LA DOULEUR DU MEMBRE FANTÔME

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13 avril 2023

Cours sciences de base

PLAN

- Épidémiologie
- Description des différentes douleurs post-amputation
- Douleur du membre fantôme
- Physiopathologie
- Facteurs de risques
- Traitements non pharmacologiques et pharmacologiques
- Prévention
- Conclusion

ÉPIDÉMIOLOGIE

- 70 à 80% des patients vont souffrir d'une douleur du membre fantôme dans les premiers jours après une amputation
- 30-40% douleur sévère
- 25% douleur modérée
- Généralement diminue dans les 6 premiers mois en intensité et en fréquence
- 25-50% auront encore une douleur sévère avec atteinte du fonctionnement à 6 mois

Schone HR, *et al. J Neurol Neurosurg Psychiatry* 2022;**93**:833–843. doi:10.1136/jnnp-2021-328428

DOULEURS POST AMPUTATION

- L'hallucinose
- Douleur dans le membre fantôme (algohallucinose)
- Douleur du moignon
  - Douleur du névrome
  - Causalgie du moignon
  - Adaptation du moignon à la prothèse
- Douleur musculo-squelettique dans le membre affecté ou ailleurs

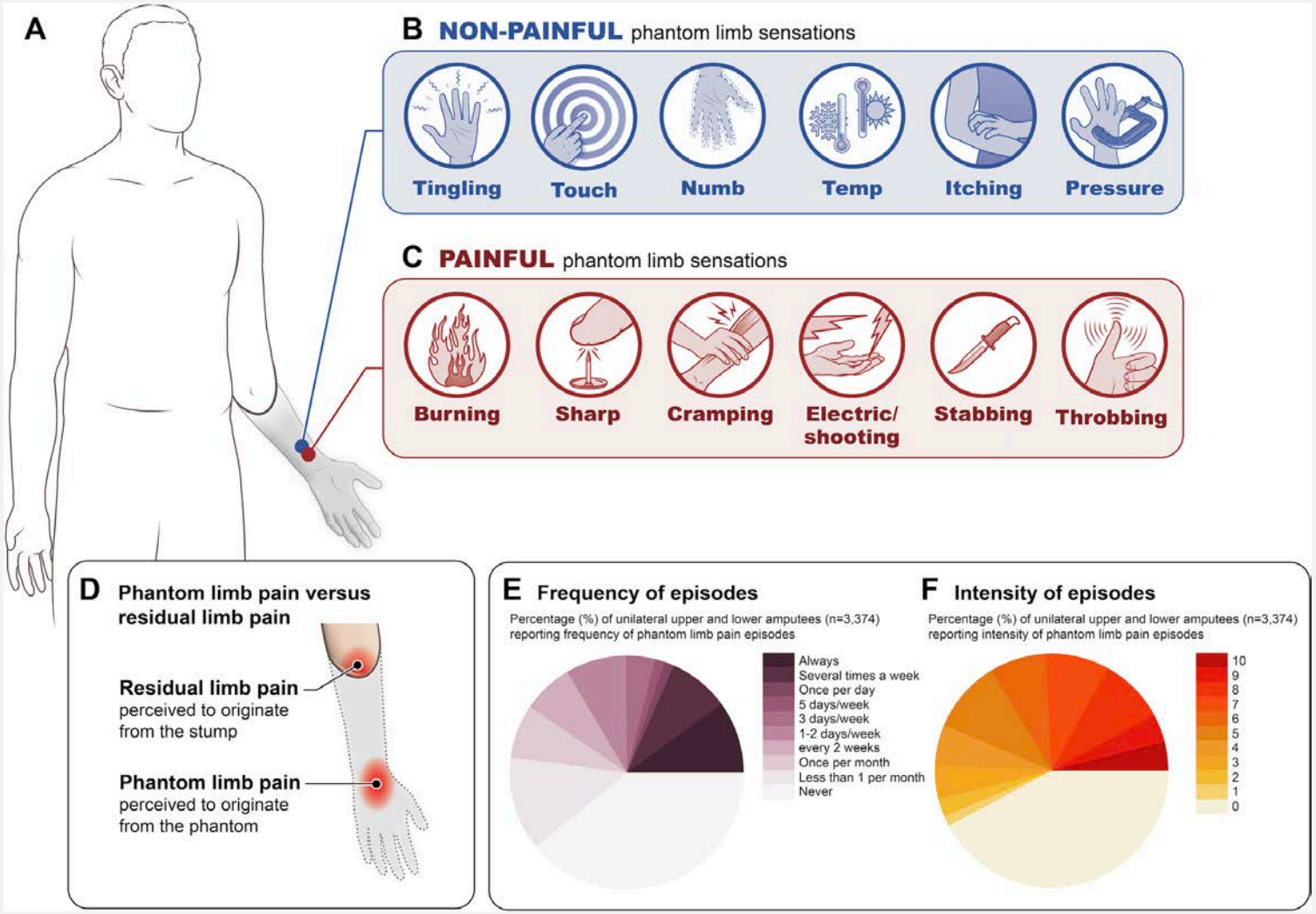

Figure 1 Phantom limb sensations. (A) Diagram of upper limb amputee with a phantom arm. Spectrum of phantom sensations from non-painful (B) to painful (C). (D) Residual limb pain (RLP) and PLP illustrated in an upper limb amputee. RLP is perceived to originate from the stump/residual limb, whereas PLP is pain perceived to originate from the phantom limb. (E) Cross-sectional surveys on PLP frequency (data adapted from figure 2 in Diers *et al*[32] with permission) and (F) average intensity (data adapted from figure 2 in Diers *et al*[32] with permission). Illustrations and remade figures are original.

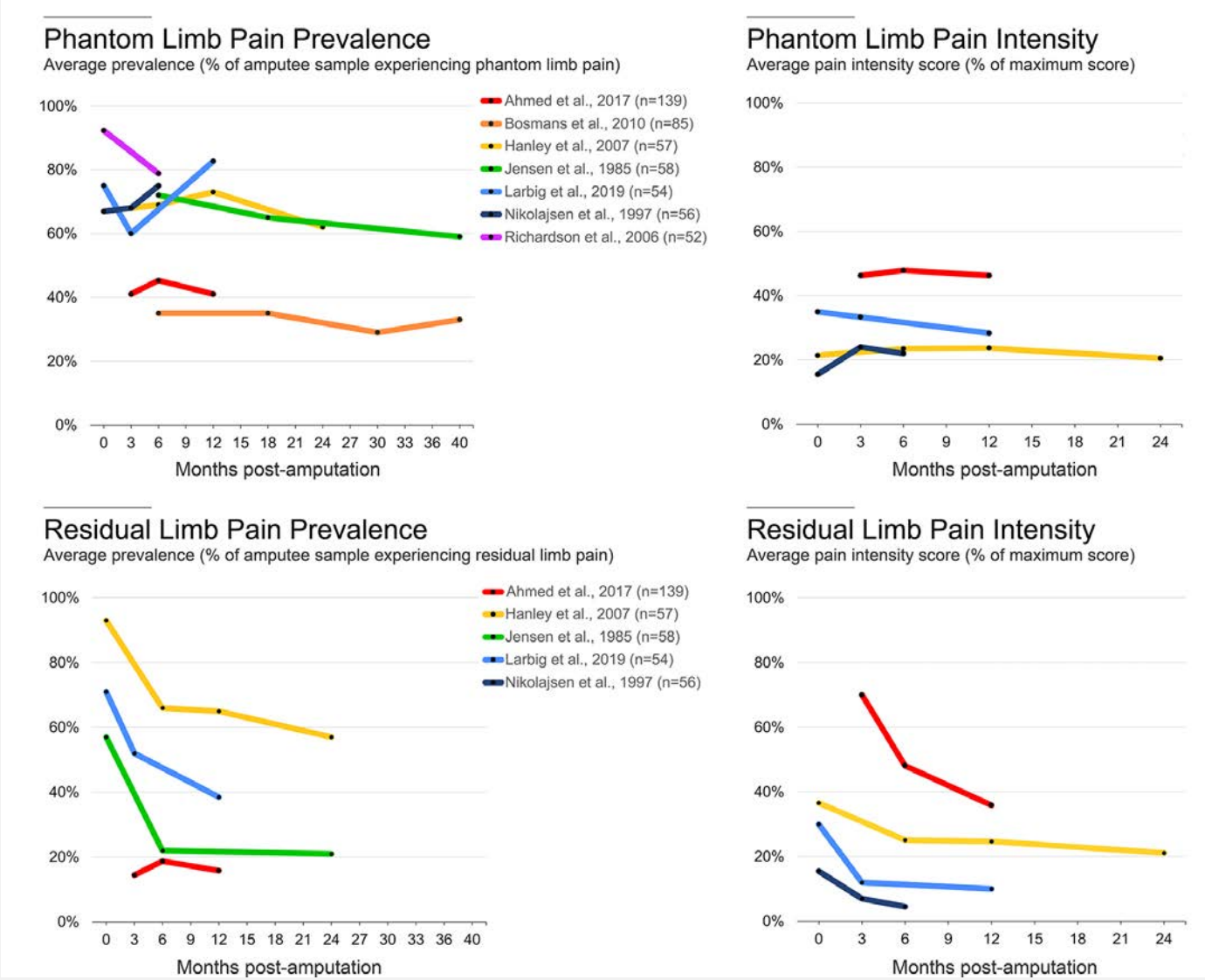

Figure 3 Time course of phantom limb pain (PLP) and residual limb pain (RLP). To characterise the time course of postamputation pain, we identified all longitudinal, peer-reviewed studies that report prevalence rates and average pain intensity values for PLP and RLP at multiple time points. In the top row, based on PLP data from prospective longitudinal studies, the number of individuals who report PLP and the intensity scores remains relatively constant with time. In the bottom row, based on RLP data from the longitudinal surveys, there is a large decrease in the number of individuals reporting RLP and in the intensity of RLP experienced in the first 6 months after amputation. Black dots represent individual timepoints. Colours depict individual studies; n values report the amputee sample sizes of each study. Patient drop-off across timepoints is not reflected in the starting sample sizes listed after references. The data used to generate these plots and a description for how the data were acquired are available at OSF (https://osf.io/3u8b4/).

