Pharmacol. Ther. Vol. 75, No. 1, pp. 1–19, 1997

ISSN 0163-7258/97 $32.00
PII S0163-7258(97)00019-3

Chronic Neuropathic Pain and Its Control by Drugs

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ABSTRACT. The medical treatment and some currently known aspects of the aetiology of five neurogenic pain states are discussed. Neurogenic pain can be described as pain resulting from noninflammatory dysfunction of the peripheral or central nervous system without nociceptor stimulation or trauma. The enormity of the field has limited this review to post-herpetic neuralgia, complex regional pain syndromes, phantom pain, trigeminal neuralgia and diabetic neuralgia. Evidence suggests that many neurogenic pain states are not effectively controlled. This may be due in part to a lack of understanding of the aetiology of these conditions and to the lack of high quality studies evaluating existing treatments. A compact review of the literature is presented with some treatment options and possible future directions. Where appropriate surgical management and physical therapy have been discussed; however, a thorough appraisal of nondrug treatments was not the main priority of this review. PHARMACOL. THER. 75(1):1–19, 1997. **© 1997 Elsevier Science Inc.**

KEY WORDS. Neurogenic pain, post-herpetic neuralgia, complex regional pain syndromes, trigeminal neuralgia, phantom pain, diabetic neuropathy.

CONTENTS

ABBREVIATIONS. CRPS, complex regional pain syndromes (Types I and II); DN, diabetic neuropathy; EPSP, excitatory postsynaptic potential; GABA, γ-aminobutyric acid; HZO, Herpes Zoster Opthalmicus; IASP, International Association for the Study of Pain; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs; PHN, post-herpetic neuralgia; PLP, phantom limb pain; PNS, peripheral nervous system; RSD, reflex sympathetic dystrophy; SMP, sympathetically maintained pain; TCA, tricyclic antidepressant; TGN, trigeminal neuralgia.

1. INTRODUCTION

Pain is an intense human experience that has defied definition and explanation for centuries. Many explanations have viewed pain as a sensory experience related to tissue injury. However, definitions based on stimulus simply suggest probable precipitating factors; they do not account for the development of chronic pain nor provide explanations for idiopathic pain. The assumption of a fixed stimulus-response scenario is not realistic, considering other events that accompany the stimulus during transmission from the peripheral nervous system (PNS) to the CNS. Firstly, there is a barrage of electrical activity resulting from the peripheral stimulus. This is accompanied by the transmission of chemical mediators centrally from the PNS. There is interaction between messages arising from different stimuli, which may inhibit or exaggerate the effects of individual stimuli. Secondly, the resulting efferent message is subject to powerful controls originating in the CNS. For these two reasons, the existence of a fixed stimulus-response relationship cannot be justified (Wall and Melzack, 1989).

The Taxonomy Committee of the International Association for the Study of Pain (IASP) describes pain as being, "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, 1986). The definition suggests that pain is a highly subjective experience that is coloured by the physical, psychological and social experiences of the patient. Pain that is reported in the absence of tissue damage historically has been considered to be of psychological aetiology. The IASP definition classifies pain resulting from a nontraumatic experience as true pain if deemed to be reported by the patient in a manner resembling that following actual tissue damage.

Neurogenic pain can be defined as pain resulting from noninflammatory dysfunction of the PNS or CNS without peripheral nociceptor stimulation or trauma. Reports have indicated that at least 1% of the population of the United Kingdom suffers from some form of neurogenic pain (Bowsher, 1991). This number is probably as high as 50% of pa-

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tients over the age of 65. Considering that the majority of admissions only experience mild amelioration of symptoms following intervention and the increasing proportion of elderly persons, neurogenic pain represents a considerable problem in the community.

Chronic pain is a long-term experience that invades the patient's life, affecting their behaviour, work, daily tasks, emotional state and social interactions. The patient's painful somatosensory state can become a preoccupation. In the case of chronic neurogenic pain, the injurious modality has usually long resolved; however, pain continues (Braune and Schady, 1993). The development of chronic pain following peripheral nerve injury has been attributed to the occurrence of three different processes in the spinal cord. These are increased excitability, decreased inhibition, and structural reorganisation of cells (Woolf and Doubell, 1994). These changes in the spinal cord become the underlying pathology of the pain state.

Neurogenic pain can result from peripheral nerve trauma (deafferentation events, entrapment, amputation), infection (post-herpetic neuralgia [PHN], human immunodeficiency syndrome-associated neuralgia), pressure due to growth (neoplasia), infarct, metabolic disturbance (diabetic neuralgia), or it may be idiopathic.

Despite the broad aetiology of neurogenic pain states, the clinical manifestations of these conditions are relatively uniform. Patients frequently present with burning sensations associated with dull or throbbing pain. They may also suffer from lancinating, shooting paroxysmal pains. The burning sensations experienced by neurogenic pain sufferers (similar to that experienced when one places a warm hand into extremely cold water) are almost diagnostic of these conditions.

Associated with these symptoms, patients may suffer from a subclinical form of sensory deficit that may or may not correspond to the somatic area of pain. This deficit is most likely to manifest as a loss of the patient's ability to differentiate between warm and cool temperatures. Paradoxically, lowered temperatures can often precipitate severe burning pain. Cold allodynia can result from a cool breeze against the face or contact with a cool surface. Tactile allodynia may result from a scarf or hair blowing against one's face. While these examples indicate provoked pain sensations, pain can also be of a spontaneous nature, especially in the deafferentation events that occur following trauma (Woolf and Doubell, 1994). Quite often the patient's symptomatology is a combination of spontaneous and evoked pains.

Aside from pain, other changes include localised hyperhydrosis, altered skin temperature and trophic changes to the nail, skin and underlying structures. A lifetime of living with constant pain can lead to personality disturbances and in some cases, suicide.

2. NEUROGENIC PAIN MECHANISMS

One factor that can contribute to development of neurogenic pain is the development of a neuroma at the site of nerve injury. When a peripheral nerve is injured, the distal length of the nerve severed from the energy-supplying cell body degenerates; however, the section of nerve proximal to the site of injury survives. At the site of injury, a neuroma forms; it is here that abnormal ectopic stimuli arise and are communicated to the CNS (Wall and Gutnick, 1974; Govrin-Lippman and Devor, 1978). The CNS interprets this discharge as originating from the affected limb and perceives pain in the limb.

The development of these abnormal ectopic discharges is fairly well understood. It involves the anterograde axoplasmic transport of cellular constituents, such as receptors and chemical mediators, from the cell body to the periphery. As the peripheral portion of the nerve has been severed, the transported mediators accumulate in the neuroma (Laduron, 1987). This leads to an increase in the excitability of the area and the generation of ectopic signals.

Impulse generation can also result from the hypersensitivity of the neuroma to stimuli such as mechanical, chemical and metabolic changes, ischaemia, inflammation, cold stimuli and circulating catecholamines. Stimulation of ectopic signals from these areas can persist for long periods of time as controlling neural input from the periphery is affected. This can lead to periods of nociceptive sensation long after the triggering stimulus has subsided. This may be followed by a nonpainful refractory period, e.g., in the case of trigeminal neuralgia (TGN) (Devor, 1991).

These sources of ectopic discharge provide the clinician with certain diagnostic criteria for the condition. The Tinel sign is a tool used in the diagnosis of mechanical hypersensitivity by tapping along the length of the nerve. They also present the clinician with the possibility of treatment, e.g., stimulation of ectopic discharge by catecholamines can be ameliorated by sympathectomy. For excellent reviews and opinions on mechanisms of neuropathic pain see Devor (1991) and Ochoa (1994).

In contrast to this train of thought, it has been suggested that ectopic discharge is not solely responsible for the maintenance of neurogenic pain, but that changes in peripheral nerves resulting from injury are communicated to the CNS, resulting in reorganisation and alterations in the receptive fields of spinal cord cells (Devor and Wall, 1981a,b; Wall and Devor, 1983; Ochoa, 1994). Evidence corroborating this includes the fact that some animal neurogenic pain models show complete resolution of ectopic discharge, yet they continue to exhibit evoked pain (Scadding, 1981). Ochoa (1994) suggests that evidence indicating that ectopic pacemaker sites are responsible for ongoing nociceptive stimuli in humans is not conclusive.

Neuroanatomical reorganisation within the CNS is an important consideration in most forms of neurogenic pain. In situations where there is complete transection of peripheral nerves, dorsal horn cells, which previously received inputs from the denervated region, begin to respond to stimulation of other body regions, often developing receptive fields in more proximal, innervated parts of the affected limb (Devor and Wall, 1978, 1981a,b; Hylden *et al.*, 1987). This process is generally thought to occur as a result of up-

regulation of existing synapses, although there is also evidence to indicate that axonal sprouting in dorsal horn cells may lead to the establishment of new synaptic connections. Myelinated axons, which normally terminate in laminae III and IV of the dorsal horn, have been shown to sprout into lamina II of the dorsal horn, potentially developing synaptic connections with intrinsic neurons involved in the transmission of nociceptive afferent inputs (Woolf *et al.*, 1992). The authors postulated that this might constitute a mechanism whereby normally innocuous afferent inputs could contribute to nociception.

