Pain Management

16

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Contents

16.1 Introduction

Neuropathic pains associated with syringomyelia are often refractory to conventional analgesic therapy, with most patients obtaining, at best, only partial relief of symptoms. There is still a tendency to treat these pains with one analgesic, or two in combination, but the pathogenesis of neuropathic pain is complex and multifactorial, so this approach is often unsuccessful. To make matters worse, there is scant scientific literature on which to base best management.

Most physicians follow a hierarchy of treatments for chronic neuropathic pain, starting with monotherapy or a combination of agents such as opioids, serotonin-noradrenaline uptake inhibitors, tricyclic antidepressants, anticonvulsants, cannabinoids and topical analgesics. Such compounds are often combined with non-pharmacological treatments like transcutaneous electrical nerve stimulation, percutaneous electrical nerve stimulation and supportive interventions such as cognitive and physical therapies.

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If patients do not respond to these approaches, then interventional procedures can be considered, such as nerve blockade, dorsal cord stimulation and intrathecal drug delivery systems. Beyond these methods there is invasive neuromodulation, such as spinal cord stimulation. Unfortunately, some patients never achieve adequate pain control, despite all such measures.

In this chapter, our current understanding of the mechanisms causing neuropathic pain and the nonsurgical therapy of syringomyelia are reviewed. Limitations of therapy are discussed, together with likely future directions for treatment. Non-pharmacological treatments, such as acupuncture, complementary medicine, cognitive therapy and neurostimulation, are also considered.

16.2 Neuropathic Pain in Syringomyelia

Clinical features of syringomyelia are diverse, but common signs include sensory deficits such as reduced thermoalgesic sensitivity, often presenting in conjunction with neuropathic pain. There is, however, much clinical variability between individual cases, ranging from asymptomatic patients, through those with mild, chronic pains to individuals with extreme and intractable pain (Tables 16.1 and 16.2). Pain in syringomyelia is often unilateral: with cervicodorsal cavities it is commonly located in the hand, shoulder, thorax or neck; in patients with dorsolumbar syringomyelia, the pain is usually in the lower limb (Attal and Bouhassira 2006). In posttraumatic syringomyelia, months or years may elapse, from the initial injury up until the onset of pain (Attal and Bouhassira 2006). Pain associated with syringomyelia may vary in intensity, and periods of both exacerbation and remission are common. Suboccipital headache is frequent and is often described as being oppressive in nature, the intensity being influenced by the sufferer's posture or their intracranial pressure. If intracranial pressure rises, such as after Valsalva manoeuvres, coughing, sneezing and defecation, both the headache and the neck pain can intensify. On the other hand, the headache might have a more nonspecific character and seem similar to a tension headache. Neck pain is frequent and characterised by an absence of accompanying radicular arm pain. It may be associated with a continuous burning, deep-seated discomfort in the shoulders, the nape of the neck, the chest or the upper limbs. Some symptoms such as hyperalgesia,[1] allodynia[2] and segmental and radicular pains can

Table 16.1 Sensory symptoms in syringomyelia

Specific and nonspecific pains (*see* Table 16.2)
Hypoaesthesia: reduced sense of touch or sensation or a partial loss of sensitivity to sensory stimuli
Hypoalgesia or *hypalgesia*: decreased sensitivity to painful stimuli
Hyperpathia or *hyperalgesia*: an excessively painful response to a mildly painful stimulus, such as a slight prick
Paraesthesia: abnormal but not unpleasant sensations, for example, tingling
Dysaesthesia: unpleasant abnormal sensations often described as a sensation of burning, pins and needles and stretching of the skin
Allodynia: a painful response to a non-painful stimulus, such as light touch
Vasoconstriction or *vasodilatation*
Hyperhidrosis or *anhidrosis*
Piloerection or *loss of piloerection*
Trophic changes, e.g. pale glossy skin with a sensation of coldness

Table 16.2 Pain-related symptoms in syringomyelia

Headache
Valsalva induced
Suboccipital
Retro-orbital
Generalised, nonspecific headache
Trigeminal pain
Orofacial pains
Neck pain
Segmental pain
Radicular pain
Back pain
Neuropathic arthropathy pains
Leg pain

[1] Increased sensitivity and lowered threshold to painful stimuli.

[2] Pain in response to something that would not typically cause pain, such as a light touch or contact with clothing.

be anatomically related to the injured neurons or territory innervated by the injured segment. There can also be spread of these symptoms to adjacent, noninjured segments or even to involve the entire body. Other symptoms, such as trophic changes,[3] are linked to the global influence of the lesion on autonomic nervous system function (Soria et al. 1989; Milhorat et al. 1996). Features such as hyperhidrosis or hypohidrosis may occur as isolated symptoms of syringomyelia, without any other associated neurological features, or they may be part of the autonomic hyperreflexia syndrome.[4] They may also be a manifestation of a developing posttraumatic syringomyelia (Sudo et al. 1999).

Scoliosis, when seen in relation to syringomyelia, presumably relates to degeneration of motor neurons innervating the spinal muscles. Once initiated, progression of the curve can occur without further motor neuron degeneration. The resulting deformity can generate discomfort of mechanical origin, in addition to the pain arising from the syrinx itself.

Following surgery for Chiari malformation, with or without syringomyelia, patients frequently enjoy a significant improvement in their quality of life (Gautschi et al. 2011; Falci et al. 2009). Headache and neck pain may diminish, as may symptoms attributable to compression of the brain stem, such as dysphagia, ataxia, nystagmus and diplopia. In contrast, symptoms directly attributable to a syrinx cavity, including pain, scoliosis, and loss of sensitivity, are the least likely to improve.

There is no clear and simple relationship between the anatomical extent of a syrinx cavity and the symptoms and signs it creates. Nor is it possible to distinguish, just by looking at their MR scans, between patients who will and those who will not develop neuropathic pain, even when this imaging is combined with electrophysiological assessments of nociceptive and non-nociceptive pathways (Hatem et al. 2010). On the other hand, higher-average daily pain intensities do correlate with greater structural damage to the spinal cord. Further, patients experiencing both spontaneous and evoked pain have less severe structural damage to the cord than do patients with spontaneous pain alone, who tend to have more severe spinal cord damage (Hatem et al. 2010).

16.3 Pain Pathophysiology and Treatment Targets

Neuropathic pain, in its various forms, is thought to result from a number of interrelated phenomena:

1. Peripheral[5] and central sensitisation[6]
2. Hyperexcitability of central nociceptive neurons
3. Altered gene expression
4. Spontaneous neuronal activity
5. Disinhibition
6. Abnormal sprouting and cellular connectivity[7]
7. Neuronal cell death

In general, we can describe the progression of acute pain into chronic neuropathic pain as taking place in five steps. Drugs based on different mechanisms of action can be used to target each step.

1. *Activation of Glutamate Receptors*
   Glutamate transmitter release results in increased activation of spinal receptors and increased neuronal excitability. Release of the

[3] Atrophic changes of the skin which becomes thin, shiny and smooth. Hair growth may be increased, especially in early stages, or it may be decreased.

[4] Autonomic hyperreflexia can occur in spinal cord-injured individuals with spinal lesions above level T6 and is characterised by paroxysmal hypertension, throbbing headaches, profuse sweating, flushing of the skin above the level of the lesion, bradycardia and anxiety.

[5] A reduction in threshold and an increase in responsiveness of peripheral nociceptive neurons.

[6] An increase in the excitability of nociceptive neurons within the central nervous system.

[7] Neuroplasticity—the process by which neurons compensate for injury and disease and adjust their activities in response to new situations or to changes in their environment. Central nervous system reorganisation occurs by processes such as 'axonal sprouting' in which axons sprout nerve endings and connect with other nerve cells, forming new neural pathways.

glutamate is calcium channel dependent. Analgesics such as gabapentin and pregabalin target these altered calcium channels and inhibit their function.

