Guidelines For Evaluation And Management Of Neuropathic Pain

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Introduction

Pain is an important physiologic mechanism that warns us about potential injury, thus an indispensible protective mechanism. Pain is often transient and resolved if underlying cause is removed or managed appropriately and adequately e.g. minor local trauma, cardiac ischemia and abscesses. On the contrary pain as a result of neuronal injury is often chronic and distressing. Though neuropathic pain can result from neuronal injury at any level of nervous system i.e. from cerebral cortex to peripheral or cranial nerve, usual cause is injury to peripheral part of nervous system e.g. peripheral or cranial nerves and nerve roots (cervical and lumbosacral).

Neuropathic pain affects about 10% of general population in West[1,2]. Though the burden of neuropathic pain in Pakistan is not exactly known, the burden is likely to be high, considering huge population[3], high prevalence of diabetes mellitus and stroke[4-7], rising trends of bomb blasts and gunshot injuries and the fact that about two fifths of our disease burden is comprised of non-communicable diseases[8].

These guidelines are focused on management of neuropathic pain in broader view and some specific pain syndromes like post herpetic neuralgia, trigeminal neuralgia, carpal tunnel syndrome, back ache and neck pain, complex regional pain syndromes and central pain syndromes including central post stroke pain syndrome.

Methods

The primary author (BK) reviewed all the data on current tools for identification of neuropathic pain, investigations to evaluate neuropathic pain, pharmacologic and non-pharmacologic strategies to manage the pain in general and for specific pain syndromes. Special attention was given to *Cochrane reviews* and recent international guidelines on the subject by professional societies.

Neuropathic pain: Definition, characteristics, burden and diagnosis

Neuropathic pain is defined by its origin i.e. nervous system. Any painful condition resulting from injury to neuronal tissue is called neuropathic pain.

Neuropathic pain is characterized by constant or paroxysmal (episodic, intermittent) burning, shooting, electric shock like, stabbing, lancinating, sharp pain which may either be spontaneous or stimulus evoked. Stimulus evoked pain may be brought on upon noxious (painful) stimulus, called Hyperalgesia or non noxious (non painful) stimulus called allodynia. Allodynia to cold stimulus is called cold allodynia[9,10].

The pain is often associated with other positive symptoms i.e. paresthesias (abnormal sensations which are not unpleasant), dysesthesias (abnormal and unpleasant sensations) and negative symptoms like sensory impairment (partial or complete) of various sensory modalities including pain, temperature, vibration and joint position sense. There may also be symptoms and signs pertaining to motor (pyramidal) system.

Epidemiologic studies from West have reported that about 10% of general population suffers from neuropathic pain[1,2]. Though data from Pakistan on this subject is lacking but considering burden of certain diseases like diabetes mellitus which afflicts about 25% of Pakistanis of age 45 years and above[4], and stroke which reportedly affects about 5% of Pakistani population over age of 40 years[6], burden of neuropathic pain in Pakistan is likely to be high. Western literature reports a prevalence of peripheral neuropathy from 8-23% while an Indian study reported the prevalence of 2.8% among Parsi adult[11-14]. Diabetes mellitus is probably most common cause of peripheral polyneuropathy. Western epidemiologic studies have clearly shown that about 50-60% of patients with diabetes mellitus have diabetic neuropathy and 11-26% has

painful neuropathies[15-17]. Though HIV is not a major health concern at present but it is emerging in our country. Frequency of painful peripheral neuropathy in HIV patients has been calculated to be 35%[18].

Postherpetic neuralgia is a very painful condition which presents with pain in dermatomal pattern, after shingles (herpes zoster). Its prevalence at 3 months in patients with herpes zoster is reported to be 7-23%[19,20].

Trigeminal Neuralgia is another very painful condition characterized by brief recurrent pain in distribution of one or more branches of trigeminal nerve (see figure 1), usually unilateral. Its reported annual incidence, based on two large population based studies is 4.7-8/100,000[21,22].

Carpal tunnel syndrome is most common compressive mononeuropathy which affects women more than man especially and obese persons. Other important high risk groups are pregnancy and rheumatoid arthritis. It presents with numbness, pain, paresthesias of the hand (usually sparing little finger) which worsens with household work, telephone use and during sleep. Its prevalence in West is reported in a range of 1-5 to 16%[18].

