Original Article

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Clinical Study and Management of Phantom Limb Pain

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Abstract

Phantom limb pain is defined as abnormal sensation from an amputated limb. 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. Phantom limb pain is a very common condition in patients with amputation. The phantom limb pain should be differentiated from non-painful phantom sensation, residual limb pain and stump pain secondary to bony overgrowths. The treatment of phantom limb pain is difficult. The evidence for the use of pharmacological approaches for 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. Multi treatment approach, tailored to the individual needs of the patients, has the best chance of improving the symptoms of phantom limb pain and functional outcome.

Keywords: Phantom Limb; Pain; Amputation.

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

a. Phantom limb pain: Painful sensations referred to the absent limb.
b. Phantom limb sensation : Any sensation in the absent limb, except pain.
c. Stump pain: Pain localized in the stump.

These elements often coexist in each patient and may be difficult to separate. A low incidence of 2% has been reported in earliest literature [1]. The occurrence of phantom pain seems to be independentof age in adults, gender and level, or side of amputation [37,45]. Phantom pain is less frequent in youngchildren and congenital amputees. The in-cidence 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 original article discusses the nature, char-acteristics, mechanisms and treatment options available for phantom limb pain.

Method and Selection Criteria

Forty patients presenting with PVD with ischemic limb, diabetic foot with spreading cellulitis, and gangrenous foot, were admitted in our Hospital.

Duration of Study - 6 Months

Period of Study - 1st June 2016 to 30th December 2016

The method of the study consisted of taking a good clinical history in achronological order as soon as the patient was operated. This study discusses

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incidence, the nature and characteristics of phantom limb pain, risk factors such as stress ,anxiety and depression associated with it. 40 patients studied over the period of 6 months at regular fallow up was done for every 1 week, 2 week, one month and 3 month.

Inclusion Criteria

All amputated patients regardless cause of amputation in our Hospital.

Exclusion Criteria

Children and Congenital deficiency of limbs.

Results

1. *Incidence:* the study showed that incidence phantom limb pain about 86%.however more recent studies report incidences of 60-80%. The occurrence of phantom limb pain seems to be independent of age in adults, gender and level or side of amputation [46,47] . It is also generally agreed that the incidence of pain is similar following civilian or military accidents [32,37].

2. *Nature and Characteristics of Phantom Limb*

1. Onset of pain: onset of pain is very early. In our study it is showed that among 40 patients 8 patients developed pain immediately after amputation, 22 patients developed in first week, 7 patients in 2nd week and 3 patients in 3rd week. 75% patients develop pain in first week itself. Several studied shows that 75% patients develops pain within the first few days after amputation.

At least three prospective studies have examined the duration phantom pain. Parkes found that 85%of 46 amputees had phantom pain immediately after amputation.

Continuous or intermittent: study shows 36 patients had intermittent pain and 4 patients had continuous pain. Some studies shows phantom pain is usually intermittent and few patient are in constant pain [46].

2. Frequency and intensity of pain: incidence and

Table 1:

Duration	No of Patients	Percentage%
Immediate	8	20%
1st week	22	55%
2nd week	7	17.5%
3rd week	03	7.5%

