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Clinical updates on phantom limb pain

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Abstract

Introduction: Most patients with amputation (up to 80%) suffer from phantom limb pain postsurgery. These are often multimorbid patients who also have multiple risk factors for the development of chronic pain from a pain medicine perspective. Surgical removal of the body part and sectioning of peripheral nerves result in a lack of afferent feedback, followed by neuroplastic changes in the sensorimotor cortex. The experience of severe pain, peripheral, spinal, and cortical sensitization mechanisms, and changes in the body scheme contribute to chronic phantom limb pain. Psychosocial factors may also affect the course and the severity of the pain. Modern amputation medicine is an interdisciplinary responsibility.

Methods: This review aims to provide an interdisciplinary overview of recent evidence-based and clinical knowledge.

Results: The scientific evidence for best practice is weak and contrasted by various clinical reports describing the polypragmatic use of drugs and interventional techniques. Approaches to restore the body scheme and integration of sensorimotor input are of importance. Modern techniques, including apps and virtual reality, offer an exciting supplement to already established approaches based on mirror therapy. Targeted prosthesis care helps to obtain or restore limb function and at the same time plays an important role reshaping the body scheme.

Discussion: Consequent prevention and treatment of severe postoperative pain and early integration of pharmacological and nonpharmacological interventions are required to reduce severe phantom limb pain. To obtain or restore body function, foresighted surgical planning and technique as well as an appropriate interdisciplinary management is needed.

Keywords: Acute pain management, Amputation, Stump pain, Regional analgesia, Coanalgesics

1. Introduction

Painful and/or nonpainful sensations in place of the missing limb are reported by almost all patients after amputation and have been described in medical literature since the 16th century. French military surgeon Ambroise Paré has been credited with first describing this postamputation phenomenon.[45] Although pain-free phantom sensations (any sensation of the missing limb, eg, feeling the posture of the former body part or feeling the limb in a static or moving condition) are most frequent and reported by almost all amputees, they seem not to have pathological value and no negative effects on patient's life and function. The same is not true with regard to painful sensations. In Western countries, most limb amputations are performed due to diabetes mellitus or vascular diseases. Less often, the reason for amputation is trauma or cancer and only a minority of patients present with congenital malformation or septic infection. Amputations worldwide are more often related to traumatic injury. They are either caused by accidents (road, at work, or agriculture) or by armed conflicts and their long-term consequences (eg, landmines).

Key Points

1. Phantom pain and other pain entities are highly prevalent (up to 80%) in patients after amputation.
2. Current evidence-based pharmacological and interventional prevention and therapy is unsatisfying, and randomized controlled trials with relevant numbers of participants are missing. However, randomized controlled trials with relevant numbers of participants remain an unresolved challenge.
3. From the clinical point of view, prevention should be focused on effective reduction of perioperative pain intensity and early restoration of the body scheme.
4. Mirror therapy, proprioceptive training, virtual reality, and modern prosthetic and surgical approaches are the most promising approaches for the treatment of established phantom limb pain.
5. Treatment should include multimodal approaches coordinated within an interdisciplinary team.

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2. Phantom limb pain

Phantom limb pain (PLP) is defined as a painful sensation referring to the missing limb, but is also described after loss of an eye, breast, or tooth.[6,10,24,28,122,123,138] The prevalence can be estimated right up to 80% of all patients after limb amputation, depending on study design and study population.[107]

The onset of PLP mostly occurs soon after surgery but can be delayed in some patients. Painful phantom sensations are usually intermittent and last from seconds to minutes, but can last for hours, or even permanently. Generally, pain diminishes in both frequency and duration during the first 6 months after amputation.[31,40,47,79,124] In a relevant proportion of patients, these sensations persist for years.[15,63,131] Prospective follow-up data are only available for some years and not for long-term outcome. The prospective study by Bosmans et al. provided follow-up data of patients of a period of 31/2 years, suggesting that the prevalence of PLP decreases only moderately. Pain intensity is reported to be severe in 30% to 40% and moderate in 25% of patients in early stages, days and weeks after surgery, with a tendency to alleviate over time.[31,111,131] About 10% of amputees will retain pain with severe intensity after 6 months and more after surgery.[31,63] Nevertheless, PLP affects patients' quality of life with 25% to 50% reporting severe pain-related impairment.[40,131,140]

