Chronic pain management: an insight into neuropathic pain

Many people suffer from chronic pain. In these patients, the most common ‘ wish’ is to be pain free. Even though modern Medicine has advanced at an unprecedented rate over the past century, approaches to chronic pain management is still not completely satisfactory. I have recently seen a patient who has been living with neuropathic pain for many years. Neuropathic pain is a type of chronic pain that is considered to be the most difficult to treat and manage, due to its complex nature in etiology and clinical manifestations. Despite the improvement in scientific understanding of pathogenesis of neuropathic pain, and utilization of newer pharmacological, surgical and cognitive approaches, diagnosing and treating neuropathic pain still poses a challenge clinically. This essay will be presenting a case history of a patient with neuropathic pain being treated at the Kent and Canterbury Hospital and this case will form the basis of discussion on the current understanding of neuropathic pain mechanisms and its management.

Patient case

Mrs L is a 58 years old medically retired office worker who has a 25-year history of multiple sclerosis. She has been coping well until 8yrs ago when her left foot suddenly experienced a “ shooting” pain on weight bearing. At first, she was maintained on paracetamol and nurofen by her GP with limited pain relief and then referred to the podiatrist, where an ultrasound scan revealed the presence of Morton’s neuroma (a benign swelling of the intermetatarsal plantar nerve causing neuropathic pain), which was causing intense pain with a severity 10/10 across her left forefoot. To help alleviate the pain, it was initially decided that surgically removing the neuroma could

achieve adequate pain relief, but this was proven to be an unrealistic goal. During the surgical intervention period, she had altogether three neuromas removed on separate occasions, with additional shaving off the bones to reduce compression on the nerve and resultant inflammation.

She was then referred to be managed at the pain clinic. While Mrs L has been under the care of the pain physicians, she was given local anaesthetics & steroid infiltration into her forefoot, cryotherapy (ice cold packs applied to tibial nerve), guanethedine block, lumbar chemical sympathectomy (with midazolam & fentanyl), acupuncture, lidocaine patches, capsaicin cream, duloxetine and co-codamol. Despite temporary pain relief provided by these therapies, there was not a long-lasting effect that allowed Mrs L to stay pain-free.

Understandably, living with an excruciating pain chronically can severely damage an individual’s psychological as well as physical health. She could no longer enjoy her hobbies, such as dancing and going to antic fairs; even daily activities such as shower would make her scream in pain. As a result, she became extremely depressed and suicidal.

Currently, she is receiving a multidisciplinary input from her GP, the specialist pain physician, specialist pain nurse, clinical psychologist, and physiotherapists and is maintained on gabapentin and diclofenac for her neuropathic pain, citalopram for her slowly recovering depression and baclofen for controlling her ongoing multiple sclerosis symptoms. She is also regularly attending chronic pain management programs, through which she

believes that she gains better appreciation for her condition and is in a better position to be in charge of her own symptoms.

This case nicely demonstrates the difficulties encountered in clinical practice in treating chronic pain. First of all, neuropathic pain is exceptionally difficult to treat, with unpredictable outcomes; secondly, most methods of pain management can only provide symptomatic relieve of pain temporarily, rather than offering a permanent cure; thirdly, chronic pain is an extremely debilitating condition to live with and its psychological impact should not be underestimated; and finally, to enable the best pain management a multidisciplinary approach is evidently the most successful and gives the patient most control over their symptoms.

What is pain?

We are all familiar with the term ‘ pain’. The International Association for the Study of Pain (IASP) defines pain as: “ An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” (IASP 2007). It is important to note that pain is a very subjective experience, which varies enormously from one individual to the next. To emphasize on the subjectivity of pain perception and the need for individualized approach to pain management, Margo McCaffery who specialized in pain management nursing in 1968 described pain as “ whatever the experiencing person says it is, existing whenever the experiencing person says it does” (Rosdahl & Kowalski, 2007). It is undeniable that psychology and physiology are interwoven in the perception of pain.

To understand pain, it is helpful to know what causes pain; as mentioned above, normally our perception of pain is triggered by a specific stimulus, such as hot, cold, or sharp objects, which could cause potential tissue irritation or injury. It is obviously advantageous in evolutionary terms to be able to sense the potential cause of injury and act via spinal reflexes to achieve self-protection, e. g. withdrawal of fingers from hot pan. This form of pain is called nociceptive pain, where the stimulus is known to be harmful in nature. This type of pain warns us of impending damage; therefore, it is regarded as the ‘ good’ type of pain.

