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Pain in neurological disease

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KEY LEARNING POINTS

- Pain in neurologic disease is common and may be severe.
- The clinical features of pain in neurologic disease are seldom disease-specific.
- Pain presentations in neurologic disease are diverse, reflecting diverse mechanisms.

- Nociceptive, as well as neuropathic, pain commonly occurs.
- Individual patients may have more than one pain phenotype.
- For each pain phenotype, the physiological nature of the generation of pain has implications for treatment.

INTRODUCTION

There is a commonly held view among many physicians (including some neurologists) that pain in the context of neurologic disease is rare, but when it does occur it is neuropathic in nature and extremely resistant to treatment. This chapter will show that the reality is that pain in neurologic disease is very common, multifactorial, and protean in its manifestations.

Despite its diversity, most pain in neurologic disease falls into one of two major mechanistic categories, and some other pain forms a third category:

1. Neuropathic pain resulting directly from the effects of the disease on somatosensory neurons – peripheral or central (for example, burning limb pain in syringomyelia, postherpetic neuralgia (PHN)).

2. Nociceptive pain resulting directly or indirectly from the motor effects of the disease on the locomotor system; activating the familiar nociceptive system responding to tissue damage (for example, painful lower limb muscle spasm in multiple sclerosis, "frozen shoulder" poststroke).

A third category can also be considered:

3. Neuropathic pain resulting from the effects of the disease on peripheral nerves/roots, secondary to motor changes (for example, meralgia paresthetica in spastic paraplegia, radiculopathy in cervical dystonia).

These distinctions are of practical value, as the rational management of each is different. In many conditions where both motor and sensory pathways are damaged

(e.g. multiple sclerosis), combinations of two or all three types of pain are seen. It follows that an assessment of the nature of pain in an individual with neurologic disease relies upon an assessment of the pathophysiologic effects of that disease in that individual. Definitive diagnosis of the primary condition *per se* will not usually clarify this.

The prevalence of chronic pain across the spectrum of neurologic disorders is unknown. However, the data available from two common disorders – multiple sclerosis and Parkinsonism – suggest that the scale of the problem of pain in those two diseases is almost certainly underestimated, which suggests that the problem is also likely to be underestimated in less common disorders.

A classification of neurologic diseases is presented in **Table 24.1**. For each category, one or two representative examples of painful disorders are given. However, it may be argued that traditional classifications such as this have limited utility in pain evaluation, in that there is usually no clear link between the pathologic nature of the disease and the presence (and type) of pain. It may be more useful to consider categories of painful disorders presenting to neurology clinics, as proposed by Cervero and Jensen (see **Table 24.2**). In some neurologic disorders, pain is a well-recognized and predominant symptom and may be a prerequisite to diagnosis. Several such disorders are deservedly allocated chapters of their own in this volume and will be discussed little, if at all, in this chapter. These are:

- trigeminal neuralgia (Chapter 35, Facial pain);
- peripheral neuropathy (Chapter 25, Peripheral neuropathies);

- postherpetic neuralgia (Chapter 32, Herpes zoster pain including shingles and postherpetic neuralgia);
- complex regional pain syndrome (Chapter 27, Complex regional pain syndromes).

Other topics that to some degree overlap with this chapter and are covered elsewhere are:

- management of painful spasticity (Chapter 33, Management of painful spasticity);
- postamputation pain (Chapter 31, Postamputation pain);
- central pain syndromes (Chapter 28, Central neuropathic pain: syndromes, pathophysiology, and treatments).

It is not possible to provide a comprehensive list of every neurologic disease that may give rise to pain in this chapter.

What follows may be considered an overview of the scope and nature of pain in neurologic disease, largely exemplified by two conditions which are common and which illustrate some important general points – multiple sclerosis and parkinsonism. Additional brief notes are included on Guillain–Barré syndrome and dystonia.

MULTIPLE SCLEROSIS

There are two reasons to choose multiple sclerosis (MS) as a representative model on which to base generalizations about pain in neurologic disease.

Table 24.1 A suggested classification of neurological diseases associated with pain.

Etiologic category	Example	Nature of pain (location of lesion)
Hereditary	DMD	Nociceptive (muscular)
	HMSN	Either nociceptive or neurogenic (sensorimotor neuropathy)
Metabolic	DM	Neurogenic (small-fiber neuropathy)
Infective – viral	Herpes zoster	Neurogenic (ganglioneuropathy)
Infective – bacterial	Syphilis (Tabes dorsalis)	Neurogenic (myelopathy)
Inflammatory	Guillain–Barré syndrome	Neurogenic (neuropathy)
Structural/degenerative	Intervertebral disk herniation	Neurogenic (compressive radiculopathy)
Developmental	Syringomyelia	Neurogenic (myelopathy)
Vascular	Cerebral infarct	Neurogenic (central)
Demyelination – central	MS	Neurogenic (central)+nociceptive (musculoskeletal)
Demyelination – peripheral	AIDP	Neurogenic
Movement disorders – hypokinetic	PD	Nociceptive+? neurogenic (musculoskeletal+? central)
Movement disorders – hyperkinetic	Primary dystonia	Nociceptive (musculoskeletal)
Trauma	Spinal cord transection	Neurogenic (myelopathy)
Iatrogenic	Radiation plexopathy	Neurogenic (plexus)
Neoplastic	Intracerebral glioma	Nociceptive (headache ↑ ICP)

