

Chronic Neuropathic Pain: Pharmacological Interventions in The New Millennium A Theory of Efficacy

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Introduction

The management of pain has been a problem since before 200 B.C. In the book, *Wisdom of Sirach*, 38:4-8, it is said: "The Lord created medicines from the earth, and a sensible man will not despise them...And He gave skill to men that they might be glorified in His marvelous works. By them He heals and takes away pain; the pharmacist makes of them a compound."¹

In the 1800s, opium was the tonic of the day. By the mid 20th century, the gate control theory of pain, as presented by Melzack and Wall, became an accepted explanation of pain pathways. During the 1970s and 1980s, the main classes of medication used to manage neuropathic pain were antidepressants, anticonvulsants, antiarrhythmics and the opioids. This methodology of pain management was only partially efficacious. During this period, monotherapy was in vogue. Compliance with therapy was compromised by adverse drug reactions, limited efficacy, contraindications and barriers to the use of opioids in chronic nonmalignant pain conditions, e.g., as in chronic neuropathic pain.

Chronic neuropathic pain is the result of multiple etiologies, often unknown, which share a common pathway of pathophysiology. Diabetic peripheral neuropathy, postherpetic neuralgia, complex regional pain syndrome type I (formerly called *reflex sympathetic*

dystrophy), fibromyalgia, postsurgical neuropathy, post-trauma neuropathy, visceral neuropathy, xenobiotic neuropathy and the idiopathic neuropathies share the same pathway of sensory input and central modulation and inhibition. The search for pharmacological interventions to more efficiently control chronic neuropathic pain has recently focused on a multifaceted approach of management. The use of multiple agents concomitantly with different mechanisms of action is anecdotally reported to increase efficacy and decrease adverse drug reactions. The routes of administration are quite varied in the contemporary setting: topical (gels, creams), oral (regular and sustained release), sublingual and buccal, nasal, rectal and infusion (peripheral, central, intrathecal, epidural).

Recent reports of N-methyl-D-aspartate (NMDA) receptor antagonists, glutamate antagonists, α_2 -agonists, gamma-aminobutyric acid (GABA) agonists, α_1 -antagonists, opioids and antioxidants in various combinations provide the contemporary rationale that is furnishing increased efficacy in the clinical management of chronic neuropathic pain, with fewer side effects.

This article will focus on this new theory as an approach, from the perspective of a compounding pharmacist, to provide better control of the agony of chronic neuropathic pain in the new millennium. Implementation of this theory in daily practice within the triad of care will enhance the odds of positive outcomes in patients suffering from chronic neuropathic pain.

Pathophysiology

Chronic neuropathic pain is the net result of sensory input greater than the central inhibitory response. It originates in either the periphery or central compartments, depending on the source of pain.² The uniqueness of chronic neuropathic pain is that its multiple etiologies share a common pathway. The insult in the periphery stimulates afferent nerve fibers to process the pain signal to the central nervous system (CNS) via the dorsal horn of the spinal cord (see Fig. 1). These afferent fibers are of two main types: the myelinated, fast A fibers and the unmyelinated, slow C fibers. The constant suffering of patients with neuropathic pain is mostly C-fiber input. Nociceptor sensory input from free nerve endings is also involved but uses the afferent nerve fibers as the pathway of input to the CNS. The gate control theory of pain explained the synapse of the afferents in the dorsal horn and the descending inhibitory control mechanisms. The idea of the synapse of sensory input in the spinal cord being "gated" before it was presented to the CNS was a significant departure from the previously held position that pain signals reached the brain directly.^{3,4} Once the pain signal interfaces the dorsal-horn synapse, it reaches the CNS via various pathways for interpretation of pain. The CNS recognition of pain stimulates the modulatory events of descending inhibitory signals. The net result is either resolution, modulation or gain of pain.