Of course, most of the long-term pains are certainly not ‘ good’ or ‘ friendly’. What distinguishes between ‘ friend’ and ‘ foe’ in the field of pain is determined by the time-course, the intensity, the cause of and the social and economic consequences of the pain. An excellent example of a ‘ bad’ pain is neuropathic pain (Figure 1):

Figure 1. Diagram showing the mechanisms behind the processing and perception of three different types of pain. Phase 1= nociceptive pain; Phase 2= inflammatory pain; Phase 3= neuropathic pain. (Cervero F, 2009)

Neuropathic pains are resulted from disease or trauma to the central or peripheral nervous system; common causes include stroke, spinal cord injury, multiple sclerosis, surgery, diabetic neuropathy, and herpes zoster virus (Jensen et al., 2007). The Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP has recently redefined neuropathic pain as “ pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (Treede et al., 2008). As a result, neuropathic pain

produces very unusual pain sensations beyond the range produced by the normal nociceptive system; these include spontaneous pain, reduced pain thresholds, and mechanical allodynia (Cervero F, 2009). As illustrated in figure 1, abnormal sensory processing is one of the landmarks for diagnosing neuropathic pains; patients often experience pain in the absence of any noxious stimuli (allodynia) and additionally produces an abnormally heightened sensory input, changing a non-noxious stimulus into a painful stimulus, producing a state called ‘ hyperalgesia’. Therefore, the main characteristic is the nearly complete lack of correlation between peripheral noxious stimuli and pain sensations perceived.

There are many types of neuropathic pain (Table 1), which can be broadly classified into four groups based on their aetiology and anatomy: peripheral nervous system focal and multifocal lesions, peripheral nervous system generalized polyneuropathies, central nervous system lesions, and complex neuropathic disorders (Freynhagen & Bennett, 2009). It is outside the scope of this essay to discuss these different types of neuropathic pain in further detail; rather, neuropathic pain as a distinct group of pain will be explored.

Table 1. Examples of neuropathic pain syndromes (Freynhagen & Bennett, 2009).

How is neuropathic pain diagnosed?

Despite its frequent occurrence, neuropathic pain still constitutes as a major diagnostic problem in clinical practice because it can present with a variety of signs and symptoms, which vary greatly even within one particular disease entity (e. g. in postherpetic neuralgia) (Geber et al, 2009). Clinical

examination and expert judgment is still the best way to make a clinical diagnosis of neuropathic pain, despite the recent development of various screening tools, such as the LANSS questionnaire (Bennette, 2001) and the Neuropathic Pain Scale (Galer and Jensen, 1997) that assist in making a diagnosis. Bedside examinations for hyperalgesia and dysthesia include assessing the effect of the same stimuli on painful areas compared to the contralateral side or an unaffected site. Allodynia is demonstrated by the experience of pain when performing light touch with cotton wool; exaggerated painful response to pin prick suggests hyperalgesia, therefore lowered pin-prick threshold. These are the typical components that define a pain as neuropathic type.

Patients are most likely to present with a mixture of pain types with a neuropathic component to it. It is important to identify the presence of such a component as the treatment recommendations are different for these. With the introduction of the new grading system for neuropathic pain by NeuPSIG group (Treede et al 2008), it is becoming increasingly recognized that chronic pain is often presented as a combination of different types of pains, rather than a clear-cut nociceptive or neuropathic type of pain. In Treede and colleagues new recommendation for the diagnosis of neuropathic pain, options of ‘ definite’, ‘ probable’ or ‘ possible’ are available for the diagnosis of a component of neuropathic pain in the disease presentations in the clinical setting, which aims to aid more accurate diagnosis of neuropathic pain (Figure 2).

Figure 2. Flow chart of grading system for neuropathic pain. The grading system is based on four criteria: pain distribution (criterion 1), the link

between pain distribution and the patient’s history (criterion 2), confirmatory tests of neurologic status demonstrating positive or negative sensory signs confined to the innervation territory of the lesioned nervous structure (criterion 3), and further confirmatory diagnostic tests to identify the lesion or disease entity underlying the neuropathic pain (criterion 4). Criteria 1 and 2 must be met to initiate the working hypothesis of possible neuropathic pain. *Patient requires follow-up and/or additional confirmatory tests. â€ The point at which the diagnosis of possible neuropathic pain should be abandoned has not been defined (Treede et al 2008).