AIDP, acute inflammatory demyelinating polyneuropathy; DM, diabetes mellitus; DMD, Duchenne muscular dystrophy; HMSN, hereditary motor and sensory neuropathy; ICP, intracranial pressure MS, multiple sclerosis; PD, Parkinson's disease.
NB Some overlap between etiologic categories occurs. Guillain–Barré syndrome/AIDP is given as an example; it may be classified either as inflammatory or peripheral demyelinating.

Table 24.2 Painful conditions presenting to neurology clinics.

Painful conditions	
Pain after nerve injury	Complex regional pain syndrome
	Painful entrapment disorders
	Pain after surgical intervention
Facial pain	Trigeminal neuralgia
	Atypical facial pain
Painful neuropathies	Painful diabetic neuropathy
	Other painful polyneuropathies
	Postherpetic neuralgia
	Postamputation pain
Central neuropathic pain	Spinal cord injury pain
	Syringomyelia
	Central poststroke pain
	Pain in multiple sclerosis
	Pain in Parkinson's disease
Others	Fibromyalgia
	Chronic low back pain
	Whiplash
	Pain in dementia

First, it is common and has a high profile in the eyes of the lay public as well as the medical establishment, with vigorous support groups funding research and disseminating information about the disease. One might therefore expect reasonably accurate epidemiologic data to be available. Despite this, the prevalence of chronic pain as a major problem for persons with MS is widely underestimated. Until recently, the disease was regarded as typically painless, and described as such[1] in authoritative texts of neurology and reviews. Even now, the myth persists; a contemporary textbook of neurology for medical generalists states that pain in MS is so rare that the diagnosis should be questioned in its presence.[2]

Second, the disease can give rise to a wide variety of pains, both neuropathic and nociceptive, encompassing most of the pain patterns observed across the entire spectrum of neurologic disorders.

The nature of the disease

MS is characteristically a disease of young adults. The etiology remains unknown but both genetic and environmental factors probably contribute; the histopathologic lesion is a central nervous system (CNS) perivenular inflammatory demyelination consistent with an autoimmune response directed at myelin antigens. These lesions can occur almost anywhere in the CNS, accounting for the great diversity of clinical presentation seen in this disease. The clinical course is notoriously variable, but is typically relapsing/remitting with a tendency to cumulative

neurologic deficit as the disease progresses. Optic neuritis or peripheral paresthesiae are the most common presenting features. Rarely, pain is the first clinical manifestation of the disease.[3] Motor and/or cerebellar symptoms tend to present later and are associated with a poorer prognosis. Approximately one-third of patients do not develop permanent functional impairment and less than one-third will become severely disabled. Typical features of the severe advanced case include spastic paraparesis or tetraparesis, variable somatosensory deficits, cerebellar ataxia with scanning dysarthria, incontinence, disorders of mood, and cognitive impairment.

Epidemiology

In northern Europe and North America, the incidence rates and prevalence of MS are in the order of 4–8 and 60–100 per 100,000, respectively. It is therefore about ten times as common as syringomyelia or myasthenia gravis.

Although the epidemiology of pain in the disease is less certain, several surveys suggest that a majority of sufferers experience pain of at least moderate severity.[4, 5, 6, 7, 8, 9] Moreover, these studies show a striking concordance in the breakdown of the distribution and probable cause of the reported pain patterns. A recent publication indicates that pain in MS is a major problem in registered sufferers in the community and not just in hospital clinic attenders (who may be more severely affected).[10] The most familiar type of pain quoted in neurology textbooks – trigeminal neuralgia – is relatively rare.[4, 5, 6, 7, 8, 9, 11] By contrast, myelopathic pain involving the lower limbs is common, as is pain of nociceptive musculoskeletal origin. This last feature should come as no surprise, as the consequences of the disease on motor function might be expected to cause nociceptive pain directly from spastic muscles and their mechanical effects on neighboring structures. In general, pain in MS appears comparable in severity to that of rheumatoid and osteoarthritis, and its intensity correlates with reduced quality of life.[12]

Patterns of pain presentation in multiple sclerosis

A suggested approach to the analysis of pain in MS is outlined in **Box 24.1**. It is intended to encourage the clinician to consider the pathophysiologic basis of the pain before considering which treatment modalities are most appropriate. Pains of primary neurogenic origin are divided into paroxysmal and nonparoxysmal. Paroxysmal pains may be more likely to respond to anticonvulsant drugs, whereas ongoing central pains may be more likely to respond to other groups of drugs such as antidepressants and *N*-methyl-D-aspartic acid (NMDA) receptor antagonists, and in some cases opioids.

