Mechanistic-Based Treatment for Common Neuropathic Pain and the Treatment Dilemma of the Elderly

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Abstract: Neuropathic pain is a complicated disorder. This complexity arises not because the characteristics of the pain differ from nociceptive inflammatory symptoms, but because of its complex mechanism. Peripheral transduction, ectopic impulse, central sensitization, low threshold A-beta fiber mediated pain, and loss of inhibitory control all play a role in the mechanism. Nevertheless, the outcomes are still unsatisfactory for physicians and patients with regards to treatment. For example, certain disorders such as central post-stroke pain are extremely difficult to treat, not only because of the intolerable side effects of the medications but also because of the unknown effectiveness of pain reduction, especially in the elderly. Under-treatment frequently occurs in the absence of attention to the pain characteristics, and because physicians are concerned of adverse effects or inappropriate up-titration of neuropathic drugs such as anti-epileptic medicines. Multidisciplinary approaches including non-pharmacological management, rehabilitation, biofeedback, acupuncture, education on stepwise pain reduction, and keeping a diary are somewhat helpful in clinical practice but not easily implemented without the cooperation of multidisciplinary teams. Physicians prescribe opioids to alleviate the symptoms, however this carries the risk of addiction. Therefore, it is important that clinicians are made aware of common neuropathic disorders in order to establish strategies to manage such types of pain.

Keywords: Neuropathic pain, mechanism-based, treatment dilemma, elderly.

PREFACE OF NEUROPATHIC PAIN

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 sculpture "Laocoön and His Sons" (Hellenistic original from ca. 200 BC., and found in the Baths of Trajan, 1506) described the Trojan priest Laocoön and his sons Antiphantes and Thymbraeus being strangled by sea serpents. This statue showed the suffering of the father with his pain expressed by his facial expression (Figure **1**). People suffering from pain may attempt suicide or self-harm, and excessive pain can transform their personality.

Figure 1: The painful expression on Laocoön’s face. (Sculptors unknown, Laocoön and His Sons, original from 200 BC., now on display in the Vatican Museum).

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Historical records of pain began with Rene Descartes (1596 ~ 1650), who wrote "…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...". This is the earliest scientific observation with regards to pain. Until 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 despite controversy over how to more comprehensively define pain. Treede 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 from scientific observations, definitions, and update revisions. It is important that clinicians understand the development of pain history to be able to fully comprehend the problems involved.

PREVALENCE OF GLOBAL NEUROPATHIC PAIN

Pain is a very common problem in the elderly, with chronic pain affecting more than 50% of those living in a community setting and more than 80% of nursing home residents. There are a number of challenges in studying the epidemiology. Neuropathic pain (NP) is a more devastating symptom of severe chronic pain. Since the emphasis is often the disease itself, NP is often under-diagnosed and under-treated, especially in the elderly. The prevalence and incidence of NP in the elderly is not clear. Bennett reported that the prevalence of NP in the US is 1-2% [3], of which low back pain, diabetic painful neuropathy (DPNP) and post-herpetic neuralgia (PHN) were the most common. In a recent report from the Netherlands which enrolled 362,693 subjects, the prevalence of NP was estimated to be 1% in the general population, and the aged specific prevalence was higher to 20% over 65 years old [4]. However, with different methodologies, non-unique randomized or matched clinical studies, wide range of sample sizes, and inconsistent validity statistics, it is difficult to calculate a unique or global rate of prevalence in NP, and especially in the elderly. IASP reviewed the relevant literature and reported that the current prevalence of NP is not known [5a]. This statement alerted clinicians to the fact that using consistent methodologies, unique definitions and randomized control trials is important to obtain an accurate prevalence rate of NP in different populations and in those with different disease entities. To date, no age-stratified prevalence rates of NP have been published in Taiwan.