Cervical radiculopathy is characterized by neck pain radiated to one or both arms in dermatomal pattern. Disc herniation with or without degenerative spondylotic changes is most common cause of cervical radiculopathy. Age adjusted annual incidence is reported to be 83.2/100,000 population, from USA[23]. An Indian study reported point prevalence of 36/100,000[24] .

Low backache is a common symptom and it affects about 37% of general population at any given time[25]. Life time prevalence of backache is even higher[25].

Central pain syndromes are not uncommon. About 8-14% of stroke patients develop post stroke pain in distribution of the motor/sensory deficits[18,26]. The pain may starts as early as one month

or as late as 3years after the stroke[27]. Similarly 40% patients with spinal cord injury (SCI) and 23% patients of multiple sclerosis (MS) develop neuropathic pain.[18]

Diagnosis of neuropathic pain is based on history and clinical examination to determine and document the characteristics and distribution of the pain, corresponding positive (allodynia, hyperalgesia) and negative (sensory impairment to touch, pain, temperature, vibration or position sense in various combinations) sensory signs. Corresponding motor symptoms and signs (weakness, wasting, change in tone i.e. hypotonia or spasticity, depressed deep tendon reflexes or hypereflexia, clonus, Hoffman's sign and Babinski's sign) support the diagnosis. The motor features also help in localizing the process to peripheral or central nervous system thus provide basis for further appropriate laboratory evaluation. Presence or absence of autonomic features like changes in sweating pattern, postural hypotension should be documented, as this helps to narrow down the differential diagnosis. The examination confirms neuro-anatomic distribution of the signs corresponding to the sensory symptoms, an important step in diagnosis and evaluation of neuropathic pain.

Simple tools are required to assess different sensory modalities and motor system i.e. common/safety pins, cotton, soft brush, 10 g monofilament, tuning fork (128Hz) and a reflex hammer.

As mentioned earlier further diagnostic evaluation is tailored according to findings of initial assessment (history and physical examination) to determine underlying etiology, severity of the process and confirm location of the pathologic process. Broadly, neurophysiologic evaluation is recommended when history and physical examination suggest site of the pain origin is in peripheral nervous system e.g. peripheral neuropathy, mononeuropathy like carpal tunnel syndrome, radiculopathy or plexopathy. If site of origin of the pain is considered to be central

nervous system e.g. central post stroke pain, spinal cord injury, multiple sclerosis, then neuroimaging (radiologic evaluation) is required.

Neurophysiological testing (EMG/NCS) helps in identifying the site of neural dysfunction along the peripheral nervous system (nerve roots to peripheral nerves), underlying pathology (axonal vs. demyelinating) and gives valuable information regarding functional status of sensory and motor nerves[28]. The routine nerve conduction studies may be normal early in course of illness particularly radiculopathies (Ist three weeks) and acute neuropathies (Initial 1-2 weeks). Furthermore, routine nerve conduction studies do not assess small nerve fibers thus these studies are negative in small fiber neuropathies[28]. In such cases laser evoked potentials (LEPs) and autonomic testing (AT) provide useful information[28,29]. LEPs currently are not available in Pakistan and availability of AT is also limited. Quantitative sensory testing (QST) is another neurophysiologic testing which may be helpful in evaluating small fiber neuropathy[28].

Neurophysiologic testing (trigeminal and blink reflex) is also useful to differentiate between classic and symptomatic trigeminal neuralgia[28,30]. Patients with symptomatic trigeminal neuralgia are more likely to have abnormal reflexes and these patients should then undergo MRI brain for further evaluation.

Neuroimaging i.e. MRI brain and spine (cervical, thoracic) are required for suspected disease processes affecting brain (stroke, multiple sclerosis, traumatic brain injury) or spine (transverse myelitis, multiple sclerosis, traumatic myelopathy). Neuroimaging is also useful in evaluation of suspected radiculopathies, especially when there are focal deficits.

Biochemical and hematologic testing is required to determine underlying etiology of peripheral neuropathy. Highest yield tests in his group are blood glucose, B_{12} and immunofixation. Glucose tolerance test is required to document glucose tolerance if blood glucose levels are normal[31].

Skin biopsy can be performed to quantify somatic intraepidermal nerve fibers (IENF), which is an established tool to ascertain diagnosis of small fiber neuropathy[28,29].

Nerve biopsy is another important tool for evaluation of neuropathy to establish underlying etiology. In clinical practice it is mainly utilized in specialized centers and considered when underlying etiology of neuropathy is unclear. It may particularly be useful in determining evidence of amyloidosis, vasculitis and demyelination[29].

