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Pharmacotherapy of Neuropathic Pain

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1. Introduction

Neuropathic pain is responsible for a significant amount of the morbidity associated with generalized and focal peripheral neuropathies (Freeman, 2005). Appropriate diagnosis and assessment are critical to the successful treatment of neuropathic pain. The diagnosis of neuropathic pain can often be challenging and diagnostic criteria are evolving. Additionally the neuropathic pain commonly coexists with other types of pain (e.g., low back pain associated with both radiculopathy and musculoskeletal abnormalities). Assessment of neuropathic pain should focus on identifying and treating the underlying disease processes and peripheral or central nervous system lesions, response to prior therapies, and comorbid conditions that can be affected by therapy. Particular attention should be paid to identifying coexisting depression, anxiety, sleep disturbances, and other adverse impacts of neuropathic pain on health-related quality of life. Both pain and its adverse effects should be reassessed frequently. Patient education and support are critical components of the successful management of neuropathic pain. Careful explanation of the cause of neuropathic pain and the treatment plan are essential. Patient's and provider's expectations regarding treatment effectiveness and tolerability must be discussed, and realistic treatment goals should be established with patients. Non-pharmacologic methods of coping with pain should be discussed, including the importance of stress reduction, good sleep hygiene, physical therapy, and other potentially useful interventions (Dworkin et al., 2007).

Although neuropathic pain occurs as a consequence of numerous peripheral and CNS disorders, a variety of agents from diverse pharmacologic classes, the so-called adjuvant analgesics, have been used to treat neuropathic pain (Table 1) (Freeman, 2005). Early recognition and aggressive management of neuropathic pain is critical to successful outcome (Hutter et al., 2007). Historically, the earliest treatment strategies for neuropathic pain were invasive in nature. It was hoped that blocking neural transmission, either temporarily using local anesthetics or permanently by surgical nerve ablation, would alleviate pain. These techniques were particularly favored in the treatment of chronic pain associated with amputations or wounds suffered by soldiers during the great wars. In 1916, Leriche suggested that vasomotor changes seen in patients with peripheral nerve damage might indicate an association between pain and abnormal vascular stimulation: this led to the use of periarterial sympathectomy in an attempt to alleviate pain. However, none of these therapies was found to be consistently successful. Oftentimes, an interdisciplinary management team provides multiple treatment modalities which includes (Chong and Bajwa, 2003):

1. Non-invasive drug therapies eg. antidepressants, antiepileptic drugs, membrane stabilizing drugs, intrathecal morphine pump systems;
2. Alternative therapies e.g. acupuncture;
3. Physical modalities eg. physical rehabilitation;
4. Psychological modalities eg. behavior modification, relaxation training;
5. Spinal cord stimulators; and
6. Invasive therapies eg. nerve blocks, ablative surgery, trigger–point injections, epidural steroids, sympathetic blocks;
7. Various surgical techniques eg. dorsal root entry zone lesions, cordotomy, and sympathectomy.

2. General principles

A set of principles for the use of medications will result in attenuation of symptoms in a significant majority of patients with neuropathic pain (Freeman, 2005). The majority of the randomized clinical trials (RCTs) are conducted for the certain types of patients with neuropathic pain only. Although the extent to which the results of RCTs of one type of neuropathic pain apply to other types is unknown, the extrapolation of efficacy of medications that have demonstrated efficacy in one or more types of neuropathic pain to other types of neuropathic pain is reasonable and often clinically necessary. Medications that have demonstrated efficacy in several different neuropathic pain conditions may have the greatest probability of being efficacious in additional, as yet unstudied, conditions. However, it is possible that some types of neuropathic pain respond differently to treatment. The few RCTs conducted for head-to-head comparisons of different medications that make it difficult to compare the relative efficacy and safety of many medications in neuropathic pain with different severities and duration of the treatment (Dworkin et al., 2007).

Unfortunately, there is insufficient evidence to rank medications for neuropathic pain by their degree of efficacy or safety. Given these limitations, clinicians must consider several other factors when selecting a specific medication for a patient with neuropathic pain, including (Dworkin et al., 2007):

1. The potential for adverse outcomes associated with medication-related side effects;
2. Potential drug interactions;
3. Co-morbidities that may also be relieved by the non-analgesic effects of the medication (e.g., sleep disturbance, depression, anxiety);
4. Costs associated with therapy;
5. The potential risks of medication abuse; and
6. The risks of intentional and unintentional overdose.