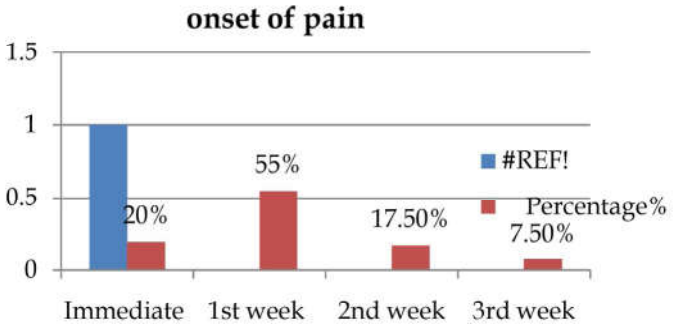

Fig. 1: Onset of pain

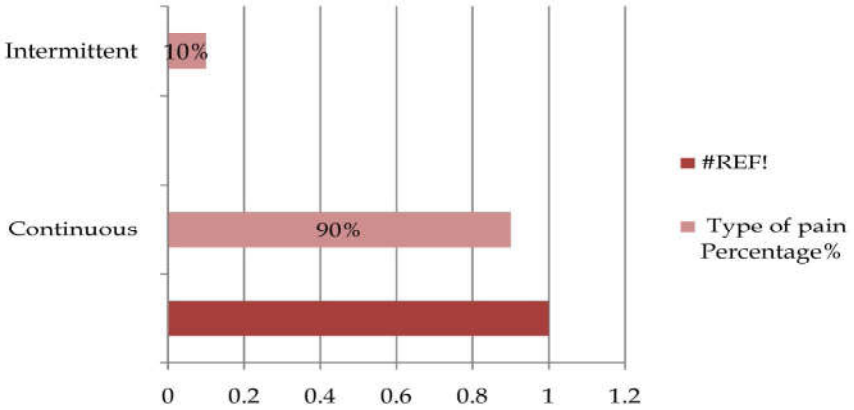

Fig. 2: Type of pain

Type of Pain	Total No Patients	Percentage%
Continuous	36	90%
Intermittent	4	10%

intensity of pain remained constant during follow up, both frequency and duration of pain attacks decreased significantly..

3. Type of pain: studied shows that 70% patients had shooting type of pain, 10% patient had stabbing type and 10% patients had squeezing or burning and boring type.
4. Location of phantom pain: location of phantom limb is usually distal part of amputated limb, toes instep, top of the foot, ankle [38].In our study it is shows that 30 patients had pain over foot, 6 patients had over the ankle joint and 4 patients shown over the foot.
5. Pain with duration of time: In our study it is

Table 2:

Character of Pain	No of Patients	Percentage %
Shooting	28	70%
Stabbing	4	10%
Squeezing or burning or boring	4	10%

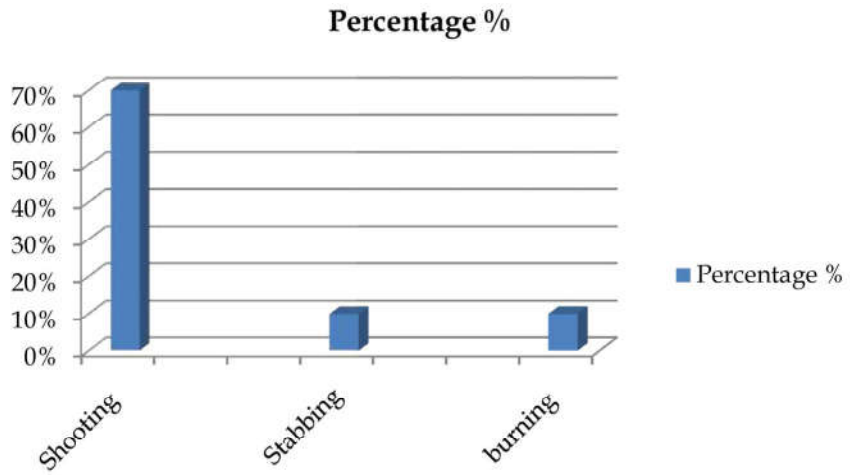

Fig. 2: Character of pain

Location of Pain	No of Patients	Percentages%
Over the foot	30	75
Over the ankle	6	15
Toes	4	10

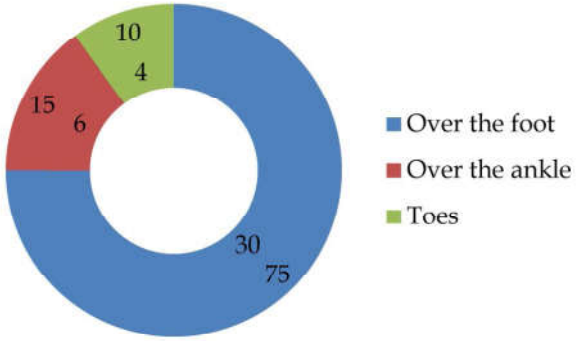

Fig. 4: Location of phantom pain

shown that 10 patients pain disappeared, decreased markedly in 12 patients, remain similar in 6 patients, increased in 2 patients. 59 Wartan and colleagues British vererans with longstanding amputations and reported that phantom limb disappeared in 16%, decreased markedly in 37%, remained similar in 44% and increased in 3% of the respondents.