CONSÉQUENCES DE L'AMPUTATION

- Morphologiques
- Psychologiques
- Neurochimiques
- Électrophysiologiques

PHYSIOPATHOLOGIE
THÉORIE PÉRIPHÉRIQUE

- Le principal facteur associé à la douleur fantôme est la douleur résiduelle au niveau du moignon.
  - Résection du nerf
  - Altérations moléculaires
  - Influx nerveux ectopiques provenant d'un névrome ou de la racine dorsale du ganglion.

A review of current theories and treatments for phantom limb pain

Kassondra L. Collins, ... , Robert S. Waters, Jack W. Tsao *J Clin Invest.* 2018;128(6):2168-2176. https://doi.org/10.1172/JCI94003.

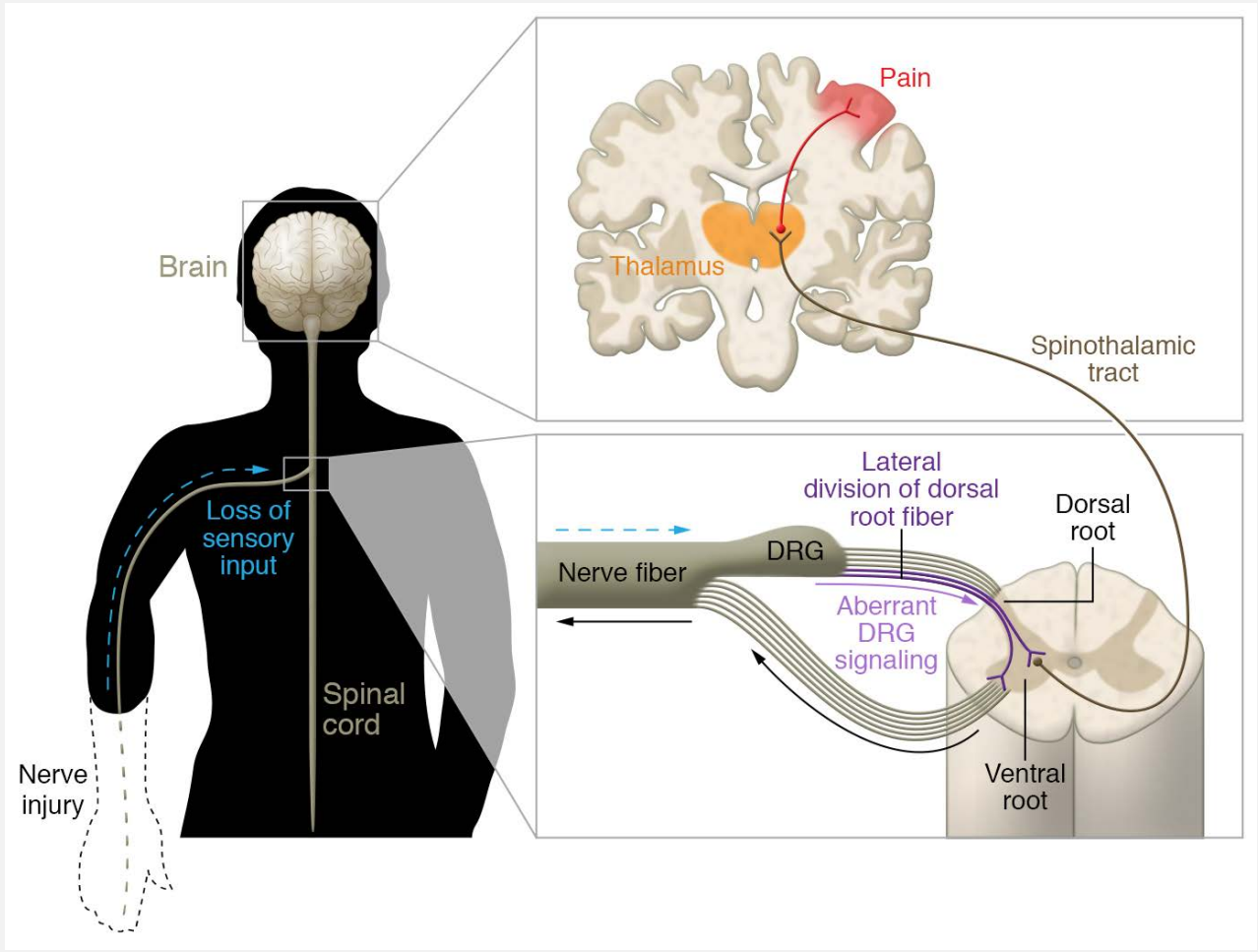

Figure 2. Proposed peripheral contributions to PLS and PLP. The dorsal root fibers of the DRG split into lateral and medial divisions (38). The lateral division sections contain most of the unmyelinated and small myelinated axons and specifically carry pain and temperature information. The medial division sections of the dorsal root fibers (not shown) contain mostly myelinated axons that convey sensory information from the skin, muscles, and joints, such as touch, pressure, proprioception, and vibration (38). When an injury occurs to the nerves, neurons in the DRG increase their nociceptive signaling through increases in neuronal excitability and the creation of ectopic discharges (25). The resulting aberrant signaling through the spinothalamic tract may produce PLP.

PHYSIOPATHOLOGIE
THÉORIE PLASTICITÉ CÉRÉBRALE

- Douleur fantôme est reliée à une plasticité mésadaptée de l'organisation neuronale.
- Perte de l'influx périphérique après une amputation pourrait causer la douleur fantôme 2nd au changement neuronal dans la représentation des parties du corps dans le cortex somatosensoriel.
- Le territoire cérébral qui supportait la partie amputée est déprivé d'influx nerveux et devient activé par les autres parties du corps.

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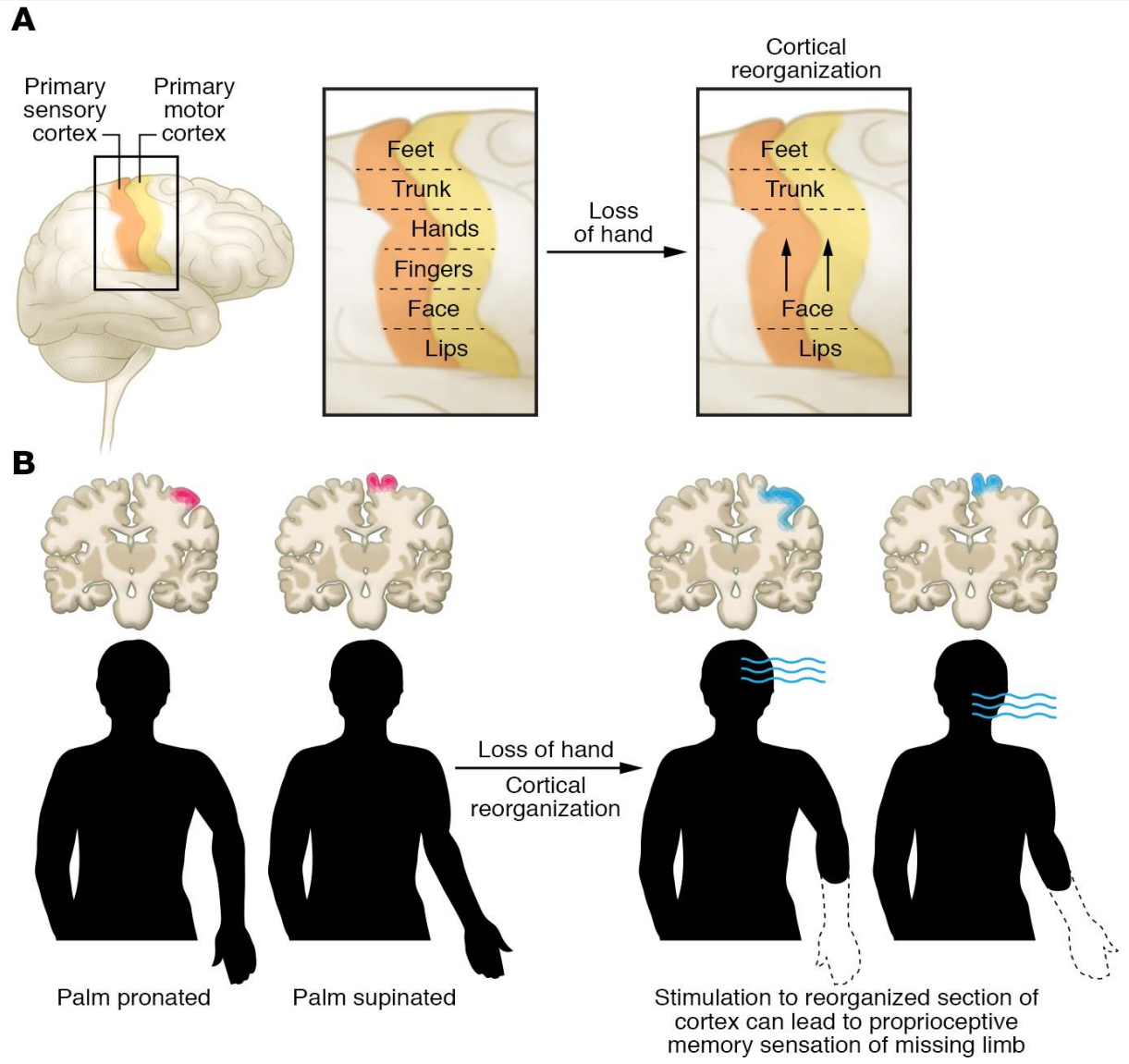

Figure 1. Cortical contributions to PLS and PLP. (**A**) Body part sensory and motor representation are laid out in a pattern that forms the cortical homunculus and receives sensory information (e.g., tactile, olfactory, or pain) from different areas of the body (24). Following amputation, a cortical region that received sensory or motor projections from the amputated limb may begin to receive sensory or motor input, respectively, from neighboring cortical regions, which expand to take over the region that previously controlled the amputated limb (27, 28). (**B**) Proprioceptive memory, which stores information about the position of the limb in space relative to the body, may influence cortical reorganization in the CNS. These memories may store information about the final position of the missing limb or, in combination with cortical reorganization, may affect PLS or PLP. This image illustrates rapid changes in cortical activation patterns that can occur simply with repositioning of the phantom limb, manifested as changes in the location of hand sensations mapped onto the face.