The key mechanism involved in the modulation of afferent signals is the NMDA receptor.⁵ Located throughout the CNS, the NMDA receptors (see Fig. 2) play a crucial role in the modulation of pain signals, the maintenance of chronic neuropathic pain and

the development of hyperalgesia and allodynia.^{6,7} This development of hyperalgesic and allodynic states (exacerbated pain response to a normally non-noxious stimulus) is the result of activation of the NMDA receptor by glutamate.⁸ Glutamate is a ubiquitous excitatory amino acid in the CNS. Noxious sensory input causes glutamate to act on the NMDA receptors and open the calcium channel, by magnesium displacement, allowing calcium to enter the intracellular space. This glutaminergic action also affects other ionic receptors, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate and nonionic receptors, metabotropic (G protein-coupled). Non-NMDA receptors are also

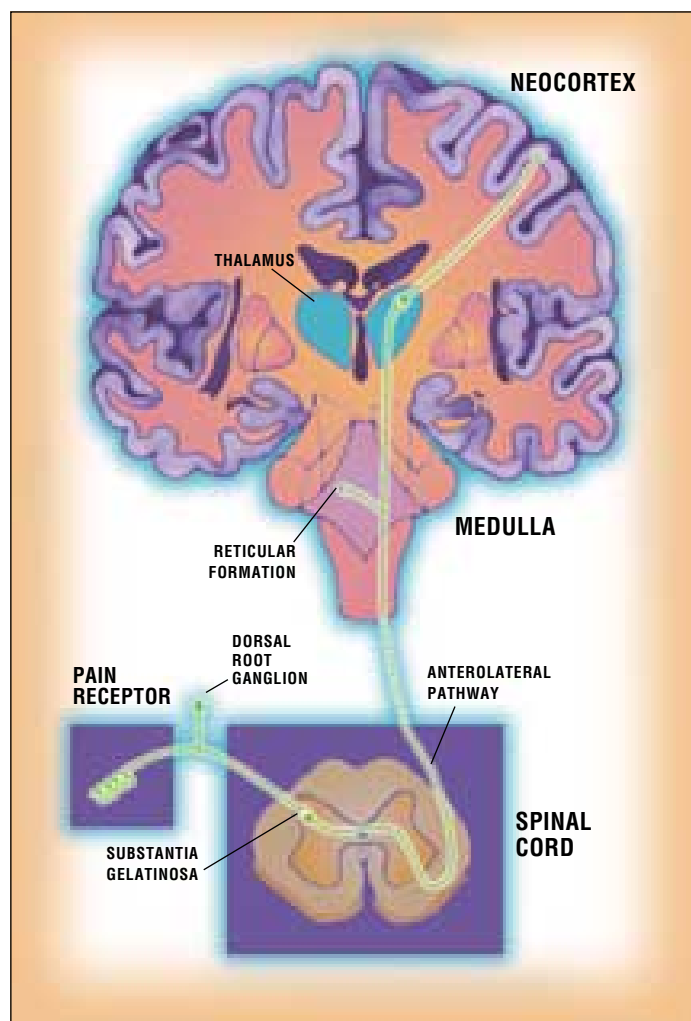


Fig. 1. Pain and temperature information travels to the brain via the anterolateral pathway. The figure is from *Human Physiology, second edition*, by Rodney Rhoades and Richard Pflanzler, copyright (©) 1992 by Saunders College of Publishing, reproduced by permission of the publisher.

referred to as *AMPA*.⁹ Intracellular calcium stimulates a cascade of events releasing protein kinase C, arachidonic acid, endothelium-derived relaxing factor and other mediators that further facilitate NMDA modulation action. This complex and multifactorial process leads to long-term potentiation via plastic changes at the dorsal-horn neurons.¹⁰ Neuronal plastic changes refer to learning and memory, kindling and long-term potentiation. The long-term potentiation results in the hyperalgesia and allodynia states commonly observed in chronic neuropathic pain.

Peripheral insult that stimulates action at the NMDA receptors also involves other systems: substance P, α agonists and antagonists, GABA agonists and the free-radical system. This brief summary of the pathophysiology of chronic neuropathic pain is

certainly not all inclusive. Much is yet to be learned regarding the pathophysiology of neuropathic pain. It is, however, a more complete basis of understanding than ever before. Manipulating the NMDA receptor with the available antagonists concomitantly with other agents is the basis for increased efficacy in managing neuropathic pain emanating from any type of noxious insult.

