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Neuropathic Pain and Its Prevalence: A Complete Review

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Abstract

Neuropathic pain (NP) is a prevalent neurological disorder that causes damaging of nerves. It mainly affects somatosensory system including both central neurons as well as peripheral fibers. Nerves over-sensitization causes extreme pain from stimuli which are normally painless. NP can be classified into central neuropathic pain (CNP), peripheral neuropathic pain (PNP), and general neuropathic pain (GNP). PNP includes diabetic peripheral neuropathy, HIV-associated NP, post-herpetic neuralgia, chemotherapy associated peripheral neuropathy, post-traumatic or postoperative peripheral neuropathy. CNP includes pain of spinal cord injury, post stroke neuropathic pain or the pain of multiple sclerosis and GNP includes both PNP and CNP. Neuropathic pain affects around 7 to 10 % of the common public globally. As per the recent reports NP is more persistent in women i.e. about 8% as compared to men i.e. about 5.7%.The most common symptoms of neuropathic pain include “sensations (burning, tingling, ants, crawling etc.), spontaneous pain, numbness or loss of sensation, allodynia (a general non-painful stimuli like touch can cause pain, hyperalgesia (Slightly painful stimuli causes exaggerated pain).

Introduction

The word neuropathic pain (NP) is related to all pain that is induced by a primary lesion or from the dysfunctioning of the nervous system [1]. The disorders that cause NP are related to lesions of central as well as peripheral nervous system. As compared to all other types of chronic pain, NP is one of the most relentless pain and is related to deterioration of day-to-day activities [1]. The symptoms of NP may include lancinating, burning or characteristics related to electric shock [3]. As compare to other etiologies, pathogenesis of NP is distinct, and that is the reason that NP is having different diagnosis as well as management. Inspite of these distinctions, many patients

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suffering from NP are not managed and diagnosed correctly. Because of such reasons, patients suffering from NP are not satisfied with the available options of treatment for NP. A better understanding of NP prevalence and at present its population impact may provide a better knowledge of NP existence. Approximately 20 million people are affected by peripheral neuropathy in the United States [4]. It has been identified that peripheral neuropathy can be of more than 100 types [4]. The overall incidence and prevalence in the general population is shown in table 1[4]. Different conditions and prevalence of neuropathic pain worldwide [5] and countrywise (USA [6], Canada [7], and India [8]) are shown in fig 1, 2, 3, 4 and 5 respectively.

2. Common symptoms of neuropathic pain (NP) [3]

- Allodynia- severe pain occurred due to stimulus or touch that normally doesn't cause any ache.
- Hyperalgesia- Slightly painful stimuli causes exaggerated pain.
- Hypoalgesia- numbness or reduced pain due to painful stimuli.
- Paresthesia- pain occurred when there is no stimuli at all.
- Hypoesthesia- reduced thermal sensitivity in response to cold or warm objects.
- Dysesthesia- a spontaneous abnormal unpleasant sensation.

3. Types of NP

3.1.Postherpetic neuralgia (PHN)

PHN includes unilateral pain in dermatomes caused by herpes zoster virus [9, 10]. Intensity and type of PHN decides the treatment to be initiated. Initially monotherapy must be started and combination therapy should be used if there is failure of monotherapy [10, 11].Location of pain and treatments used for PHN is mentioned in Table2 [12].

3.2. Complex regional pain syndrome (CRPS)

CRPS is a form of chronic pain that affects limbs and should be diagnosed by neuropathic specialist[12].Various medications including antispastic drugs, bisphosphonates and invasive

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procedures are used to treat CRPS. Physical therapy and psychological therapies are also used for the treatment of CRPS [13, 14-17].

3.3. Diabetic polyneuropathy (DPN)

DPN can be caused by either diabetes mellitus – I or diabetes mellitus – II. It affects feet, may extends up to thighs, lower legs and hands. Maintaining proper level of blood glucose can prevent DPN [18, 19]. Initially first-line drugs are used to treat DPN and in case first-line drugs got failed, alternate therapies including second-line drugs, natural or synthetic drugs that have different mechanism of action, or combination of drugs are used [20-23].

3.4. Trigeminal neuralgia (TN)

TN is a condition where chronic NP occurs in the area of trigeminal nerve [24, 25]. Carbamazepine, clonazepam, antiepileptics and baclofen are used for the treatment of TN. In case of failure of these medications, surgery is suggested. Before surgery, botulin toxin is recommended [26-29].

3.5. Post-amputation pain

Post-amputation pain also called as phantom pain occurs in amputated patients that surrounds post-surgical stump scar [30]. Neurodistruction can occur during stump pain while peripheral nerves stimulation and spinal cord thermo lesion are effective in phantom pain[31-33].Strong opioids, gabapentin, tramadol, lidocaine infusions, amitriptyline, calcitonin pregabalin, physiotherapy and psychotherapy are most common treatments used to treat post-amputation pain.

3.6. Post-traumatic pain (PTP) and Post-operative pain (PPP)

PTP as well as PPP both are the chronic pains related to trauma or surgery and take more time to heal as compare to normal tissue healing [34]. To prevent PTP and PPP, prophylactic measures before surgeries, use of epidural anesthesia, use of local anesthetics to treat surgical wounds, use of gabapentin or pregabalin during preoperative phase, use of intravenous infusions of lidocainefor all the affected groups etc. are recommended. Causative management and lidocaine

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(5%) individually can be combined with systemic drugs and considering interventional methods are recommended to treat PPP [13].

