treatments with NNT>10. The higher the numerical value, the lower the susceptibility to bias. If the susceptibility to bias is less than 400, a new study with fewer than 400 participants with no effect could change the NNT to a level that is not clinically meaningful; however a study with a susceptibility to bias score higher than 400 will not.[34] †Susceptible to reporting bias.

Table 1: **Pain response, withdrawals, and susceptibility to reporting bias based on number needed to treat**

A Comprehensive Algorithm for Management of Neuropathic Pain

Pain Med. 2019 Jun; 20(Suppl 1): S2–S12



Mechanisms of Botulinum Toxin Type A Action on Pain

Ivica Matak et al. Toxins august 2019

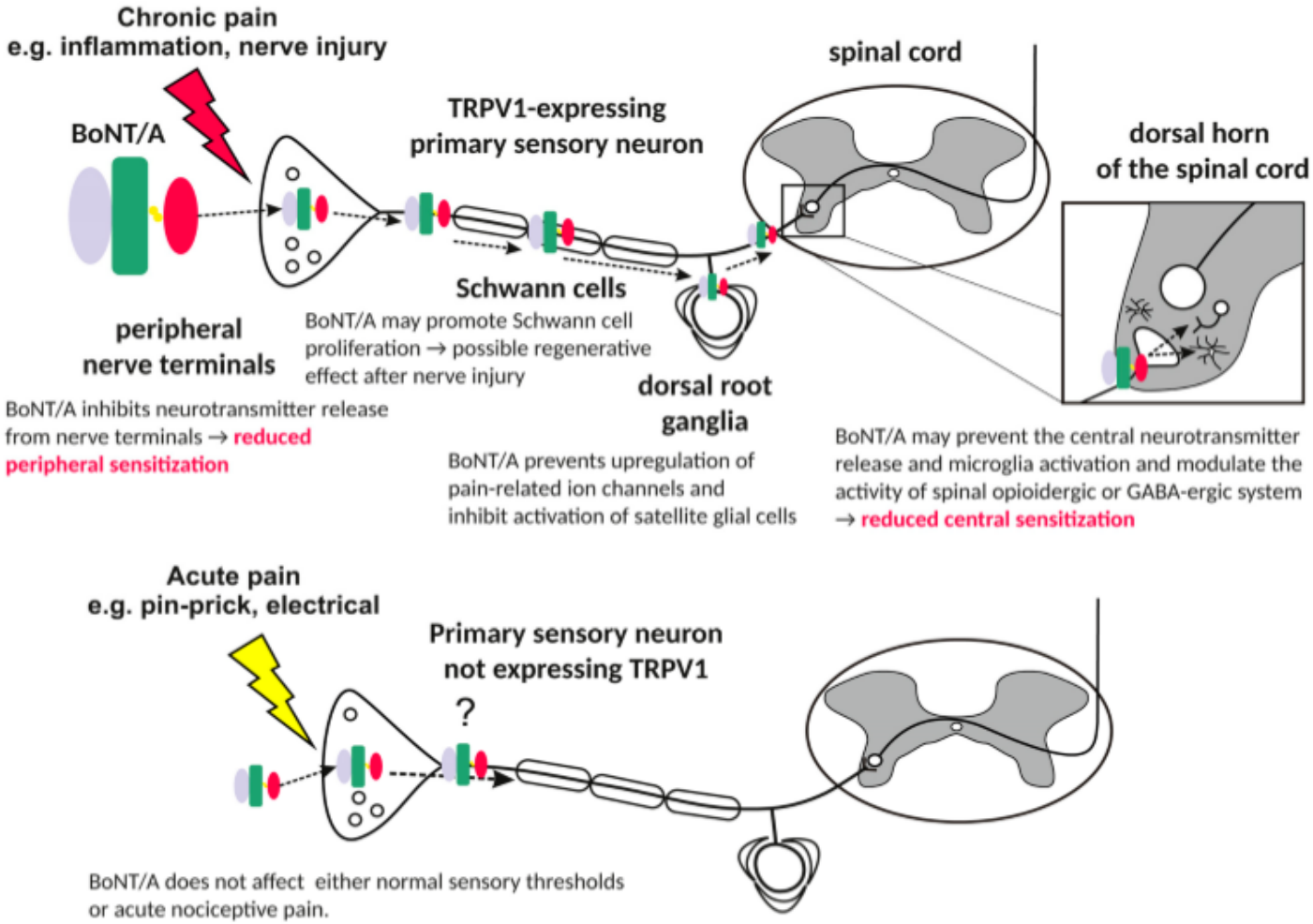
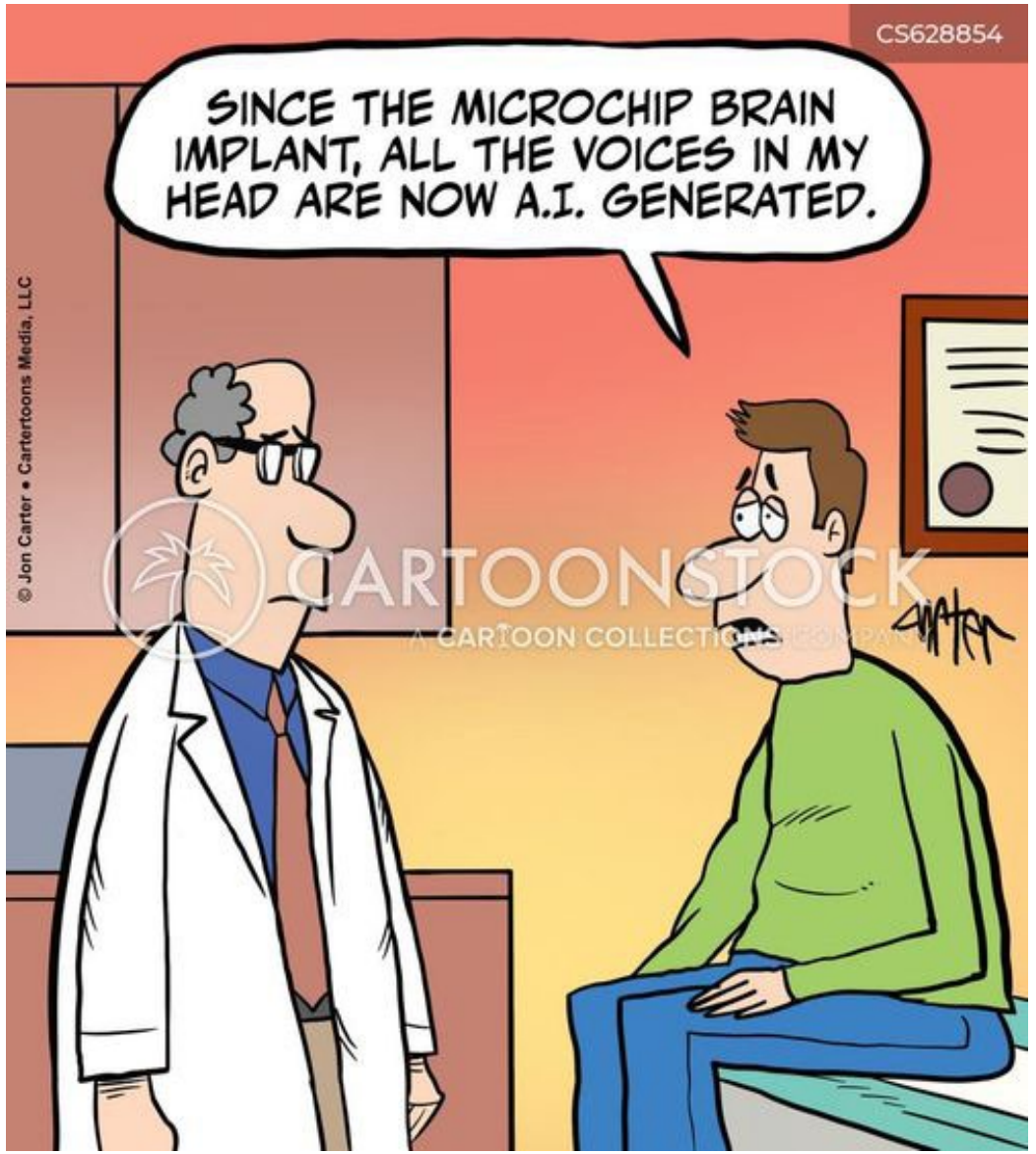