Box 24.1 Pain classification in multiple sclerosis

- Pains of primary neurogenic origin
  - Paroxysmal
    - Trigeminal neuralgia
    - Lhermitte's phenomenon
    - Seizures
- Painful spasms
- Visceral pain
  - Nonparoxysmal central pain
- Nociceptive musculoskeletal pain
  - Chronic back pain
  - Peripheral muscle spasticity/spasm
- Miscellaneous
  - "Mechanical" neuropathic
- Nonspecific exacerbating factors
  - Infection
  - Iatrogenic

PAINS OF PRIMARY NEUROGENIC ORIGIN

Paroxysmal

Trigeminal neuralgia occurs in multiple sclerosis approximately 300 times more often than in the general population. It is generally similar in its presentation to the idiopathic condition, but tends to occur at a younger age and is more likely to be bilateral (which is extremely rare in the idiopathic disorder). It is generally responsive to treatment along similar lines to idiopathic tic douloureux,[13] although microvascular decompression (in a small series) appeared less effective,[14] and there also appears to be relative refractoriness to neurolytic surgical procedures.[15] A 1994 study[7] suggests a prevalence in the order of 5 percent (rather higher than formerly believed). Unlike most pain syndromes in MS, trigeminal neuralgia may be a presenting symptom of the disease, and the underlying diagnosis should therefore be considered particularly in a young patient or one with bilateral symptoms. The clinical manifestations and treatment of trigeminal neuralgia are discussed at greater length in Chapter 35, Facial pain.

Lhermitte's phenomenon is a classical finding in MS. It consists of rapidly evolving paresthesiae or dysesthesiae, provoked by neck flexion, and typically spreading down the back and into the extremities. It is suggested that traction on the dorsal columns actively involved in the inflammatory process is the trigger. A recent study indicates that it may occur in over 41 percent of individuals with MS at some point in the course of their disease, and is significantly correlated with magnetic resonance imaging (MRI) signal change in the cervical cord.[16]

Epileptiform seizures are rare in MS, and in general are a rare cause of pain. However, a syndrome of spreading dysesthesiae and muscle spasm, either spontaneous or evoked by trivial stimuli such as light touch, active or passive movement, or a startling event, is recognized. The prevalence of this symptom complex varies in the limited literature describing it.[7, 17]

Nonparoxysmal central pain

This is probably the most common neurogenic pain manifestation in MS. It is typically burning and/or aching in quality[4, 5, 7, 11] and often anatomically extensive (e.g. from the waist down). Although it is impossible to exclude supraspinal mechanisms in the genesis of pains of this sort, it seems likely that demyelinating myelopathy is the primary cause in most cases. This may be inferred from the similarity of the pain to that described in many cases of traumatic spinal cord damage with no evidence of rostral neural injury.[18] This type of pain is much more common in the lower extremities than the upper. A characteristic complaint is of a sensation of constriction of the painful territory, like wearing a tight corset or an undersized boot. Allodynia undoubtedly occurs but is uncommon in the author's experience and most published material.

Nociceptive musculoskeletal pain

There is no doubt that many patients with MS suffer pains in this category – perhaps in the order of 20 percent – and that such pains are more troublesome than in the general population. It seems obvious that many patients with myelopathy and/or cerebral disease will be susceptible to pains of both true central and peripheral nociceptive nature, the latter consequent on spasticity and immobilization. In some cases, analysis of the separate pain components may be difficult on clinical grounds. Nevertheless, it seems desirable to try to separate central neurogenic and peripheral nociceptive components of pain because of the different implications for treatment.

Painful spasticity of muscles, particularly of the spinal muscles and muscles of the lower limbs, is a common problem in advanced MS.[13] The management of painful spasticity is covered elsewhere in this volume (Chapter 33, Management of painful spasticity).

Low back pain is common and probably the consequence of a combination of factors. Lumbar paraspinal muscle spasticity may result directly in muscular pain and also produce increased mechanical stress on nonmuscular components of the spine (such as ligaments, disks, and zygapophysial joints). Additionally, the immobilization and weakness that occurs with advancing disability may predispose to musculoskeletal spinal pain in the same way as is believed to occur in patients with chronic back pain without neurologic disease.

Miscellaneous

"Mechanical neuropathic"

On the basis of the above, one would expect lumbar radiculopathic pain to be more common in people with MS than in the general population. Analysis of pain

patterns in the aforementioned prevalence studies identifies pain of this type. The author has seen a number of patients with meralgia paresthetica associated with flexor spasms of the thigh.

