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The Pharmacologic Management of Chronic Orthopaedic Pain

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Abstract: This article will: 1) define nociceptive and neuropathic chronic pain; 2) describe the different pharmacologic agents that may be used to treat orthopaedic patients who have chronic pain; and 3) provide a rationale for the use of nonsteroidal anti-inflammatory medications (NSAIDs), opioids, tricyclic antidepressants (TCAs), and membrane-stabilizing agents based on an understanding of the neuroanatomy and neurophysiology of nociceptive and neuropathic pain.

Introduction

Before it is possible to discuss the management of chronic pain, we must first define pain as a conceptual entity. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [8]. Thus, pain is both a physiologic process as well as a subjective and emotional experience. This definition asserts that "pain" implies the *perception* of a number of biochemical and physiologic processes. Without perception and a concomitant emotional experience, we have only a series of complex electrophysiologic events but not true pain [8].

There are two types of pain: nociceptive and neuropathic pain. *Nociceptive* pain is mediated by a number of discrete nerve pathways and neurotransmitters. It implies activation and/or sensitization of these nerves (nociceptors). Four physiologic processes are involved in nociception: (a) *transduction,* whereby nociceptors in the periphery change noxious stimuli into electrochemical impulses, (b) *transmission* of these electrochemical impulses to the spinal cord and further into the central nervous system, (c) *modulation* by a number of endogenous analgesic substances, and (d) *perception*.

Nociceptive pain can be further divided into both somatic and visceral subtypes. Somatic pain involves nociception in bone, periarticular soft tissue, joints, and muscles. Somatic pain is typically well localized in the patient's description of pain. Moreover, the patient uses adjectives such as "aching, gnawing, throbbing, or cramping" to describe somatic pain.

Visceral pain is mediated by a different set of nociceptors in the cardiovascular, respiratory, gastrointestinal, and genitourinary systems. The pathways and physiologic processes underlying the visceral afferent sensory system are not as well described as those subserving somatic pain. However, visceral pain pathways share many common features with somatic nociception. Typically, visceral pain is described as "diffuse" and is less topographically distinct than somatic pain. Other adjectives used to describe visceral pain are "colicky or squeezing."

There are no discrete preformed nerves, neural pathways, or neurotransmitters subserving *neuropathic* pain. Neuropathic pain results from injury to neural structures within the peripheral or central nervous system. The injury to these nerves generates spontaneous action potentials. Moreover, noxious stimuli may cause a reorganization of the nervous system. This is referred to as *neuroplasticity*.

There are three subsets of neuropathic pain described by the location of the injury. The pain of cervical or lumbar radiculopathy, spinal nerve lesions, or brachial or lumbosacral plexopathy are examples of *peripherally-generated* neuropathic pain. *Central* pain is caused by injury to the spinal cord or higher rostral centers. Examples of central pain syndromes include thalamic stroke and phantom limb pain. *Sympathetically-maintained* pain may be generated peripherally or centrally and is characterized by autonomic dysregulation. In the past, sympathetically-maintained pain has been referred to as reflex sympathetic dystrophy or causalgia. More recently, a new nomenclature has been devised referring to these entities as complex regional pain syndrome, Types I and II, respectively.

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Nonsteroidal anti-inflammatory medications

Nonsteroidal anti-inflammatory medications (NSAIDs) are the most commonly used medications for treatment of orthopaedic pain. Table 1 lists the families of NSAIDs in common use in the United States. The majority of NSAIDs are derivatives of carboxylic acid. The individual carboxylic acid families of NSAIDs are: the salicylic acids, the acetic acids, the propionic acids, and the anthranilic acids (Table 1).