Figure 1. Actions of BoNT/A along the pain pathway.

Starting point:
Allodynia pain NRS 7-8
SMART goal: Pain NRS 3-4

Where are we going in the future



Reference: Google Picture

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Table 1. Treatment protocols for targeting the peripheral nervous system.

Type	Treatment Protocol	Treatment Mechanism
Medical treatments	Alpha-adrenergic antagonists (Prazosin, Phenoxybezamine)	• Decreasing adrenergic sensitivity in the nociceptive afferents
	Glial-modulating agents	• Decreasing glial cell activation • Inhibiting pro-inflammatory cytokine synthesis • Antagonism of pro-inflammatory cytokines
	Immune-modulating agents	• *TNF-α Antagonists:* Reduces elevated TNF-α levels in patients with neuroinflammation during acute CRPS • *Recombinant IL-10 (rIL-10):* Alleviates mechanical allodynia by modulating microglial activation in the early phase of CRPS
	IV immunoglobulin (IVIG) Therapies	• Downregulation of autoantibody production by B cells • Inhibition of cytotoxic T cells • Elimination of autoantibodies • Elimination of pro-inflammatory cytokines • Anti-inflammatory action
	Plasma exchange therapies	• Elimination of autoantibodies • Elimination of pro-inflammatory cytokines • The treatment has specific benefits, especially for patients with small fiber neuropathy and CRPS
	Free radical scavengers	• Reduce the risk of developing CRPS by lowering proinflammatory cytokines and oxidative stress • Show potential as a preventive treatment
	Alpha-lipoic acid (ALA)	• Reduce oxidative stress and enhance blood flow to the nerves • Neutralize various reactive oxygen species, inhibit generators of these reactive molecules, and repair damage caused by oxidants
	Dimethyl fumarate (DMF)	• Prevent nociceptive sensitization and reduce the accumulation of oxidative stress markers • Inhibit the development of pro-nociceptive serum antibodies and diminish innate inflammatory responses
	AMPK activators—Metformin	• Influence nociceptive processing • Decrease the excitability of sensory neurons
	Tadalafil (phosphodiesterase-5 inhibitor)	• Improve microcirculation • Decrease temperature difference between affected and unaffected feet
Interventional	peripheral nerve stimulation (PNS) treatments	• It applies electrical current to the myelinated fibers of peripheral nerves, thereby suppressing synaptic activity

Candan B, Gungor S. Current and Evolving Concepts in the Management of Complex Regional Pain Syndrome: A Narrative Review. Diagnostics (Basel). 2025 Feb

Table 2. Treatment protocols for targeting the central nervous system.