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PHYSIOPATHOLOGIE

- Le développement d'un névrome au niveau du nerf réséqué avec activité neuronale spontanée anormale.
- Les changements centraux et périphériques sont associés à une augmentation des canaux sodiques et une augmentation de l'activité des fibres C nociceptives et une activité spontanée du ganglion dorsal.
- Au niveau de la moelle, une sensibilisation a aussi été décrite
- Diminution de l'activité des neurones inhibitrices

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DOULEUR FANTÔME
FACTEURS DE RISQUE

Cognitive neurology

Most common factors associated with PLP

FACTORS OF INTEREST	NUMBER OF STUDIES REPORTING EACH FACTOR	STRENGTH OF ASSOCIATION	MEASURE OF ASSOCIATION	SAMPLE SIZE	REFERENCES
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

¶ Pearson's univariate correlation test; § Chi-squared; † Relative risk; ‡ Odds ratio
* Classified as a *risk factor*, in that the factor of interest precedes the typical onset of PLP (following the amputation event)
ULA=upper-limb amputee; LLA=lower-limb amputee

Figure 2 Factors positively associated with phantom limb pain (PLP). Most common factors associated with PLP identified in the meta-analysis by Limakatso *et al*.[33] In selecting these factors, we chose to report those that met the following two criteria: reported in at least two studies and have a positive association that was moderate to very strong in strength. Data adapted from Table 3 in Limakatso *et al*., 2020 with permission.

Limakatso K, Bedwell GJ, Madden VJ, *et al*. The prevalence and risk factors for phantom limb pain in people with amputations: a systematic review and meta- analysis. *PLoS One* 2020;15:e0240431–21

IMPACT FONCTIONNEL

- Impact majeur sur la qualité de vie
- Impact sur le sommeil
- Impact sur l'humeur
- Isolement

Challenges in methodology	**Limitations** in prior studies	**Recommendations** for future studies
Low prevalence of amputation	Small sample sizes leading to low statistical power	- Multi-center clinical research collaborations to increase study sample sizes and to accelerate cross-centre replications
No clear criteria for establishing a PLP diagnosis	Different inclusion criteria for PLP patients across studies	- Develop a set of comprehensive measures for PLP which incorporate presence, intensity, frequency, duration of episodes and quality of PLP
Setting exclusion criteria given heterogenous amputation-related factors	Limited exclusion criteria (i.e., high heterogeneity in samples)	- Develop a better understanding of amputation-related comorbidity - Increase sample size to enable regression of covariates
Lack of standard pain measures and instructions	Different pain measures and instructions given to patients across studies	- Develop a set of standard quantifiable and objective measures for PLP
Lack of hypothesis driven research	Exploring too many outcome measures leading to opportunities for selective reporting	- Pre-register reporting of outcome measures of interest - Correct for multiple comparisons
Inadequate adoption of clinical trial standards	Lack of randomization, double-blinding	- Adopt CONSORT recommendations for conducting and reporting clinical trials - Randomization or matching active and control groups based on amputation-related factors (e.g. baseline pain levels) - Double blinding for treatment outcomes where possible
Establishing appropriate treatment controls	No or weak treatment controls	- Develop clearer standards for active controls - Control for patient's expectations, engagement with experimenter and task demands
Conducting longterm prospective studies	Few prospective studies and very few with follow-ups beyond 1 year	- Increase funding to facilitate longterm research studies
Systematic reviews and meta-analyses	- Absence of pre-registration - Poorly specified search terms - Lack of risk of bias assessment	- Pre-register protocols with PROSPERO or similar database - Adopt PRISMA/STROBE guidelines and recommendations for systematic reviews and meta-analyses - Conduct risk of bias assessments of existing literature

Schone HR, *et al. J Neurol Neurosurg Psychiatry* 2022;**93**:833–843. doi:10.1136/jnnp-2021-328428

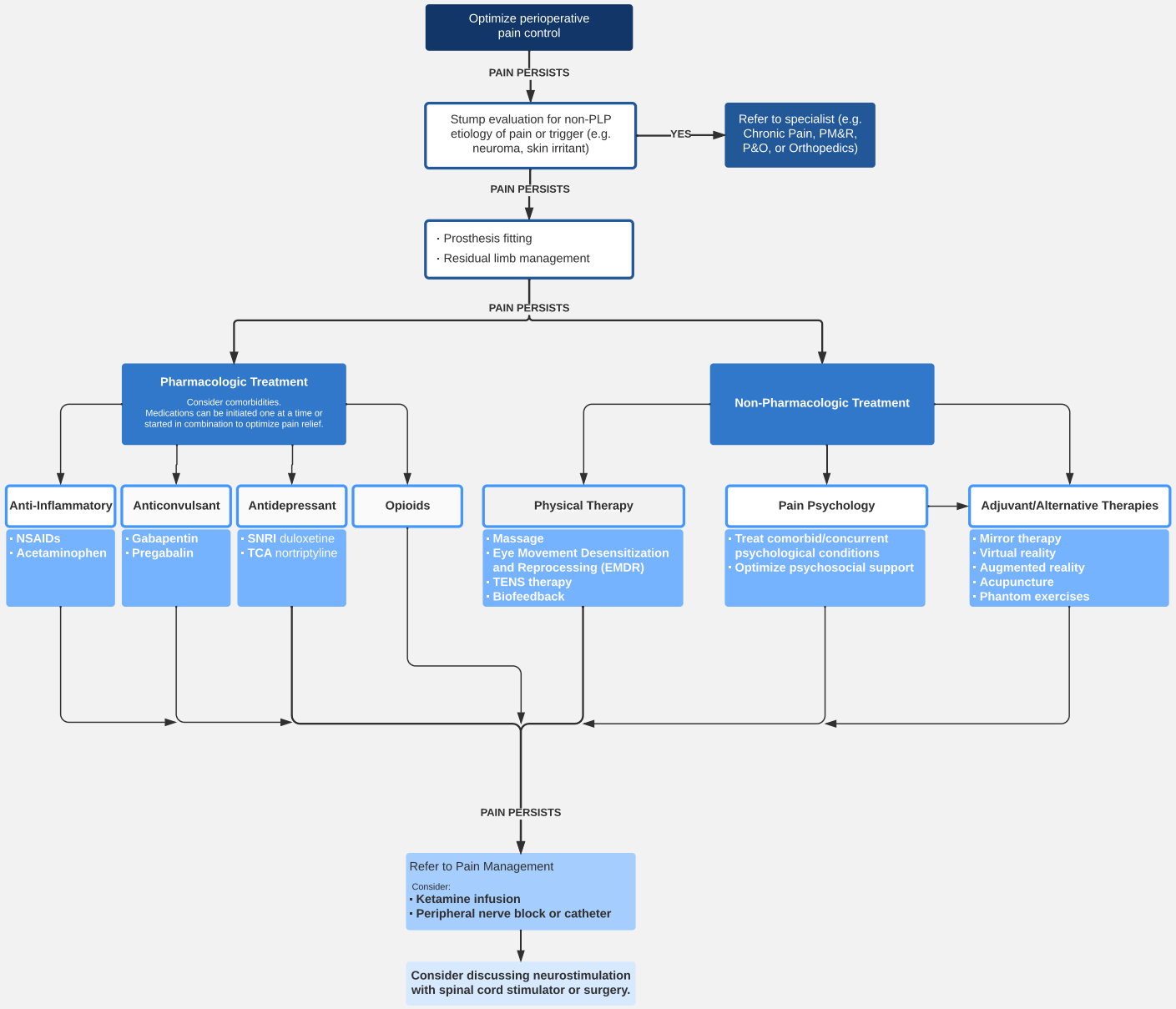


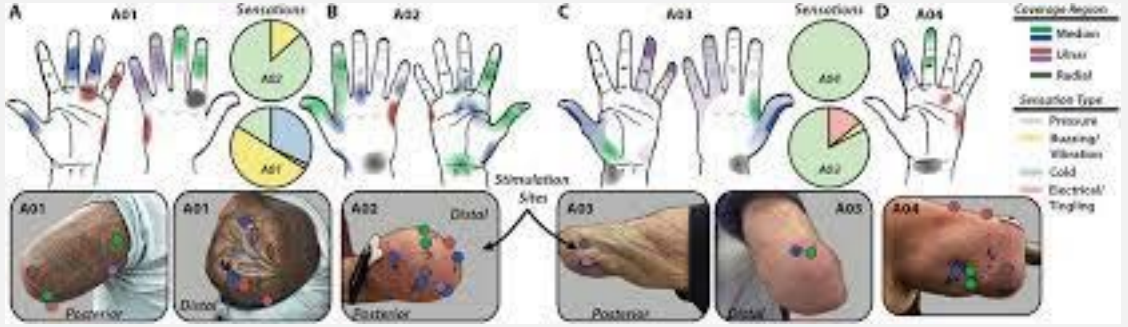
Figure 1 Management algorithm for phantom limb pain. Algorithme 2022 équipe virginie