Evidence

In 1996 Klarica and colleagues, and in 1997 Wei and colleagues respectively, announced the presence of NMDA-receptor subtypes in the spinal cord.^{11,12} Carlton and colleagues, in April 1998, suggested that NMDA receptors were located in the periphery on unmyelinated axons at the der-

mal-epidermal junction. This discovery of the presence of local NMDA receptors in the periphery was significant. It provides support for the theory of the existence of primary afferents that may behave as central neurons.¹³

A local response to glutamate action resulting in long-term potentiation from plastic changes on local NMDA receptors to express hyperalgesia and allodynia is an interesting theory. Plastic changes in the CNS, including the spinal cord, are well documented to result from NMDA receptors' stimulation and resultant calcium flux to the intracellular space. Kumazawa reported that plastic changes lead to "crosstalk among neural networks" (see Fig. 3). This communication establishes a persistent memory-like state that leads to long-lasting pain. This chronic neuropathic pain requires treatment from a multidisciplinary perspective.¹⁴

Eide added evidence in September 1998 of sodium-channel involvement in NMDA-receptor modulation. Intracellular sodium indirectly induces the reduction of the GABA and opioid inhibitory systems as the glutamergic surge stimulates the NMDA channel to allow calcium influx to trigger intracellular activity.¹⁵ The role of sodium in the excitotoxicity of neurons is thought to be additive to the NMDA receptor. The AMPA receptor is intimately involved with the NMDA receptor.¹⁶

In July 1998 and November 1998 it was independently reported that peripheral and dorsal-horn sites are active in sodium-channel receptors. These neurons were responsible for sodium flux after AMPA activation. The result was delayed calcium rise intracellularly and an increase in excitotoxicity.^{17,18} Excitotoxicity is a precursor to long-term potentiation.

The AMPA receptors are located in close proximity to the NMDA receptors. The AMPA and kainate receptors mediate fast pain to NMDA areas. N-methyl-D-aspartate responds to this input in a secondary but significant manner by producing plastic changes that result in long-term potentiation states of hyperalgesia and allodynia. This activity of AMPA, kainate and NMDA

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receptor interaction is communicated from various neighboring neurons.¹⁰ Shi and colleagues reported in June 1999 the observation that AMPA action required the synaptic activation of NMDA receptors before the interaction could potentiate the development of long-term potentiation, thus, its polymodal complexity.¹⁹

In October 1998 Coutinho reported that visceral hyperalgesia is the result of NMDA receptor activation and confirmed the role of glycine as a co-agonist of glutamate at the NMDA receptor.²⁰ The NMDA receptor noncompetitive antagonists are reported to inhibit glycine's role in increasing the efficiency of glutamate action.²¹ Joint pain was described as being associated with AMPA and NMDA receptors by Neugebauer and colleagues in May 1993.²² The nociceptive input from the joint was received by the NMDA receptors and the mechanical input by the AMPA receptors. This again demonstrates the complex role of multimodal involvement in neuropathic pain. Carlton discovered a peripheral site of action for gabapentin in May 1998.²³ The mechanism of action is uncertain; however, it is known that gabapentin is a glutamate antagonist due to its anticonvulsant action. Davidson, in March 1997, reported localized glutamate receptors discovered on cutaneous axons. He concluded that a topical route of administration would avoid medication side effects from systemic dosing.²⁴

The involvement of free radicals in excitotoxicity was first reported by Schulz in May 1995.²⁵ This *in vivo* study provides evidence for the use of antioxidants in the treatment of chronic neuropathic pain.

Drummond and colleagues discovered α_1 -receptors in the epidermis.²⁶ The concentration was greater in the epidermis and dermal papillae than further down in the dermis. The comparison of hyperalgesic to normal human skin demonstrated a significant mean density increase in the patients with neuropathic pain.