Type	Treatment Protocol	Treatment Mechanism
Medical treatments	Ketamine	• The antagonism of NMDA receptors results in pain relief • Blocking NMDA receptors downregulates heightened NMDA receptor activity in the CNS • It reduces the temporal summation of pain and modulates antinociception • Prevents central sensitization in dorsal horn neurons
	Low-dose naltrexone (LDN)	• Regulation of glial cell function to reduce the release of inflammatory cytokines in the CNS • Effects on neuropathic pain modulation by antagonizing TLR4 receptor, which blocks TLR4 signaling and potentially prevents and reverses central neuroinflammation and neuropathic pain.
	Glial-modulating agents	• Disruption of glial activation • Disrupting pro-inflammatory cytokine signaling and synthesis • Inhibition of pro-inflammatory cytokine synthesis • Antagonism of pro-inflammatory cytokines
	AMPK activators (e.g., Metformin)	• Influence nociceptive processing • Inhibit pathological pain signaling and reduce the excitability of dorsal root ganglion (DRG) neurons
Interventional treatments	Spinal cord stimulation (SCS)	• Electric stimulation on the dorsal column inhibits pain sensation • Suppressing ascending nociceptive signals • Enhancing descending inhibitory pathways • Stimulating supraspinal brain regions
	Dorsal root ganglion (DRG) stimulation	• Modulate pain signaling more directly at the site of pain transmission
	Repetitive transcranial magnetic stimulation (rTMS)	• Stimulating the brain cortex by magnetic pulses can induce cortical excitability, leading to a pain-reducing effect by altering pain perception

Candan B, Gungor S. Current and Evolving Concepts in the Management of Complex Regional Pain Syndrome: A Narrative Review. Diagnostics (Basel). 2025 Feb

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Perineural Injections of Inco-BTX-A for diabetic Neuropathic Pain on the Lower Extremities (PINBOT study)

ClinicalTrials.gov PRS
Protocol Registration and Results System

Contact ClinicalTrials.gov PRS
Org: Rigshospitalet User: BBiering-Soerensen

Home > Record Summary > Protocol Section

ID: PINBOT | Perineural Injections of Incobotulinumtoxin-A for Diabetic Neuropathic Pain of the Lower Extremities | NCT05623111

Protocol Section

Record Summary | Preview | Edit All | Help | Definitions

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Study Identification

Unique Protocol ID: PINBOT
Brief Title: Perineural Injections of Incobotulinumtoxin-A for Diabetic Neuropathic Pain of the Lower Extremities (PINBOT)
Official Title: Perineural Injections of Incobotulinumtoxin-A for Diabetic Neuropathic Pain of the Lower Extremities: A Double-blind, Randomized, Placebo-controlled Study
Secondary IDs:

Edit

Study Status

Record Verification: November 2023
Overall Status: Recruiting
Study Start: August 1, 2023 [Actual]
Primary Completion: November 1, 2025 [Anticipated]
Study Completion: February 1, 2026 [Anticipated]

Edit

Sponsor/Collaborators

Sponsor: Rigshospitalet, Denmark
Responsible Party: Principal Investigator
Investigator: Bo Biering-Soerensen [bbiering-soerensen]
Official Title: Senior Physician
Affiliation: Rigshospitalet, Denmark
Collaborators: Merz Pharmaceuticals GmbH
Toyota Foundation Denmark
Steno Diabetes Center Zealand Region
Shipwright Per Henriksen, R., and wife Foundation