Clinically, PLP is often projected to the distal parts of the missing limb (eg, foot, toes, hand, or fingers), which might be related to the larger representation of distal body parts in the somatosensory cortex compared with the proximal limb.[47,48] Patients often describe PLP with characteristics typically associated with neuropathic pain (burning, stabbing, and pricking).[31] Although PLP is usually classified as neuropathic, patients often describe their pain with terms, suggesting more nociceptive pain experiences such as squeezing or crushing of the hand, finger, or toe, as if "a car is driving over the foot" etc. Perception of the limb may also change over time, with effects such as telescoping (feeling that the phantom limb is gradually shrinking/shortening over time).

3. Mechanisms

Although several potential mechanisms for development and maintenance of PLP have been described, the persistence of PLP most likely is a multifactorial process driven by somatic, psychological, and social factors (similar to other chronic pain conditions),[47,55] despite a seemingly universal cause in the unavoidable nerve injury with respective peripheral and central changes in the nervous system.[5]

Differentiating early factors might be the extent of tissue damage, edema, and disorders of the cell membrane, and damage of the perineurium. In the periphery, regenerative processes are initiated, like sprouting of damaged neurons and development of neuroma on the tail of the injured nerve with abnormal spontaneous activity generating afferent input. Central and peripheral changes are also associated with an increased expression of sodium channels and higher activity of nociceptive C fibers and spontaneous activity of dorsal root ganglion neurons.[12,112]

At the spinal cord level, sensitization has been described, while the activity of inhibitory interneurons has been shown to be reduced.[47] Also, an increased activity of spinal pronociceptive excitatory systems, with increased activity of glutamate and the N-methyl-D-aspartate receptor system, has been indicated.[108]

Neuronal plasticity and reorganization of the somatosensory cortex have been demonstrated after amputation.[52] Cortical reorganization is a process by which neighboring regions of the area representing the lost limb expand along the cortical map thereby coactivating neurons formerly receiving and processing peripheral input from this limb. This is accompanied by the expansion of neuronal receptive fields. Importantly, the degree of cortical reorganization correlates with severity of PLP.[51] Therapy focusing on limb perception (such as mirror therapy and prosthesis use) could prevent, reduce, and even reverse these changes in cortical reorganization.[47] Interestingly, research by Makin et al. suggests that PLP might rather be driven by the disruption of interregional functional connectivity rather than by changes in the local cortical representation.[94] They could show that multiple factors contribute to PLP, including a preserved structural representation of the area of the amputated hand.[93] However, maladaptive reorganization and persistent representation of the limb are not necessarily mutually exclusive and may depend on the task used to measure cortical changes. For example, in a computational model of PLP, Bostrom et al.[16] showed that both the amount of reorganization during tactile stimulation (used by Flor et al.[51]) and the level of cortical activity during phantom movements (used by Makin et al.[94]) were enhanced in a scenario with strong phantom pain as compared to a scenario with weak phantom pain (for a further discussion see Refs. 4 and 50). Thus, depending on the experimental context or method chosen, one might find evidence for either cortical reorganization or preservation of the amputated limb representation. Both cortical reorganization and preservation might not be contradictory, but rather complementary, which should be considered in future PLP models.

4. Psychosocial factors

Affective burden such as depression is not linked to occurrence of PLP, but may instead affect the course and the severity of the pain.[54,65,85,134] A passive coping style before amputation was associated with PLP, as well as catastrophizing as a maladaptive response.[124] Cognitions, coping style, and social environmental variables predicted 43% of the variance of PLP intensity.[72] Furthermore, personality factors such as rigid and compulsive self-reliant personality assessed directly after the amputation were significantly correlated with a higher PLP intensity 1 year after the amputation.[114,134] Nevertheless, not all studies could find such a relationship.[134]