The diagnosis of neuropathic pain can be categorized as possible, probable or definite based on level of certainty[32]. The diagnosis is considered to be 'possible neuropathic pain', if examination and diagnostic tests are negative but history clearly suggest neuropathic pain in appropriate neuroanatomic distribution. If negative or positive sensory signs are confirmed on neurologic examination, in appropriate neuroanatomic distribution or diagnostic tests confirm pathologic process which could explain the neuropathic pain, a diagnosis of 'probable neuropathic pain is made and if both the examination and diagnostic tests support the diagnosis, the pain is considered to be 'definite neuropathic pain'

Etiology of neuropathic pain

The etiologic processes are myriad and are summarized in table 1*.

Symmetric polyneuropathies
Metabolic (Diabetes mellitus, impaired glucose tolerance, uremia, hypothyroidism)
Toxic (Chemotherapeutic agents, metronidazole, mega dose of vitamin B_6)
Nutritional (Vitamin B_{12} deficiency, Vitamin B_1 deficiency alcoholism)
Immune mediated (GBS, CIDP, gammopathies, associated with connective tissue disorders)
Infections (HIV associated neuropathy)
Neoplastic (Cancer related / paraneoplastic neuropathy)
Hereditary
Idiopathic
Mononeuropathies
Compressive (Carpal tunnel syndrome, cubital tunnel syndrome, tarsal tunnel syndrome, peroneal neuropathy at fibular head, Saturday night palsy/radial neuropathy in spiral groove)
Traumatic
Mononeuritis multiplex (multiple mononeuropathies); immune mediated
Radiculopathies
Disc disease (cervical and lumbosacral/sciatica)
Diabetes mellitus (cervical, thoracic, lumbosacral)
Infections like HIV, CMV, TB, Lyme disease
Radiation induced
Malignancies
Trauma

Plexopathies
Diabetes mellitus (Lumbosacral)
Trauma
Idiopathic
Other peripheral neuropathic pain syndromes
Trigeminal Neuralgia; classic (Idiopathic/classic), symptomatic
Post herpetic neuralgia
Central causes
Brain related (stroke, multiple sclerosis)
Spinal cord related (traumatic, compressive, infective, ischemic and post radiation myelopathies)
Complex regional pain syndrome (CRPS)
Type I and type II (previously called reflex sympathetic dystrophy and causalgia)

*GBS=Guillian Barre syndrome, CIDP=Chronic inflammatory demyelinating neuropathy

HIV=Human immunodeficiency virus, CMV=Cytomegalovirus, TB=Tuberculosis

Management of Neuropathic Pain

Painful peripheral neuropathy: Pharmacologic management

Several pharmacologic agents have been tested for management of neuropathic pain of various etiologies and multiple high quality randomized trials and systematic reviews provide evidence for efficacy several classes of pharmacologic agents.

TCAs (Tricyclic antidepressant agents; nortriptyline, amitriptyline, imipiramine, desipramine), SNRIs (serotonin and norepinephrine receptor inhibitors; duloxetine, venlafaxine) and certain antiepileptic medications (gabapentin, pregablin) are first line therapies for neuropathic pain. Side effect profile, cost, comorbid conditions, drug-drug interaction, risk and potential of abuse, and age determine selection of the medications in a particular patient. There are only few head to head trials and they have shown that the efficacy is similar of the agents e.g. venlafaxine and imipiramine were found to be equally effective in one trial and another trial concluded that gabapentin and nortriptyline have similar efficacy[33,34]. However, combination therapy may be superior[34]. Another trial reported that combination of venlafaxine and gabapentin is superior to gabapentin alone[35]. A recent metanalysis concluded that duloxetine, pregablin and gabapentin are probably equally effective for diabetic painful neuropathy.[36] Recently published guidelines (by American Academy of Neuromuscular and Electrodiagnostic Medicine, American Academy of neurology and American Academy of Physical Medicine and rehabilitation) on management of painful diabetic neuropathy concluded that strongest evidence is for pregablin then all the other agents, and have mentioned this as first line therapeutic agent[37]. They used stricter criteria for the trials to be considered as class I studies as compared to prior published guidelines by other professional societies[38,39] and furthermore they did not consider Cochrane

