PHANTOM LIMB PAIN: REVIEW OF LITERATURE

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ABSTRACT

Phantom limb pain is described as abnormal sensation (painful or non painful) from an amputated limb. Phantom limb pain is a very common condition in patients undergoing amputation regardless of the cause of amputation. The condition can be very disabling and therefore should be differentiated from non-painful phantom sensation, residual limb pain and stump pain secondary to bony overgrowths. There is overwhelming evidence regarding central nervous system changes in phantom limb pain, however the role of peripheral mechanisms and psychological factors are as important in the pathogenesis of phantom limb pain. The treatment of phantom limb pain is difficult and challenging. The evidence for the use of pharmacological approaches fro phantom limb pain is weak and non-pharmacological approaches do not work for most of the patients. Prolonged phantom limb pain interferes with the ongoing rehabilitation and prosthetic fitting leading to poor functional outcome. The prognosis of phantom pain varies and in some cases spontaneous resolution can occur following few years.

KEY WORDS: Phantom, Limb, Pain.

INTRODUCTION

Phantom limb pain can be defined as pain or discomfort felt by an amputee in the area of the missing limb[1]. Approximately 60 to 80% of individuals with an amputation will experience phantom sensations in their amputated limb, and the majority of the sensations are painful[1]. A low incidence of 2% has been reported in earliest literature[2]. Phantom limb pain is more common in upper limb amputee as compared to lower limb amputee[3] and in females than males[4]. It is less common in young children and congenital limb deficiency [2]. Wilkins et al[5] compared the incidence of phantom limb pain in children with congenital deficiency of the limb and the traumatic amputee. The incidence in congenital limb deficiency was 3.7% when compared to the traumatic group (48.5%). There is no relationship between the age in adults, gender, side or level of amputation, general health status and the phantom limb pain.[2,6-8] This review article discusses the nature, characteristics, mechanisms and treatment options available for phantom limb pain.

Research strategy and selection criteria

The published articles for the review of phantom limb pain were identified from Medline and Science direct databases. The search was carried between April 2012 and May 2012. The search terms used were phantom limb pain, management, treatment and mechanism. Additional references were obtained from books relevant to phantom limb pain and from the references of the selected articles. Articles published in English, French, Italian, or German was included. The abstracts and reports from scientific meetings were not included in the review.

Nature and Characteristics of Phantom Limb Pain

Phantom limb pain usually develops very early following the amputation. The literature suggests that 75% of patients develop phantom limb pain within the first week of their amputation.[8,9] However phantom limb pain has also been reported to occur months or years following the amputation.[10] Phantom limb pain is usually intermittent. The frequency and intensity of the pain is variable and generally tends to decrease with time. Nikolajsen et al[8] questioned 56 patients who underwent amputation of the lower limb at 1 week, 3 months and 6 months. They found that although the incidence and intensity of the pain remained constant but the frequency and duration of the pain attacks decreased significantly. Wartan and colleagues[11] surveyed 526 British veterans with longstanding amputations and reported that phantom pain disappeared in 16%, decreased markedly in 37%, remained similar in 44% and increased in 3% of the respondents.

The amputees describe phantom pain as stabbing, boring, shooting, squeezing, throbbing or burning in nature. It is usually intermittent and very occasionally constant. The phantom pain attacks can range from few times per day to few per week[12]. The location of the phantom limb pain is usually in the distal parts of the amputated limb. Hence upper limb amputee pain is experienced in fingers and palms and for lower limb amputee painful areas are toes, top of the foot and ankle.[8,13]

Risk Factors for Phantom Limb Pain

There is a strong relationship between preamputation pain and phantom limb

pain, which has been identified as a risk factor for phantom limb pain.[12,14,15] Stress, anxiety, depression, and other emotional triggers contribute to the persistence or exacerbation of phantom limb pain. The results of a national survey in 2005 showed that amputees with depressive symptoms were more likely to characterize their pain as more severe than those without depressive symptoms[16]. The risk factors for the development of phantom limb pain following an amputation are female sex, upper extremity amputation, and presence of pre-amputation pain, anxiety, depression and stress[17].