TRAITEMENTS PHARMACOLOGIQUES

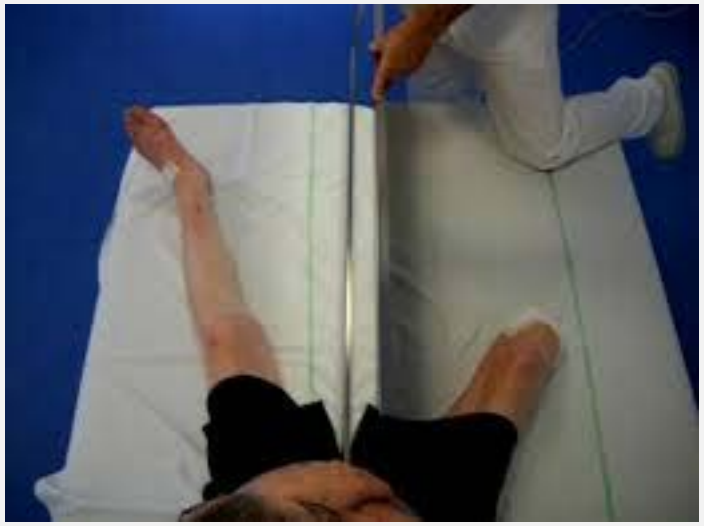
- Selon comorbidités du patient
- Anticonvulsivants (gabapentin ou prégabaline)
- ISRN (duloxétine, venlafaxine) (trouble dépressif)
- ADT (amitriptyline, desipramine, nortriptyline)(trouble du sommeil)
- Combinaison de plusieurs agents souvent nécessaire
- Crème lidocaine, crème kétamine/amitriptyline
- Perfusion kétamine/lidocaïne
- AINS et Tylenol (en aigu et si douleur d'irritation/inflammation moignon)

ENTRAÎNEMENT DE DISCRIMINATION SENSORIELLE

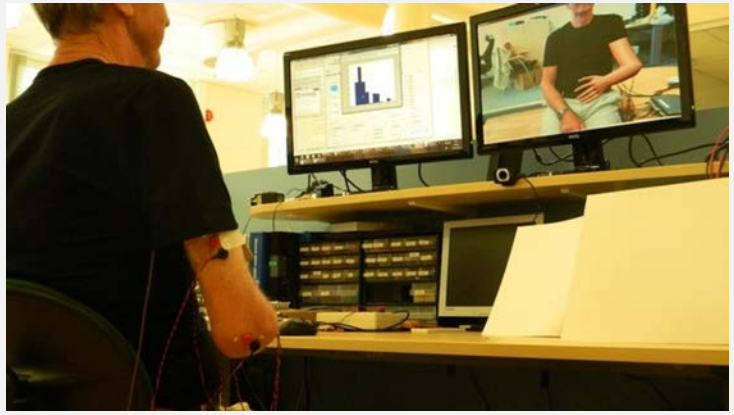
- Stimulation des nerfs qui innervait la partie amputée
- Patient doit discriminer la fréquence et localisation de la stimulation 90 min/jr x 2 semaines
- Diminution de la douleur chronique
- Peut être effectué par un membre de la famille avec du coton ou tout stimuli tactile.

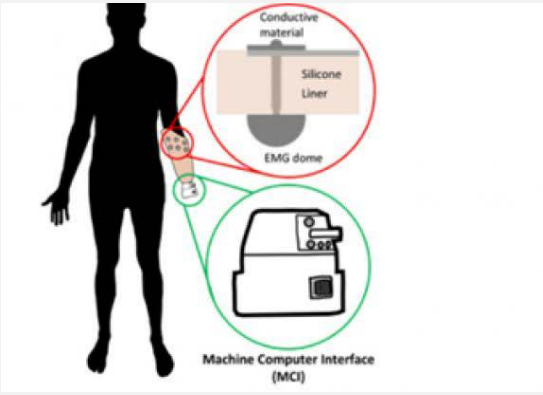


MIRROR AND MOTOR IMAGERY TRAINING



RÉALITÉ VIRTUELLE





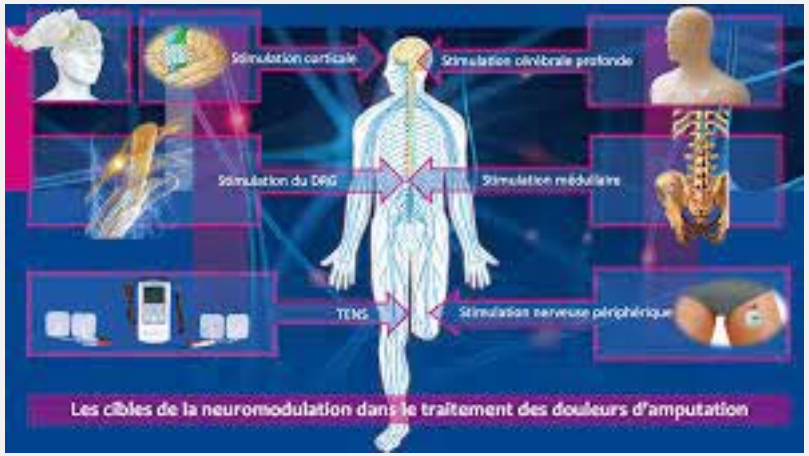
STRATÉGIES AU NIVEAU DE LA PROTHÈSE

- Utilisation d'une prothèse bien adaptée diminue la douleur fantôme
  - Reconstruit le feedback sensoriel
  - Diminution de l'incongruence sensorimotrice et de l'image corporelle

- En 1990 : prothèses myoélectriques
  - Récepteurs sensoriels dans la prothèse qui reçoivent les signaux électriques et les transforment en commande motrice ce qui permet de bouger la prothèse.

NEUROMODULATION

- Stimulation transcrânienne électromagnétique
- Stimulation électrique transcutanée
- Technique invasive de neuromodulation
  - Nerf périphérique
  - Moelle épinière
  - Stimulation du ganglion dorsal



TRAITEMENTS

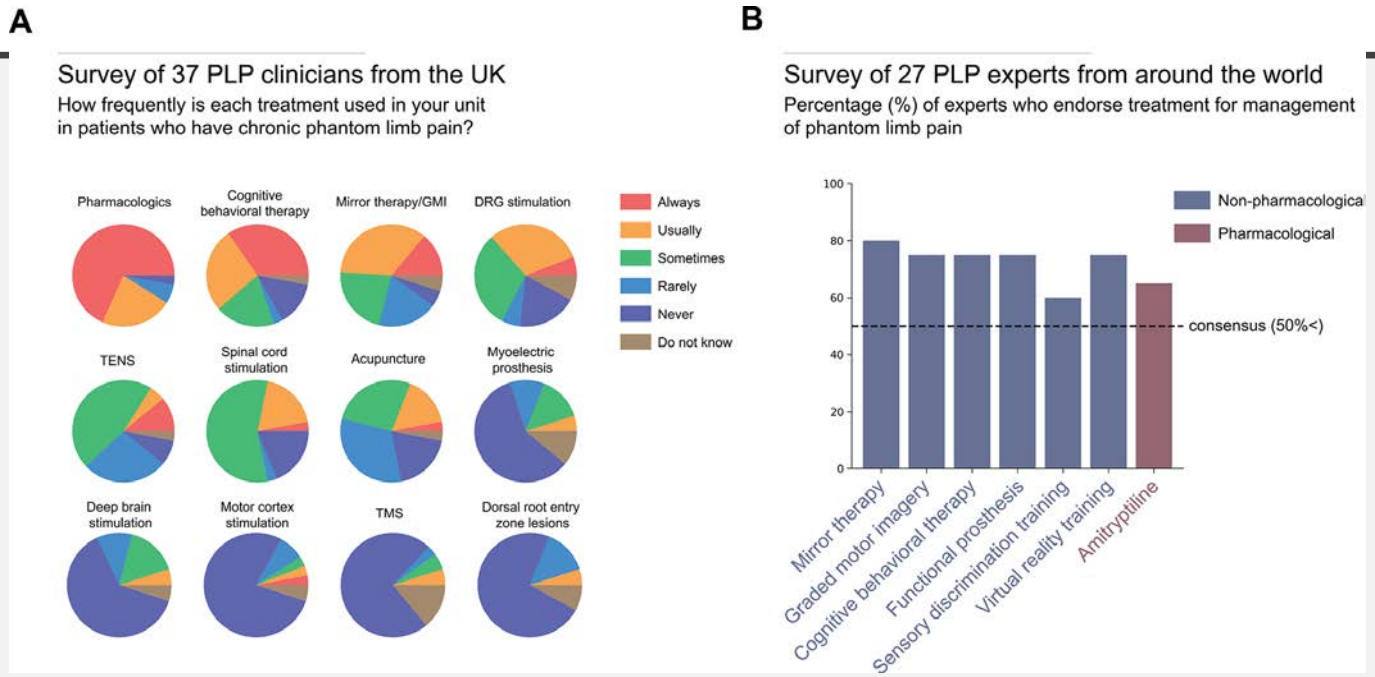


Figure 4 Therapies and treatments for phantom limb pain (PLP). (A) A recent survey of 37 PLP clinicians, 23 pain physicians, 11 neurosurgeons, 2 anaesthetists and 1 rehabilitation physician, across 30 UK hospitals, revealed that most clinicians are primarily using pharmacological treatments for chronic PLP patients, as well as a combination of non-pharmacological and brain stimulation therapies. Data adapted from Table 27 in Corbett *et al*[4]. (B) A global Delphi review of PLP treatments used by PLP experts, three anaesthetists, three physiatrists, two psychologists, two neurologists, eight physiotherapists, one nurse and one occupational therapist, revealed that most consensus treatments were non-pharmacological. Graded motor imagery (GMI); transcutaneous electrical nerve stimulation (TENS); transcranial magnetic stimulation (TMS). Data adapted from Table 2 in Limakatso and Parker[3] with permission.