reviews in their analysis. Considering these facts, as well as our economic status, we suggest TCAs as first line therapeutic agents, in addition to the antiepileptic agents and SNRIs. TCAs[38-40] are cheapest of all available first line agents. Their effective dose range is 25-150 mg daily as single bed time dose. Secondary amine TCAs (nortriptyline, desipramine) are probably safer than other TCAs[39]. The Cochrane reported that number needed to treat (NNT) for TCAs was 3.6 (95% CI 3 to 4.5) to obtain moderate pain relief[40]. Their added advantage is their role in depression which may coexist in patients with chronic neuropathic pain. Though, neuropathic pain may respond to low dose, as little as 25 mg/day, minimum effective dose for depression is 75 mg/ day. Common side effects are sedation and dry mouth. These medications should be avoided in patients with glaucoma, benign prostatic hypertrophy, elderly and cardiac disorders. SNRIs i.e. duloxetine and venlafaxine are among 1st line treatment, specially for painful diabetic peripheral neuropathies at doses of 60-120 mg daily (in single dose) and 150-225 mg daily (in two divided doses) respectively[38-41]. Duloxetine is as effective as gabapentin and pregablin[36]. NNT for venlafaxine are 3.1 (2.2 to 5.1) and for duloxetine are 6 (95% CI 5 to 10) when > 50% reduction in pain is considered and for > 30% improvement of pain NNT are 5 (95% CI 3 to 8)[41]. Its common side effects are gastrointestinal symptoms, hyperhydrosis (excessive sweating), dizziness, insomnia, excessive sleepiness, tremor (especially at 120 mg/d) and non significant elevation in blood pressure[38,41]. Rarely, it causes hepatotoxicity[38]. Venlafaxine causes significant EKG changes in 5% of the patients and also hypertension so EKG and blood pressure monitoring is required[38]. Like TCAs these are also effective antidepressant agents and additionally SNRIs also work well in fibromyalgia. Number needed to harm (NNH) for duloxetine is reported to be 17 (95%CI 12 to 50), if harm is considered to stop treatment because of side effects[41].

Antiepileptic agents (only gabapentin and pregablin) are effective first line agents for painful peripheral neuropathies[38,39]. Effective dose of pregablin (PGB) is 300-600 mg daily in divided doses[42]. A lower dose of 150 mg/day is not effective for peripheral neuropathy[42]. Dry mouth, dizziness, weight gain, peripheral edema and sleepiness are common side effects. The side effects may occur in as high 45% at dose of 600 mg/day[42]. Another major problem is high percentage (20%) of withdrawal at doses of 600mg/ day[38,42]. NNT for PGB to cause pain improvement above 50% of baseline in painful diabetic neuropathy were calculated to be 5.0 (95% CI; 4.0 to 6.6), in the Cochrane review[42]. Gabapentin (GBP) is effective at doses of 900 mg/ day to 3600 mg/ day (in three divided doses)[38,43]. Side effects are more or less similar to pregablin. About 10% may have diarrhea[43]. NNT for painful diabetic neuropathy are 3.7 (95% CI; 2.4 to 5.4)[43]. The pain reduction effect may be noticed as early as second week if the drug is titrated up rapidly and with PBG maximum benefit may be achieved within two weeks[39]. Both of these drugs are easily available in Pakistan and these drugs do not have significant drug-drug interactions. These are also safe in patients with liver disorders, which are very common in Pakistan. Pregablin has advantage of having additional anxiolytic effect and proven efficacy in fibromyalgia. In elderly titration should be cautious and slow and dose of gabapentin has to be reduced by half in patients with renal failure.

Opioids and tramadol are other useful medications for pain control in neuropathy and should be considered if an adequate trial (adequate dose and duration of trial) of first line therapy fails or not tolerated well[37,38,44].Tramadol can be used in doses of 100-400 mg/day, in divided doses[44]. Common side effects are dizziness, central nervous system effects, incoordination, nausea, autonomic dysfunction, dry mouth, sedation, constipation and rarely seizures.[44]. NNT for at least 50% reduction in pain was found to be 3.8 (95% CI; 2.8 to 6.3) and NNH leading treatment

discontinuation was 8.3 (95% CI; 5.6 to 17)[44]. Opioids like morphine sulphate and oxycodiene up to doses of 120 mg/day and dextromethorphan at dose of 400mg/day are opioids, useful in controlling neuropathic pain of patients with diabetic polyneuropathy [37,45]. Risk of this particular aspect should be assessed in every patient. Main concern with these medications is abuse and addiction potential. The people who have personal or family history of substance abuse (illegal drug or prescription drug), young age (16-45 years), underlying mental disorders (obsessive-compulsive disorder, bipolar disorder, attention-deficit hyperactivity disorders, Depression, and schizophrenia) and history of preadolescence sexual abuse, especially in women predict risk of opioid abuse.

