

*Highlights of the Society for Medicines Research Symposium  
held June 26, 2003, in London, United Kingdom.*

# Pharmacotherapy for Neuropathic Pain: Progress and Prospects

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by *Sandy Pullar  
and Alan M. Palmer*

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**O**n June 26, 2003, the Society for Medicines Research held a very successful and well-attended symposium at the Eli Lilly Research Centre at Erl Wood Manor, Windlesham, United Kingdom. The meeting focused on the progress that has been made in the discovery and development of new drugs for the treatment of neuropathic pain and looked forward to assess the prospects for the emergence of new medicines for this chronic debilitating disorder. The meeting was organized by Sandy Pullar (Eli Lilly, U.K.) and Alan M. Palmer (Pharmidex, U.K.), who, together with Ian Regan (Eli Lilly, U.K.), chaired the proceedings.

Now let's set the scene: Imagine a pain so excruciating that words fail to describe it and doctors can't explain it. A pain that may in fact worsen over time. Tragically, some people don't have to imagine such pain, they expe-

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## *Summary*

Neuropathic pain, a persistent chronic pain resulting from damage to the central or peripheral pain signaling pathway, has become an area of intense research activity—largely because it represents a disorder with high unmet medical need. It is not a single disease entity, but rather includes a range of heterogeneous conditions that differ in etiology, location and initiating cause. Despite this diversity, the clinical presentation is frequently surprisingly similar, which suggests a common biological basis. Until recently, little was known of the mechanisms underlying the various neuropathic pain conditions, making the directed development of novel therapies almost impossible. However, the steady increase in our understanding of the anatomical, cellular and molecular basis of neuropathic pain, coupled with the advent of a number of experimental models of neuropathy, has permitted relatively rapid progress, and the prospects for the emergence of new, more effective therapies look very good. Gabapentin (Pfizer), which appears to act by blocking calcium channels, is the first drug to acquire widespread regulatory approval for the treatment of neuropathic pain. The Society for Medicines Research symposium held June 26, 2003, considered this treatment modality alongside other approaches to therapy, such as N-methyl-D-aspartate receptor antagonists and cannabinoid receptor agonists. The whole meeting provided an excellent description of the challenges facing neuropathic pain drug discovery—at both the research and the development phases of the value chain. © 2003 Prous Science. All rights reserved.

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rience it, and it makes their life unbearable. Neuropathic pain, as it is called, can be described as a malfunction in the nervous system that usually follows injury to the nerve or to certain regions of the spinal cord or brain. It is the most severe form of pain and the only one that leads patients to commit suicide. It

is triggered by conditions such as diabetic neuropathy, AIDS-related neuropathy, postherpetic neuralgia, chronic degenerative spinal disease, sympathetic dystrophies, postamputation stump (phantom limb pain), trigeminal neuralgia and multiple sclerosis. Multiple changes in the processing of

pain signals from peripheral nerves to the cerebral cortex do occur following nerve injury, and the relative clinical significance of these is still being determined. However, neurons that are normally concerned with the processing of innocuous sensation (e.g., touch) sprout into areas of the dorsal horn that normally mediate nociceptive processing. Thus, there is a “rewiring” of the dorsal horn so that innocuous tactile stimuli are interpreted by the brain as painful, such as occurs in allodynia (Table I) or trigeminal neuralgia.

Estimates of the potential market for neuropathic pain range from 400,000 to 900,000 patients annually in the United States alone, where the market is valued at \$450 million. The market for pain drugs is considered to be in the early stages of development, with potential for significant and rapid growth.

Neuropathic pain (unlike acute pain) is not adequately managed with available medications and so represents a substantial unmet medical need. There are currently very few truly effective, well-tolerated therapies for this neuropathic pain. Opiates (which work well for acute pain) are not particularly effective. Tricyclic antidepressants (which act by blocking the uptake of the neurotransmitters noradrenaline or serotonin, or both) have been used “off label” and claimed to be effective, but they suffer from undesirable side effects. Also, some of the more recently introduced antiepileptic agents have been claimed to be effective, for example, lamotrigine and gabapentin; the latter compound has now been approved for the treatment of neuropathic pain. Other approaches to therapy include N-methyl-D-aspartate (NMDA) receptor antagonism, sodium channel blockade<sup>1</sup> and cannabinoid receptor agonists. Such approaches to therapy will be considered today alongside a description of the challenges facing neuropathic pain drug discovery at both the research phase (e.g., how do we predict efficacy) and development phase (e.g., what type of neuropathic

**TABLE I. DEFINITIONS OF CERTAIN TYPES OF NEUROPATHIC PAIN**

Allodynia	Pain following a normal innocuous stimulation
Hyperalgesia	Pain disproportionate to a noxious stimulation
Hyperpathia	Increasing pain with repetitive stimulation: <ul style="list-style-type: none"> <li>• After response (continued exacerbation pain after stimulation)</li> <li>• Radiation of pain to adjacent areas after stimulation</li> </ul>

pain should we target first and what are the best outcome measures).