Etiology and Mechanisms of Phantom Limb Pain

Different theories have been proposed for phantom limb pain over the years. Initially it was thought to be a psychiatric illness[17]. Later the dominant theory for the cause of phantom limb pain was severed nerve endings and formation of neuroma. With the accumulation of research in recent years, phantom limb pain is thought to develop due to the changes in the both peripheral and central nervous system. However, none of these theories tends to explain the phenomenon of phantom limb pain very clearly and multiple mechanisms are likely responsible[17].

a. **Peripheral mechanisms:** Phantom pain is significantly more prevalent in those amputees who have long-term stump pain than without any stump pain[13]. During the amputation operation various peripheral nerves are cut, resulting in massive tissue and neuronal injury. The severed nerve endings then sprout to form neuromas. There is increased accumulation of sodium channels in these neuromas that causes increased excitability and spontaneous discharge (abnormal peripheral activity). This abnormal peripheral activity secondary to upregulation of sodium channel causes stump and phantom pain[18]. The fact that sodium channel blocking agents help to reduce the phantom limb pain, provide addation evidence to support this theory[19,20]. The cells in the dorsal root ganglion also undergo changes following injury to the nerves resulting in upregulation of the sodium channel. The upregulated sodium channels in the dorsal root ganglion cells have increased sensitivity to mechanical and neurochemical stimulation causing stump and phantom limb pain[21].

b. **Role of sympathetic nervous system in phantom pain:** The role of sympathetic nervous system has been studied in animal models whereby application of norepinephrine or activation of the post-ganglionic sympathetic fibers excites and sensitizes damaged but not normal nerve fibers[22]. Sympatholytic blocks have been shown to abolish phantom limb pain and injection of norepinephrine into the skin causes the phantom pain to return[23]. Similarly injection of norepinephrine around the stump neuroma is painful even long after an amputation[24].

c. **Changes at the Level of Spinal Cord:** Abnormal connections are established between the proximal section of the amputated peripheral nerve and the neurons in the spinal cord. Some of the neurons in the spinal cord that are not involved in pain transmission also sprout into the lamina II (area involved in transmission of the nociceptive afferent input) [18]. This abnormal sprouting causes increased neuronal activity, expansion of the neuronal receptive field and hyperexcitability within the spinal cord, a process called central sensitization. At the same neurotransmitters like substance P, tachykinins and neurokinins mediate increased activity at the NMDA receptors[25]. All these changes at the spinal cord level causes upregulation of the receptors at the spinal cord level and this phenomenon is called "windup phenomenon"[25]. Changes in the descending inhibitory pathways are also observed in phantom limb pain where the target neurons for these inhibitory pathways may be lost resulting in the nociceptive inputs reaching the supra spinal centers without any spinal cord inhibition.

d. **Changes at the Level of Brain (Cortical Reorganization and Body Schema):** The reorganization of the motor and sensory cortex can help to explain the painful sensations in the phantom limb pain. This phenomenon has been studied extensively in both animals and human models following amputation and deafferentation. The process of cortical reorganization means that the areas of the brain representing the amputated limb are taken over by the neighboring zones in both the primary motor and sensory cortex[18,26,27]. The extent of cortical reorganization is directly related to the degree of pain. Several imaging studies have correlated that greater extent of somatosensory cortex involvement is associated with more intense phantom limb experience[28-30].

Head and Holmes, almost a century ago, first proposed the concept of "body schema". According to this concept the entire body is represented onto the brain as template and any changes in the body such as amputation result in the perception of phantom limb pain[31]. A further expansion of the body schema concept is the "neuromatrix and neurosignature" hypothesis proposed by Ronald Melzack in 1989. The neuromatrix is the just a network of neurons within the brain that integrates numerous inputs from various areas including somatosensory, limbic, visual, and thalamocortical components. It then

results in an output pattern that evokes pain or other meaningful experiences. The term "neurosignature" refer to the patterns of activity generated within the brain that are continuously being updated based upon one's conscious awareness and perception of the body and self. The deprivation of various inputs from the limbs to the neuromatrix causes an abnormal neurosignature to be produced that results in the generation phantom limb pain[32-34].

