



Neuropathic and mixed pain: Post amputation pain

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No conflicts of
interest



Objectives

- Describe briefly the concept of **mixed pain**
- Different aspects of pain in **post-amputation pain (PAP)** patients
- Detailed the presentation of **phantom limb pain** and **residual limb pain**
- Outline the **treatment options**
- Explain the importance of **improving coordination** amongst **interprofessional team members** to **optimize outcomes of rehabilitation** for these patients

Pathophysiology of pain

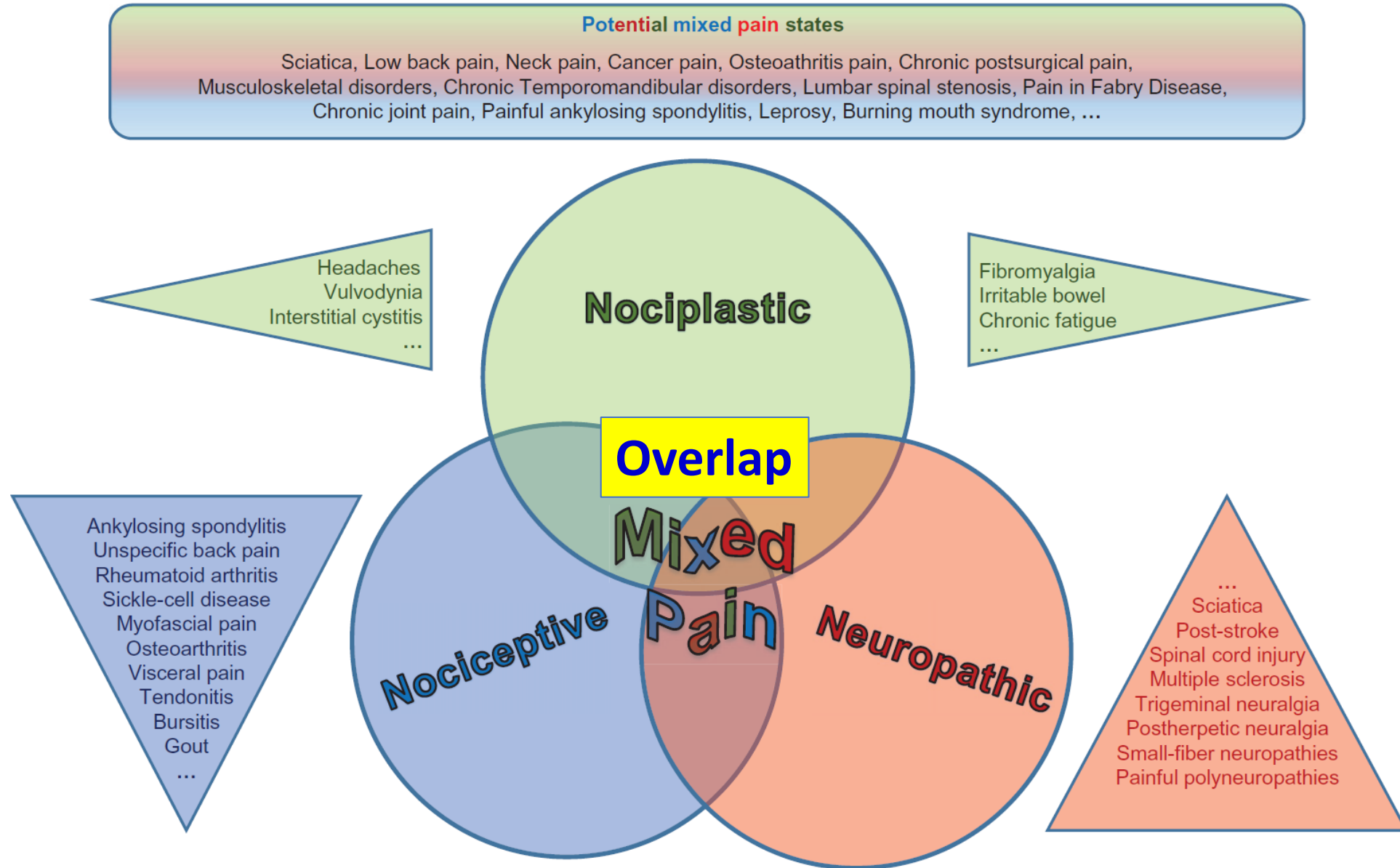


Figure 1. The three different types of pain defined by the IASP give rise to overlap which can be acknowledged as “mixed pain” (Freynhagen©). Conditions described as “mixed pain” in the literature share a common characterization of manifesting clinically with a substantial overlap of the different known pain types.



REVIEW

 Check for updates

Current understanding of the mixed pain concept: a brief narrative review

Rainer Freynhagen^{a,b}, Harold Arevalo Parada^c, Carlos Alberto Calderon-Ospina^{d,e}, Juythel Chen^f, Dessy Rakhmawati Emrii^g, Freddy J. Fernández-Villacorta^h, Hector Francoⁱ, Kok-Yuen Ho^j, Argelia Lara-Solares^k, Carina Ching-Fan Li^l, Alberto Mimenza Alvarado^m, Sasikaan Nimmaanratⁿ, Maria Dolma Santos^{o,p} and Daniel Ciampi de Andrade^q

Mixed pain: practice pearls

- The **diagnosis of mixed pain** is made based on **clinical judgment** following detailed **history-taking** and thorough **physical examination**
- When encountering a patient who presents with an **overlap of nociceptive and neuropathic symptoms**, consider **mixed pain** as a working diagnosis
- Set early treatment with a **combination of agents** targeting **nociceptive and neuropathic mechanisms**
- Also perform a careful evaluation for **comorbidities** (e.g. disturbed sleep, mood alterations, sarcopenia...) and **manage accordingly**



The global burden of traumatic amputation in 204 countries and territories



OPEN ACCESS

EDITED BY
Mary Sheehan,
Queensland University of Technology,
Australia

REVIEWED BY

Bei Yuan, Dong Hu, Suxi Gu*, Songhua Xiao* and Fei Song*

- **Amputation** causes disability and severe impairments in human mobility, physical and emotional functions, with a strong impact on the QOL
- Significant global health economic burden
- The leading cause of amputation varies from region to region:
- Peripheral vascular disease and diabetes are the most important causes of amputation in developed countries
- In developing countries, **trauma** is still the main cause of amputation



- The **number** of patients living with amputations **is increasing**, with approximately 115 000 amputations performed annually, and is predicted to increase from 2 million to more than 3.5 million by the year 2050 in the USA
- A major challenge with studying PLP is that it is **a multifaceted experience**
- There are the **combined sensory, emotional, and cognitive domains**
- How **pain** is experienced is modulated by **multiple dynamic factors**, such as **genetics, personal experiences of the loss of the limb, sleep, general health status, and psychosocial factors**

