Treatment of Neuropathic Pain: Historical Aspects

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Introduction

Since the earliest descriptions of pain related to injury of the nervous system, it has been recognized that the characteristics of this type of pain differ markedly from those of pain due to non-neural tissue damage. Later, as new analgesics were developed, it became clear that neurogenic pain was very often refractory to these drugs. This brief article considers some historical aspects of the development of treatments for neuropathic pain. All pain clinicians would accept that the current armamentarium of therapies for neuropathic pain is limited, a fact that reflects our poor understanding of the pathophysiology of neuropathic pain and inability to target treatments specifically and selectively. Closely related to this is the continuing debate over exactly what we mean when we use the term neuropathic pain.

Early Clinical Descriptions of Neuropathic Pain

Fothergill is credited with the earliest description of trigeminal neuralgia, though he did not use the term neuralgia, which came into use some years later [1–3]. There followed descriptions of pain arising as a result of both central and peripheral nervous system damage. Important landmark descriptions of central nervous system pathology causing pain included those of vascular lesions [4,5]. Dejerine and Roussy described the thalamic syndrome in 1906 [6] and, in a masterpiece of clinicopathologic correlation, Head and Holmes [7] detailed the sensory consequences (including pain) of cerebral lesions at different sites. Holmes later recognized that similar pain could be caused by spinal cord lesions [8]. Behan [9] coined the term “central pain” (CP), and Riddoch [10] provided a definition of CP that has stood the test of time.

Pain resulting from peripheral nerve and root lesions was well recognized and recorded during the earlier part of the 19th century. Silas Weir Mitchell’s descriptions of pain following peripheral nerve trauma and, particularly, his detailed accounts of causalgia [11] in casualties of the American Civil War are widely regarded as marking the start of the systematic scientific approach to the study of the clinical features and pathophysiology of peripheral neuropathic pain. However, Denmark had, much earlier, given a detailed description of causalgia in a soldier with a radial nerve injury caused by a musket ball, sustained in the Spanish Peninsular War [12]. Paget independently described a similar syndrome in the same year as Weir Mitchell and his colleagues [13].

Pain Theories

The development of ideas about the pathophysiology of neuropathic pain is linked with theories that attempted to understand sensory physiology more broadly. A discussion of specificity theories [14], pattern theories [15], affect theory [16], the early powerful and enduring influence of the theory of epicritic and protopathic divisions of sensation and their relation to peripheral neuropathic pain [17], other sensory interaction theories [18], and the later highly influential gate control theory [19] is beyond the scope of this article.

The Definition of Neuropathic Pain

One might be forgiven for thinking that, after some 150 years of careful clinical observation and scientific investigation, there would be unanimity about the definition of neuropathic pain. The fact that there is not, emphasizes the limitations in our
understanding of the underlying pathophysiology of neuropathic pain and, in addition, a terminologic confusion that has its roots in the changing usage of words. Neuralgia, defined as “pain arising in the distribution of a nerve or nerves” [20], is a term that remains in widespread use. At some stage, though historically not clearly defined exactly, the term neuropathic pain came into use to describe conditions affecting peripheral nerves (i.e., peripheral mononeuropathies, mononeuritis multiplex, and polyneuropathies) that give rise to pain. Central pain was the term used to refer to the pain associated with central nervous system lesions. Neurogenic pain was an all-embracing term, referring to pain of both peripheral and central origin.

It is only in recent years that the definition of neuropathic pain has been widened to include both peripheral and central causes [20]. However, the most contentious issue is the inclusion of “dysfunction of the nervous system” in the International Association for the Study of Pain’s definition of neuropathic pain. Thus, neuropathic pain is defined as “pains resulting from disease or damage of the peripheral or central nervous system, or to dysfunction of the nervous system” [20]. This dysfunctional category of neuropathic pain allows the inclusion of organic pain states (i.e., not primarily psychologically determined states) in which the clinical features, including the nature of the pain and the presence of allodynia, hyperalgesia, and hyperpathia, do not result from an identifiable primary lesion of the nervous system. Notably, this wider definition leads to the inclusion of complex regional pain syndrome type I (CRPS I, previously known as reflex sympathetic dystrophy [21,22]) as a category of neuropathic pain.

The debate continues, with both those for [23] and against [24] the inclusion of dysfunction in the definition producing cogent reasons for their stances, stimulating others to consider means of clarifying and validating the definition and description of neuropathic pain [25]. The ongoing debate again underlines the fact that we are still at the stage of definition in clinical syndrome terms. Although there are numerous candidate mechanisms for ongoing pain allodynia, hyperalgesia and hyperpathia, peripheral and central, we are not yet in a position to dependably link symptoms and signs with specific pathophysiologic properties [26,27].

For the moment, it has to be accepted that, if dysfunctional neurologic pain symptoms are included as part of neuropathic pain, the clinical limits of neuropathic pain are broad and difficult to recognize. This is an issue of considerable importance to workers in the field. However, exclusion of this type of pain ignores the clinical reality of the existence of similar pain states—one provoked by neurologic damage and the other by damage to nonneural tissues.