Nonspecific exacerbating factors

Infections in persons with MS may worsen spasticity and spasm.[14] Pressure sores may be painful although typically they are not.

Iatrogenic

This includes pain, for example, related to surgical procedures such as intrathecal pump implants.

ACUTE INFLAMMATORY POLYNEUROPATHY (GUILLAIN–BARRÉ SYNDROME)

Guillain–Barré syndrome (GBS) is an acute onset, predominantly motor polyneuropathy with an immunologic basis. There is often an antecedent history of infection or immunization but in many cases no such trigger can be identified. Despite the predominance of motor over sensory deficit, pain is common (approximately 50–70 percent of cases in a fairly recent review[19]) and may manifest itself in a wide variety of ways including both neurogenic and nocigenic presentations. A more recent prospective study suggests an even higher frequency (nearly 90 percent), with nearly 50 percent reporting pain "distressing" or worse.[20] Pain can be a prominent symptom even in otherwise mild cases.[21] The most commonly encountered pains were deep, aching back/leg pain and dysesthetic extremity pain. Although complete recovery has widely been considered to be the rule, more recent data suggest that many patients report aching and cramping pain years after the onset of symptoms, that the pain is correlated with persisting sensory, but not motor, deficits,[22] and gabapentin appears to be effective.[23, 24][II]

MOVEMENT DISORDERS

Many neurologic diseases may result in disordered movement. However, those conditions traditionally grouped together under the heading "movement disorders" comprise a collection of disorders in which disease or dysfunction of the extrapyramidal system is the principal feature.

In common with multiple sclerosis, it seems likely that pain is underestimated in these conditions, although there are fewer data available from the medical literature to support this assertion. The likelihood of nociceptive pain in patients with impaired/involuntary movement seems intuitively obvious, but there is evidence of neuropathic pain in some of these disorders as well, focusing attention on involvement of sensory, as well as motor tract pathology.

Movement disorders can be subdivided into two categories: **hypokinetic**, characterized by impaired volitional

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Box 24.2 Causes of parkinsonism

- Parkinson's disease
- "Parkinson plus" syndromes
  - Progressive supranuclear palsy
  - Multiple system atrophy
  - Spinocerebellar ataxias
  - Corticobasal degeneration
- Other
  - Drug-induced/toxic
  - Vascular
  - Infectious/transmissible (including Creutzfeldt–Jakob disease)

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movement, of which parkinsonism is much the commonest (see **Box 24.1**), and **hyperkinetic**, characterized by involuntary movements of various types (see **Box 24.2**).

Notes on some terms relating to movement disorders

A number of descriptive terms are used to differentiate patterns of disordered muscle tone and movement, and may give rise to confusion among non-neurologists. Some of these terms, and their corresponding meanings, are listed below:

- Spasticity is the type of muscle hypertonia seen following a lesion of the corticospinal tract. Resistance to passive movement of an affected limb is maximal at its outset and reduced once movement is initiated ("clasp-knife" effect). Tendon reflexes are increased. The Babinski response is extensor. Clonus (rhythmic repetitive contractions) may occur.
- Rigidity is a uniform increase of muscle tone seen in extrapyramidal lesions, notably parkinsonism. Resistance to passive movement is evenly encountered throughout the range ("lead-pipe" rigidity). In cases where tremor is superimposed, rapid fluctuations in the degree of resistance may be felt ("cog-wheel" effect).
- Dyskinesia is a term used to cover the range of involuntary movements seen in extrapyramidal disturbance:
  - chorea: jerky, quasi-purposive movements, typically of the face/upper limbs;
  - athetosis: slower, more writhing movements;
  - hemiballismus: violent excursions of an entire limb;
  - dystonia: sustained, often repetitive, muscle contraction, typically giving rise to twisting movements and/or abnormal postures;
  - tremor: rhythmic rapid oscillations;
  - myoclonus: brief isolated jerks which may involve part of a muscle, an entire muscle, or several muscle groups.

PARKINSONISM

The distinction should be made between the broad clinical syndrome of bradykinesia, rigidity, and tremor (parkinsonism) – which may result from several causes – and the idiopathic condition, Parkinson's disease (PD). Causes of parkinsonism are listed in **Box 24.2**. The relevance of the distinction between these conditions from the pain management perspective is that some of these conditions may be associated with somatosensory deficit, increasing the likelihood of neuropathic pain (although this has been proposed in idiopathic PD as well).

The nature of the disease

In contrast to MS, PD is typically a disorder of the middle-aged and elderly. Some secondary causes of parkinsonism may present earlier. Pain in PD has been the subject of a recent review article.[25]

Parkinsonism provides a useful second model of a neurologic disorder in which chronic pain is both common and underestimated.[26, 27] The etiology very probably involves both genetic and environmental factors; various toxic environmental chemicals have been implicated in the disease, as well as familial clustering of cases consistent with autosomal dominant inheritance. Concerning the pathology, degeneration of dopaminergic neurons of the substantia nigra is the hallmark of the idiopathic disease. The prevalence in the USA is in the order of 0.4 percent overall, increasing to 1 percent in individuals over age 55.