These potentially competing factors must be prioritized according to the specific needs of each patient with neuropathic pain. Individual variation in the response to the medications used to treat neuropathic pain is substantial and unpredictable. Although evidence-based recommendations encourage the use of specific medications, the overall approach should be recognized as a stepwise process intended to identify the medication, or medication combination, that provides the greatest pain relief and fewest side effects for a given patient. If a trial of one medication fails to adequately relieve pain or causes intolerable side effects, treatment should be discontinued and a different medication should be selected. If a medication is well tolerated and provides partial pain relief, it should be continued and a second medication with a distinct mechanism of action could be added (Dworkin et al., 2007).

In addition to potential additive analgesic benefits, combination therapy may provide analgesia more quickly by combining a medication with a rapid onset of effect with one that requires several weeks of treatment before maximum benefit is achieved. These potential advantages of combination therapy must be weighed against the possibility of additive adverse effects, drug interactions, increased cost, and reduced adherence to a more complex treatment regimen. In one of the RCTs of combination therapy in neuropathic pain, gabapentin and morphine combination provided superior pain relief to either medication alone and to placebo. However, a recent RCT evaluating nortriptyline, morphine, and their combination in patients with chronic lumbar root pain found no greater efficacy with the combination than with either medication alone or placebo (Dworkin et al., 2007).

The pharmacologic regimen for each patient should be individualized. Pharmacotherapy should be initiated with a low dose of medication, particularly in the elderly and patients susceptible to medication side effects. Most agents should be slowly titrated to minimize side effects. Since the pain of peripheral neuropathy is characteristically worse at night, it may be helpful to weight the dosing of short-acting medications to the evening hours. The onset of the therapeutic effect may be gradual and sufficient time should elapse before a conclusion is drawn, as to the success or failure of a drug. The combination of one or more drugs from a different class may result in an additive or even synergistic effect. Once patients are pain free for several months, a gradual medication taper should be considered (Freeman, 2005).

3. Pharmacological treatment of neuropathic pain

Pharmacotherapy of neuropathic pain is still difficult despite of new treatments, and there is no single treatment that works for all conditions and their underlying mechanisms. Given the increasing evidence for effective treatments of neuropathic pain, it is important for the clinician to know which drugs are most effective in relieving pain and associated with the fewest adverse effects and there is a need for an evidence-based algorithm to treat neuropathic pain conditions (Finnerup et al., 2005). Pharmacological management will produce the desired analgesia in some, but not all, patients. In those who fail to respond, other modalities of treatment may be considered, ranging from behavior modification and fostering of coping skills to the more major invasive medical techniques (McCleane, 2003). It is accepted that nociceptive pain may be relieved by morphine and non-steroidal anti-inflammatory drugs (NSAIDs). However, with neuropathic pain, some studies suggest analgesia with morphine (Kupers et al., 1991; Rowbotham et al., 1991) or NSAIDs (Cohen and Harris, 1987; Benedittis et al., 1992), while others demonstrate no analgesia with morphine (Arner and Meyerson1988; Eide et al., 1994) or NSAIDs (Weber et al., 1993; Max et al., 1988). However, the most neuropathic pain responds poorly to NSAIDS and opioid analgesics (Talati et al., 2011).

The mainstays of treatment of neuropathic pain are predominantly the tricyclic antidepressants (TCA's), the anticonvulsants, and the systemic local anesthetics (Talati et al., 2011; Vranken et al., 2001). Other pharmacological agents that have proven efficacious include the corticosteroids, topical therapy with substance P depletors, autonomic drugs, and N-methyl D-aspartate (NMDA) receptor antagonists (Talati et al., 2011). While many other agents may be used in treating neuropathic pain, although their use is not verified by appropriate studies. It is hoped that the rational use of drugs increases the chance of achieving analgesia in the patient with neuropathic pain. However, no one therapeutic intervention is guaranteed the success. Consequently, it may often be necessary to work ones way through a list of treatment options before analgesia is achieved. Inevitably, any relief produced may be tempered by the

associated side effects of that drug so that improvement in quality of life (pain reduction, mood elevation, increased mobility, better sleep with minimal side effects from treatment) is the therapeutic goal. Poly pharmacy is a real danger, with patients staying on medication in hope of relief when none is actually apparent. Trials of medication for a defined period with assessment before and after may be more appropriate (McCleane, 2003).