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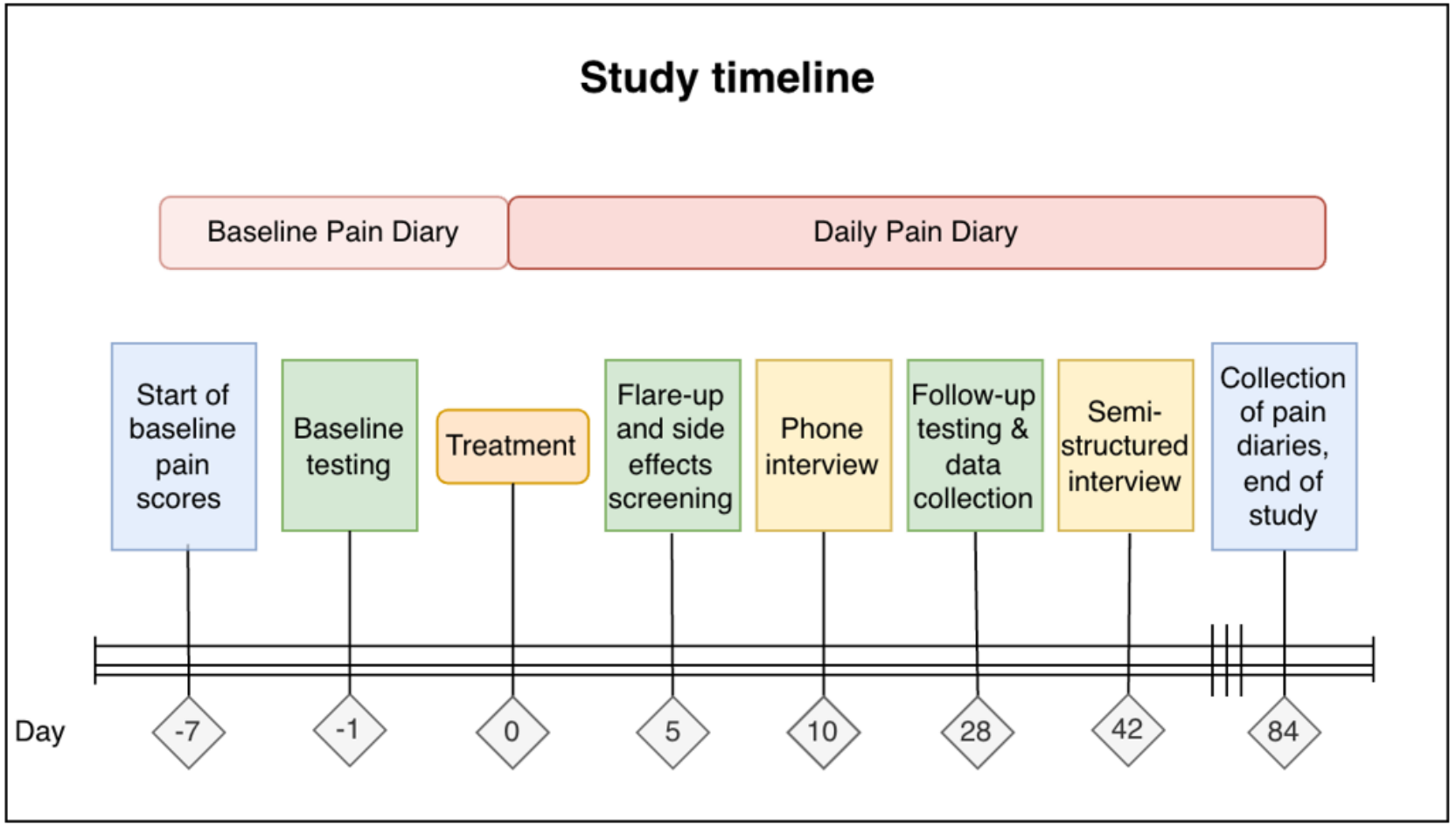
Perineural incobotulinumtoxin-A for CRPS type 1 – an open-label pilot study investigating feasibility and tolerability

Inclusion criteria

Participants eligible for the study will be those who:

- Are over the age of 18
- Have a diagnosis of CRPS type 1 in either one upper or 1 lower extremity which
  - Fulfils the Budapest research criteria
  - Have had the condition for at least 6 months
- Rate CRPS as their primary pain condition
- Have been on a stable analgesic regimen, including any rescue medications, for at least 1 month prior to the study and intend to maintain this regimen throughout the study.



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Memantin (NMDA receptor antagonist) for CRPS

Receptors play a critical role in amplifying pain signals in the central nervous system and have a significant effect on the development of central sensitization, spontaneous pain, and hyperalgesia

Week	Dose (mg/day)	Comment
1	5 mg once in the evening	Start low, assess tolerance.
2	5 mg twice daily	Monitor for dizziness, headache, fatigue.
3	10 mg morning, 5 mg evening	Increase gradually if well tolerated.
4	10 mg twice daily (20 mg/day)	Maintain for 4 weeks.
8+	15–20 mg twice daily	Further titration after 4 weeks up to a maximum of 60 mg/day.