3.7. Neuropathic cancer pain

There may be different causes and mechanisms related to neuropathic pain in cancer patients as mentioned in Table including cancer metastasis, anticancer therapy, and diseases related to cancer, and diseases that are not related to cancer. According to intensity of NP tramadol is recommended in case of moderate intensity and opioid in case of high intensity. To reduced opioid doses and for enhanced effectiveness combinations of the drugs mentioned previously along with pregabalin and gabapentin are used. In post-chemotherapy duloxetine and venlafaxine are recommended [13, 35].

3.8. Neuropathic pain due to HIV infection

This pain may occur either due to anti-retroviral therapy or the HIV virus itself. Treatments included combination of capsaicin patch (8%), gabapentin and lamotrigine. Lidocaine patches (5%), amitriptyline and pregabalin are also used for the treatment but are less effective [13, 36].

3.9. Central neuropathic pain (CNP)

The cause for CNP in patients is CNS injuries. Treatments include pregabalin (first-line agent) and TCA (first-line agent) in case of insomnia and depression [13, 37].

3.10. Peripheral nerve injury and neuropathic pain

Peripheral nerve injury and neuropathic pain is directly related to the age factor at which the destruction has been happened [38]. The mechanical hypersensitivity occurs but in the later stages of life that can be tested by weight bearings tests or cold stimulation [38]. The pain can be treated by initiating pre-treatment using pro-inflammatory polarized microglia inhibitor minocycline [39, 40].

3.11. Osteoarthritis (OA) neuropathic pain

Osteoarthritis is the disorder of muscle skeleton that includes joint pain due to sensitization of peripheral joint and central pain pathways. Nociceptive mechanisms cause changes in the bones and inflammation of local joints [41].The causes are not well understood but centrally acting drugs can treat OA pain [42,43]. The mechanism behind OA pain includes increased sodium channels, sensitization of dorsal-horn nerves leads to NP modulation central point causing

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secondary hyperalgesia and N-methyl-D-aspartate(NMDA) receptors activation resulting in inclined calcium influx [37,44,45]. Treatments include hydrotherapy, physiotherapy, use of heat packs or cold packs, nerves electrical stimulation, combination of centrally acting drugs, analgesic drugs and anti-inflammatory drugs are used. Other options that are under investigation include strontium ran elate and bisphosphonates for methotrexate [46].

4. Common causes, location of pain and treatments for non-malignant and malignant neuropathic pain

There are various causes for PNP including post-herpetic neuralgia, trigeminal neuralgia, painful neuropathies, limb amputation, radiculopathy etc. The various causes of PNP and CNP including location of pain, sensory signs and various treatments are mentioned in Table 2 [12]and Table 3 [47]. Similarly different causes of NP in cancer patients including anti-cancer therapy, cancer metastasis etc. their mechanism of action and various treatments for the same are mentioned in Table 4 [48].

5. Mechanisms causing symptoms of NP

5.1. Nociceptors sensitization

Nociceptors are triggered by either endogenous substances or exogenous substances involving mediators of inflammation (prostaglandins, bradykinin, prostaglandins, and various derivatives of arachidonic acid), growth factors and neurotransmitters [noradrenalin, neurokinins, histamine, stimulatory-amino acids and 5-hydroxy tryptamine (5-HT) [49-51]. Growth factors, inflammatory mediators and proinflammatory cytokines are released when degeneration of peripheral nerve axon occurs after injury. This leads to allodynia and hyperalgesia [52-54].

5.2. Irregular ectopic excitability of afferent neurons

Burning and stinging pain occurs as a result of irregular excitability of C and Aδ fibers, leads to symptoms caused by sodium channels. Na_v(1.7, 1.8 and 1.9) and voltage-gated ion channels play a major impact in pain perception [55-57].

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5.3. Central reorganization phenomena

Patients having phantom-limb pain (PLP) are admitted and significant cortical reorganization is examined. Pain intensity is directly linked to the cortical reorganization quantity i.e. the body part (exposed and broader) is not intricate into the excised part, leads to extreme PLP [58].

5.4. Pronociceptive facilitation of spinal dorsal horn

A stimulatory pain neurotransmitter, Glutamate which is caused by CNS and the glutamate receptors are involved in conduction of peripheral pain signals. Ionotropic-glutamate NMDA receptors gets disinhibited that leads to entangling of substance P and peptide called as calcitonin- gene related peptide. Also, these metabolic-glutamate receptors lower the pain signals conductions as well as suppresses the adenylyl-cyclase [58-60].

5.5. Spinal inhibitory disinhibition of pain

In the spinal cord, non-noxious cold stimulus causes loss of inhibition those results into thermal-grill illusion.This TGI causes loss of inhibition of peripheral as well as central toxic thermal responsive pathways [58, 61, and 62].

5.6. Mechanism of sympathetically controlled pain

This mechanism included both direct and indirect pain. Neuropathic pain involves coupling of efferent sympathetic signaling and nociceptive input. The similar pain is caused by subcutaneous presence of noradrenalin after continuous sympathetic blockage. This sympathetic trunk stimulation causes pain and hyperalgesia [63, 64].

6. Lines of Treatment for neuropathic pain

To treat neuropathic pain, number of different treatments are available including first-line treatments (TCAs or Tricyclic antidepressants, and SNRIs or Serotonin noradrenaline reuptake inhibitors , Local anesthetics ,Calcium channel alpha 2 delta,) second-line treatments (Opioids) and third-line treatments (Mexiletine, other anticonvulsants, Topical capsaicin, N-methyl-D-aspartate receptor antagonists) as shown in Table 5 [65].

7. Animal models used for neuropathic pain

Various models of animals are developed for NP including CCI model, sciatic nerve injury model, trigeminal neuralgia model, caudal trunk resection model, spared nerve injury model etc.

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The different types of models, their principle and types of species used in each model are described in Table 6 [66].