e. **Psychogenic Mechanism:** The literature does not support the concept that phantom limb pain is psychogenic in nature despite the fact that stress, exhaustion and depression tends to aggravate the phantom limb pain[35]. A recent cross-sectional study found that amputation in people with personality traits characterized by passive coping styles and catastrophizing behavior was associated with the development of phantom limb pain independent of anxiety and depression[36]. Most research on the relationship between psychological symptoms and phantom limb pain has been retrospective and cross sectional rather than longitudinal and thus limited inferences can be derived from them.

Management of Phantom Limb Pain

There are no agreed specific treatment guidelines for phantom limb pain. The aim is self-management of the pain and rehabilitation of the patient with multidisciplinary involvement. This can be done through pharmacological and no-pharmacological approaches.

1. **Pharmacological Approaches:** Various medications have been used to treat phantom limb pain with varying results.

   a. **Preemptive use of analgesics and anesthetics** during the preoperative period is believed to prevent the noxious stimulus from the amputated site from triggering changes and central neural sensitization. This in turn may prevent the amplification of future impulses from the amputation site[37]. Karanikolas et al[19] in a prospective randomized clinical trial in 2011 showed a decrease in phantom limb pain at six months following amputation when optimized epidural analgesia or intravenous patient controlled analgesia was started between 48 hours preoperatively and 48 hours postoperatively. Similarly prolonged postoperative perineural infusion of ropivacaine 0.5% has been reported to prevent or reduce phantom limb pain after lower extremity amputation[20]. Ketamine, on the other hand was not found to significantly reduce acute central sensitization or the incidence and severity of postamputation pain[38].

   b. **Non-steroidal Anti-Inflammatory Drugs (NSAIDs)** in a cross sectional study was found to be the most common medications used in the treatment of phantom limb pain[39]. The analgesic mechanism of NSAIDs is inhibition of the enzymes needed for the synthesis of prostaglandin and decreasing the nociception peripherally and centrally.

   c. **Tricyclic antidepressants (TCA)** are among the most commonly used medications for various neuropathic pains including phantom limb pain. Although the TCAs are very effective in treating neuropathic pain but their role in treating phantom limb pain is not very well established. The analgesic action of tricyclic antidepressant is mainly due to the inhibition of serotonin- norepinephrine uptake blockade, NMDA receptor antagonism, and sodium channel blockade[40]. A recent study reported excellent phantom limb pain control with an average dose of 55mg of amitriptyline[41], but there are others in which tricyclic antidepressants had no effect on phantom limb pain control[42]. Nortriptyline, imipramine and desipramine are equally effective in treating phantom limb pain when compared with amitriptyline with fewer side effects[43].

   d. **Serotonin Norepinephrine reuptake inhibitors (SNRI)** like duloxetine is very effective in peripheral diabetic neuropathy. There is no strong evidence in the literature to suggest its effectiveness in phantom limb pain and further research is need in this field. There are case reports demonstrating good effect of duloxetine in the treatment of phantom limb pain[44]. A small case series also demonstrated the effectiveness of mirtazapine, an alpha 2-receptor antagonist with fewer side effects than tricyclic antidepressants in the treatment of phantom limb pain[45].

   e. **Anticonvulsants** like antidepressants have shown mixed results in phantom limb pain. Gabapentin is the agent with most convincing evidence in phantom limb pain but again with mixed results[46-48]. Carbamazepine, a non-specific sodium channel blocker, has been reported to reduce the brief stabbing and lancinating pain associated with phantom sensations[17]. Oxcarbazepine, pregabalin and Lamotrigine all may have a role in the treatment of phantom limb pain, but further studies are required[17, 49].

