Treatment Guidelines for Neuropathic Pain in Clinical Practice in Taiwan

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Abstract

Neuropathic pain is a complicated symptomatic disease. This complexity is not because the characteristics of the pain differ from nociceptive inflammatory symptoms, but because of its complex mechanism. Peripheral sensitization, ectopic discharge, central sensitization, central re-organization and loss of inhibition play roles in the mechanism. However, with regards to treatment, the outcomes are unsatisfactory for both physicians and patients, for example in central post-stroke central pain (CPSP). Under-treatment by physicians frequently occurs due to fear of adverse effects or abuse of anti-neuropathic pain drugs. Therefore, a multidisciplinary approach including non-pharmacological management, rehabilitation, careful explanation, stepwise pain reduction, daily diary record, and tailored individual planning for medications are helpful. Pharmacological treatment is the treatment of choice for many conditions including post-herpetic neuralgia (PHN), diabetic painful neuropathy (DPNP), central post-stroke pain (CPSP), trigeminal neuralgia (TN), complex regional pain syndrome (CRPS), cancer pain, and failed back syndrome, while polypharmacy is also practiced. Tricyclic antidepressants (TCA), gamma-aminobutyric acid (GABA), voltage-dependent calcium channel blockers (CCB), selective non-epinephrine reuptake inhibitors (SNRI), opioids and morphine are evidence-based medicines (EBM) with different outcomes per individual. Acupuncture is effective to some extent and is used commonly in Taiwan with a perceived placebo benefits, however there is a lack of randomized control studies to clarify the effects. In this study, we review the guidelines for total pain management in Taiwan, and compare them to the guidelines used in Europe and the US.

Key words: neuropathic pain, complex mechanisms, pharmacological and non-pharmacological treatment, guidelines comparison, patient education
**Introduction**

The popular expression, “No pain, no gain”, tells us that there are no rewards without effort. From a medical point of view, pain allows for escape from physical or psychological injury, however excessive pain not only causes fear and recall of the traumatic event, similar to post-traumatic stress disorder (PTSD), but also causes psychological or physical consequences such as disability, insomnia or depression (1). The famous "Paradise Lost" (written by John Milton, painted by William Blake) described mostly biblical stories. The painting showed an archangel who had fallen to Earth trying to tempt a child with a pure spirit to commit a crime. The suffering shown on the face of the archangel expressed pain. People suffering from pain may have suicidal or violent moods. Excessive pain can even make an angel become a devil. (Figure 1)

Historical records of pain began with Rene Descartes (1596 ~ 1650). “...If for example fire comes near the foot, the minute particles of this fire, which as you know move with great velocity, have the power to set in motion the spot of the skin...”, was the earliest scientific observation about pain. In 1973, the International Association for the Study of Pain (IASP) established the first definition of pain as, "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” This definition was used until 2007 due to some controversial issue as malingering or hysteria associated with pain. In 2008, Tradee and his colleagues modified the definition to, “Pain arises as a direct consequence of a lesion or disease affecting the somatosensory system” (2). This definition provides a modern medical viewpoint of scientific evolution. It is important for clinicians to understand the development of pain history from a global point of view.

**Prevalence**

The prevalence and incidence of neuropathic pain is not clear. Bennett reported the prevalence of neuropathic pain in the US to be 1-2% (3), of which low back pain, diabetic painful neuropathy (DPNP) and post-herpetic neuralgia (PHN) were the top three causes. This was similar to Europe and Asia with rough estimation in the past. In a recent study in the Netherlands with 362,693 subjects, the prevalence of neuropathic pain was estimated to be 1% of the general population (4). However, with different methodologies, heterogeneity of clinical trials, non-unique randomized or matched studies, wide range of sample sizes, diverse races and genetic issues, and inconsistent validity statistics, it is difficult to estimate the unique and global rates of the prevalence of neuropathic pain (5). The IASP reviewed the relevant literatures in
2010 and reported that the current prevalence of neuropathic pain is not known (www.iasp-pain.org). This statement alerted clinicians to the fact that consistent methodologies, unique definitions and randomized control trials are important to obtain the prevalence of neuropathic pain in different population groups.