8. Conclusion

Various causes as well as symptoms of NP have been described and at present the incidences of NP are inclined globally. The increased incidences could be the result of increased population, diabetes mellitus, chemotherapy, inhibitory and excitatory somatosensory signaling imbalance, ion channels alterations etc. Poor management and complex treatments of NP leads to the unsatisfactory outcomes. Instead of advanced treatments and continuous efforts from the researchers, the life quality of folks suffering from NP is affected as a result of prescribed drugs and regular visits to health care centers. Various personalized treatments and diagnostic procedures are under progress and development, but still a multidisciplinary approach is still needed.

9. Figures and tables

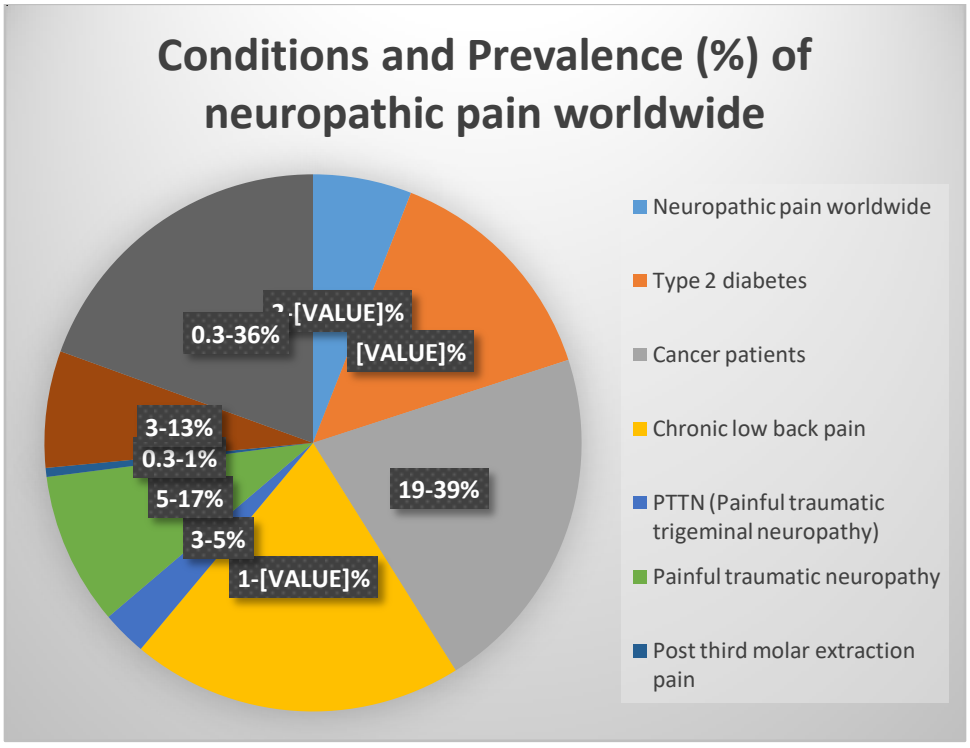

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Fig 1.Conditions and Prevalence (%) of neuropathic pain worldwide