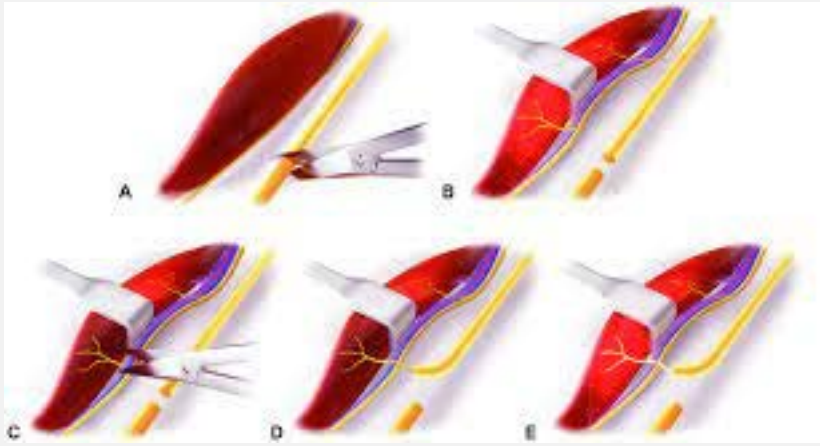
Schone HR, *et al*. *J Neurol Neurosurg Psychiatry* 2022;**93**:833–843. doi:10.1136/jnnp-2021-328428

TRAITEMENTS INTERVENTIONNELS POUR DOULEUR FANTÔME CHRONIQUE

- Infiltration du névrome
- Blocs nerveux
- Radiofréquence pulsée des nerfs distaux ou du névrome
- Cryothérapie du névrome ou du nerf terminal si bloc diagnostique positif
- Infiltrations autres 2nd à l'atteinte de la démarche (atteinte facettaire, SI, arthrose hanche etc.)
- Neurostimulateurs

PRÉVENTION
TMR(TARGETED MUSCLE REINNERVATION)

- Effectué par plasticien lors de l'amputation.
- Permet reconstruction bionique
- Nerfs résiduels du membre amputé sont transférés sur un nouveau muscle.
- Améliore le contrôle de la prothèse
- Diminue la douleur
- Diminue l'incidence de douleur fantôme



Prevention is better than cure: Surgical methods for neuropathic pain prevention following amputation – A systematic review
J.W.D. de Langea, C.A. Hundepoola, D.M. Powerb, V. Rajaratnamc, L.S. Durakud, J.M. Zuidama,*

TMR

- Mécanisme pas complètement élucidé
  - Restauration de la continuité physiologique
  - Restauration de la morphologie du nerf myélinisé
  - Meilleure fonction de la prothèse
  - Prévention de névrome
  - Effets sur la réorganisation corticale.

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PRÉVENTION

- Approche préventive :
  - Technique chirurgicale adéquate pour optimiser et normaliser la fonction et le body scheme.
  - Meilleure adaptabilité à la prothèse et la capacité de mise en charge
  - Réduction de la douleur pré-op, périop et PO.
  - Techniques régionales devraient toujours être considérées pour s'assurer d'un contrôle suffisant des douleurs en PO.
- Les études d'utilisation et comparaison des techniques régionales incluent un petits nombres de patients, méthodologies différentes, différents groupes contrôles, différents temps d'initiation et donc résultats différents…

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PRÉVENTION

- Les études nous permettent pas actuellement de conclure quelle technique est la plus efficace ou quel timing utiliser.
  - Pré-op jour 1
  - Pré-op quelques jours avant
  - Directement pré-op
- On manque de données pour comparer la péridurale à un bloc péri-nerveux et leur effet sur la prévention de la douleur fantôme.
- L'utilisation d'une péridurale ou d'un bloc nerveux diminuent l'incidence de la douleur fantôme.
- Techniques régionales diminuent la consommation d'opiacés en PO.

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PRÉVENTION
TECHNIQUES RÉGIONALES

- Sélection de la technique et du timing est basé sur les risques individuels des patients et leurs conditions cliniques.
- Si douleur pré-op sévère réfractaire malgré analgésie
  - Initiation d'une péridurale ou d'un bloc périneural quelques jours à un jour avant la chirurgie peut être indiquée lorsque c'est possible.
    - Logistique et selon disponibilité des lits
  - Toujours tester sa péridurale ou son bloc avant la chirurgie !!! Le plus important est d'avoir un bloc qui fonctionne.

PRÉVENTION

- L'étape la plus importante !!
- Rôle de tous les anesthésiologistes peu importe le milieu d'exercice
- Toujours penser au risque de douleur fantôme, douleur chronique lors d'une amputation.
- Facteur de risque le plus important est la douleur périopératoire.
- RÉGIONALE !!!
- On a tous un rôle à jouer!!!
- Penser à diminuer l'utilisation des opioïdes en douleur chronique et diminution des méfaits.

CRISE DES OPIOÏDES AU CANADA ET AU QUÉBEC

- 3 556 décès dus à la toxicité des opioïdes sont survenus de janvier à juin 2022. Cela représente environ 20 décès par jour.
- Dans les années précédant la pandémie, il y avait entre 8 (2016) et 12 (2018) décès par jour.
- 9,6 % des adultes canadiens qui ont pris des médicaments opioïdes en 2018 ont dit en avoir fait un usage problématique.
- Crise avec les opiacés d'ordonnance!
- 104 visites urgences/mois Montréal
- De moins en moins indiqués de les prescrire pour douleur chronique non cancéreuse.

NOTRE EXPÉRIENCE CLINIQUE HMR

- Pain board
  - Chirurgiens orthopédiques et plasticiens
  - Cliniciens de la clinique de la douleur
  - Infirmières SAPO
  - Réunions une fois /mois

PAIN BOARD

- Présentation de cas

  - Douleur pré-op importante non contrôlée
  - Risque de douleur PO important
  - Amputation haute, désarticulation de la hanche, hémipelvectomie

PAIN BOARD

- Suggestions pour améliorer l'analgésie pré-op
- Organisation d'un RV avec un algologue pour organiser un plan de match
  - améliorer le contrôle de la douleur pré-op
  - Plan chirurgical
- Suivi SAPO et suivi PO transitoire (infirmière SAPO et algologue) pour le retour à la maison afin de s'assurer d'une bonne évolution des symptômes et du sevrage des opioïdes s'il y a lieu.

PAIN BOARD
NOTRE PRATIQUE HMR

- Pour amputation haute (désarticulation hanche, hemipelvectomie)
  - Péridurale tunnelisée :
    - Permettant un sevrage lent de la péridurale selon la sévérité de douleur fantôme (en moyenne 10 à 15 jours).
  - Si douleur fantôme malgré péridurale :
    - Ajouter anticonvulsivants, ADT ou ISRN selon comorbidités du patient et augmentation rapide des doses selon la tolérance des effets secondaires.
    - Perfusion kétamine si douleur sévère malgré péridurale.
    - Opiacés PRN

PAIN BOARD

- Pour amputation MS :
  - Bloc infra-claviculaire continu tunnelisé
- Pour amputation plus distale Minf :
  - Péridurale versus bloc sciatique continu tunnelisé si douleur importante pré-op et consommation élevée de narcotiques
  - Non tunnelisé si peu de facteurs de risque.
- INDIVIDUALISER LE TRAITEMENT SELON FACTEURS DE RISQUE ET COMORBIDITÉS

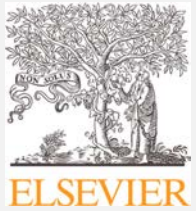
CONCLUSION

- Prévention is the key!!!
- Un bon contrôle de la douleur péri-opératoire est primordiale
- Toujours penser à utiliser l'anesthésie régionale pour toute amputation plus majeure qu'une amputation d'orteils.
- Analgésie multimodale
- Pathologie avec impact fonctionnel majeur et coût sociétaire
- Toujours penser à limiter la consommation des opioïdes en douleur chronique non cancéreuse
- Assurer un suivi post hospitalier transitoire

- Questions ???

INNOVATIONS CHIRURGICALES

Journal of Plastic, Reconstructive & Aesthetic Surgery 75 (2022) 948–959



Review

Prevention is better than cure: Surgical methods for neuropathic pain prevention following amputation – A systematic review

J.W.D. de Lange[a], C.A. Hundepool[a], D.M. Power[b], V. Rajaratnam[c], L.S. Duraku[d], J.M. Zuidam[a,*]

Table 1

Effects of regional anesthesia on phantom limb pain.