Marketing

According to global market research in 2003 (MarketResearch.com), the most common drugs used to treat neuropathic pain were non-steroid anti-inflammation drugs (NSAIDs) (42%), non-narcotic analgesics (21%), anti-epileptic drugs (14%), and potent opiates (4%). However, to date, treating neuropathic pain with NSAIDs has been found to be ineffective, indicating that most clinicians are not familiar with the principles for neuropathic pain control. In contrast, a European marketing survey in 2010 (www.qrxpharma.com) found that the most common drugs used to treat neuropathic pain were strong opioids (30%) followed by NSAIDs (22%) and anti-epileptic drugs (12%). Culture differences, the low rate of law-suits for opioids misuse, or disease severity may explain this difference. According to World Health Organization (WHO) analgesic ladder updated in 2011 (Figure 2), NSAIDs or non-narcotic analgesics should be used as first-line drugs if the pain scores are from 1 to 3 (scale 1-10). For pain scores from 4 to 6, weak opioids or short-acting analgesics should be used, and for pain scores from 7 to 10 powerful opiates can be considered. The pharmacological effects of opiates are complex, acting not only on pre-synaptic areas to reduce the release of excited ions, but also on post-synaptic receptors to stabilize potassium channels and hyper-polarization. Opiates can also act on general μ and δ receptors throughout the whole body to relieve systemic pain. Addiction or tolerability will occur if they are used too frequently or in inappropriate doses. Therefore, opiates should be considered as a second or third line of treatment in pain control. In certain circumstances, they can be used as first-line treatment especially in terminal cancer patients.

Mechanisms of pain

Realizing that neuropathic pain treatment should be based on a mechanism-based approach is important (6-8). Pain is derived from surrounding nociceptors by the release of neurotransmitters (e.g., substance-p and glutamate) stimulating peripheral nerve fibers (C or Aδ). This signal is transmitted through the spinal thalamic tract via the spinal cord reaching the ventral posterior nucleus of the thalamus, and is then projected to the limbic system and cortical parietal lobe to feel and recognize the pain. Based on this anatomical pathway, five mechanisms have been proposed to explain
pain:

1. Peripheral sensitization. Following a peripheral nerve injury, a sensitization occurs which is characterized by spontaneous activity by neurons, a lowered threshold for activation and increased response to a given stimulus. Zoster-associated pain, tissue injury and osteoarthritis with pain are attributed to this kind of mechanism, with characteristics of burning, heating, hyperalgesia or allodynia (9). This pain is more acute, occurring within 2~3 months of symptomatic attacks, and anti-inflammatory drugs or steroids usually have some benefits (10).

2. Ectopic discharge. Ectopic neuronal pacemakers can occur at various sites along the length of the nerve. Increased densities of abnormal or dysfunctional sodium channels are thought to be the cause of this ectopic activity. This pain is not uncommon, and sudden, brief, short-term lancinating or sharpening in character, with most complaints related to migration. Since channel pumping is malfunctioning, the use of sodium channel blocker seems to be effective in this mechanism (11, 12). This may explain the rationale of treatment with lidocaine, mexiletine, phenytoin, carbamazepine and lamotrigine.

3. Central sensitization and plasticity. NMDA (N-methyl-D-aspartate) receptors play a critical role in synaptic plasticity within pain transmission pathways and are thus likely to be important in neuropathic pain (13, 14). This mechanism is mainly caused by excessive excitation signals into the spinal cord or brain. Under normal circumstances, NMDA is plugged by magnesium ions. When noxious stimuli induce the release of interleukin and glutamate excitatory substances, post-synaptic AMPA and neurokinin-I are elicited as a binding complex with gate control of NMDA, un-plugging the magnesium ions and freeing calcium influx into the cellular membrane to activate depolarization (15). Ketamine and dextromethorphan are major two drugs used for this kind of pain. However, in clinically assessed NMDA antagonists, the narrow separation between effectiveness and liability, such as sedation, memory impairment, motor in-coordination and psychotomimetic effects, has severely hampered their utility for the treatment of neuropathic pain (16).

