Summary of Phantom Limb Pain studies

Robinson et al

Methods	Randomized controlled trial
Participants	Thirty-nine persons with amputation-related pain lasting more than 6 months
Interventions	Six-week trial of amitriptyline started at 10mg daily (titrated up to 125mg/d) or an active placebo (benztropine mesylate).
Outcomes	Primary outcomes - average pain intensity scores Secondary outcomes - disability, satisfaction with life, handicap
Results	No significant effect on pain scores between the two groups
Conclusions	The authors did not support the use of amitriptyline in the treatment of post amputation pain

Bone et al

Methods	Randomized, double-blind, placebo-controlled, cross-over study
Participants	Nineteen patient with phantom limb pain
Interventions	Six-week trial treatment of both placebo and gabapentin titrated in increments of 300 mg to 2400 mg or the maximum tolerated dose. One week washout period between therapies
Outcomes	Primary outcome - visual analogue scale (VAS) pain intensity difference (PID) compared with baseline at the end of each

	treatment. Secondary outcome - indices of sleep interference, depression (Hospital Anxiety and Depression [HAD] scale), and activities of daily living (Bartel Index)
Results	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 =.03). No significant differences between placebo and gabapentin therapy in terms of the number of tablets of rescue medication required, sleep interference, HAD scale, or Bartel Index
Conclusions	After 6 weeks, gabapentin monotherapy was better than placebo in relieving post amputation phantom limb pain

Smith et al

Methods	Randomized, double-blind crossover trial
Participants	Twenty-four adults with phantom limb pain (PLP) and/or residual limb pain (RLP) with pain >3 on NRS
Interventions	Six-week trial treatment of both placebo and gabapentin titrated in increments of 300 mg to 2400 mg or the maximum tolerated dose. One week washout period between therapies
Outcomes	Primary - pain intensity Secondary - pain interference, depression, life satisfaction, and functioning
Results	No significant differences between gabapentin and placebo on measures of pain

	intensity
Conclusions	Gabapentin does not provided significant pain relief for patients with PLP

Nikolajsen et al

Methods	Randomized trial
Participants	Forty-six patients scheduled to undergo lower limb amputation were randomly assigned to receive oral gabapentin or placebo
Interventions	Treatment was started on the first postoperative day and continued for 30 days. The daily dose of gabapentin or placebo was gradually increased to 2,400 mg/day
Outcomes	Primary - intensity of stump and phantom pain. Five interviews were performed after 7, 14, and 30 days and after 3 and 6 months
Results	Risk of phantom pain (gabapentin vs. placebo) was 55.0% versus 52.6% (risk difference, 2.4%; 95% confidence interval, -28.9 to 33.7%; P = 0.88; 30 days) and 58.8% versus 50.0% (risk difference, 8.8%; 95% confidence interval, -23.3 to 40.9%; P = 0.59; 6 months). The median intensity of phantom pain (gabapentin vs. placebo) was 1.5 (range, 0-9.0) versus 1.2 (range, 0-6.6) (P = 0.60; 30 days) and 1.0 (range, 0-6.0) versus 0.5 (range, 0-5.0) (P = 0.77; 6 months). The median intensity of stump pain was 0.85

	(range, 0-8.2) versus 1.0 (range, 0-5.4) (P = 0.68; 30 days) and 0 (range, 0-8.0) versus 0 (range, 0-5.0) (P = 0.58; 6 months)
Conclusions	Gabapentin administered in the first 30 postoperative days after amputation does not reduce the incidence or intensity of post amputation pain.

Eichenberger et al

Methods	Randomized **,** double-blind, crossover
Participants	Twenty patients with chronic PLP
Interventions	4 i.v. infusions of: 200 IE calcitonin; ketamine 0.4 mg/kg (only 10 patients); 200 IE of calcitonin combined with ketamine 0.4 mg/kg; placebo, 0.9% saline
Outcomes	Primary - VAS for PLP intensity recorded before, during, at the end, and the 48 h after each infusion Pain thresholds after electrical, thermal, and pressure stimulation were recorded before and during each infusion.
Results	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 side 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.
Conclusions	Ketamine, but not calcitonin, affects central sensitization processes that are probably involved in the pathophysiology of phantom limb pain.