Comparison	Intervention	Endpoint/follow-up period	No. of inclusions	Effects
Preoperative and postoperative epidural bupivacaine/fentanyl and epidural anesthesia vs preoperative i.v. PCA fentanyl, epidural anesthesia, and postoperative epidural bupivacaine/fentanyl vs preoperative and postoperative i.v. PCA fentanyl and epidural anesthesia vs preoperative and postoperative i.v. PCA fentanyl and general anesthesia vs preoperative and postoperative analgesia with pethidine, codein/paracetamol, and general anesthesia for AKA and BKA (Randomized, Karanikolas et al.[75])	a: Preoperative epidural bupivacaine 2 mg/mL fentanyl 2 μg/mL 4–8 mL/h for 48 hours, epidural anesthesia, postoperative epidural analgesia as preop for 48 hours b: Preoperative i.v. PCA fentanyl for 48 hours, epidural anesthesia, postoperative epidural infusion as in A for 48 hours) c: Preoperative i.v. PCA fentanyl for 48 hours, epidural anesthesia, postoperative i.v. PCA fentanyl for 48 hours d: Preoperative i.v. PCA fentanyl for 48 hours, general anesthesia, postoperative i.v.-PCA fentanyl for 48 hours e: Preoperative and postoperative analgesia with pethidine 50 mg i.m. 4–6 times per day, codeine 30 mg/paracetamol 500 mg 3–5 times per day p.o., general anesthesia	Outcome assessment at 24 hours, 4, 10 days, and 6 mo after surgery	65	"At 6 months, median (minimum-maximum) PLP and *P* values (intervention groups vs control group) for the visual analogue scale were as follows: 0 (0–20) for Epi/Epi/Epi ($P = 0.001$), 0 (0–42) for PCA/Epi/Epi ($P = 0.014$), 20 (0–40) for PCA/Epi/PCA ($P = 0.532$), 0 (0–30) for PCA/GA/PCA ($P = 0.008$), and 20 (0–58) for controls. The values for the McGill Pain Questionnaire were as follows: 0 (0–7) for Epi/Epi/Epi ($P < 0.001$), 0 (0–9) for PCA/Epi/Epi ($P = 0.003$), 6 (0–11) for PCA/Epi/PCA ($P = 0.208$), 0 (0–9) for PCA/GA/PCA ($P = 0.003$), and 7 (0–15) for controls. At 6 months, PLP was present in 1 of 13 Epi/Epi/Epi, 4 of 13 PCA/Epi/Epi, and 3 of 13 PCA/GA/PCA patients vs 9 of 12 control patients ($P = 0.001$, $P = 0.027$, and $P = 0.009$, respectively). Residual limb pain at 6 months was insignificant. Optimized epidural analgesia or intravenous PCA, starting 48 hours preoperatively and continuing for 48 hours postoperatively, decreases PLP at 6 months"
Epidural bupivacaine and diamorphine preoperatively and postoperatively vs continuous sciatic or tibial or common peroneal nerve block with bupivacaine for AKA and BKA (Randomized, Lambert et al.[84])	a. Epidural bupivacaine 0.166% 2–8 mL/h, diamorphine 0.2–0.8 mg/h 24 hours preop and 72 hours postoperatively b. Continuous sciatic (AKA) or tibial or common peroneal (BKA) nerve block with bupivacaine 0.25% 10 mL/h 72 hours postoperatively	Outcome assessment 6, 24 hours, 2, 3 days, and 12 months after surgery	30	"Stump pain scores in the first 3 days were significantly higher in the perineural group compared with the epidural group ($P < 0.01$). After 3 days, 4 (29%) patients in the epidural group and 7 (44%) in the perineural group had phantom pain ($P = 0.32$). Numbers of patients with phantom pain for epidural vs perineural group were: 5 (63%) vs 7 (88%) ($P = 0.25$) at 6 mo; 3 (38%) vs 4 (50%) ($P = 0.61$) at 12 mo. Stump pain and phantom sensation were similar in both groups at 6 and 12 months."
Preoperative and postoperative bupivacaine + morphine vs epidural saline + morphine i.m/p.o. preoperatively and epidural analgesia with bupivacaine + morphine postoperatively for AKA, BKA, and through knee joint (Randomized, Nikolajsen et al.[109])	a. Epidural bupivacaine 0.25% 4–7 mL/h, morphine 0.16–0.28 mg/h median 18 hours preoperatively and median 166 hours postoperatively b. Epidural saline 4–7 mL/h i.m./po morphine median 18.5 hours preoperatively and epidural analgesia with bupivacaine 0.25% 4–7 mL/h, morphine 0.16–0.28 mg/h median 166 hours postoperatively	Outcome assessment at 1 wk, 3, 6, 9, and 12 mo after surgery	60	"After 1 week, 14 (52%) patients in the blockade group and 15 (56%) in the control group had phantom pain (95% CI −30.6 to 22.7, $P = 0.9$). The figures for blockade vs control group were: 14 (82%) vs 10 (50%; 4.0–60.8, $P = 0.09$) at 3 mo; 13 (81%) vs 11 (55%; −2.7 to 55.3, $P = 0.2$) at 6 mo; and 9 (75%) vs 11 (69%; −27.0 to 39.6, $P = 1.0$) at 12 mo. Intensity of stump and phantom pain and consumption of opioids were similar in both groups at all 4 postoperative interviews."

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Table 1 (*continued*)

Effects of regional anesthesia on phantom limb pain.

Comparison	Intervention	Endpoint/follow-up period	No. of inclusions	Effects
Epidural ketamine + bupivacaine vs epidural saline + bupivacaine for AKA and BKA (Randomized, Wilson et al.[147])	a. Epidural bolus ketamine 0.5 mg/kg and bupivacaine 0.5% 1 mg/kg preoperatively, continuous ketamine 3.3 mg/kg/L and bupivacaine 0.125% 10–20 mL/h with the aim of VAS <30 48–72 hours postoperatively b. Epidural bolus saline + bupivacaine 0.5% 1 mL/kg before start of operation, continuous infusion saline + bupivacaine 0.125% 15 mL/h 48–72 hours postoperatively	Outcome assessment at 8 days, 6 wk, 3 mo, 6 mo, and 12 mo	53	"Persistent pain at one year was much less in both groups than in comparable studies, with no significant difference between groups (group K = 21% (3/14) and 50% (7/14); and group S = 33% (5/15) and 40% (6/15) for stump and phantom pain, respectively). Postoperative analgesia was significantly better in group K, with reduced stump sensitivity. The intrathecal/epidural technique used, with perioperative sensory attenuation, may have reduced ongoing sensitization, reducing the overall incidence of persistent pain. The improved short-term analgesia and reduced mechanical sensitivity in group K may reflect acute effects of ketamine on central sensitization. Longer-term effects on mood were detected in group K that requires further study."
Epidural bupivacaine + fentanyl + calcitonin vs epidural bupivacaine + fentanyl + saline for AKA, BKA, minor amputations below ankle (Randomized, Yousef and Aborahma[150])	A: Epidural bolus bupivacaine 0.5% 10 mL and fentanyl 0.1 mg and calcitonin 100 I. U. preoperatively, and once a day 2 days postoperatively B: Epidural bolus bupivacaine 0.5% 10 mL and fentanyl 0.1 mg and saline 1 mL preoperatively, and once a day 2 days postoperatively	Outcome assessment at 1, 6 wk, 3, 6, and 12 mo	60	"There was statically significant improvement in the grade of phantom pain in the BCF group at 6 and 12 mo after surgery ($P = 0.033$ and 0.001, respectively). A significantly higher number of patients developed allodynia in the BF group at 6 ($P = 0.039$) and 12 ($P = 0.013$) months and hyperalgesia at 12 months ($P = 0.025$). The preventive use of epidural calcitonin improved the grade of phantom pain and reduced the incidence of allodynia and hyperalgesia in patients undergoing lower-limb amputation under combined spinal–epidural anesthesia during 1 year of follow-up."
Epidural bupivacaine and morphine vs paracetamol + NSAIDS + opioids for BKA (Prospective controlled trial, Bach et al.[9])	a: Epidural bupivacaine 0.25% and morphine 72 hours preoperatively until amputation b: Various analgesics: Paracetamol, NSAIDs, opioids starting 72 hours before amputation	Follow-up before limb amputation, 7 days, 6 months, and 1 year after limb amputation	25	"Seven days after operation, 3 patients in the LEB group and 9 patients in the control group had phantom limb pain ($P < 0.1$). After 6 months, all patients in the LEB group were pain-free, whereas 5 patients in the control group had pain ($P < 0.05$). After 1 y, all the patients in the LEB group were still pain-free, and 3 patients in the control group had phantom limb pain ($P < 0.20$). Preoperative lumbar epidural blockade with bupivacaine and morphine reduces the incidence of phantom limb pain in the first year after operation."
Epidural bupivacaine + clonidine + diamorphine vs opioid analgesia as needed for AKA and BKA (Prospective, controlled trial, Jahangiri et al.[71])	a: Epidural bupivacaine 75 mg, clonidine 150 μg, diamorphine 5 mg in 60 mL of saline 1–4 mL/h 24–48 hours preoperatively and 72 hours postoperatively b: Opioid analgesia as needed	Outcome assessment at 7 days, 6 months, and 1 y after amputation	24	"At 1-y follow-up, one patient in the study group and 8 patients in the control group had phantom pain ($P < 0.002$) and 2 patients in the study group vs 8 patients in the control group had phantom limb sensation ($P < 0.05$). There was no significant improvement in stump pain. We conclude that perioperative epidural infusion of diamorphine, clonidine, and bupivacaine is safe and effective in reducing the incidence of phantom pain after amputation."

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Table 1 (*continued*)

Effects of regional anesthesia on phantom limb pain.