Another form of neuroanatomical reorganisation has been demonstrated following a constriction injury to a peripheral nerve (McLachlan *et al.*, 1993). These authors demonstrated that following sciatic nerve ligation in rats, noradrenergic perivascular axons sprout into dorsal root ganglia and form basket-like structures around large-diameter sensory neurons. The noradrenergic terminals located around the dorsal root ganglia somata may be responsible for sympathetically mediated paraesthesias as a result of initiating afferent activity during ongoing and reflex sympathetic postganglionic discharge (McLachlan *et al.*, 1993). As a result, pain might be generated if central nociceptive neurons become sensitised to activity in large-diameter afferent fibres. Activity in large dorsal root ganglion cells initiated by the release of noradrenaline onto their somata, therefore, might be converted into nociceptive signals within the CNS (McLachlan *et al.*, 1993).

Implication of the excitability of central neurons in the maintenance of neurogenic pain introduces the concept of primary and secondary hyperalgesia. These terms were first coined by Hardy in 1950 (Hardy *et al.*, 1950). Primary hyperalgesia occurs as a result of sensitisation of primary mechano- and heat-sensitive nociceptors in the immediate area of tissue damage. Secondary hyperalgesia occurs in a referred area around the zone of tissue damage and is typically mechanosensitive only. Microneurography studies (Torebjork *et al.*, 1992) have strongly implicated the process of central sensitisation as a basis for the development of secondary hyperalgesia.

Woolf (1994) has described central sensitisation as "Those changes in the excitability of neurons within the central nervous system that contribute to abnormal pain sensibility." Much of the early research in this field was carried out by the group at University College London headed by Wall and Woolf. They showed that low-frequency electrical stimulation of unmyelinated nociceptive afferents would produce an increase in the excitability of spinal cord neurons (Wall and Woolf, 1984). This phenomenon was termed "windup." The capacity of unmyelinated afferents to produce "windup" and consequent central sensitisation has been linked to their ability to produce slow excitatory postsynaptic potentials (EPSPs) (Woolf, 1994). In contrast to myelinated afferents that produce very short-duration EPSPs (in the order of a few milliseconds), unmyelinated afferents produce much longer EPSPs lasting up to 20 sec (Thompson *et al.*, 1990). Repetitive stimulation of unmyelinated afferents results in temporal summation of slow EPSPs in second-order neurons and a nonlinear cumulative depolarisation of the neuronal membrane. Subsequently, spinal cord neurons will exhibit a reduced threshold for activation and spontaneous activity, which are the primary characteristics of sensitisation. Unmyelinated afferent input appears to be crucial for the induction of central sensitisation; however, Woolf (1983) and Coderre and Melzack (1987) have shown that once a state of central sensitisation is induced, it can be maintained even after peripheral nociceptive afferent input is blocked by the administration of local anaesthetic. Central sensitisation, therefore, can be seen as a phenomenon that is spatially, temporally and mechanistically distinct from peripheral sensitisation.

The release of tachykinins, such as substance P and neurokinin A, and an associated up-regulation of the N-methyl-D-aspartate (NMDA) receptor appear to be key factors in the induction of central sensitisation. Substance P and neurokinin A are released from primary afferents in response to nociceptive stimulation and are spread widely through the dorsal horn, potentially influencing a large number of neurons (Duggan *et al.*, 1990). These neuropeptides bind with neurokinin receptors (NK1 and NK2), triggering the release of intracellular calcium (Woolf, 1994). Release of intracellular calcium increases neuronal excitability and facilitates the up-regulation of the NMDA receptor. At normal resting membrane potentials, the NMDA receptor's ion channel is blocked by the physical presence of a magnesium ion (Woolf, 1994). However, this blockade is voltage-dependent and so, an increase in intracellular calcium levels will lead to partial depolarisation of the membrane, displacing the Mg^{2+} and allowing the receptor's ion channel to become patent. When it is patent, the NMDA receptor provides a divalent cation channel. Binding of excitatory amino acid neurotransmitters (such as glutamate) released from primary afferents as a result of nociceptive stimulation will then result in an influx of Ca^{2+}, as well as Na^{+}, into the cell, further contributing to the increased excitability of the neuron.

Maintenance of this state of central sensitisation is related to a number of mechanisms that are induced by the action of Ca^{2+} as an intracellular second messenger (Woolf, 1994). These include activation of protein kinase C, phospholipase C, nitric oxide synthetase, and the induction of early gene expression. These mechanisms have all been implicated in the maintenance of central sensitisation. For example, protein kinase C can phosphorylate the NMDA receptor, causing a sustained reversal of the Mg^{2+} blockade and leaving the receptor channel in a permanently patent state (Woolf, 1994). Nitric oxide has been implicated in the process of central sensitisation, although its exact mechanism of action remains a matter of debate. One proposal is that nitric oxide produced by the postsynaptic neurons diffuses out and is taken up by presynaptic neurons, where it can up-regulate activity in the presynaptic membrane, leading to enhanced synaptic efficacy (Meller and Gebhart, 1993). Increased activity of phospholipase C will

ultimately lead to the production of prostaglandins, which may contribute to the development of sensitisation. The generation of diffusible prostaglandins that can spread to increase the excitability of adjacent neurons has been proposed as an important mechanism underlying the spread of central sensitisation. The protein products of the proto-oncogenes *c-fos* and *c-jun* may be important in a prolonged sensitisation process (Carr, 1990), and persistent increases in fos expression have been demonstrated following sciatic nerve transection (Chi *et al.*, 1993).

3. NEUROGENIC PAIN THERAPY

The treatment of neurogenic pain is a highly contentious area. Davies *et al.* (1993) reported considerable disagreement between respondents to a questionnaire mailed to consultant physicians involved in neurogenic pain management. Many physicians did not agree on the appropriateness of various treatments for neurogenic pain. This occurred both between and within speciality fields. The majority of respondents, however, did agree that the use of opioid analgesics for the treatment of neurogenic pain was not generally effective and was limited to pain resulting from a tumour either applying pressure to or infiltrating a nerve.

Generally, neurogenic pain states are considered to be opioid unresponsive (Arner and Meyerson, 1988). Evidence suggests there is a reduction in the number of opioid receptors expressed on C fibre afferents following peripheral trauma, which may reduce the effectiveness of opioids in this kind of injury (Dickenson, 1994). This paper also implicates cholecystokinin and NMDA excitatory amino acids in the reduction in opioid responsiveness.

Portenoy *et al.* (1990) suggest that while neurogenic pain may be less responsive to opioids than nociceptive pain, overcoming this is merely a matter of dose titration, considering both the characteristics of the pain and the patient when determining a final dosage end point. They further suggest that historically, opioids have been underutilised in neurogenic pain treatment paradigms due to unresponsiveness from "usual doses" and a fear of introducing side effects at higher doses. Whatever the reason, opioid analgesics tend to be conspicuously missing from neurogenic pain control regimens. Treatment often involves the utilisation of other compounds that are not conventionally recognised as analgesics.

Indeed, the compounds used to control neurogenic pain are a relatively esoteric group. In general, anticonvulsant drugs, such as carbamazepine and sodium valproate, are used to control the lancinating or stabbing pain component, and antidepressants, such as amitriptyline and imipramine, and the sodium channel blocker mexiletine are used to treat the constant burning pain component of the condition.

4. POST-HERPETIC NEURALGIA

PHN is probably the most common form of neurogenic pain. It is accepted as being pain that persists or recurs 1 month or more following the initial eruption of Herpes Zoster infection of the skin or eye. Herpes Zoster is the most common disease affecting the nervous system. PHN is a complication of Herpes Zoster infection; it is not a symptom of continued or subsequent infection.

Patients usually describe severe aching and burning sensations in the dermatome affected (most commonly the thoracic dermatomes). This area can also be associated with a sensory deficit that is not usually witnessed in the non-PHN Zoster patient. Chronic symptoms are often associated with shooting, stabbing paroxysms. Symptoms extend from the acute stage of the infection into the post-infective condition; however, in many cases, the intensity of pain subsides with time. The pain of Herpes Zoster infection can stretch from 3 weeks prior to the eruption (most commonly only 2–3 days) and may not fully resolve for several years in the case of the post-eruptive condition. Spontaneous resolution of pain can occur within a 3- to 6-month period following onset; however, it is unlikely to resolve spontaneously after this period.