Parkinsonian syndromes classically present with a triad of features:

1. bradykinesia – slowness of spontaneous movement;
2. rigidity;
3. tremor – typically at rest.

Of this triad of components, it is usually the first two which are associated with pain.

PD is now hardly ever seen in its unmodified form in advanced cases as treatment with L-dopa and other dopaminergic drugs is more or less universal in developed countries. While L-dopa therapy has dramatic therapeutic benefit early on, its continued use ultimately typically gives rise to a state of clinical fluctuation between bradykinesia/rigidity and dyskinesia ("on–off" phenomenon). In this state, the parkinsonian patient may exhibit pain associated with both hyperkinetic and hypokinetic disorder.

Although pain has long been recognized in PD, there were few data on which to base estimates of its prevalence until the important paper by Snider et al. in 1976.[28] On the basis of this study, the prevalence is probably in the order of 40–50 percent (similar to MS), although the authors quote a lower figure on the basis of excluding burning sensations and also muscular pains clearly resulting directly from increased tone. A later study by Goetz et al.[29] closely mirrors these findings; however, Snider et al. attribute much of the limb pain to central mechanisms, whereas Goetz's paper places more emphasis on nociceptive pain attributable to the effects of the disease on muscle tone, movement, and posture.

Although Snider et al. cite a lack of correlation between muscle hypertonia and pain as evidence of a central cause for the pain, it is usually worse on the side with most motor dysfunction, and the character of the pain suggests a musculotendinous origin. In advanced treated cases with an "on–off" pattern, pain may be a feature of both the "on" and the "off" phase. Sufferers typically complain of a constant aching, cramp-like discomfort of the muscles while "off," and "muscle-strain" pain while "on."

However, some pains cannot be explained on this basis and seem likely to be neuropathic in nature, such as the reports of oral/genital pain.[30, 31] A fairly recent study suggests that in approximately 8 percent of parkinsonian patients with pain, the pain is neuropathic.[27] A small proportion of patients with PD have sensory symptoms (including pain) which precede any clinically apparent motor effects of the disease. Burning pain is often, though not invariably, related to L-dopa therapy.

There is evidence that the prevalence of pain in multiple system atrophy, the most common cause of secondary parkinsonism, is similar to that of PD.[32]

Quinn et al.[33] have proposed a classification of pain in Parkinson's disease largely based on its relation to medication, although this sheds no light on putative pain mechanisms.

HYPERKINETIC DISORDERS

Hyperkinetic disorders are categorized in **Box 24.3**. Usually, pains in these conditions are considered to be nociceptive and muscular/arthralgic in origin. However, a recent paper on pain in spasmodic torticollis,[34] the most frequent form of cervical dystonia, questions this and suggests that central mechanisms may be an important cause. This suggestion is largely based on the observation

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Box 24.3 Classification of hyperkinetic disorders

- Chorea/athetosis/hemiballism
- Dystonia
- Myoclonus
- Tics

that the correlation between markedly hypertonic muscles and pain in those muscles is weak, rather than on any positive evidence of central sensory disturbance.

Neuropathic pain may undoubtedly occur if sensory pathways are damaged, in which case clinical evidence of such damage should be apparent. Certainly, dyskinesia giving rise to abnormal mechanical stress on the axial skeleton may cause radicular pain. In a study of cervical dystonia, Jancovic et al.[35] reported evidence of secondary radiculopathy in 32 percent of their patients.

MANAGEMENT OF PAIN IN NEUROLOGIC DISEASE

General considerations

Effective treatment of pain in neurologic disease is seldom, if ever, disease specific. Burning central neuropathic pain is probably as likely to respond to a tricyclic antidepressant whether the disorder responsible is syringomyelia, multiple sclerosis, or spinal cord injury. Conversely, an antiepileptic drug that successfully treats trigeminal neuralgia in a patient with MS may be completely ineffective for lumbar back pain in the same patient. Rational management of pain in any patient with neurologic disease must start with an attempt to identify the nature of the likely pathophysiology giving rise to the pain (or pains).

The following fundamental questions may form a useful starting point:

- Is the pain nociceptive or neurogenic?
- If neurogenic, is it central or peripheral?
- If peripheral, is it directly due to the primary disease process or the result of motor dysfunction?
- If nociceptive, is there spasticity, rigidity, or dyskinesia?