4. Central reorganization. Peripheral nerves have the characteristic of regeneration. After nerve injury, reconstruction will occur over a period of time. Sprouting errors (e.g., Aβ cross-linked to C fibers) lead to previously painless areas experiencing unendurable sharpening pain (ephaptic cross talk). This phenomenon can be seen in patients with spinal cord injuries or syringomyelia (17, 18). The mechanism mainly
consists of sodium channel excitability, synaptic sprouting, and spinal cord re-organization or hyper-excitability (19, 20). It is difficult to treat, and GABA-like inhibitory drugs or voltage-dependent channel blockers are mainly used. Nevertheless, in a recent animal study, the sprouting and regeneration errors were not found to play a major role in eliciting pain (21).

5. Loss of descending inhibition control. Researchers have suggested that a part of the cause of neuropathic pain is due to the inefficiency of endogenous inhibitory systems (3, 22). Descending pain transmission inhibitory control originates from brainstem centers located at periaqueductal gray matter (PAG), locus ceruleus (LC), and ventral-medial medulla area (23). This descending inhibitory control system is mediated by some peptides, serotonin and non-epinephrine transmission to modulate the pain (24). Experimental and empirical studies have confirmed that inhibition of the conduction of both transmitters has a better effect for pain control than inhibiting only one or other antidepressant (25, 26). This can also improve mood and depressive disorder. For this reason, serotonin and non-epinephrine reuptake inhibitors (SNRI) have been found to have better outcomes than selective serotonin reuptake inhibitors (SSRI) alone in pain control in clinical practice (27, 28).

In addition to the above mechanisms, neuro-immune dysfunction, genetic factors, low-threshold Aβ fiber-mediated pain, and ion channel interactions are all likely to be relevant to neuropathic pain (29). Clinicians should be aware of these mechanisms in order to have a better understanding of treating neuropathic pain syndromes.

Etiologies

Various etiologies (30) cause neuropathic pain, including vascular factors (central post stroke pain), infection (post-herpetic neuralgia), trauma (amputated phantom pain), toxin-related (arsenic, cadmium poisoning), alcohol-related (alcoholic polyneuropathy), metabolic abnormalities (diabetes, steroids or thyroid neuropathy), immune-related response (multiple sclerosis, acute inflammatory disseminating polyradiculoneuropathy or human immune-virus neuropathy), compression (carpal-tunnel syndrome or spinal stenosis), cancer-related (paraneoplastic syndrome or cancer pain), vitamin deficiency (subacute combine degeneration), and genetic abnormalities (Fabry disease)(31). It is imperative to reverse these causal factors to cure or alleviate pain. Distinguishing symptoms of burning, pricking, lightening or signs of hyperalgesia, allodynia or causalgia from neuropathy is difficult. Patients always have similar complaints of neuropathic pain at clinical visits (32).
Diagnosis of neuropathic pain

A rapid useful clinical technique is taught to the residents of our hospital, a tertiary medical center (2000-bed available) and also in community hospitals in southern Taiwan which is simply, “3Ls - listen, look, and location”. Listening to the descriptions of the patients with regards the pain characteristics, duration and onset of time, intensity, and relapse or remission periods offer a reliable clue in clinical diagnosis. Looking for blisters of the skin (zoster-associated pain), scarring along the nerves (post-herpetic neuralgia), neurological signs such as Lhermitte or Laseque tests (cervical or lumbar rooting involvement, with or without disc hernia), and locations at the wrist (carpal-tunnel syndrome) or thigh (meralgia paresthetica) with aggravated precipitation is a consistent diagnostic method compared to using nerve conductive velocity (NCV) or quantitative sensory tests (QST) (33, 34). We have used pain questionnaires such as The Leeds Assessment of Neuropathic Pain Symptoms and Signs (LANSS) Pain Scale, Neuropathic Pain Questionnaire (NPQ), Douleur Neuropathique 4 questions (DN4), and ID pain in Chinese version (35). In addition, electromyography (EMG), histamine tests and thermography can also be used as diagnostic tools (36). It is notable that small fiber disease can not be excluded if nerve conductive velocity is within normal range. It is worth taking repeat histories, neurological examinations, imaging studies or skin-punch biopsies if the patients have persistent complaints of neuropathic-like symptoms (37, 38)