Comparison	Intervention	Endpoint/follow-up period	No. of inclusions	Effects
Continuous nerve block + bolus + pethidine i.m. vs parenteral opioids for AKA and BKA (Observational study, historical control group, Fisher et al.[46])	a: Block with bupivacaine 0.25% 10 mL/h For 72 hours + bolus 20 mL + pethidine i.m. b: Parenteral opioids	Outcome assessment monthly for 6 months, then 3 monthly for up to 1 y	31	"Effective amputation stump analgesia was obtained, significantly reducing the need for on-demand narcotic analgesics during this time to a mean dose equivalent of 1.4 mg of morphine compared with a retrospective control group who received the equivalent of a mean dose of 18.4 mg of morphine ($P < 0.0001$). No complications related to the technique were observed. A follow-up of the group receiving continuous postoperative regional analgesia for up to 12 months showed a total absence of phantom pain despite the presence of preoperative limb pain."
Continuous nerve block + various analgesics vs various analgesics for AKA and BKA (Retrospective comparison, Grant and Wood.[60])	a: Sciatic or tibial nerve block postoperatively for 1–8 d (3.4) with bupivacaine 0.5% 3–4 mL/h and various analgesics b: Various analgesics (paracetamol, dihydrocodeine, and morphine)	Time point not reported	64	"64 patients had a major lower-limb amputation (31 patients treated routinely, and 33 patients had an intraneural anesthetic (INA) catheter placed). In the INA group, median postoperative opioid analgesia requirement was 10 mg vs 74 mg ($P = 0.0002$, Mann–Whitney U) and postoperative prescription of amitriptyline for phantom pain was less common (4 patients vs 11 patients; $P = 0.0281$, Mann–Whitney U)."
Continuous nerve block + bolus vs parenteral opioid analgesia and/or epidural opioid for AKA, BKA, partial resection, and hemipelvectomy **(Observational, historical comparative group, Malawer et al.[95])**	**a: Sciatic, femoral, or lumbar nerve block with bupivacaine 0.25% 2–4 mL/h and 0.25%–0.5%, bolus 10–20 mL for 72 hours postoperatively b: Parenteral opioid analgesia and/or epidural opioid**	**Outcome assessment at 72 hours after amputation**	**34**	**"Eleven of the 23 patients on PICRA required no supplemental narcotic agents. The mean level of the narcotic agents required by the remaining 13 PICRA patients was approximately one-third of that required by the matched group of 11 patients receiving epidural morphine. Overall, the patients on PICRA had an 80% reduction of narcotic requirements when compared to the historical controls."**
Continuous wound infiltration + various analgesics vs various analgesics for AKA **(Observational study, divided to groups to the side amputated, Uhl et al.[137])**	**a: Sciatic nerve block with 0.375% ropivacaine 5 mL/h for 72 hours + various analgesics b: Various analgesics**	**Outcome assessment at day 1–5 after amputation**	**42**	**"The study demonstrated a significantly reduced postoperative VAS score for stump pain in group 1 for the first 5 days. Furthermore, the intake of opiates was significantly reduced in group 1. There were no significant differences between the 2 groups, neither in phantom pain intensity at discharge nor postoperative complications and death."**
Preoperative vs postoperative continuous nerve block + bolus **(Observational, van Geffen et al.[141])**	**a: Sciatic, femoral, or brachial nerve block preoperatively with ropivacaine 0.75% 0.3 + 0.1 mL/kg bolus, bupivacaine 0.25% (or 0.125% if 2 catheters) 0.1 mL/kg/h max 6 mL/h under ultrasound guidance for 5 days b: Postoperative neural blockade for 5 days as in a.**	**Outcome assessment at day 1–5 after amputation**	**11**	**"We conclude that ultrasonography facilitated the performance of successful peripheral nerve blocks in amputee patients in whom other pain-relieving techniques failed or where contraindicated."**

The retrospective comparison of Ayling 2014[8] was not included into this overview because the results only reported general postoperative pain intensity.

AKA, above-knee amputation; BCF, Bupivacaine/Calcitonin/Fentanyl; BF, Bupivacaine/Fentanyl; BKA, below knee amputation; Epi, epidural anesthesia; GA, general anesthesia; INA, intraneural anesthetic; LEB, lumbar epidural block; MPQ, McGill Pain Questionnaire; PCA, patient-controlled analgesia; PICRA, postoperative infusional regional analgesia; RCT, randomized controlled trial; RLP, residual limb pain; VAS, visual analogue scale; pts, patients; VRS, visual rating scale.

Table 1 (*continued*)

Effects of regional anesthesia on phantom limb pain.

Comparison	Intervention	Endpoint/follow-up period	No. of inclusions	Effects
Continuous sciatic or tibial nerve block with bupivacaine + PCA opioid vs continuous nerve block with placebo (saline) + PCA opioid for AKA and BKA (Randomized, Pinzur et al.[118])	a: Continuous Sciatic or tibial nerve block with bupivacaine 0.5% 1 mL/h 10 mL bolus, for 72 hours postoperatively and PCA opioid b: Continuous nerve block with placebo (saline) 1 mL/h 10 mL placebo bolus, for 72 hours postoperatively and PCA opioid	Outcome assessment at 1, 2, 3 days, 3, and 6 mo after amputation	21	"We concluded that continuous perineural infusion of an anesthetic seems to be a safe, effective method for the relief of postoperative pain but that it does not prevent residual or phantom limb pain in patients who have had an amputation of the lower extremity because of ischemic changes secondary to peripheral vascular disease."
Various nerve blocks with prolonged postoperative infusion for AKA and BKA (Observational study, no comparative group, Borghi et al.[14])	a: Various nerve blocks (sciatic, femoral, posterior lumbar) with ropivacaine 0.5% 5 mL/h (perineural sciatic, femoral, lumbar plexus), prolonged postoperative infusions for median 30 (4–83) days. b: No comparative group	Outcome assessment at the end of 12-month evaluation period.	62	"Median duration of the local anesthetic infusion was 30 days (95% confidence interval, 25–30 d). On postoperative day 1, 73% of the patients complained of severe-to-intolerable pain (visual analogue scale >2). However, the incidence of severe-to-intolerable phantom limb pain was only 3% at the end of the 12-mo evaluation period. At the end of the 12-month period, the percentage of patients with VRS pain scores were 0 = 84%, 1 = 10%, 2 = 3%, 3 = 3%, and 4 = none. However, phantom limb sensations were present in 39% of patients at the end of the 12-mo evaluation period. All patients were able to manage the elastomeric catheter infusion system at home."
Continuous nerve block + bolus + analgesics vs various analgesics incl. Opioids for AKA and BKA (Observational study, historical control group, Elizaga et al.[44])	a: Sciatic or tibial nerve block with bupivacaine 0.5% 2–6 mL/h + bolus 10–20 mL, 3–7 d or boluses + analgesics b: Various analgesics, opioids	Outcome assessment on day 3 after amputation and follow-up for up to 20.2 ± 8.1 months in Bupivacaine group (n = 9) and 13.8 ± 7.8 months in control group (n = 12).	59	"Bupivacaine 0.5% 2–6 mL/h was infused through a polyamide 20-gauge catheter inserted into the sciatic or posterior tibial nerve sheath under direct vision at the time of surgery. All patients, treated and control, received opioid analgesics systemically during the 72-hour period of study. The postoperative opioid analgesic requirement of treated patients was compared with that of control patients who received opioid analgesics alone. 72-hour opioid consumption (mean ± SD): a: 132.7 ± 92.8 mg b: 151.3 ± 124.3 mg The differences between study groups in the descriptor profiles and descriptor intensity ratings from the short form MPQ were not statistically significant, nor were pain intensity ratings different. The onset of phantom pain, temporal properties, change since amputation, impact on daily activity and sleep, use of prostheses, and variety of pain treatments used were also comparable between groups.

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Continuous nerve block + various analgesics vs various analgesics for AKA and BKA (Retrospective comparison, Grant and Wood.[60])	a: Sciatic or tibial nerve block postoperatively for 1–8 d (3.4) with bupivacaine 0.5% 3–4 mL/h and various analgesics b: Various analgesics (paracetamol, dihydrocodeine, and morphine)	Time point not reported	64	"64 patients had a major lower-limb amputation (31 patients treated routinely, and 33 patients had an intraneural anesthetic (INA) catheter placed). In the INA group, median postoperative opioid analgesia requirement was 10 mg vs 74 mg ($P=$ 0.0002, Mann–Whitney U) and postoperative prescription of amitriptyline for phantom pain was less common (4 patients vs 11 patients; $P = 0.0281$, Mann–Whitney U)."
Continuous nerve block + bolus vs parenteral opioid analgesia and/or epidural opioid for AKA, BKA, partial resection, and hemipelvectomy **(Observational, historical comparative group, Malawer et al.[95])**	**a: Sciatic, femoral, or lumbar nerve block with bupivacaine 0.25% 2–4 mL/h and 0.25%–0.5%, bolus 10–20 mL for 72 hours postoperatively b: Parenteral opioid analgesia and/or epidural opioid**	**Outcome assessment at 72 hours after amputation**	**34**	**"Eleven of the 23 patients on PICRA required no supplemental narcotic agents. The mean level of the narcotic agents required by the remaining 13 PICRA patients was approximately one-third of that required by the matched group of 11 patients receiving epidural morphine. Overall, the patients on PICRA had an 80% reduction of narcotic requirements when compared to the historical controls."**
Continuous wound infiltration + various analgesics vs various analgesics for AKA **(Observational study, divided to groups to the side amputated, Uhl et al.[137])**	**a: Sciatic nerve block with 0.375% ropivacaine 5 mL/h for 72 hours + various analgesics b: Various analgesics**	**Outcome assessment at day 1–5 after amputation**	**42**	**"The study demonstrated a significantly reduced postoperative VAS score for stump pain in group 1 for the first 5 days. Furthermore, the intake of opiates was significantly reduced in group 1. There were no significant differences between the 2 groups, neither in phantom pain intensity at discharge nor postoperative complications and death."**
Preoperative vs postoperative continuous nerve block + bolus **(Observational, van Geffen et al.[141])**	**a: Sciatic, femoral, or brachial nerve block preoperatively with ropivacaine 0.75% 0.3 + 0.1 mL/kg bolus, bupivacaine 0.25% (or 0.125% if 2 catheters) 0.1 mL/kg/h max 6 mL/h under ultrasound guidance for 5 days b: Postoperative neural blockade for 5 days as in a.**	**Outcome assessment at day 1–5 after amputation**	**11**	**"We conclude that ultrasonography facilitated the performance of successful peripheral nerve blocks in amputee patients in whom other pain-relieving techniques failed or where contraindicated."**

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Table 2

Evidence of randomized controlled trials of pharmacological intervention.