Ideally, the drug choices in an evidence-based algorithm would be based on direct comparisons of one drug with another, for both efficacy and side effects. There are very few such direct comparisons available. An alternative approach is to estimate relative treatment efficacy and safety using RCT data, which is based on the number needed to treat (NNT) and number needed to harm (NNH). NNT is defined as the number of patients needed to treat with a certain drug to obtain one patient with a defined degree of pain relief, at least 50% pain relief. If 50% pain relief could not be obtained, then the number of patients reporting at least good pain relief or reporting improvement was used to calculate NNT. NNT was only calculated when the relative risk was statistically significant. NNH indicates the number of patients that need to be treated for one patient to drop out due to adverse effects. TCA's and the anticonvulsants gabapentin and pregabalin were the most frequently studied drug classes. In peripheral neuropathic pain, the lowest NNT was for TCA's, followed by opioids and the anticonvulsants gabapentin and pregabalin. Whereas, for central neuropathic pain there is limited data. NNT and NNH are currently the best way to assess relative efficacy and safety, but the need of dichotomous data estimated retrospectively for old trials, and the methodological complexity of pooling data from small cross-over and large parallel group trials, remain as limitations of NNT and NNH (Finnerup et al., 2005).

3.1 Drug classification (Offenbaecher and Ackenheil, 2005; Freeman, 2005; NICE clinical guideline, 2010)

Drug class: subclass	Drugs
Opioid analgesics	Buprenorphine, co-codamol, codeine phosphate, co-dydramol, dihydrocodeine, fentanyl, morphine, oxycodone, tramadol
Antidepressants: Tricyclic antidepressants (TCAs)	 Amitriptyline, clomipramine, desipramine, dosulepin (dothiepin), doxepin, imipramine, lofepramine, nortriptyline, trimipramine
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, fluoxetine, paroxetine, sertraline
Serotonin–norepinephrine reuptake inhibitors (SNRIs)	Duloxetine, venlafaxine
Anti-epileptics (anticonvulsants)	Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, sodium valproate, topiramate
CCK antagonists	Proglumide
NMDA antagonists	Ketamine, dextromethorphan, riluzole, memantine, MK801
Topical treatments/ membrane stabilisers	Capsaicin, lidocaine, tocainide, mexiletine
Miscellaneous drugs	Clonidine, cannabinoids, tetrahydrocannabinol

Table 1. Drugs used for the treatment of neuropathic pain

3.1.1 Opioid analgesics

Tramadol ((1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclo-hexanol) is a synthetic opioid from the aminocyclohexanol group. It is an analgesic with opioid agonist properties that acts on the neurotransmission of noradrenaline and serotonin. In comparison with typical opioid agonists such as morphine, pethidine and the partial agonist buprenorphine, and tramadol, it rarely causes respiratory depression or physical dependence. Tramadol activates the spinal pain inhibitory system. In patients with postoperative pain of moderate or severe intensity, tramadol administered *iv* or *im* is equivalent to the analgesic potency of pethidine and pentazocine (oral route). In patients with postoperative pain of moderate intensity, tramadol analgesia (when administered *iv* in doses of 50–150 mg) is equivalent to the analgesic efficacy of morphine in doses of 5–15 mg, although during epidural administration, tramadol possesses 1/30 of the analgesic efficacy of morphine. Tramadol's main adverse reactions are nausea, dizziness, sedation, dry mouth, and sweating. Tramadol may be particularly useful for patients, who are more sensitive to the adverse effects of strong opioids (e.g., sedation, fatigue, constipation) (Leppert, 2009).

Morphine and other analogues are of limited value in most of the neuropathic pain states. Only in diabetic peripheral neuropathy oxycodone has a positive effect on pain. A special role has tramadol, which already has been proposed as an antidepressant. This unique agent combines opiate receptor agonist activity with NA reuptake inhibition, and recent research has suggested that it also has agonist activity at the 5-HT receptor. Due to this dual action it seems to have some value in the treatment of chronic neuropathic pain and can be recommended for treatment attempts (Offenbaecher and Ackenheil, 2005).

Alfentanil (active placebo), μ-opioid receptor agonist, in neuropathic pain syndromes showed significant and marked reductions of hyperalgesia to cold and also significantly reduced ongoing pain and mechanical hyperalgesia. However, no firm conclusion can be made on the long-term effect and the clinical usefullness of alfentanil (Ko et al., 2009; Offenbaecher and Ackenheil, 2005).