Almost all treatment modalities advocated and practiced in the treatment of pain in neurologic disease are described and discussed at length in the relevant chapters on treatments elsewhere in this volume. They will therefore be considered relatively briefly here, with the focus of attention on their use in the context of neurologic disorders and neuropathic pain states. As in other chapters, they will be discussed under the following headings:

- Pharmacologic;
- Physical treatments;
- Invasive treatments;
- Surgical treatment;
- Psychologic treatment;
- Alternative medicine.

The evidence scores given for each treatment modality generally refer to efficacy in treating neuropathic pain.

Pharmacologic

The pharmacologic treatment of neuropathic pain, including topical as well as systemic administration, has been the subject of a recent publication by a Task Force of the European Federation of Neurological Societies.[36]

TOPICAL TREATMENTS

Nonsteroidal anti-inflammatory drugs, capsaicin, and local anesthetics may be useful in clinical situations where pain is evoked or exacerbated by superficial nociceptors (or in some cases non-nociceptive afferents). Topical treatments are discussed in depth in Chapter 17, Topical analgesics for neuropathic pain, and their use in postherpetic neuralgia in Chapter 32, Herpes zoster pain including shingles and postherpetic neuralgia.

OPIOIDS

Some controversy still exists concerning the value of potent opioids such as morphine in chronic non-malignant pain generally, as well as whether these drugs are effective in neuropathic pain. These issues are discussed in depth in Chapter 16, Opioids and chronic noncancer pain, but it is perhaps appropriate to cite here one well-conducted study demonstrating efficacy of opioids in neuropathic pain,[37][II] and another publication[38] reporting little or no benefit.

A reasonable interpretation of the medical literature overall addressing this issue is that there are some individual patients with individual neuropathic pains that are opioid responsive and others which are not. Whether or not a given individual will prove responsive to this group of drugs is not reliably predictable on the basis of pathologic diagnosis. A suggested practical management approach is to offer patients a limited trial of opioid therapy if it seems justified by clinical need, only continuing treatment in the long term if the trial results in substantial symptomatic and functional benefit without unacceptable side effects.

In general, nociceptive pain in neurologic disease should respond to opioids in a manner similar to that in the patient without neurologic disease.

ANTIDEPRESSANTS

The use of antidepressants in neuropathic pain has been subject to recent systematic review.[39, 40][I] This can be briefly summarized by stating that there was clear benefit compared with placebo in a variety of conditions, including diabetic neuropathy, PHN, and central pain. The number needed to treat (NNT) for pooled data was between two and three. Amitriptyline, in particular, appears effective in central poststroke pain.[41][I] Selective

serotonin-reuptake inhibitors (SSRIs) generally appeared less effective than tricyclic antidepressants (although they were associated with fewer side effects), suggesting that the noradrenergic action of some tricyclics may be important for their analgesic effect. In this review, the character of the pain was not predictive of response to these drugs, and favorable response was typically achieved in a few days.

Beneficial effects of antidepressants on pain have been demonstrated in a wide variety of pain syndromes, including rheumatoid arthritis, low back pain, tension headache, and cancer pain. It is clear that these drugs may be helpful for both neurogenic and nociceptive pains. It is reasonable to try them in patients with neurologic disease whose pain falls into either category or both categories. The evidence of benefit in MS is conflicting. Clifford and Trotter[11][V] report relief of pain by tricyclic antidepressants in more than 50 percent of their series of patients, whereas Moulin et al.[5][V] found this group of drugs relatively ineffective.

ANTICONVULSANTS

The use of anticonvulsants in chronic pain has also been subject to fairly recent systematic review.[42][I]

To summarize the findings, the majority of studies were of neuropathic pain states, with three examining diabetic neuropathy. Results were conflicting. Overall, NNT for both effectiveness and adverse effects were similar to the corresponding figures for the antidepressants. The relatively new adjunctive anticonvulsant gabapentin was not included in this review, but a number of subsequent publications report benefit in pains associated with multiple sclerosis,[43, 44, 45, 46][V] diabetic neuropathy, PHN, and other neuropathic pain states. Pregabalin is also clearly effective,[47] although good evidence of superiority over gabapentin is lacking. There is also growing evidence of benefit from lamotrigine in central pain.[41][I], [48][V] Adverse effects frequently limit the practical utility of antiepileptic drugs, with a recent study of patients with MS showing that carbamazepine was associated with worse adverse effects than either gabapentin or lamotrigine, in some cases mimicking disease relapse.[49]

SYSTEMIC SODIUM CHANNEL BLOCKERS

Although this group of drugs comprises the local anesthetics and related "membrane-stabilizing" cardiac antiarrhythmics, it should be appreciated that sodium channel inhibition is a property of many other groups of drugs, including many anticonvulsants, antidepressants, and "mainstream" analgesics such as pethidine (meperidine), and it is possible that at least some of the therapeutic effects of these drugs are mediated through sodium channel inhibition.