NEUROPATHIC PAIN DRUGS MARKETING

According to global market research in 2003 (MarketResearch.com), the most commonly used drugs to treat NP were non-steroid anti-inflammation drugs (NSAIDs) (42%), non-narcotic analgesics (21%), anti-epileptic drugs (14%), and potent opioids for (4%). However, NSAIDs have been shown to be ineffective in treating NP, indicating that most physicians are not familiar with the mechanistic basis of neuropathy. A prescribing data from the General Practice Research Database in UK demonstrated amitriptyline or gabapentin is the most common first-line treatment in DPNP and phantom limb pain, while amytriptyline or codeine-acetaminophen mixed pill is for PHN [5b]. Recently, a European marketing survey found that strong opioids (30%) had become the most commonly used drug to treat NP, followed by NSAIDs (22%) and AEDs (12%), and that the use of strong opioids was predicted to be much higher in 2020 [6]. This demonstrates greater changes in drug misuse in Western countries, which may have devastating consequences in those with NP, especially for the vulnerable sufferers. Cultural differences, drug misuse or disease severity may be the reasons for the increasing use of opioids, and giving strong opioids for pain control and improving the quality of life in hospitals are most likely the iatrogenic etiologies. According to the World Health Organization (WHO) analgesic ladder (Figure **2**), NSAIDs or non-narcotic analgesics should be used as first-line drugs for pain scores between 1-3 (scale 1-10), while powerful opioids should be considered for pain scores between 7-10 [7]. The pharmacological effects of opioids are complex, acting not only on pre-synaptic areas to reduce excited ions, but also on post-synaptic receptors to stabilize potassium channel-induced hyper-polarization. Opioids can also act on general μ, kappa and δ receptors to relieve systemic pain [6, 7]. However, addiction or tolerability will occur if they are used too frequently or in inappropriate doses. The side effect of opioids is similar for all age groups; yet the elderly is at a greater risk with co-morbidities or multiple drugs usages. Therefore, knowing how to increase and switch between the different classes of medications is necessary in the safe and successful management of pain, and adjuvant therapy with other non-opioid painkillers should be encouraged in pain management. Opioids should remain as a second- or third-tier treatment in pain control.

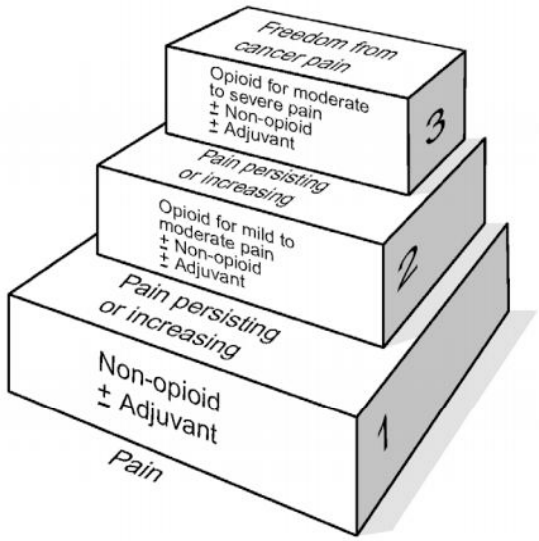

Figure 2: The World Health Organization pain ladder, 2011.

MECHANISTIC RULES OF NEUROPATHIC PAIN

Realizing that neuropathic pain treatment should be based on a mechanism-based approach is important [8-11]. Pain is derived from surrounding nociceptors by the release of neurotransmitters (e.g., substance-p and glutamate) stimulating peripheral nerve fibers (C-fiber 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 connecting networks with limbic systems, frontal area, cingulate gyrus, brain stem nucleus and widespread cortical areas to downward regulate and modulate pain. Based on the anatomical pathway, several common mechanisms have been proposed:

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

2. Ectopic impulse. 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 frequently occurs in clinical practice. Sudden, brief, short-term pain of lancinating or sharpening characteristic with migration is most commonly complained of by patients. Since ion channel pumping is not functioning properly, the use of sodium channel blockers seems to be effective to reduce pain in this mechanism [12]. This may explain the rationale of treatment with lidocaine, mexiletine, phenytoin, carbamazepine and lamotrigine for NP control.

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 NP [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. Ketamine and dextromethorphan are two examples of drugs used for such 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 severely hampers their utility for the treatment of NP [15].