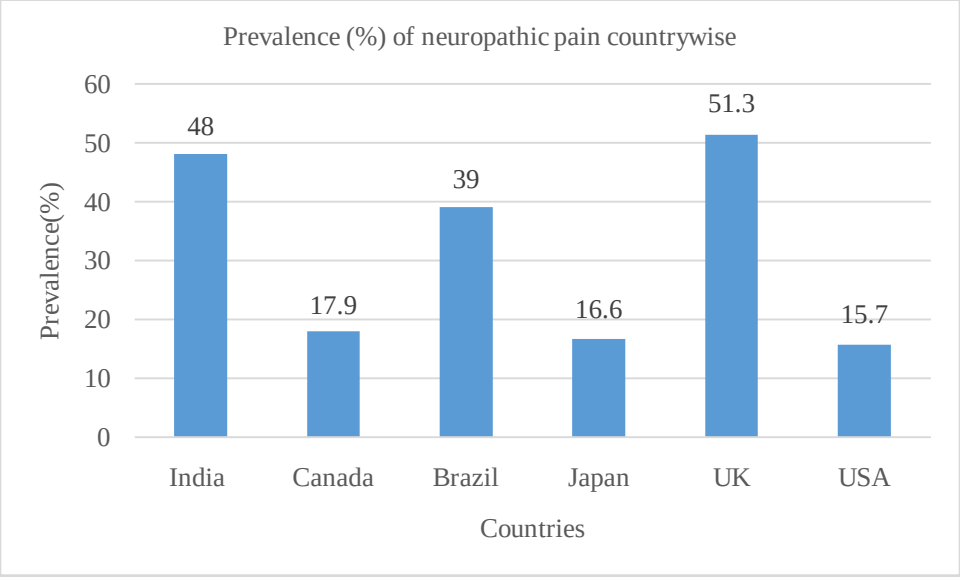

Fig 2. Prevalence (%) of neuropathic pain country wise

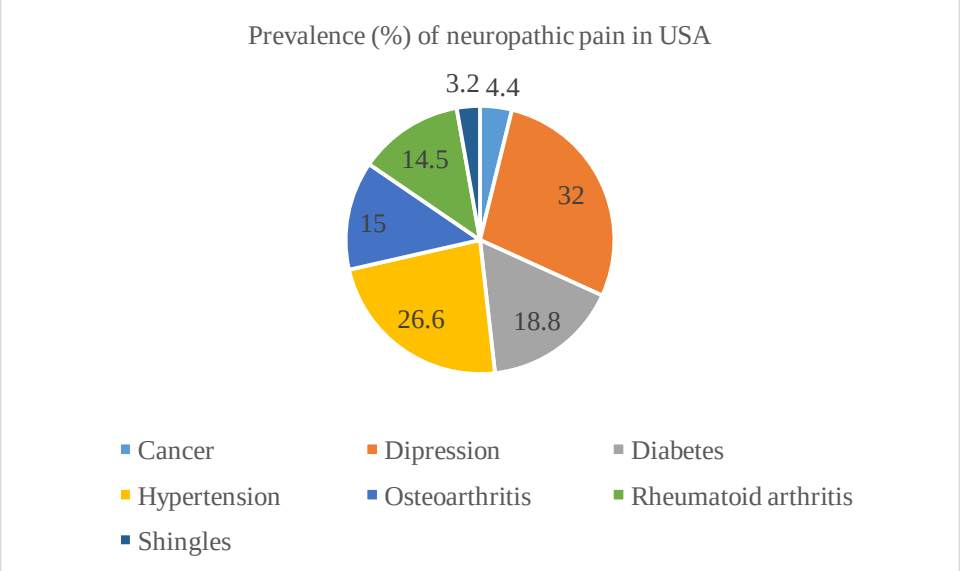

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Fig 3. Prevalence (%) of neuropathic pain in USA

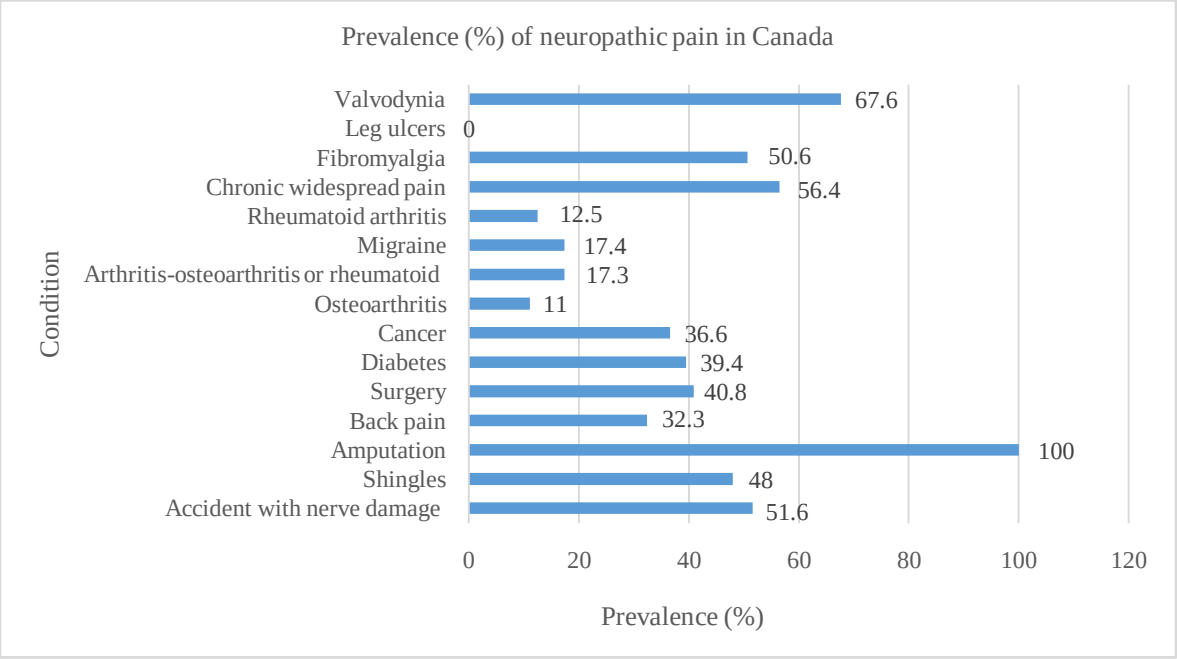

Fig 4.Prevalence (%) of neuropathic pain in Canada

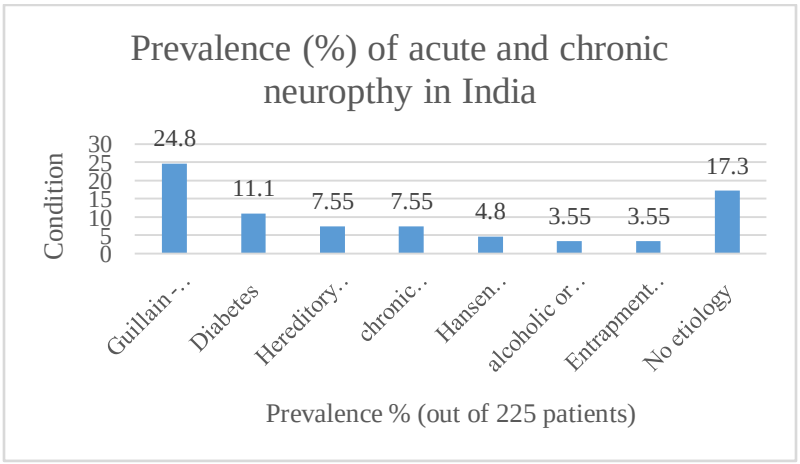

Fig 5.Prevalence (%) of acute and chronic neuropathy in India

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Table 1. Incidence and Prevalence estimates in general population

S.No.	Country	Incidence rate (95% CI)	Prevalence estimates (95%CI)
1.	France	N/A	6.9% (6.6%-7.2%)
2.	United states	4.7 per 100,000 population [3.6-5.8]	N/A
3.	United states	0.8 per 100,000 population [0.3-1.2]	N/A
4.	United states	0.007% at 60 days (4.5% of HZV)	N/A
5.	United states	N/A	Clinical examination : 9.8% [6.2%-13.4%] S-IANSS:8.8% [7.9%-9.8%] Berger criteria: 3.0%[2.5%-3.6%] Self- reported: 12.4%[11.4%-13.6%]
6.	UK	11/100,000/year [6.0-17.0] 8.0/100,000/year[4.0-13.0]	0.7 per 1000[0.4-1.0] 0.7 per 1000[0.4-1.0]
7.	UK	N/A	0.8%
8.	UK	40.2/100,000 PY[39.5-40.9] 26.8/100,000 PY[26.2-27.4]	N/A