Opioids and tramadol can be used as first line therapy for acute exacerbations of pain and during early phase of therapy or in patients with concomitant nociceptive pain[39].

Carbamazepine and phenytoin have some role to control pain in peripheral neuropathies and be considered third line pharmacologic therapeutic agents[38]. These are cheap as compared to SNRIs and GBP, PGB.

Valproate has been found effective to control pain of diabetic painful neuropathy at doses of 500-1200mg/d[37]. Though this drug is freely available and is relatively cheap but considering its side effect profile, including potential to worsen glycemic control, this drug should be considered third line therapy.

Topiramate and SSRI (selective serotonin receptor inhibitors) i.e. fluoxetine have controversial role in management of diabetic painful poluneuropathy[37,38]. Similarly, utility of vitamins and lipoic acid is also unclear[37].

Lamotrigine, oxcarbamazepine and lacosamide have no role in management of neuropathic pain in peripheral neuropathies[37,38,46].

Other tested drugs which were found to be ineffective to control neuropathic pain include clonidine, mexiletine and petoxifylline[37].

Local application of capsaicin 0.075% four times a day is a useful in controlling neuropathic pain[37,47]. Single application of high dose patch (8%) over the painful site, for 30-90 minutes, is also effective and may be an alternative to daily multiple low dose topical application[45].

Other efficacious topical applications include lidocaine patch and isosorbide dinitrite spray, which may be used in patients with localized pain[37]. These are useful options in elderly especially those with history of falls[37,38].

Above mentioned therapies are particularly useful for painful diabetic peripheral neuropathy. Other neuropathies may not respond to the drugs, discussed above, in similar way.

In HIV neuropathy only effective therapies are cannabis, capsaicin patches. In a subgroup of patients who are on antiretroviral therapy, lamotrigine is effective at dose of 300 mg /day. Amitriptyline and GBP are not effective in HIV neuropathy[38].

Posttraumatic or postsurgical neuropathies are not responsive to GBP, venlafaxine and capsaicin. There is only modest efficacy of amitriptyline and botox A[38].

Cancer neuropathic pain is responsive to GBP. Amitriptyline and tramadol are second line agents[38].

There is limited evidence of utility of GBP in GBS patients to control neuropathic pain[38].

<u>Painful peripheral neuropathy: Non pharmacologic management</u>

A recently published analysis of available literature suggests that TENS is an effective nonpharmacologic modality to control pain in peripheral neuropathy, especially mild diabetic neuropathy[37,48].

Other nonpharmacologic modalities i.e. electromagnetic field treatment including magnetized shoe insoles, low intensity laser treatment and Reiki therapy are not effective so are not recommended in painful diabetic neuropathy[37].

Effect of rTMS in neuropathic pain of peripheral nerve origin is only transient[49].

Post herpetic neuralgia: Pharmacologic management

GBP, PGB and TCAs are first line oral agents for treatment of post herpetic neuralgia[38,50]. NNT for these medications are 2.2 (95% CI; 1.7 to 3.0), 3.3 (95% CI; 2.3 to 5.9) and 1.6 (95% CI; 1.2 to 2.4) respectively[50]. Pregablin may be effective at lower dose i.e. at 150 mg/d[42]. Lidocaine patch may be considered as first line agent especially in elderly.

Lidocaine should be avoided in patients with severe hepatic dysfunction. Topical capsaicin and opioids (morphine and methadone) are second line agents. High concentration (8%) capsaicin patch has advantage over oral medications as well as low concentration capsaicin, since single application for 30-90 minutes is effective for 3 months[38]. Though opioids have been found to be superior to the TCAs[50], in head to head comparisons, their potential for abuse and addiction as well as side effect profile these agents are recommended as second line therapeutic agents. Role of COX 2 inhibitors, mexilitene and tramadol is not established.

Short course of steroids during acute phase may be helpful in controlling acute pain[51].

Post herpetic neuralgia: Non pharmacologic management

Evidence of nonpharmacologic measures in management of PHN is unclear.