5. Other postamputation pain syndromes

Not all painful sensations after amputation are related to phantom pain. To provide the patient with sufficient therapy, it is important to distinguish and assess them using an interdisciplinary approach. In the immediate postamputation period, about 50% of patients experience amputation residual limb pain (RLP).[19] There is a strong correlation between RLP and PLP: patients affected with PLP show a higher presence of RLP in comparison to patients without PLP.[19,110] In some patients, RLP persists or develops in the context of wound healing disorders, osteitis, osteomyelitis, local circulatory disorders, neuroma, hematoma, or seroma.[56,82,131] Residual limb pain is also associated with inappropriate preparation of the stump (eg, unfavorable formation of the bony stump end), inaccurate alignment of bone lengths in stumps with 2 or more bones (eg, metatarsus, lower leg, or forearm), and missing fat pad under mesh-graft after surgical treatment of soft tissue injuries resulting in improper fit of the prosthesis. In addition, structural changes of the stump and its surrounding tissue can develop over time, such as bony

extractions, exostosis, disturbing scar tissue, surplus skin, reduced soft tissue covering of the stump due to lack of pretension of the musculature or muscle atrophy, and onset of (pseudo) bursae due to mechanic stress or skin lesions through the prosthesis. Neuromas can not only trigger PLP but can also cause localized allodynia, hyperalgesia, and pain hindering prosthesis use. In addition, hyperhidrosis of the stump might trigger sensitization and painful discomfort. This can further be deteriorated by mechanical stress through rubber stockings of the prosthesis. Being less mobile, compensating the missing limb, or adapting unfavorable movement patterns (eg, by walking with a prosthesis) can contribute to musculoskeletal pain disorders. These pain conditions can also radiate into the rest of the limb, or the stump and must be distinguished from PLP (eg, piriformis syndrome, myofascial trigger points, radiculopathy, lower back pain, and osteoarthritis of adjacent joints, eg, hip osteoarthritis).[1,33,34,78,83]

6. Treatment options

Although this has not been shown in dedicated studies, patients with postamputation pain syndromes probably benefit from assessment, treatment, and monitoring within an interdisciplinary team—including surgeons, anesthetists and pain physicians, psychologists, occupational therapists and physiotherapists, and orthopedic technicians. This should allow for optimizing potential synergistic effects and careful differential diagnosis. Main treatment options (for both prevention and established PLP) can be summarized under the following categories: surgical technique, prosthetic supply, pharmacotherapy including regional anesthesia, nonpharmacological treatment, education, and cognitive-behavioral therapy (possibly trauma-focused or eye movement desensitization and reprocessing therapy in case of posttraumatic stress disorder).[30,129] Due to few randomized controlled trials, case series with significant methodological weaknesses, lack of control groups, and small case numbers, currently there is limited evidence base for pharmacological and nonpharmacological prevention and treatment of PLP. In addition to consequent treatment of severe perioperative pain, the essential aspect seems the early restoration of body scheme and function if possible associated with sensomotoric efference input.[119] This review aims to provide an interdisciplinary overview of recent evidence-based and clinical knowledge as well as current trends and potential promising future developments in the management of PLP. It is based on an interdisciplinary review of the recent literature in the respective fields of the contributing authors, focusing on available systematic or narrative reviews, and relevant publications as identified by the authors with no predefined time window.

7. Procedures for preventing phantom limb pain

Preventive approaches include adequate surgical techniques to optimize/normalize function and body scheme postamputation by achieving the best possible adaptability to the prosthesis and static load capacity. Although studies on preamputation pain as risk factor for later PLP showed contradictory results,[107] severe preoperative and postoperative pain are the most consistent risk factors for chronic postsurgical pain per se.[69,76] Consequent reduction of preoperative and postoperative pain thus may contribute to the prevention and modulation of PLP. Regional anesthesia techniques should be considered to ensure sufficient symptom control after surgery. Studies using regional anesthesia for amputation included only a small number of patients, were heterogeneous regarding technique, time of initiation of the technique, and control group, and yielded conflicting results. On the one hand, regional anesthesia techniques led to a reduction of postoperative opioid consumption. On the other hand, the studies do not allow to draw conclusions about the selection of a specific procedure or for specific timing (at preoperative day, or earlier vs immediately preoperative).[107] There is also a lack of meaningful comparison between epidural and perineural infusion on their effect of the prevalence of PLP. A current systematic review of regional techniques after major limb amputation from von Plato et al. found 19 studies (9 randomized controlled trials [RCTs] and 10 observational studies) including 949 subjects. Only one of these studies provided a direct comparison (**Table 1**), showing no differences in long-term outcome.[142] Therefore, selection and timing of the technique should primarily be based on the patient's individual risk and clinical condition. If preoperative pain is severe and systemic analgesia insufficient, initiation of a continuous epidural or perineural infusion even days before surgery can be indicated. In addition, certain surgical techniques require intraoperative nerve stimulation and muscle localization if a myoelectric prosthesis is planned. Therefore, neurological limitations due to the intraoperative effects of local anesthetics have to be prevented. If the regional catheter is placed on the day before the operation, the regional technique can be initiated intraoperatively immediately after the stimulation.