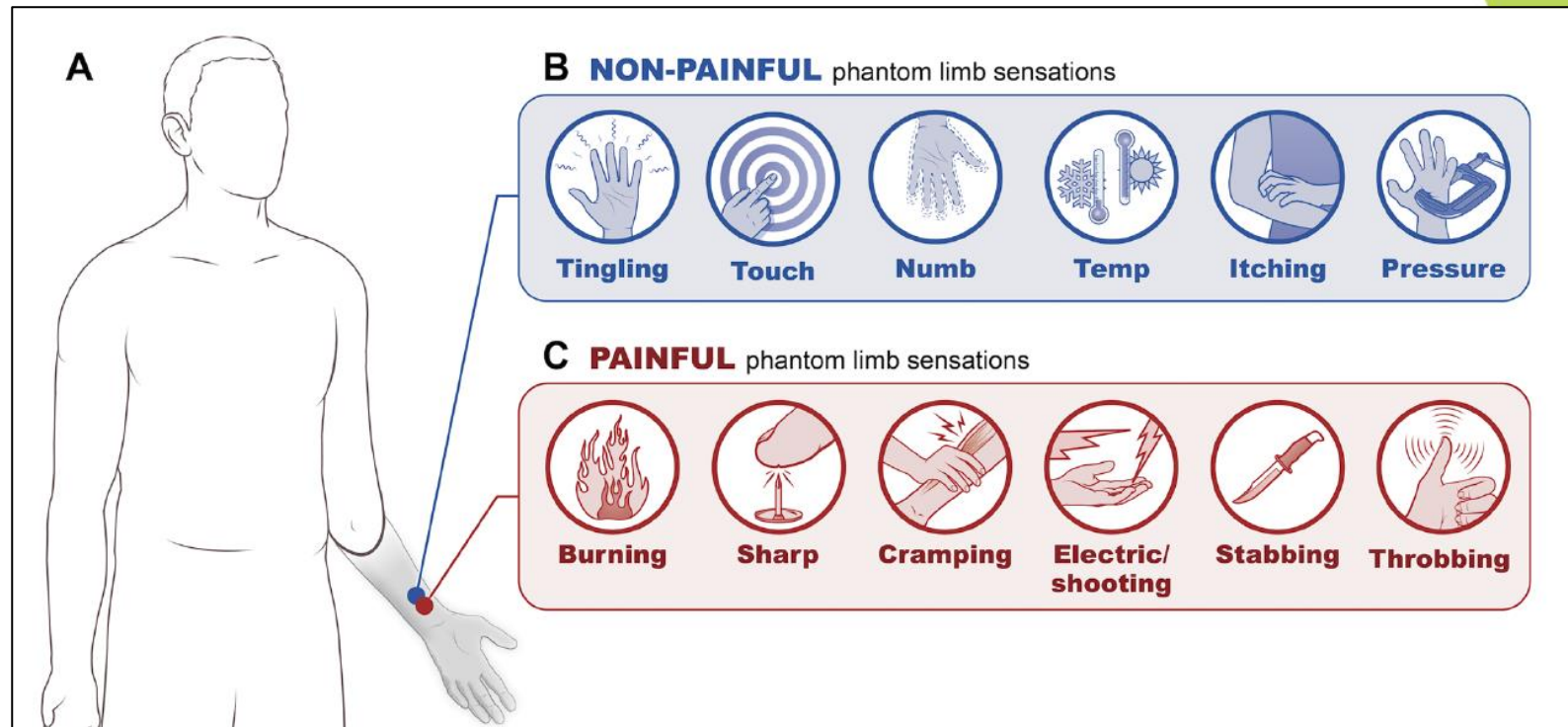
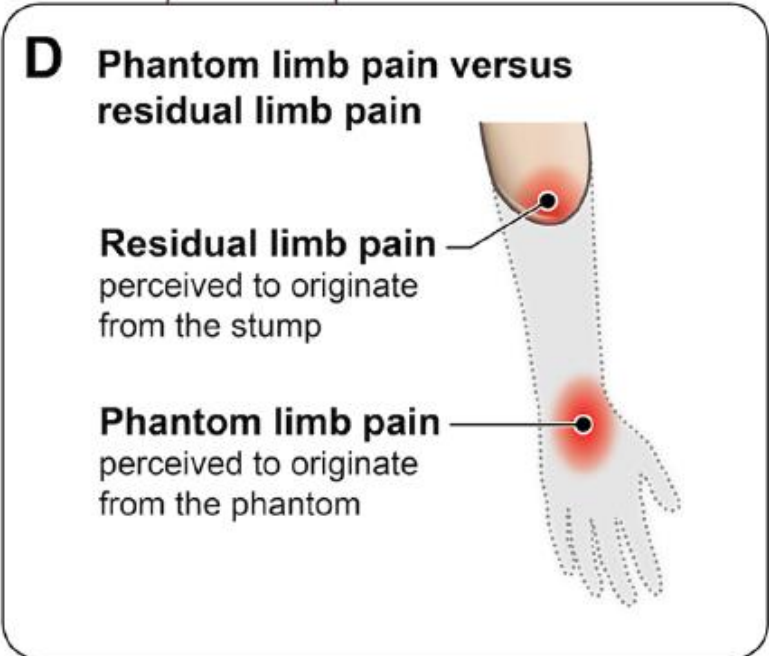


Review

Making sense of phantom limb pain

Hunter R Schone ^{1,2}, Chris I Baker ¹, Joel Katz ^{3,4}, Lone Nikolajsen ^{5,6},
 Katleho Limakatso ⁷, Herta Flor ^{8,9}, Tamar R Makin ²

Schone HR, et al. *J Neurol Neurosurg Psychiatry* 2022;**93**:833–843.






Phantom limb pain (PLP)

- Phantom limb pain (PLP) is a common consequence of limb amputations, occurring in 60%–68% of cases (**mean: 64%**)
- 10%–15% experience severe pain episodes
- 50%–85% may develop chronic PLP
- Among those with chronic PLP, **up to 25% endure significant pain-related disability**



Risk factors for PLP

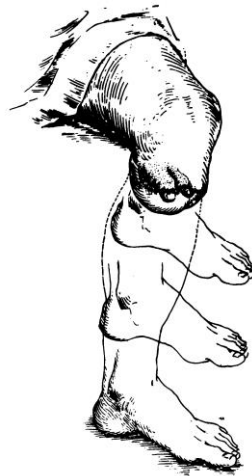
FACTORS OF INTEREST	NUMBER OF STUDIES REPORTING EACH FACTOR	STRENGTH OF ASSOCIATION	MEASURE OF ASSOCIATION	SAMPLE SIZE	REFERENCES	
<p>Most common factors associated with PLP</p> 	Residual limb pain	5	Very strong Very strong Strong Strong Moderate	31.2 (8.97-108.50) [‡] 11.17 (p<0.01) [‡] 7.03 (1.34-36.82) [‡] 3.90 (p<0.001) [‡] 3.90 (p<0.01) [§]	139 (ULA/LLA) 141 (ULA) 52 (LLA) 536 (ULA/LLA) 52 (ULA/LLA)	Ahmed et al., 2017 Desmond et al., 2010 Richardson et al., 2007 Dijkstra et al., 2002 Larbig et al., 2019
	Pre-amputation pain*	4	Very strong Strong Moderate Moderate	10.40 (p=0.002) [‡] 6.36 (p=0.024) [‡] 4.22 (p<0.01) [§] 2.83 (1.38-5.76) [‡]	391 (ULA/LLA) 44 (ULA/LLA) 52 (ULA/LLA) 139 (ULA/LLA)	Yin et al., 2017 Noguchi et al., 2019 Larbig et al., 2019 Ahmed et al., 2017
	Non-painful phantom sensations	3	Very strong Strong Strong	19.50 (p<0.001) [‡] 107.30 (p<0.0001) [§] 4.94 (P<0.05) [§]	536 (ULA/LLA) 526 (ULA/LLA) 22 (ULA/LLA)	Dijkstra et al., 2002 Wartan et al., 1997 Razmus et al., 2017
	Proximal amputation*	2	Very strong Moderate	15.65 (p<0.001) [‡] 1.60 (0.038) [‡]	104 (LLA) 536 (ULA/LLA)	Gallagher et al., 2001 Dijkstra et al., 2002
	Lower limb amputation*	2	Strong Moderate	2.50 (1.3-4.7) [‡] 5.60 (p<0.001) [‡]	914 (ULA/LLA) 536 (ULA/LLA)	Ephraim et al., 2005 Dijkstra et al., 2002
	Diabetic cause of amputation*	2	Strong Moderate	4 (p<0.001) [‡] 2.24 (p=0.032) [‡]	536 (ULA/LLA) 44 (ULA/LLA)	Dijkstra et al., 2002 Nogucji et al., 2019
	Post-amputation depression	2	Strong Moderate	3.86 (1.75-8.53) [‡] 2 (1.3-3.1) [‡]	139 (ULA/LLA) 914 (ULA/LLA)	Ahmed et al., 2017 Ephraim et al., 2005
	Use of prosthesis	2	Moderate Moderate	2.83 (1.19-4.76) [‡] 4.23 (p<0.05) [¶]	139 (ULA/LLA) 57 (LLA)	Ahmed et al., 2017 Hanley et al., 2009



