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Phantom limb pain: a review of pharmacological management

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Abstract

Introduction: Phantom limb pain (PLP) is a complex condition resulting in pain in the missing limb affecting 60–80% amputees. Increasing number of patients are undergoing amputations. Approximately 1 per every 1000 people in the United Kingdom is an amputee. Incidence of PLP can be as high as 80% following amputation. PLP can be severe and difficult to treat. A range of pharmacological interventions exist yet little is known about them in respect to PLP. This article will address the effectiveness of both single pharmacological, therapy as well as drug combination therapy.

Methods: We reviewed all literature looking at the evidence for the efficacy of both single and combined pharmacological therapy in the management of phantom limb pain. Not all commonly prescribed analgesic agents have been studied in the use of PLP and in these cases, the evidence of their efficacy in neuropathic pain was reviewed

Conclusion: It is difficult to draw definitive conclusions on the pharmacological management of PLP based on current available evidence. Most trials involved small cohorts and were not specific to the PLP. The trials which looked specifically at the PLP population gave conflicting results. Only the *N*-methyl-D-aspartate (NMDA) receptor antagonist class demonstrated consistent positive results. Most notably ketamine did produce a reduction in pressure pain thresholds and pain windup associated with PLP, although the numbers in these studies remain small. This benefit was not demonstrated across all NMDA receptor antagonists. Combination therapy has demonstrated effectiveness in previous studies for neuropathic pain but this has never been tested specifically against a PLP cohort. Therefore, combination treatment of agents with proven efficacy in PLP such as opioid and gabapentin deserves a closer examination in a controlled study against a placebo as well as single drug therapy

Keywords
Phantom Limb, chronic pain, pain, intractable, postoperative

Introduction

Phantom limb pain (PLP) is a complex condition resulting in pain in the missing limb. It affects 60–80% amputees'.[1] Increasing number of patients are undergoing amputations.[2] The prevalence rate for amputation within the United Kingdom is 26.3 per 100,000.[3] More than half are due to peripheral vascular disease (PVD) or diabeties.[2] The incidence related to PVD alone is estimated up to 50 per 100,000 and this number is forecast to increase be 50% over the next 15 years secondary to an ageing population.[4] PLP reduces quality of life[5] and has a big impact on society with only 43% patients returning to work following amputation.[6]

Post amputation phenomenon can consist of three elements:[5]

1. PLP: painful sensations referred to the absent limb

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2. Phantom limb sensation: any sensation in the absent limb, except pain;
3. Stump pain: pain localized in the stump.

Incidence of PLP can be as high as 80% following amputation.[7,8] This estimate has risen in recent times from the initial estimate of 2–4%. Risk factors include female sex,[9,10] pre-amputation pain[11] and depression.[1] Over recent years more has been understood of the changes that develop in the central and peripheral nervous system.

Initial transection of the peripheral nerves brings about an increased release of histamine, bradykinin and prostaglandins. Sensitivity of the nociceptors to these chemicals increases leading to an increased firing of afferent neurones. There is a concurrent alteration in the sodium channel membrane potential.[12] This lowered threshold potential further increases the rate of neurone impulse transmission.

Following transection of peripheral axons sprouting occurs of the ventral terminals of the large myelinated axons. This sprouting allows the sensory axons to terminate in lamina II instead of laminae III or IV. This means that the 'wrong connections' are made and sensory neurones responsible for touch might connect with the inter-neurones that normally receive input from nociceptors.[12] As a result, even light touch can cause a lot of discomfort.

The increased neuronal activity leads to a central sensitization or 'Wind-up phenomenon'.[13] The final factor is cortical reorganization. Once the limb has been amputated, the brain still has the old geography wired in. This leads to excessive activity in the neuromatrix due to lack of signals from the limb.[14] The neuromatrix theory of pain states that the perception of painful stimuli does not result from the brain's passive registration of tissue trauma, but from its active generation of subjective experiences through a network of neurones known as the neuromatrix.[15]

PLP can be severe and difficult to treat. A range of pharmacological interventions exist; yet little is known about them in respect to PLP. This article will address the effectiveness of both single pharmacological therapy and drug combination therapy.