It is likely that an elderly person will suffer some degree of pain throughout the infective or post-infective period. It has been estimated that by age 85, an individual has a 50% chance of suffering a Herpes Zoster eruption (Hope-Simpson, 1975), and that up to 50% of these cases may develop some kind of post-eruptive pain (Bowsher, 1994). The incidence of PHN has been reported to be between 9 and 14.3% of all Herpes Zoster cases. The percentage of these patients that continue suffering pain for 3 months after the initial eruption is between 35 and 55%, and those continuing for up to 1 year, between 22 and 33% (Scadding, 1994). As age increases, the incidence of PHN significantly increases.

Living with PHN is extremely difficult. Pain is often associated with unpleasant sensations in localised areas of the skin that may be hyper- or hypaesthesic and itchy. Allodynia may be present, and pain can be evoked by clothes brushing against the affected area, changes in temperature, movement of the skin when walking, and emotional states. Patients are often forced to take long periods of time off from work, which may adversely affect their careers. Elderly people often withdraw from society and become lonely, isolated, and depressed.

If the nasocilliary nerve is involved in the eruption, Herpes Zoster Opthalmicus (HZO) may result. This condition represents 10–17% of Herpes Zoster cases (Harding, 1993). Harding reported that 93% of HZO patients suffered from acute pain and 31% developed a chronic condition. The list of other complications involved with ocular infection is considerable and includes optic inflammatory conditions, neuritis, keratitis, and meningoencephalitis.

Electrophysiological studies of Herpes Zoster patients have failed to show significantly different extents of peripheral nerve damage between patients developing PHN and those not developing the condition. Mondelli *et al.* (1996) reported that in 64 Herpes Zoster patients, the severity of sensory axonopathy was variable, and concluded that damage to peripheral sensory fibres was not the cause of PHN.

This suggests that development of PHN may result from either CNS infection or central changes resulting from peripheral nerve infection. This is further corroborated by post-mortem studies that report dorsal horn atrophy only in Herpes Zoster patients suffering PHN (Watson *et al.*, 1991). Another study, however, showed a significantly reduced neurogenic axon reflex flare response to topical capsaicin, suggesting the possibility of disrupted primary afferent function and/or autonomic instability (Morris *et al.*, 1995).

4.1. *Medical Management*

Whilst the development of antiviral drugs has had an effect on the treatment of Herpes Zoster, the ability of antivirals to prevent the development of PHN is controversial. It is widely recognised that systemic antivirals, administered in the prodromal period of the infection (approximately within 72 hr of the development of the initial stage), can reduce the presentation and spread of the eruption, the period of healing, the incidence of HZO and its long-term complications, and recurrence in immunocompromised patients (Wagstaff *et al.*, 1994). Whether systemic antivirals can prevent or significantly reduce the incidence of PHN is still a matter of considerable debate. There is clear evidence that administration of acyclovir does not have a significant effect on the development of PHN (McKendrick *et al.*, 1989); however, evidence also exists to the contrary (Wagstaff *et al.*, 1994).

A wide variety of pharmacological treatments have been tried in the management of PHN. These include tricyclic antidepressants (TCAs); anticonvulsants; sodium channel blockers, e.g., mexilitine; neuroleptics; and steroids. Their success is variable between individuals and is dose-dependent. Several topical treatments have been used to treat PHN. These include capsaicin, aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and local anaesthetics. Other treatments include local anaesthetic nerve blocks, transcutaneous electrical nerve stimulation, biofeedback, and acupuncture.

The TCA amitriptyline has a long-established place in the treatment of PHN. Its pain relieving efficacy is independent of its antidepressant action (Bowsher, 1994). This is evident as the dose required for analgesia is lower than the usual antidepressant dose, and amitriptyline is effective as an analgesic in PHN patients who are not clinically depressed. It has been suggested that drugs of this group are more effective against constant burning-type pain rather than lancinating pain. Other members of the group, including imipramine, nortriptyline, and desipramine, have also been shown to be effective. It has been suggested that the efficacy of the antidepressants is dependent on their inhibition of neurotransmitter re-uptake, possibly involving both serotonin and noradrenaline (Ardid and Guilbaud, 1992; Watson, 1995). Unfortunately, the TCAs have side effects that may affect patient compliance. These include anticholinergic effects, such as dry mouth, urinary retention, constipation, and also sedation.

The dose of amitriptyline is individually titrated to the patient's requirements to allow for response and to minimise side effects. Initially, 10–25 mg is administered at night. This is increased weekly by 10–25 mg, to a maximum of approximately 75 mg at night. Doses higher than 75 mg are advocated by some physicians, whereas others will consider alternative or co-treatments. Controlled clinical trials administering 25–75 mg of amitriptyline nightly have proven its success in pain reduction (Watson *et al.*, 1982). The biological half-life of amitriptyline is 12–36 hr, allowing once daily dosage. Due to the sedating effects of the drug, it is preferably administered at night. Therapy is maintained for at least 3 months following onset of pain control, and is then slowly reduced, e.g., by 10–25 mg/month. If pain recurs, therapy should be reinstated.

Treatment of pain associated with HZO is as for dermal PHN. The use of ocularly applied steroids in cases of inflammatory complications may be warranted; however, in most cases, this is not indicated and may be harmful. The co-administration of oral acyclovir also appears to improve the effectiveness of pain treatments (Harding, 1993). Regular intraocular application of a 3% acyclovir ointment may also be used.

It is apparent that the initiation time of amitriptyline therapy in reference to acute Herpes Zoster infection is critical. There has been a reported difference of 50% in successful amelioration of pain between patients receiving amitriptyline in the first 3–6 months following acute Herpes Zoster and those receiving it after 2 years (Bowsher, 1994). It has been suggested that the TCAs should be used as a prophylactic therapy in elderly patients during the prodromal stage of the condition in order to prevent the development of PHN. Pain relief is reported to occur 6–8 weeks following initiation of amitriptyline therapy, with a reduction of 75% in pain score after approximately 11 months (Bowsher, 1994). This period can be reduced to 5 months in patients who received acyclovir therapy (800 mg 5 times daily for 7–10 days) during the prodromal period. Therefore, while the antiviral agents alone may not have an effect on PHN, they positively effect pain relief outcomes elicited by the TCAs.

While the TCAs are one of the main treatments in the management of PHN, they at best can only reduce pain to a tolerable level. One controlled clinical trial suggests that the success rate with amitriptyline is as low as 50% (Max *et al.*, 1988). Subsequently, this has prompted some clinicians to resort to the use of high-dose oral opioids, such as morphine, oxycodone, hydromorphone, and methadone, to overcome inadequacies and intolerable side effects of the tricyclics (Pappagallo and Campbell, 1994; Watson, 1995).

Capsaicin is a natural product extracted from hot chilli peppers (*Capsicum* spp). It causes the release of substance P and other neuropeptides from the terminals of slow-conducting unmyelinated C fibres. Substance P is a peptide that plays an important role in nociception by initiating neurogenic inflammation and stimulating other neurokines and inflammatory mediators in response to trauma. Sub-

TABLE 1. Summary of Usual Pharmacotherapy for Various Neurogenic Pain Conditions

Condition	Drug Therapy	Dose	Duration Of Therapy	Side Effects	Comments
PHN	Amitriptyline (antidepressant) (also imipramine, desipramine and nortriptyline)	Amitriptyline: 10–25 mg nightly increased weekly by 10–25 mg as necessary Maximum usual dose of 75 mg	Onset of pain relief delayed by 6–8 weeks. Approximately 3 months after pain control, may be reduced or discontinued.	Dry mouth, urinary retention, sedation, constipation	The TCAs are the mainstays of drug therapy; however, reported pain relief is as low as 50%.
	Mexiletine	50 mg 3 times daily, increasing to 200 mg 3 times daily if necessary	Long-term administration, acts as an adjuvant analgesic during period of administration.	Arrhythmia, tremor	Treats continous burning pain. May be combined with Na valproate to treat the lancinating pain.
	Capsaicin cream (depletes substance P - counter irritant)	0.025% or 0.075% cream applied to the area 5 times daily	Frequent use maintained for few days, then reduced to 3 times daily.	Burning and hyperalgesia that reduces over time if regular use is maintained.	Often used in combination with oral therapy. Rarely used as monotherapy.
	Acyclovir (antiviral) (also ganciclovir, and famcyclovir and valacyclovir)	Acyclovir: 800 mg 5 times daily	Duration: 7–10 days. Initiation: within first 24–48 hr. of initial eruption	Very well tolerated	Research suggests antiviral use prevents pain; however, this is still tenuous.
CRPS	Local anaesthetics	Bupivicaine: 0.25% ganglion block Lignocaine: 0.5% infusion	Infused over 0.5 hr duration of pain relief only 3–4 hr due to short half-life.	Paraesthesias, arrhythmia, surgical complications	May provide longer relief if administered early or via a catheter.
	Guanethidine (adrenergic blocking drug)	10–30 mg via intravenous regional blockade or via topical iontophoresis	Cuff remains in place for 20 min, long-term pain relief may result from 3 or 4 injections.	Side effects include hypotension and bradycardia; however, are not significant if cuff pressure is adequate.	Evidence suggests the placebo effect is more significant in this procedure.
	Chemical neurectomy	Phenol 7–10% Ethanol 50–100%	Results in death of the nerve, causing long-term local anaesthesia.	May cause toxic side effects, also neurosurgical complications	Generally performed if other treatments are not effective or inappropriate.
	Adrenergic blocking agents	β: propranolol 320 mg daily α: Prazocin 4 mg daily and clonidine 50–100 μg 2–3 times daily	Long-term administration, relieves systemic effects of sympathetic hyperactivity during administration.	Hypotension, syncope, sedation, asthma (propranolol)	Used as adjuvant analgesics in SMP.
	Nifedipine and other calcium channel blockers	Nifedipine: 10–30 mg 3 times daily	Nifedipine may provide long-term pain relief.	Hypotension, peripheral oedema	Pain relief mechanism not well understood.