4. Low threshold A-beta fiber mediated pain. Peripheral nerves are able to regenerate, and over a period of time after nerve injury, collateralized reconstruction occurs. Sprouting errors (e.g., Aβ cross-linked to C fibers) lead to previously painless areas experiencing unendurable of sharpening pain. This phenomenon can be seen in patients with spinal cord injuries or syringomyelia [16]. The mechanism mainly consists of sodium channel excitability, synaptic sprouting, and spinal cord hyper-excitability [17]. It is difficult to treat, and γ-amino butyric acid (GABA)-like inhibitory drugs or calcium-channel blockers are mainly used. Nevertheless, in recent animals study, the sprouting and regeneration errors were not found to play a major role in eliciting pain [18].

5. Loss of descending control. Researchers have suggested that a part of the cause of NP is due

to the inefficiency of endogenous inhibitory systems. Descending modulatory pathways appear to influence dorsal horn sensitization. Cortical, thalamic, and periaqueductal inputs converge on the rostral ventromedial medulla. This center gives rise to both inhibitory and excitatory inputs to the dorsal horn *via* a regulating process and periaqueductal gray matter, and the locus ceruleus also plays a role. This descending control system is mediated by serotonin and non-epinephrine to modulate the pain. Experimental and empirical studies have confirmed that inhibition of both transmitters has a better effect for pain control than inhibiting one alone [19]. This can also improve mood and depressive disorder. There is evidence that using serotonin and non-epinephrine reuptake inhibitors (SNRI) provide better pain control than selective serotonin reuptake inhibitors (SSRI) in clinical practice [20].

COMMON ETIOLOGIES OF NEUROPATHIC PAIN

Various etiologies cause NP including vascular factors (e.g., embolism, thrombosis, venous thrombosis induced post-stroke pain), infection (e.g., post-herpetic neuralgia), trauma (e.g., amputated phantom pain), toxin-related (e.g., arsenic and cadmium poisoning, platinum, taxane-based chemotherapy, isoniazid), alcohol-related (e.g., alcoholic polyneuropathy), metabolic abnormalities (e.g., diabetes, steroids or hypothyroidism neuropathy), immune-related response (e.g., multiple sclerosis, acute inflammatory disseminating polyradiculoneuropathy or human immune-virus neuropathy), compression (e.g., entrapment syndrome, carpal tunnel syndrome, or spinal stenosis), cancer-related (e.g., paraneoplastic syndrome, carcinomatosis), vitamin deficiency (e.g., subacute combine degeneration, beriberi, pellagra), and genetic abnormalities (e.g., Fabry disease). These etiologies may partially explain the reasons for neuropathic involvement. However, it is imperative to reverse these factors to cure or alleviate pain as much as possible, especially as the cause of NP is not identified in one third of sufferers. Distinguishing neuropathy by symptoms of burning, prickling, lightening or signs of hyperalgesia, allodynia or causalgia alone makes it difficult to clarify the etiology. Elderly patients in particular have similar complaints of NP during clinical visits [21].