Methods

The literature was sourced from Pubmed, Embase and Cochrane central register of controlled trials (CENTRAL) up to February 2017. Search for a wide range of classes' of medications was conducted against PLP.

Pharmacological agents searched included analgesics, anticonvulsants, antidepressants, NSAID, SSRIs, opioids, tramadol, *N*-methyl-D-aspartate (NMDA) receptor antagonists given either in single or combination. Primary interventions were not included. Levels of evidence used in this review are as follows:

- Level 1: meta-analysis or systemic reviews
- Level 2: one or more well-powered randomized controlled trials
- Level 3: retrospective studies. open-label trials, pilot studies
- Level 4: anecdotes, case reports, clinical experience and so on.

All studies contained human subjects only. The primary outcome measure was change in pain intensity pre and post treatment on any recognized scale. Secondary outcomes included withdrawals from studies, side effect profile, patient satisfaction, function, mood, sleep, and quality of life.

Single pharmacological therapy

Tricyclic antidepressant

The most commonly used medications for the treatment of PLP are tricyclic antidepressant (TCA). Their analgesic effect may be related to the SSRI (selective serotonin–norepinephrine uptake inhibition).[16]

Robinson et al.[17] examined the effect of the TCA amitriptyline in a randomized controlled study. The effect of amitriptyline versus an active placebo was measured over a 6 week period in a total of 39 participants. All participants had amputation-related pain. The primary outcome measure was patient-reported average pain intensity. Amitriptyline was started at 10 mg per day and increased to a maximum of 125 mg per day. There was no difference between the two groups. As a result the conclusions did not support the use of amitriptyline in the treatment of post amputation pain.

The use of TCA's in PLP is not supported by the evidence to date. Certainly, the level of side effects experienced by patients on this medication during the Robinson et al.[17] study remained high and must be considered in its use.

Serotonin–norepinephrine reuptake inhibitor

Venlafaxine is an SNRI (serotonin–norepinephrine reuptake inhibitor). It is important to note that venlafaxine is not recommended to date under the NICE or the Scottish SIGN guidelines as an option for neuropathic pain in non-specialist settings. The reuptake effects are dose dependent. At low doses (< 150 mg/day), it acts only on serotonergic transmission. At moderate doses (> 150 mg/day), it acts on serotonergic and

noradrenergic systems, whereas at high doses (> 300 mg/day), it also affects dopaminergic neurotransmission.[18]

No studies measuring the effectiveness any SNRI's in relation to PLP could be found. It is worth noting a large multicentre, double-blind, randomized, placebo-controlled study examining the use of venlafaxine in painful diabetic neuropathy found a low side effect profile.[19] This was not the case with duloxetine where most duloxetine users in the trial demonstrated at least one side effect.[20]

Anticonvulsants

Gabapentin is an anticonvulsant commonly used to treat pain since the 1960s. The action of gabapentin is complex and may inhibit the release of excitatory neurotransmitters and reduce glutamate availability at NMDA and non-NMDA receptors.[21] However, its main action in respect to neuropathic pain is believed to be via the binding to the α-2-delta subunit of voltage-dependant calcium channels. This leads to reduction of the influx of calcium into neurones.[22]

A randomized, double-blind, placebo-controlled, crossover study examined the effect of gabapentin alone in PLP. Nineteen patients were randomized. The primary outcome measure was visual analogue scale (VAS) pain intensity difference (PID) compared with baseline at the end of each treatment. Daily doses of up to 2400 mg were used. PID was significantly greater in the gabapentin group (3.2 ± 2.1 vs 1.6 ± 0.7, $P = .03$), with no effect on activities of daily living. The authors concluded after 6 weeks that gabapentin monotherapy was better than placebo in relieving post amputation PLP.[23]

Smith et al. examined 24 patients in a double-blind crossover trial. Inclusion criteria consisted of lower limb amputation more than 6 months prior and an average pain of at least 3 on a 0–10 numerical rating scale (NRS). The primary outcome measure was NRS. The effect of gabapentin up to a higher maximum dose of 3600 mg was compared against placebo over a 5-week period. More than half of the participants reported improved functioning, satisfaction and global improvement, although no discernible difference in the primary measure (NRS) between groups. This was compared to about one-fifth who reported a meaningful decrease in pain during the placebo phase.[24]

The above gabapentin studies involved only small numbers of subjects. It is therefore difficult to draw any meaningful conclusions regarding the specific clinical effectiveness of the drug in PLP.