Even if there is insufficient evidence for effective prophylaxis of PLP, from the clinical point of view, anesthetic procedures should also include the use of preoperative and intraoperative coanalgesics. For preoperative gabapentinoids, there is evidence to reduce postoperative pain.[43,86] The American "Guidelines on Management of Postoperative Pain" provide strong recommendation for preoperative gabapentinoids in all surgeries associated with substantial pain, and for patients with long-term opioid use as part of an multimodal analgesic concept (eg, 150–300 mg pregabalin, or 600–1200 mg gabapentin administered 1–2 hours preoperatively).[23] Also, the intraoperative use of ketamine or lidocaine may be useful (ketamine: preoperative bolus of 0.5 mg/kg followed by an infusion at 10 μg/kg/min intraoperatively in addition to a regional technique; lidocaine for patients without regional technique: preoperative bolus of 1.5 mg/kg followed by 2 mg/kg/h intraoperatively).[23]

8. Pharmacotherapy for early and established phantom limb pain

Several recent reviews have summarized the limited evidence for the pharmacological treatment of PLP.[2,61,107,125] A current Cochrane analysis on pharmacologic interventions for treating PLP included 14 studies (randomized and quasirandomized trials) with only a total of 269 study participants.[2] Morphine (oral and intravenous) and gabapentin were effective in decreasing pain intensity, both with limiting side effects. Intravenous ketamine had analgesic effects only for the time of application, but no relevant long-term effects. Orally available N-methyl D-aspartate receptor antagonists had either no analgesic effects on PLP (memantine) or short-term effects in a small study (dextromethorphan). In these controlled trials, botulinum toxin and amitriptyline were not effective in reducing intensity of PLP, whereas the results for intravenous application of calcitonin were variable, with one problematic yet positive study (**Table 2**). However, in a case series, some of these therapeutic approaches have shown a positive benefit for the patient (eg, botulinum toxin Refs. 73 and 79).

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 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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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.

Studies indicated in bold evaluated phantom limp pain in the immediate postoperative period only.

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."

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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 with a decrease in the rating of stump and phantom limb pain assessed using visual analogue scale (VAS) and McGill Pain Questionnaire (MPQ). Ketamine increased pressure-pain thresholds significantly. Wind-up like pain (pain evoked by repeatedly tapping the dysaesthetic skin area) was reduced significantly by ketamine. By contrast, no effect was seen on pain evoked by repeated thermal stimuli. Side 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 calcitonin, reduced phantom limb pain. The combination was not superior to ketamine alone. There was no difference in basal pain thresholds between the amputated and contralateral sides except for pressure pain. Pain thresholds were unaffected by calcitonin. The analgesic effect of the combination of calcitonin and ketamine was associated with a significant increase in electrical thresholds, but with no change in pressure and heat 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 not in the placebo group, 4 individuals remained pain-free without a second infusion. Any further treatment was performed with s-CT. One week after the first PLP treatment, 19 patients (90%) had pain relief of more than 50%, 16 (76%) were completely pain-free, and 15 (71%) never experienced PLP again. One year later, 8 out of the 13 surviving patients (62%) still had more than 75% PLP relief. After 2 y, PLP exceeded 3 on NAS in 5 individuals (42%), and the remaining 12 patients presented the same PLP as after 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 injection, a statistically significant greater relief of phantom limb pain was observed after using local anaesthetic than when using saline injection ($P = 0.003$). Bupivacaine consistently reduced/abolished the phantom sensation in 6 out of 8 patients. These effects on phantom sensation were not observed after saline injections."

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Table 2 (*continued*)

Evidence of randomized controlled trials of pharmacological intervention.