The GABA agonist action is inhibitory to pain signals. Specifically, the GABA_b receptor is a member of the metabotropic (G protein-coupled) complex associated with

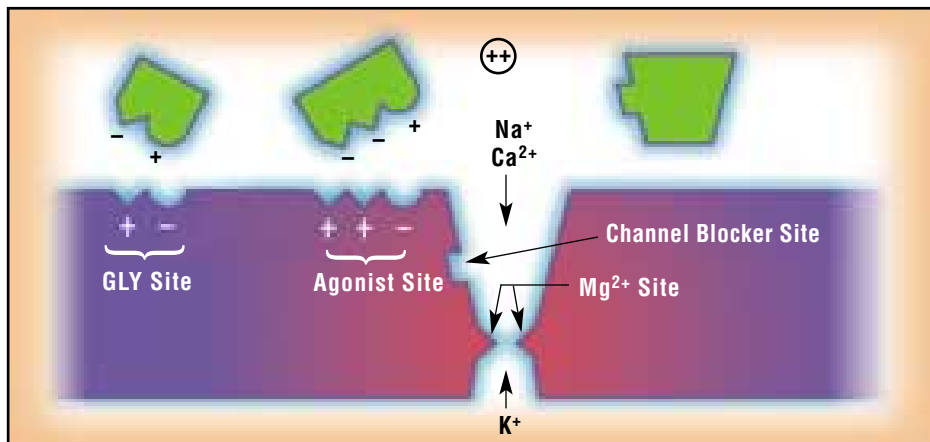


Fig. 2. Basic scheme of the NMDA receptor complex. GLY site is glycine receptor. Agonist site is glutamate receptor. Channel blocker site is NMDA antagonist receptor. Source: Collingridge GL, Watkins JC. The NMDA Receptor, ed 2, 1994, p.17.



Fig. 3. Illustration depicting how scores of nerves interconnect between axon to dendrite - a virtual network of signals passing from one to another.

the NMDA receptor modulation of sensory input.¹⁰ Agents that are agonistic at the GABA_b receptor are useful concomitantly with NMDA antagonists to mitigate glutaminergic calcium influx more effectively

than either alone. Evans describes baclofen as a myorelaxant GABA_b agonist possessing presynaptic depressant action at NMDA and non-NMDA receptors.²⁷

The α_2 -adrenergic receptors are located

Table 1. Mode of Action (MOA) Table.

MOA (Classification)	Drug or Drug Class	Route of Administration
NMDA Ca ²⁺ channel antagonist	Ketamine, amantadine, dextromethorphan, memantine,* orphenadrine, haloperidol, nylidrin	Topical, oral, injection, sublingual,** buccal,** nasal,** rectal**
Glutamate antagonist	Gabapentin	Topical, oral
AMPA (Na ⁺ channel)	Gabapentin, carbamazepine, valproic acid, phenytoin	Topical, oral, rectal**
α_2 -Agonists	Clonidine, tizanidine	Topical, oral, injection
NE reuptake inhibitors	Tricyclic antidepressants	Topical, oral
α_1 -Antagonists	Prazosin, phentolamine	Topical,** oral, injection**
GABA _b agonists	Baclofen	Topical, oral, injection, sublingual, rectal
Non-NMDA Ca ²⁺ channel blocker	Nifedipine	Topical
* investigational in US **does not apply to all		
<i>Note: This table is intended only as a quick reference guide. It is not complete.</i>		

in the periphery and the CNS. Agonists of these receptors block norepinephrine release from sympathetic nerve endings. The α_2 -agonists also potentiate the effects of anesthetics and opiates.^{10,28} Interestingly, Aley and Levine stated, in January 1997, evidence for μ -agonist action of clonidine, a known α_2 -agonist. They further concluded that multiple mechanisms of action, i.e., μ -agonist and α_2 -agonist, are required for peripheral antinociception.²⁹ The opioid receptors are located in the CNS and periphery. At least three sites have been identified: primary afferent nerves, postsynaptic spinal neurons and the central spinothalamic tract. Opioid receptor agonists block substance P release and dull the sensation of pain. The opioids do not ameliorate neuropathic pain very effectively when used as monotherapy. A feature of opioid use is tolerance. The NMDA antagonists are known to block morphine tolerance.³⁰ Muller and Lemos assessed the addition of ketamine, a noncompetitive NMDA antagonist, to an intrathecal mixture of morphine, clonidine

and lidocaine. The patients also received oral sustained-release morphine. The addition of ketamine gave significant additional pain relief without side effects and the dose demands of oral sustained-release morphine were reduced.³¹