### Symptomatology

Neuropathic pain is not a single entity, but rather includes a range of heterogeneous conditions that differ in etiology, location and initiating cause. The clinical picture was clearly and graphically described by John Wedley (Guy’s and St. Thomas’ Hospital, London). Clinical diagnosis is made on the basis of emergent characteristics—the description from patients is not reliable and often made in emotional terms. It may be accompanied by characteristic sensory changes such as allodynia and hyperpathia (Table I).

The physical findings reflect the etiology and will be greater where there is peripheral nerve injury (e.g., complex regional pain syndrome, CRPS) and least where the cause is entirely central (e.g., thalamic pain). Most patients present with a mixed picture. Even where the original tissue injury is entirely peripheral there will be central changes. An understanding of these changes both facilitate drug discovery and provide a framework for rational drug therapy.

The treatment of neuropathic pain falls into three categories, psychotherapy, drug treatment and nerve ligation/stimulation. In the rare condition CRPS type I, which is caused by soft tissue damage, patients should be encouraged to use the affected limb, as this can lead to improvement. It is probably for this reason that psychotherapy is effective in this condition. In the more common CRPS type II, which results from nerve damage after such things as a prolapsed intervertebral disc, herpes zoster infection, spinal cord injury and amputation

(phantom limb pain), nerve ligation is effective but only for a short time. It may lead to a long-term exacerbation of the pain. Anticonvulsants such as carbamazepine seem to work, but their usefulness is limited by side effects. For atypical facial pain, tooth pain that persists even after removal of the tooth, tricyclic antidepressants such as amitriptyline are effective, as are high doses of selective serotonin reuptake inhibitors (SSRIs).

Increasing awareness of the plasticity of the nervous system and replacement of the “hard-wired” model with that of a matrix has enhanced the movement away from neurodestructive techniques to neuromodulatory treatments such as transcutaneous nerve stimulation and spinal cord stimulation, although neurodestructive procedures may still have a place in the treatment of cancer pain. Neuropathic pain remains the most difficult form of pain to treat. Pain may be reduced but very rarely eliminated. It often leads to one or a combination of the following:

- immobility
- insomnia
- anorexia
- anxiety
- depression
- reductions in quality of life

Multidisciplinary cognitive- and behavior-based pain management programs optimize the patient’s quality of life. As someone who sees patients suffering from neuropathic pain on a regular basis, Dr. Wedley pointed to three key additional tools to add to analgesic armamentarium. These are:

- better ketamine
- long-acting local anesthetic
- drugs with multiple actions.

## Biological basis

A key prerequisite for meeting the need for better treatment is a clear understanding of the biological basis of neuropathic pain. This topic was well covered by Tony Dickenson, (Dept. Pharmacology, University College, London). This approach to therapy was largely stimulated by the Gate theory of pain (1965), which predicted that pain could be modulated. Damage to a nerve should only lead to sensory loss, but the incidence of spontaneous pain (allodynia and hyperalgesia; Table I) indicate marked changes in the nervous system that are possible compensations for the loss of normal function. Neuropathic pain arises from initiating changes in the damaged nerve, which then alter function in the spinal cord and the brain and lead to plasticity in areas adjacent to those directly influenced by the neuropathy. The peripheral changes drive central compensations so that the mechanisms involved are multiple and located at a number of sites.

Nerve damage increases the excitability of both the damaged and undamaged nerve fibers, neuromas and the cell bodies in the dorsal root ganglion. These peripheral changes are substrates for the ongoing pain and the efficacy of excitability blockers such as carbamazepine, lamotrigine and mexiletine (Fig. 1).

A better understanding of ion channels at the sites of injury has shown important roles of particular sodium, potassium and calcium channels in the genesis of neuropathic pain. In peripheral pain, there is a clustering of sodium channels. Three types of channels seem to be involved. One of these channels, which normally disappears after birth but returns after injury, has a unique profile in that it is only poorly sensitive to tetrodotoxin. Within the spinal cord, increases in calcium channel activity appear to play a role in neuropathic pain. Such channels have been subdivided with specific ligands into N-type ( $\omega$ -conotoxin), P-type ( $\omega$ -agatoxin), T-type (ethosuximide) and L-type (verapamil). N-type voltage-

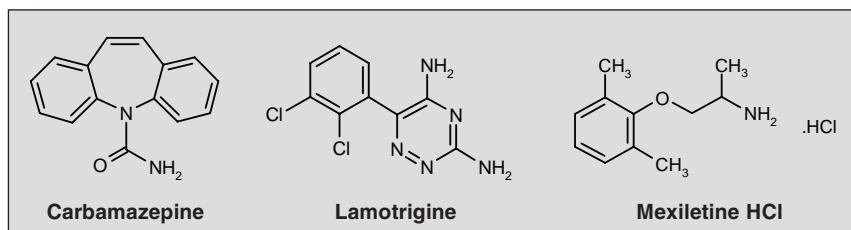


Fig. 1. Excitatory blockers.