RAPID DIAGNOSIS OF NEUROPATHIC PAIN

A rapid useful clinical technique is taught to the residents including a tertiary medical center (2000-bed available) and 2 regional (800-bed available) hospitals in southern Taiwan, which is simply “3Ls - listen, look, and location”. Listening to the descriptions of the patients with regards to the pain characteristics (tingling, sharpening, lightening, prickling, crawling, or burning etc.), the duration and onset of time (acute or chronic), pain intensity (mild, moderate or severe) , and relapse or remission periods (inflammation, nociceptive or neuropathic) offers a reliable clue for the clinical diagnosis. For example, looking for acute skin blisters and pain (e.g., zoster-associated pain), scarring along thoracic, lumbar areas or trigeminal branches with sharpening pain (e.g., post-herpetic neuralgia), neck pain with positive Lhermitte sign (e.g., cervical cord lesion), back pain with positive Lasegue tests (e.g., lumbar disc herniation), pain along the wrist of 1^{st}-3^{rd} fingers which is relieved by shaking hands (e.g., carpal-tunnel syndrome), lateral thigh numbness without referring pain (e.g., meralgia paresthetica), with pain downstream (e.g., spinal nerve lesions), pain triggered by a light touch on face (e.g., allodynia of trigeminal neuralgia), stroke with unilateral painful limb numbness (e.g., central post-stroke pain), painful amputated stumps (e.g., phantom limb pain), injured arms/legs with swelling and discoloration of the skin (e.g., complex regional pain syndrome-type I), stock and glove sensation of the four limbs (e.g., polyneuropathy), painful proximal muscle atrophy (e.g., diabetic amyotrophy), pain after back surgery (e.g., failed back surgery syndrome), chronic generalized somatic pain and fatigue (e.g., fibromyalgia), cancer with metastatic pain (e.g., mixed pain), is a consistent diagnostic method compared to using nerve conductive velocity (NCV) or quantitative sensory tests (QST). With more reliable evidence for diagnosis, pain questionnaires such as the Leeds Assessment of Neuropathic Pain Symptoms and Signs (LANSS), Neuropathic Pain Questionnaire (NPQ), painDETEC**T**, ID pain (Chinese version), Douleur Neuropathique en 4 questions (DN4), and Neuropathic Pain Symptom Inventory (NPSI) have also been used [22-24]. Beyond these clinical tools, laboratory tests are useful in confirming the neuropathic diagnosis. For example, small fiber disease of neuropathic origin should be considered if NCV is normal, since the fast and large myelinated diameter nerves (A fibers) can be detected only by electrophysiological studies. QST are performed to define the patch or small lesion of neuropathic symptoms, and performing a skin biopsy to count the fiber density with uncertain peripheral nerve lesions is suggested if needed. In summary, the diagnosis of neuropathic pain using the 3Ls (listen, look and location) is practical and easily carried out, and

supplementary tests as NCV and QST can be implemented to detect the neuropathic characteristics, regardless of small or large fiber neuropathic disorders. In addition, the utility of imaging studies or other laboratory data to exclude pain-related lesions (tumor, compression, or inflammation) can sometimes helpful. Therapeutic drug trials can provide useful information from referral cases, especially in the elderly initially treated at community hospitals where the ability to perform neurological tests is usually lacking [25].

NON-PHARMACOLOGICAL MANAGEMENT IN NEUROPATHIC PAIN

Non-pharmacological treatments such as biofeedback, relaxation therapy, occupational therapy, transcutaneous electrical nerve stimulation (TENS), and cognitive-behavior therapy (CBT) seem to be preferable for frail people, with less adverse effects detected in migraine prevention [26, 27], however the reasons behind the efficacy are not clear [28-30]. Acupuncture is popular in Taiwan, and although there is some evidence of success in treating migraines [31], there is a lack of evidence of the effectiveness for reducing NP, and any effects may be related to a placebo effect. The Cochrane collaboration started a similar project to discover the effectiveness of acupuncture in 2011, however the results have not yet been published. Other aspects of Chinese culture such as daily exercise ("Chi") and meditation ("Zen"), for pain suppression, were reported to have efficacy in a local symposium, however there is a lack of evidence to support these findings. Evidence with regards to the effects of "Zen" meditation is based on the hypothesis of the Brain-Gate theory proposed by Melzack and Wall in 1965 [32], in which small fiber (C-fiber) conducting pain can be suppressed by large fibers when stimulated at the same time, thereby lessening pain. In our experience, beneficial effects can be achieved by rubbing or pressing near the injected site to alleviate the feeling of pain when children receive injections. Melzack *et al*. amended the theory in 1982 [33] by adding the perception of awareness or ignorance to pain itself (e.g., focusing on other things). Further research on meditation and Zen was presented by Prof. James H. Austin in his book "Zen and the Brain"[34], which was translated into Chinese in 2010 (by Prof. Nai-Shin Chu, Department of Neurology in Chang Gung Memorial Hospital in Taiwan). One chapter described a study of monks with different ecclesiastic hierarchies. During meditation, the brain recordings revealed a high-frequency of 30-70 gamma waves which synchronized whole 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 during meditation without painful sensations longer than ordinary people or low-hierarchy monks. This is an example of gate control theory by focusing the mind with regards to inattention or self-controlled awareness. However, not everyone has this kind of training of self-awareness. From an evidence-based point of view, this effect of medication in the reduction of pain is still inadequate.