Jaeger et al

Methods	Randomized **,** double-blind, crossover
Participants	Twenty patients with chronic PLP who underwent major amputations and developed severe PLP 0-7 days after surgery
Interventions	For each patient a matched pair of infusions was prepared containing either 200 IU of s-CT or placebo. When PLP reached a level of more than 3 on a numeric analogue scale (NAS) the first infusion was administered
Outcomes	primary - NAS pain scores
Results	Using s-CT infusion, PLP was eased from a median of 7 to 4 on NAS in both groups (P less than 0.001) Placebo did not change pain scores (median 7 on NAS, P greater than 0.1)
Conclusions	s-CT is a valuable treatment for PLP in the early postoperative period

Nikolajsen, Hansen et al

Methods	Double-blind saline-controlled study
Participants	11 patients with established stump and phantom limb pain
Interventions	Ketamine (bolus at 0.1 mg/kg/5 min

	followed by an infusion of 7 micrograms/kg/min) was administered intravenously
Outcomes	Primary - visual analogue scale (VAS) and McGill Pain Questionnaire (MPQ)
Results	Ketamine increased pressure-pain thresholds significantly Wind-up like pain (pain evoked by repeatedly tapping the dysaesthetic skin area) was reduced significantly by ketamine no effect was seen on pain evoked by repeated thermal stimuli
Conclusions	NMDA receptor antagonists may have a potential in the treatment of stump and phantom limb pain.

Abraham et al

Methods	Double-blind crossover trial
Participants	3 cancer amputee patients
Interventions	Oral dextromethorphan (120-180 mg daily) was administered to three selected cancer patients during a 3-week period and an additional 1 month of treatment
Outcomes	Primary - pain intensity Secondary – mood, sedation levels
Results	All patients reported a >50% decrease in pain intensity, better mood, and lower sedation
Conclusions	Dextromethorphan reduces persistent phantom limb pain satisfactorily

Wiech et al

Methods	Placebo-controlled double-blinded crossover trial
Participants	8 patients with chronic PLP
Interventions	30 mg memantine
Outcomes	Primary - intensity of PLP was rated hourly by the patients on a visual analog scale during baseline and both treatment periods Secondary – functional organization of the primary somatosensory cortex (SI) was determined by neuromagnetic source imaging.
Results	No effect on the intensity of chronic PLP. No significant changes in the functional organization of SI observed
Conclusions	Memantine is ineffective in the treatment of chronic PLP and is also ineffective for the reduction of associated neural plasticity in the primary SI

Schley et al

Methods	Randomized, double-blind, controlled trial
Participants	9 patients with acute traumatic amputation of the upper extremity
Interventions	All patients received postoperative analgesia by continuous brachial plexus anesthesia (ropivacaine 0.375% 5ml/h) for at least 7 days. In addition, the patients received either memantine (20–30mg daily, *n*=10) or placebo (*n*=9) for 4 weeks.
Outcomes	Primary - Number of ropivacaine bolus injections required

	Secondary - PLP prevalence and intensity
Results	Memantine treatment reduced the number of requested ropivacaine bolus injections during the first week and resulted in a significant decrease of PLP prevalence and intensity at 4 weeks and 6 months follow up, but not at 12 months follow up.
Conclusions	Memantine can reduce intensity of phantom limb pain and might also prevent the development of PLP. However, despite the very early begin of treatment; no long-term effect on established PLP was evident.

Huse et al

Methods	Double-blind crossover design
Participants	12 patients with phantom limb pain after unilateral leg or arm amputation
Interventions	Two treatment phases of 4 weeks each were initiated with an intravenous test infusion of MST or Placebo. The titration phase was 2 weeks. The dose of MST was titrated to at least 70 mg/day and at highest 300 mg/day.
Outcomes	Primary - Pain intensity was assessed hourly on visual analogue scales during a 4-week treatment-free phase, both treatment phases and at two follow-ups (6 and 12 months). Secondary - Perception and pain thresholds

Results	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. Neuromagnetic source imaging of three patients showed initial evidence for reduced cortical reorganization under MST concurrent with the reduction in pain intensity
Conclusions	Opioids show efficacy in the treatment of phantom limb pain and may potentially influence also cortical reorganization

Wu et al

Methods	Randomized double-blind, active placebo-controlled, crossover trial
Participants	31 patients. Eleven subjects had both stump and phantom pains, 11 and 9 subjects had stump and phantom pain alone, respectively
Interventions	An intravenous bolus followed by an intravenous infusion of morphine (0.05 mg/kg bolus + 0.2 mg/kg infusion over 40 min), lidocaine (1 mg/kg bolus + 4 mg/kg infusion) and the active placebo, diphenhydramine (10 mg bolus + 40 mg infusion), were performed on three consecutive days.
Outcomes	Phantom and stump pain ratings and sedation scores were recorded at 5-min intervals using a 0-100 visual analog scale. Pain measures were initiated 30 min before drug infusion and continued until 30 min

	after the end of infusion. Subjects' self-reported pain relief and satisfaction were assessed at the end of each infusion.
Results	Compared with placebo, morphine reduced both stump and phantom pains significantly ($P < 0.01$). In 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 ($P < 0.01$), while 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).
Conclusions	Stump pain was diminished both by morphine and lidocaine, while phantom pain was diminished only by morphine, suggesting that the mechanisms and pharmacological sensitivity of stump and phantom pains are different