f. **Opioids** use in phantom limp pain is controversial and their use is limited due to the side effects and potential for abuse. Opioids bind to the peripheral and central opioid receptors and provide analgesia. They may also diminish cortical reorganization and disrupt one of the proposed mechanisms of phantom limb pain[50]. Randomized controlled trials have demonstrated the effectiveness of opioids (oxycodone, methadone, morphine, and levorphanol) for the treatment of neuropathic pain including phantom limb pain[17]. Comparative trials have also shown benefit with opioids when compared with tricyclic antidepressants and gabapentin though the opioids were associated with more frequent side effects[51]. The total amount of opioid required to achieve analgesia may be less when used together with other agents, such as tricyclic antidepressants or anticonvulsants, which also have use in neuropathic pain modulation[17]. Tramadol is an analgesic with both with monoaminergic and opioid activity and can be used as an alternative to strong opioids as tolerance and dependence with tramadol long-term use are uncommon[2].

g. **Other medications** that have been used in phantom limb pain with varying results are calcitonin[52], NMDA receptor antagonist (memantine)[53], beta blockers (propranolol)[49], and calcium channel blockers (nifedipine)[49]. The mechanism of action of these medications in phantom limb pain is unclear and further studies are required to show their effectiveness.

2. **Nonpharmacological Approaches:** The combination of pharmacological and nonpharmacological approaches together can help to manage the phantom limb pain.

a. **Transcutaneous Electrical Nerve Stimulation (TENS)** has been traditionally used in the management of phantom limb pain. It is portable, easy to use, cheap and without any side effects. There have been various studies showing the effectiveness of TENS in the phantom limb pain[54].

b. **Mirror therapy** was first introduced by Ramachandran[55] in 1996, and help to resolve the visual-proprioceptive dissociation in the brain[56]. Although the use of mirror therapy has been shown to be effective in some cases there is still no widely accepted theory of how it works. In a 2010 study of phantom limb pain, Martin Diers[57] and his colleagues in a randomized, controlled trial that used graded motor imagery and mirror training, found that patients with phantom limb pain showed a decrease in pain as well as an improvement in function post-treatment and at the 6-month follow-up. However, they also showed that mirrored imagery produced no significant cortical activity in patients with phantom limb pain and concluded that the optimal method to alter pain and brain representation, and the brain mechanisms underlying the effects of mirror training or motor imagery, are still unclear.

c. **Other nonpharmacological approaches** with some beneficial effects in the management of phantom limb pain include biofeedback[58], guided imagery[28], relaxation techniques[59] and hypnosis[60]. There are case reports of the beneficial effect of acupuncture for phantom limb pain[61] and case series on the effectiveness of cognitive behaviour therapy[62].

3. **Surgical interventions** are usually used when other treatment methods have failed. Stump revision is offered only when the cause of phantom limb pain is secondary to stump or wound problems. If a neuroma is diagnosed clinically and confirmed on the scan then neurectomy is the treatment of choice. There is no role of sympathectomy, cordotomy and local nerve blocks in the treatment of phantom limb pain. A case report showed that, for selected patients, who have not obtained adequate relief with medical management, spinal cord stimulation was found to be effective[63]. Case reports of improvement of phantom limb pain with deep brain stimulation of the periventricular gray matter and thalamic nuclei have been published[64]. Motor cortex stimulation was also found to be helpful in a case of phantom limb pain[65]. A case report of electroconvulsive therapy (ECT) showed positive outcome even though the mechanism and role of ECT in phantom limb pain is unclear[66].

CONCLUSION

Phantom limb pain is relatively common condition and causes marked functional and psychological disability. These are no agreed pathophysiological mechanism for the condition. Specific treatments are still evolving and majority of the treatments are based on the treatment recommendations for chronic neuropathic pain. Multi-treatment approach, tailored to the individual needs of the patient, has the best chance of improving the symptoms of phantom limb pain and the functional outcome. Moreover pre-amputation consultation with a specialist in pain or rehabilitation medicine with regular follow-up in the post-amputation period can have positive impact of functional outcomes.