TGN	Carbamazepine (sodium channel blocker/ anticonvulsant)	100 mg 4 times daily for 4 weeks. Dose may be increased to 200 mg 4 times daily. Higher doses have been used.	Dose may be reduced if pain relief is attained. Serious side effects may considerably limit dose elevation.	Sedation, blood dyscrasias (carbamazepine may be replaced by other drugs with fewer side effects, e.g., valproate and gabapentin).	Pain of a lancinating nature is suggested to respond better to carbamazepine than dull aching pain.
	Phenytoin (sodium channel blocker/anticonvulsant)	100 mg 3 times daily. Increased if necessary.	As for carbamazepine	May be co-administered with carbamazepine to reduce side effects of both.	Swapping carbamazepine for phenytoin due to side effects may not be useful.
	Baclofen (spasmolytic-GABAergic)	5 mg 2–3 times daily. May be increased every 3 days to a usual maximum of 60–80 mg daily.	Long-term administration, acts as an adjuvant analgesic during period of administration.	Generally well tolerated; however, may cause problems in renal failure in elderly patients.	Suppresses muscle convulsion by mimicking the inhibitory neurotransmitter GABA.
DN	Insulin	As required by the individual	Early therapy is advocated to reduce the incidence of pain in later life.	Hypoglycaemia, coma	Glycaemic control is the major component in the prevention of painful DN.
	Paroxetine (SRI)	20 mg daily	Long-term administration, delay in pain control may be a few weeks.	Very well tolerated	The only SRI that has been effective in the treatment of neurogenic pain.
	Tolrestat (aldose reductase inhibitor)	200–400 mg daily	Prophylactic administration may be advantageous.	Relatively well tolerated, possible dizziness	May block the progress of DN.
PLP	Acute pain management (epidural)	Lignocaine 3 mg/kg for 20–30 min	Pain relief lasts 2–3 hr.	Contraindicated in patients with heart block	Co-administration of lignocaine and fentanyl used to reduce side effects and extend duration.
		Fentanyl 20–40 μg/hr	Longer pain relief than lignocaine.	Respiratory depression	
	Chronic pain management	Conventional analgesics, e.g., paracetamol, NSAIDs narcotic analgesics plus antidepressants, β-blockers and anticonvulsants	Long-term administration. Act as analgesics during period of administration.	NSAIDs: GIT ulceration and CNS depression. Narcotics: respiratory depression, addiction, and constipation.	Conventional analgesics appear to provide better pain relief in PLP than other neurogenic pain.

SRI, serotonin reuptake inhibitor; GIT, gastrointestinal tract.

stance P is also found in some fast-conducting A fibre terminals; however, these are not involved in the capsaicin effect. This has led some researchers to question the mechanism of action of capsaicin in neurogenic pain disorders predominantly involving A fibre activity.

Initial application of capsaicin cream (0.025 or 0.075%) to the skin causes burning and hyperalgesia as a result of substance P release. This eventually diminishes as substance P becomes depleted from C fibre terminals. The burning sensation can persist if the frequency of application is not adequate, and this can cause problems with patient compliance. Most clinicians recommend application of a sparing amount, 3–5 times daily. Gradually, desensitisation to the burning sensation occurs, indicating that neuropeptide depletion has occurred.

Capsaicin has been shown to be more effective than placebo in controlled studies involving PHN; however, it has not been shown to be more effective than other conventional therapies (Rains and Bryson, 1995). Other authors suggest that while the successes reported with topical capsaicin are interesting, there is limited evidence to support its effectiveness (Zhang and Li Wan Po, 1994). Realistically, capsaicin probably has a place as a therapeutic adjunct in the management of PHN rather than as the primary analgesic agent.

Measurement of treatment outcome in PHN studies is confounded by the variability that occurs in the clinical presentation of this condition. For example, amitriptyline treatment is more successful when initiated in the first 3–6 months following eruption; however, this is also the period when patients are most likely to demonstrate spontaneous remission. Many studies fail to adequately control for the variable natural history of the disorder, with consequent limitations to their findings. However, there is mounting evidence advocating early administration of an antiviral agent and possible co-administration with a TCA for prevention or control of this condition. The goal of research is to develop effective treatments that can control the acute condition and prevent the development of PHN (see Wood, 1994; Crooks *et al.*, 1991; Benoldi *et al.*, 1991).

Case Study 1: PHN

A 72-year-old male awoke one morning with severe one-sided chest pain. He believed the pain to be musculo-skeletal in origin, resulting from his previous day of gardening. Whilst taking a shower, he noticed blisters across his right chest wall immediately below the level of his nipple. As the pain was worsening, he decided to see his local physician.

On presentation to his physician his major complaints included:

- a blistering rash that covered a narrow band of his right chest wall, extending from the spine, posteriorly, to the lower border of the sternum anteriorly;
- a severe constant aching and burning pain, with occasional sharp lancinating pains; and
- inability to tolerate clothing contacting the area.

His local physician made the diagnosis of shingles (rash resulting from Herpes Zoster infection). The infection was confined to a single dermatome, in this instance the right T6 dermatome.

The patient was immediately commenced on a course of acyclovir and given paracetamol and codeine for pain.

Six weeks later, the red rash had faded; however, some scarring was evident. The patient was still complaining of both severe constant aching pain, as well as frequent lancinating pains, which he described as "electric shocks".

Following advice from a local pain clinic, his physician commenced him on amitriptyline (25 mg at night) and sodium valproate (200 mg twice daily). If pain relief was not achieved within a few weeks, mexiletine (50 mg 3 times daily, increasing to 200 mg 3 times daily) was to be trailed. The patient was also treated with transcutaneous electrical nerve stimulation administered by a physiotherapist.

5. COMPLEX REGIONAL PAIN SYNDROMES

The group of conditions that are described under the heading complex regional pain syndromes (CRPS) historically were known as reflex sympathetic dystrophy (RSD) and causalgia. The second edition of the IASP Classification of Chronic Pain Syndromes recognises two different types of CRPS. Type I, formerly known as RSD, does not involve obvious injury to the nervous system, whereas Type II, formerly known as causalgia, refers to the situation where a nerve injury has occurred. The IASP have also classified the term sympathetically maintained pain (SMP) as one that can be used in the description of these various disorders. A condition is considered to be sympathetically maintained if the majority of the pain is influenced by sympathetic nervous system activity. If only a small component of the pain is maintained by the sympathetic nervous system, it is considered to be sympathetically independent pain.

Replacement of the terms RSD and causalgia occurred as a result of their misuse and the subsequent loss of their diagnostic contrasts. RSD refers to a condition involving sympathetic hyperactivity; however, scientific discussion and clinical observation cannot totally agree on this matter. Research suggests that sympathetic nervous system hyperactivity exists (Merskey, 1986). However, it is becoming clear that pain is not always dependent on the presence of sympathetic hyperactivity. It is also possible that while tissues may become hypersensitive to noradrenaline release from sympathetic nerves, there may be a reduction in sympathetic nervous system activity associated with the condition.

Changes in the CNS resulting from peripheral nerve injury and maintained by sympathetically dependent or independent peripheral input are important (Gracely *et al.*, 1992). This led some researchers to question the regular use of sympathetic blockade in the diagnosis and treatment of CRPS and to suggest that in many cases, pain relief is dependent on the placebo response (Ochoa and Verdugo, 1995). The term RSD also implies soft tissue changes resulting from a reflex or the sympathetic nervous system,

which is not always the case. For an overview of the new taxonomy, refer to Stanton Hicks *et al.* (1995).