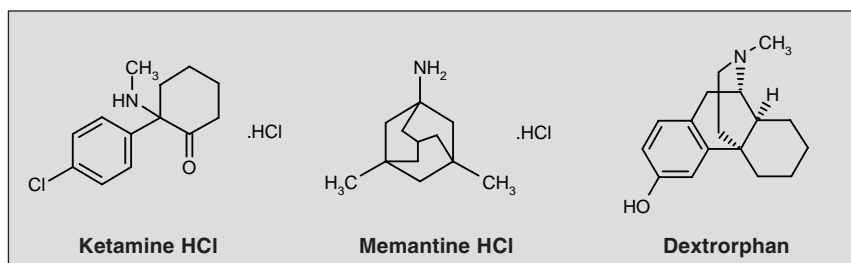


Fig. 2. NMDA receptor blockers.

dependent  $\text{Ca}^{2+}$  channels are enhanced after nerve injury; P-type channels are important in pain but are unaltered by nerve damage and L-type channels seem to be uninvolved. There is now evidence emerging to suggest that gabapentin may interact with a modulatory ( $\alpha_2$ ) subunit of calcium channels.

Receptors for excitatory amino acids, especially the NMDA receptor, are also thought to play a key role in neuropathic pain. NMDA receptors, for example, trigger wind-up and central hyperexcitability. Increases in transmitter release, neuronal excitability and the size of the receptive field then ensue. Examples of NMDA receptor blockers (Fig. 2) include ketamine (a dissociative anesthetic), memantine (a new medicine to treat Alzheimer's disease) and dextrorphan (an analgesic).

In addition to these spinal mechanisms of hyperexcitability, lamina I cells participate in a spinal-supraspinal loop that involves the part of the brain responsible for affective responses to pain; it also engages descending excitatory systems. These pathways become more active after nerve injury and molecular microsurgery using

SP-saporin, which has been used to ablate lamina I neurons. Similar efficacy has been obtained by blocking  $5\text{HT}_3$  receptors with the  $5\text{HT}_3$  receptor antagonist ondansetron. This has been shown to mimic the effect of SP-saporin on mechanical and thermal coding of spinal neurons.

It can be said that at present our understanding is that neuropathic pain is associated with:

- peripheral changes in sodium and potassium channels
- ectopic, hepatic, sympathetic activity
- increased NT release from intact fibers
- increased central NMDA and N-type calcium channel activity
- possible changes in opioid, noradrenaline (NA) and serotonin (5-HT) systems.

A better understanding of the multiple mechanisms of neuropathic pain should lead to a more effective use of existing drugs and provide a basis for the development of potential new therapies.

## Experimental models

To establish that potential drug candidates are likely to be efficacious in the clinic, it is essential to have predic-

**TABLE II. PREDICTIVE VALIDITY OF ANIMAL MODELS OF NEUROPATHIC PAIN<sup>5</sup>**

MODEL	GENERAL SENSITIVITY (%)	EXPERIMENTAL VS. CLINICAL EFFICACY	GENERAL SPECIFICITY	EXPERIMENTAL VS. CLINICAL EFFICACY
Chronic constriction injury	88	94 animal studies +ve when 107 were expected be so on basis of clinical data	0	0 animal studies -ve when four expected to be so on basis of clinical data
Spinal nerve ligation	68	63/93	60	6/10
Partial sciatic ligation	61	8/13	N/A	No data
Streptozocin	70	26/37	60	2/3

tive experimental models of neuropathic pain. Alyson Fox (Novartis Institute for Medical Sciences, London) reviewed this topic.

Until recently, little was known of the mechanisms underlying the various neuropathic pain conditions, making the directed development of novel therapies almost impossible. However, the advent of a number of animal models of neuropathy has led to a huge increase in research activity into neuropathic pain. These animal models should be predictable, reproducible and have a relationship to the disease. Ideally, they should be experimentally straightforward, have a reasonable throughput and be mechanistically based. If they can be carried out in the mouse, it would enable the use of receptor knockout animals. The animal models are divided largely into groups of those with peripheral nerve injury and those mimicking a particular disease condition. The most widely used are the nerve injury models, principally the partial sciatic ligation model,<sup>2</sup> the chronic constriction injury model<sup>3</sup> and the spinal nerve ligation model.<sup>4</sup> All these models show behavioral signs characteristic of clinical neuropathic pain conditions including mechanical and thermal hyperalgesia, tactile allodynia and cold allodynia. Mechanistic studies with these models have highlighted the huge number of plastic changes occurring in the nociceptive pathway following nerve injury such as phenotypic changes in peripheral sensory nerves, spontaneous activity in sensory fibers and central sensitization. While arguably less is known of the underlying mechanistic processes, disease models such as the streptozotocin-induced model of dia-

betic neuropathy and chemotherapy-induced neuropathy are becoming more widely used. These models display a number of the key features of neuropathic pain states seen in humans, including tactile hypersensitivity, and both static and dynamic allodynia. The major concern currently with these models is that of clinical predictability. The conclusions of a systematic analysis of the predictive validity of animal models of neuropathic pain<sup>5</sup> that looked at nine drug classes (tricyclic antidepressants [TCAs]; other antidepressants; opioids, membrane stabilizers; anticonvulsants; GABA receptor agonists; NMDA-receptor antagonists;  $\alpha$ -adrenergic agonists and nonsteroidal anti-inflammatory drugs) can be found in Table II.