Trigeminal neuralgia: Pharmacologic treatment

Carbamazepine (200-1200 mg/d) is first line agent for pain control in classic trigeminal neuralgia[30]. Second and third line therapies include OXC (600-1800 mg/d) and LTG[30]. There is

also low level of evidence of efficacy of baclofen and pimozide[30]. There is not enough evidence to make firm recommendations regarding efficacy of clonazepam, gabapentin, phenytoin, tizanidine, topical capsaicin, and valproate for controlling pain in patients with CTN[30].

Topical ophthalmic anesthesia is probably ineffective for controlling pain in patients with CTN.

Efficacy of pharmacologic treatment for symptomatic trigeminal neuralgia is not established[30].

Trigeminal neuralgia: Interventional treatment including surgery

A recent analysis of available evidence suggests that surgical interventions are useful to control the pain. However, optimum timing for surgical intervention is unclear. Microvascular decompression (MVD) is probably the best of available procedures as it provides longer duration of pain control and over 70% of patients are pain free 5 years post surgery[30] Other options include percutaneous procedures on Gasserian ganglion and gamma knife.

The peripheral techniques using streptomycin/lidocaine are ineffective in controlling pain of trigeminal neuralgia[30].

Central pain syndromes: Pharmacologic treatment

Pregablin and TCAs are first line agents to treat central post stroke pain (CPSP) and spinal cord injury (SCI)[38]. Role of TCAs in CPSP is particularly seen in depressed patients at higher dose (150 mg/d). Lamotrigine, tramadol and opioids are second line agents for central pain syndromes, however, they have differential effects in different pain syndromes of central origin[38]. Lamotrigine works for CPSP (200 mg/d in two divided doses) but not SCI and tramadol works for SCI. Skin rash has been reported in 10% of patients treated with lamotrigine. There is also high quality evidence of efficacy of cannbanoids (oral spray) in central pain secondary to MS[38]. This agent is not freely available in clinical practice, yet.

Central pain syndromes: Non pharmacologic treatment

Utility of non pharmacologic therapeutic modalities like neurostimulation procedures (TENS, rTMS, spinal cord stimulation, direct current motor cortex stimulation) and acupuncture is not established in central pain syndrome[38,49]. However, there is recent growing evidence that neurostimulation procedures are useful in management of central pain syndromes and to some extent in peripheral pain syndromes[52-54].

Neck pain, backache, radiculopathies: Pharmacologic therapies

Available literature suggests that TCAs, SSRIs, venlafaxine, morphine and TPM are not effective in chronic radiculopathies and chronic low back pain[55]. NSAIDs are effective for short term pain control in low back pain without sciatica[56].

Neck pain, backache, radiculopathies: Non pharmacologic therapies

Though it is not available in Pakistan currently, spinal cord stimulation is an effective procedure in management of failed back surgery syndrome (FBSS). This modality has been found to be useful for FBSS compared to reoperation or addition to medical treatment[49,54]. Its role in other neuropathic pain syndromes is not yet established.

TENS is routinely used in clinical practice for backache, neck pain. However, a recent review of available literature suggest that it is effective in painful diabetic peripheral neuropathy but not for chronic backache[48]. Role of TENS in acute backache and in neck pain is not known.

The current literature does not support or refute the efficacy or effectiveness of continuous or intermittent traction for pain reduction, improved function or global perceived effect when compared to placebo traction, tablet or heat or other conservative treatments in patients with chronic neck disorders[57]. Role of mechanical traction in acute cervical radicular pain is unclear.

Mobilization and manipulation are moderately effective in acute and subacute neck pain at short term and intermediate term follow up[58]. However, Role of massage in neck pain is not clear[59].

Role of Chinese herbal medication to control pain in patients with degenerative cervical disc disease (with radicular symptoms or myelopathy) is not clear[60].

There is evidence that multimodal approach consist of manipulation/mobilization with exercises is effective to control pain in mechanical neck disorders with or without headache[61]. Efficacy of this approach in neck pain with radicular symptoms is not known[61].

There is moderate evidence of efficacy of acupuncture at short term in chronic mechanical neck disorders and chronic neck pain with radicular symptoms[62].

Role of surgery in cervical spondylotic radiculopathy and myelopathy is not very clear. Low quality evidence suggests that surgical intervention may help in faster pain relief in short term but in long term its efficacy is similar to hard collar immobilization or physiotherapy[63].

Acupuncture and dry needling are useful in controlling pain in short term and are effective than no treatment. These should be considered useful adjuncts to other therapeutic intervention for chronic low back pain[64]. However, utility of acupuncture in acute backache is not known[64].