Non-painful phantom sensations

- Approximately **80%** of amputees experience some form of **non-painful phantom sensations**:
- **Kinetic** (perception of phantom movement)
- **Kinaesthetic** (awareness of phantom's size, shape, and position)
- **Exteroceptive** (tactile, pressure, temperature, etc.)

- **Telescoping**



25% a 75%

Prevalence of residual limb pain and symptomatic neuromas after lower extremity amputation: a systematic review and meta-analysis

Emile B. List*, David D. Krijgh, Enrico Martin, J. Henk Coert

PAIN 162 (2021) 1906–1913

- **Residual limb pain (RLP)** has **multiple etiologies**, comprising **both somatic and neuropathic pain in the stump**, with **possible overlaps**
- **Somatic pain** is commonly caused by infection, vascular insufficiency, bone spur formation, unstable scar, myofascial pain, and soft tissue inflammation inhibiting or related to the prosthetic use
- **Neuropathic RLP** can often be attributed to the presence of neuromas, nerve compression, complex regional pain syndrome
- The pooled prevalence in this meta-analysis was 59% (95% CI: 51-67), with high heterogeneity between studies
- RLP pain may also be **multifactorial** in nature, increasing the difficulty with its management

Postamputation Residual Limb Pain Severity and Prevalence: A Systematic Review and Meta-Analysis

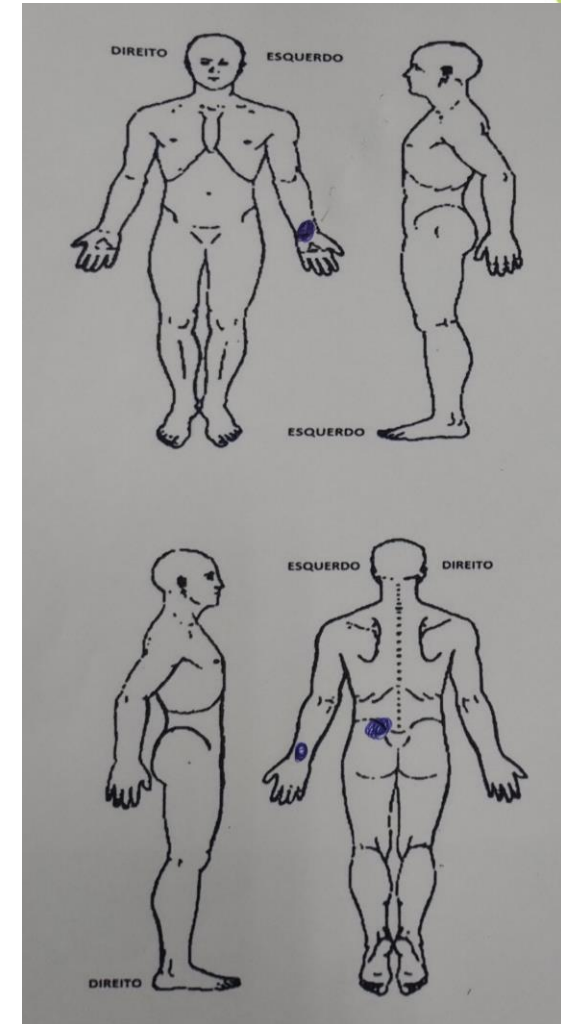
Plastic Surgery
2022, Vol. 30(3) 254–268
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Adam G. Evans, MD¹, Sara C. Chaker², Gabrielle E. Curran²,
Mauricio A. Downer, Jr., BS¹, Patrick E. Assi, MD³,
Jeremy T. Joseph, MD³, Salam Al Kassis, MD³, and
Wesley P. Thayer, MD³

- 2022: Twenty clinical trials (1347 patients)
- Mean patient ages ranged from 38 to 77
- **Prevalence of RLP at 1 week was 50%, 1 month was 11%**
- From 3 months to 2 years, **the prevalence** of RLP remained **relatively stable** and was between **22%** and **27%**
- **RLP is more common after upper extremity amputation** than lower extremity amputations
- **The most severe pain** is reported by patients undergoing amputations due to **cancer, followed by traumatic amputations**, while vascular amputation patients report lower pain severity

Painful spasms of residual limb

43% of our patients with chronic post-amputation pain (cPAP) presented myofascial pain syndrome





Pathophysiology

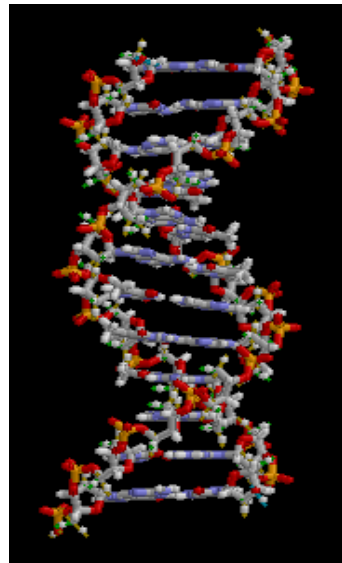
- A major difficulty in developing targeted PLP treatments relies on **a partial understanding of its pathophysiological mechanisms**
- There are **complex interactions** within the **peripheral, spinal, and brain systems**, with **functional and anatomical changes**
- **Deafferentation, sensitization, and hyperexcitability** of the nervous system
- Peripheral changes as **neuroma development** and **irregular nerve activities**
- **Facilitation** of ascending nociceptive input and a **decrease** in descending pain modulation



- The most common changes are **somatosensory cortex, motor cortex, and thalamic alterations**, indexed by neuroimages
- **Altered persistence of the cortical representation of the amputated limb, motor cortex disorganization, sensorimotor cortex hyperactivity, and hyperconnectivity between the insula and the sensorimotor cortices (S1/M1)**
- **Chronic pain**, in turn, induces observable brain changes, including **gray matter reduction**, associated with **emotional and cognitive disturbances**



Neuromatrix



Encoded by DNA
Network with spatial
distribution and synaptic
connections genetically
determined