2. *Activation of the N-methyl-D-aspartate (NMDA) Receptor*
   In the spinal cord, release of peptides and glutamate activates the NMDA receptor, which, in concert with other spinal systems, generates a persistent pain state. Wind-up[8] and long-term potentiation[9] are key processes related to chronic activation of NMDA receptors. Wind-up is induced by C-fibre and A-delta fibre inputs and, once produced, enhances all responses, including those from low-threshold inputs. If the peripheral sensory input declines, there might be a slow return of neuronal responses back to baseline, so blocking such peripheral drives should attenuate central sensitisation. Unfortunately, in some cases chronic pain does not cease, most probably because of glial activation (see below). Long-term potentiation is a longer-lasting version of wind-up, where high-frequency C-fibre input produces chronic excitability, an event that persists even though the input is terminated. Ketamine blocks the NMDA receptor complex, and use of NMDA antagonists has been a useful tool for demonstration of NMDA receptor-mediated hypersensitivity in patients with neuropathic and complex regional pain syndrome pains (Azari et al. 2010).
3. *Temporal Summation* (*Wind-up and Further Wind-Up*)
   If the nociceptive input continues, neuronal responses remain elevated, resulting in a cascade of detrimental neuronal overactivity. By this process weak stimuli may evoke pain, if repeated or if their duration is prolonged.
4. *Glial Activation* (*See Below*)
5. *Cortical Reorganisation* (*See Below*)

Spinal cord neurons that become hyperexcitable, as a result of the mechanisms described above, show reduced thresholds to normal sensory inputs, greater evoked responses to such input, increased receptive field sizes[10] and ongoing stimulus-independent activity. These processes are all important factors in the pathogenesis of allodynia, hyperalgesia and spontaneous pain. Overactive neurons in the central nervous system can be inhibited via drugs that target neural cells directly such as antidepressants, antiepileptics, GABAergic agonists (benzodiazepines) and opioids. A common feature of these drugs is that their targets are ion channels and receptors on nerve endings (synapses).

16.4 The Role of Glial Cells in Neuropathic Pain

Virchow (1821–1902) first described and depicted glia as gelatinous material giving structural support to the nerve cells. In 1894 Franz Nissl described the morphological changes seen in glial cells following spinal cord injury, regarding these as a biological response to promote nerve repair. These days we are increasingly aware of other roles played by the glial cells, including in the development of neuropathic pain. Until recently development of new analgesics and treatment of neuropathic pain has focused on neuronal targets. The vital role played by glial and inflammatory cells has been overlooked but is now a fast-emerging area of research (Bulanova and Bulfone-Paus 2010). A concept, which the author refers to as 'the hexapartite synapse', describes six interconnecting elements that play a functional role in neurotransmission of pain (Fig. 16.1). The hexapartite synapse consists of two neurons making synaptic contact, a microglial cell, an astrocyte, a T-cell lymphocyte and a mast cell. All these

[8] Wind-up pain is a mechanism leading to chronic pain via the constant bombardment of the second-order neurons in the dorsal horn of the spinal cord.

[9] Long-term potentiation (LTP) is a long-lasting enhancement in signal transmission between two neurons as a consequence of stimulation.

[10] The receptive field of a sensory neuron is a term originally coined by the famous neurophysiologist Sherrington to describe an area of the body surface where a stimulus alters the firing of that neuron. In neuropathic pain, repetitive painful stimulation results in an expansion of the receptive fields.

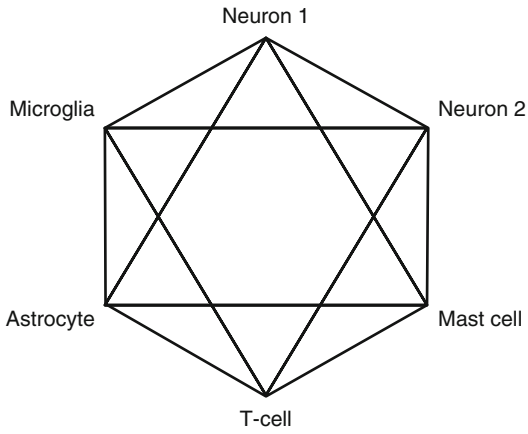

Fig. 16.1 The hexapartite synapse. Six cellular elements play a functional role in the genesis and maintenance of neuropathic pain: two neurons, a microglia cell, an astrocyte, a mast cell and a T lymphocyte. The non-neuronal cells play an underestimated role in neuropathic pain, and failure to deal with this is one of the major reasons for unsatisfactory control of neuropathic pain

neuronal and non-neuronal cells function as a unit, and non-neuronal cells can influence the generation of electric impulses. The familiar paradigm of one afferent and one efferent neuron with a synapse in between is obsolete, and consequently therapies that only target the neuron are likely to be inadequate (Fields 2009; Keppel Hesselink 2011).

Damage to the sciatic nerve in rats causes astrocytes in the dorsal horn of the spinal cord to increase in volume and to multiply, a pivotal factor in the development of neuropathic pain (Garrison et al. 1991). Low-grade inflammation also develops in the spinal cord dorsal horn and along the pain pathways to the thalamus, as well as further upstream, as far as the parietal cortex (Saade and Jabbur 2008). A consequence of this neuro-inflammation is glial cell activation, especially of the microglia (Aldskogius 2011; Gao and Ji 2010a). This activation also takes place in central pain (Wasserman and Koeberle 2009). Activated microglia and astrocytes then release many irritant molecules such as proinflammatory cytokines, including interleukins, chemokines and tumour necrosis factor (TNF)-alpha, which contribute to chronic pain states. Hyperactive neurons produce comparable compounds, such as growth factors which in turn activate spinal cord microglia and astrocytes, and a vicious circle emerges, where both cell types wind up each other and neuropathic pain is both initiated and maintained (Graeber 2010). In the rat spinal cord, astrocytes are responsive to the pain neurotransmitter substance P (Marriott et al. 1991). There is an intimate interaction between neuronal and non-neuronal cells. For example, following nerve cell injury, certain enzymes are activated, such as c-Jun N-terminal kinase in spinal cord astrocytes, leading to the expression and release of monocyte chemotactic protein-1 (MCP-1). Monocyte chemotactic protein-1 is a cytokine which increases pain sensitivity via direct activation of NMDA receptors in the spinal cord. c-Jun N-terminal kinase plays a key role in the body's response to stressful stimuli such as inflammatory signals and changes in levels of reactive oxygen species. c-Jun N-terminal kinase activity regulates several important cellular functions, including cell growth, differentiation, survival and apoptosis, and pharmacological inhibition of c-Jun N-terminal kinase attenuates neuropathic pain in animal models (Wang et al. 2011). In addition to spinal wind-up phenomena like these, cortical reorganisation adds to the complexity of the central sensitisation processes (Dimcevski et al. 2007). The term cortical reorganisation refers to the functional changes that occur in parts of the brain. An extensive network of brain regions often referred to as the 'pain matrix' frequently show abnormalities on functional imaging studies in chronic pain states, and changes in the motor and sensory homunculus have also been described (Henry et al. 2011).

There are currently five major neurobiological pathways known to activate microglia (Fig. 16.2) (Smith 2010).

1. *Fractalkine* (also known as chemokine (C-X3-C motif) ligand 1 or neurotactin) is a chemokine[11] produced by a variety of cells, including neuronal and glial cells. It induces microglia chemotaxis. Microglia are the

[11] Chemotactic cytokines are small proteins capable of inducing chemotaxis (migration) of nearby responsive cells such as microglia.