Non- and pharmacological treatment

Non-pharmacological management such as EMG biofeedback, relaxation therapy, occupational therapy, transcutaneous electrical nerve stimulation (TENS), and cognitive-behavior therapy (CBT) are evidence-based (EBM) techniques in migraine prevention (39, 40), however these effects in treating neuropathic pain are insufficient evidences (19, 41, 42). Acupuncture is popular in Taiwan, and the results were still in controversy to some extent (43). The Cochrane review in 2011 undertook similar research, and the study is ongoing at present (www.thecochranelibrary.com). With regards meditation or “Zen” for pain suppression, the evidences are scanty with some theories postulated (44). According to the brain-gate theory proposed by Melzack and Wall in 1965 (45), small fiber (C-fiber) conducting pain can be suppressed by large fibers on stimuli at the same time, therefore lessening the pain. This is the reason why rubbing or pressing around an injected site will alleviate the pain after receiving an injection. Melzack et al. amended the theory in 1982 (46), by adding the perception of awareness or inattention to the pain itself (e.g., focus on other things). Regarding the
research on meditation and Zen, Prof. James H. Austin published a book, “Zen and the Brain” in 1998 (47) (which was translated into Chinese in 2010, by Prof. Nai-Shin Chu, Department of Neurology in Chang Gung Memorial Hospital in Taiwan). One chapter describes a study in monks with differing ecclesiastic hierarchies. During meditation, brain recording revealed a high-frequency of 30-70 gamma waves which synchronized all brain activity and spread to the prefrontal lobe and limbic system to reduce pain and calm emotions. High-hierarchy monks were able to put their hands in ice water for many hours during meditation without painful sensations compared to ordinary people or low-hierarchy monks. This is an example of gate control theory, by focusing the mind with regards attention or self-control awareness. However, not everyone has this kind of training. From an EBM point of view, the effect resulting from meditation to reduce pain is still inadequate.

Pharmacological treatments for pain medications and updated guidelines have been reviewed (10, 27, 37, 48-52). The evidence of strength based on the study methods, clinical efficacy, and scientific measures are graded into A, B, C, U, with A being the most recommended, while U having inadequate or conflicting evidence and should be avoided if possible (appendix).