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		1.5/100,000 PY[1.3-1.6] 15.3/100,000PY[14.9-15.7]	
9.	UK	N/A	8.2% [7.2%-9.2%]
10.	UK	N/A	0.9% No 95% CI reported
11.	UK	Age -standardized 27.3/100,000 PY[27.0-29.5] 26.7/100,000 PY[26.1-28.6] 0.8/100,000 PY[0.6-1.1] 26.7/100,000PY[26.0-28.4]	N/A
12.	UK	N/A	1.3% No 95%CI reported
13.	UK		
14.	Brazil	N/A	10% No 95% CI reported
15.	Netherlands	0.009% population/ year	N/A
16.	Netherlands	8.2/1000 PY[8.0-8.4] 41.8/100,000 PY[38.1-45.7] 28.9/100,000 PY[25.8-32.1] 0.40/100,000PY[0.1-	N/A

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		0.9]	
17.	Netherlands	38.7/100,000 PY[34.9-42.9] 3.9/100,000 PY[2.7-5.3] 12.6/100,000 PY[10.5-15.1] 0.2/100,000PY[0.0-0.7]	N/A
18.	Netherlands	47.5 per 10,000 [40.6-54.4] 5.8% [5.0-6.6] 2.2% [1.71-2.71]0.7%[0.41-0.97]	N/A
19.	Austria	N/A	3.3% No 95% CI reported
20.	Taiwan	42.0/100,000 PY No 95% CI reported	N/A
21.	Italy	N/A	0.09% CI reported
22.	Canada	N/A	17.9 % [15.8%-20.2%]

*CI- confidence interval, HZV-Herpes Zoster Virus, N/A- Not applicable, PY- Person years, S-LANSS- Self-complete leads assessment of Neuropathic Symptoms and signs

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Table 2.Common causes of non-malignant peripheral neuropathic pain (PNP)

S.N.	Peripheral neuropathic pain (PNP) disorders	Location of pain and sensory signs	Treatment
1.	Painful polyneuropathies (diabetic and non-diabetic)	In feet, may include thighs, lower legs and hands .	• Gabapentin • Pregabalin • Venlafaxine ER • TCAs • Duloxetine • Opioids • tramadol
2.	Post-herpetic neuralgia (PHN)	Affects nerve fibers and skin	• Amitriptyline • Opioids, • 5% lidocaine • Pregabalin • Gabapentin • 8%capsaicin.
3.	Trigeminal neuralgia	Trigeminal nerve that brings	• Carbamazepine

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		sensation from face to brain is affected	• Clonazepam • Baclofen • Antiepileptic's (lamotrigine, gabapentin or pregabalin) • Surgery
4.	Brachial plexus injury and limb amputation (Phantom limb pain)	In the missing body part and/or in the residual limb	• Opioids • Tramadol • Gabapentin • Calcitonin pregabalin • Lidocaine infusions • Amitriptyline • Physiotherapy • Psychotherapy
5.	Post-surgical and post-traumatic neuralgias	Pain occurred in the body part after traumatic nervous injury	Prevention • Prophylactic measures before surgeries • Epidural anesthesia

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			• Local anesthetics to treat surgical wounds • Gabapentin or pregabalin during perioperative phase • Lidocaine intravenous infusions Treatment • Causative management • Lidocaine (5%) alone or in combination with systemic drugs • Interventional methods
6.	Complex regional pain syndromes	It affects one limb (arm, hand, leg or foot), mostly occurs after an injury (arm, hand, leg or foot)	• Antispastic drugs • bisphosphonates • invasive procedures • Physical therapy • Psychological therapy
7.	Radiculopathy	Spinal nerve gets compressed. Affects any part of the spine, most commonly lower back and neck.	

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8.	Peripheral nerve injury pain	Affects sensory nerve connected with skin, motor nerve connected with muscles and autonomic nerves connected with internal organs	• Pre-treatment using inhibitor of pro-inflammatory polarized microglia, minocycline
9.	HIV related neuropathic pain		• Combination of capsaicin patch (8%), gabapentin and lamotrigine. • Lidocaine patches (5%) • amitriptyline • pregabalin

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Table 3.Common causes of non-malignant central neuropathic pain (CNP)

S.N.	Central neuropathic pain (CNP) disorders	Location of pain and sensory signs	Treatments
1.	Post stroke pain	Felt on part or all the side of body affected by stroke including face, leg, arm and torso.	• Pregabalin • TCA
2.	Injury of spinal cord	Below the lesion of spinal cord	
3.	Multiple sclerosis	Combination of symptoms occurred in post stroke pain and due to injury of spinal cord	
4.	Central neuropathic pain (CNP) disorders	Location of pain and sensory signs	

Table 4.Common causes of malignant neuropathic pain

S.N.	Cause of NP in cancer patient	Mechanism	Treatments
1.	Anticancer therapy	Intraoperative destruction of nervous system	• Tramadol • Opioid • Combination of opioid along with pregabalin and gabapentin Post-chemotherapy • Duloxetine • venlafaxine
2.	Cancer metastasis	Infiltration of cancer into the CNS or PNS	
3.	Disease related to cancer	Post-herpetic neuralgia and acute varicella zoster	
4.	Disease which are not related to cancer	Diabetic polyneuropathy	

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Table 5. Lines of treatment for neuropathic pain