Historical review shows that this debate is not new. Livingston lucidly discussed the confusion produced by different terminological usages and definitions, including major and minor causalgia and posttraumatic pain syndromes [28]. Reappraisal of his thoughtful writings now illustrates both how the basic neuroscience pertaining to pain mechanisms has developed and how we are embroiled in an almost identical terminologic conundrum today as in the 1940s.

Historic Aspects of Specific Treatments for Neuropathic Pain

The other papers in this supplement examine, in detail, treatments for neuropathic pain. Here, the origins of some current treatments are outlined, but the following account does not attempt comprehensive coverage of all the many modalities of treatment employed for neuropathic pain.

Pharmacologic Treatments

Antidepressants

Chronic pain and depression frequently coexist, and there is a complex relationship between the two disorders [29]. An analgesic effect of tricyclic antidepressant (TCA) drugs was first reported over 40 years ago [30]. Several strands of evidence indicate separate and distinct mechanisms of action of antidepressants (TCAs and monoamine oxidase inhibitors) in depression and pain. The onset of an analgesic effect often occurs earlier than that of an antidepressant effect [31], and an analgesic effect can be obtained in some patients without relief of the associated depression (e.g., in atypical facial pain [32]) and in patients with chronic pain who are not depressed (e.g., in patients treated for tension headache [33]).

From a historical perspective, despite a wealth of good evidence accumulating over the past 40 years concerning the analgesic efficacy of TCAs [34–36], it is interesting to note that the treatment of chronic neuropathic pain became a licensed indication for TCAs only relatively recently in most countries. A greater awareness of the burden of neuropathic pain in recent years is possibly responsible for a shift in attitudes involving doctors as well as pharmaceutical companies and licensing
authorities. The rapid licensing of gabapentin for the treatment of neuropathic pain following large trials in North America (see below) may be a reflection of this awareness and of the pressing need for more effective treatments for neuropathic pain.

Other Psychotropic Drugs
Analgesic effects of a variety of other psychotropic drugs, including neuroleptics and anxiolytics, have been claimed over the last 5 decades.

Neuroleptics were first reported to have analgesic effects in the 1950s in various pain states, including peripheral neuropathic pain and central pain [37–39]. The adverse effects of long-term neuroleptic drug treatment have, understandably, led to a reluctance to use these agents for the treatment of chronic pain for periods of months or years. The best quality evidence for the efficacy of neuroleptics derives from the treatment of acute pain, though positive results of combined treatment with antidepressant medication in various pain states, both nociceptive and neuropathic, have been reported, mainly during the 1970s [29]. Doubt remains concerning the efficacy of neuroleptic medication given as the sole agent in chronic pain states.

Anxiolytics (benzodiazepines) have been used as adjunctive treatments in pain states for their anxiolytic, sedative, or muscle spasm relieving actions. There is no convincing evidence concerning the use of anxiolytic drugs for the treatment of neuropathic pain. They have nearly always been used in combination with analgesics or other psychotropic medication, and it is difficult to identify an independent analgesic action. A possible exception may be clonazepam; in one study, it was effective in relieving lancinating phantom limb neuropathic pain [40] but, in another study, lorazepam did not help postherpetic neuralgia [41]. Nonetheless, the anxiolytic and short-term muscle relaxant properties of the benzodiazepines have ensured their continued use, though long-term administration has been considerably reduced in recent years in the light of increasing evidence of the potential for serious dependence.

Anticonvulsant Drugs
Blom [42] demonstrated the remarkable efficacy of carbamazepine in trigeminal neuralgia, and the drug remains the mainstay of medical treatment for this condition. Early hopes that this medication, and other antiepileptic drugs, might hold the answer to the treatment of other types of neuropathic pain were sadly not realized [43]. The exception is gabapentin, shown in recent large trials of postherpetic neuralgia [44,45] and painful diabetic neuropathy [46] to have a clinically significant analgesic effect. This action, combined with the drug’s low toxicity, has established it as a primary choice of medication in neuropathic pain of peripheral origin. Its position in the treatment of neuropathic pain of central origin requires further investigation.

Opioids
The history of opioid use (or nonuse) in neuropathic pain is instructive. The natural reluctance to prescribe opioids to patients with neuropathic pain of benign cause was, for many years, reinforced by the received wisdom that opioids were ineffective in neuropathic pain, based on weak evidence. It took many years before this “truth” was questioned. Reexamination in the later 1980s [47] was followed by controlled studies that clearly substantiated an important analgesic action of morphine and fentanyl [48] and, later, other opioids [49] in neuropathic pain.

Antiarrhythmics
Blockade of voltage-dependent sodium ion channels using local anesthetics may be highly effective in producing short-term analgesia in neuropathic pain due to, for example, neuromas or painful scars; lidocaine has been used in this way for many years. More recently it was shown that lidocaine, given by intravenous (IV) infusion, could also relieve neuropathic pain [48]; it is now widely used to predict the response to oral drugs such as mexiletine, flecainide, and tocainide. However, results of oral treatment have been disappointing, and the dangerous adverse effects of this class of drugs have precluded their use by most clinicians, particularly as none of the drugs are licensed for the treatment of neuropathic pain.