REFERENCES

1. Sherman RA, Sherman CJ, Parker L. Chronic phantom and stump pain among American veterans: Results of a survey. Pain 1984; 18: 83-95.
2. Nikolajsen L, Jensen, TS. Phantom Limb Pain. Br J Anaesth 2001; 87(1): 107-16.
3. Davidson JH, Khor KE, Jones LE. A cross-sectional study of post-amputation pain in upper and lower limb amputees, experience of a tertiary referral amputee clinic. Disability and Rehabilitation 2010; 32 (22): 1855-86.
4. Hirsh AT, Dillworth TM, Ehde DM, Jensen MP. Sex differences in pain and psychological functioning in persons with limb loss. J Pain 2010; 11(1): 79- 86.
5. Wilkins KL, McGrath PJ, Finley GA, Katz J. Phantom limb sensations and phantom limb pain in child and adolescent amputees. Pain 1998; 78: 7-12.
6. Kooijman CM, Dijkstra PU, Geertzen JHB, Elizinga A. Sxhans CP. Phantom pain and phantom sensations in upper limb amputees: An epidemiological study. Pain 2000; 87: 33-41.
7. Montoya P, Larbig W, Grulke N, Flor H, Taub E, Birbaumer N. The relationship of phantom limb pain to other phantom limb phenomena in upper extremity amputees. Pain 1997; 72: 87-93.
8. Nikolajsen L, Ilkjaer S, Krøner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. Pain 1997; 72: 393-405.
9. Krane EJ, Heller LB. The prevalence of phantom sensation and pain in pediatric amputees. J Pain Sympt Manage 1995; 10: 21-29.
10. Rajbhandari SM, Jarett JA, Griffiths PD, Ward JD. Diabetic neuropathic pain in a leg amputated 44 years previously. Pain 1999; 83: 627-629.
11. Wartan SW, Hamann W, Wedley JR, McColl I. Phantom pain and sensations among British veteran amputees. Br J Anaesth 1997; 78: 652-9.
12. Katz J, Melzack R. Pain 'memories' in phantom limbs: review and clinical observations. Pain 1990;43:319-36.
13. Jensen TS, Kerbs B, Nielsen J, Rasmussen P. Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation pain. Pain 1985; 21: 267-278.
14. Houghton AD, Nicholls G, Houghton AL, Saadah E, McColl L. Phantom Pain: natural history and association with rehabilitation. Ann R Coll Surg Engl 1994; 76: 22-25.
15. Hanley MA, Jensen PM, Smith DG, Ehde DM, Edwards WT, Robinson LR. Preamputation pain and acute pain predict chronic pain after lower extremity amputation. J Pain 2007; 8(2): 102-109.
16. Ephraim PL, Wegener ST, MacKenzie EJ, Dillingham TR, Pezzin LE. Phantom pain, residual limb pain, and back pain in amputees: Results of a national survey. Archives Physical Med Rehab 2005; 86(10): 1910-19.
17. Subedi B, Grossberg GT. Phantom Limb Pain: Mechanism and Treatment Approaches. Pain Res Treat; 2011: Article ID 864605, doi:10.1155/2011/864605.
18. Flor H, Nikolajsen L, Jensen TS. Phantom limb pain: a case of maladaptive CNS plasticity? Nature Reviews Neuroscience 2006; 7(11): 873-881.
19. Karanikolas M, Aretha D, Tsolakis I, Monantera G, Kiekkas P, Papadoulas S, et al. Optimized perioperative analgesia reduces chronic phantom limb pain intensity, prevalence, and frequency: a prospective, randomized, clinical trial," Anesthesiology 2011; 114(5): 1144-54.