Table 1. Pharmacologic nomenclature of the NSAIDs

Carboxylic acids	
Salicylic Acids	**Propionic Acids**
Acetylsalicylic acid (Aspirin)	Phenylpropionic acids
Nonacetylated salicylates	Ibuprofen (Motrin)
Choline magnesium trisalicylate	Fenoprofen (Nalfon)
(Trilisate)	Flurbiprofen (Ansaid)
Salicyl salicylate (Disalcid)	Ketoprofen (Orudis)
Diflunisal (Dolobid)	Naphthylpropionic acids
Acetic Acids	Naproxen (Naprosyn,
Indoles	Anaprox)
Indomethacin (Indocin)	**Anthranilic Acids**
Sulindac (Clinoril)	Fenamates
Etodolac (Lodine)	Meclofenamic acid
Pyrolle acetic acids	(Meclomen)
Tolmetin (Tolectin)	Mefenamic acid
Ketorolac (Toradol)	(Ponstel)
Phenyl acetic acids	
Diclofenac (Voltaren)	
Naphthyl acetic acid	
Nabumetone (Relafen)	
Oxicams	
Piroxicam (Feldene)	
Pyrazoles	
Phenylbutazone (Butazolidin)	

Mechanism of action

It was originally thought that nonsteroidal anti-inflammatory drugs derived their analgesic properties via peripheral inhibition of the enzyme cyclooxygenase (prostaglandin synthetase) [46]. During inflammation, cell membrane phospholipids are released and catalyzed by the enzyme phospholipase into arachidonic acid intermediates. The enzyme cyclooxygenase catalyzes the conversion of arachidonic acid intermediates into cyclic endoperoxide intermediates. These endoperoxide intermediates are unstable and go on to form the various clinically relevant prostaglandins: prostacyclin (PGI_2), thromboxane (PxA_2), and the tissue prostaglandins (PGE_2, PGF_{2alpha}). Recently, a central analgesic mechanism has been proposed [22,41].

As prostaglandins produce pain, a reduction in their quantity causes pain relief. Prostaglandins contribute to the process of transduction in conjunction with a number of other chemical algesic mediators (e.g., histamine, serotonin, bradykinin). Prostaglandins are known to sensitize the ability of nerves to generate action potentials. Thus, a reduction in the synthesis of prostaglandins decreases the ability of a noxious stimulus to be transduced into nerve action potentials. This is believed to be the peripheral analgesic mechanism underlying the use of NSAIDs.

Side effects

The side effects of NSAIDs are either prostaglandin-mediated or nonprostaglandin-mediated effects. The non-prostaglandin-mediated interactions are sometimes called "idiosyncratic." They will not be discussed further because of their rarity. The prostaglandin-mediated side effects include gastropathy, disorders of hemostasis, and nephrotoxicity.

Gastropathy

Prostaglandins are involved in gastric mucosal cytoprotection and inhibition of ulcerogenesis [3]. Prostaglandins are autocoids (locally generated hormones that act at the site of secretion) within the body of the stomach. Therefore, ulcerogenesis is promoted by the inhibition of prostaglandin synthesis by NSAIDs. The symptoms of NSAID gastropathy include dyspepsia, epigastric pain, anorexia, esophagitis, constipation, and diarrhea.

The issues surrounding the prophylaxis and treatment of NSAID gastropathy are complex [17,39]. Alcohol ingestion and smoking should be stopped. Patients should be questioned regarding their possible use of multiple NSAIDs. Such practice has no therapeutic benefit (as NSAIDs have a ceiling effect with respect to analgesia) and will only increase the risk of development of an ulcer or gastropathy. Prophylaxis of the development of gastropathy may be accomplished by the use of nonacetylated salicylates because their use carries a reduced risk [10,19]. Moreover, sulindac (Clinoril), nabumetone (Relafen), and salicyl salicylate (Disalcid) are also relatively gastric sparing. These drugs are inactive prodrugs, which must be converted by metabolic transformation into active metabolites [4,37]. Misoprostol (Cytotec) may also be used for prophylaxis of gastropathy in high-risk patients. Misoprostol is an analog of prostaglandin and causes gastric mucosal cytoprotection [15,36].

H_2-antagonists, antacids or sucralfate, should be used if gastropathy does occur. If ulceration develops, NSAIDs should be discontinued. If this is not possible, the dosage should be minimized, and treatment should be instituted with Misoprostol or H_2-antagonists.