Whilst the nature of the initial insult is different between the two types of CRPS, both conditions have similar features. These include peripheral spontaneous pain, allodynia or hyperalgesia that is disproportionate to the original insult, a history of oedema, integumentary cardiovascular anomaly, bone demineralisation, and altered sudomotor activity. The nature of the pain may be an intense burning sensation, occasionally in combination with stabbing paroxysms also involving allodynia and hyperpathia.

CRPS Type I involves deep diffuse pain brought on by minor injury resulting from inflammation, surgery, infection, bone fracture, myocardial infarct, stroke, degenerative joint disease, frostbite, and burns (Payne, 1986). Other cases of CRPS have resulted from prolonged nerve compression following application of a plaster cast and swelling due to injury and arthroscopy (Hendler and Raja, 1994). Historically, symptoms were organised into three progressive stages that involved the spread of localised spontaneous pain that may lessen as time progresses. The new taxonomy does not include the concept of disease progression.

CRPS Type II is related to neural tissue injury and typically, diagnosis is made 5–6 weeks following pain onset. Generally, after this period, non-neural tissue injury has resolved, thus precluding pain of this type (Payne, 1986). The areas of the body affected are almost invariably the hand and foot, as the most common nerves involved are the median, sciatic, tibial, and ulnar nerves. Pain can spread proximally to involve the entire limb, and may also involve unrelated structures.

Trophic changes to the skin, nail, bone, muscle, and joint can follow the onset of pain. The skin can become reddish, cold and hyperhydrotic. The affected body part may suffer sensory and motor loss due to injury of the innervating nerve. Pain typically can become aggravated by environmental stimuli, such as changes in temperature, mechanical stimuli, or movement of the affected limb. Pain can be brought upon by emotional states, such as stress, fear, or anger.

CRPS Type II persists in 85% of cases for greater than 6 months and continues for 1 year or more in approximately 25% of cases (Payne, 1986). Such long-term intense pain affects every aspect of life, and often develops into mental anguish. The patient may become removed from society as the pain becomes the pivotal point of their existence.

The involvement of the sympathetic nervous system does not form part of the differential diagnosis of CRPS. While sympathetic hyperactivity may be an aspect of the condition, it is not a requirement for diagnosis. It is possible that sympathetic nervous system activity contributes to the pain state in many ways; however, reduction in pain resulting from sympatholytic block may not be diagnostic of CRPS.

The new IASP definition for CRPS allows for the development of various subgroups under the umbrella of CRPS. These subgroups may involve patients who respond to sympathetic blocks and those who do not, or patients who present with the classical symptoms of CRPS associated with another condition outside the existing definition. The new definition places less emphasis on the involvement of sympathetic activity and provides a simpler method of diagnosis, allowing for anomalies to be classified.

There is a considerable debate between groups involved in research into CRPS. This is especially true in relation to the involvement of the sympathetic nervous system in the disorder, methods of pain measurement used, the appropriateness of regional blocks in diagnosis, and the placebo effect associated with diagnostic blocks. Until many of these questions can be resolved, it will be difficult to develop a more definitive treatment for CRPS.

5.1. *Medical Management*

The management of CRPS involves a stepwise approach depending on the severity and progression of the condition. Initial treatment usually will involve a sympathetic regional block targeted at the stellate or lumbar sympathetic ganglion pertaining to the somatic area involved. Local anaesthetics such as bupivicaine (0.25%) provide short-term pain relief for approximately 3–4 hr when injected directly into the ganglion. However, more prolonged analgesia may occur (Payne, 1986). Success of the procedure depends on the skill of the physician. Complications may include paraesthesia, bradycardia, and vessel perforation. Regional blockade is regularly combined with physical therapy to address the dystrophic changes in connective tissue that are part of the condition.

If a sympathetic block provides successful pain relief initially, but relief is only temporary, a chemical or surgical sympathectomy may be indicated. Chemical sympathectomy involves the injection of either 7–10% phenol or 50–100% ethanol into the affected ganglion. Surgical procedures involve the positioning of appropriate neural lesions by the surgeon in order to affect the desired region. There is currently a tendency to avoid destructive techniques such as sympathectomy.

As an alternative to invasive, ganglion-targeted sympathetic blockade, intravenous regional sympathetic blockade can be performed. This procedure involves isolating the affected limb with a tourniquet and administering an adrenergic blocking agent such as guanethidine (10–30 mg) intravenously (Hannington-Kiff, 1979). The tourniquet remains in place for 20 min following the administration of guanethidine to keep the agent localised in the limb, thus preventing systemic side effects such as hypotension. Guanethidine acts to block adrenergic nerve function by depleting intraneural vesicles of noradrenaline. It is actively taken up into the nerve by the noradrenaline reuptake mechanism. Guanethidine causes an initial release of noradrenaline, which eventually subsides as it occupies adrenergic vesicles. This inhibits adrenergic nerve impulse transmission.

It generally is accepted that administration of regional guanethidine is more effective early in the condition and provides a longer period of relief. However, this concept

was refuted in a multicentre study performed with CRPS Type I patients who were administered regional guanethidine within 3 months of initial pain symptoms (Ramamurthy and Hoffman, 1995). This study also questioned the difference between placebo and guanethidine administration; however, the placebo used (lignocaine 0.5%) may have provided significant pain relief itself. Indeed, it has been suggested that simply applying a pressure cuff to the extremity provides significant pain relief due to ischaemia (Raja *et al.*, 1991).

An alternative to this method of guanethidine localisation is transdermal delivery of the compound utilising an electromotive driving force. Iontophoresis increases tissue penetration of charged molecules, delivered across the skin, by the application of a weak electric field. Positive results in CRPS Type I patients have been demonstrated following iontophoretic administration of guanethidine (Bonezzi *et al.*, 1994). This was achieved without systemic side effects and without the possibility of tourniquet-induced analgesia.

A systematic review of similar controlled studies up to 1993 revealed no significant pain relief reported following regional guanethidine block (Jadad *et al.*, 1995). A study published in the same article also failed to demonstrate a statistically different effect between guanethidine and saline. It has been suggested that poor results reported in studies of this kind indicate incorrect diagnosis of SMP. It has been further suggested that clinical reports should include detailed diagnostic protocols used in the study and that standardised predictors of success such as the intravenous phentolamine test should be utilised (Arner, 1991). Current reported data tend to suggest that the use of regional guanethidine block may not be warranted in the treatment of CRPS.

As an adjunct to procedures performed by the physician, patients are regularly maintained on oral therapy. This usually involves the administration of sympatholytic agents such as the β-blockers (e.g., propranolol up to 320 mg daily), or α-adrenergic blocking agents (e.g., prazosin 2 mg twice daily or phenoxybenzamine 40-120 mg daily). Potential side effects of propranolol include CNS depression, hypotension, sexual dysfunction, and Reynaud's syndrome. Propranolol is contraindicated in asthmatic patients. Prazosin may cause postural hypotension with initial administration. Nifedipine (10-30 mg 3 times daily) has been trailed successfully in CRPS Type I patients exhibiting cold allodynia (Prough *et al.*, 1985). Nifedipine is a peripheral calcium channel blocker that causes vasodilatation and may be effective against the vasomotor aspect of CRPS. There is a possibility that it also limits Ca^{2+} influx into neural tissue, thus reducing ectopic discharge.

In some pain centres, indwelling pumps to provide a continuous infusion of spinally administered opioids or implanted electrodes to provide continuous spinal cord stimulation are used as a means to provide ongoing pain relief so that physical therapies can be used to restore function to the affected limb. Restoration of function is seen as being the ultimate aim of treatment.

Other pharmacological treatments include TCAs, anticonvulsants, and anti-inflammatory agents.

Case Study 2: CRPS

A 26-year-old female fell at work and suffered a right wrist sprain. The wrist was strapped and the patient returned to work. Three days later, the patient visited her local doctor complaining of worsening pain in the wrist and swelling in the right hand. The general practitioner suspected a bone in the wrist may be fractured and ordered plain X-rays, which indicated no fractures present. A diagnosis of ligamentous injury was made, and the patient was sent for physiotherapy.

Over the next 4 weeks, the hand became more painful and swollen. The patient also noticed that her right hand had taken on a mottled appearance, was sweating profusely, and was warm to the touch. She was referred to an orthopaedic surgeon, who diagnosed RSD.

The patient was referred to a psychologist who specialised in pain management techniques and to a physiotherapist for an intensive graduated exercise program. She was given a short course of oral opioids, and was administered a series of four local anaesthetic injections to temporarily anaesthetise her right arm and thereby interrupt the chronic pain cycle.