Mechanisms of neuropathic pain

Broadly speaking, neuropathic pain arises from the peripheral nervous system (ectopic impulse generation due to abnormal sodium channel expression), or from the central nervous system (central sensitization, disinhibition and plasticity) (Scadding, 2003).

The key behind the generation of neuropathic pain is the abnormal neurological changes to the sensory system resulting in an abnormal hyperalgesic state, achieved through three processes: 1) the activation and sensitization of peripheral nociceptors, which are responsible for sensing peripheral noxious stimuli; 2) the abnormal amplification, rather than the suppression as in the normal states, of the central nervous system, known as central sensitization, caused by the strengthening of the synaptic connections between the peripheral and central nervous systems, producing a persistent pain state; 3) the change in the central actions of the undamaged afferents, so that a non-noxious tactile stimulus sensed by these receptors are converted into nociceptive information and processed as pain,

rather than a light touch (Cervero F, 2009). This also further leads to secondary hyperalgesia, which means that instead of relieving the nociceptive pain by rubbing on the painful area (tactile stimulus), the tactile movement of rubbing will actually produce the opposite effect of enhancing the existing pain.

Figure 3. The pain signaling and modulation pathways. F Cx: frontal cortex; SS Cx: somatosensory cortex; Hyo: hypothalamus. (Ro & Chang, 2005)

As shown in Figure 3, the physiological pain mechanisms include the pain signaling pathway from nociceptors to peripheral nervous system to spinal dorsal horn cells to thalamus and finally to the cortex, and the pain control system from the cortext to periaqueductal grey to raphe nucleus to spinal dorsal horn (Ro & Chang, 2005). In normal circumstances, there is a balance between signal transduction and pain modulation, therefore the individual recovers from that episode of pain. However, when this balance is disturbed, i. e. when there is a lesion within the primary somatosensory system, then the individual experiences neuropathic pain. The lesion may occur anywhere along the pathways of the somatosensory system, and it could be as a result of compression, inflammation, ischaemia, trauma, tumour invasion, nutritional deficits, or degenerative processes to the neurons (Ro & Chang, 2005). Some of these important mechanisms will be discussed individually below.

Local nerve injuries

After the occurance of local nerve damage, in an attempt to repair, a neuroma forms at the proximal stump of the damaged nerve. A neuroma is a

tangled mass of regenerating axons embedded in connective tissues. The axons within a neuroma not only fail to regenerate properly, but also develop abnormal electrical activities (England et al, 1996). This neuroma sprout then begins to fire abnormal signals with a heightened excitability, which stimulates regenerating C-fibers. After a period in the growth of these fibers, erratic impulse generator will develop, which sends abnormal signals into the central nervous system, perceived as dysthesia, parasthesia, itching or electrifying sensations (Liu et al, 2002).

Sodium channel accumulation

Sodium channel density is increased in areas of axons proximal to the injury site, as shown by England et al (1996) when the excised neuromas were studied from patients who suffered from painful traumatic neuromas (Figure 4). This specific type of sodium channel accumulated have a faster recovery time after inactivation, therefore, they are able to conduct ectopic impulses in neuropathic states. The ectopic activity then maintains the central sensitization process, resulting in great amplification of peripheral afferent signals. In neuropathic pain, there is a change in ionic channels composition and functions, such an accumulation of sodium channels which leads to hyperexcitability of these nerve terminals. These are found to be accumulating in neuropathic damaged areas of the nerve, such as in neuromas and demyelinated areas (Devor, 2006). In a normal axon, the transportation of sodium ion channels is preprogrammed via endoplasmic vesicles along the axons to be distributed in the nodes of Ranvier and peripheral sensory endings; there is a low density of sodium channels on the myelinated axonlemma. However, as a consequence to neuropathic damage,

the set program of ionic channel settlement is disturbed, and these ion channels end up being located at a high concentration at the areas of neuromas, demyelination and sprouting (Aurilio et al, 2008). Such important roles played by sodium channels means that by blocking these channels, neuropathic pains could be reduced. Indeed, sodium channel blockers open up a major therapeutic channel for neuropathic pain treatment.

Figure 4. Sodium channel immunocytochemistry of neuromas. (a, b, c) Sodium channel-specific immunoreactivity is present throughout the axons of th these neuromas. (d) Control showing the nonspecific immunofluorescence. Scale bar = 10 micrometer (England et al, 1996).