PHARMACOLOGICAL TREATMENT IN NEURO-PATHIC PAIN

Pharmacological treatments for pain medications and updated guidelines have been reviewed [25, 28, 35-42]. The level of recommendations differs among countries. The strength of evidence based on study methods, clinical efficacy, and scientific measures are classified as I, II, III, and IV, and summarized as level A, B, C, and U, with A being the most recommended and U having inadequate or conflicting evidence and should be avoided if possible (Table **1**). The four most common NP syndromes in Taiwan are summarized below, with the aim of raising clinicians' awareness and also the dilemma of treatment in the elderly based on the review and also on our own experience.

a. Post-Herpetic Neuralgia (PHN). Approximately 2.2-3.4/1000 person-years of herpes zoster occur in the US and Europe each year [43, 44a]. The prevalence in Taiwan is estimated to be around 0.42/1000 person-years, with the elderly suffering from a higher rate (>80 years, 13.69; < 20 years, 2.07) [44b]. In general, PHN occurs 3 months after skin blisters have healed or the resulting scarring. Immune response and age are the two major predictors. The drugs based on the American Academy of Neurology (AAN) guidelines in 2004 and reaffirmed in 2008, gabapentin, 5% lidocaine patch, pregabalin, oxycodone, and tricyclic anti-depression agents (TCA) 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, ketamin, and methyl-prednisolone are rated as having limited or ineffective benefits (level U), and should be avoided. In comparison, the European Federation of Neurological Society guidelines

Table 1: Evidenced-Based Classification and Recommendations

Class I	Prospective randomized control trial (RCT) with outcome assessments, with primary outcome and exclusion/inclusion criteria are clearly defined. Also adequate accounting for dropouts and crossovers with minimal bias, and appropriate statistical adjustment for differences are provided.
Class II	Prospective matched group cohort study with outcome assessments defined.
Class III	Controlled trials in a representative population where outcome assessment is independent of patient treatment.
Class IV	Uncontrolled studies, case series, case reports, or expert opinions
Level A	One class I or two class II studies. Established as effective, ineffective or harmful for the given condition in a specified population.
Level B	At least one class II or three class III studies. Probably effective, ineffective, or harmful results.
Level C	At least two class III studies. Possibly effective, ineffective, or harmful outcomes.
Level U	Data inadequate or conflicting or treatment is unproven.

(Modified from the Taiwan Headache Society in the treatment of migraine with evidence-based medicine, 2008).

(EFNS) in 2005 and revised in 2010, recommend TCA (mainly consisting of amitriptyline), gabapentin, pregabalin, and 5% lidocaine plasters (level A), followed by strong opioids, tramadol, and 0.075% capsaicin cream (level B). The central-acting NMDA antagonists and mexiletine lack efficacy and should not be used (level A). This is the reason why ketamin is theoretically effective for PHN, but proof with evidence-based medicines is lacking. With regards to lidocaine patches, no more than 3 patches per day should be used, and be given within 12 hours to avoid addiction or failure of efficiency [45]. In 2009, the FDA approved 8% capsaicin patches in treating PHN to reduce substance-p release, with moderate pain reduction, and are now available in the US and Europe [39, 46, 47]. Due to adverse effects such as skin allergy, and reddish, itching papules, they are not yet marketed in Taiwan.