Line of treatment	Treatment	Symptoms of neuropathic pain
First-line treatment	Tricyclic antidepressants (TCAs)	
	• Desipramine	
	• Imipramine	BRP,STP
	• Amitriptyline	BRP
	SNRIs or Serotonin and noradrenaline reuptake inhibitors	BRP,STP
	• DXH	
	• Venlafaxine	STP
	Calcium channel alpha 2 delta	-
	• Pregabalin	
	• Gabapentin	
	Local anesthetics	
	• Topical 5% patches of lidocaine	HPA,ADA,STP,BRP
		HPA,ADA,STP,BRP
		HPA,ADA
Second-line treatment	Opioids	
	• Morphine	ADA
	• Tramadol	ADA
Third-line treatment	Other anticonvulsants	
	• Carbamazepine	STP

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• Lamotrigine	STP
Others	
• Mexiletine	HPA, ADA
• N-methyl-D-aspartate receptor antagonists.	-
• Topical capsaicin	-

*HPA= Hyperalgesia, ADA= Allodynia, BRP burning pain, STP= Shooting pain

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Table6. Various models of animals for neuropathic pain has been developed

S.N.	Type of model	Model principle	Type of species used
1.	Chronic constriction injury (CCI)	Sciatic nerve is ligated by four loose ligatures	Rats and mice
2.	Ligation of spinal nerve to sciatic nerve (SNL)	• Spinal nerves (L5, L6) are tightly ligated • Ligation of nerves of spinal cord (L7)	Rats and Macacafascicularis
3.	Partial sciatic nerve ligation (pSNL)	• Tight ligation of sciatic nerve approximately one third to half	Rats and mice
4.	Sciatic nerve axotomy	• Sciatic nerve is completely transected.	Rats
5.	Spared nerve injury	• Common and tibialperoneal nervesaxotomy	Rats and mice
6.	Trigeminal neuralgia	• Trigeminal ganglion is compressed • CCI is done to infra-orbital nerve	Rats
7.	Transection of tibial and sural nerve	• Axotomy of sural and tibial nerves	Rats
8.	Common peroneal nerve ligation	• Ligation of Common peroneal nerve	Mice
9.	Cryoneurolysis of sciatic nerve	• Sciatic nerve is freezed	Rats
10.	Resuction of caudal trunk	• Caudal trunk resection	Rats and mice
11.	Sciatic inflammatory neuritis	• Human menopausal gonadotropins (HMG)	Rats and mice

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		injection, zymosan injection and TNF-alpha injection around sciatic nerve	
12.	Sciatic nerve injury caused by cuffing	• Polyethylene cuff is implanted around sciatic nerve	Rats and mice
13.	Sciatic nerve injury by photochemicals	• For the purpose of thrombosis in small vessels supplying sciatic nerve, photosensitizing agents like laser and dyes are used	Rats and mice
14.	Sciatic nerve injury by laser	• Radiations causes blood supply reduction to sciatic nerves	Rats
15.	Weight drop spinal cord injury	• Weight is dropped on spinal cord after exposing it	Rats and mice
16.	Excitotoxicinjury of spinal cord	• Excitatory amino acids are intraspinally injected	Rats and mice
17.	Spinal cord injury by photochemicals	• For the purpose of thrombosis in small vessels supplying sciatic nerve, photosensitizing agents like laser and dyes are used	Rats
18.	Spinal hemisection	• T11-T12 segments undergo laminectomy	Rats
19.	Drugs induced	• These drugs are directly injected to PNS	(a) Rats, guinea

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	(a) Anti- HIV agents like didanosine (b) Anti-cancer agents like cisplatin, paclitaxel	nerves	pigs and mice (b) Rats and rabbits
20.	NP induced by diabetes (a) NP induced by streptozotocin (b) Genetic models	• Persistent hyperglycemia causes alterationin nerves	Rats and mice
21.	Models of bone cancer pain (a) Cancer pain in humerus, calcaneus, femur, tibial bone (b) Cancer pain due to neuropathy (c) Skin cancer pain	(a) Cancerous cells are inoculated into bones (b) Tumor growth in sciatic nerve vicinity (c) Melanoma cells are injected in plantar region og hind paw	(a) Rats and mice (b) Mice (c) Mice
22.	Neuropathic pain due to HIV	• HIV- protein gp120 is delivered to sciatic nerve	Rats
23.	Post- herpetic neuralgia (a) Herpes simplex virus (b) Varicella zoster virus (c) Non- viral model	(a) Cells infected by virus are injected in the footpad (b) capsaicin-sensitive is depleted (c) Afferents with resiniferotoxin	(a) Rats (b) Rats and mice (c) Rats
24.	Chronic ethanol consumption or withdrawal	• Ethanol consumption over extended period about 70 days	Rats
25.	Acrylamide induced pain	• Acrylamide is administered for prolonged	Rats

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		period	
26.	Orofacial pain	• Carragenan or formalin is injected into temporomandibular joints and maxilla	Rats and mice
27.	Pain due to Pyridoxine	• Pyridoxine is administered for long period	Dogs and rats