A systematic review has been undertaken of systemic local anesthetic-type drugs in chronic pain.[50][I] The findings can be summarized as follows: the most convincing evidence for benefit is seen in neuropathic pain of peripheral nerve injury or peripheral neuropathy, with no evidence of benefit in dysesthesia from spinal cord injury or painful neuropathy (including plexopathy) in malignant disease. However, one recent publication supports their use in MS.[51][V]

NEUROLEPTICS

At the time of writing, the author is unaware of any convincing evidence in support of the use of these drugs for any pain-related indication. In addition, the risk of producing persisting tardive dyskinesia should be borne in mind by anyone tempted to prescribe these drugs on the basis of anecdotal evidence.

BENZODIAZEPINES AND OTHER GABA–AMINOBUTYRIC ACID AGONISTS

Generally speaking, drugs of the benzodiazepine group have been viewed with caution in long-term pain management because of the increasingly recognized problems of tolerance and dependence. However, although under most circumstances they are not analgesic, they are anxiolytic and, to varying degrees, antispastic. This last property may be valuable in the treatment of pain associated with muscular hypertonia. Spasticity may be relieved by both benzodiazepines and baclofen. Dantrolene, which acts peripherally on striated muscle, is of dubious value as a sole antispastic agent but may act synergistically with baclofen.[14] Baclofen has an antinociceptive action distinct from its antispastic effect, but the clinical effect in most pain associated with neurologic disease is probably marginal when it is given systemically (see below under Spinal drug administration).

Tizanidine, a centrally acting α_2-agonist, has also been reported as beneficial in a variety of spastic disorders, including MS.[52][II]

NMDA RECEPTOR ANTAGONISTS

The availability of drugs for human use with established effects on the NMDA receptor is limited. It is postulated, but not proven, that gabapentin may exert some effect through this mechanism; drugs with an established action are ketamine, dextromethorphan, and amantadine, all of which have been shown to be effective in studies of neuropathic pain.[53, 54, 55] The practical utility of these drugs is limited by side effects which, so far, seem inextricably linked with the desired pharmacologic effect. In addition, ketamine has well-recognized abuse potential and uncertain long-term adverse effects.

CANNABINOIDS

The use of cannabinoids as specific analgesics in neuro-pathic pain remains controversial. A recent study of a cannabis-based preparation in the treatment of pain in MS indicated that it was effective and well tolerated.[56][II]

Physical treatments

Included in this category are the range of "hands-on" techniques of physiotherapy, osteopathy, and chiro-practic and the treatment modalities of transcutaneous electrical nerve stimulation (TENS) and acupuncture which are often offered by physiotherapists but which are also extensively practiced by other healthcare profes-sionals. There is also some overlap with the treatment modalities espoused by alternative and complementary medicine.

An increasingly recognized role of physiotherapists in pain management is their contribution to cognitive/behavioral programs which will not be discussed further here.

Evidence-based evaluation of physical treatments is inherently difficult, partly because of the problems of blinding of the recipient and providing a placebo that is both credible and physiologically inert, and partly because of the difficulty of standardizing many of these treatments.

Not surprisingly, most clinical studies of physical treatments have focused on musculoskeletal/inflamma-tory disorders and there is little information about out-come when these techniques are applied specifically to sufferers of neurologic disease. A number of studies have reported reduction of spasticity following topical cooling, but the effects have generally been too brief to suggest a practical role for such treatment.

The problems of evaluating the use of TENS in chronic pain generally are discussed in a systematic review by McQuay and Moore,[57][I] who conclude that there is no good evidence in support of its use and that more studies are needed. Only one of the 38 rando-mized controlled trials included in this study looked specifically at a neurologic disorder (postherpetic neu-ralgia) and this compared TENS with acupuncture, as did many of the studies in this paper. The difficulty of blinding (especially the recipient) seems insuperable at present, but some problems with much of the literature to date can be remedied – larger numbers of subjects, longer periods of use of the treatment, and longer fol-low up. Evidence-based evaluation of acupuncture pre-sents similar problems. At the time of writing, the author is unaware of any specific unimodal physical therapy of proven value for treatment of pain in neu-rologic disease. Kidd *et al.*[58][V] draw attention to the value of rehabilitation in the global management of patients with MS, but it is unclear whether there is any specific effect on pain.

Invasive treatments

There is an inevitable overlap between these therapies and (systemic) pharmacologic treatments, which is perhaps most obvious in the use of implanted spinal drug delivery systems to increase the therapeutic effect, and/or reduce side effects, of a drug previously given systemically.

Invasive treatments can be classified as follows:

- reversible local/regional block with local anesthetic, with or without the use of additional corticosteroid;
- spinal injection/infusion of some drugs considered largely effective only by this route (e.g. benzodiazepines, clonidine) or more effective/better tolerated in selected cases (e.g. opioids, baclofen);
- neurolytic procedures;
- botulinum toxin injection;
- miscellaneous.