b. Diabetic Painful Neuropathic Pain (DPNP). The prevalence of diabetes mellitus (DM) in Taiwan is to be estimated 7.5% in those above 15 years of age (M: F=8.2: 6.8), and 15.5% in those above 45 years of age (M: F=15.5:14.0). The prevalence of DPNP was estimated to be 26.8% in patients with type II DM in one large-scale survey [48]. In the US, the prevalence of type II DM with DPNP has been reported to be 16.2% lower than in Taiwan [49], and from 7-26% in Europe [50]. The clinical diagnosis of DPNP is based on four indicators: pre-prandial blood sugar ≥ 126 mg, and post-prandial blood sugar (2 hours) ≥ 200 mg; NCV studies confirming the neuropathy; pain originating with neuropathic characteristics; excluding non-diabetic factors. Based on these criteria, the initial guidelines were proposed by the Mayo Clinic in 2006, in which duloxetine, oxycodone CR, pregabalin, and TCAs were the first tier of recommendations (level A), and carbamazepine, gabapentin, lamotrigine, tramadol, and venalfaxine ER 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 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 as the second line (level B) [51]. In Taiwan, duloxetine and pregabalin received approval from the Health Insurance Bureau in 2012, with an adaptable dose from 60-120 mg/d for duloxetine and 150-300 mg/d for pregabalin, and slow titration was advised for both [24]. Comparing the EFNS guidelines in 2010 with those of the AAN in 2011, sodium valproate was not recommended in Europe, and TCAs not recommended as first-line treatment in the US. However, both agreed that tramadol and opioid-like substances should be regarded as second-line medications. The pharmacological management is similar to the Canadian Pain Society and IASP [28, 52].

c. Trigeminal Neuralgia (TN). The incidence of TN in Taiwan is unknown, while it is estimated to be about 0.15~0.4% in the US [53], and 0.3% in Germany [54]. According to the International Classification of Headache Disorders (ICHD-II) in 2004 [55], typical TN (classic TN) is diagnosed as follows: A. Paroxysmal attacks of pain lasting from a fraction of a second to two minutes, with

or without persistent aching between paroxysms, affecting one or more divisions of the trigeminal nerve and fulfilling the criteria of B and C; B. Pain with 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. Distinguishing symptomatic TN from classic TN has reliable sensitivity with regards to abnormal blinking reflex, sensory deficits and bilateral trigeminal involvement [56]. Patients with the above symptoms/signs of trigeminal pain should receive neuroimaging studies to confirm the etiology of tumors or vascular lesions. For TN, the most effective recommended treatment in the US, Europe and Taiwan is carbamazepine as the first tier (level A), and oxcarbazepine as the second-line (level B). The FDA only endorses carbamazepine for the treatment of TN. Other drugs such as baclofen, lamotrigine, 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), in which severe adverse effects of skin toxic dermatitis, generalized eruptions, or lethal events have been reported due to genetic risk factors. Therefore, surveys of blood HLA-B1502 to confirm a negative reaction before use is important. The odds ratio (OR) was 1357 times for positive HLA-B1502 higher than for a negative reaction to have SJS [57].

d. Central Post-Stroke Pain (CPSP). This kind of pain is the most difficult to treat, 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 [58-60]. 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 derangement as well as functional changes in the brain [61]. Despite these findings, it is notable that no single drug can suppress this widely activated system. In a literature review [62-64] and Medscape website search, only TCAs, lamotrigine and opioids are suggested as second-line drugs (level B), indicating mild efficacy. In addition, SSRI, transcranial magnetic stimulation, and passive range of motion exercises (PROM) were all reported to have evidence of level C. The European guidelines in 2011 suggested pregabalin, gabapentin, and TCAs as first-line medications, while cannabinoids (in multiple sclerosis), lamotrigine, opioids and tramadol (in spinal cord injury) as second-line drugs [39]. The optimum dosage for treating CPSP with lamotrigine was reported to be 200 mg/d, and should be titrated at an initial 25 mg/d to avoid SJS [65]. Pregabalin 300-600 mg/d has been suggested with mild to moderate effectiveness ranging from 30-60% [66-68]. The TCA amitriptyline (~75 mg/d titrated from 10 mg/qn) has been shown to have a moderate effect. In our experience, combined drug therapy seems to be more beneficial for pain sufferers with less adverse effects, and especially in the elderly. However, evidence from long-term follow-up studies is still lacking. Clinicians should be aware of the benefit-versus-risk in treating CPSP to balance the adverse effects and efficacy [69]. After all, this kind of pain is difficult to “cure”, but “remission”, and flare symptoms frequently occur unpredictably. In summary, patients with negative symptoms (hypoesthesia, numbness) are less likely to have significant improvement than those with positive symptoms of tingling, lightening, burning or allodynia in CPSP as in other NP syndromes.