Environments



Sensory, visual and motor stimuli
Behavioral experiences



**Plastic changes in
neuronal synapses**

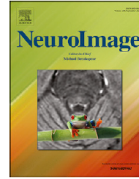


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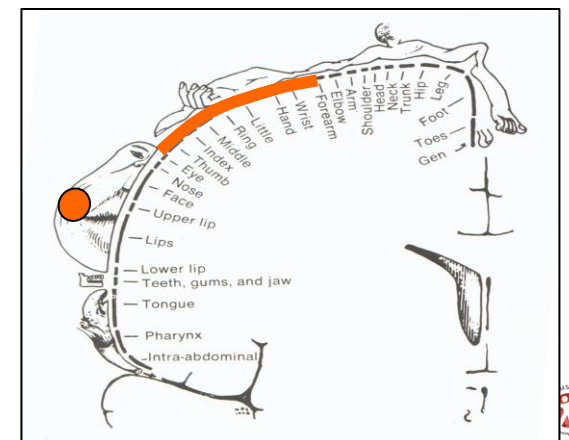
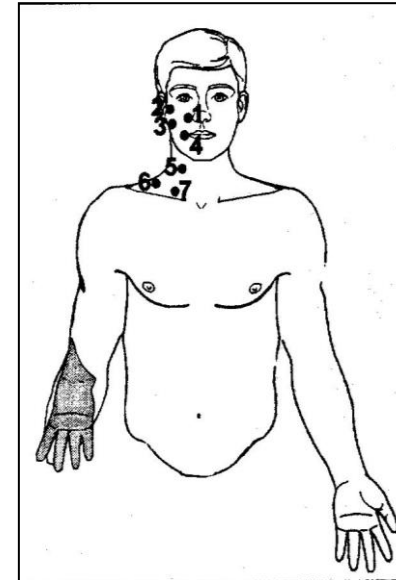


Brain (re)organisation following amputation: Implications for phantom limb pain

Tamar R. Makin ^{a,b,*}, Herta Flor ^{c,d,e}



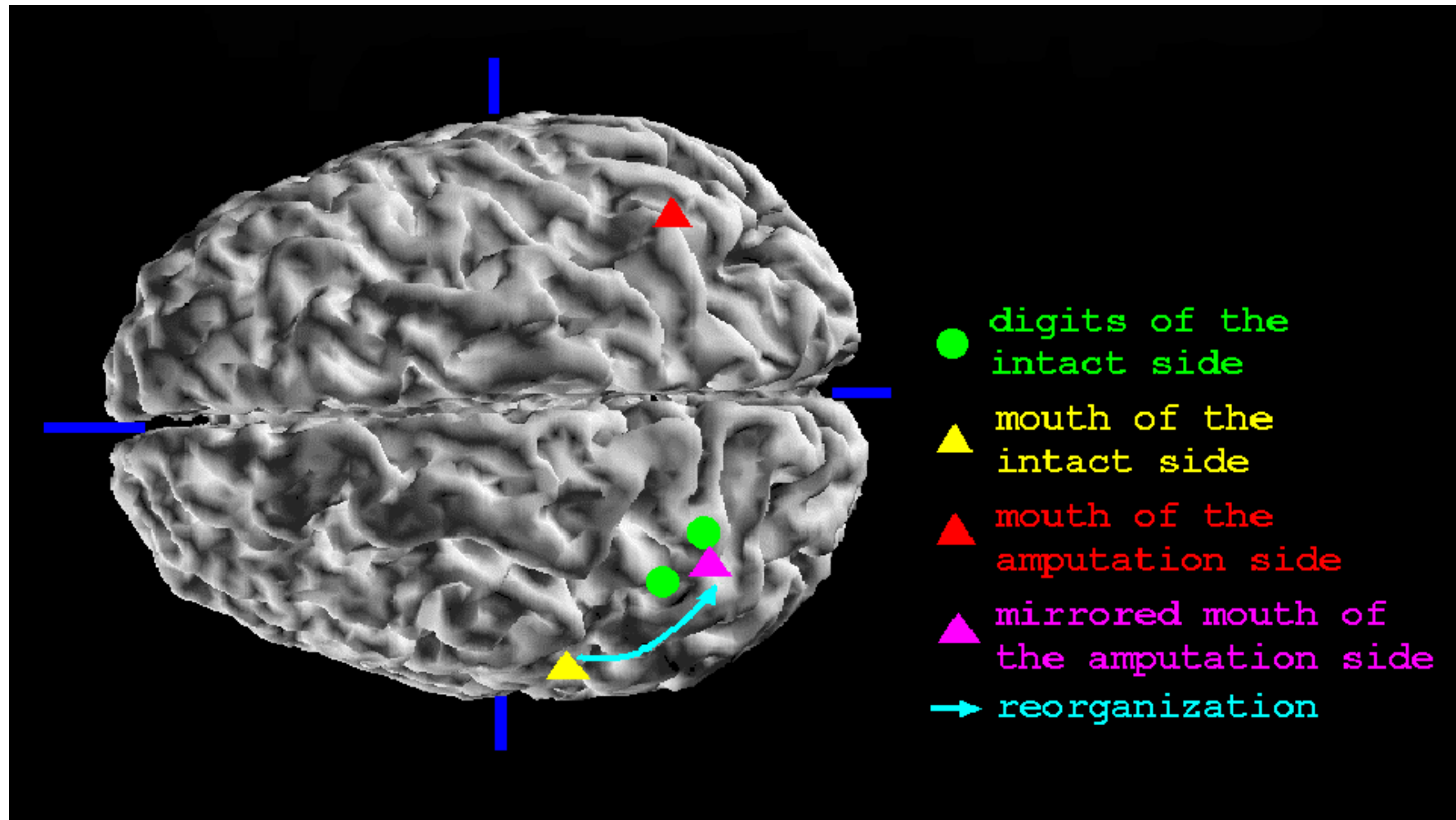
- **Stimulation of the face** may induce **painful sensations in the phantom limb**
- **Penfield's homunculus:** the face is beside the hand
- Amputation: **invasion of deafferented neighboring body parts**
- **Maladaptive reorganization in the somatosensory and motor remapping**