Five common types of neuropathic pain

a. Post-Herpetic Neuralgia (PHN). Approximately 2.2-3.4/1000 person-year of herpes zoster occurs in the Europe and US (53, 54), however, the prevalence in Taiwan has not been estimated. In general, PHN occurs 3 months after skin blisters have healed or scarred. Immune response and age are two major predictors to have devastating pain. The drugs based on the American Academy of Neurology (AAN) guidelines in 2004 were gabapentin, 5% lidocaine patch, pregabalin, oxycodone, and tricyclic anti-depressive agents (TCAs) are recommended as first-line drugs (level A). However, the US Food and Drug Administration (FDA) have only endorsed three (gabapentin, pregabalin, and 5% lidocaine patch). For second-line use, 0.075% capsaicin, aspirin cream and intrathecal methylprednisolone injection are recommended (level B), while camabazepine, ketamine, and methyl-prednisolone are rating as limited or ineffective benefits (level U), and should be avoided. Compared to the European Federation of Neurological Societies guidelines (EFNS) in 2005, TCAs (mainly amitriptyline), gabapentin, pregabalin, and 5% lidocaine patch are recommended (level A), followed by strong opioids, tramadol, and 0.075% capsaicin (level B). The central-acting NMDA antagonists and mexiletine lack efficacy and should not be used (level A). This is why ketamine is not used to treat PHN although
According to the International Classification of Headache Disorders (ICHD-II) in 2004, typical trigeminal neuralgia (classic TN) is diagnosed as follows: A. Paroxysmal attacks of pain lasting from a fraction of a second to two minutes, with or without a prodrome of burning or tingling, occurring usually without warning and usually without a trigger. B. The attacks are usually unilateral and are usually of slight to moderate intensity. C. The attacks are typically unilateral, and the pain is usually unilateral. D. The attacks are usually unilateral, and the pain is usually unilateral. E. The attacks are usually unilateral, and the pain is usually unilateral. F. The attacks are usually unilateral, and the pain is usually unilateral. G. The attacks are usually unilateral, and the pain is usually unilateral. H. The attacks are usually unilateral, and the pain is usually unilateral. I. The attacks are usually unilateral, and the pain is usually unilateral. J. The attacks are usually unilateral, and the pain is usually unilateral. K. The attacks are usually unilateral, and the pain is usually unilateral. L. The attacks are usually unilateral, and the pain is usually unilateral. M. The attacks are usually unilateral, and the pain is usually unilateral. N. The attacks are usually unilateral, and the pain is usually unilateral. O. The attacks are usually unilateral, and the pain is usually unilateral. P. The attacks are usually unilateral, and the pain is usually unilateral. Q. The attacks are usually unilateral, and the pain is usually unilateral. R. The attacks are usually unilateral, and the pain is usually unilateral. S. The attacks are usually unilateral, and the pain is usually unilateral. T. The attacks are usually unilateral, and the pain is usually unilateral. U. The attacks are usually unilateral, and the pain is usually unilateral. V. The attacks are usually unilateral, and the pain is usually unilateral. W. The attacks are usually unilateral, and the pain is usually unilateral. X. The attacks are usually unilateral, and the pain is usually unilateral. Y. The attacks are usually unilateral, and the pain is usually unilateral. Z. The attacks are usually unilateral, and the pain is usually unilateral. 

b. Diabetic Painful Neuropathic Pain (DPNP). The prevalence of diabetes mellitus (DM) in Taiwan is estimated to be 7.5% in those above 15 years of age (M: F=8.2: 6.8), and 15.5% (M: F=15.5:14.0) in those above 45 years of age. The prevalence of DPNP was estimated to be 26.8% in patients with type II DM in a large-scaled survey (58). In the US, the prevalence of type II DM with DPNP was 16.2% less than in Taiwan (59, 60), and varying from 7-26% in Europe (61). The clinical diagnosis of DPNP is based on four indicators: preprandial blood sugar ≥ 126 mg, and post-prandial blood sugar (2 hours) ≥ 200mg; NCV studies confirming the neuropathy; pain originated as neuropathic characteristics; excluding non-diabetic factors(62). Based on these criteria, the initial guidelines were proposed by the Mayo Clinic in 2006, in which duloxetine, oxycondone CR, pregabalin, and TCAs were the first tier of recommendations (level A). Carbamazepine, gabapentin, lamotrigine, tramadol, and venalfaxine ER were recommended as second tier drugs (level B). As previously mentioned, opioids should not be used for first-line treatment, so the new guidelines of the AAN in 2011 amended the priority, with pregabalin 300-600 mg/d recommended as first tier (level A), followed by gabapentin 900-3600 mg/d, venalfaxine ER 75-225 mg/d, sodium valproate 500-1200 mg/d, duloxetine 60-120 mg/d, amitriptyline 25-100 mg/d, and tramadol 210 mg/d etc, as second-line medications (level B) (50). In Taiwan, only duloxetine has been approved by the Bureau of Health Insurance to date, with an adaptable dose from 60-120 mg/d and slow titration (36). Comparing the EFNS guidelines in 2010 and AAN in 2011, sodium valproate was not suggested for use in Europe, and TCAs not recommended as first-line treatment in the US. However, both agreed that tramadol and opioid-like substances should be second-line medications. The pharmacological principles are also similar in the IASP and CPS (Canadian Pain Society) (63, 19).