Advising strict bed rest to patients with lumbosacral radiculopathy (sciatica) is a common practice. However, available literature does not support this approach. Rest or staying active does not change the functional outcome of patients with sciatica[65,66]. However, staying active may be helpful in improving acute low back pain[65].

For chronic and recurrent low back ache, back schools in occupational setting improve pain, functional status and time to return to work in short term and intermediate term follow up.

Back schools may be useful to control pain, improve functional status and speedy return to work for chronic and recurrent nonspecific low back pain[67-69].

For chronic low back pain operant and behavioral therapies are useful in short term and for chronic low back pain behavioral therapies and group exercises are equally effective in long

term[70]. Exercise therapy is especially useful in healthcare setting. Operant therapy is based on conditioning principle and involves measures to avoid behaviors which reinforce the pain and promote healthy behaviors which might help to relieve pain or return to work early. This strategy often requires active role of caregiver, spouse and trained staff to positively reinforce the patient's efforts towards healthy behavior like graded exercise increments.

Use of injection therapy (epidural or facet joint injection) is not supported by available evidence for subacute and chronic low back pain[71]. The epidural injections may improve pain in short term in selected patients but overall it has no impact on functional improvement, need of surgery or long term pain control[71,72].

Role of lumbar supports and chiropractic intervention to treat low back pain is unclear[73,74].

Massage is useful to treat subacute or chronic nonspecific low back pain and effect is long term after end of the treatment[75]. Different massage modalities i.e. Swedish massage, Thai massage and acupuncture massage are effective for this purpose[75].

After completion of formal treatment of low back pain, general exercises like stretching, strengthening, endurance training and posture training are useful to prevent recurrence of low back pain[76]. In patients with acute or subacute low back pain, intensive individual patient education sessions are useful to their swift return to work[77].

Prolotherapy is an injection based treatment strategy whereby periodic injections of irritant material is given in ligaments are tendineous attachments in order to improve joint stability. This mode of treatment may or may not be effective when used alone but when combined with other conservative measures like exercise or spinal manipulation may be more useful[78].

<u>Complex regional pain syndrome (CRPS)</u>

Complex regional pain syndrome encompasses two syndromes previously known as causalgia and reflex sympathetic dystrophy. This is a painful condition that affects limbs as result of any type of injury and is categorized in to type I if results from tissue damage and type II if inciting event is nerve injury[79]. Most common inciting event is bone fracture which was to be inciting event in 44% of the patient in a recent population based study[80]. Same study reported an incidence of 26.6/100,000 person years. It affects women three times more than men and is more common in postmenopausal women[80]. The diagnosis is clinical and based on presence of continuing pain usually disproportionate to the inciting injury with signs and symptoms involving sensory, motor, autonomic systems including vasomotor and sudomotor components[79]. Thus these patients would have pain, allodynia, hyperalgesia, hypoesthesia, edema, temperature and skin color changes, sweating, weakness, tremor and trophic changes in various combinations[79].

Effective treatment strategies for CPRS include topical application of 50% DSMO (dimethyl sulphoxide) four times daily and systemic administration of N-acetylcysteine 200 mg three times daily 600 mg daily[81]. There is also evidence of anti-inflammatory medications especially steroids in acute settings[82]. Other symptomatic measures like analgesics, neuropathic pain modulators, vasodilators and spasmolytics may be of some help[79]. There is some evidence that bisphosphonates may be useful in treatment of CRPS I[83]. If conservative measures fail, interventional therapies should be considered. Most useful interventional therapies are stellate ganglion block, lumbar sympathetic block and spinal cord stimulation[79]. Spinal cord stimulation is useful especially in patients with CRPS type I[49]. Role of brachial plexus block and epidural analgesia is unclear[79].

Parsonage turner syndrome

This syndrome also known as brachial neuritis may be acquired (post trauma, post surgery, post infectious or post vaccine) or hereditary and is characterized by severe upper extremity pain followed by weakness and wasting. There is little data on its management but anecdotal evidence and a single retrospective case series suggest that early (within four weeks of onset) corticosteroid therapy may have a positive influence on pain in some patients, and possibly speed up recovery in a few[84].