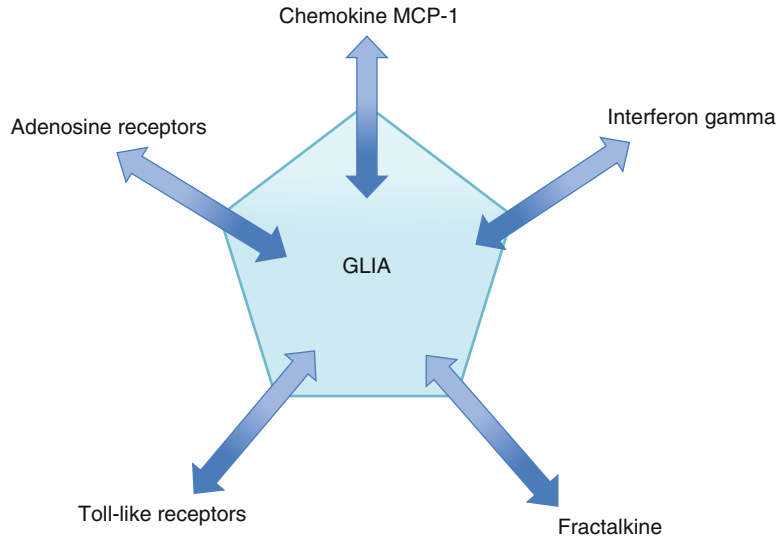

Fig. 16.2 Microglia-activating pathways. There are many targets to inhibit overactive glia in neuropathic pain

only central nervous system (CNS) cells that express the fractalkine receptors, which are upregulated in pain states. Upon activation, microglia secrete proinflammatory mediators such as prostaglandins, proteases, cytokines (TNF-alpha, interleukin-1 beta, interleukin-6) and excitatory amino acids, whose receptors are expressed on dorsal horn neurons. It is speculated that it is by this process that microglia alter sensory neuronal activity (Owolabi and Saab 2006).

2. *Interferon gamma* (INF-γ) is a cytokine with antiviral, immunoregulatory and antitumour properties. Interferon gamma alters transcription in up to 30 genes producing a variety of physiological and cellular responses. After becoming activated with INF-γ, microglia release further interferon gamma which activates more microglia and initiates a cytokine-induced activation cascade, rapidly activating all nearby microglia.
3. *Monocyte chemotactic protein-1* (MCP-$_1$) is also known as chemokine (C-C motif) ligand 2 (CCL2) or small inducible cytokine A2. Monocyte chemotactic protein induces monocyte, macrophage, basophil and mast cell migration and is synthesised by monocytes, macrophages, dendritic cells and astrocytes (Deshmane et al. 2009). This cytokine contributes to the pathogenesis of monocyte-dependent tissue injury, and release is triggered by increasing NMDA concentrations (Szaflarski et al. 1998). The consequence of increased MCP-1 concentrations and upregulation of the chemokine receptor CCR2 and MCP-1/CCL2 is an enhanced and prolonged persistent pain state (White and Wilson 2008; Gao and Ji 2010b).
4. *Toll-like receptors* (TLR) are membrane-spanning receptors that have a pivotal role in the innate immune response[12] in particular cellular activation and cytokine production in response to microbes. In the CNS TLR4 is expressed exclusively by the microglia, and TLR4 mRNA expression is significantly increased in experimental neuropathic pain states (Smith 2010) (Fig. 16.3).
5. *P2X receptors* (receptors for the nucleotide adenosine). Nucleotides that are released and leaked from cells are involved in cell-to-cell communication in physiological and pathophysiological conditions (Smith 2010). The upregulation of P2X4 receptor in microglia appears to be an important process in contributing to neuropathic pain (Smith 2010).

It is increasingly recognised that these phenomena play a central role in neuropathic pain.

[12] The innate immune system (nonspecific immune system) is the body's first line of defence and comprises the cells that recognise and respond to pathogens in a generic way and defend the host from infection by organisms.

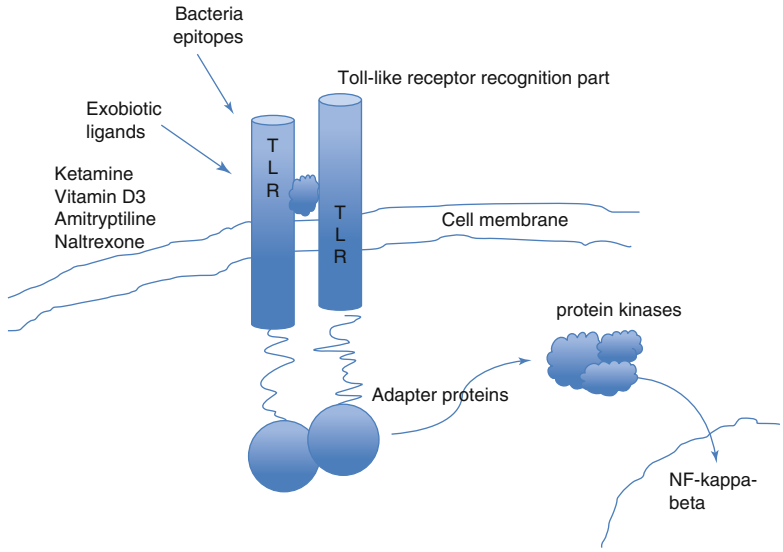

Fig. 16.3 Toll-like receptors. The Toll-like receptors are membrane-spanning receptors (named TLR1 to TLR13). The receptors function as dimers, and after activation, for instance, by an analgesic drug, Toll-like receptors recruit adapter molecules within the cytoplasm of cells to propagate a signal leading to the induction in the nucleus of certain key genes or the suppression of other genes that orchestrate the inflammatory response and chronic pain states. Toll-like receptors can be found on mast cells, glia and many immune-competent cells as well as on neurons. These receptors might play an important role in glia modulation by drugs such as ketamine, propofol, vitamin D3 or low-dose opiate antagonists such as naltrexone

Gliopathic or asteropathic pain may become new synonyms for neuropathic pain, and glia-modulating drugs may become a new class of neuropathic pain drugs (Ohara et al. 2009). Other non-neuronal targets, for instance, gap junctions and connections,[13] are still in an early phase of research and development. These new non-neuronal targets will also lead, hopefully, to additional avenues of pain medication (Wu et al. 2012).

16.5 Traditional Pharmacological Therapies

Most outcome studies looking at the treatment of neuropathic pain are focused on painful peripheral polyneuropathies, especially diabetic and postherpetic neuralgias. Studies of central neuropathic pain are few in number, largely because it is laborious to recruit sufficient patients for entering into clinical trials. There is therefore little data on nonsurgical management of neuropathic pain secondary to Chiari malformation and syringomyelia and certainly no methodologically sound outcome studies. The literature is confined to anecdotal recommendations, case reports and series with small patient numbers. In addition, the majority of the animal models used in drug trials are not representative of the real-life situation for human patients. The only comparable animal models relevant to syringomyelia are some breeds of toy dog, especially Cavalier King Charles Spaniels (see Chap. 14), which have a high prevalence of syringomyelia (Knowler et al. 2011). The opportunities that this model may represent have not yet been realised, with only a few unpublished clinical trials having taken place.

Drawing conclusions about what is the most effective therapy is even more difficult when one has to take into account the many differences in study design (Table 16.3).

Whilst our understanding of neuropathic pain-generating mechanisms has grown considerably, this has not been translated into a similar improvement in treatment efficacy, and most

[13] Gap junctions are channels between cells allowing a direct connection between the cytoplasm and allowing passage of molecules and ions. One gap junction channel is composed of two connections (or hemichannels).

Table 16.3 Variations in study design between different trials

Population differences
Race
Sex
Age
Patient numbers
Power calculations
Estimated magnitude of effect
Number of subjects included
Number of subjects dropping out
Trial duration
Inclusion and exclusion criteria
Pain intensity
Outcome measures

neuropathic pain patients are still left with insufficient pain relief (Finnerup et al. 2010). Clear insights into why some patients are nonresponders remain absent. Given the high variability in intensity, severity and location of symptoms, each patient must receive an individualised treatment plan.

The analgesics most often used for treatment of spinal cord injury-related pain are nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen (paracetamol) and non-opioid muscle relaxants, such as baclofen and tizanidine. Generally, these analgesics are not prescribed by pain physicians but are purchased by patients themselves or prescribed by general practitioners. As single agents, or in combination, they are, unfortunately, ineffective in many spinal cord injury patients (Cardenas and Jensen 2006). They also have potential risks due to gastrointestinal, renal and hepatic toxicity, especially with prolonged use and higher dosage.