Although the patient's recovery was slow, after 3 months of physical therapy, she had recovered 90% of the normal function of her right hand and only suffered minimal pain.

6. TRIGEMINAL NEURALGIA AND ATYPICAL FACIAL PAIN

TGN, or tic douloureux, is possibly the most excruciating of the neurogenic pain syndromes. It is most common in elderly people. Painful events usually occur in cycles that may be separated by pain-free periods lasting years. Tic douloureux is characterised by certain specific features that provide the differential diagnosis between it and atypical facial pain, another affliction of the face. Tic douloureux involves brief stabbing pains followed by pain-free periods. Pain is triggered abruptly, usually by a non-noxious stimulus, and it normally occurs unilaterally. Pain occurs in the distribution of the trigeminal nerve involving the third or mandibular division, possibly in combination with the second or maxillary division. In rare cases, pain may also occur in areas innervated by the glossopharyngeal nerves (Olds *et al.*, 1995). TGN is not usually associated with a sensory deficit of the affected area (Loeser, 1994).

Precipitating stimuli are usually innocuous and occur during everyday life. A simple light touch of the cheek by a hand or scarf may send the patient into a painful spasm. Pain brought upon by chewing may prevent the patient from enjoying a proper diet, and they may stop eating altogether to prevent attacks. Pain can be precipitated by a cool breeze, thus preventing the patient from venturing outdoors. Personal grooming and hygiene may cease due to

pain resulting from brushing one's hair, cleaning one's teeth, or shaving one's face.

These symptoms are contrary to those suffered in atypical facial pain, which is characterised by a burning pain that is constant in nature, and may be bilateral or extend to include the cervical dermatomes. Atypical facial pain does not involve the facial or glossopharyngeal nerves. Often it is associated with a sensory deficit. Atypical facial pain may develop due to facial lacerations, neoplasia, infection, or in tic douloureux sufferers, following trigeminal denervation surgery. Pain is not triggered by any specific stimulus and does not respond to interventions involving the trigeminal nerve or any other conventional treatment. Surgical denervation is generally considered useless and may cause further painful symptoms.

Other conditions that manifest as facial pain also include dental neuralgia, cluster headache, migraine, and idiopathic facial pain (Feinmann and Peatfield, 1993).

The pathological findings of TGN patients generally involve neurovascular compression of the trigeminal nerve as it leaves the brain stem. This has been documented preoperatively by magnetic resonance tomographic angiography; however, the exact pathophysiology is still considered to be incompletely understood (Meaney *et al.*, 1995). A small group of patients can develop TGN symptoms as a result of other compression events, e.g., posterior fossa tumours (Barker *et al.*, 1996a).

6.1. *Surgical Management*

Neurovascular compression lends itself to surgical microvascular decompression, which generally is considered to be the mainstay of treatment for this condition. Microvascular decompression involves removal of the involved vessel or separating the vessel from the nerve root (e.g., using a piece of sponge). There are many other surgical procedures available to treat TGN, including γ-knife radiosurgery (Regis *et al.*, 1995), percutaneous stereotactic radiofrequency rhizotomy (Taha *et al.*, 1995), and glycerol rhizotomy (Bergenheim and Hariz, 1995; Tan *et al.*, 1995). Rhizotomy offers an alternative to microvascular decompression in patients who are considered to be at high risk of adverse effects following posterior fossa procedures such as the elderly.

A large long-term prospective study performed in Boston, MA, USA on TGN patients following microvascular decompression found the procedure to be safe and effective in the treatment of TGN with longterm amelioration of pain (Barker *et al.*, 1996b). The study revealed that 30% of patients suffered recurrence during the median 6-year follow-up period. Recurrence of symptoms occurred most commonly in females who lacked immediate pain relief following the procedure. Kaplan-Meier analysis determined that 70% of patients continued to enjoy significant pain relief 10 years following the procedure.

Another factor that seems to have an impact on recurrence of painful attacks is treatment history. Barker *et al.* (1996b) reported that a radiofrequency trigeminal ganglion lesion performed prior to decompression increased the incidence of facial pain on follow-up. Another study showed that previous glycerol rhizotomy reduced the effectiveness of subsequent glycerol or radiofrequency treatment (Bergenheim and Hariz, 1995).

Obviously, as with any surgical procedure, there are risks to consider. Major adverse events, ranging from hearing loss, to brain stem infarction, to death, have been reported following posterior fossa surgery. The incidence of adverse events ranges from 0.1% (Barker *et al.*, 1996b) to 1% (Sidebottom and Maxwell, 1995). Whilst the greatest success in controlling TGN has arisen out of surgery, other methods, including pharmacotherapy, transcutaneous electrical nerve stimulation, and acupuncture, can be considered as primary treatments in high-risk patients (Guo *et al.*, 1995; Holt *et al.*, 1995).

6.2. *Medical Management*

Pharmacotherapy of TGN usually involves the use of an anticonvulsant, such as carbamazepine, sodium valproate, or phenytoin. Therapy may also involve administration of a benzodiazepine, e.g., clonazepam, or the skeletal muscle relaxant baclofen. The nature of ectopic focal discharge witnessed in the condition and the success of carbamazepine in the management of TGN has lead one researcher to describe TGN as "a sort of sensory reflex epilepsy" (Pagni, 1993).

The success of carbamazepine in treating TGN has been attributed to its sodium channel blocking function and consequent membrane stabilising ability. This may cause inhibition of the lancinating aspect of the condition; however, the exact mechanism of pain relief is not fully understood. Doses of carbamazepine generally are titrated to the patient's requirements, and typically begin at around 100 mg 3 times daily for 4 weeks. This can be increased to 200 mg 3 times daily; however, much higher doses have been used in clinical trials. Unfortunately, the large number of significant side effects experienced with carbamazepine often leads to withdrawal of the drug from the pain control regimen. The most common side effect is CNS depression, which is experienced mainly in elderly patients. However, more serious side effects are experienced with higher doses, including blood disorders and severe erythematous rashes.

Carbamazepine may be replaced by phenytoin if side effects are considerable or if the condition is not adequately controlled. Phenytoin has the same action on Na^+ channels as carbamazepine, but it can also influence K^+ and Ca^{2+} channels. The side effect profile of phenytoin is similar to carbamazepine; therefore, transferring a patient to phenytoin may not be advantageous. In some instances, the two anticonvulsants may be administered concomitantly to allow a reduction in the dose of both drugs. Other anticonvulsants used include valproic acid and clonazepam. Some clinicians suggest that valproic acid should be considered as a replacement for carbamazepine, as its side effect profile is less problematic. This is also true for some of the new gen-

eration anticonvulsants, e.g., gabapentin, which may be of clinical use in the treatment of TGN.

If anticonvulsant drugs are not successful, baclofen may be administered. Baclofen, a spasmolytic, mimics the action of γ-aminobutyric acid (GABA), a CNS inhibitory neurotransmitter. There is also evidence that suggests it is capable of inhibiting Ca^{2+} channels. It is usually administered as 5 mg 2–3 times daily, with the dose titrated upwards every 3 days until analgesia is achieved or side effects become problematic. The maximum recommended dose is 60–80 mg daily. Relatively high doses of 150 mg daily may be required by some individuals. While it is relatively well tolerated, baclofen should be used with extreme caution in the elderly or those suffering renal insufficiency as it is excreted almost entirely unchanged in the urine.

Correct clinical diagnosis is of paramount importance in determining the appropriate treatment for chronic orofacial pain. While surgical decompression has proven to be extremely effective in the treatment of TGN, its use in atypical facial pain is questionable and may be ill advised. Studies have shown that decompression surgery has a profound long-term effect on the pain of TGN, with severe adverse events occurring in frequencies probably not greater than those witnessed following other surgical procedures (Barker *et al.*, 1996b). In many instances, successful surgery allows the sufferer to enjoy life again without the need for pharmacotherapeutic maintenance with its associated side effects. A systematic review on the use of anticonvulsants to manage pain has been undertaken by McQuay *et al.* (1995). They reviewed papers published over the last 28 years and presented collated information on a range of anticonvulsants. Over this period, there has been a lack of controlled scientific experiments, despite the popularity of this group of drugs in clinical practice. However, available studies appear to warrant the use of the anticonvulsants in TGN.

Case Study 3: TGN

A 69-year-old female was referred to a multidisciplinary pain management centre with acute severe facial pain. Four weeks previously she had awoken one morning with episodes of lancinating pain across the left side of her face, immediately below the left eye.

She described an excruciating pain, similar to an electric shock, which occurred once or twice a minute and lasted 1 or 2 sec. The pain was triggered by touching the left side of her face, by a breeze blowing across her skin, or even by walking into an air-conditioned room.