3.1.2 Antidepressants

Antidepressants and anticonvulsants are used as first-line therapy for the treatment of neuropathic pain. A meta-analysis of antidepressant use in randomized placebo-controlled trials revealed that TCAs provided at least a 50% reduction in pain intensity in 30% of individuals with neuropathic pain. Moreover, amitriptyline's a tertiary amine, is the best-studied TCA. It has been shown, in numerous randomized, blinded, placebo-controlled clinical trials, to significantly improve neuropathic pain. Amitriptyline's side effects include drowsiness, constipation, dry mouth, weight gain, and orthostatic hypotension. The secondary amines, nortriptyline and desipramine, have less troublesome side-effect profiles. The use of these agents is preferable, particularly in the elderly and side-effect prone patients, although their efficacy may not be as great. Due to possible cardiotoxicity, TCAs should be used with caution in patients with known or suspected cardiac disease (Freeman, 2005).

Current data suggest that SSRIs are not as effective as TCAs in the management of neuropathic pain. Small studies with the selective serotonin reuptake inhibitors (SSRIs), citalopram and paroxetine, have shown some improvement in symptoms of neuropathic pain in patients with painful peripheral neuropathy. The non-TCA bupropion, an Serotonin–norepinephrine reuptake inhibitor (SNRI), and a weak inhibitor of dopamine reuptake, was effective in a small, placebo-controlled trial of patients with neuropathic pain

of diverse etiology, during which it was administered at 150–300 mg/day in its sustained-release form (Freeman, 2005).

The SNRIs, venlafaxine, duloxetine, and milnacipran, may prove useful in the treatment of painful diabetic peripheral neuropathy. These agents inhibit reuptake of serotonin and norepinephrine without the muscarinic, histaminic, and adrenergic side effects that accompany the use of TCAs. Venlafaxine has shown effectiveness in the treatment of neuropathic pain. In a three-way crossover trial of patients with painful neuropathy, venlafaxine 225 mg/day and imipramine 150 mg/day reduced pain scores significantly more than placebo. Surprisingly, there was no difference in the effectiveness or the side-effect profile of these two active drugs. Side effects of venlafaxine include nausea, dizziness, dry mouth, sexual dysfunction, hypertension, and irritability. Similar results were obtained with doses between 150–225 mg/day in patients with painful diabetic peripheral neuropathy (Freeman, 2005).

The SNRI duloxetine, a secondary amine, may be a more potent reuptake inhibitor in vitro than the tertiary amine SNRIs venlafaxine and milnacipran. The clinical significance of this in vitro difference in potency is uncertain. Based on evidence that duloxetine ameliorates the painful physical symptoms of depression, clinical trials were performed in patients with diabetic peripheral neuropathy. There is supporting preclinical evidence of effectiveness of duloxetine in a rodent model of neuropathic pain as well as duloxetine reverses mechanical allodynia behavior in the L5/L6 spinal nerve ligation model. Food and Drug Administration approved duloxetine for the treatment of neuropathic pain in diabetes. Common side effects of duloxetine include nausea, headache, insomnia, constipation, dry mouth, dizziness, and fatigue (Freeman, 2005).

3.1.3 Anti-epileptics (anticonvulsants)

Anticonvulsant agents have been used in pain management over the last few decades due to the clinical impression that they are effective in alleviating certain forms of pain for example neuropathic pain especially lancinating and burning pain (Todorovic et al., 2003), cancer pain (Keskinbora et al., 2007). Gabapentin has attracted recent attention because of its effectiveness against neuropathic pain in both controlled clinical trials and animal models (Kayser and Christensen, 2000).

It has been reported that, in addition to the anti epileptic activity, gabapentin also displays antinociceptive (Cheng and Chiou, 2006; Taylor et al., 1998), antihyperalgesic (Garry et al., 2005; Reyes-Garcia et al., 2004), and antiallodynic (Garry et al., 2005; Suzuki et al., 2005) activity in various animal pain models e.g. models of sciatic nerve chronic constriction injury (Joshi et al., 2006), spinal nerve ligation (Abdi et al., 1998; Joshi et al., 2006), diabetic neuropathy (Cheng and Chiou, 2006), acute herpes zoster infection (Cheng and Chiou, 2006), thermal injury (Garry et al., 2005; Hanesch et al., 2003) and postoperative pain (Cheng and Chiou, 2006; Field et al., 1997; Otari et al., 2010). In addition, gabapentin was shown to reduce hyperalgesia and inhibit C-fibre responses to noxious stimuli in animal models of inflammatory pain (injection of formalin or carrageenan)(Hanesch et al., 2003).