Calcium channels and signaling in injury

Calcium channels are also involved in contributing to neuropathic pains, as intracellular calcium determines the phosphorylation of the membrane proteins (Aurilio et al, 2008).

The inflammatory neuropeptides, calcitonin gene-related peptides (CGRP), are released from injured nerve endings. They have a role in acting as co-transmitters in the spinal cord, therefore are involved in the central sensitization and hyperalgesic states found in neuropathic pain. An in vitro study identified that the release of CGRP entirely depended on the presence of extracellular calcium ions; this process involves particularly the N- and L-type calcium channels (Kress et al, 2001). Selective calcium channel blockers, such as gabapentin and lamotrigine may have significant potential in treating neuropathic pain.

Cytokines in neuropathic pain

Cytokines such as interleukins and tumour necrosis factors are well known mediators of inflammatory responses. Additionally, they are involved in neurogenic inflammations and are thought to play a role in the generation of neuropathic pains. In an established experimental model of neurogenic hyperalgesia and allodynia, mice with chronic constrictive injury to one sciatic nerve, the usage of interleukin-1 antagonist has been found to significantly yield in a reduction in the pain responses (Sommer et al, 1999) (Figure 5). Since TNF- ¡ immunoreactivitiy is found to be higher in nerve biopsies from patients with neuropathic pain, directing treatments to reducing the level of cytokines in the nervous system may also be helpful in relieving neuropathic pains (Empl et al, 2001). Indeed, combined neutralizing therapies against IL-1 and TNF- ¡ produced additive effects in experimental models (Schafers et al, 2001).

Figure 5. Hyperalgesia to thermal stimuli following unilateral sciatic nerve injury in six groups of mice. a negative difference score is an indicator of hyperalgesia in the experimental/treatment limb. Hyperalgesia is present throughout the experimental period in the sham-treated group of mice. Treatment with anti-IL1 reduces hyperalgesia in a dose dependent manner (Sommer et al, 1999).

Central inhibition inefficiency and sensitization

The pain transmission system is under continuous inhibitory control from the brainstem centers, such as periaqueductal grey and locus coeruleus. Many studies have been conducted in laboratory animals for studying the pain mechanisms in neuropathic pain. It is found that in animals with neuropathic

pain their central descending inhibition is nearly 50% lower than normal (Zimmermann 2001).

Additionally, there is a hypersensitized central nervous system in neuropathic pain. Normally central sensitisation process would return back to baseline level when the tissue heals and inflammation subsides (Dworkin et al, 2003), but in neuropathic pain states this is not the case. The plasticity and sensitisation following peripheral nerve injury was thought to be caused by the long-term potentiation mechanism (Liu & Sandkuhler, 1995). It is thought that after local nerve damage peripherally, growth factors such as nerve growth factors (NGF) can no longer be taken up into the dorsal ganglion neurons; this alters the nervous system at the transcription and protein synthesis level. NGF is a trophic molecule essential in the development maturation of the nervous system, and it is found to be elevated in conditions which pain is a predominant feature. This change to the composition to the nervous system also results in changes in the activities of aspartate and NMDA, which leads to an influx of calcium ions that indirectly contributes to the sensitisation and hyperalgesia of the spinal cord dorsal ganglion cells (Ro & Chang, 2005).

Peripheral inhibition inefficiency

In addition, there also is a reduction in the response to endorphin molecules in patients with neuropathic pain than other pain mechanisms (Terenius 1979); therefore, there is a reduction in the sensation of pain relief centrally. Peripheral nerve lesion was simulated in rats by rhizotomy, a technique which severs the spinal roots, and this has demonstrated a decreased opioid receptor binding in the spinal cord (Zajac et al, 1989).

Living with neuropathic pain

From a patent's perspective, pain is something they have to learn to live with, however bad it is. Patients who suffer from chronic pain not only have to go through the physical anguish exerted by the pain, but being in pain also hinders them from normal day to day functioning; from not being able to stay independent or taking care of themselves, to losing jobs, family and friends, lack of support and results in social isolation. A patient has once told me that: " because what I'm going through (pain) is not readily recognized by others, the way other people acted towards me put me under lots of frustration and made me socially unaccepted". It is crucial to bear in mind the wider impact of living with neuropathic pain when formulating a management plan for that individual.

Not surprisingly, neuropathic pain is linked to significant reduction in the patients' health-related quality of life (HRQoL) as well as creating substantial costs to the health service. It is reported that generally, patients with neuropathic pain have higher pain rating scores and lower HRQoL (Jenson et al, 2007).