The patient was diagnosed as having TGN involving the second division or maxillary branch of the left trigeminal nerve. An MRI scan was performed to exclude any tumour of the above nerve.

Treatment was commenced with oral carbamazepine and later baclofen. When pain proved difficult to control, a neurosurgeon was asked to consult. In view of the patient's age, the neurosurgeon recommended a neuroablative technique rather than a craniotomy to decompress the trigeminal nerve. The patient underwent a radiofrequency neurotomy of the second division of the left trigeminal nerve with complete pain relief and only partial sensory loss in the previously painful area.

7. PHANTOM PAIN

Reports of amputees experiencing pain and other sensations from their amputated limbs can be traced back hundreds of years. Many battleground surgeons reported that the majority of amputees complained of pain or sensation from limbs that clearly no longer existed. Today, these phenomena are categorised into three different groups: phantom pain (pain referred to the amputated limb), stump pain (pain at the amputation site), and phantom limb (nonpainful sensations referred to the amputated limb). This review will concentrate on phantom pain.

Precise epidemiological statistics on the incidence and prevalence of phantom pain are difficult to collate due to unreliable reporting of the existence of pain in an amputated limb. Unfortunately, reporting of pain referred to an amputated limb often goes unheeded by a physician and may be considered as a psychological confluent of the trauma of amputation. Whilst psychological well-being is an important aspect in the treatment of amputee patients, there is no evidence that any psychological disorder is responsible for the development of phantom limb pain (PLP) (Katz, 1992). It is suggested, however, that the psychological status of the patient affects the manner of pain reporting (Sherman, 1980). Reports indicate that as many as 85% of amputees suffer from phantom pain (Sherman and Sherman, 1983). The majority of patients experience significant lifestyle changes following limb amputation, with ongoing pain being a major contributor to these changes (Jones and Davidson, 1995).

The majority of cases experience pain in the first week following surgery; however, some instances may not occur for several months. It generally is accepted that pain attacks will either diminish significantly or self-resolve within 1–2 years; however, this is not always the case.

The location of the pain is usually in the distal regions of the limb. In most cases of above the knee amputation, pain is referred to the foot or calf and seldom occurs in the thigh. Pain has been described as being burning or a painful numbness (Sherman, 1994). However, some patients experience feelings of abnormal nociceptive input, e.g., pain resulting from a squeezing sensation or as if the toe- or fingernails are digging into the skin.

While the existence of phantom pain has long been recognised, the mechanism for its development has remained a mystery. With the development of cortical mapping, researchers have been able to theorise as to the aetiology of this condition. Case studies have been reported indicating that patients experience referred phenomena in a phantom upper limb following stimulation of other areas of the upper body (regularly the face), which is suggestive of cortical reorganisation (Halligan *et al.*, 1993). Flor *et al.* (1995) ob-

served that the amount of cortical reorganisation and the degree of PLP were directly proportional and that the degree of cortical reorganisation was significantly higher in patients suffering painful phantom sequelae than those suffering nonpainful sequelae.

Another report suggests that pain experienced in the limb prior to amputation correlates with the degree of pain in the phantom (Katz, 1992). Katz also suggests that afferent nociceptive information from the stump is being processed by regions in the cortex that were once responsible for receiving input from the amputated limb, thus referring pain to the phantom. It is likely that the development of phantom pain is due to a variety of factors that are present to varying degrees in individuals and that treatment of this condition should address this individuality.

The management of PLP reflects the diverse nature of the clinical picture. As a result of this diversity, there are a considerable number of treatments available to the physician.

7.1. *Surgical Management*

Historically, the mainstay of surgical intervention involved transection of neuromas formed as a consequence of the initial injury of surgery. The proximal end of the cut nerve is then implanted into a nearby anatomical site, often an adjacent bone. This procedure may only provide short-term pain relief as a subsequent neuroma can develop at the transection site. Various other neurosurgical procedures, including peripheral nerve stimulation, spinal cord stimulation, dorsal root rhizotomy, and deep brain stimulation, are available; however, these will not be discussed in this review.

7.2. *Medical Management*

Pharmacotherapy of PLP is similar to that of the other conditions discussed in this review. Oral treatment involves the use of β-blockers, TCAs, and anticonvulsants (Iocono *et al.*, 1987). Other more conventional analgesics, such as narcotic analgesics, paracetamol and the NSAIDs, may be considered before antidepressants or anticonvulsants are tried.

Epidural administration of local anaesthetics, e.g., bupivacaine, and narcotic analgesics, e.g., fentanyl, are also used in the treatment of PLP. Epidural administration of narcotic analgesics may introduce some potentially serious side effects, such as delayed respiratory depression, nausea, and vomiting. These problems have been addressed in some studies by combining a local anaesthetic and a narcotic analgesic in an infusion, thus allowing the dose of both the narcotic and local anaesthetic to be reduced (Jahangiri *et al.*, 1994). Epidural analgesia is regularly used prior to and for approximately 72 hr following amputation in response to the observation discussed in Section 7 involving the link between the degree of preoperative pain and the degree of postoperative pain.

Systemic administration of a local anaesthetic has also been advocated, although they may cause serious myocardial abnormalities. Five daily doses of intravenous lignocaine (3 mg/kg) injected slowly over 30 min may bring about prolonged pain relief. Alternatively, a continuous intravenous or subcutaneous infusion of lignocaine may be used.

Case Study 4: PLP

A 24-year-old male sustained a compound fracture of the left ankle in a motorcycle accident. Despite internal fixation of the fracture, the bone would not unite and the ankle became infected. Three months later, the patient continued to suffer from osteomyelitis and excessive pain in the ankle. Following consultation with the patient, the orthopaedic surgeon performed a below the knee amputation of the left leg.

Postoperatively, the patient complained of severe pain in the stump, as well as a painful phantom limb. Upon consultation with a pain specialist, three distinct types of neuropathic pain were identified. These included:

- continuous crushing pain in the region of the phantom ankle very similar to the preoperative pain, but worse;
- constant pain of a burning nature deep within the stump; and
- lancinating pains within the left thigh.

The patient's wound pain was well controlled with intramuscular morphine; however, this did not provide relief for any of the other conditions.

Initial management involved the insertion of a lumbar epidural catheter for a continuous infusion of bupivicaine and fentanyl over 4 days. Concern was expressed that the patient had not received similar treatment prior to surgery to desensitise central neurones.

When the epidural catheter was removed 4 days later, the patient complained of only marginal improvement of the phantom pain; however, both the burning and lancinating pains in the stump were considerably better. He was commenced on amitriptyline (25 mg at night) for pain relief and sedation. He was administered intravenous lignocaine (3 mg/kg over 20 min) daily for 4 days. This resulted in significant reduction in phantom pain and the size of the phantom limb. The patient was discharged to a rehabilitation unit and commenced on mexiletine (50 mg 3 times daily), slowly increased to 200 mg 3 times daily.

The patient still suffers with a certain degree of PLP; however, he is learning to cope with the aid of psychiatric care.

8. DIABETIC NEUROPATHY

Diabetes is a disorder affecting the metabolism of sugar and results in abnormally high glycaemic levels, amongst other metabolic changes. Diabetic neuropathy (DN) is the most common example of a metabolic disorder causing neuropathic pain. One study reported that 7.5% of patients being treated at a diabetes clinic presented with neuropathic pain (Chan *et al.*, 1990).

The most common complication associated with diabetes, particularly in the elderly, is peripheral neuropathy

(Sima and Greene, 1995). In the group of patients who have suffered diabetes for a period of at least 25 years, the prevalence of peripheral neuropathy is 50%. There seems to be no apparent difference in prevalence of neuropathy between those suffering insulin-dependent diabetes mellitus and those suffering noninsulin-dependent diabetes mellitus (Pirart, 1978). However, there is evidence that the mechanism involved in the development of neuropathy in these two groups may be different (Sima *et al.*, 1988). DN, therefore, is likely to result from uncontrolled hyperglycaemia and other factors, rather than the underlying diabetogenic pathophysiology.

In general, DNs are classified as subclinical or clinical, depending on their presentation. The most common form of DN is a distal, symmetrical sensorimotor polyneuropathy also called diabetic peripheral neuropathy and DN. This condition is associated with progressive nerve fibre loss, tissue atrophy and injury, and may involve neuropathic pain. The clinical symptoms of DN are progressive insensitivity to external painful stimuli and limb deformity. It is the most common cause of ulceration and amputation in the diabetic patient due to incidental tissue damage resulting from sensory loss (Boulton, 1994). Neuropathic pain suffered by the patient may result from deafferentation effects, nerve fibre regeneration, or injury to the distal limb as a result of these sensory and other changes.