A New Approach

Considering the barriers to effective pain management shared by patients and providers, it is time to consider a different approach to the problem as we enter a new millennium. The problem of side effects can be minimized by using low-dose concomitant agents with complementary modes of action. Also, knowledge of receptor location (see Fig. 4) provides different routes of administration to avoid oral or infusion systemic doses when it becomes necessary to decrease the risk of side effects. Selection of oral dosing over injection is an option to decrease problems, i.e., ketamine. Oral ketamine has relieved "stump pain" from amputation without side effects.³² Al-

ternative low-dose infusions, in combination with other agents, are an option. Low-dose ketamine infusion was added to escalating oral opioid doses in terminal patients with intractable pain. This intervention resulted in profound analgesia, eliminated the need for further opioid dose increases and provided a calming effect on patients.³³

Gabapentin has been used orally for chronic neuropathic pain for years. Recent studies confirmed anecdotal reports.^{34,35} It is fortunate that gabapentin has a low profile of unwanted effects and interactions with other medications due to the high doses required to achieve neuropathic pain relief. Somnolence can be profound and discourage compliance, a barrier often overlooked. Another compliance issue with gabapentin is cost; in the United States it is expensive. Carlton suggested topical gabapentin may be novel.

Theories related to receptor location involvement offer new approaches to pain management. Drummond and Davidson reported α_1 receptors and glutamate receptors located in the periphery. Opioid and α_2 -agonist receptors are known to exist locally. Evidence of NMDA receptors in the epidermal-dermal junction was reported by Carlton.^{23,24} The AMPA receptors are located in close proximity to NMDA receptors. Coutinho expanded the thought process on NMDA receptor involvement in visceral hyperalgesia,²⁰ thus opening up a new approach to reduce suffering and side effects by combining low-dose ingredients with additive modes of action. Olivar and Laird confirm the involvement of NMDA receptors in processing and modulating visceral pain. Interestingly, ketamine and memantine were used in this study and gave independent positive results.³⁶ This is suggestive of different NMDA receptor subgroups as a site of action for these two noncompetitive antagonists of the NMDA complex.

The existence of multiple NMDA receptors is well documented. Sundstrom observed several subtypes of NMDA receptors in human spinal cord.³⁷ The subtypes were listed as: NR1, NR2A, NR2C and

NR2D, with the NR1 subtype found predominately in the dorsal half of the cord. The discovery of additional populations of subtypes, coupled with drugs possessing specific action at those receptor subtypes, will expand the NMDA antagonist market for the management of chronic neuropathic pain.

Apoptosis (cell death) is a well-known central event to constant glutamate insult at the NMDA receptor. Little is known about spinal apoptosis. Azkue and colleagues expanded the current knowledge in a June 1998 study.³⁸ This group gave a significant conclusion. Early signals from injured afferent nerves processed and modulated by NMDA receptors produced apoptosis predominately in the superficial ipsilateral dorsal horn. In groups treated with continuous NMDA antagonists, no apoptosis occurred. This provides a theory that early intervention with NMDA antagonists in neuropathic pain to block the glutamate shower of the NMDA receptor would prevent the calcium intracellular cascade of events that result in long-term potentiation and/or apoptosis.

Nifedipine is a non-NMDA, voltage-sensitive calcium-channel blocker. Robertson, in 1992, reported data on nifedipine as providing direct vasodilatory effect on vessels, nerve conduction, hypoxic resistance and capillary density in diabetic rats.³⁹ Pei and colleagues studied cortical neurons in 1996 and observed an additive protective effect of topical ketamine and nifedipine in combination greater than either alone in blocking glutamate insult when added to the cortical neuron culture.⁴⁰ Carins reported that NMDA and AMPA receptors are located in the temporomandibular joint (TMJ).⁴¹ Parada also found NMDA receptors located in the temporomandibular area.⁴² Clinical information on topical treatment of TMJ disorder pain with an NMDA antagonist is known from open-label evaluations.