Table 3:

Pain with Duration of Time	No of Patients	Percentage%
Disappeared	10	25
Decreased	12	30
Remain similar	6	15
Increased	2	5

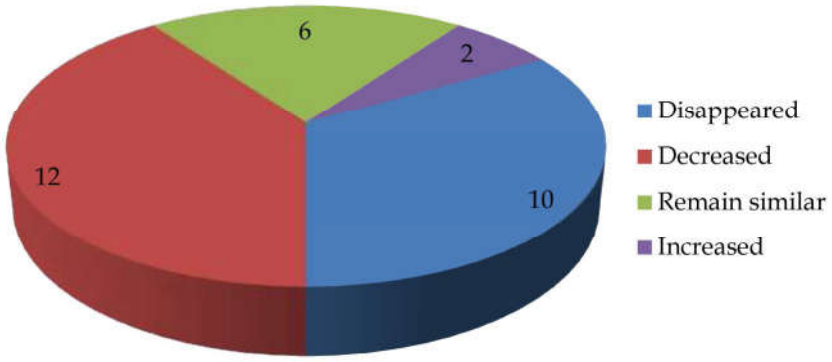

Fig. 3: Pain with duration of time

3. *Risk Factors Associated with Pain*

a. Relationship between pre amputation pain and phantom limb pain: in our study it is shown that der is significant association between preamputation pain and phantom limb pain

b. Factors that modulate the experience of phantom limb pain. Some patients with anxiety/ emotional distress had experienced phantom limb pain. Using prosthesis also aggrevated phantom pain in some patients.

c. Depression vs severity of pain

4. Management of phantom limb pain: our study shows non steroidal anti inflammatory drugs more effective by its mechanism of inhibition of the enzymes needed for the synthesis of prostaglandin and decreasing the nociception peripherally and centrally.

Tricyclic antidepressants used in few patients but role is not well established. A recent study reported excellent phantom limb pain control with an average dose of 55mg amitriptyline.

Serotonin norepinephrine reuptake inhibitors had little role in phantom limbs as shows in our study.

Case Disscussion

The first medical description of post-amputation sensation was given by Ambroise Pare Â (1510±1590), a French militarysurgeon, who noticed that patients may complain of severe pain in the missing limb following amputation. In his 'Haquebusses and other guns', PareÂ characterized the post amputation syndrome and proposed different models to explain the pain. 45 Subsequent studies by Charles Bell (1830), Magendie (1833), Rhone (1842), GueÂniot (1861) and others provided detailed descriptions of the phenomenon and, in 1871, Mitchell coined the term phantomlimb [25].

Phantom limb pain can be defined as pain or discomfort felt by an amputee in the area of the missing limb [1]. Approx-imately 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]. Phantom limb pain is more common in upper limb amputee as compared to lower limb amputee [3] and in females than males

The phantom complex includes three different

elements.

- Phantom limb pain: Painful sensations referred to the absent limb. .
- Phantom limb sensation: Any sensation in the absent limb, except pain.
- Stump pain: Pain localized in the stump

These elements often coexist in each patient and may be difficult to separate.

It is now clear that nerve injury is followed by a series of changes in the peripheral and the central nervous system and that these changes may play a role in the induction and maintenance of chronic phantom pain. Although phantom pains may occur following amputation of body parts other than limbs. There is no relationship between the age in adults, gender, side or level of amputation, general health status and the phantom limb pain. This study discusses risk factors, the nature, char-acteristics, mechanisms and treatment options available for phantom limb pain.

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].

The amputees describe phantom pain as stabbing, boring, shooting, squeezing, throbbing or burning in nature. It is usu-ally 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].

Phantom limb pain usually develops very early following the amputation. The literature suggests that 75% of pa-tients 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 frequen-cy and intensity of the pain is variable and generally tends to decrease with time in 44% and increased in 3% of the respondents.

Etiology and Mechanisms of Phantom Limb Pain

Different theories have been pro-posed 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 accu-mulation 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 oper-ation various peripheral nerves are cut, resulting in massive tissue and neuronal injury. The severed nerve endings then sprout to form neuro-mas. 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 up-regulation of sodium channel causes stump and phantom pain [18]. 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 in-creased sensitivity to mechanical and neurochemical stimulation causing stump and phantom limb pain [21].

B. Role of Sympathetic Nervous Sys-tem 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 fibres excites and sensi-tizes 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. 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 neurotrans-mitters 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 re-ceptors at the spinal cord level and this phenomenon is called "windup phenomenon"[25]. Changes in the de-scending 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 centres 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 sen-sations in the phantom limb pain. This phenomenon has been studied extensively in both animals and hu-man 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 [28,29,30].

E. Psychogenic Mechanism

The liter-ature 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 pain35. A recent cross-sectional study found that amputation in people with personality traits characterized by passive coping styles and catastro-phizing behevior 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 effective in There are no agreed specific treat-ment 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.