In a cross-sectional evaluation of the impact of neuropathic pain on patients and their quality of life conducted in the Spanish population, it was found that pain substantially interfered with work and family life in these patients. Over 95% of the 1519 patients recruited for this study had either neuropathic pain or a mixed neuropathic and nociceptive pain. Younger patients tend to report a lower quality of life than that of the elderly population in both the physical and mental components of life (Figures 6a & 6b); possibly due to having fewer comorbidities in younger patients helps to

exaggerate the perceived deleterious effects of neuropathic pain on their daily functioning. Using the Sheehan’s disability scale, the younger patients are also shown to have generally a higher perceived stress compared to the older patients (Galvez et al, 2007).

It is important to analyse the effects that neuropathic pain exerts upon its sufferer, not only because we start to appreciate the level of impairment on the quality of life this chronic illness can cause to the patients, but also to further explore areas that could be perhaps better dealt with in terms of treatment (Jenson et al, 2007). As was reflected by the outcome of the Spanish study, 43% of patient had extreme disability; these included disability for work (51%), 47% for social life, 42% for family life. 38% of the patients also reported extreme stress and 19% perceived that they received little or no social support (Galvez et al, 2007). This shows that living with neuropathic pain is not just leading to physical disability, but also psychological and social dysfunctioning. Having known this nature of neuropathic pain, it important to consider both a pharmacological and psychosocial approach when prescribing treatment and formulating management plans.

Figure 6. Scatter graph showing the linear relationship between age (years) and quality of life of the patient; physical (6a) and mental (6b) components, given as a standardised score relative to the reference Spanish population (SDS). SDS score is shown for each patient adjusted for type of neuropathic pain, center, and present pain intensity, age, and sex. SD, standard deviation; 95% CI, 95% confidence interval. (Galvez et al, 2007)

b.

a.

Management of neuropathic pain

The management of neuropathic pain involves a number of well-established pharmacological therapies, as well as utilizing the psychosocial aspects of the neuropathic pain nature fully to best control the patient's pain symptoms.

Non-Pharmacological approaches

As the symptoms of pain are not just derived purely from a physical entity, psychotherapy should be considered as part of the management program for neuropathic pain. At an early stage, patients should be educated on the nature of the condition and to have realistic expectations with regards to treatment options; especially the current management for neuropathic pain is still mainly palliative in nature, with main aims to reduce symptomatic complaints of pain, but not a curative fix. To be able to alleviate the pain and achieve symptomatic relieve, even if only temporarily, may be the only attainable goal (CREST, 2008).

Since non-pharmacological treatments have the lowest risks of adverse side effects these must be offered early. These include a combination of physiotherapy, occupational therapy, psychotherapy and pain management programs that are adjusted to the individual's psychological and physical needs. The main aims for physiotherapy is to provide pain relieve wherever possible, but also focuses on the restoration of normal functioning and helping the patient to return to normal physical activities, such as going back

employment (Serpell et al, 2008). The low risk physiotherapy modalities include TENS (transcutaneous electrical nerve stimulation) and acupuncture are offered, along with appropriate education, advice and exercise. Functional difficulties in areas of personal care, work and leisure could be managed best by the input of occupational therapists, who may work around the needs of the individual in adjusting the arrangements at home/work to best allow the patient to function despite the pain. In Mrs L's case, she had shower rails and hand-held tools to pick up distant objects without exerting strain on her back/affected limbs; these were extremely helpful to her.

Of course, to maximize the outcome of pharmacological treatment, psychological therapy is essential in addressing the disability, emotional impacts and general life interruptions that are consequences of neuropathic pain. Apart from pharmacotherapy, psychotherapy is the best evidence-based therapy for the treatment of chronic pains like neuropathic pain (Morley et al, 2000).

Additionally, patients living with chronic pain often suffer from other comorbidities. Frequently these are not treated alongside the treatment for the chronic pain, therefore, a limited effect of the pain treatment may be observed. Behavioral and psychiatric conditions are especially common in patients with neuropathic pain; recognizing and treating these will aid in improved quality of life and better pain relief overall (Fishbain, 1999). An recent eight-week study of the effects of cognitive behavioural therapy (CBT) on chronic pain-induced insomnia has found that patients who received CBT exhibited significant reductions in sleep latency, number of awakenings

during sleep and overall quality of sleep (Jungquist et al, 2010). This offers further hope for patients who suffer from pain-related insomnias.