TAIWAN GUIDANCE FOR NEUROPATHIC PAIN TREATMENT

A consensus was reached by an advisory committee composed of specialists in the fields of anesthesia, neurology, endocrinology, rheumatology, orthopedics, and psychiatry for pain management in Taiwan in 2010 (Table **2**). This consensus provided useful reference guidelines for Taiwanese being treating for NP. The Taiwan Guidance for Total Pain Management is briefly introduced below. As yet, no suggested doses are recommended in these guidelines due to inter-rater variability and the lack of large-scale clinical trials, except for TN [24].

1. Painful polyneuropathy (PPN). The recommended medications are TCAs, pregabalin, and gabapentin (level A) for first-line drugs; the SNRIs duloxetine and venalfaxine (level B) for the second-line; and tramadol,

Table 2: Comparison of Guidelines Among US, Europe and Taiwan

Taiwan guidelines (2010) European revised guidelines (2010) AAN (2004, 2008)	1st recommended drugs	2nd or 3rd recommended drugs
Post-herpetic neuralgia	Gabapentin[a,b,c], Pregabalin[a,b,c], Lidocaine patch[a,b,c], TCA[a,b,c], Oxycodone or morphine sulfate, controlled release[c]	Capsaicin[a,b,c], Opioids[a,b], Tramadol[a], Valproate[a], Aspirin in cream or oitment[c], Methyl-prednisolone intrathecal[c],
Trigeminal neuralgia	Oxcabazapine[a,b,c], Carbamazepine[a,b,c]	Surgery[a,b,c]
Central pain	Amitriptyline[a,b] Gabapentin[a,b] Pregabalin[a,b], TCA[b]	Cannabinoids (MS) [a,b] Lamotrigine[a,b], Opioids[a,b], Tramadol (SCI)[b]
Painful polyneuropathy or Diabetic painful polyneuropathy	Gabapentin[a,b], Pregabalin[a,b], TCA[a,b], Venalfaxine[b], Duloxetine[b]	Lamotrigine, Opiates, SNRI, Tramadol[b], Opioids[b]
AAN guidelines (2011)	Level A	Level B
Diabetic painful polyneuropathy	Pregabalin 300-600mg/d	Gabapentin 900-3600mg/d, Amitriptyline 25-75mg/d, Venalfaxine 75-225mg/d, Duloxetine 60-120mg/d, Sodium vaproate 500-1200mg/d, Tramadol 210mg/d, Capsaicin 0.075% qid, Detromethophran 400mg/d. (Oxcabazapine, Lamotrigine are not recommended)

1. Adapted from TOPMAN[a] (Total Pain Management by Advisory Committee in Taiwan, 2010), Europe[b] (European Federation of Neurological Society, 2010), and AAN[c] (American Academic Neurology, 2004 and 2008).
2. TCA-tricyclic antidepressant, SNRI-serotonin and non-epinephrine reuptake inhibition, MS-multiple sclerosis, SCI-spinal cord injury.
3. Level A as 1st recommendation and level B as 2nd or 3rd recommendation in the American Academic Neurology (AAN) guidelines.
4. AAN did not have central pain treatment guidelines by 2013.

lamotrigine, opioids (level B) for the third-line; while capsaicin, mexiletine, oxcarbazepine, SSRI, and topiramate were determined to be ineffective (negative level A).

2. Post-herpetic neuralgia (PHN). The first-line recommendations are TCAs, pregabalin, gabapentin and 5% lidocaine patches (level A); capsaicin, tramadol, opioids, and valproate as second- or third-line (level B); mexiletine, lorazepam, and NMDA antagonists were determined to be ineffective (negative 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 and should not be used (level B).