Current evidence exists for a new approach in the management of chronic neuropathic pain. Compounding pharmacists interact intensely with patients and providers. This communication should be

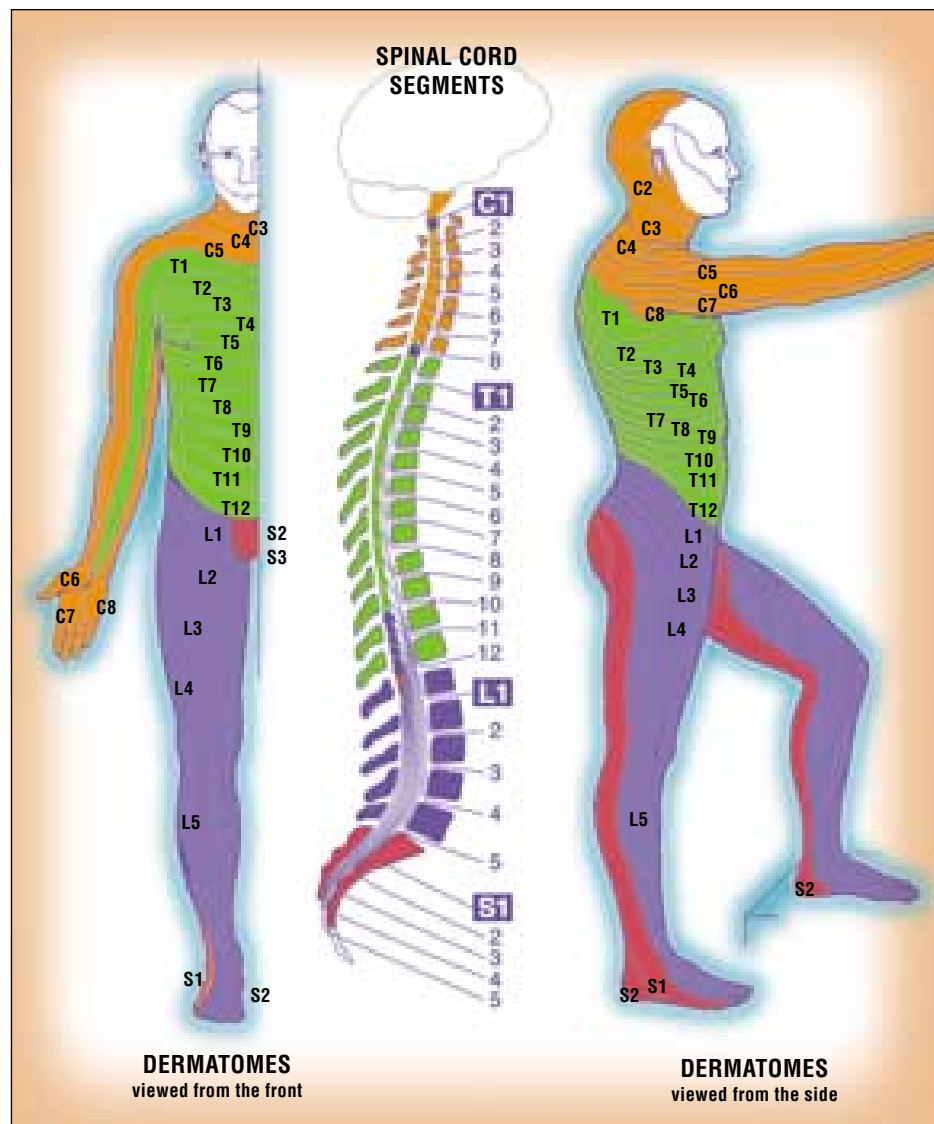


Fig. 4. The 31 segments of the spinal cord are linked to areas of the skin known as dermatomes.

used to overcome the barriers to effective pain management. Informed patients and practitioners are better prepared to understand the innovations available to them. Based on evidence presented and avoidance of problems, the choice of dose administration is a topical route of administration.