PLP

Cortical reorganization



Flor et al.: Nature 375, 482-484, 1995



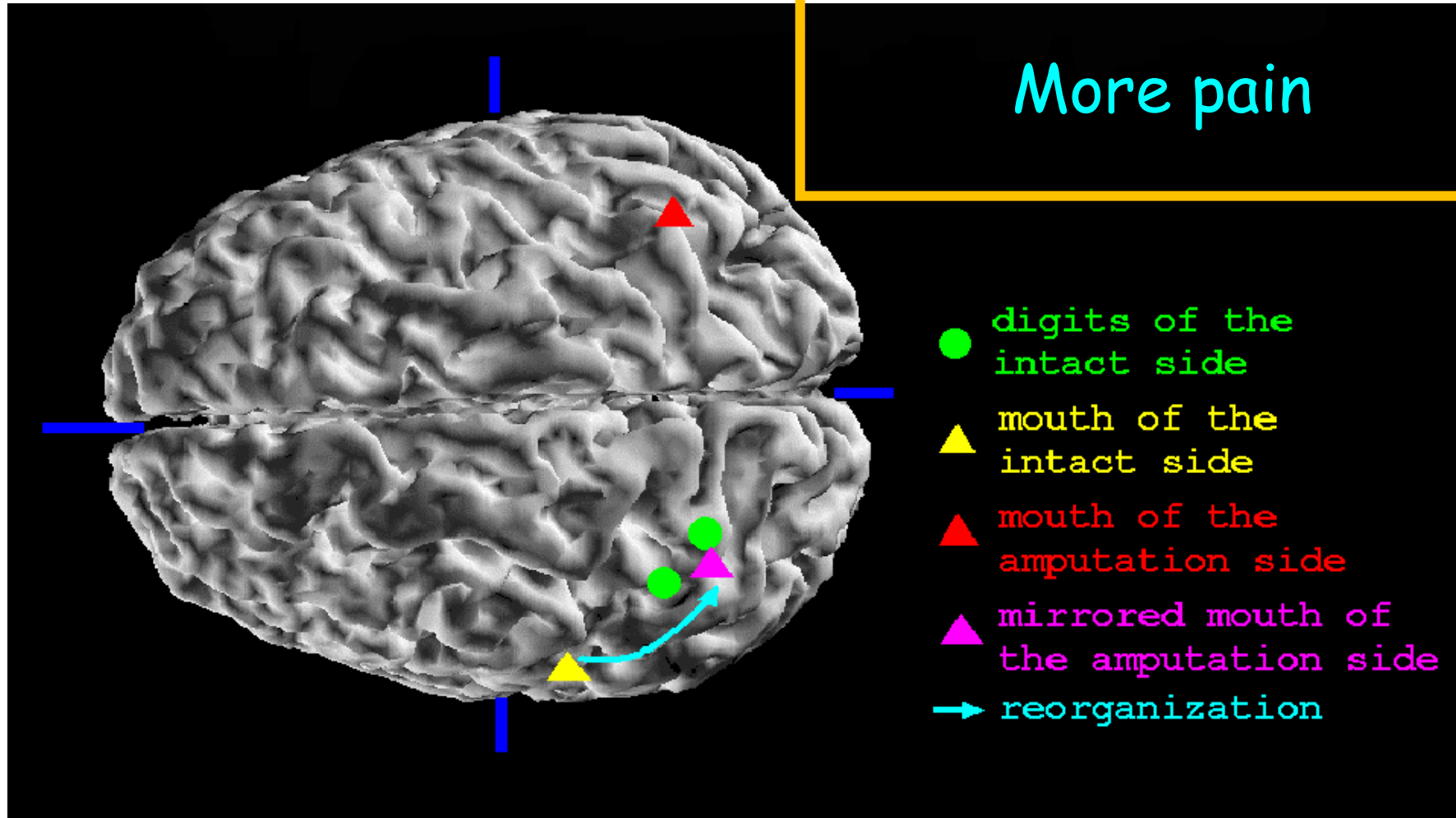
PLP

Maladaptative reorganization

The greater alterations



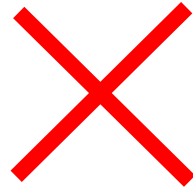
More pain



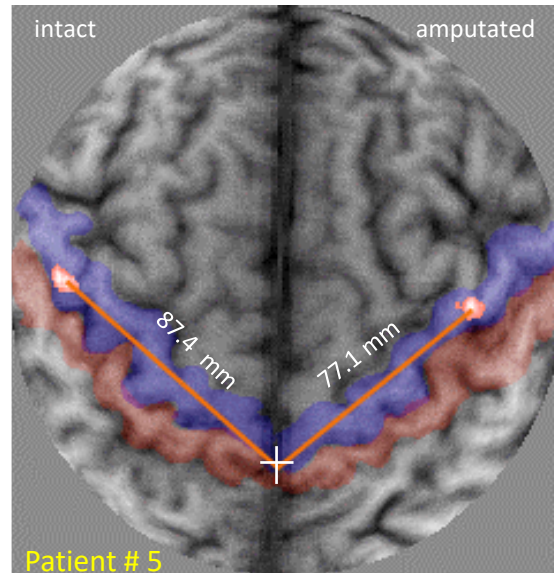


Motor activity and brain reorganization

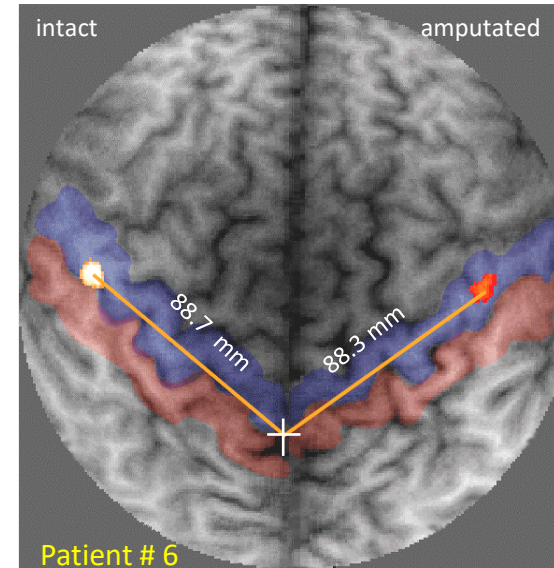
PLP



Without PLP



Δ 5.8 mm



Δ 0.4 mm

A SURVEY OF CURRENT PHANTOM LIMB PAIN TREATMENT IN THE UNITED STATES

RICHARD A. SHERMAN *, CRYSTAL J. SHERMAN and NORMAN G. GALL

- The survey identified 68 treatment methods
- Only a few treatment methods were even moderately successful after one year

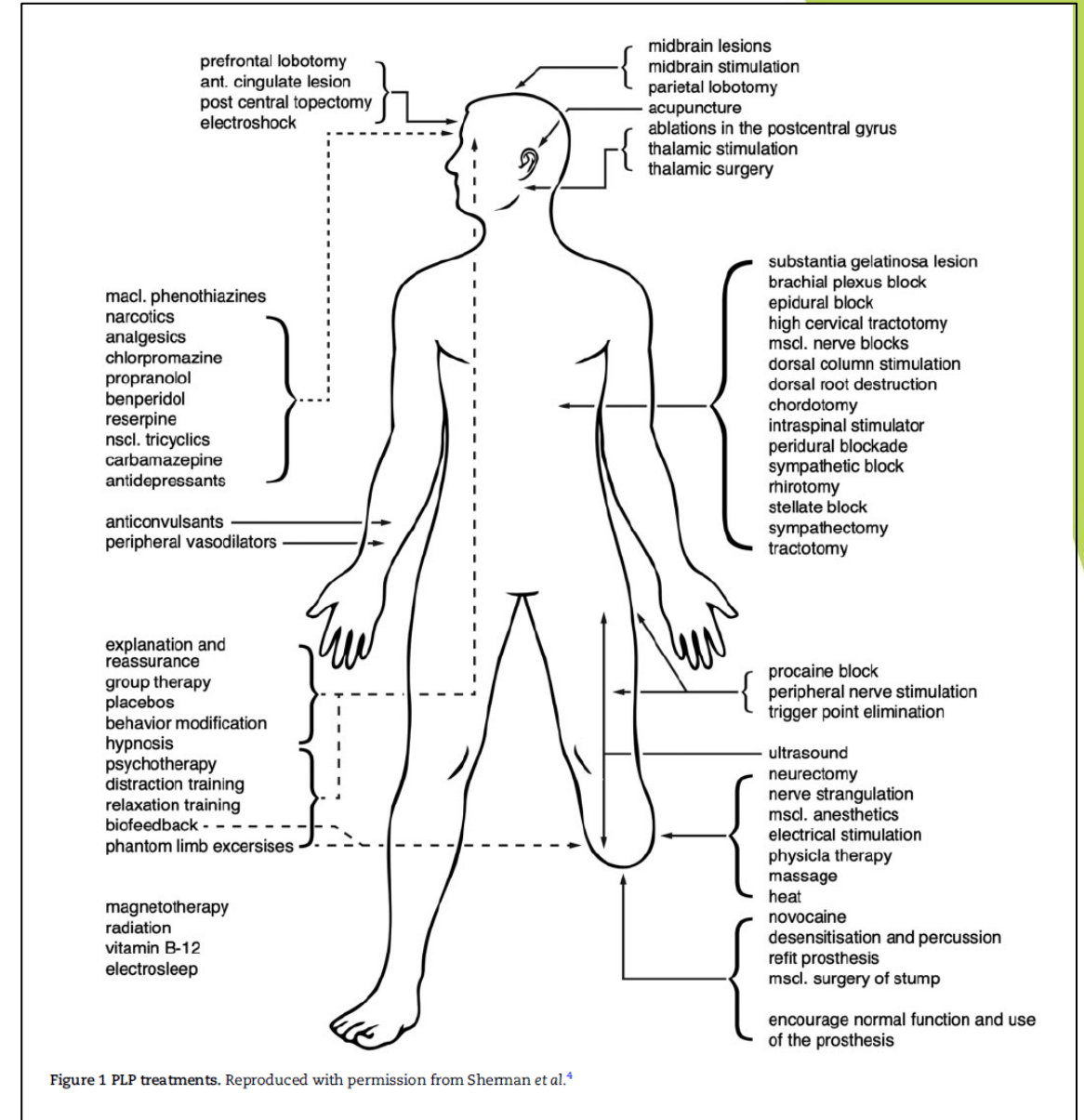
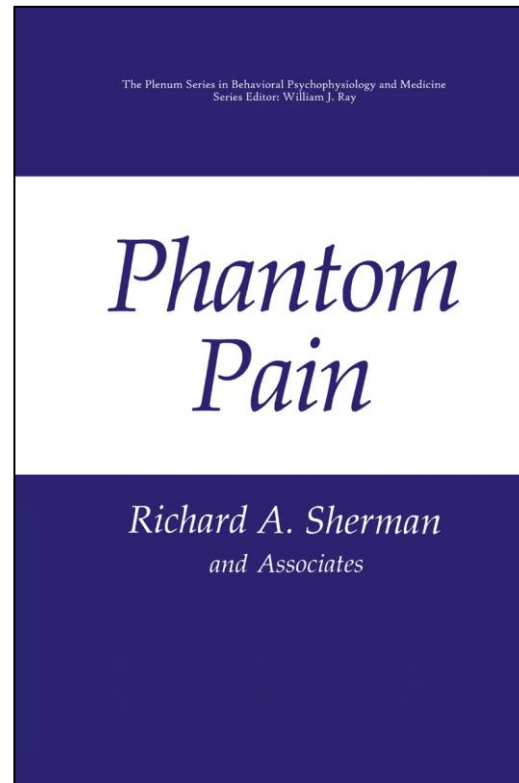