Comparison	Intervention	Endpoint/follow-up period	Inclusions	Clinical effects
Botulinum toxin vs lidocaine and methylprednisolone (Randomized, DB, Wu et al.[149])	Injection of each painful side with botulinum toxin A, 1 mL = 50 units once or injection of each painful side with combination of 0.75 mL lidocaine 1% and 0.25 mL methylprednisolone (=10 mg)	Outcome assessment monthly up to 6 months	14 patients with PLP or/and RLP, pain intensity at least 5/10 and unresponsive to conventional therapy	"Botox and lidocaine/Depomedrol injections resulted in immediate improvements of RLP (Botox: P= 0.002; lidocaine/Depomedrol: P = 0.06) and pain tolerance (Botox: P= 0.01; lidocaine/Depomedrol: P= 0.07). The treatment effect lasted for 6 months in both groups. The patients who received Botox injection had higher starting pain than those who received lidocaine/Depomedrol injection (P = 0.07). However, there were no statistical differences in RLP and pain tolerance between these 2 groups. In addition, no improvement of PLP was observed after Botox or lidocaine/methylprednisolone injection."

BID (bis in diē): twice a day; DB double-blinded; HAD scale, Hospital Anxiety and Depression Scale; MPQ, McGill Pain Questionnaire; NAS, numeric analogue scale; NNT, number needed to treat; NMDA, N-methyl-D-aspartate; PLP, phantom limb pain; RCT, randomized controlled trial; RLP, residual limb pain; VAS, visual analogue scale.

Kern et al.[77] described a promising observation applying cutaneous 8% capsaicin in a case series. Capsaicin treatment resulted in reduced PLP of at least 30% to up to 70% within the second to seventh week, of the 12-week follow-up period. After the seventh week, PLP intensity increased again. Mean of absolute reduction of intensity of PLP at the end of the 12-week period was −2,4 (numeric rating scale 0–10).

From a clinical perspective, it seems reasonable to consider the use of other medications typically used to treat neuropathic pain, including weak and strong opioids, other anticonvulsants (pregabalin, carbamazepine, and oxcarbazepine) and antidepressants (duloxetine and venlafaxine), as well as cannabinoids.[64]

9. Sensory discrimination training

Stimulation-related procedures delivering intense peripheral input into the cortical representation area of the amputated limb were found to be effective in reducing chronic pain. In one study, electrodes were closely spaced over the amputation stump in a region where stimulation excited the nerve that supplied the amputated portion of the arm. Patients then had to discriminate the frequency and location of the stimulation in an extended training period that lasted 90 min/d over a 2-week period. Substantial improvements to both two-point discrimination and PLP were demonstrated in the trained patients. These improvements were accompanied by changes in cortical reorganization, indicating a normalization of the shifted mouth representation in the primary somatosensory cortex.[49] An asynchronous peripheral stimulation of the stump and also the lip yielded a significant reduction in PLP too, suggesting that the separation of overlapping cortical networks involved in pain may be important.[68] Recently, it could be demonstrated that this training approach is also working with tactile stimuli using cotton swaps, which could easily be applied by the relatives of the patient.[143]

Innovative methods use sensory feedback to interact with phantom limb motor control and thus reduce PLP (see also prosthesis strategies). Using both visual and tactile feedback to influence and train muscular activity at the stump reduced PLP 32.1% up to 6 weeks after a two-week training period.[29]

10. Mirror and motor imagery training

Ramachandran et al. was the first to suggest that the use of a mirror might reverse the reorganizational changes observed in patients with PLP. There is evidence that viewing movements of one's intact hand in a mirror, which provides the impression of viewing the amputated hand, leads to better movement of and less pain in the phantom limb.[121] In a study by Brodie, lower-limb amputees reported a significantly greater number of movements in the phantom limb when a mirror box was used.[18] Hunter et al. showed that a single trial mirror box intervention led to a more vivid awareness of the phantom limb and a new or enhanced ability to move the phantom limb.[66] By contrast, Brodie et al. reported that both movements in front of a mirror as well as movements without a mirror attenuated PLP and phantom limb sensation.[17] Contrary to these findings, which were based on a single trial, only 4 weeks of mirror training led to a significant decrease in acute PLP compared to training with a covered mirror or mental visualization in lower-limb amputees.[22] Taken together, this suggests that PLP can be altered by visual feedback.