Multiple ingredients with complementary modes of actions (see Table 1) address the complex nature of chronic neuropathic

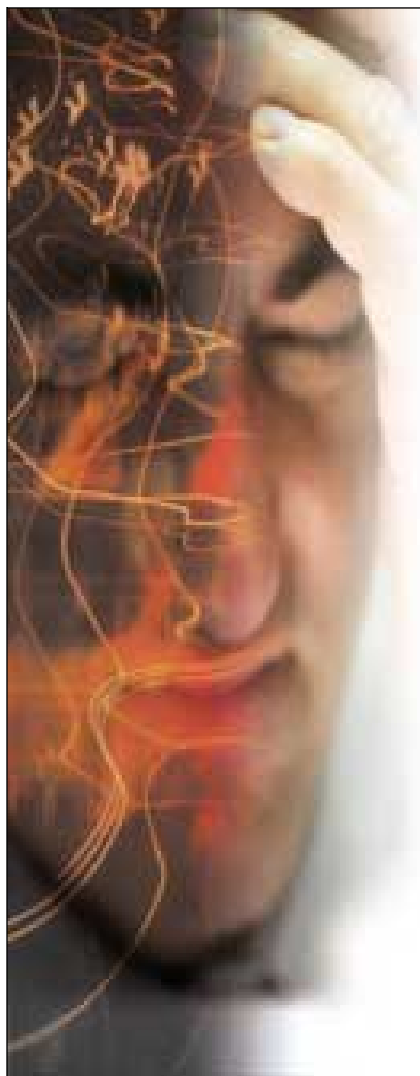
ic pain. The receptors for these medications are documented to be resident in the local tissues. A compounded base that contains penetration enhancers is preferred and clinically proven to be more efficacious than simple creams, gels and ointments. These enhanced bases are readily compounded: Pluronic[®] lecithin organogel (PLO), speed gel, vanishing penetrating cream (VanPen), and DemiGel. These bases affect the stra-

tum corneum in various degrees, depending on the formulation and preparation. The first choice should be the PLO or speed gel. If the clinical response suggests, the other bases are then available for selection. Based on the key role that the NMDA receptor performs in causing pain and suffering, an NMDA antagonist should be the first additive (see Table 1), a glutamate/AMPA antagonist second and either an α_2 -agonist, α_1 -antagonist or GABA_b agonist third. Next additional items from the third choice should be added. The theory of low-dose, multiple, concomitant, complementary therapy starts with three medications incorporated into a base, normally applied at eight-hour intervals on a regular basis and as often as every two hours as needed for breakthrough pain. Dose escalation can occur daily or every other day until pain is relieved or, rarely, side effects occur. Additional medication from a different mode of action should be added within one or two weeks after the

start of therapy, if needed. Again, dose escalation and evaluation should be repeated. Then another medication with a different mode of action should be repeated. Based on the apoptosis evidence, the new approach would include topical ketamine and low-dose nifedipine for diabetics with sensory peripheral neuropathy in an attempt to prevent the development of diabetic neuropathy from neuronal apoptosis numbness and the resultant high risk of amputation.

Clinical Compounding Success

Implementing this treatment algorithm involves a process of thoughtful consideration for the specific patient. A hypothetical Type II diabetes patient with a greater than five-year diagnostic history, normal- or low-risk cardiovascular status, elevated glycosylated hemoglobin (HbA1c), and chief complaint of pain in the legs would be considered for treatment with the following: ke-



THE PSYCHOLOGY OF PAIN

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All pain has a psychological component and the psychological factors surrounding pain are important during all stages of pain. The literature is replete with reference to the subjective nature of pain. Even the thought of pain is sufficient psychological motivation to keep some patients out of the dentist's chair.

There is growing evidence for the theory that pain-related fear in back pain patients may be more disabling than the pain itself. The fear was described as fear of pain, fear of loss of physical activity or fear of reinjury.¹ Concerns about pain and treatment were particularly associated with anxiety.² The avoidance of physical activity and fear of pain's returning were the two main factors directly associated with back pain patients. These two factors limited a return to physical activity, even though the majority of the patients believed strongly that being physically active helped ease their low back pain.³

In my personal clinical experience dealing with the concept of hospice care, the most important parameter from a pharmacological perspective is control of pain and the associated anxiety. It is my observation that significant pain control frequently abates anxiety. The experience of pain is

subjectively different from the fear of and anxiety caused by threats of pain. Anticipation of pain can in its own right cause mood changes and behavioral adaptations that exacerbate the suffering experienced by chronic pain patients.⁴