From the perspective of most pain specialists, antidepressants, antiepileptics and opioids are the best established and most commonly used adjuvant analgesics. Most have similar equivalent efficacy, with a number needed to treat[14] (NNT) of 3–6, but the adverse effect profiles differ (Finnerup et al. 2010).

[14] The NNT is defined as the number of patients that need to be treated, in a clinical trial, for one to benefit, as compared with the control group (Laupacis et al. 1988). The ideal NNT is 1, where every patient improves with treatment and no one improves with control. The higher the NNT, the less effective is the treatment.

16.5.1 Tricyclic Antidepressants

Tricyclic antidepressants such as amitriptyline and nortriptyline have 'dirty'[15] pharmacology, which is perhaps the reason for their efficacy in pain states with complex pathophysiology. Pharmacologically dirty drugs, which bind to multiple receptors, tend to be more effective for neuropathic pain but have more potential adverse effects. The therapeutic effect of the classical tricyclic antidepressants is mediated by their inhibition of the reuptake of noradrenaline and of serotonin. However, they also interact with the muscarinic acetylcholine receptor, the histamine-1 receptor, the alpha-1 adrenergic receptor and sodium ion channels (Pancrazio et al. 1998). The more receptors that are triggered, then the greater the biological effect. If only one receptor in a complicated network is influenced, then this impact will ultimately be neutralised. If multiple sites are affected, then the network is more likely to be broken and for longer. There have been some anecdotal reports that tricyclic antidepressants are effective for neuropathic pain following spinal cord injury in the presence of depressive symptoms and less effective in patients not suffering from signs of depression (Attal et al. 2009; Rintala et al. 2007).

Tricyclic antidepressants are mostly metabolised by cytochrome P450 2D6 (CYP2D6); therefore drug interactions and high serum concentrations can occur, as this hepatic enzyme plays an important role in the metabolism of many different drugs and compounds. The same dose can result in 10- to 30-fold variation in serum concentration between different patients. Patients who metabolise the drug slowly may sometimes develop a toxic serum concentration following just a single oral dose or, rarely, even after topical application. At the same time, even a small amount of amitriptyline can have a positive effect. For example, 10 mg amitriptyline before bedtime may improve sleep and decrease nocturnal pains.

[15] Drugs that bind to many molecular targets or receptors with a wide range of effects and possibly negative side effects. Novel drugs tend to be 'cleaner' and have a more selective action with fewer adverse reactions. There may, however, be advantages in using drugs that exhibit multi-receptor activity, and, depending on the perspective, sometimes these drugs are referred to as 'enriched'.

16.5.2 Serotonin Antagonist and Reuptake Inhibitors

Serotonin antagonist and reuptake inhibitors are a class of drugs, most commonly prescribed for depression, which act by antagonising serotonin receptors and/or inhibiting the reuptake of serotonin, norepinephrine or dopamine. Additionally, most also act as alpha1-adrenergicreceptor antagonists. Examples of this class of drugs include venlafaxine, duloxetine and trazodone. Compared to tricyclic antidepressants, SARIs have a more selective action, and as they are cleaner in their receptor affinities, there are fewer histaminergic and muscarinergic adverse effects. Whether this theoretical advantage translates into better tolerability for neuropathic pain has not been substantiated in comparison trials. Compared to amitriptyline, serotonin antagonist and reuptake inhibitors have a higher NNT and are therefore less efficacious for neuropathic pain. A recent trial compared duloxetine and pregabalin for patients with diabetic peripheral neuropathic pain, who had inadequate pain control following gabapentin monotherapy. Duloxetine was not superior to pregabalin as a monotherapy, and there was no synergistic effect with combination therapy. On the contrary, the efficacy of the combination was less than the efficacy of duloxetine alone. In addition, adverse effects such as nausea, insomnia, hyperhidrosis and decreased appetite were more common with duloxetine than pregabalin (Tanenberg et al. 2011).

16.5.3 Antiepileptic Drugs

Carbamazepine seems to be effective for peripheral neuropathic pain but has not been subjected to a clinical trial lasting longer than 4 weeks (Wiffen et al. 2011b). In patients with central, post-stroke pain, there was no difference in efficacy between amitriptyline and carbamazepine (Selph et al. 2011).

Gabapentin and pregabalin target the alpha-2-delta subunit of the voltage-dependent calcium channel. The efficacy of both is comparable, but due to the higher affinity of pregabalin for the receptor, a lower dose is required to achieve optimal analgesia. Gabapentinoids have been evaluated specifically in spinal cord injury pain, with positive effects (Vranken et al. 2008; Tai et al. 2002; Levendoglu et al. 2004). A Cochrane review investigating gabapentin in randomised trials for acute, chronic or cancer pain concluded that gabapentin was superior to placebo in 14 of 29 studies (Moore et al. 2011). Patients taking gabapentin can expect to have at least one adverse event (66 %), and some will withdraw because of such effects (12 %). Common side effects include dizziness (21 %), somnolence (16 %), peripheral oedema (8 %) and gait disturbance (9 %). To date, no head-to-head comparison studies are available for clinicians to determine whether one of these drugs is superior for central neuropathic pain (Tzellos et al. 2008). These studies are not popular to conduct and are very rarely, if ever, sponsored by the manufacturer.

Benzodiazepines may inhibit some of the ectopic activity[16] in peripheral nerves following nerve injury and consequently may be used in the management of neuropathic pain, but efficacy has never been proven in well-controlled trials (Reddy and Patt 1994). There are a few old reports, from small, open-label trials,[17] where clonazepam was successfully used to treat burning mouth syndrome and trigeminal neuralgia (Smirne and Scarlato 1977; Court and Kase 1976). It is not uncommon for clonazepam to be used for spinal cord injury pain, but supportive data is lacking. Doses of up to 8 mg of clonazepam often result in marked drowsiness, so, typically, a lower dose of up to 2 mg is used. Although not supported by enough data, sometimes one may want to explore the usefulness of clonazepam in central neuropathic pain, especially in case of muscle spasms.

Lamotrigine initially appeared promising in animal models of peripheral neuropathic pain and perhaps more effective than compounds such as carbamazepine and gabapentin (Chogtu et al.

[16] After nerve injury, spontaneous neuronal ectopic activity may occur, leading to more pain.

[17] Open-label trials are clinical trials where both the participant and the researchers know what treatment is being administered. They may be randomised, e.g. comparing two treatments, but are generally not controlled, i.e. there is no placebo group.

2011). Clinical trials have not, however, been convincing, and there is no solid evidence supporting the use of this drug in neuropathic pain (Selph et al. 2011).

A number of antiepileptic drugs have been investigated and have shown no efficacy for pain management in patients after spinal cord injury. These include valproic acid and its sodium salt (Drewes et al. 1994; Gill et al. 2011), levetiracetam (Finnerup et al. 2009) and lamotrigine (Wiffen et al. 2011a). Compounds such as phenytoin, topiramate and carbamazepine have not been studied in post spinal cord injury pain.

For spinal cord pain and post-spinal cord injury neuropathic pain, there is enough evidence to support the use of gabapentin and pregabalin (Ahn et al. 2003; Siddall et al. 2006; Putzke et al. 2002). Evidence to support the use of other antiepileptic drugs is less substantial, and results of long-term studies have not yet been published (Eisenberg et al. 2007).

16.5.4 Opioids

Opioids have been used for pain management for thousands of years and are mentioned in pivotal medical texts of the ancient world. They were used extensively for chronic pain management and palliative care in the nineteenth and early twentieth century. In the 1970s and 1980s, opioids were not considered useful for the management of neuropathic pain, and one definition of neuropathic pain was that which was unresponsive to opioids (Arner and Meyerson 1988). This view, which was founded on results from small, mostly short duration and uncontrolled trials, is no longer held. Even so, trials of opioid use in central neuropathic pain are still scarce. Tramadol and tapentadol have been evaluated in peripheral neuropathic pain conditions, but the efficacy in central neuropathic pain states is not widely tested. One relatively small but randomised trial does, however, support their use in post-spinal cord injury pain (Norrbrink and Lundeberg 2009).