20. Borghi B, D'Addabbo M, White PF, Gallerani P, Toccaceli L, Raffaeli W, et al. The use of prolonged peripheral neural blockade after lower extremity amputation: the effect on symptoms associated with phantom limb syndrome. Anesthes Analges 2010; 111(5): 1308-15.
21. Kajander KC, Wakisaka S, Bennett GJ. Spontaneous discharge originates in the dorsal root ganglion at the onset of a painful peripheral neuropathy in the rat. Neurosci Latt 1992; 138: 225-8.
22. Devor M, Hainf W, Michaelis M. Modulation of activity in dorsal root ganglion neurons by sympathetic activation in nerve-injured rats. J Neurophysiol 1994; 7: 28-47.
23. Torebjork E, Wahren L, Wallin G, Koltzenburg M. Noradrenaline-evoked pain in neuralgia. Pain 1995; 49: 439-41.
24. Chabal C, Jacobson L, Russell L, Burchiel KL. Pain responses to perineuromal injection of normal saline, epinephrine and lidocaine in humans. Pain 1992; 49: 9-12.
25. Baron R. Mechanisms of disease: neuropathic pain — a clinical Perspective. Nature Clinical Practice Neurology 2006; 2(2): 95-106.
26. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. The Lancet Neurology 2010; 9(8): 807-19.
27. Ramachandran VS, Brang D, McGeoch PD. Dynamic reorganization of referred sensations by movements of phantom limbs. Neuro Report 2010; 21(10): 727-30.
28. MacIver K, Lloyd DM, Kelly S, Roberts N, Nurmikko T. Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. Brain 2008; 131 (8): 2181-91.
29. Spring J. Neural plasticity and the progress of phantom pain research mind matters. Wesleyan J Psychol 2010; 5:13-26.
30. Roux FE, Ibarrola D, Lazorthes Y, Berry I. Chronic motor cortex stimulation for phantom limb pain: a functional magnetic resonance imaging study: technical case report. Neurosurgery 2008; 62(6 Suppl 3): 978-85.
31. Head H, Holmes G. Sensory disturbances from cerebral lesions. The Lancet 1912; 179(4612): 144-52.
32. Giummarra MJ. Gibson SJ. Georgiou-Karistianis N, Bradshaw JL. Central mechanisms in phantom limb perception: the past, present and future. Brain Research Reviews 2007; 54(1): 219-32.
33. Melzack R. Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture. Presented at the Third World Congress of World Institute of Pain, Barcelona 2004," Pain Practice 2005: 5(2): 85-94.
34. Iannetti DG, Mouraux A. From the neuromatrix to the pain matrix (and back)," Experimental Brain Research 2010; 205(1): 1-12.
35. Berger H, Bacon DR Historical notes on amputation and phantom limb pain: "All Quiet on the Western Front? Gundersen Lutheran Med J 2009; 6(1): 26-9.
36. Richardson C, Glenn S, Horgan M, Nurmikko T. A prospective study of factors associated with the presence of phantom limb pain six months after major lower limb amputation in patients with peripheral vascular disease. J Pain 2007; 8(10): 793-801.
37. Reuben SS, Buvanendran A. Preventing the development of chronic pain after orthopaedic surgery with preventive multimodal analgesic techniques. J Bone Joint Surg 2007; 89(6): 1343-58.
38. Hayes C, Armstrong-Brown A, Burstal R. Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: A randomized, controlled trial. Anaesthes Intensive Care 2004; 32(3): 330-8.
39. Hanley MA, Ehde DM, Campbell KM, Osborn B, Smith DG. Self-reported treatments used for lower-limb phantom pain:

descriptive findings. Archives Physical Med Rehab 2006; 87 (2): 270-7.

40. Verdu B, Decosterd I, Buclin T, Stiefel F, Berney A. Antidepressants for the treatment of chronic pain. Drugs 2008; 68(18): 2611-32.

41. Wilder-Smith CH, Hill LT, Laurent S. Postamputation pain and sensory changes in treatment-naive patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo. Anesthesiol 2005; 103(3): 619-628.

42. Robinson LR, Czerniecki JM, Ehde DM, Edwards WT, Judish DA, Goldberg ML, et al. Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study, Archives Physical Med Rehab 2004; 85(1): 1-6.

43. Jefferies K. Treatment of neuropathic pain. Seminars in Neurology 2010; 30(4): 425-32.

44. Spiegel DR, Lappinen E, Gottlieb M. A presumed case of phantom limb pain treated successfully with duloxetine and pregabalin. General Hospital Psychiatry 2010; 322: 46.

45. Kuiken TA, Schechtman L, Harden RN. Phantom limb pain treatment with mirtazapine: a case series. Pain Practice 2005; 5(4): 356-60.

46. Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain. Cochrane Database of Systematic Reviews 2005;3. Article ID CD005452.

47. Smith DG, Ehde DM, M. Hanley A, Campbell KM, Jensen MP, Hoffman AJ, et al. Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. J Rehabil Res Dev 2005; 42(5): 645-654.

48. Nikolajsen L, Finnerup NB, Kramp S, A. Vimtrup S, Keller J, Jensen TS. A randomized study of the effects of gabapentin on postamputation pain. Anesthesiology 2006; 105(5): 1008-15.

49. Casale R, Alaa L, Mallick M, Ring H. Phantom limb related phenomena and their rehabilitation after lower limb amputation. Eur J Physical Rehab J 2009; 45(4): 559-566.

50. Weeks SR, Anderson-Barnes VC, Tsao JW. Phantom limb pain: theories and therapies. Neurologist 2010; 16(5): 277-86.

51. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med 2009; 122(10): S22-S23.

52. Eichenberger U, Neff F, Sveticic G, Björgo S, Petersen-Felix S, Arendt-Nielsen L, et al. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. Anesthes Analges 2008; 106(4): 1265-73.

53. Hackworth RJ, Tokarz KA, Fowler MI, Wallace SC, Stedje-Larsen ET. Profound pain reduction after induction of memantine treatment in two patients with severe phantom limb pain. Anesthes Analges 2008; 107(4): 1377-9.

54. Giuffrida O, Simpson L, Halligan PW. Contralateral stimulation, using tens, of phantom limb pain: two confirmatory cases. Pain Medicine 2010; 11(1): 133-41.

55. Ramachandran VS, Rogers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. Proceedings of the Royal Society B: Biological Sciences 1996; 263: 377-86.

56. Feinberg TE. Brain and self: bridging the Gap. Conscious Cogn 2011; 20(1): 2-3.

57. Diers, M, Christmann, C, Koeppe, C, Ruf, M, Flor, H. Mirrored, imagined, and executed movements differentially activate sensorimotor cortex in amputees with and without phantom limb pain. Pain 2010; 149(2): 296-304.

58. Harden RN, Houle TT, Green S, Remble TA, Weinland SR, Colio S, et al. Biofeedback in the treatment of phantom limb pain: a time-series analysis. Applied Psychophysiology Biofeedback 2005; 30(1): 83-9.

59. Ramachandran VS, Brang D, McGeoch PD. Size reduction using mirror visual feedback (MVF) reduces phantom pain. Neurocase 2009; 15(5): 357-60.

60. Cassileth BR, Keefe FJ. Integrative and behavioral approaches to the treatment of cancer-related neuropathic pain. Oncologist 2010; 15: 19-23.

61. Bradbrook D. Acupuncture treatment of phantom limb pain and phantom limb sensation in amputees. Acupuncture Med 2004; 22(2): 93-7.

62. Wetering EJVD, Lemmens KMM, Nieboer AP, Huijsman R. Cognitive and behavioral interventions for the management of chronic neuropathic pain in adults — a systematic review. Eur J Pain 2010; 14(7): 670-81.

63. Viswanathan A, Phan PC, Burton AW. Use of spinal cord stimulation in the treatment of phantom limb pain: case series and review of the literature. Pain Practice 2010; 10(5): 479-84.

64. Bittar RG, Otero S, Carter H, Aziz TZ. Deep brain stimulation for phantom limb pain. J Clin Neurosci 2005; 12(4): 399-404.

65. Fagundes-Pereyra JW, Teixeira MJ, Reyns N, Touzet G, Laureau E, Blond S. Motor cortex electric stimulation for the treatment of neuropathic pain," Arquivos deNeuropsiquiatria 2010; 68(6): 923-9.

66. Rasmussen KG, Rummans TA. Electroconvulsive therapy for phantom limb pain. Pain 2000; 85(1-2): 297-9.

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