Figure 1 PLP treatments. Reproduced with permission from Sherman et al.⁴



Treatment and potential perioperative prevention strategies

- ✓ To date, there is **no single treatment** has been found to **effectively prevent or treat chronic Post Amputation Pain (cPAP)**
- ✓ **Severe perioperative pain** after amputation has been associated with a **higher prevalence of cPAP**
- ✓ Thus, aggressive efforts to **control pain perioperatively** may potentially decrease the prevalence of cPAP
- ✓ Based on this pathophysiology, **pharmacological prevention and treatment options target different areas of the pain transduction and perception pathway**



Prevention of PAP

- ✓ Matheny et al proposed the **Lower Extremity Amputation Protocol (LEAP)**, a combination of **pre, intra- and postoperative interventions**, including:
 - ✓ **Preoperative assessment and counseling**
 - ✓ The employment of **multimodal and regional anesthesia**
 - ✓ **Early fitting** of limb protector
 - ✓ **Physical and occupational therapies**
 - ✓ Standardized **prosthesis fitting**
 - ✓ The results suggest a **lower incidence of PLP**, and **faster prosthetic use**



Treatment planning

- ✓ Clinically identifying the **source(s) that increase the pain sensitivity** may aid **decision-making** regarding **appropriate therapeutic interventions**
- ✓ Patients with **increased amputated-region sensitivity, without** signs and symptoms of **central sensitization**, may benefit from **locally targeted treatment** as desensitization exercises and physical therapy
- ✓ Patients who demonstrate **signs of peripheral and central sensitization**, may benefit most from **multidisciplinary, locally and centrally targeted treatment, combined with pain neuroscience education, graded motor imagery (that included mirror therapy), and pharmacological agents targeting reduced nervous system sensitivity**

Goals of Rehabilitation



- **Education, adherence, and self-efficacy**
- **Correction** of triggering and perpetuating factors
- **Improvement** of the habits, lifestyles, ergonomics
- **Restful sleep**
- **Proper eating and nutrition**
- Adjustments or implementation of **physical activities**
- **Control of psychosocial stressors**
- **Decrease hypervigilance, catastrophism, fear and avoidance**
- **Proper pain and symptom management**
- **Therapeutic strategies (pharmacological and non-pharmacological methods)**
- **Multimodal, multi/interdisciplinary treatment**
- **Early diagnostic and treatments** → **better prognosis**



PM R 13 (2021) 1216-1226



www.pmrjournal.org

Original Research—CME

Treatment Recommendations for Phantom Limb Pain in People with Amputations: An Expert Consensus Delphi Study

Katleho Limakatso, MSc , Romy Parker, PhD



- In PLP, its **pharmacological management** is based on recommendations for **neuropathic pain syndromes**
- However, current systematic review evidence from **Cochrane (2016)** suggests that three recommended **pharmacological treatments** (amitriptyline, duloxetine, and pregabalin) **are no more effective than placebo** for reducing PLP
- **The lack of effectiveness** of these treatments may be because they **do not target maladaptive cortical reorganization**, which has been shown to be strongly associated with the maintenance of PLP
- Given the difficulty in conducting a meta-analysis for nonpharmacological treatments and the weak evidence for pharmacological treatments for PLP, **consensus on the first-line management of PLP needs to be reached using alternative methods**



PM R 13 (2021) 1216-1226



www.pmrjournal.org

Original Research—CME

Treatment Recommendations for Phantom Limb Pain in People with Amputations: An Expert Consensus Delphi Study

Katleho Limakatso, MSc , Romy Parker, PhD

- ❖ Objective: To reach **expert consensus** and make **recommendations on the effective management of PLP**
- ❖ The study included **27 clinicians and researchers** from various health disciplines who are **experts** in PLP management




PM R 13 (2021) 1216-1226

Original Research—CME



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Treatment Recommendations for Phantom Limb Pain in People with Amputations: An Expert Consensus Delphi Study

Katleho Limakatso, MSc , Romy Parker, PhD



The rationales and percentage of experts who provided supporting rationale for each treatment