LOCAL ANESTHETIC BLOCK

The indications for local anesthetic nerve blocks have been categorized by Bonica into:

- diagnostic;
- prognostic;
- prophylactic;
- therapeutic.

The practical value of this classification is as relevant to pain in neurological disease as in any other clinical con-text. The indications for, and practical use of, peripheral nerve blocks is discussed in Chapter 23, Peripheral nerve blocks: practical aspects in the *Practice and Procedures* volume of this series. It now seems clear that serial local anesthetic blocks – with or without the addition of corticosteroid – may provide extended periods of relief of chronic pain, long outlasting the anticipated direct duration of action of the local anesthetic drug.[59][V] More studies are needed to establish the indications and general utility of this form of treatment for pain in various neurologic disorders. The role, if any, of steroids is not established.

SPINAL DRUG ADMINISTRATION

Intrathecal baclofen is clearly effective in reducing spas-ticity and would therefore be expected to reduce noci-ceptive pain directly attributable to spasticity.[14][V] However, there is also evidence that it might be effective in the treatment of central pain.[60, 61][V]

There is some evidence of benefit from spinally administered clonidine in neuropathic pain of multiple sclerosis/spinal cord injury[62] and cancer,[63][V] and a study indicating pain relief in relapsing MS from spinally administered corticosteroid (triamcinolone).[64][III]

Spinal opioid delivery is discussed in Chapter 21, Spinal administration.

NEUROLYTIC PROCEDURES

There is some evidence for benefit from procedures in this category in the treatment of pain in neurologic disease, especially characterized by disabling and painful spasticity. Favorable results using hyperbaric intrathecal phenol in such cases were reported nearly 50 years ago by Nathan,[65][V] and similar results have emerged from a study by the author and others in patients with advanced MS.[66][V]

Use of neurolytic procedures interrupting sensory pathways in an attempt to relieve pain may expose the patient to the risk of recurrent, resistant central pain consequent upon deafferentation, which may be extremely difficult to treat. By contrast, treatment of nociceptive, spasticity-contingent pain by selective motor neuronal/axonal lesioning should be free of this risk provided it is sufficiently selective.

Because of the invasive and potentially irreversible nature of these treatments, they have been largely restricted to patients with severe pain and disability; there are some data concerning their use in neurologic disease with severe spasticity.

BOTULINUM TOXIN

Botulinum toxin injection is now a well established treatment for disorders of muscular hypertonia; it is discussed in a separate chapter (Chapter 33, Management of painful spasticity) and will not be further considered here.

Surgical treatment

Most surgical interventions deemed appropriate for pain in neurologic disease involve interruption or augmentation of neural pathways and therefore lie within the province of the neurosurgeon. However, there are obvious special situations where other surgical specialists may contribute to relief of pain as well as other symptoms – tenotomy, plastic surgical treatment of pressure sores, etc. A recent large review of neurosurgical interventions in MS suggests that good outcomes can be achieved with appropriate selection criteria.[67][III] Neurosurgical procedures for treating chronic pain are discussed in Chapter 28, Central neuropathic pain: syndromes, pathophysiology, and treatments and Chapter 20, Neurostimulation techniques, and will not be considered further here.

Psychologic treatment

The application of psychology-based treatment to chronic pain is extensively covered in Chapter 13, Self-regulation skills training for adults, including relaxation; Chapter 14, Biofeedback; Chapter 15, Contextual cognitive-behavioral therapy; and Chapter 16, Graded exposure *in vivo* for pain-related fear in the *Practice and Procedures* volume of this series. In principle, the management approach is as appropriate to chronic pain sufferers with neurologic disease as to other groups, with perhaps two qualifications.

First, cognitive impairment is a feature of some neurologic disorders and may limit the feasibility of cognitive modification.

Second, physical disability in many painful neurologic diseases may be directly attributable to motor/sensory deficit or dysfunction, in contrast with, for example, the patient with musculoskeletal back pain without neurologic disease whose disability is pain contingent. This may limit the capacity for improving physical function with a cognitive–behavioral management approach.

Alternative medicine

The evidence for efficacy of complementary and alternative medicines in MS has been the subject of a recent review by Huntley,[68][III] in which the paucity of well-conducted studies is emphasized and no firm conclusions reached for any specific therapy. A review of acupuncture concluded that there was no good evidence for symptomatic benefit from this treatment in either MS or PD, but highlighted the difficulties of trial design.[69][III]

CONCLUSION

Pain in neurologic disease is frequently underestimated in its importance, both in terms of its seriousness to those afflicted and its prevalence. Pains may be neuropathic or nociceptive, and the two types of pain frequently coexist in individual cases. Pain phenotype in neurologic disease is hardly ever disease-specific, and attention should be focused on likely mechanisms of pain generation in an attempt to determine the likelihood of response to therapeutic interventions.

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