A study comparing methadone to placebo, for neuropathic pain, demonstrated evidence of analgesic effect at a dose of 20 mg/day but not at a dose of 10 mg/day (Cherny 2011). Methadone does have several distinct advantages over other opioids, particularly as it has no active metabolites. Classic opioids like morphine, oxycodone and fentanyl are broken down into metabolites that are 'hyperalgesic', that is, molecules that can cause pain when they accumulate under conditions of chronic administration. This means that patients taking opioids may experience more pain or even allodynia, a phenomenon referred to as opioid-induced hyperalgesia Consequently, methadone is a good alternative when intolerable adverse effects from another opioid limit further dose escalation. Often a much lower dose is required than would be expected from equianalgesic conversion tables. In addition, methadone is comparatively inexpensive, and with chronic use, the long duration of analgesia allows less-frequent dosing than is required with other opioids. Methadone is therefore often regarded as a logical choice for controlling malignant and non-malignant chronic pain (Portenoy and Foley 1986) although this view is not universally held, partly because of the risk of fatal overdose. Some recommend that methadone should not be the first-choice drug for pain and nor should it be used in opioid-naive patients (Terpening and Johnson 2007). Nor is there a clear consensus on the appropriate interval for dosing of methadone with recommended intervals ranging from 3 to 24 h (Ripamonti et al. 1997). The duration of analgesia following a single dose of methadone is 4–6 h. One study in which patients controlled their own dosing interval, at a fixed 10 mg dose, showed that after a week of repeated dosing, the initial 3- to 7-h interval lengthened to an average of 10 h (Sawe 1986). The recommended starting dose in an opioid-naive patient is 2.5 mg orally every 8 h. Frail elderly patients may require a lower initial dose, and 2.5 mg orally, once daily, has been suggested (Toombs and Kral 2005).

There is some limited data supporting intravenous use of opioids (oxycodone) for spinal cord injury patients with anticonvulsant refractory neuropathic pain (Barrera-Chacon et al. 2011). A 3-month follow-up prospective, multicentre study, following 54 patients, concluded that oxycodone, in combination with anticonvulsants, decreased pain intensity and diminished the impact of pain on physical activity and sleep.

However, half of the patients showed at least one treatment-related adverse event, with constipation being the most frequent, in one-third of patients.

16.5.5 NMDA Receptor Antagonists

Ketamine is an anaesthetic drug and an N-methyl-D-aspartate (NMDA) receptor antagonist. It also inhibits pain by a number of other routes, including depression of the Toll-like receptor 3 pathway, via certain ion channels and downregulating activated glia (Hayashi et al. 2011; Mei et al. 2011a, b). Ketamine is an old drug which has been in clinical practice for nearly 40 years and may have a valuable role in management of refractory neuropathic pain patients (Cohen et al. 2011; Truin et al. 2011; Zhou et al. 2011). The effective dose for analgesia is much lower than that required for anaesthesia. This is thought to be due to a second mechanism of action, most likely via the Toll-like receptors on the glia (Mei et al. 2011b).

The usefulness of ketamine, delivered via a patient-controlled intravenous delivery system, has been reported in a single patient with cervical syringomyelia (Cohen and DeJesus 2004). The regime used resulted in a significant lessening of the pain, permitting a reduction in opioid dosage (Cohen and DeJesus 2004). It has also been reported that relative short courses (4 days) of intravenous ketamine infusion could trigger long periods (11 weeks) of decreased pain in complex regional pain syndrome type I (Sigtermans et al. 2009). The intravenous preparation can also be given orally, sublingually or rectally or as a spray for intranasal delivery.

16.5.6 Other Agents

Intravenous lidocaine infusion can be used for treating post-spinal cord injury pain in the short term but is not an option for chronic therapy (Attal et al. 2000). In syringomyelia, spasticity contributes to a patient's discomfort, and spasmolytics such as baclofen and tizanidine can be useful co-analgesics (Devulder et al. 2002). Intrathecal baclofen is also useful for reducing pain and spasticity after spinal cord injury (Lind et al. 2004).

Pharmaceutical trials of drug therapy for hyperhidrosis caused by spinal cord lesions are few and are not supportive for their given therapies, for example, dextropropoxyphene hydrochloride (Andersen et al. 1992).

16.6 Novel Drug Therapies

16.6.1 Cannabis and Endocannabinoids

Cannabinoids such as tetrahydrocannabinol, cannabidiol and nabilone can be useful in several pain states including central and peripheral neuropathic pain, rheumatoid arthritis and fibromyalgia (Lynch and Campbell 2011). Smoked cannabis is a method used by a number of individuals with chronic, noncancer pain as well as by some patients with multiple sclerosis. Many natural and synthetic cannabinoids are therefore under investigation as potential anti-neuropathic pain drugs (Rahn and Hohmann 2009). Despite several papers supporting the efficacy and safety of cannabis and cannabinoids for various pain states, the medical use of cannabis is forbidden in many countries.

Palmitoylethanolamide is an endogenous fatty acid amide which can be found in tissues of all mammals, including man, and some foods, such as eggs and milk (Costa et al. 2002). It functions as a ubiquitous signalling molecule and is formed in the brain from the membrane phospholipid N-acylated phosphatidylethanolamines (Hansen 2010). It mimics several endocannabinoid-driven actions, even though it does not bind to cannabinoid receptors 1 and 2 (Scuderi et al. 2012). Palmitoylethanolamide can activate many receptors, most notably the peroxisome proliferator-activated receptors. These are cell nuclear receptors, mediating several physiological functions including lipid metabolism, energy balance and inflammation. There have been many scientific studies detailing palmitoylethanolamide's neuroprotective, antiepileptic, anti-inflammatory and analgesic

properties (Lo Verme et al. 2005; Koch et al. 2011; Esposito et al. 2011; Loria et al. 2008; Gatti et al. 2012). Palmitoylethanolamide also downregulates hyperactive mast cells and is a possible candidate for treating several chronic inflammatory diseases (Aloe et al. 1993) including neuroinflammatory disorders (Skaper and Facci 2012). Palmitoylethanolamide is available for clinical use for the treatment of chronic pain and chronic inflammation in some parts of Europe. A suggested dosing regimen for chronic pain is 600 mg palmitoylethanolamide twice daily for 3 weeks followed by single daily dosing in addition to standard analgesic therapies or as single therapy (Gatti et al. 2012). To date no drug-to-drug interactions have been documented (Gatti et al. 2012).

Other endocannabinoids include oleoylethanolamide, stearoylethanolamide, 2-lineoylglycerol, 2-palmitoylglycerol and anandamide or arachidonoylethanolamide. Many of these have anti-inflammatory and/or analgesic actions and have been investigated for potential therapeutic benefit (LoVerme et al. 2006; Calignano et al. 2001; Costa et al. 2008; Conigliaro et al. 2011; Indraccolo and Barbieri 2010).