Preclinical studies using these models have confirmed the antihyperalgesic and antiallodynic profile of gabapentin and the increased potency of pregabalin. In addition to providing a predictor of clinical efficacy, these models have contributed (or have the potential to contribute) in three other areas:

- They provide an opportunity to explore their mechanism of action. The hope is that with the increasing knowledge of neuropathy gained using these models we may be able to arrive at a more mechanistic classification of neuropathic pain conditions in the clinic, rather than one based solely on etiology. In the first instance, this may allow a targeted patient selection process for clinical trials in an area notorious for its high placebo effect and number of failed trials.

- They may lead to a more accurate drug selection tailored for each patient, thereby avoiding the “polypharmacy” approach and the greater risk of adverse effects.
- They can assist in the identification of a surrogate marker of neuropathic pain. This would be extremely helpful in clinical trials, but no such marker exists at present.

### **NMDA receptor antagonists**

Chris G. Parsons (Merz Pharmaceuticals, Frankfurt, Germany) provided a detailed presentation of the role of NMDA receptor antagonists in neuropathic pain.<sup>6</sup> He indicated that glutamate is the major fast excitatory neurotransmitter in the central nervous system (CNS) and that it has been implicated in a wide variety of neurological diseases. Ionotropic glutamate receptors are classified into two major subclasses: AMPA/kainate and NMDA. Preclinical evidence indicates that hyperalgesia and allodynia following peripheral tissue or nerve injury depends on NMDA receptor-mediated central changes in synaptic excitability. Functional inhibition of NMDA receptors can be achieved through actions at subsites distinct from the NMDA binding site. These include the co-agonist, strychnine-insensitive glycine site (glycine<sub>B</sub>), polyamine site (NR2B) and the uncompetitive (PCP) channel site. Uncompetitive NMDA receptor antagonists act in a “use-dependent” manner, meaning that they only block the channel when it is in the open state.

Antagonists can impair normal synaptic transmission and cause side effects, such as memory impairment,



psychosis, ataxia and motor incoordination. The challenge has therefore been to develop NMDA receptor antagonists that prevent the pathological activation of NMDA receptors but allow their physiological activation.

Uncompetitive NMDA receptor antagonists with rapid unblocking kinetics but somewhat less pronounced voltage-dependency than  $Mg^{2+}$  seem to be able to antagonize the pathological effects of the sustained, but relatively small, increases in extracellular glutamate concentration but, like  $Mg^{2+}$ , leave the channel as a result of strong depolarization following physiological synaptic activation. Thus, uncompetitive NMDA receptor antagonists with moderate, rather than high, affinity may be desirable. Memantine, amantadine, ketamine and dextromethorphan are clinically used agents that belong to this category. The uncompetitive NMDA antagonist neramexane (Fig. 3) has characteristics similar to those of memantine and is active in the carageenin pain model.

Another promising target for NMDA receptor antagonism is the glycine<sub>B</sub> modulatory site. Recent data indicate that systemically active glycine<sub>B</sub> antagonists have potential utility as analgesic, neuroprotective, anxiolytic and antiepileptic drugs. In contrast to high-affinity, uncompetitive antagonists, glycine<sub>B</sub> antagonists do not have psychotomimetic effects. They have minor negative effects on learning, and even very high doses do not cause any neurodegenerative changes in the cingulate/retrosplenial cortex of rats. Glycine<sub>B</sub> antagonists presently under development and with therapeutic potential in the treatment of pain include GV-196771A, licostinel (ACEA-1021), ZD-9379 and MRZ-2/576 (Fig. 4).

The NR2B-selective agents traxoprodil (CP-101606) and (±)-Ro 25-6981 (Fig. 5) have also been reported to be effective in suppressing hyperalgesia in animal models of chronic pain at doses devoid of negative side effects on motor coordination or behavior

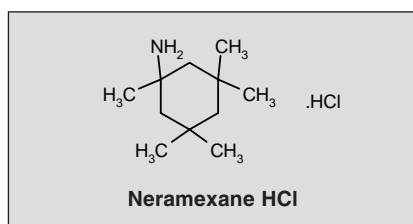


Fig. 3. Uncompetitive NMDA antagonist.

(including in humans). This indicates that NR2B-selective antagonists may also have clinical utility for the treatment of neuropathic and other pain conditions in humans with a reduced side effect profile. These therapeutically safe NMDA receptor antagonists are also able to slow or prevent the development of opioid tolerance, indicating the synergistic utility of their combination with opiates in the treatment of chronic pain, both in terms of symptomatic analgesic effects and prevention of the development of chronic pain states.

### NA and 5-HT uptake inhibitors

David G.S. Perahia (Eli Lilly, Windlsham, U.K.) considered the use of NA and 5-HT uptake inhibitors in the treatment of neuropathic pain. NA and 5-HT uptake inhibitors have been successfully utilized in the treatment of depression since the introduction of

TCAs such as imipramine in the late 1950s. The TCAs, while enhancing NA and 5-HT neurotransmission to varying degrees, also have affinity for a variety of other neuronal receptors that mediate a number of their undesirable effects. It was this lack of selectivity that was one of the drivers behind the search for more selective, “cleaner” antidepressant agents, culminating in the discovery of SSRIs such as fluoxetine (*Prozac*) in the 1980s.