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10. References

[1]. Jensen, S. Troels S., et al, "A new definition of neuropathic pain," Pain, vol. 152(10), pp. 2204-2205, 2011.
[2]. Bouhassira, Didier, et al, "Development and validation of the neuropathic pain symptom inventory," Pain, vol. 108.3, pp.248-257, 2004.
[3]. https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM542169.pdf (Accessed on 8th December 2019)
[4]. OV. Hecke, SK. Austin, RA. Khan, BH. Smith, N.Torrance," Neuropathic pain in the general population: A systematic review of epidemiological studies," vol.155, pp.654-662, 2014.
[5]. J.Khan, "Neuropathic pain," The Journal of Indian Prosthondontic Society, vol.16 (2), pp.114-5, 2016.
[6]. MD. Dibonaventura, A. Sadosky, K. Concialdi,M.Hopps, Ian. Kudel, B. Parson et al, "The prevalence of probable neuropathic pain in the US: results from a multimodal general – population health survey," Journal of Pain Research, Vol.10, pp. 2525-2538, 2017.
[7]. EG. Vandenkerkhof, EG.Mann, N.Torrance, BH. Smith,A.Johnson, I. Gilron, "An epidemiological study of neuropathic pain symptoms in Canadian adults," Pain Research and Management, 1-13, 2016.
[8]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5586108/?report=reader#!po=4.05405. (Accessed on 8th December 2019)
[9]. RH. Dworkin, RK. Portenoy, "Pain and its persistence in herpes zoster," Pain, Vol. 67(2-3), pp.241-51, 1996.
[10]. HG. Thyregod HG, et al, "Natural history of pain following herpes zoster," Pain, vol. 128(1-2), pp. 148-56, 2007.
[11]. BF. Jung BF, et al, "Risk factors for postherpetic neuralgia in patients with herpes zoster,"Neurology, vol. 62(9), pp.1545-51, 2004.
[12]. RN.Harden, et al, "Proposed new diagnostic criteria for complex regional pain syndrome," Pain Med, vol.8 (4), pp.326-31, 2007.
[13]. Szczudlik A, et al, "Diagnosis and management of neuropathic pain: review of literature and recommendations of the Polish Association for the Study of Pain and the Polish Neurological Society-Part Two," NeurolNeurochir Pol, vol.48 (6), pp.423-35, 2014.
[14]. PE. Zollinger,et al, "Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study," J Bone Joint Surg Am, vol. 89(7), pp.1424-31, 2007.
[15]. BH. Lee BH, et al, "Physical therapy and cognitive-behavioral treatment for complexregional pain syndromes," J Pediatr, vol.141 (1), pp.135-40, 2002.

ISSN: 0971-1260
Vol-22-NO-30 Special Issue-December-2019

[16]. GL. Moseley, "Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb? A randomised clinical trial," Pain, vol.114 (1-2), pp.54-61, 2005.

[17]. HM, Oerlemans, et al, "Evaluation of three methods to rate impairment in patients with complex regional pain syndrome I of one upper extremity," ClinRehabil, vol.14 (3), 331-9,2000.

[18]. J. Partanen , et al, "Natural history of peripheral neuropathy in patients with noninsulin-dependent diabetes mellitus, N Engl J Med, vol.333(2), pp.89-94, 1995.

[19]. M. Zychowska,et al, "Mechanisms and pharmacology of diabetic neuropathy - experimental and clinical studies," Pharmacol Rep, vol. 65(6), pp. 1601-10, 2013.

[20]. AJM. Boulton, et al, "Diabetic Neuropathies: A statement by the American Diabetes Association, "Diabetes Care, vol.28 (4), 956-62, 2005.

[21]. V. Bril , et al, "Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation," Neurology, vol. 76(20), pp. 1758-65,2011.

[22]. S. Tesfaye S, et al, "Painful diabetic peripheral neuropathy: consensus recommendationson diagnosis, assessment and management," Diabetes/Metabolism Research and Reviews, vol.27 (7), pp.629-38,2011.

[23]. K. Raafat, A.El-Lakany, "Acute and subchronicin-vivo effects of Ferula hermonis L. and Sambucusnigra L. and their potential active isolates in a diabetic mouse model of neuropathic pain," BMC Complement Altern Med, vol. 15, pp.257, 2015.

[24]. JS. Koopman ,et al, "Incidence of facial pain in the general population," Pain, vol.147(1-3), pp. 122-7, 2009.

[25]. JM. Zakrzewska, "Diagnosis and differential diagnosis of trigeminal neuralgia," Clin J Pain, vol. 18(1), pp.14-21, 2002.

[26]. EA. Childs, et al, "Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy," Neurology, vol. 52(3), pp. 607-13, 1999.

[27]. G. Gronseth, et al, "Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies, "Neurology, vol.71(15), pp. 1183-90, 2008.

[28]. G. Cruccu , A. Truini , "Refractory trigeminal neuralgia. Non-surgical treatment options," CNS Drugs, vol. 27(2), pp.91-6, 2013.

[29]. JSHA. Koopm, et al, "A nationwide study of three invasive treatments for trigeminalNeuralgia,"Pain, vol. 152(3), pp.507-13, 2011.