16.6.2 Naltrexone

Experiments in animals have demonstrated that a transient blockade of opioid receptors, by low doses of an antagonist such as naltrexone, can stimulate increased production or upregulation of mu-opioid receptors in pain centres in the brain (Mannelli et al. 2006). Low doses of opioid antagonists have therefore been postulated to 'reset' the opioid-receptor system for a period of time. In addition, low-dose naltrexone also inhibits glial cell activation, via Toll-like receptor 4, which might have an analgesic effect (Inceoglu et al. 2006; Mattioli et al. 2010). It has been suggested that naltrexone has two dose-related effects: at a low dose of 1–5 mg, the Toll-like receptors are targeted and opioid receptors are reset, and at 10 mg and above, opiate receptors are blocked. A low dose of an antagonist transiently blocks the opioid receptors, resulting in increased production, or upregulation, of mu-opioid receptors in regions of the brain that control pain responses. After the antagonist effects wear off (depending on the agent and dose, this may take minutes to hours), then there are increased numbers of receptors able to bind endogenous or exogenous opioids. In addition, the body responds to the temporary opioid-receptor blockade by increasing production of endorphins. This upregulation of the opioid receptions can also 'reset' the opioid receptors from the desensitisation which occurs during chronic opioid treatment. However, practical use of naltrexone is still experimental and requires experience in pain management, in particular, and knowledge of the half-life of the opioids that the patient is already receiving. Typically low-dose naloxone is not combined with opioids, and patients are advised to take 1.5–4.5 mg at bedtime. Occasionally patients do report adverse effects, such as vivid dreams, nightmares or night-time waking. For these patients a morning prescription of low-dose naltrexone can be taken. Although this is contrary to normal practice, we have not found any sound scientific data indicating that low-dose naltrexone should not be administered in the morning (Leavitt 2009).

16.6.3 Magnesium

Magnesium is a physiological blocker of the NMDA receptor, and it has been suggested that magnesium supplementation may have an antinociceptive effect. Although initial studies looked promising (Lee et al. 2012), their findings were not supported in a recent clinical trial (Pickering et al. 2011). This trial, however, had a high placebo response, making interpretation more difficult. In addition, only one dose was tested. Anecdotally, the authors have found that adding oral magnesium sulphate to an existing analgesic regimen, at 500 mg three times daily, may be effective, especially if the patient complains of painful muscle spasms.

16.7 Management Strategies for Central Neuropathic Pain

If the results of the efficacy of analgesics and co-analgesics in neuropathic pain are reviewed, a clear picture emerges. Firstly, most drugs are less efficacious for central as compared to peripheral neuropathic pain. Secondly the NNT of all of the most commonly prescribed drugs are similar, between three and nine (Finnerup et al. 2010). Amitriptyline is the oldest and most active compound with an NNT just below three. The NNT have actually increased for drugs evaluated in more recent clinical trials, but this is probably related to more stringent trial methodology (Finnerup et al. 2010). Patients themselves are also important sources of information about drug efficacy, if not the most important source. They report that, after titrating up the dose, most of these drugs begin to produce side effects, making optimal dosing difficult, if not impossible, in many individuals. Drowsiness, inability to drive a car and 'feeling like a zombie' are common complaints. Patients with spinal cord pain also suggest that drugs such as antidepressants are less effective, when compared to other interventions, such as acupuncture (Heutink et al. 2011).

A review of all available comparison trials for neuropathic pain has been undertaken. This included industry-sponsored and other unpublished studies involved in the drug approval process (Watson et al. 2010). For instance, they reported a clinical trial with reasonable methodology (Jadad score of 3 [18]) which compared amitriptyline to pregabalin. For patients treated with amitriptyline, 46 % had 50 % or greater relief in pain. In comparison, 50 % or greater relief from pain was documented in 40 % of patients treated with pregabalin and 30 % of patients receiving a placebo. They used the same methodology to describe all trials comparing two or more drugs and came to the following conclusions:

1. There is no evidence supporting the efficacy of the benzodiazepine lorazepam, the phenothiazine fluphenazine and the sodium channel-blocking agent mexiletine or carbamazepine for neuropathic pain (trigeminal neuralgia was excluded).
2. There is no evidence for the superiority of gabapentinoids over tricyclic antidepressants, either regarding pain or adverse effects, although the nature of the latter differs with the two agents.
3. There are nonsignificant trends suggesting the superiority of opioids over tricyclic antidepressants and gabapentinoids.

16.7.1 Combinations of Analgesics

Neuropathic pain is generated by a biochemical network of maladaptive neurons and glia. It is therefore unlikely that monotherapy will ever produce sufficient analgesia, and in practice, neuropathic pain is managed with combination of analgesics and co-analgesics. A well-known early combination was the Brompton cocktail, named after the Royal Brompton Hospital in London (Mount et al. 1976). It was a potent elixir of alcohol, cocaine, morphine and flavouring. Since many patients vomited on this concoction, antiemetics were added. Happily this type of polypharmacy is now obsolete, but the general idea of combining drugs with different but synergistic mechanisms of action is the accepted best practice for management of neuropathic pain, as recommended by the World Health Organization and many professional associations. If there is a synergistic effect between two drugs, then the dose of each individual drug and, therefore, dose-related side effects are reduced, ensuring a better balance between efficacy and safety. Take the example of drug A, which achieves analgesia at a maximal dose of at 150 mg twice daily, and drug B, which gives sufficient analgesic at a maximal dose of 25 mg twice daily. If the same efficacy is achieved by combining these two drugs at

[18] The Jadad score (Oxford quality scoring system) is used to classify clinical trials into 'rigorous' and 'poor' trials from a trial methodological perspective. A score of 1 or 2 is considered to have poor methodology, 3 is acceptable and scores of 4 and 5 are considered to have good methodology.

half doses, i.e. drug A at 75 mg twice daily and drug B at 12.5 mg twice daily, then this merely shows an additive effect. If, however, comparable or better analgesia is achieved with the two drugs combined at lower dosages—say drug A at 50 mg twice daily and drug B at 10 mg twice daily—then the drugs are synergistic (Smith and Argoff 2011). Another effective means of combining drugs is according to speed of onset and duration of action. If a fast-onset but short-acting analgesic is combined with a slower-onset but longer-acting agent, then the outcome may be a more rapid onset of pain relief and a longer duration of benefit. Combining analgesics also provides a means of transferring patients from one type of monotherapy to another.

There is an active debate as regards whether a stepwise approach should be adopted, i.e. increasing the first drug up to its maximal tolerated dose before then adding a second drug, or whether a combination should be used from the outset. Some argue that the first option is the only way to determine which drug is beneficial. Many favour the second approach because the sooner one reaches acceptable analgesia the better. They also reason that combining different drugs from different classes is in line with the complex pathophysiology of neuropathic pain (Harvey and Dickenson 2008).

Some studies on the safety and efficacy of combination therapy have been published. Gabapentin and nortriptyline, used alone and in combination, in patients with neuropathic pain due to diabetes mellitus or herpes zoster, were studied in a double-blind study. Drug dosages were increased in a stepwise manner, up to the subjectively effective dose or to the maximum tolerated dose, with a limit of 3,600 mg gabapentin daily and 100 mg nortriptyline daily. The visual analogue score[19] was 3.2 (2.5–3.8) for gabapentin, 2.9 (2.4–3.4) for nortriptyline and 2.3 (1.8–2.8) for combination treatment. In other words the pain score with combination treatment was significantly lower than with gabapentin or nortriptyline alone. Furthermore, the mean dose administered was lower in combination therapy compared to traditional monotherapy: for gabapentin 2,180 mg versus 2,433 mg and for nortriptyline 50.1 mg versus 61.6 mg (Gilron et al. 2009).

In a similar study design, gabapentin and morphine were compared and combination therapy was again superior (Gilron et al. 2005). At a maximum tolerated dose of drug, the visual analogue scale pain scores were 5.72 at baseline, 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine and 3.06 with the gabapentin-morphine combination.

In another study a combination of gabapentin and oxycodone was evaluated in patients with neuropathic pain associated with diabetes mellitus (Hanna et al. 2008). Results were also in favour of the combination treatment, with significantly improved pain relief, less use of escape medication,[20] fewer nights of disturbed sleep and fewer discontinuations due to lack of therapeutic effect. In addition, opiate-induced adverse events were not exacerbated by the combination of oxycodone and gabapentin.

Palmitoylethanolamide (600 mg twice daily) was added to pregabalin in previously pregabalin refractory patients; pain decreased from a visual analogue score of above 7 to below 3 (Desio 2010). In a second, open-label trial[17], difficult to treat patients had low-dose oxycodone (5 mg twice daily) added to their palmitoylethanolamide regimen, with an improvement of the visual analogue score from 7 to 2.5 at day 30 (Desio 2011).