In addition to their well-established efficacy in depression, TCAs have long been known for their efficacy in chronic, especially neuropathic, pain. Their analgesic effects are likely mediated by dual 5-HT and NA reuptake inhibition. This is based on preclinical evidence comparing dual with single NA and 5-HT uptake inhibition. In one such study (using the formalin paw test), a combination of paroxetine (an SSRI) and thionisoxetine (a noradrenaline reuptake inhibitor) had greater efficacy than either drug alone. Clear efficacy was also demonstrated in this model with the dual serotonin, noradrenaline reuptake inhibitor duloxetine, which was also shown to be efficacious in the Chung model of neuropathic pain and to reverse capsaicin-induced mechanical allodynia

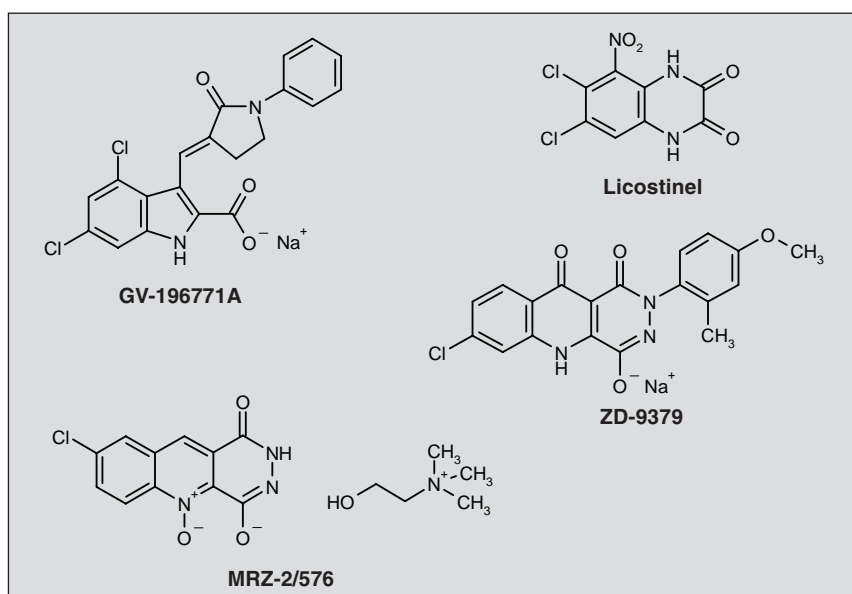
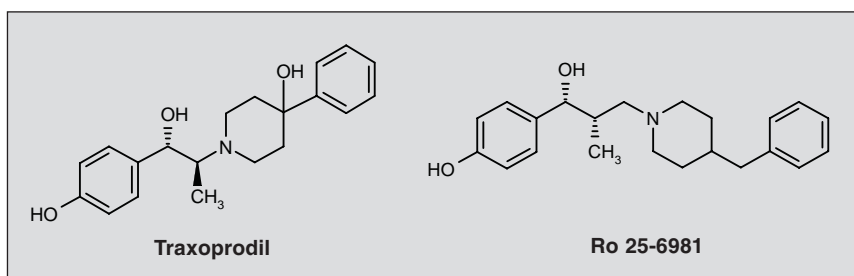


Fig. 4. Glycine<sub>B</sub> antagonists with therapeutic potential for neuropathic pain.



**Fig. 5.** NR2B-selective NMDA receptor antagonists.

Numerous double-blind, placebo-controlled studies of TCAs are discussed in the literature, together with a multitude of case reports and reviews showing consistent evidence of efficacy of imipramine and amitriptyline in neuropathic pain. These trials provide evidence that the dose and the choice of the TCA itself in terms of relative effects on 5HT/NA, are factors influencing efficacy.

There have been fewer placebo-controlled studies of SSRIs, and the evidence of efficacy is weaker. However, some of the studies have provided positive results. For example, in a trial of the SSRI paroxetine, 10 out of 20 patients showed improvement on paroxetine and only 3 out of 20 on placebo. As with the trials of dual reuptake inhibitors, the number of patients in each group is limited. An analysis of the clinical effectiveness of TCAs and SSRIs indicates that they are more effective when given in combination.

Since the introduction of SSRIs, novel agents have been developed that recreate the dual 5-HT and NA reuptake inhibition of some TCAs, but with less of the safety and tolerability limitations of the older antidepressants. These novel agents include venlafaxine, milnacipran and duloxetine (Fig. 6).