Peripheral sensory input to the central nervous system becomes dynamic from the psychosocial component. AIDS patients with pain, as compared to AIDS patients without pain, have significantly more symptoms on the Beck Depression Inventory. Of significant note were hopelessness and greater overall psychological distress.^{5,6} In a pilot study, AIDS patients with pain were twice as likely to have suicidal ideation (40%) as those without pain (20%).⁷

Often people with chronic pain suffer from depression, anger, anxiety, sleeplessness, sexual concerns, drug-related problems and suicidal ideation (Fig. 1). Chronic pain goes beyond the patient to family members, employment, leisure activities and life goals. A history of trauma or violence adversely affects chronic pain sufferers through coping difficulties and ineffective management of pain.⁸ Patients and caregivers need instruction about the facts of tolerance and addiction. Patient fears regarding tolerance have been rated higher

tamine 10%, gabapentin 6%, clonidine 0.2% and nifedipine 2% in a penetrating enhanced-gel base, e.g., PLO. Instructions for application would be one gram every eight hours and as needed. In addition, α -lipoic acid would be taken by mouth 100 mg three times a day and increased to 300 mg three times a day over a 30-day period. Citrus bioflavonoids and vitamins C and E would also be taken orally every day, along with CoEnzyme Q₁₀ taken sublingually. The patient would be encouraged to comply with medication to reduce the HbA1c to within normal limits. Metabolic control is very important to prevent complications of diabetes. Pain control and vascular improvement will give the patient hope for preventing further complications.

Conclusion

The numbers are staggering. According to *Business Week*

(1999;1:103-110), the world market for analgesics is about \$7.7 billion in US currency and growing at 7% per year. Fifty million Americans are partially or totally disabled due to chronic pain. Americans spend about \$3 billion per year on over-the-counter (OTC) analgesics. The American Pain Society estimates 45% of the population seeks medical help for persistent pain at some point. In the United States alone estimates for total cost of pain, including lost workdays and physician visits, is in excess of \$100 billion per year. The market is out there waiting for help. How many patients are spending serious money on over-the-counter (OTC) medication, not really aware that ibuprofen and acetaminophen are not that benign? In addition, knowing that most pain possesses a neuro-pathic component, it is easy to see that these OTC agents are not that effective. Communication is the central ingredient to expand the knowledge of effective and innovative treatment plans. Inter-

than the fear of addiction. The resultant loss of pain control and increased anxiety and depression are a large price to pay for lack of information.⁹

The large number of patients seeking euthanasia and physician-assisted suicide as a result of unrelenting pain and depression is the ultimate loss. A recent report in *JAMA* revealed that 15.8% of reporting oncologists had participated in euthanasia or physician-assisted suicide; a large number of patients both initiated and repeated their requests for euthanasia or physician-assisted suicide. Most were experiencing unremitting pain. The impact of this decision has long-lasting effects on both the patient's family and physician.¹⁰

Relief of pain has a positive impact on the psychology of pain. Compounding pharmacists are in a unique position in the triad of care to increase the efficacy of pain management. Communication with physicians and patients is key to effective control. Use of simple tools to assess pain, i.e., a visual analogue scale or numerical scale, is a critical parameter to management success. Only the patient can describe the level of pain; the practitioner must accept this information and act on it in a positive manner. The barrier of psychological input into the development of pain can be overcome with adequate control of pain. A team effort to attain this goal seems the most effective.



Fig. 1. Psychological stress factors associated with pain.

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act with your patients and inform them of choices. Both of you will be rewarded.

As the new millennium begins, be respectful of past endeavors to deal with the problem of chronic neuropathic pain. They were then where we are now as the next millennium rolls around. The theory of a new approach of pharmaceutical interventions to treat chronic neuropathic pain presented here is a synthesis of clinical feedback to the author since the beginning of 1999. The evidence-based ideas, presented as pieces of a puzzle, have one by one come together as part of a logical thought process to determine how to effectively manage a very frustrating problem: the agony and suffering of patients dealt the problem of chronic neuropathic pain. The efficacy is significant using this approach. The problems encountered are significantly rare, especially when the patient is monitored in a multidisciplinary manner. Compounding pharmacists are positioned to make an impact on this huge market. The subjective nature of pain is a personal assessment. The reward for ameliorating pain is personal satisfaction. The positive outcome is the personal thank you received from the patient.

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