Comparison	Intervention	Endpoint/follow-up period	Inclusions	Clinical effects
Morphine vs placebo (Randomized, cross-over, Huse et al.[67])	Oral morphine sulfate (MST) titrated up to 300 mg/d, or the max. tolerable dose for 4 weeks	Outcome assessment at the end of the 4-week application period	12 patients with PLP, at least 3/10 VAS, upper extremity and lower extremity	"A significant pain reduction was found during MST but not during placebo. A clinically relevant response to MST (pain reduction of more than 50%) was evident in 42%, a partial response (pain reduction of 25%–50%) in 8% of the patients."
Morphine vs lidocaine vs placebo (diphenhydramine) (Randomized, DB, Wu et al.[148])	40 minutes IV infusion of morphine 0.2 mg/kg, 40 minutes IV infusion of lidocaine 4 mg/kg	Outcome assessment 30 minutes after end of the IV infusion	31 patients with persistent postamputation pain at least 6 months, upper extremity and lower extremity	"Compared with placebo, morphine reduced both stump and phantom pains significantly ($P < 0.01$). By contrast, lidocaine decreased stump ($P < 0.01$), but not phantom pain. The changes in sedation scores for morphine and lidocaine were not significantly different from placebo. Compared with placebo, self-reported stump pain relief was significantly greater for lidocaine ($P < 0.05$) and morphine ($P < 0.01$), whereas phantom pain relief was greater only for morphine ($P < 0.01$). Satisfaction scores were significantly higher for lidocaine (mean ± SD: 39.3 ± 37.8, $P < 0.01$) and morphine (45.9 ± 35.5, $P < 0.01$) when compared with placebo (9.6 ± 21.0)."
Gabapentin vs placebo (Randomized, DB, Bone et al.[13])	Oral gabapentin titrated up to 2400 mg/d or the max. tolerable dose for 6-week period	Outcome assessment weekly and at the end of the 6-week application period	19 patients, pain at least 6 months, intensity at least 40/100 VAS, upper extremity and < lower extremity	"Both placebo and gabapentin treatments resulted in reduced VAS scores compared with baseline. PID was significantly greater than placebo for gabapentin therapy at the end of the treatment (3.2 ± 2.1 v 1.6 ± 0.7, $P = 0.03$). There were no significant differences between placebo and gabapentin therapy in terms of the number of tablets of rescue medication required, sleep interference, anxiety, depression, and daily function."
Gabapentin vs placebo (Randomized, DB, cross-over, Smith et al.[135])	Oral gabapentin titrated up to 3600 mg/d for 6-week period	Outcome assessment at the end of the 6-week application period	24 patients with PLP and residual limb pain, upper extremity and lower extremity, amputation at least 6 months; traumatic, cancer, infectious etiology	"Both placebo and gabapentin treatments resulted in reduced VAS scores compared with baseline. Pain-intensity difference was significantly greater than placebo for gabapentin therapy at the end of the treatment (3.2 ± 2.1 v 1.6 ± 0.7, $P = 0.03$). There were no significant differences between placebo and gabapentin therapy in terms of the number of tablets of rescue medication required, sleep interference, HAD scale, or Barthel Index. The medication was well tolerated with few reports of adverse effects"
Amitriptyline vs benztropine mesylate (Randomized, DB, Robinson et al.[126])	Oral amitriptyline 10 mg/d titrated to max of 125 mg/d, oral benztropine mesylate 0.5 mg/d, each for 6 week	Outcome assessment at the end of the 6-week application period	39 patients with PLP and residual limb pain, upper-limb and lower-limb amputation, amputation at least 6 months, pain at least 3 months, pain intensity at least 2/10 NRS	Primary outcome average: pain intensity; secondary outcomes: disability, satisfaction with life, handicap; "No significant differences were found between the treatment groups in outcome variables when controlling for initial pain scores."

Table 2 (*continued*)

Evidence of randomized controlled trials of pharmacological intervention.

Comparison	Intervention	Endpoint/follow-up period	Inclusions	Clinical effects
Memantine vs placebo (Randomized, DB, Maier et al.[92])	Oral memantine 30 mg/d; for 3 weeks	Outcome assessment at the end of the 3-week application period	36 patients with history of PLP of at least 12 months, pain intensity at least 4/10 NRS, upper extremity and lower extremity	"In both groups, PLP declined significantly in comparison with the baseline (verum: 5.1 [±2.1] to 3.8 [±2,3], placebo from 5.1 [±2.0] to 3.2 [±1.46] NRS) without a rerising of the PLP during the washout period. Mean pain relief was 47% in the memantine group (10 patients reported more than 50% relief), 40% in the placebo group (6 > 50%): NNT were 4.5 (KI: 2.1–10.6). Analysis of covariance demonstrated a significant impact only on the prior PLP intensity, but no treatment effect. Two patients have demonstrated long-term pain relief under memantine until now (16 months). The total number of slight adverse events was comparable in both groups, but the overall number of severe events was higher in the memantine group ($P < 0.05$)."
Memantine oral vs placebo (Randomized, DB, cross-over, Wiech et al.[146])	Oral memantine up to 30 mg/d; for 4 weeks	Outcome assessment at the end of the 4-week application period	8 patients with chronic PLP, upper extremity, traumatic etiology	"In comparison to baseline and placebo, the NMDA receptor antagonist had no effect on the intensity of chronic PLP. In none of the periods were significant changes in the functional organization of SI observed."
Memantine oral vs placebo (Randomized, DB, Schwenkreis et al.[133])	Oral memantine titrated up to 30 mg/d; for 3 weeks	Outcome assessment at the end of the 3-week application period	16 patients with PLP at least 12 months, upper extremity, traumatic etiology	"Mean phantom pain was reduced in both the placebo (median − 0.9, range −3.2 to +1.2) and in the memantine group (median −2.5, range −6.3 to +0.3) in the course of the study. However, a comparison of both groups revealed no significant difference."
Dextromethorphan vs placebo (Controlled clinical trial; DB followed by open phase, 3-period, cross-over, Ben Abraham et al.[11])	Oral dextromethorphan 2 arms: 120 mg/d and 180 mg/d for 10 days	Outcome assessment at the end of the 10-day application period	10 patients with severe PLP, pain at least 1 mo, upper extremity and lower extremity, cancer etiology > traumatic, vascular	"All patients reported a >50% decrease in pain intensity, better mood, and lower sedation in each treatment phase. Four individuals reported this level of pain relief with the 60-mg and one with the 90-mg BID regimen during the double-blind phase, whereas 2 amputees benefited from the 60-mg and 3 from the 90-mg thrice-daily regimen in the open-phase trial. One reported exacerbation of pain with the 90-mg BID regimen, and 3 reported pain rebound at the 1-mo posttreatment follow-up phase. Three patients stopped all previous analgesic use during the study."

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Table 2 (*continued*)

Evidence of randomized controlled trials of pharmacological intervention.

Comparison	Intervention	Endpoint/follow-up period	Inclusions	Clinical effects
Ketamine vs placebo (Controlled clinical trial; DB followed by open phase, 3-period, cross-over, Nikolajsen et al.[108])	45 min IV infusion of ketamine 0.5 mg/kg	Outcome assessment at the end of the application	11 patients with stump and PLP, upper extremity and lower extremity, cancer etiology > traumatic, infection, reflex dystrophy, vascular	"All 11 patients responded decrease in the rating of st and phantom limb pain ass using visual analogue scale and McGill Pain Questionna (MPQ). Ketamine increased pressure-pain thresholds significantly. Wind-up like p (pain evoked by repeatedly tapping the dysaesthetic sk area) was reduced significar ketamine. By contrast, no e was seen on pain evoked b repeated thermal stimuli. Si effects were observed in 9 patients."
Ketamine vs ketamine vs calcitonin, vs combination of ketamine/calcitonin vs placebo (Randomized, DB, cross-over, Eichenberger et al.[42])	1 hour IV infusion of ketamine 0.4 mg/kg, 1 hour IV infusion of calcitonin 200 IU, IV infusion 1 hour IV infusion combination of ketamine 0.4 mg/kg and calcitonin 200 IU, IV	Outcome assessment at 30 min and 60 min of infusion and 48 hours after the end of the application	20 patients (only 10 received ketamine) with PLP at least 6 months, mean pain intensity at least 3/10 VAS, upper extremity and lower extremity, vascular, traumatic, cancer, chronic pain etiology	"Ketamine, but not calciton reduced phantom limb pain combination was not superi ketamine alone. There was difference in basal pain thresholds between the amputated and contralatera sides except for pressure p Pain thresholds were unaffe by calcitonin. The analgesic of the combination of calcit and ketamine was associat with a significant increase i electrical thresholds, but wi change in pressure and hea thresholds."
Calcitonin vs placebo (saline) (Controlled clinical trial, cross-over, Jaeger and Maier[70])	20 minutes IV infusion of 200 IU calcitonin	Outcome assessment at 24 hours after application, follow-up 7–152 days with weekly assessments	21 patients PLP in the first 7 days after amputation, upper extremity and lower extremity (only 1 upper), vascular, traumatic, cancer and infectious etiology	"In the calcitonin group, but the placebo group, 4 indivi remained pain-free without second infusion. Any furthe treatment was performed w CT. One week after the firs treatment, 19 patients (90 pain relief of more than 50 (76%) were completely pair and 15 (71%) never experie PLP again. One year later, 8 the 13 surviving patients (6 still had more than 75% PL relief. After 2 y, PLP exceed on NAS in 5 individuals (42 and the remaining 12 patie presented the same PLP as 1 y"
Calcitonin vs ketamine (see above, Eichenberger et al.[42])				
Bupivacaine vs placebo (saline) (Randomized, DB, cross-over, Casale et al.[20])	One contralateral myofascial injection of 1 mL of bupivacaine 2.5 mg/mL	Outcome assessment one hour after injection	8 patients with PLP at least 6 months, lower extremity, vascular, traumatic etiology	"Sixty minutes after the inje a statistically significant gre relief of phantom limb pain observed after using local anaesthetic than when usin saline injection ($P = 0.003$ Bupivacaine consistently reduced/abolished the phar sensation in 6 out of 8 pati These effects on phantom sensation were not observe saline injections."

(*continued on nex*