Venlafaxine has shown clear efficacy for diabetic neuropathic pain, and a number of studies suggest the drug's efficacy for fibromyalgia, neuropathic pain following breast cancer treatment, tension headache and chronic headache. Similarly, duloxetine has been shown to be effective in treating

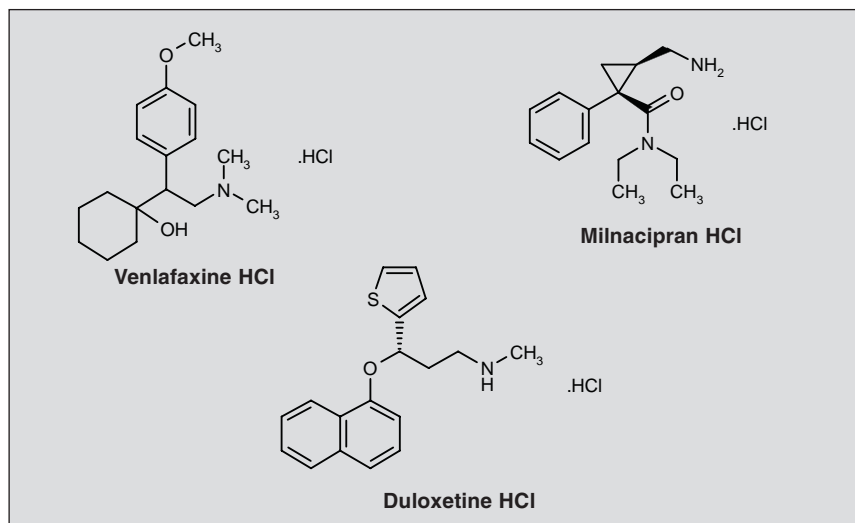
the neuropathic pain associated with diabetes on the basis of both primary and secondary efficacy measures without any changes in mood or anxiety.

### Cannabinoid receptor agonists

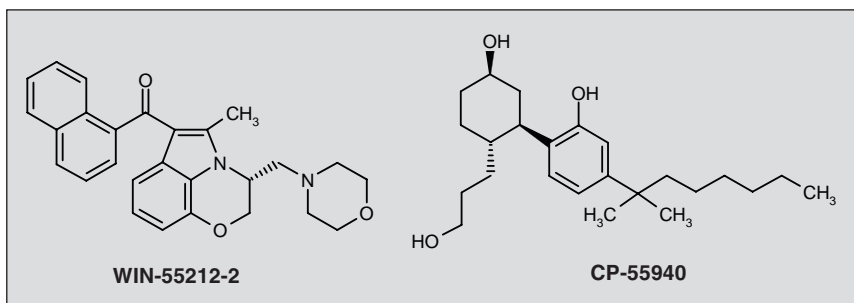
Stuart Bevan (Novartis Institute for Medical Sciences, London) reviewed the use of cannabinoid receptor agonists for neuropathic pain. The efficacy of these agonists for neuropathic pain is supported by considerable pre-clinical and clinical evidence, and there are anecdotal reports to suggest that smoking cannabis may relieve the pain and spasticity in multiple sclerosis sufferers. Limited clinical trials using various forms of THC, the major active component of cannabis, have shown the agent to have analgesic activity in forms of neuropathic pain. However, in all cases the efficacy was reported to be limited by adverse CNS side effects. It

is now known that the effects of cannabinoids are mediated via an interaction with CB<sub>1</sub> and CB<sub>2</sub> receptors. Both these receptors are G-protein-coupled receptors negatively linked to adenylate cyclase, but they have markedly differing distributions, with CB<sub>1</sub> receptors having a widespread distribution in the central and peripheral nervous systems, and CB<sub>2</sub> receptors restricted largely to cells of the immune system. In animals, cannabinoids have long been known to be analgesic in models of acute pain, an effect which is now known to be mediated through spinal and brain CB<sub>1</sub> receptors. More recently, it has been shown that synthetic cannabinoids such as WIN-55212-2 and CP-55940 as well as the endogenous CB agonist anandamide are effective in models of chronic neuropathic and inflammatory pain, reversing established mechanical or thermal hyperalgesia and tactile allodynia.

However, systemic administration of cannabinoids also produces a characteristic set of behavioral effects, including catalepsy, hypothermia and motor dysfunction, due to activation of central CB<sub>1</sub> receptors. There is little separation between the antihyperalgesic activity and these side effects. While the analgesic effects of cannabinoids in models of chronic pain are at least partly mediated via central CB<sub>1</sub>



**Fig. 6.** Novel agents that recreate the dual 5-HT and NA reuptake inhibition of some tricyclic antidepressants.



**Fig. 7.** Synthetic cannabinoids effective in models of chronic neuropathic and inflammatory pain.

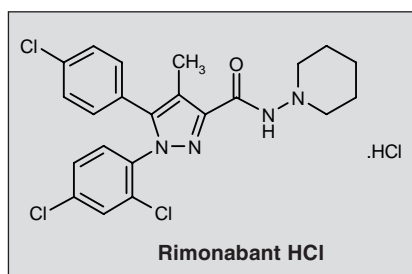
receptors, emerging evidence suggests that activation of peripheral CB receptors may also mediate analgesia. CB<sub>1</sub> receptors are expressed by sensory nerves and have been shown to be transported to their peripheral terminals. Electrophysiologic studies have shown that WIN-55212-2 inhibits calcium currents in dissociated DRG neurons, and it inhibits mechanically induced firing of single sensory fibers in an isolated skin-nerve preparation. In behavioral studies, injection of WIN-55212-2 or anandamide directly into the ipsilateral but not contralateral paw has been shown to inhibit hyperalgesia in models of neuropathic and inflammatory pain. Importantly, this effect of locally administered WIN-55212-2 in the model of neuropathic pain was inhibited by systemic but not intrathecal administration of the CB<sub>1</sub> antagonist rimonabant (SR-141716A; Fig. 8), implying a peripheral mode of action.