Finally, the Pain Management Program is a multi-disciplinary approach to pain control that is tailored to each patient's individual needs. Patients are typically referred to this program if they have been living with chronic pain for a number of years and suffer from significant physical, social and psychological functional difficulties. Many have become dependent on medications and acquired a number of side effects from these medications which are slowly eroding the quality of their lives. In the pain management programs, the goals are to reduce the subjective experience of pain, learning new coping strategies to control pain and improve physical and emotional functioning. Indeed, the pain management programs have been found to achieve a reduction in medication and enhanced rates of returning to work (CREST 2008 & NRH 2009).

Pharmacological therapies for neuropathic pain

In most cases, patients with neuropathic pain will need to be started on analgesic medication after failure to respond to non-pharmacological treatments. Although opioid and non-opioid analgesics, such as codeine and diclofenac respectively, have a role in dampening pain transmission in within the CNS in neuropathic pain states, it is far more effective to target the sodium, calcium and NMDA receptors, which are altered during nerve injury. Generally speaking, the clinical effectiveness of these drugs is limited by their narrow therapeutic indexes, i. e. the difference between the number needed to treat (NNT) and the number needed to harm (NNH) is very small (Rice & Hill, 2006).

Neuropathic pain is appreciably a very complex condition and treatment for this can be a real challenge, as most patients do not respond to conventional analgesics. The main problems lie within the inadequate diagnosis, lack of understanding of the pain mechanisms, inappropriate selection of therapies, and insufficient management of comorbidities that could delay the response to neuropathic pain therapies (Ro & Chang, 2005). Recently a review of the guidelines by O'Connior & Dworkin has resulted in the formulation of a stepwise approach to neuropathic pain management in primary care (Table 2). It is important to highlight that the first step of the management plan includes the identification of comorbidities, and relevant patient education as discussed above in the non-pharmacological managements of neuropathic pain to fully prepare the patient for adequate treatment.

Table 2. Stepwise pharmacologic management of neuropathic pain (O'Connor & Dworkin, 2009)

According to a recent review and recommendation by Dworkin et al, three lines of pharmacological treatment have been advised for neuropathic pain treatment. The first line treatments include tricyclic antidepressants (TCA), selective serotonin noradrenaline reuptake inhibitors (SSNRI), Ca2+ channel ligands (e. g. gabapentin & pregabalin) and topically applied 5% lidocaine; second line treatments including opioid analgesics & tramadol; and third line treatments are the other antiepileptics (e. g. Carbamazepine, lamortigine), other antidepressants (e. g. citalopram), N-methyl-D-aspartate (NMDA) antagonists and topically applied capsaicin (Dworkin et al, 2007 and O'Connor & Dworkin, 2009).

TCAs

The administration of TCAs such as amytriptyline and nortriptyline will benefit patients with neuropathic pain as TCAs have been shown consistently to be more efficacious than placebos in a number of randomized controlled trials (Saarto & Wiffen 2007), and especially beneficial for patients who have a comorbidity of depression. They act via histaminic, muscarinic and serotoninergic receptors both peripherally and centrally. However, one should note that the possibility of cardiac toxicity hinders its administration in patients with pre-existing cardiac conditions, especially arrhythmias; they should also be avoided in patients who have suicide risk or poor impulse control (Serpell et al, 2008). A large, retrospective cohort study reported that there was an increased risk to sudden cardiac death at dosages higher than 100mg/day (Ray et al, 2004). Because the recommended dose of TCA can range from 25mg at the starting dose to 150mg/day as the maximum dose (Dworkin et al, 2007), administering TCA should be a cautious exercise. In general, TCAs should be started at low dosages, administered at night to minimize sedative effects, and titrated up slowly to be continued for 6-8 weeks to allow analgesic effects (O'Connor & Dworkin, 2009).

SSRNIs

SSNRIs such as duloxetine and venlafaxin are less effective than TCAs, but have a better safety profile. Duloxetine has consistently demonstrated efficiency in treating painful diabetic peripheral neuropathy (Dworkin et al, 2007), although its effects in other types of neuropathic pain have not been studies extensively, therefore its efficacy in those types of pain are still uncertain.

Calcium channel ligands

Calcium channel ligands, e. g. gabapentin and pregabalin, bind to the voltage-gated calcium channels at the Î±2- ¤ subunit to modulate neurotransmitter release from presynaptic nerve terminals (Figure 7). Both drugs have been shown to be efficacious