The possible mechanisms involved in the multiple therapeutic actions of gabapentin have been actively studied. Several hypothesis were raised. Despite its structural similarity to GABA, gabapentin has no discernible action at $GABA_A$ or $GABA_B$ receptors nor does it have any effect on either the uptake or degradation of GABA. However, it interacts specifically with the $\alpha_2\delta$ subunit of voltage sensitive calcium channels, a subunit ubiquitous to all calcium channel types, suggesting that the $\alpha_2\delta$ subunit is involved in the antinociceptive action of gabapentin

(Cheng and Chiou, 2006; Hanesch et al, 2003). Of the different subtypes, N-type calcium channels acquire greater functional roles after nerve injury and evidence exists for an upregulation of the $\alpha_2\delta$ -1 subunit and the N-type pore-forming α_1 or β subunit in this pain state (Suzuki et al., 2005). Pregabalin, a gabapentin analogue, is also effective in the management of neuropathic pain and exerts its pharmacological effects via the same mechanism as that gabapentin. The N-type calcium channel is Cav2.2 and it is unique to sensory nerve terminals in the dorsal horns of the spinal cord controlling neurotransmitter release (Cheng and Chiou, 2006). By binding to the $\alpha_2\delta$ subunit, gabapentin might affect Ca^{2+} currents to modulate neurotransmitter release or neuronal excitatibility and synaptic transmission. Gabapentin reduced excitatory amino acid (glutamate and aspartate) release in the spinal cord in several pain models (Cheng and Chiou, 2006).

3.1.4 CCK antagonists

After systemic injection, mechanical allodynia was reduced by higher doses of cholecystokinin-B (CCK B) receptor antagonist, CI-988 (10 and 20 mg/kg). Intrathecal CI-988 (100, 200 and 500 microg) dose-dependently increased the paw withdrawal threshold in both paws after spinal cord hemisection in rats. It was suggest that up-regulation of spinal CCK may contribute to maintenance of mechanical allodynia following spinal cord injury (SCI) and that clinical application of CI-988 or similar drugs may be useful therapeutic agents for management of central neuropathic pain (Kim et al., 2009).

It was demonstrates that, the antinociception by RB 101, a complete inhibitor of enkephalin-catabolizing enzymes, was induced by elevation of extracellular levels of endogenous enkephalins, and can be extended to neuropathic pain in diabetic rats. Furthermore, blockade of CCK-B receptors potentiated antinociceptive effects elicited by RB 101. Moreover, its coadministration with CI-988, a C CK-B receptor antagonist, has been shown to strongly enhance its antinociceptive effect in normal rats (Coudore-Civiale et al., 2001).

3.1.5 NMDA antagonists

An NMDA antagonist, which is metabolized to dextrophan has therapeutic effects on neuropathic pain as well. In patients with posttraumatic neuropathic pain, Dextromethorphan resulted in a significant (30%) reduction of pain. Most patients (76%) experienced one of the milder to moderate dose-related adverse effects, such as light-headedness and drowsiness this may limit further use of dextromethorphan. This indicated that dextrophan is the therapeutic agent for neuropathic pain. Whereas, another NMDA receptor antagonist, memantine was also effective in patients with diabetic neuropathy and post-herpetic neuralgia (Offenbaecher and Ackenheil, 2005).

Ketamine, in patients with long lasting peripheral neuropathic pain, produced significant reduction in mean pain, measured with a visual analog scale. The clinical usefulness is however, limited by disturbing side effects mainly somnolence, light-headedness, paraesthesia etc. Ketamine in neuropathic pain syndromes showed significant and marked reductions of hyperalgesia to cold and also significantly reduced ongoing pain and mechanical hyperalgesia. However, no firm conclusion can be made on the long-term effect and the clinical usefullness of ketamine (Offenbaecher and Ackenheil, 2005).

A glycine antagonist, in patients with neuropathic pain of mixed origin, in order to reduce pain failed to show a positive effect in comparison with placebo (Offenbaecher and Ackenheil, 2005).