The visual system has a perceptual dominance in intersensory conflicts because of stronger spatial solution provided by vision compared to the other senses (including touch), even if the information based on touch would have been more correct.[62,101,127] An fMRI study observed that amputees with PLP were unable to activate the sensorimotor cortex opposite to the amputated limb when the intact hand was moved in front of a mirror (appearing as movement of the phantom). A similar lack of activation was, however, also present with executed movements of the intact hand and with imagery of the phantom hand.[36] Moreover, PLP was inversely correlated with activation on the hemisphere contralateral to the amputation suggesting that mirror training may not be specific.[100] In a 4-week mirror training program in patients with chronic PLP, treatment effects were predicted by a telescopic distortion of the phantom limb, with those patients who experienced telescoping profiting less from treatment. fMRI data analyses revealed a relationship between change in pain after mirror training and a reversal of dysfunctional cortical reorganization in primary somatosensory cortex.[53]

Reports on imagined phantom limb movements in amputees showed activation in primary sensorimotor cortex representing the amputated limb in pain-free amputees and healthy controls but not in patients with PLP.[87,89,130] This was supported by results from transcranial magnetic stimulation, which showed that perceived phantom hand movement could be triggered by stimulation over the motor cortex in an area that represented the amputated limb.[97] Giraux and Sirigu as well as MacIver et al.[57,91] showed that imagery alone also affects the cortical map representing the amputated limb and relieves PLP. By contrast, Chan et al. did not find changes in PLP related to imagery but did not assess cortical changes.[22,57,91] These studies suggest that several types of modification of input into the affected brain region may alter pain sensation. A review on the effects of mirrored and imagined movements was published by Moura et al.[102]

11. Virtual reality approaches to mirror training and robotic applications

Using a mirror box has some technical limitations. The intact limb has to move symmetrically with the mirrored limb. This is especially unnatural for the leg. This led to the invention of virtual reality (VR) and augmented reality mirror boxes (for a review see Ref. 25). In a first approach, the perceived phantom arm was presented on a flat screen in 3D and controlled through a wireless data glove on the intact arm.[32] The advantage of the VR mirror box is the possibility of incongruent movements between the intact hand with the data glove and the virtual phantom hand. In this study, patients reported that some of the virtual/phantom fingers appeared to be frozen and movement of the complete phantom hand led to more pain. The number of moved phantom fingers was thus gradually increased resulting in relaxation and less pain sensation in 2 of the 3 cases. A different approach used immersive VR (IVR) to transpose the movements made by an amputee's remaining anatomical limb into movements of a virtual limb.[103] The authors found a reduction of PLP intensity in 2 of 3 cases.[104,105] The advantage of this system is that the entire body is implemented in the IVR and thus complex hand–eye coordination is possible. A novel variation on this method is using motion capture to collect data directly from a patient's stump and then transforming it into goal-directed, virtual action in the VR environment.[26] In a first experimental study with 14 patients, 72% reported the ability to move the phantom limb and a reduction in PLP. Another possibility is an augmented reality home training system. Here, several training tasks can be implemented to make the training more exciting and increase the commitment of the patients. It works through a head-mounted display equipped with cameras that captures a handheld camera in front of the body and then mirrors it and displays it in real time.[136] These VR applications are promising and could be extended in the future. With the rubber hand illusion, it could be shown that the transfer of tactile sensations from the stump to a prosthetic limb by tricking the brain is possible.[41] This is an important contribution to the field of neuroprosthetics where a major goal is to develop artificial limbs that feel like a real part of the body.

12. Neuromodulation

Due to its noninvasive nature, transcutenous electrical nerve stimulation can be a good therapeutic option for peripheral stimulation.[74,115] Even if case studies demonstrated some relief of PLP, there is a lack of high-quality evidence and mixed results for its efficiency on PLP in one systematic review.[115] External brain stimulation using transcranial direct current stimulation or repetitive transcranial magnetic stimulation have shown clinical effects during the stimulation periods in several small studies, but failed to induce longer-lasting effects—limiting their clinical applicability.[80,106] Invasive techniques of neuromodulation, such as peripheral nerve, spinal cord, or dorsal root ganglion stimulation, have not received widespread clinical adaption. Evidence is lacking, except for small cohort studies with mixed results.[115]