c. Trigeminal Neuralgia (TN). The lifetime prevalence in German is 0.3% (64), and around 0.15-0.4% in US (65). The prevalence in Taiwan is still not estimated.
without persistent aching between paroxysms, affecting one or more divisions of the trigeminal nerve and fulfilling the criteria of B and C; B. pain has at least one of the following characteristics: (1) intense, sharp, superficial or stabbing; (2) precipitating from trigger areas or by trigger factors; C. Attacks are stereotyped in the individual patient. D. No causative lesions or vascular compression are demonstrated. E. Non-attributable to other disorders (66). Distinguishing symptomatic TN from classic TN has reliable sensitivity with regards abnormal blinking reflex, sensory deficits and bilateral trigeminal involvement (67). Patients with the above symptoms/signs of trigeminal pain should be arranged for neuroimaging studies to confirm the etiology of tumors or vascular lesions. Age, poor response to medication or V1 branch involvement are less sensitive to predict symptomatic TN, and should be not used as absolute predictors (68). For trigeminal neuralgia, the most effective treatment regardless of whether in the US, Europe or Taiwan, is carbamazepine as the first-line (level A), with oxycabazepine as the second-line (level B). The FDA only endorses carbamazepine to treat TN. Other drugs such as baclofen, lamotrigiene, and gabapentin do not seem to be very effective and should not be used as first- or second-line (level C or U). When using carbamazepine in Taiwanese patients, clinicians should be aware of Steven-Johnson syndrome (SJS), with which severe adverse effects of skin toxic dermatitis, generalized eruptions, or lethal events have been reported due to genetic risks. Therefore, surveys of blood HLA-B1502 to confirm a negative reaction before use is important. The odds ratio (OR) for positive HLA-B1502 is 1357 times risky higher than for a negative reaction to have SJS (69).

d. Central Post-Stroke Pain (CPSP). This kind of pain is the most difficult to treat or cure of all types of neuropathic pain, not only because of a poorly understood and complex mechanism, but also because of a lack of understanding of how the descending modulating system works (70-73). From functional magnetic resonance studies, it has been found that unilateral stroke in the brainstem, thalamus or cortical area, can elicit a wide range of hot-spot reactions cross linked to both sides. Persistent pain can even cause structural changes as well as functional derangement in the brain (74). As such widespread areas are involved in CPSP, it has been speculated that no single drug can suppress this widely activating system. From a recent literature review (75-78), no recommended level A drugs but TCA (amitriptyline), lamotrigine, and opioids drugs are suggested as second-line (level B) implicated the mild to moderate strength of evidence. In addition, SSRI, transcranial magnetic stimulation, and passive range of motion exercises (PROM) were reported as level C suggestions. The European guidelines in 2011 suggested pregabalin, gabapentin, and TCA as first-line medications, while cannabinoids (in multiple sclerosis), lamotrigine, opioids and
tramadol (in spinal cord injury) as a second-line drugs (79). The most common dosage for treating neuropathic pain with lamotrigine was 200 mg/d with slow titration at an initial 25 mg/d to avoid SJS (75, 80). Pregabalin 300-600 mg/d in Europe has been used with better tolerance and efficacy, varying from 30-70% (81-83). TCA of amitriptyline 75 mg/d (titrated from 10 mg/d) has been shown to have a moderate effect, but clinicians should be aware of side effects or cardiac death (Tosade de’ point) especially in the elderly. In summary, negative symptoms (hypoesthesia, numbness) are less likely to have significant improvement than positive symptoms of tingling, lightening, and burning or allodynia (84, 85).