The pathological changes in nerve fibres in the diabetic patient are many and varied, and despite a large amount of scientific and clinical observations, are not completely understood. Different mechanisms for the development of neural changes and pain have been postulated. They include transmission alterations in pain fibres (Price, 1988), microvascular abnormalities (Johnson *et al.*, 1986), altered vascular metabolism (Greene *et al.*, 1993), and peripheral vascular disease (Fry *et al.*, 1962). There seems to be agreement that hyperglycaemia plays an important role; however, the exact mechanism is unclear. It is possible that hyperglycaemia may lead to the development of DN via a metabolic or microvascular pathology (Tesfaye *et al.*, 1994).

Another factor that may be involved in the development of DN includes overactivation of the polyol pathway, leading to increased intracellular sorbitol and fructose and depletion of myoinositol. Ineffectual glycaemic control leads to an increase in plasma glucose levels, which is shunted through the polyol pathway where aldose reductase converts it to sorbitol and causes a reduction in myoinositol. Myoinositol depletion causes a reduction in Na^+/K^+-ATPase and subsequent slowing of nerve conduction. Aldose reductase inhibitors such as tolrestat are currently being tried clinically, following successful results in animal experiments (Yagihashi *et al.*, 1990). Early indications suggest that they significantly reduce sorbitol levels, leading to beneficial neuroregenerative effects (Sima *et al.*, 1993).

Reduced nerve growth factor (NGF) in retrograde axoplasmic transport and alterations in other growth factors have been demonstrated in diabetic neurons, leading to a loss of nociceptive sensation (Brewster *et al.*, 1994; Hellweg and Raivich, 1994; Hellweg *et al.*, 1994; Thomas, 1994; Anand *et al.*, 1996). Administration of NGF has been reported to reverse some of the changes witnessed in diabetic neurons, and whilst it may not be the cause of DN, NGF may play an important role in the development of the condition. As sensory loss is directly implicated in the development of skin ulceration, NGF administration may provide a possible preventative measure in the future.

Altered lipid metabolism has also been implicated in the development of DN. Whilst evidence suggests that lipoprotein levels do not correlate with sensory nerve dysfunction (Maser *et al.*, 1996), there has been a suggested link between serum phospholipid autoantibody concentrations and the extent of DN (Vinik *et al.*, 1995).

While these proposed mechanisms provide insight into possible preventative treatments, it still is not clear if there is actually a difference between the occurrence of these changes in the elderly diabetic and non-DN sufferer (Bradley *et al.*, 1990). Similarly, there may not be measurable nerve fibre functional differences between painless and painful DN (Veves *et al.*, 1994). Owing to the diffuse nature of diabetes, the list of implicated factors is considerable and difficult to cover in depth.

8.1. *Medical Management*

Pharmacotherapy of DN involves the use of a range of TCAs, such as amitriptyline, imipramine, and desipramine. The newer serotonin-selective reuptake inhibitors have not been studied extensively as adjuvant analgesics except for paroxetine, which has shown some positive results (Sindrup *et al.*, 1990). Other treatments include anticonvulsants and lignocaine. One factor that is clear, however, is that the most effective preventative therapy for DN and other diabetes complications is good glycaemic control (Santiago, 1993). Rigorous glycaemic control includes self-monitoring of blood glucose concentration using portable blood glucose monitors and adherence to insulin or oral hypoglycaemic regimens. Other good health factors, including diet and weight control, ceasing cigarette smoking, regular exercise, and regular foot assessment, are also important. Early detection of the disease is important, which is reflected in a report indicating that intensive insulin therapy reduced the incidence of DN in later life by 61% (Feldman and Stevens, 1994). Unfortunately, currently there is little evidence suggesting that intensive insulin therapy reduces existing neuropathy.

Other pain control therapies include the TCAs, which may be combined with phenothiazines, e.g., fluphenazine (1 mg 3 times daily), if monotherapy is unsuccessful. Intravenous infusions of sodium channel blockers such as lignocaine (3 mg/kg over 30 min) can provide pain relief for up to 3 weeks (Bach *et al.*, 1990). Oral sodium channel blockers, such as phenytoin (100 mg 3 times daily), carbamazepine (200 mg 3 times daily), and mexiletine (200 mg 2–3 times daily), have also been used with success. Capsaicin cream has also been used in the treatment of DN. A

systematic review of the literature has been published, which discusses the relative efficacy of a range of treatments (Wright, 1994). This report suggests that some currently used treatments are based on case reports and have not been subjected yet to controlled scientific investigation to prove their value.

Currently, the mainstays of DN treatment remain normoglycaemic control with a TCA added into the regimen as the drug of choice if necessary. Some physicians and researchers recommend a stepwise approach to the treatment of DN to prevent mismanagement of the condition (James and Page, 1994). Unfortunately, in many cases, long-term sensory deficit results in foot amputation, leading to further neurogenic pain problems. A lack of controlled experimental and clinical data has limited the development of more definitive treatments; however, this is being rectified and hopefully, better control of the condition will be available in the near future.

Case Study 5: Diabetic Peripheral Neuropathy

A 58-year-old male complained of bilateral burning pain involving both feet. Radiological investigations revealed no abnormal pathology in the lumbosacral spine apart from mild degenerative changes. Upon closer investigation, the patient revealed that the pain predominantly involved the feet; however, the pain also radiated upwards over his ankles. There was no back pain nor was there pain radiating from the back down the legs. He described the pain as a constant burning sensation, and stated that it frequently felt like he was walking on glass.

The patient suffered from diabetes mellitus, and for some years, had been taking oral medication to control his elevated blood sugar. A neurologist and an endocrinologist were asked to assess the patient and determine the possibility of diabetic peripheral neuropathy. The diagnosis was confirmed and the patient commenced on regular subcutaneous insulin therapy to better control his blood sugar level.

Pain management commenced with a trial of oral amitriptiline (25 mg at night). After 1 week, oral mexilitine was added at a dose of 50 mg 3 times daily. The mexilitine dose was slowly increased over a 3-week period, up to 200 mg 3 times daily.

The combination of better blood glucose control and oral amitriptiline and mexilitine resulted in a 60% reduction in the patient's pain.

9. FUTURE THERAPY

Misunderstanding of the mechanisms behind the development and maintenance of neuropathic pain has meant that the mainstays of treatment for these conditions have not significantly improved in some clinical settings for many years. Unfortunately, this has resulted in a large number of ineffective, risky surgical procedures being performed, with the only outcome being short lived remittance of pain followed by a lifetime of further procedures, analgesics, and side effects for the patient. Today, whilst surgery is still an important component of treatment of some conditions, it is generally not accepted to be prudent or advantageous in others (Burchiel *et al.*, 1993).

As a result of this, pharmacotherapy is becoming the mainstay of neuropathic pain management. Unfortunately, condition-specific treatments are rare, and sometimes long periods of manipulating the drug regimen may be necessary before an acceptable level of pain relief is reached. This problem is due to the fact that neuropathic pain symptoms are common across the spectrum of disorders, while their degree and variability of expression is extremely high. Whereas one particular drug at a particular dose is adequate for the pain of one TGN sufferer, it may be totally useless in another. This may lead to a lengthy period of dose titration, nondirectional drug swapping, and polypharmacy.

Due to a lack of definitive understanding of the underlying pathophysiology of these conditions, symptomatic relief is the aim of treatment. Until the mechanisms of cause and maintenance of neuropathic pain are better understood, clinicians and scientists will not be able to design more effective treatments.

Nevertheless, research and treatment have progressed considerably from the days when pain was considered to be purely of peripheral sensory origin with a fixed stimulus-response relationship, and neurogenic pain was considered to be more psychogenic than physiological. Research into new treatments for neurogenic pain is based on current knowledge of the aetiology and maintenance of these disorders. Treatment options include preventing central sensitisation (Woolf and Chong, 1993), the use of cyclo-oxygenase inhibitors (Malmberg and Yaksh, 1992; Brune, 1994), NMDA receptor antagonists (Mao *et al.*, 1992; Kolhekar *et al.*, 1993; Mao *et al.*, 1993; Tal and Bennett, 1993; Eide *et al.*, 1994; Tal and Bennett, 1994; Eide *et al.*, 1995; Mathisen *et al.*, 1995; Persson *et al.*, 1995), nitric oxide synthesis inhibitors (Malmberg and Yaksh, 1993), calcium channel blockers (Azmitia, 1989; Sucher *et al.*, 1991; Lipton, 1994a,b), and axoplasmic transport modifiers (Csillik *et al.*, 1982; Knyihar-Csillik *et al.*, 1982; Porubcsanszki and Csillik, 1992). In the future, the judicious combination of appropriate treatment options may result in more effective treatment for patients with neurogenic pain.

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