Other studies have shown that activation of CB<sub>2</sub> receptors may also inhibit hyperalgesia in models of inflammatory pain, although the role of these receptors in neuropathic pain remains less certain. Taken together, these studies in animals show that CB receptor agonists have considerable potential utility in the treatment of neuropathic pain. However, it is clear that if they are to be used routinely in the clinic then they must have analgesic efficacy without the CNS side effects, which are known to limit the use of available cannabinoid preparations. While one approach would be to develop CB<sub>2</sub> agonists, a potentially more promising mechanism offering

greater efficacy and broader use would be the development of peripherally restricted CB<sub>1</sub> receptor agonists.

### Gabapentin and pregabalin

Dic Williams (Pfizer Global Research and Development, Sandwich, U.K.) reviewed the gabapentin story. As the first approved treatment for neuropathic pain, gabapentin (Fig. 9) has made a major impact on the lives of thousands of patients suffering from this condition. Gabapentin is now widely recognized as a treatment of choice for neuropathic pain, although there still exists a need to develop more potent, easier-to-use products that are supported by strong clinical evidence. Pregabalin (Fig. 9) was specifically designed to be an advance in the treatment of neuropathic pain and is supported by the largest group of controlled clinical trials in neuropathic pain of any agent, including gabapentin. The studies have demonstrated that pregabalin is a potent, efficacious and well-tolerated compound with linear absorption kinetics. A large body of evidence, which has emerged over several years, indicates that these agents act through a novel mechanism that is

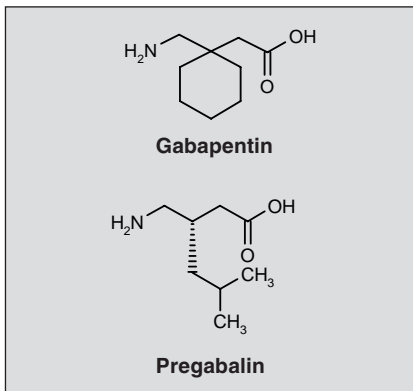


**Fig. 8.** CB<sub>1</sub> antagonist.

involved with the peripheral and central changes in pain processing associated with neuropathic pain.

Pregabalin and gabapentin bind to a single high-affinity binding site, widely distributed in the central nervous system. This has been identified as the  $\alpha_2\delta$  accessory protein of voltage-gated calcium channels. The binding protein is upregulated in primary afferents in animal models of neuropathic pain. These compounds are structurally similar to the major inhibitory neurotransmitter GABA. However, they do not bind to GABA<sub>A</sub> receptors. It has been suggested that they activate postsynaptic GABA<sub>B</sub> receptors, specifically those heterodimers expressing the GABA<sub>B1a</sub> subunit. However, two more recent studies provide evidence that they are not GABA<sub>B</sub> receptor agonists.

There is evidence that these  $\alpha_2\delta$  ligands may act at both central and peripheral sites. Thus, pregabalin and gabapentin decrease the ectopic primary afferent discharges associated with nerve injury; there is evidence that they have peripheral actions against nociceptive responses to formalin, and they block substance P potentiation of potassium-evoked glutamate release in spinal cord slice preparations. These ligands are efficacious following intrathecal administration in inflammatory and neuropathic pain models, they attenuate hyperalgesia induced by intrathecal substance P and decrease the after-discharge and wind-up of dorsal horn neurons responding to high-threshold sensory nerve stimulation in hyperalgesic rats but not in normal controls. Attenuation of calcium currents by  $\alpha_2\delta$  ligands in cultured sensory nerves and in *in vitro* preparations of central neurons have been described. While electrophysiologic studies on neurons in normal spinal cord slice preparations have shown a complex pattern of action, it seems clear that the relevant mechanisms may only be revealed in preparations showing hyperalgesia and allodynia.



**Fig. 9.** Agents used in the treatment of neuropathic pain.

Taken together, the evidence summarized above supports a role of  $\alpha_2\delta$  in the development and maintenance of hypersensitive states such as those seen in neuropathic pain, and that this protein constitutes the primary mechanism through which gabapentin and pregabalin exert their therapeutic actions. The central effects of pregabalin extend beyond its antiallodynic and antihyperalgesic actions, since they also include anxiolysis and improved sleep quality. It therefore seems likely that neural modulation via the  $\alpha_2\delta$  protein may involve a number of integrative processes in the CNS and that pregabalin may correct the dysfunction associated with neuropathic pain via actions at multiple sites in the neuraxis.