Nikolajsen et al. also examined the effects of early gabapentin post amputation against placebo. Forty-one patients were included and treatment was started on the first postoperative day and continued for 30 days. A maximum dose of gabapentin 2400 mg was used. The authors concluded that there was no reduction in incidence or intensity of post amputation pain between the two groups.[25]

Topiramate is a gamma-aminobutyric acid (GABA) agonist, sodium channel blocker and kainate antagonist. A pilot prospective, double-blind, randomized, placebo-controlled study examined the effect of topiramate on four PLP patients. A statistically significant reduction of 70–80% VAS was observed between daily doses of 25–800 mg.[26] Although well tolerated, side effects including acute myopia have been reported in the first 4 weeks of topiramate treatment.[27] It is hard to draw any conclusion however from such a small cohort of patients, although the drug potentially warrants a more definitive study. The use of pregabalin in PLP has not been examined to date.

Calcitonin

The outcomes of calcitonin therapy in PLP have produced mixed results. The use of calcitonin (200 IE) was examined in chronic PLP against and in combination with ketamine (0.4 mg/kg) infusion in a 20 participant randomized, double-blind trial. Intensity of phantom pain (VAS) was recorded before, during, at the end and 48 h after each infusion. Ketamine, but not calcitonin, reduced PLP. The authors concluded that ketamine but not calcitonin affects central sensitization occurring in PLP.[28]

A double-blind crossover comparison of Calcitonin 200 IU infusion against a placebo recruited 21 patients who had undergone major amputations and developed severe PLP up to 7 days postoperatively. Calcitonin infusion reduced pain levels on a numeric analogue scale (NAS) from a median of 7 to 4. Placebo had no effect of pain scores. There was evidence of some longer lasting effects. One week after 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 years PLP exceeded 3 on VAS in 5 individuals (42%), and the remaining 12 patients presented the same PLP as after 1 year. The authors therefore concluded that calcitonin is effective for the prophylaxis of PLP in the early postoperative period.[29]

NMDA receptor antagonists

Hyperactivity of NMDA receptors may be one of the factors in the maintenance of persistent stump and PLP.[30] Nikolajsen et al. examined the effect of ketamine on PLP. They infused ketamine (bolus at 0.1 mg/

kg/5 min followed by an infusion of 7 μg/kg/min) administered to 11 patients with established PLP. Ketamine resulted in a reduction in pain in all 11 patients (VAS and McGill Pain Questionnaire). Ketamine increased pressure pain thresholds significantly. Wind-up like pain was also reduced. The authors therefore concluded that NMDA receptor antagonists might be effective in stump and PLP.[30] This was further re-enforced by Eichenberger et al.[28] as described above that ketamine potentially affects central sensitization occurring in PLP.

This would warrant further study with a larger cohort to ascertain the effect of ketamine in PLP. Ketamine has a substantial side effect profile. This has been known since 1960s when it was introduced in Anaesthesia practice. Side effects include cystitis, hallucinations and cardiovascular effects.

Dextromethorphan has been shown to alleviate pain in both human and animal models. A pilot double-blind crossover trial of three patients with cancer amputation pain showed oral dextromethorphan 120–270 mg daily effectively reduced PLP. Pain recurred in one patient a month after stopping treatment.[32] Again an adequately powered clinical trial is required to explore this further since the drug possibly offers a less severe side effect profile in comparison to ketamine.

Wiech et al.[33] conducted a placebo-controlled randomized crossover trial of Memantine (30 mg daily) in eight PLP patients. The drug had no effect on chronic PLP. This was further demonstrated by a randomized, double-blind controlled trial with 19 patients undertaken by Schley et al. Memantine (20–30 mg daily) was used against placebo and demonstrated a reduction in PLP intensity at 1 month, 6 months but not at 12 months. As a result, the authors concluded that no long-term effect on established PLP was evident.[34]

Opioids

Randomized control trials have demonstrated a benefit of opioids in PLP. It is hypothesized that they may also reduce cortical reorganization.[35].