3.1.6 Miscellaneous drugs

Imidazoline receptors (IRs) are widely distributed in mammalian cells of the central (CNS) and peripheral (PNS) nervous systems, liver, kidney and heart. CR4056 is a new ligand of the imidazoline-2 sites (I2R) with efficacy in several models of pain. CR4056 is a very effective analgesic compound active in several preclinical models relevant for important human pathologies including fibromyalgia and diabetes-induced neuropathy. CR4056 has now completed preclinical development and a phase I safety study in humans has now been designed to finally develop the compound as a first I2 ligand in chronic and neuropathic pain conditions (Ferrari et al., 2011).

Administered adenosine led to a significant reduction in spontaneous pain and hyperalgesia in individuals with neuropathic pain of various etiologies. The role for intrathecal adenosine is very limited for the treatment of neuropathic pain. The cholecystokinin (CCK) 2 antagonist, L-365, in patients receiving morphine for chronic neuropathic pain was not superior (Offenbaecher and Ackenheil, 2005).

4. Combination pharmacotherapy

Clearly, numerous pharmacological agents are available for the treatment of neuropathic pain. The definitive drug therapy has however remained elusive. Given the limited effectiveness of current treatments, combining different drugs may result in improved results at lower doses and with fewer side effects. Many patients with neuropathic pain currently receive drug combinations, albeit in the absence of supportive evidence. Oftentimes triple drug therapy with TCA's, anti–convulsants, and a systemic local anesthetic is necessary. Occasionally, there is the patient who requires chronic opioid therapy in conjunction with the above medications. In a recent RCT, analgesia with a morphine-gabapentin combination was superior to treatment with either drug alone. In a study involving 11 patients who did not respond to gabapentin, a gabapentin-venlafaxine combination was superior to gabapentin alone. In another RCT, the addition of the neuroleptic fluphenazine to amitriptyline therapy provided no benefit. Future trials are needed to evaluate optimal drug combinations and dose ratios as well as safety, compliance, and cost-effectiveness. When patients fail failed to showresponce to systemic treatments, the implantable systems such as a spinal cord stimulator or intrathecal morphine pumps are available. Recently, the spinal cord stimulator has been shown to attenuate the augmented dorsal horn release of excitatory amino acids via a GABAergic mechanism in rats. Rarely, surgical intervention is required (Gilron et al., 2006).

5. Studies in progress

There are preliminary studies in neuropathic pain and fibromyalgia with very promising results. Pregabalin belongs to the class of AEDs, which modifies intracellular calcium levels and decreases norepinephrine (NE), 5-HT, and dopamine secretion. It improves diabetic neuropathy and seems to be effective in fibromyalgia patients. Another group of drugs are newer antidepressants (duloxetine and milnacipram) which inhibit NE and 5-HT reuptakte more specifically than the classic antidepressants, meaning that they have almost no effect on other transmitters and therefore have more favorable side effects. The results of these studies were reported at the 2004 Myopain Congress in Munich, Germany (Offenbaecher and Ackenheil, 2005).

Kamata and colleagues evaluated the efficacy of milnacipram, a novel serotonin-norepinephrine reuptake inhibitor, in a series of five patients with chronic pain of mixed

origin. Four out of five patients experienced a pain reduction between 42% and 86% during a 12-week treatment period (Offenbaecher and Ackenheil, 2005).

In a phase II study, reported at Collegium Internationale Neuro-Psychopharmacologicum Paris in 2004, milnacipram was used in 125 patients with fibromyalgia. Administration of milnacipram either four times daily or twice daily showed that the latter was better tolerated and resulted in significant improvements of several outcome variables such as pain (37% reported a 50% reduction), fatigue, stiffness, and physical functioning. Overall, 273 adverse events were reported of which 49% were mild, 38% moderate, and 13% severe (Offenbaecher and Ackenheil, 2005).

The results of a study by Detke was presented in a congress report by Susmanon investigations on duloxetine in patients with diabetic neuropathy. Duloxetine is a potent and balanced dual reuptake inhibitor of both 5-HT and NE, possessing comparable affinities in binding to NE and 5-HT transport sites, in contrast to most other dual-reuptake inhibitors. In 457 patients with diabetic neuropathy receiving placebo or three different doses of duloxetine in a 12-weeks, multicentre, double-blind study, 60 mg and the 120 mg dose were significantly more effective in reducing 24-hour pain. In the highest dose, patients displayed more side effects, such as nausea, somnolence, dizziness, and increased appetite. This clinical results provided evidence that duloxetine 60 mg/day and duloxetine 60 mg BID is effective in the treatment of pain associated with diabetic neuropathy. These positive results of duloxetine on pain were further supported by a currently published study by Goldstein and colleagues. Data from 3 different studies investigating primarily the effect of duloxetine on mood in patients with major depression were analysed concerning painful symptoms, as secondary outcome in these studies. The authors found that compared to placebo, duloxetine reduces significantly painful physical symptoms in these patients (Offenbaecher and Ackenheil, 2005).