ISSN: 0971-1260
Vol-22-NO-30 Special Issue-December-2019

[30]. RL. Rauck ,et al "Treatment of post-amputation pain with peripheral nerve stimulation,"Neuromodulation, vol. 17(2), pp.188-97, 2014.
[31]. J. Rosenstock J, et al, "Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial," Pain, vol. 110(3), pp. 628-38, 2004.
[32]. CH. Wilder-Smith, LT. Hill, S. Laurent, "Postamputation pain and sensory changesin treatment-naive patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo," Anesthesiology, vol. 103(3), pp.619-28, 2005.
[33]. H. Knotkova H, et al, "Current and future options for the management of phantomlimbPain," J Pain Res, vol. 5, pp. 39-49, 2012.
[34]. F. Perkins, J. Ballantyne, "Postsurgical Pain Syndromes, in Evidence-Based ChronicPain Management," pp.194-203,2010.
[35]. MT. Fallon, "Neuropathic pain in cancer," Br J Anaesth, vol. 111(1), pp. 105-11, 2013.
[36]. A. Verma A, "Epidemiology and clinical features of HIV-1 associated neuropathies," J PeripherNervSyst, vol.6(1), pp.8-13, 2001.
[37]. RD.Treedeet al, "Neuropathic pain: redefinition and a grading system for clinical and research purposes," Neurology, vol. 70(18), pp.1630-5, 2008.
[38]. M. Fitzgerald, R. McKelvey, "Nerve injury and neuropathic pain - A question of age," ExpNeurol, vol. 275(2), pp.296-302,2016.
[39]. GJ. Hathway ,et al, "Brief, low frequency stimulation of rat peripheral C-fibres evokes prolonged microglial-induced central sensitization in adults but not in neonates," Pain, vol.144(1-2), pp.110-8, 2009.
[40]. K. Kobayashi, et al, "Minocycline selectively inhibits M1 polarization of microglia," Cell Death Dis, vol.4, pp525, 2013.
[41]. L. Sharma, D. Kapoor , S. Issa , "Epidemiology of osteoarthritis: an update," CurrOpinRheumatol, vol. 18(2), pp.147-56, 2006.
[42]. J. Zhang ,et al, "Risk factors for and prevalence of knee osteoarthritis in the rural areas of Shanxi Province, North China: a COPCORD study," RheumatolInt, vol. 33(11), pp.2783-8, 2013.
[43]. SJ. Nho ,et al, "The burden of hip osteoarthritis in the United States: epidemiologicand economic considerations, " J Am AcadOrthopSurg, vol. 21(1), pp.6-44, 2013.
[44]. C. Sommer, "Painful neuropathies," CurrOpinNeurol, vol. 15(5), pp.623-8, 2003.
[45]. KA, Moore ,et al, "Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord," J Neurosci, vol. 22(15), pp.6724-31,2002.

ISSN: 0971-1260
Vol-22-NO-30 Special Issue-December-2019

[46]. T. Dimitroulas ,et al., "Neuropathic pain in osteoarthritis: a review of pathophysiologicalmechanisms and implications for treatment," Semin Arthritis Rheum, vol.44(2), pp. 145-54, 2014.

[47]. Kılınç, Muhammed, et al, "Effects of transcutaneous electrical nerve stimulation in patients with peripheral and central neuropathic pain," Journal of rehabilitation medicine, vol. 46.5, pp.454-460, 2014.

[48]. Becker, Niels, et al, "Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center," Pain, vol.73.3,pp.393-400,1997.

[49]. D. Julius , AI. Basbaum, "Molecular mechanisms of nociception," Nature, vol. 413(6852), pp.203-10,2001.

[50]. R. Schmidt ,et al, "Novel classes of responsive and unresponsive C nociceptors in human skin," J Neurosci, vol. 15(1), pp.333-41,1995.

[51]. H. Ueda, "Peripheral mechanisms of neuropathic pain-involvement of lysophosphatidicacid receptor-mediated demyelination," Mol Pain, vol.4, pp.11, 2008.

[52]. M.Inoue ,et al, "Initiation of neuropathic pain requires lysophosphatidic acid receptorSignaling," Nat Med, vol. 10(7), pp.712-8, 2004.

[53]. G. Moalem, DJ. Tracey, "Immune and inflammatory mechanisms in neuropathic pain," Brain Res Rev, vol. 51(2), pp. 240-64, 2006.

[54]. J. Scholz , CJ. Woolf CJ, "The neuropathic pain triad: neurons, immune cells and glia," Nat Neurosci," vol. 10(11), pp.1361-8, 2007.

[55]. R. Amir , M. Michaelis , M. Devor, " Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain," J Neurosci, vol. 19(19), pp.8589-96,1999.

[56]. M. Tal , PD. Wall , M. Devor, " Myelinated afferent fiber types that become spontaneously active and mechanosensitive following nerve transection in the rat," Brain Res, vol.824(2), 218-23,1999.

[57]. TR. Cummins , PL. Sheets , SG. Waxman SG, "The roles of sodium channels in nociception: Implications for mechanisms of pain," Pain, vol. 131(3), pp.243-57, 2007.

[58]. FT. Nickel ,et al, "Mechanisms of neuropathic pain. EurNeuropsychopharmacol," vol.22(2), pp. 81-91,2012.

[59]. ME. Fundytus ,et al, "In vivo antinociceptive activity of anti-rat mGluR1 and mGluR5 antibodies in rats," Neuroreport, vol. 9(4), pp.731-5, 1998.

[60]. WL. Wu W, et al, " Discovery of orally efficacious tetracyclic metabotropic glutamate receptor 1 (mGluR1) antagonists for the treatment of chronic pain," J Med Chem, vol. 50(23)pp.555-3, 2007.

ISSN: 0971-1260
Vol-22-NO-30 Special Issue-December-2019

[61]. J. Knabl ,et al, "Reversal of pathological pain through specific spinal GABAA receptorSubtypes," Nature, vol. 451(7176), pp.330-4, 2008.
[62]. HU. Zeilhofer, WT, Ralvenius, MA, Acuna, "Restoring the spinal pain gate: GABA(A)receptors as targets for novel analgesics," AdvPharmacol, vol.73, pp.71-96, 2015.
[63]. J. Sato, ER. Perl, "Adrenergic excitation of cutaneous pain receptors induced by peripheral nerve injury," Science, vol. 251(5001), pp.1608-10,1991.
[64]. E. Torebjork E, *et al*, "Noradrenaline-evoked pain in neuralgia," Pain, vol. 63(1), pp.11, 1995.
[65]. PM. Scholten, RN. Harden, "Assessing and Treating Patients WithNeuropathic,"Pain, vol. 7(11), pp.257-69, 2015.
[66]. 66. Jaggi.AS, Jain.Vivek, Singh.Nirmal, "Animal models of neuropathic pain," Fundamental & Clinical Pharmacology, vol.25, pp.1-28, 2011.