The percentage of experts who provided a rationale for supporting each treatment

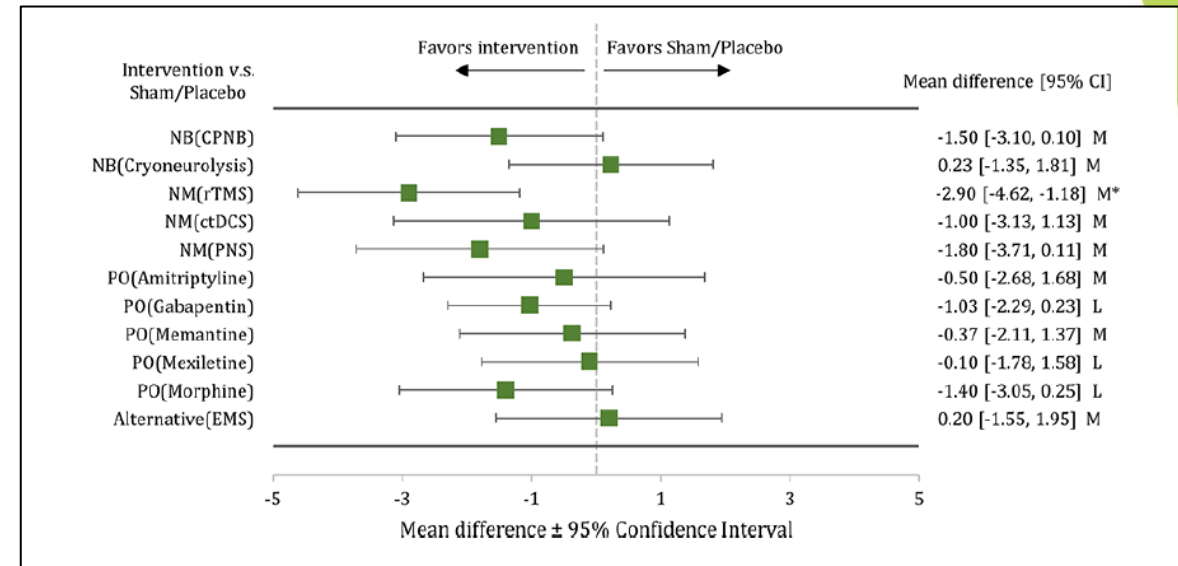
Treatment	There is some scientific evidence supporting the effectiveness of the treatment	The treatment is effective in clinical practice	There is some scientific evidence supporting the effectiveness of the treatment and the treatment is effective in clinical practice	Total percentage of experts who provided supporting rationale for treatment
Mirror therapy	21.1	15.8	57.9	94.8
Graded motor imagery	26.3	26.3	42.1	94.7
Cognitive behavioral therapy	5.3	36.8	36.8	78.9
Sensory discrimination training	21.1	21.1	26.3	68.5
Virtual reality treatment	10.5	36.8	21.1	68.4
Use of functional prosthesis	22.2	16.7	27.8	66.7
Amitriptyline	23.5	5.9	35.3	64.7



Beyond traditional therapies: a network meta-analysis on the treatment efficacy for chronic phantom limb pain

Chung S-M, et al. *Reg Anesth Pain Med* 2024;0:1–12.

- 2024: The NMA incorporates **12 RCTs** (783 participants)
- **Changes in pain intensity**
- Compared with the sham/placebo group, the summary MD of changes in pain intensity:
- **-2.90 points (95% CI: -4.62 to -1.18) for rTMS;**
- **-1.00 points (95% CI: -3.13 to 1.13) for ctDCS;**
- **-1.80 points (95% CI: -3.71 to 0.11) for PNS;**
- **-1.50 for CPNB (95% CI: -3.10 to -0.10);**
- 0.23 for cryoneurolysis (95% CI: -1.35 to 1.81);
- **-0.50 for oral amitriptyline (95% CI: -2.68 to 1.68);**
- **-1.03 for oral gabapentin (95% CI: -2.29 to 0.23);**
- -0.37 for oral memantine (95% CI: -2.11, 1.37);
- -0.10 for the oral mexiletine method (95% CI: -1.78 to 1.58);
- **-1.40 for oral morphine (95% CI: -3.05 to -0.25)**
- 0.20 for the alternative EMS (95% CI: -1.55 to 1.95)





OPEN ACCESS

Beyond traditional therapies: a network meta-analysis on the treatment efficacy for chronic phantom limb pain

Chung S-M, et al. *Reg Anesth Pain Med* 2024;**0**:1–12.

Adverse event rate

Eight trials with a total of 466 participants

In comparison with the sham/placebo group, the summary ORs for adverse event rate were:

0.60 (95% CI: 0.01 to 32.56) for rTMS

1.00 (95% CI: 0.02 to 53.89) for ctDCS

1.17 (95% CI: 0.02 to 63.97) for PNS

6.04 (95% CI: 2.26 to 16.12) for oral morphine

OR less than 1 indicates fewer adverse events



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Available online at
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 www.sciencedirect.com

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 www.em-consulte.com



Practice guidelines

Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations



X. Moisset^{a,b,*}, D. Bouhassira^{c,d}, J. Avez Couturier^e, H. Alchaar^f,
 S. Conradi^g, M.H. Delmotte^h, M. Lanteri-Minet^{a,i}, J.P. Lefaucheur^{j,k},
 G. Mick^l, V. Piano^m, G. Pickering^{a,n}, E. Piquetⁱ, C. Regis^o, E. Salvat^p,
 N. Attal^c

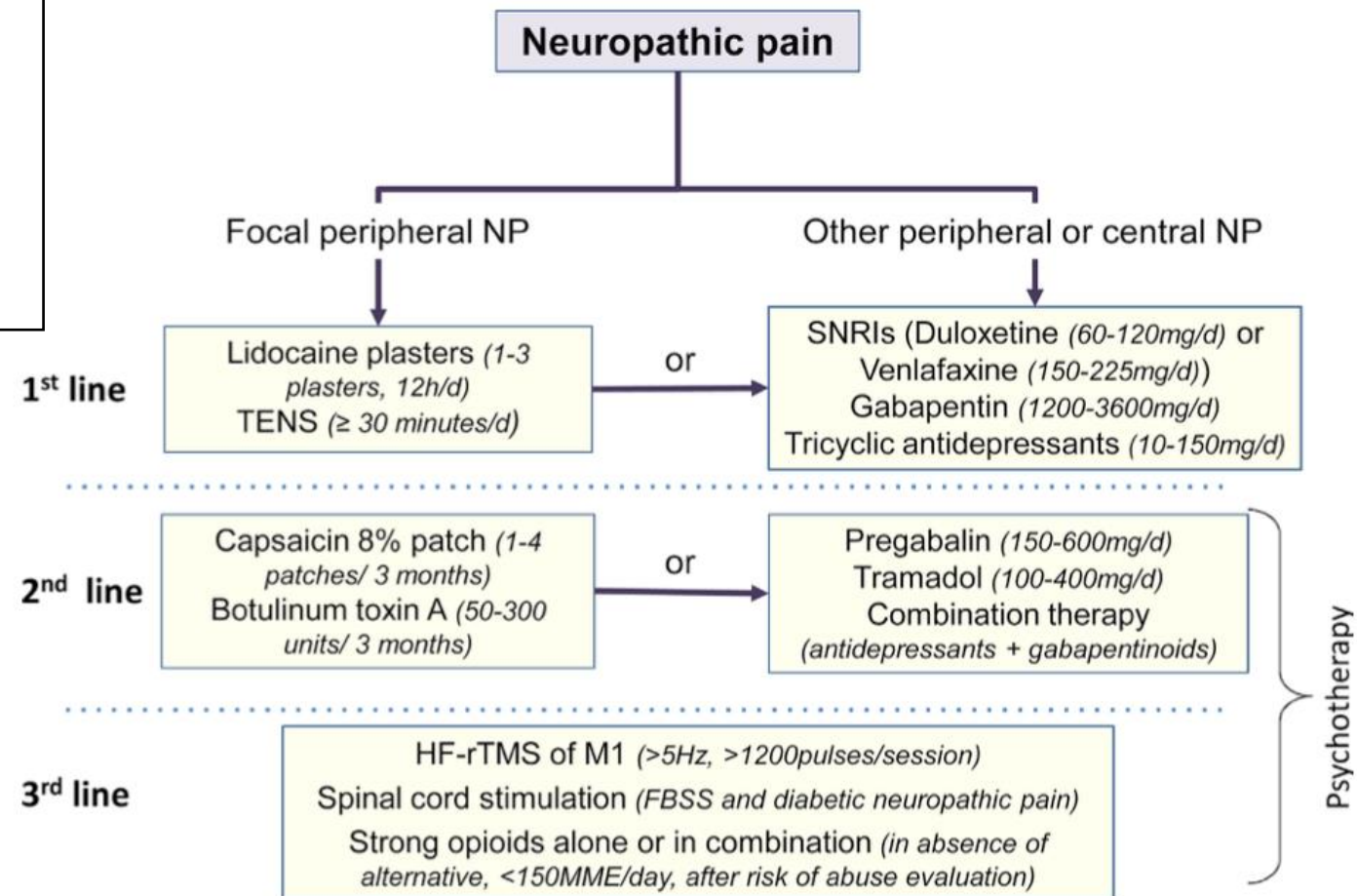


Fig. 2 – Proposed therapeutic algorithm for neuropathic pain treatment in adults. Only treatments available in France in June 2019 were considered. For practical considerations, see Table 4. NP: neuropathic pain; TCAs: tricyclic antidepressants; TENS: transcutaneous electrical nerve stimulation; HF-rTMS: high-frequency repetitive transcranial magnetic stimulation; M1: primary motor cortex; BTX-A: botulinum toxin type A; FBSS: failed back surgery syndrome; MME: mg morphine equivalent.