Telephone follow-up (15 minutes) is conducted by the pain nurse at week 4, week 8, and week 12, with additional follow-up in case of continued dose escalation. The purpose of the follow-up is to monitor treatment efficacy, assess potential side effects, and provide ongoing guidance for possible further titration

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Amitriptyline-ketamine cream for patients with allodynia related to complex regional pain syndrome (CRPS) type 1 or type 2.

- The purpose of the project is to investigate the efficacy and tolerance of treatment with **amitriptyline-ketamine cream in 30 ml tubes:**
  - **Concentration: 2% amitriptyline/1% ketamine containing 600 mg amitriptyline and 300 mg ketamine**
  - **Concentration: 4% amitriptyline/2% ketamine containing 1,200 mg amitriptyline and 600 mg ketamine.**

- **Design: Randomized, double-blind, cross-over with three arms**
- One week baseline – 1st treatment – washout – 2nd treatment – washout – 3rd treatment
- **The cream is intended for the relief of allodynia in a well-localized area where first-line treatment has not provided sufficient effect**

29 year old woman with dystonia distally in the left lower extremity as a result of CRPS in the left leg. CRPS 4 years

- Implanted with SCS in March 2020, which has had an effect on the pain—reduced by about 20%—but no effect on the dystonia
- **Primary issue with the dystonia:** flexion of all toes, plantar flexion of the ankle, and tendency toward inversion. Pain worsens to NRS-9 when untreated

Current analgesic treatment:

- Contalgin 5 mg, 2 tablets twice daily
- Duloxetine 120 mg at night
- Lyrica (pregabalin) 150 mg twice daily
- Morphine 10 mg as needed
- Panodil (paracetamol) 1 g as needed

Other current medication:

- Akineton 1 mg twice daily
- Rivotril (clonazepam) 0.5 mg twice daily

Previous medication:

- Gabapentin – adverse effect: urticaria (hives)
- Saroten (amitriptyline) – adverse effect

Baseline in relation to goal: Dystonia pain NRS-9.

GAS goal: Dystonia pain NRS 5–6. Greater extension/straightening of toes

- EMG- and ultrasound-guided, using Botox 100 IU diluted in 2 ml NaCl, injections were given into the following muscles (for flexor digitorum brevis and quadratus plantae diluted in 1 ml):
- Left tibialis posterior: 100 IU
- Left flexor digitorum longus: 60 IU
- Left flexor digitorum brevis: 50 IU
- Left quadratus plantae: 30 IU
- Left flexor hallucis longus: 70 IU
- Left peroneus longus and brevis: 30 IU
- Left soleus: 100 IU
- Left gastrocnemius: 110 IU
- Total: 550 IU Botox
- **Nerve block: Performed higher up on the sciatic nerve from the popliteal region. Effect observed with calmness in the entire foot and reduction of neuropathic pain to NRS-5. However, the whole foot is unstable when the patient attempts to stand, though it is also noted that the heel almost reaches the floor with PROM 90 degrees. Thus, not purely contractures. Cramps reappeared in the evening**

- Operated on 22.02.23 with neurectomy, where branches to the medial and lateral heads of the gastrocnemius were severed, as well as Achilles tendon lengthening and tenotomy of flexor digitorum longus (FDL) 1–4

- 03.10.23 - The patient has achieved flat-foot position and is able to walk without crutches. Has even started “running”. Maximum walking distance is about 100 m before the pain becomes too severe.

Conclusion

- CRPS is a severe, disabling condition that is difficult to treat
- Treatment of CRPS should follow a multimodal approach
- Patient education is a cornerstone in the management of CRPS
- There is still a lack of well-designed, large randomized controlled trials evaluating the many interventions proposed for CRPS treatment
- Botulinum toxin type A may be effective in treating pain in both neuropathic pain conditions and pain caused by muscle overactivity
- Emerging therapies focus on patient-centered, mechanism-based approaches

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Questions?

Reference: Google Picture