Carpal tunnel syndrome (CTS)

Several treatment options are available for treatment of CTS[85-88]. Non surgical treatment options include wrist splints, local steroid injections and short course of oral steroids[85,86,88-90]. Two dosing schedules were found to be useful, in controlled trials, i.e. 25 mg daily for 10 days or 20 mg daily for 10 days followed by 10 mg daily for days[89,90]. All of these are effective in short term (3 months) and if one modality fails, other may be tried[88]. Surgical intervention should be considered if nonsurgical therapies fail or evidence of axonal injury noted on electrodiagnostic studies[88]. Early surgery is an option if patient wants so[88].

Foot care and prevention of complications[91]

Impaired feet sensations increase the risk of trauma, ulcers and gangrene leading to amputation. Simple measures, as mentioned below, are helpful to prevent such complications.

Diabetes mellitus rampant in current era and is also a common cause of neuropathy so strict control of diabetes is utmost importance as tight control of diabetes mellitus decrease complication (including neuropathy) rate. Vascular insufficiency / peripheral vascular disease, either as a result of diabetes mellitus or atherosclerosis, increases risk of foot complications so control of risk factors for atherosclerosis is also vital. Thus a healthy and appropriate diet plan,

daily brisk walk for 30 minutes, avoiding smoking, monitoring, recording and controlling blood pressure and blood sugar are important measures to prevent devastating complications.

Checking feet daily for cuts, cracks, sores and blisters help in early identification and early management of the problem.

Keeping skin clean, smooth and moist, cutting nail regularly, always wearing slippers or shoes, putting on socks, avoiding tightly fit and pointed shoes, looking each time inside shoes before putting these on are important measures to prevent the complications. Drinking adequate amount of water is also important to keep skin healthy.

Prevention of neuropathic pain

Painful diabetic neuropathy is among most important cause of neuropathic pain of peripheral origin. A tight control of diabetes mellitus is important to prevent development of neuropathy. Similarly stroke is most important cause of central pain syndrome and strategies for primary stroke prevention (optimal care and control of diabetes mellitus and blood pressure, regular physical exercise and smoking cessation) are important to reduce prevalence of central post stroke pain.

Vitamin C 500mg daily for two months after wrist fracture has been found to reduce risk of CPRS[92,93].

Neither steroids nor acyclovir prevent PHN in patients with shingles[94,95]. However, steroids may reduce acute pain in acute settings[94]. On the contrary vaccination against herpes zoster not only reduces the risk of shingles but also that of post herpetic neuralgia, especially in people over age of 60 years[96].

Definitive treatment options

Definitive treatment options are limited. Trials of aldolase reductase inhibitors failed to treat diabetic polyneuropathy[97]. Surgical treatment for trigeminal neuralgia and carpal tunnel syndrome, vide supra, may be considered as specific therapies for these ailments. Neuropathic pain resulting from autoimmune neuropathies like GBS, CIDP and vasculitic neuropathies may responds to treatment of underlying disease processes. Therapeutic options for GBS are plasmaphresis or intravenous immunoglobulins (IVIG) while that for CIDP include IVIG, steroids and other immunosuppressive agents[98,99]. The vasculitic neuropathies also require immunosuppressive therapy[100].

Summary

A stepwise approach should be applied for neuropathic pain, starting with recognition of symptoms suggestive of neuropathic pain followed by detailed history and physical examination in order to confirm the diagnosis and to determine underlying etiology. This should be followed by appropriate targeted work up to support the diagnosis and confirm underlying etiology. One of the first line therapeutic agents i.e. a tricyclic antidepressant, SNRI or the antiepileptics (gabapentin and pregablin) should be started, depending on comorbidity. If an adequate trial (usually 4-8 weeks) at optimal dose fails to control the pain, another agent should be tried. Combination therapy may be considered if two first line agents fail or provide only partial relief. Second line agents (tramol or opoids) are options if first line agents fail or there is acute exacerbation of pain or the pain is very severe. Local application of capsaicin, lidocaine or isosorbid dinitirite spray is a useful option for localized pain especially in elderly and people at risk of falls.

Future directions and need

Population based studies are required to establish local epidemiology of neuropathic pain.

Randomized head to head drug trials, as well trials involving alternative therapies and neurostimulation techniques are required in native population to establish cost effective therapeutic strategies.

Therapeutic trials for acute radicular pain are warranted to determine efficacy of different therapeutic options including medications, neurostimulation techniques (especially TENS), physical therapy, patient education and alternative therapies like massage and acupuncture. Such trials will also help to establish best therapeutic paradigm for management of acute radicular pain syndromes.

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