13. Prosthesis strategies

There are several studies indicating that prosthetic usage decreases PLP.[145] The usage of a prosthetic replacement of the missing limb reestablishes different pathologies underlying and causing PLP, ie, reconstruction of sensory feedback of the lost extremity, reduction of sensomotory incongruence, and body image through embodiment of the prosthesis. Most of the studies were performed in upper-limb amputees and are limited in size. Among amputees, the rejection rates of prosthetic devices are very high, especially for nonfunctional cosmetic prosthesis.[27,90,113,117] In addition to the general correlation between usage of the prosthesis and reduction of PLP, there might be a further correlation between functionality of the prosthesis and the level of reduction of PLP. A study performed in the late nineties revealed that a functional prosthesis facilitating prosthetic movements by contraction and relaxation of residual-limb nearby remaining muscles ("Sauerbruch-Prosthesis"), and thereby reestablishing some somatosensory feedback, decreased PLP in comparison to a cosmetic, nonfunctional prosthesis.[144] In the nineties, myoelectrically controlled prosthesis entered the market. A myoelectric-controlled prosthesis is externally powered and controlled by electrical signals, generated naturally by muscle activity. Sensors fabricated into the prosthetic socket receive the intended electrical signals and relay the information to a controller, which translates the data into commands for the electric motors that finally move the joints of the prosthesis. Invasive procedures as described above could be replaced by emerging technologies. With myoelectric-controlled prosthesis, amputees may even use the phantom limb to control the prosthetic device.[21]

In addition, it was shown that enhanced use of a myoelectric prosthesis in upper-extremity amputees was associated with reduced PLP and even reduced cortical reorganization.[88] The more the user experiences that the discharged motor output of the prosthesis corresponds visually and functionally to the representations of the lost limb, the more relief of PLP will be achieved by using the prosthesis.[36,58,89] The new technology enables the amputee to actively engage with the prosthetic limb, by their sense of proprioception. This phenomenon is described by the term "embodiment."[58,59] The overall embodiment and reduction of PLP seems to be profound when the prosthesis provides additional cutaneous (sensory) feedback to the residual limb. Furthermore, there is a significant increase of functionality of the prosthesis by feedback mechanism, ie, for the grip strength, walking parameters.[35,37,38,96,116,128,132] A prosthesis with a feedback function seems to be a promising therapeutic tool to reduce PLP because it addresses sensomotory incongruences after amputation.[7,99]

14. Bionic reconstruction

Bionic reconstruction describes a combined surgical and rehabilitation technique. It allows for changes to the anatomy of a patient surgically, and for transfer of technology to rehabilitate the patient so they can make best use of advanced prostheses to

replace lost extremity function.[3] It has been shown that targeted muscle reinnervation (TMR) allows for bionic reconstruction, improves prosthetic control, and furthermore reduces pain.[39,98] The functional motor units generated by TMR may reverse the pathologic cortical reorganization associated with PLP.[88,120] The mechanism by which TMR reduces PLP is not entirely clear. Currently, researchers have suggested mechanisms like the restoration of physiological continuity (restoration of myelinated nerve morphology after TMR surgery),[81] improved prosthetic function, neuroma prevention, and potential effects on cortical reorganization. As the TMR approach reestablishes natural control of the prosthesis and seems to decrease PLP,[3] immediate surgical intervention of amputated nerves with TMR at the time of limb loss should be considered to prevent PLP after amputation.[3,139]

15. Discussion and clinical approach

After amputations, most patients experience PLP. From a clinical perspective, the current evidence for pharmacological and interventional prevention as well as therapy of established PLP is unsatisfying. A pragmatic clinical approach might be to reduce perioperative pain intensity as effectively as possible. Approaches should include the use of techniques of regional anesthesia, the perioperative combination of analgesics and of coanalgesics as well as nonpharmacological procedures. Multimodal approaches should be pursued in an interdisciplinary team. In the case of established pain after amputation, the focus should be on differential diagnosis, mechanistic- and function-oriented therapy, coordinated within the interdisciplinary team. The early restoration of the patients' body scheme to reduce sensomotory incongruences by using nonpharmacological treatments, such as mirror therapy and proprioceptive training, has promising potential to reduce PLP, possibly further enhanced by VR and sensory feedback approaches. Innovative prosthetic and surgical approaches can support the reestablishment of body scheme and proprioceptive input.

Disclosures

The authors have no conflicts of interest to declare.

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