Treatment of mixed pain

- **Analgesics & NSAIDs**
- **Opioids:** tramadol, tapentadol, buprenorphine, methadone
- **Tricyclic antidepressants:** amitriptyline, nortriptyline, imipramine 25 – 75 mg/d
- **SNRIs:** duloxetine: 60-120 mg; venlafaxine 75 mg a 150 mg/d
- **Anticonvulsivants:** pregabalin ≥ 150 mg 2x/d, gabapentin ≥ 300 mg, 3x/d; carbamazepine 200 mg, 2-3x /d; oxcarbazepine 150 mg, 2x/d,
- **Sleep:** TA, trazodone 50 – 150 mg /d, doxepin 3-6 mg, ramelteon 8 mg, neuroleptics
- **Botulinum toxin**
- **Neuroleptics:** chlorpromazine, levomepromazine, periciazine 4%, 3-15 gts, 3x/d
- **Local anesthetics:** lidocaine patch or topics
- **Capsaicin** 8% patch
- **Avoid or suspension of** benzodiazepines and Z-drugs



Treatment of mixed pain

- Analgesics & NSAIDs
- Opioids: tramadol, tapentadol, buprenorphine, methadone
- Tricyclic antidepressants: amitriptyline, nortriptyline, imipramine 25 – 75 mg/d
- SNRIs: duloxetine 50 mg/d
- Anticonvulsiva: gabapentin, pregabalin, carbamazepine 200 mg, 2-3x /d;
- Sleep: TA, trazodone 50 – 150 mg/d, doxepin 5-6 mg, ramelteon 8 mg, neuroleptics
- Botulinum toxin
- Neuroleptics: chlorpromazine, levomepromazine 12.5 mg, 3x/d
- Local anesthetics: lidocaine patch or topics
- Capsaicin 8% patch
- Avoid or suspension of benzodiazepines and Z-drugs

**NNT:
30 - 50% of
improvement is already
significant!!!**

**It's not good
enough!!!**

Polypharmacy

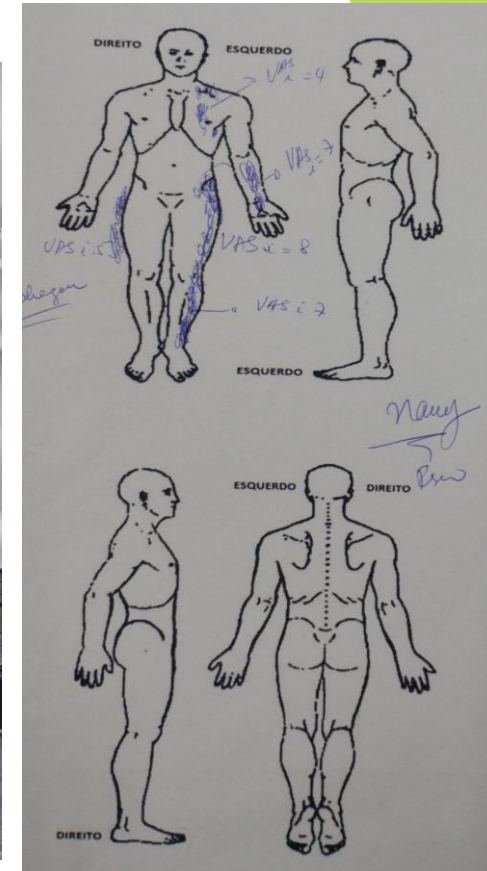
MAR, 64 y.o.

Car accident in 1977; using an aesthetic prosthesis

Pain since 2012, worsening in last few years

05.2024, VAS of PLP was 8;

Other parts of the body: 4-8





After physical therapy, VAS came to ZERO



AMPUTADA - Antes

Protocolo de entrevista interdisciplinar
Data: 24/05/24

Maria Aparecida Reis
1
24/06/2024

PINTE NO DESENHO A BAIXO AONDE VOCÊ SENTE DOR

Após físico

VAS = 0

- cabeça/nuca
- braço
- costas
- nádegas
- coxa
- joelho
- tornozelo
- pé

mas a dor (de qualquer lado) melhorou



Hypnosis




Botulinum toxin application



**Graded motor imagery
with mirror therapy
included**



Botulinum toxin therapy for management of phantom and residual limb pain following amputation: A systematic review


Courtney Frengopoulos¹ , Ramona Neferu¹, Matthew Pasquali², Ricardo Viana^{3,4}, Tom Miller^{3,4} and Michael Payne^{3,4}

Prosthet Orthot Int. 2024 Mar 22.

- 2024: 11 studies with 89 individuals with pain, 53 had Residual Limb Pain (RLP) and 63 had Phantom Limb Pain (PLP) **using botulinum toxin injection**
- There was significant variation in botulinum toxin type, injection method, and dosage
- Twenty-one **(53.9%) participants had improvement in PLP**
- Twenty-seven **(64.3%) had improvement in RLP**
- Therefore, there is **potential for use of botulinum toxin for the treatment of PLP and RLP**
- However, due to the minimal number of studies, small sample sizes, and heterogenous methodologies, our ability to conclude with certainty the efficacy of botulinum toxin injection on the treatment of PLP and RLP following amputation is limited



Motor cortex stimulation for chronic neuropathic pain: results of a double-blind randomized study

 Clement Hamani,^{1,2,†} Erich T. Fonoff,^{1,†} Daniella C. Parravano,¹ Valquiria A. Silva,³ Ricardo Galhardoni,³ Bernardo A. Monaco,¹ Jessie Navarro,¹ Lin T. Yeng,³ Manoel J. Teixeira^{1,3} and Daniel Ciampi de Andrade^{1,3}

- 18 patients with chronic neuropathic pain
- **2 phantom limb pain patients presented a good response to MCS**

rTMS

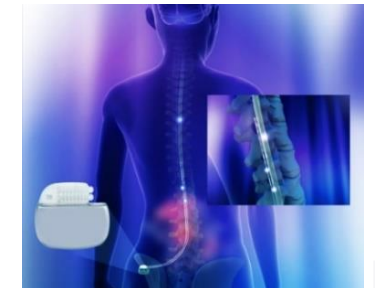




Multimodal & multidisciplinary treatment



Holistic evaluation
Adjustment of lifestyle
Adhesion
Integrative treatment
Biopsychosocial support





X CINDOR

CONGRESSO
INTERDISCIPLINAR
DE DOR DA USP

30 DE OUTUBRO A 02 DE NOVEMBRO DE 2024

Centro de Convenções Rebouças – São Paulo

Salve a data!

*A conexão que transforma:
a essência do cuidado integrado na dor*

Venha para o
CINDOR 2024!

contato.cindor@gmail.com



Thank you very much for your attention!!

lintyeng@uol.com.br