Huse et al. examined the efficacy of morphine sulphate orally (MST) against placebo in a double-blinded crossover design in 12 patients with PLP. A dose of 70–300 mg/day showed a short-term clinically relevant response to MST (pain reduction of more than 50% on VAS) was evident in 42%, a partial response (pain reduction of 25–50%) in 8% of the patients. Interestingly, neuromagnetic source imaging of three patients showed evidence for reduced cortical reorganization with MST. The authors therefore concluded that opioids show promise in reducing PLP and potentially influence cortical reorganization.[31] It must be noted opioid-induced hyperalgesia is a risk at higher doses. Furthermore, the recommendation from Public Health England states any dose above 120 mg/day oral morphine equivalent risk of harm increases substantially with no increased benefit.[36]

Wu et al. measured the effects of intravenous lignocaine and morphine administered to post amputation stump and PLP patients (31) over three consecutive days. They infused 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). Compared with the placebo, morphine reduced both stump and phantom pains significantly ($P < 0.01$). In comparison lidocaine decreased stump ($P < 0.01$), but not phantom pain. Stump pain was reduced both by morphine and lidocaine, while phantom pain was reduced only by morphine. The conclusion enhanced the theory that stump pain and PLP have a different underlying pathophysiology. This was however only a short-term study with pain scores only measured 30 minutes post infusion.[37]

A double-blind, randomized, placebo-controlled, crossover study in adult patients with post amputation pain of 6 months or longer and greater than 3 on a 0–10 numeric pain rating scale was conducted by Wu et al. They examined three treatment periods (morphine, mexiletine or placebo) included a 1-week drug-free interval followed by 4-week titration, 2-week maintenance and 2-week drug-taper phases. The primary outcome measure was change in average pain intensity from the drug-free baseline to the last week of maintenance. Morphine, but not mexiletine, resulted in a decrease in intensity of post amputation pain but were associated with a higher rate of side effects and no improvement in self-reported levels of overall functional activity and pain-related interference in daily activities.[38]

Long-term safety remains an issue with chronic opioid usage. The debate on the long-term opioid usage in chronic pain is out of the scope of this article.

Conclusion

It is difficult to draw definitive confusions on the pharmacological management of PLP based on current available evidence. Most trials involved small cohorts and gave conflicting results. Mixed results arguably reinforces our understanding that the management of PLP is complex and the answers do not lie in pharmacology alone.

Only the NMDA receptor antagonist class demonstrated consistent positive results. Most notably ketamine did produce a reduction in pressure pain thresholds and pain windup associated with PLP,

although the numbers in these studies remain small. Timing may be important with this class of agents. Memantine given early postoperatively following amputation has resulted in a decreased PLP, although this effect was not maintained long term.[37] The well recorded side effects of long-term ketamine including the potential for ketamine cystitis may be an obstacle to long-term use.[39]

When considering where future studies for the effectiveness of pharmacological agents in PLP should lie, evidence can be drawn from other neuropathic pain conditions. TCAs such as amitriptyline have in the past been a mainstay in the treatment of neuropathic pain.[40] However, alternative agents such as Venlafaxine are potentially demonstrating the same efficacy need to be investigated further.[18] They may offer a solution to PLP with the advantage of a lower side effect profile.[19] SSRI and SNRI agents such as Duloxetine have been shown to be effective in the treatment of diabetic neuropathy pain and may have a place in the management of PLP.[20]

Pregabalin has proven effectiveness in various causes of neuropathies.[41] Its efficacy in PLP remains unknown. There has been increasing use of this drug over the last few years and therefore increasing understanding of its side effect profile with regard to a potential trial.

Combination therapy was shown to be effective in previous studies for neuropathic pain.[42–44] Therefore, combination treatment such as opioid and gabapentin for PLP deserves a closer examination in a controlled study against a placebo as well as single drug therapy.

Conflict of interest

The authors declare that there is no conflict of interest.

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