Crofford and colleagues investigated the efficacy and safety of pregabalin in 529 patients with fibromyalgia. In this multicenter study three different doses of pregabalin 150 mg, 300 mg, and 450 mg were compared with placebo over an 8-week period. It was found that, the highest pregabalin dose produced a significant pain reduction (change from baseline of two points on a visual analog scale). Additionally, other outcome (eg, sleep quality, fatigue, and health-related QOL) improved as well. However, a high proportion of the patients reported side effects such as dizziness, somnolence, headaches, and others (Offenbaecher and Ackenheil, 2005).

6. Conclusion

In clinical practice the most frequently prescribed drugs in chronic neuropathic pain are classic TCAs and AEDs, both of them have the well-known side effects, which limit their long-term administration (Offenbaecher and Ackenheil, 2005).

However new studies using randomized, double-blind, placebo controlled trials are increasing to support evidence based algorithm to treat neuropathic pain conditions. The neuropathic pain is a devastating chronic condition that generally can be diagnosed by history and findings on physical examination. For some neuropathic pain syndromes, available treatments are tolerable and afford meaningful relief to a considerable proportion of patients. Nevertheless, many patients report intractable and severe pain and better treatment strategies are desperately needed. Furthermore, the coexistence of neuropathic, nociceptive, and occasionally, idiopathic pain in the same patient leads pharmacotherapy difficult. Also, neuropathic pain has historically been classified according to its etiology (e.g.

painful diabetic neuropathy, trigeminal neuralgia, spinal cord injury) without regard for the presumed mechanism(s) underlying the specific symptoms. Hence, currently, no consensus on the optimal management of neuropathic pain exists and practices vary greatly worldwide. The treatment of neuropathic pain is largely empirical, often relying heavily on data from small, generally poorly-designed clinical trials or anecdotal evidence.

It is still reassuring, however, to realise that in the future we have the prospect of additional agents with more specific sodium channel blocking effects, calcium channel blockers and new generation anticonvulsants and capitalise on the major expansion in knowledge generated from the work of the basic scientists. The field of neuropathic pain research and treatment is in the early stages of development, with many goals yet to be achieved. In particular, future laboratory, clinical, and epidemiologic research into pathogenesis, treatment, and prevention of neuropathic pain is expected as well as improved dissemination of new information to health professionals and the public. Over the years to come, many upcoming advances are expected in the basic and clinical science of neuropathic pain as well as in the implementation of improved therapies for patients who continue to experience these devastating conditions.

Recently, the problem has been recognized—there is possible shift from rheumatology to psychiatry—and newer studies have been published or are still in progress. These newer drugs—on the one hand, specific dual NE/5-HT reuptake inhibitors, and on the other hand newer AEDs—are promising in terms of efficacy and fewer side effects (Offenbaecher and Ackenheil, 2005).

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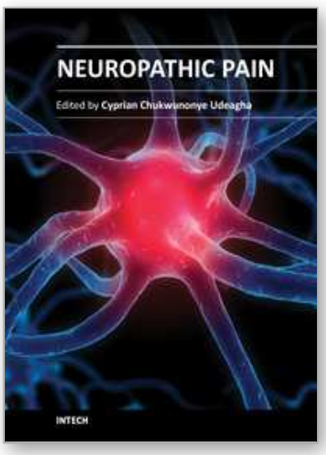

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Neuropathic pain is known to be pain with nerve involvement. The intensity of which depends on the severity, pain threshold and the ability of suffers to cope. Neuropathic pain may need mono-therapy or combination of therapies to be resolved. Neuropathic pain may not resolve completely, therefore patient's compliance and understanding is essential in its management. Awareness and patient's education on targets may be of help during therapies for neuropathic pain. All chapters treated introduction, characteristics, diagnosis and randomized interventions to certain management of neuropathic pain. We acknowledge all those involve in the making of this book.

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