### Clinical trials in neuropathic pain

The final presentation of the day was from Andrew Rice (Imperial

College, London) and focused on key issues relating to clinical trials in neuropathic pain. The first issue is that the likelihood of success in the clinic is directly proportional to the predictive value of the experimental models used. There are clear limitations associated with the current animal models of neuropathic pain:

- They are designed to yield a high incidence of pain-related outcomes following peripheral nerve injury.
- Outcome measures reflect evoked reflex response to sensory stimuli rather than integrated behavioral response to ongoing pain.
- They usually share similar methods of inducing partial nerve injury that have limited relevance to human disease.
- There is strain/genetic/dietary variability of rodent responses to injury and analgesics.

Key issues in clinical trials include:

- What clinical conditions are commonly studied for regulatory trials
- How to define a responder
- Single disease-based studies versus generic neuropathic conditions
- Single therapy versus combination therapy
- Head-to-head comparisons.

Two common types of neuropathic pain used in clinical trials are postherpetic neuralgia (PHN) and painful diabetic neuropathy. The relative merits and drawbacks of each model are summarized in Table III. Gabapentin, the first neuropathic pain agent to acquire widespread regulatory approval, has

shown efficacy in both of the above models, as well as in mixed neuropathy.<sup>7-9</sup>

Some of the practical issues relating to a clinical trial for neuropathic pain were also considered.<sup>7</sup> The suggested inclusion criteria for PHN include: 1) the presence of pain for more than 3 months after healing of the acute herpes zoster skin rash; and 2) completion of at least four daily pain scores during the 7 days prior to randomization, with an average score of greater than or equal to 4 over the past 7 days on the daily pain diary.

Once the above issues have been addressed, the next issue is what efficacy measures should be used. The possibilities include:

- change in average daily pain score on 11-point Likert scale from baseline to final week
- Short Form McGill Pain Questionnaire
- Clinician and Patient Global Impression of Change
- Sleep Interference Diary
- SF-36 Health Survey.

A further practical issue is whether it is possible to compare a test compound with placebo or whether the comparison has to be made against a comparator compound. The *Declaration of Helsinki, 2000* (<http://www.wma.net>) states that “the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods.” This does not exclude the use of place-

**TABLE III. TWO COMMON TYPES OF NEUROPATHIC PAIN USED IN CLINICAL TRIALS**

TYPE OF PAIN	ADVANTAGES	DISADVANTAGES
Postherpetic neuralgia	Common Simple diagnosis Usually stable once established Unilateral (QST) Regulator familiarity	Elderly population Median 75 years Accessibility of population Distributed across multiple care providers
Painful diabetic neuropathy	Diabetes is common although there may be a decreasing incidence of neuropathies Younger population than postherpetic neuralgia Mean 53 years Regulator familiarity	Co-morbidity of other diabetic complications Symmetrical—QST Trial effect of glucose control Accessibility of population Unstable disease process



bo, where no proven prophylactic, diagnostic or therapeutic method exists, but clearly with therapies (such as gabapentin) reaching the market, it provides a standard that has to be improved on.

## Conclusion

Considerable progress has been made in understanding the anatomical, cellular and molecular basis of neuropathic pain, and this forms a solid foundation for the emergence of new therapies for the effective treatment of this debilitating disorder. Although, at present, gabapentin is the clear forerunner in this process, promising research holds out the possibility of alternative future treatments.

Prous Science has collaborated with the Society to make the symposium available, free of charge, in a Webcast format ([http://www.prous.com/webcaster/smr\\_june2003](http://www.prous.com/webcaster/smr_june2003)). Visitors to the Webcast can hear each

speaker's voice synchronized with the complete set of slides, graphics and photographics.

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Sandy Pullar and Alan M. Palmer are Conference Organizers and Members of the Society for Medicines Research. The SMR Committee organizes conferences on behalf of the Society for Medicines Research four times a year. These one-day conferences are of a multidisciplinary nature, therapeutically focused and normally staged in or around London. Details about forthcoming meetings can be obtained from: SMR Secretariat, 20/22 Queensberry Place, London SW72DZ, U.K. Tel: +44 171 581-8333; Fax: +44 171 823-9409; E-mail: [smr@iob.org](mailto:smr@iob.org); URL: <http://www.socmr.org>.

### CLINICAL TRIAL EVALUATES CC-8490 FOR BRAIN CANCER

Celgene Corporation announced October 31, 2003, that **CC-8490**, a new anticancer compound from Celgene's proprietary class of benzopyrans, is being evaluated as a potential therapy for brain cancer in a new clinical trial. Celgene recently signed a Cooperative Research and Development Agreement (CRADA)

with the National Cancer Institute (NCI) to collaborate on clinical and preclinical development of CC-8490 and other agents that specifically target the destruction of brain cancer cells. As part of this 4-year agreement, CC-8490 is evaluated in biochemical and cell-based assays, as well as assays directed at measuring antitumor effects.

CC-8490 and its analogues are studied *in vitro* and *in vivo* in order to advance the most promising agents for use in clinical trials. Phase I and II trials will follow successful research. Previously, Celgene worked with the NCI to study the potential antiglioma activity of CC-8490 using multiple cell lines. The mechanism for this antitumor effect may be novel and is being further explored.