e. Complex Regional Pain Syndrome (CRPS). This kind of pain mainly affects the hands, shoulders, elbows and feet, and can be categorized into two types (86). The common type I was previously known as reflex sympathetic dystrophy (RSD). The etiology is not well understood. It is generally considered to involve nerve injury with messages to the brain, followed by excessive descending inhibition of spinal sympathetic activity resulting in reflex vasoconstriction with excitatory transmitter release. The extravasation of substances stimuli the pain receptors and uploading message to the brain induced another vicious cycle (87). In practice, local edema on the affected extremities with pale skin and tenderness are seen. Based on the consensus of the International Coalition on Neuropathic Pain (ICNeP) in 2002, the recommended sequences are surgery, nerve block, and supplementary medications as gabapentin, opioids, TCAs, or combination therapy. However, the updated treatment in Hong Kong recommended multidisciplinary approach including cognitive behavior therapy, medical treatment, occupational therapy and intervention at the same time (88). According to the pharmacological guidelines by Perez et al and task force, and the outcome evaluation in literatures (89, 90), there are insufficient evidences for acute treatment with NSAIDs, botulism toxin, steroids, opioids or oral muscle relaxants (level C), anticonvulsants (pregabalin, carbamazepine, phenytoin) (level C or U), capsaicin or antidepressants (level U) and gabapentin 600–1800 mg/d (level B). Of note, to prevent CRPS after wrist fracture, 500 mg/d of vitamin C is recommended with moderate efficacy (level B). Another Type II CRPS, known as causalgia, is also caused by nerve injury with inappropriate pain, and more manifestations of skin or local sympathetic changes. In briefly, there are poor pharmacological effects in treating CRPS but for prevention.

Taiwan guidelines for neuropathic pain treatment
In 2010, an advisory committee composed of specialists in the fields of anesthesia, neurology, endocrine, rheumatology, orthopedics, and psychiatry for pain management was established in Taiwan. These experts reached a consensus and provided a reference guideline for Taiwanese patients being treated for neuropathic pain. The Taiwan Guidance for Total Pain Management is briefly introduced below with the four common pain types. As yet, wide range of inter-rater variability in individuals, no recommended doses except for trigeminal neuralgia are provided in the consensus guideline (36).

1. Painful polyneuropathy (PPN). The recommended medications are TCA, pregabalin, gabapentin (level A) for first-line drugs; SNRIs ( duloxetine and venlafaxine) (level B) for the second-line; and tramadol, lamotrigine, opioids (level B) for the third-line; while 0.075% capsaicin, mexiletine, oxcarbazepine, SSRI, and topiramate for PPN were determined to be ineffective (level A).

2. Post-herpetic neuralgia (PHN). The first-line recommendations are TCA, pregabalin, gabapentin and 5% lidocaine patch (level A); 0.075% capsaicin, tramadol, opioids, valproate as second or third-line (level B); mexiletine, lorazepam, and NMDA antagonists were determined to be invalid (Level A).

3. Central pain (CP). The first-line recommendations are TCA (amitriptyline), pregabalin and gabapentin (level B); lamotrigine, cannabinoids and opioids as second- or third-line (level B or C); valproate and mexiletine were determined to be ineffective (level B).

4. Trigeminal neuralgia (TN). The first-line recommendations were carbamazepine 200-1200 mg/d (level A) and oxcarbazepine 600-1800 mg/d (level B); the second-line was surgery or micro-decompression (level B). Lamotrigine or baclofen as alternative medications in patients unwilling to receive surgery (level C or U).