16.7.2 Topical Analgesics

A great variety of drugs can be applied as topical formulations, such as creams, gels or ointments. Topical treatment also has the advantage that it is

[19] The visual analogue scale (VAS) is a means of assessing subjective parameters which are difficult to measure. It is a common tool for monitoring intensity of pain. Typically patients are asked to indicate on a line where the pain is in relation to two extremes, for example, between no pain (0) and the worst possible pain (10). The line may be graduated and/or is a known length (typically 10 cm).

[20] Escape medications are analgesics given to patients during clinical trial; if not enough analgesia occurs after a predefined period of time.

relatively cheap and associated with few adverse effects. Even applying creams that do not contain any active ingredients may be of benefit. Applying cream to painful feet has a treatment effect which is more than just placebo. Patients suffering from painful feet tend to avoid touching these body parts; by prescribing a cream the patient may be encouraged to accept the painful appendages as still being part of their body. Topical lidocaine cream (compounded or commercial) is often used to provide relief for peripheral neuropathic pain. In Europe, commercial topical tetracaine and ropivacaine creams are also used. A commercial cream containing adelmidrol, the precursor of the endocannabinoid palmitoylethanolamide, together with a low dose (0.01 %) of capsaicin, is frequently used in various European countries with anecdotal positive effects.

Topical treatment, however, is not supported by well-controlled clinical trials, partly because most drugs used topically are off-licence, and no commercial party will invest in a trial. A trial of commercially available 1.25 mg nitroglycerine patches found that they alleviated pain in spinal cord injury patients suffering from shoulder tendinopathies (Giner-Pascual et al. 2011).

In our clinic we prepare several of our own creams; examples include 5 and 10 % amitriptyline, 5 % baclofen and 10 % racemic ketamine. Of these we most commonly prescribe 5 or 10 % topical amitriptyline cream, which patients rub on the affected region up to three times daily. Patients report onset of pain relief approximately 15 min after application (Liebregts et al. 2011).

16.7.3 Intrathecal Infusions

Intrathecal infusion has been used for many years to treat chronic pain. Spinal infusion systems comprise an implantable pump for controlled drug administration and a catheter through which the medication is infused directly into the cerebrospinal fluid bathing the spinal cord. Implantation of both elements allows for prolonged therapy. Drugs used most often with this system include morphine, bupivacaine, clonidine and baclofen. Intrathecal morphine, at 44 μg/day via pump delivery, in combination with the centrally acting alpha 2 adrenergic agonist clonidine, is reported to have a synergistic analgesic effect in patients with intractable neuropathic pain (Uhle et al. 2000). A 10-year clinical experience of pain reduction using combined intrathecal baclofen-morphine therapy for spinal pain and spasticity suggested little evidence of its efficacy in neuropathic pain and no evidence for any benefit in treating the pain of syringomyelia (Saulino 2012).

16.8 Non-pharmacological Therapies

16.8.1 Acupuncture

Treatments perceived by patients as being the most effective may not be traditional analgesics but rather acupuncture, physiotherapy, exercise, massage therapy and relaxation (Heutink et al. 2011). Chronic pain is one of the most well-documented indications for treatment with acupuncture, with good proof of safety. Moreover, patients seem to prefer acupuncture to pharmacotherapy with co-analgesics like amitriptyline (Heutink et al. 2011). A literature review on the efficacy of acupuncture for spinal cord injury-related conditions, including pain, spasticity and syringomyelia, concluded that acupuncture may be a useful treatment modality (Paola and Arnold 2003). A significant decrease in chronic shoulder pain in 17 spinal cord injury wheelchair users was reported in both the acupuncture and the sham acupuncture groups, with decreases of 66 and 43 %, respectively (Dyson-Hudson et al. 2007). Twice weekly massage or acupuncture was evaluated in 30 individuals with spinal cord injury and neuropathic pain (Norrbrink and Lundeberg 2011). At the end of the 6-week treatment course, 8 out of 15 individuals receiving acupuncture and 9 out of 15 receiving massage reported an improvement; the positive effect from acupuncture lasted longer. Unfortunately, well-controlled, full-powered and methodologically sound trials evaluating the effects of acupuncture for spinal cord injury neuropathic pain have not been performed to date.

16.8.2 Massage and Other Complementary Therapy

There is very little evidence on the effects of complementary therapy in central neuropathic pain. A review of the literature, to evaluate the usefulness of a number of techniques for spinal cord injury, including physiotherapy, heat therapy, ice therapy, cold therapy, massage, ultrasound and occupational therapy, concluded that there was not enough evidence to recommend any of these methods (Fattal et al. 2009). Many patients nevertheless prefer these interventions, especially massage, over pharmacotherapy (Fattal et al. 2009; Heutink et al. 2011). A positive benefit from massage for spinal cord injury and neuropathic pain has also been reported (Norrbrink and Lundeberg 2011). Since these therapies are generally free from troublesome adverse effects, they could certainly be considered before using more invasive therapeutic approaches.

16.8.3 Psychological Interventions

Data from the Coping with Neuropathic Spinal Cord Injury Pain (CONESCI) trial indicated that a multidisciplinary cognitive behavioural treatment programme is useful, to alleviate neuropathic pain associated with spinal cord injury (Heutink et al. 2011). The intervention consisted of educational, cognitive and behavioural elements. A significant decrease in pain intensity, pain-related disability, anxiety and increased participation in activities was seen in the intervention versus the waiting list control group (61 patients).

16.8.4 The Placebo Response

In studies on analgesic drugs, a 30 % rate of positive response to placebo treatment has been reported (Beecher 1955). For neuropathic pain the placebo effect is lower but still significant. Data from 14 studies, analysing the efficacy of gabapentin versus placebo in postherpetic neuralgia, diabetic neuropathy, cancer-related neuropathic pain, phantom limb pain, Guillain–Barré syndrome and spinal cord injury pain, reported an average placebo response of 19 % (Wiffen et al. 2005). Frustrating as the placebo response might be in clinical trials, it should not be forgotten that it can be exploited as a benign and potentially effective part of the therapeutic process (Dumitriu and Popescu 2010).

16.9 Neurostimulation Techniques

Neurostimulation therapies are considered an option for treatment of severe neuropathic pain that is refractory to pharmacological treatment (Table 16.4). Treating chronic pain using electricity and magnetism is not a new technique as electromagnetic therapies emerged as medical interventions for pain following the development of the first electricity accumulator, the Leyden jar, in 1745. Electro-acupuncture started in the early nineteenth century, and peripheral nerve stimulation became very popular at the end of the ninetieth century. Spinal cord stimulation started to gain momentum simultaneously with the emergence of the gate theory of pain, which gave a more solid scientific basis for this treatment (Melzack and Wall 1965). Increasingly, neurostimulation became considered as a more viable option than the neuroablative methods.

It should, of course, be remembered that all of these interventions also have a significant placebo effect. Furthermore, the potential adverse effects of the more invasive types of neurostimulation must be carefully considered, before giving a balanced judgment as to whether any one method is justified for a given patient.

Techniques such as transcutaneous electrical nerve stimulation and percutaneous electrical nerve stimulation are safe, if applied correctly. They are easy to administer and relatively inexpensive. They have not, however, been subjected to rigorous efficacy studies. A randomised, double-blind, placebo-controlled parallel study in 225 patients analysed whether repetitive and cumulative exposure to low-frequency pulsed electromagnetic fields was safe and effective,

Table 16.4 Neurostimulation techniques available—listed in order from non-invasive to those requiring surgery

Transcutaneous electrical nerve stimulation
Photon stimulation
Pulsed electromagnetic fields
Repetitive transcranial magnetic stimulation
Transcranial direct current stimulation
Electro-acupuncture
Percutaneous electrical nerve stimulation
Spinal cord stimulation
Motor cortex stimulation
Deep brain stimulation

in diabetic painful neuropathy (Weintraub et al. 2009). The results were not impressive; there were no significant differences between pulsed electromagnetic fields and sham groups.