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

COMPARING GUIDELINES OF NEUROPATHIC PAIN

Comparing the guidelines in the US, Europe and Taiwan, there are some similarities (Table **2**). Tricyclic antidepressants (e.g., amitriptyline) are recommended for all kinds of NP, and are effective in pain reduction with a number needed to treat (NNT) of about 3~4. The US FDA does not endorse TCAs for treating NP due to the possibility of adverse effects such as double vision, dry mouth, new onset glaucoma, urinary retention, cardiac arrhythmia, Torsade de points, or cardiac death, especially in frail patients [70, 71]. In our experience, TCAs have more adverse effects than SNRI or calcium channel blockers (CCB) such as pregabalin, even with titration. Imipramine can be used as a replacement for pain reduction, however the efficacy is mild to moderate when titrated up to 75-100 mg/d. There are disparities in the priority of use of the medications between the guidelines [36-42]. In Europe, SNRIs such as duloxetine or venlafaxine are the first choice, while selective CCBs such as pregabalin or gabapentin are more popular in the US. Selective CCBs play a major role in modulating pain due to pre-ganglionic α2δ voltage-gate calcium channel control reducing excitatory substance release [72, 73]. However, adverse effects such as sedation, dizziness and unsteady gait occur more frequently [68, 74] even with dose adjustment (3~5-fold more than a placebo in the elderly in our cases). The different mechanism of

SNRIs in descending inhibitory control to modulate pain has shown evidence-based efficacy for DPNP and fibromyalgia [75]. Gastrointestinal distress, nausea and vomiting, and disturbed sleep quality limits its dose to a maximum of 90 mg in our patients (~3-fold more than a placebo in the elderly), although the evidence-based maximal dose reaches 120 mg/d in the literature. Unless the use of the aforementioned drugs is thoroughly explained to the patients, most cannot tolerate doses of SNRI (> 90 mg), pregabalin (> 300 mg), gabapentin (> 2400 mg), TCAs (amitriptyline > 75 mg; imipramine > 100 mg) due to adverse effects in our own experience, especially in frail patients. In addition, off-label use for NP in Taiwan seems to incur more legal problems if adverse effects occur. Therefore, sodium channel blockers such as phenytoin and mexiletine, glutamate-inhibitors such as benzo-diazepam, and GABA-inhibitors such as baclofen, are seldom used for pain control by clinicians in Taiwan, even though they have some effect in pain control by inhibiting repetitive firing of excitatory neurons or interfering with ion channels in certain conditions [76].

EDUCATION AND INDIVIDUAL TAILOR ARE IMPORTANT IN TREATING NEUROPATHIC PAIN

An important issue with regards to successful pain reduction is educating and explaining the condition to the pain sufferers, and especially the elderly [77]. The dynamic and kinetic differences in pharmacological distribution, the co-administration of multiple drugs, the metabolite and excretion ability, and the vulnerable idiosyncrasy limit the maximal effect of pain-control drugs [78, 79] without slow titration or thorough education in addition to the pharmacists' regular explanation. Once adverse effects occur, even established evidence-based drugs are easily withdrawn by the patients. A step-by-step therapeutic strategy is better than rapid titration or combined therapy in such subjects [80]. Although multiple drug therapy is frequently used in clinical practice, the patients who have not been educated will have inferior results [75]. Tailoring treatment for each patient, inquiring about their drug history, and recording a diary of visual analogue scales are mandatory in analyzing treatment outcomes. NP is difficult to cure, although this is usually the expectation of the sufferers. Gradually escalating to a suitable dose and maintaining an adequate period are favored if the medication is effective, although a combination of multiple drugs was favored in a recent review [75]. Dose adjustment depending on an individual's need differs between Eastern and Western patients, and some patients need a long-term course to avoid flare-ups, especially in PHN, CPSP and elderly patients. A multidisciplinary approach with approved medication, non-pharmacological biofeedback, TENS, meditation or acupuncture may be helpful to alleviate devastating pain, although the evidence is currently insufficient [81]. However, as meditation is a part of Chinese culture, people who meditate may experience some placebo benefits to reduce pain even though the mechanism is unknown. In summary, NSAIDs are mostly ineffective in treating NP, and opioids should be kept as second- or third-line treatment options. 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 every 3-5 years to improve patient care and quality of life for pain sufferers.

CONCLUSIONS

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 who have pain sensors and nerve free endings can 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 better patient-care strategies and a better approach to treat this symptomatic disease.

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DISCLOSURE

All authors have no conflicting interests to declare.

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