Pharmacological Approaches

Var-ious medications have been used to treat phantom limb pain with varying results.

- *Preemptive Use of Analgesics and Anesthetics: d*uring 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 am-putation 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.
- *Non-Steroidal Anti-Inflamma-tory 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 mecha-nism of NSAIDs is inhibition of the enzymes needed for the synthesis of prostaglandin and decreasing the nociception peripherally and centrally.
- *Tricyclic Antidepressants (TCA)* are among the most com-monly used medications for var-ious 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 anti-depressant is mainly due to the inhibition of serotonin-norepi-nephrine 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 de-sipramine are equally effective in treating phantom limb pain when compared with amitriptyline with fewer side effects [43].
- *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 ef-fectiveness 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].
- *Anticonvulsants* like antidepres-sants 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 asso-ciated 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].

- *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]. Ran-domized 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 antide-pressants and gabapentin though the opioids were associated with more frequent side effects. The total amount of opioid required to achieve analgesia may be less when used together with other agents, such as tricyclic antide-pressants or anticonvulsants, which also have use in neuropathic pain modulation [17]. Tramadol is an analgesic with both with mono-aminergic and opioid activity and can be used as an alternative to strong opioids as tolerance and dependence with tramadol long-term use are uncommon.

Nonpharmacological Approaches

The combination of pharmacological and nonpharmacological approaches together can help to manage the phantom limb pain.

- *Transcutaneous Electrical Nerve Stimulation (TENS)* has been traditionally used in the man-agement 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.
- *Mirror Therapy* was first intro-duced by Ramachandran in 1996, and help to resolve the visual-pro-prioceptive dissociation in the brain. Although the use of mirror therapy has been shown to be some cases there is still no widely accepted theory of how it works. In a 2010 study of phan-tom limb pain, Martin Diers and his colleagues in a randomized, controlled trial that used graded motor imagery and mirror training, found that patients with phan-tom 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.

Surgical Interventions

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 sympa-thectomy, 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. Case reports of improvement of phantom limb pain with deep brain stimulation of the periventricular gray matter and thalamic nuclei have been published. Motor cortex stimulation was also found to be helpful in a case of phantom limb pain. A case report of electroconvulsive therapy (ECT) showed positive outcome even though the mechanism and role of ECT in phantom limb pain is unclear.

Conclusion

Phantom limb pain is relatively com-mon condition and causes marked functional and psychological disability. These are no agreed pathophysiological mechanism for the condition. Specific treatments are still evolving and major-ity of the treatments are based on the treatment recommendations for chronic neuropathic pain. Multi-treatment ap-proach, 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 psycholog-ical 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 ampu-tees. 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: 3-41.
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, Chris-tensen 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, Mc-Coll 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 obser-vations. 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-am-putation pain. Pain 1985; 21: 267-278.
14. Houghton AD, Nicholls G, Houghton AL, Saadah E, McColl L. Phantom Pain: natural.
15. Hanley MA, Jensen PM, Smith DG, Ehde DM, Edwards WT, Robinson LR. Preampu-tation 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. Ar-chives Physical Med Rehab 2005; 86(10): 1910-19.
17. Subedi B, Grossberg GT. Phantom Limb Pain: Mechanism and Treatment Ap-proaches. 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 re-duces 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 amputa-tion: 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. Modu-lation 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, Kolt-zenburg M. Noradrenaline-evoked pain in neuralgia. Pain 1995; 49:439-41.
24. Chabal C, Jacobson L, Russell L, Burchiel KL. Pain responses to perineuromal in-jection of normal saline, epinephrine and lidocaine in humans. Pain 1992; 49:9-12.
25. Baron R. Mechanisms of disease: neu-ropathic pain — a clinical Perspective. Nature Clinical Practice Neurology 2006; 2(2):95-106.
26. Baron R, Binder A, Wasner G. Neuro-pathic 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 sen-sations 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):181-91.
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-Karis-tianis N, Bradshaw JL. Central mechanisms in phantom limb perception: the past, present and future. Brain Research Re-views 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 neu-romatrix 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, Nur-mikko T. A prospective study of factors associated with the presence of phantom limb pain six months after major lower limb amputation in patients with periph-eral 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 treat-ments used for lower-limb phantom pain.
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. Po-stamputation 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 mir-tazapine: 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, Camp-bell 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 random-ized study of the effects of gabapentin.