**Guidelines in the US, Europe and Taiwan**

Comparing the guidelines in the US, Europe and Taiwan, there are some similarities (Table 1 ~ 3). Tricyclic antidepressants are recommended for all kinds of neuropathic pain, and are effective with a number-needed to treat (NNT) of about 3-4. However, the FDA in the US has not endorsed TCA for treating neuropathic pain. There is concerned relevant to the adverse effects including double vision, dry mouth, glaucoma, urinary retention, cardiac arrhythmia, Torsades de pointes, or death, especially in the elderly. There are disparities in the priority of the medications between the guidelines (48-52, 91). In Europe, TCAs or SNRIs ( duloxetine or
venlafaxine) are trend to be recommended first, while calcium channel blockers (CCB) (pregabalin and gabapentin) are more popular in the US. Selective CCB play a major role in modulating preganglionic α2δ voltage-gate channel reducing the release of excitatory substances, and therefore reducing pain (82, 92). However, CCB have side effects of central inhibition such as drowsiness, dizziness, unsteady gait, and pitting edema (93). Pregabalin is a new generation of CCB and has been extensively studied in treating neuropathic pain with moderate to good effects. Its good tolerability, dose-linear relationship, and rapid pharmacokinetic action promise it a potential drug in treating neuropathic pain. In addition, sodium channel blockers including carbamazepine, phenytoin and mexiletine, glutamate-inhibitors such as benzodiazepam, and GABA-inhibitors such as baclofen play roles in pain control by inhibiting repetitive firing of excitatory neurons or interfering with ion channels.

**Education and individual treatment are important**

Another issue with regards successful treatment is related to education and adequate dose. Patients who are given medications without a thorough explanation by physicians/pharmacists may have results of inferiority than those do receive a well explanation before taking the medication (94). Tailoring the dosage for each patient, asking about a history of drug tolerability, recording a diary of pain using a visual analogue scale (VAS), and explaining the stepwise pain reduction are mandatory for analyzing treatment outcomes. Ultimately, neuropathic pain is difficult to “cure” but always “remission” that is habitually over-expectations by the sufferers. Gradual escalation to a suitable dose and maintaining an adequate period are favored if the medication is effective. Adjusting the dose based on an individual’s need is different between patients in the East and West, and some patients need to receive a long-term course to avoid flare-ups, especially in cancer pain, PHN, CPSP and CRPS. A multidisciplinary approach with combined medications, non-pharmacological biofeedback, TENS, meditation, spiritual encouragement, religion or acupuncture may be helpful to alleviate severe pain although the current evidence is insufficient (95). As meditation is a part of Chinese culture, however, people who meditate may experience some placebo benefits to reduce pain even though the mechanism is not well known. In summary, NSAIDs are mostly ineffective in treating neuropathic pain, and opioids should be kept as second- or third-line treatment. Antiepileptic drugs are currently popular for pain control by modulating different mechanistic-based approaches. The guidelines of a patient’s country should be followed for optimum pain control, and the guidelines should be updated at least every three years to improve the care and quality of life in sufferers.
Conclusion

Two kinds of people never experience pain according to the literature, those with leprosy (Hansen’s disease) and those with a congenital indifference to pain. People have pain sensors and nerve free endings can themselves feel pain. Excessive pain, however, leads to fear, anxiety, depression, stress, or sickness with physical and psychological burdens. Encouraging people to endure pain is a philosophical ideal, however not really healthy from a neuropsychological perspective. Understanding the mechanisms of neuropathic pain and treatment guidelines will hopefully prompt clinicians to develop new approaches to deal with this complicated symptomatic disease.
References:

17. Huco T, Levine JD: Signaling pathways in sensitization: toward a nociceptor
36. Taiwan Guidance for Total Pain Management. 台灣全方位疼痛處置諮詢委員會編制。2010年11月，頁數1-83。
47. Austin JH. Zen and the Brain. MIT Press, Cambridge, Mass and London,


73. Zhao P, Waxman SG, Hains BC. Modulation of thalamic nociceptive processing


92. Fehrenbacher JC, Taylor CP, Vasko MR. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. Pain 2003;105:133–41.


Figure 1: The painful expression of an archangel to tempt a child with a pure spirit. (Painted by William Blake, 1757-1827)
Figure 2: The pain ladder by World Health Organization, 2011
Additional files provided with this submission:

Additional file 1: Table1.doc, 29K
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