16.9.1 Photon Therapy

The finding that low-energy stimulation of tissues, by lasers, could enhance wound healing led to the development of laser therapy. Photon stimulation is a modern version of this treatment and is sometimes referred to as pulsed infrared light therapy, or photobiomodulation. Light, in the near-infrared wavelengths (750–1,300 nm), is delivered by arrays of light-emitting diodes. It penetrates skin and tissue to a depth of approximately 2–3 cm. A randomised, double-blind, placebo-controlled trial, in patients with diabetic neuropathy, who received photon stimulation versus sham treatment, demonstrated a decrease in pain intensity and pain quality scores, with improvements in pain relief, sensation and quality of life. It is questionable if the study had enough power as power calculations and expected magnitude of effect[21] were not included (Swislocki et al. 2010).

16.9.2 Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation is thought to suppress brain excitability non-invasively and to do so for a period beyond the duration of the session, although just how long this period can be remains unclear. Transcranial direct current stimulation is a more recent variation. Repetitive transcranial magnetic stimulation has been used and evaluated in a variety of chronic pain states, from fibromyalgia to central pain secondary to spinal cord lesions (O'Connell and Wand 2011). A meta-analysis of all randomised controlled trials (1 parallel, 4 crossover) suggested that repetitive transcranial magnetic stimulation is more effective for centrally than for peripherally originating neuropathic pain (Leung et al. 2009). This would seem plausible, but no rigorous comparison studies have been conducted. Drawing conclusions about the effectiveness or otherwise of repetitive transcranial magnetic stimulation is hampered by suboptimal study methodology. Shortcomings include small sample sizes, failure to include power calculations, estimated magnitude of effect,[21] intention to treat analysis,[22] cost–benefit analysis,[23] information on NNT and failure to take account of the placebo effect. Furthermore, the follow-up time in all studies is short, the longest being 1 month (O'Connell et al. 2011). Therefore, all the studies reported so far can only be regarded as pilot

[21] Estimated magnitude of (treatment) effect is used in power analysis and to calculate the study population size. The effect size should represent the smallest clinically significant effect and will vary depending on the severity of the illness. For example, a drug which decreases mortality by 10 % has more potential benefit than a drug which decreases signs of neuropathic pain by 10 %. The smaller the treatment effect, then the larger the population size required to have confidence in the results.

[22] The intent to treat (ITT) analysis is a statistical procedure employed to avoid misinterpretation of results, for example, because of patient dropout. The principle of ITT is that all study participants are included in the final analysis whether or not they completed the trial. This is particularly important because if a treatment is ineffective, then more severely affected patients are more likely to drop out. If those patients are not included, then the treatment may be interpreted to be more beneficial than it actually was.

[23] Cost–benefit analysis is a process by which the total expected cost of each treatment option is compared to the total expected benefits in other words establishing if the benefits outweigh the costs and by how much and therefore whether it is justifiable. This can also provide a basis for comparing different treatments.

studies, and if repetitive transcranial magnetic stimulation was a new drug, it would not have been licensed for the treatment of chronic neuropathic pain. The general feeling in the research community is that repetitive transcranial magnetic stimulation creates a significant decrease in pain but that the magnitude of the effect is small and, based on the published literature, its clinical usefulness is debatable. Most probably patients need repeated weekly sessions, and this must be taken into account when evaluating the economic cost of this intervention.

16.9.3 Spinal Cord Stimulation

Spinal cord stimulation has shown value in the treatment of selected types of chronic pain syndromes, such as failed back surgery syndrome (Sears et al. 2011) and peripheral neuropathic pain (Sokal et al. 2011). Spinal cord stimulation is sometimes used for complex regional pain syndromes and phantom limb pain, but it does not alleviate acute nociceptive pain. Worldwide, more than 30,000 spinal cord stimulation systems are currently implanted every year (Craig et al. 2007). The relative effectiveness of this method, compared with conventional, nonsurgical central neuropathic pain management, has not been assessed in a placebo-controlled, randomised trial setting. The 'Prospective Randomised Controlled Multicentre Trial of the Effectiveness of Spinal Cord Stimulation' (PROCESS) recruited 100 patients with failed back surgery syndrome and randomly assigned then to receive spinal cord stimulation plus conventional medical management or conventional medical management alone, for at least 6 months (Kumar et al. 2007). Conventional management included oral medications such as opioids, nonsteroidal anti-inflammatory drugs, antidepressant and antiepileptic drugs, nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy and chiropractic care. At 6-month follow-up, 48 % of the spinal cord stimulation group versus 9 % of the conventional medical management group achieved 50 % or more limb pain relief. The complication rate was high, with 32 % of spinal cord stimulation patients experiencing a total of 40 device-related complications, and 21 reoperations were required. The study was not blinded and there was no independent assessment. The presence of allodynia and/or hyperalgesia was the best predictor for long-term success in a recent retrospective study of 244 patients who underwent spinal cord stimulation (Williams et al. 2011). Data is not available for appropriateness or success of using spinal cord stimulation for syringomyelia.

16.9.4 Motor Cortex Stimulation

Neurostimulation of the motor cortex, for a disease-causing sensory disturbance, may seem illogical, but stimulation of the motor cortex can, in fact, give better results than the stimulation of the sensory cortex. Indeed, the latter may sometimes cause pain to worsen. Motor cortex stimulation is used more frequently than deep brain stimulation,[24] mainly because it is less invasive and less complex. It might also have a wider range of indications (Nguyen et al. 2000, 2008). The mechanism by which motor cortex stimulation affects neuropathic pain is unproven. It has been suggested that it induces endogenous opioid secretion (Maarrawi et al. 2011), and functional imaging has suggested that motor cortex stimulation triggers rapid and phasic activation in the lateral thalamus, which over a delayed time course of hours leads to a cascade of events in medial thalamus, anterior cingulate/orbitofrontal cortices and periaqueductal grey matter (Garcia-Larrea and Peyron 2007). There is also modulation of the spinal dorsal horn neuron activity (Senapati et al. 2005; Pagano et al. 2011). Small controlled pilot trials have suggested that motor cortex stimulation may be effective for treatment of various types of neuropathic pain, especially trigeminal neuralgia and thalamic pain syndrome. The use of motor cortex stimulation in pain states such as in

[24] Deep brain stimulation (DBS) involves surgical implantation of a stimulator which sends electrical impulses to electrodes implanted in deep brain structures such as the internal capsule, ventral posterolateral nucleus and ventral posteromedial nucleus and interferes with neural activity.

syringomyelia has not been explored, but it most probably this intervention will not lead to pain reduction, as the major 'lesion' is spinal.

Conclusions

Central neuropathic pain is difficult to treat, and controlling pain from syringomyelia remains a challenge. The best nonsurgical therapy is multimodal, and the following is approach is recommended:

(a) Combination therapy (2, 3 or 4 agents) of the following co-analgesics, slowly increasing the dose: amitriptyline (10–30 mg once daily before sleep), together with gabapentin (300–600 mg three times daily) or pregabalin (75 mg twice daily) and oxycodone (starting at 5 mg twice daily) and/or any other co-analgesic such as clonazepam. The question whether to take a stepwise approach or polypharmacy from the start has yet to be resolved.

(b) Topical analgesic self-compounded or commercial creams can be considered.

(c) Add second-line co-analgesics such as phenytoin or palmitoylethanolamide. Even though these compounds have not been proven efficacious in vigorous clinical trials, individual patients may respond.

(d) Add acupuncture or massage and/or transcutaneous electrical nerve stimulation or percutaneous electrical nerve stimulation.

(e) In severe refractory cases intrathecal infusions and neuromodulation techniques can be explored. At present spinal cord stimulation seems the most appropriate. There is little evidence to support the use of repetitive transcranial magnetic stimulation. Deep brain stimulation should only be considered when less invasive interventions fail.

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