Sympatholytic Treatment
Leriche was the first to describe relief of causalgia with sympathectomy [50] and following this, preganglionic sympathectomy soon became established as standard treatment for painful nerve injuries (including many nerve-injured combatants and civilians during World Wars I and II). Later, Hannington-Kiff introduced IV regional sympathethic blockade using guanethidine [51]. Arner developed the IV phentolamine test to identify patients with what had become known as sympathetically maintained pain (SMP) and to predict the response to subsequent longer term
sympathetic block or sympathectomy [52]. The concept and existence of SMP remain controversial subjects. While short-term pain relief may be obtained in some patients in open-label situations, controlled studies have not demonstrated any long-term benefit [53,54].

The lesson of history in relation to sympatholytic therapy can be likened to that of opioids but, in this case, the received wisdom was that sympatholytic treatment was definitely effective. In each case, it took many years for practice to change, and this only occurred as a result of challenge of dogma and careful scientific reevaluation.

Surgery for Neuropathic Pain

A full account of the historical aspects of surgical treatment for neuropathic pain is beyond the scope of this article, and only a brief chronology is given here. The first open cordotomy was performed by Spiller and Martin [55], followed much later by the technique of percutaneous cervical anterolateral cordotomy [56]. Other landmark dates in the development of neurosurgical treatments for neuropathic pain include commissural myelotomy in 1927 [57], thalamotomy in 1949 [58], mesencephalic spinothalamic tractotomy in 1962 [59], selective dorsal root lesioning in 1974 [60], and dorsal root entry zone lesioning in 1976 [61]. Numerous sites in the brain have been targeted. A reasonable summary concerning efficacy is that, although lesioning often produces short-term analgesia, long-term results are poor. Furthermore, neuropathic pain may develop as a result of the surgical procedure, together with other adverse effects, not infrequently severe. Surgery for trigeminal neuralgia is the exception; as Fields et al. [49] succinctly stated: “Outside of trigeminal neuralgia, there are no surgical approaches with established efficacy in neuropathic pain.”

Counterstimulation, Spinal Cord Stimulation, and Deep Brain Stimulation

Acupuncture, vibration, transcutaneous electrical nerve stimulation (TENS), and other methods of counterstimulation are generally regarded as the least well validated of all pain treatments by the scientific community, and there is some justification for this view. However, acupuncture, vibration, and TENS have each been shown to have therapeutic effects in nociceptive and neuropathic pain [62].

Simple methods of counterstimulation for pain are probably as old as humankind itself. Acupuncture was incorporated as part of traditional Chinese medicine, with accounts dating from 200 B.C. [63]. It is perhaps surprising that the scientific study of vibration and acupuncture did not occur until the 1980s [62].

Renewed interest in electrical stimulation occurred a little earlier in the modern era. From a historic point of view, the value of electrical shocks in producing analgesia was recognized in ancient times [64]; electrotherapy was used in more recent times during the 19th and early 20th centuries. However, it took the gate control theory [19] to reawaken serious scientific inquiry into the therapeutic potential of electrical stimulation.

Again, good-quality evidence concerning TENS is limited; adequately controlled studies clearly pose particular difficulties with this modality of treatment. Limited evidence indicates an analgesic effect both for nociceptive pain and for neuropathic pain [62].

Spinal cord stimulation, a logical extension of TENS, introduced by Shealy et al. [65], now has wide applications in the therapies for nociceptive and neuropathic pain.

The early pioneers of deep brain stimulation, targeting the ventral posterolateral (VPL) nucleus of the thalamus, were Mazars et al. [66]. The later animal experimental finding that periaqueductal grey (PAG) stimulation could induce powerful analgesia [67] provoked a search for additional therapeutic targets in the human brain: PAG, the sensory thalamus (VPL and ventral posteromedial nuclei), and the posterior limb of the internal capsule. Results have been mixed. The more recently developed stimulation of the surface of the motor cortex shows greater promise.

Conclusion

In this brief survey, historical aspects of the development of selected treatments for neuropathic pain have been outlined. A broader discussion about the nature of neuropathic pain reveals that there is still no universally agreed upon definition of neuropathic pain and, in this respect, a view could be taken that we have not advanced a great deal since the 1940s. Set against that, there have been huge strides in the understanding of the basic science relating to pain, though there is a continuing, frustrating inability to translate this new knowledge into a specific linkage of underlying physiology to symptoms and signs, thereby helping to identify clear targets for treatment.

While there have been major advances in drug trial methodology and new therapeutic agents have
been developed, the majority of the currently available treatments has limited efficacy in neuropathic pain. Ablative surgical treatments do not appear to hold the answer to the relief of neuropathic pain.

Finally, recent therapeutic advances, described in the following articles, give some grounds for optimism that neuropathic pain will become more amenable to effective treatment in the foreseeable future.

References

55 Spiller WG, Martin E. The treatment of persistent pain of organic origin in the lower part of the body by division of the anterolateral column of the spinal cord. JAMA 1971;218:1489–90.