Disorders of hemostasis

Although blood dyscrasias can occur, the most common hematologic side effect of NSAIDs is platelet dysfunction. Nonsteroidal anti-inflammatory drugs affect platelet aggregation and the platelet release reaction, thereby prolonging platelet bleeding time. All NSAIDs, except for acetylsalicylic acid (aspirin), competitively inhibit platelet cyclo-oxygenase [1]. Platelets are unable to participate in the release reaction until the drug is effectively cleared from the plasma (five half lives). Aspirin irreversibly inhibits platelet

cyclooxygenase [1]. The platelet will be unable to function in either the release reaction or aggregation for its lifetime, thereby prolonging the bleeding time for 6--10 days [6].

Nephrotoxicity

Glomerular filtration and renal blood flow are normally not prostaglandin-dependent. Prostaglandins are important as protective mechanisms against renal ischemia. In the clinical settings of dehydration, congestive heart failure and hepatic cirrhosis, renal blood flow and glomerular filtration become prostaglandin-dependent. Administration of an NSAID in these clinical settings may decrease renal blood flow and glomerular filtration by inhibiting prostaglandin synthesis [9,26]. The use of NSAIDs is not contraindicated absolutely in the aforementioned clinical scenarios. Caution should always be exercised. Any deterioration in renal function must generate immediate cessation of NSAID therapy.

Opioid therapy for chronic nonmalignant pain

Historically, long-term opioid administration had been viewed as ineffective and unsafe. Over the last 20 years, however, studies have demonstrated that this view may be inaccurate in selected subpopulations of patients with chronic pain [28--31]. Critical issues surrounding the protracted use of opioids for nonmalignant pain include: (1) therapeutic efficacy, (2) the potential for adverse pharmacologic outcomes, and (3) the risk of addiction.

Although an exhaustive review is beyond the scope of this paper, the data from nine surveys that support the use of chronic opioids for nonmalignant pain are outlined in Table 2.

Table 2. Surveys suggesting efficacy of opioid therapy

Author	N	Duration of therapy	Efficacy
Taub [42]	34	Up to 6 years	All benefited
Tennant and Uelmann [43]	22	Not states	Not stated
France et al. [13]	16	6--22 months	Sustained relief = 12
Portenoy and Foley [30]	38	6 months--10 years	Adequate = 24
Urban et al. [45]	5	12--26 months	All >50% relief
Portenoy et al. [31]	20	6 months--10 years	Adequate = 19
Tennant et al. [44]	52	Average > 15 years	Adequate 88%
Zenz et al. [47]	10	14--1472 days	Adequate 79%
Kell [18]	16	less than equal to 3 years	All benefited

No data exist that nonmalignant pain (in general), any patient subgroup, or any particular diagnosis (e.g., neuropathic pain) is inherently unresponsive to opioid therapy. It was traditionally viewed that neuropathic pain was more refractory to opioid therapy [2,21]. However, clearly there can be a

therapeutic response to opioids in any individual patient with neuropathic pain, though opioids should not be used as the first-line drugs of choice [31]. It is no longer tenable to believe that neuropathic pain or any other pain state denies the patient access to opioids on the presumption of inefficacy.

Of most concern to practitioners is the potential development of addiction in patients chronically using opioids. Three studies have been performed to determine the actual incidence of addiction with chronic opioid therapy. In the Boston Collaborative Drug Surveillance Project, only four cases of addiction were identified among 11,882 patients [32]. However, no cases of addiction could be identified in a survey of 10,000 burn patients treated for a protracted period with opioids [27]. In a headache population, only three patients were identified among 2,369 who eventually developed any type of drug-seeking behavior [24].

These data must be compared with the incidence of addiction to alcohol and other substances in the United States. The prevalence of alcoholism in the general population in the United States is 3--16% [34]. The incidence of other forms of substance abuse in the general United States population is 5--6% [34]. Thus, the data are compelling evidence that the potential for iatrogenic induction of addiction with prolonged opioid use is small in comparison to the prevalence of addiction to alcohol and other drugs in the United States population if appropriate patients are placed on chronic opioid therapy.

How should one proceed when an individual patient is possibly a candidate for this therapy? Evaluation for institution of opioids for chronic nonmalignant pain is a valid reason for referral to a pain center. Psychometric testing, psychological evaluation, and trial titration of medication will allow determination as to whether a patient is an appropriate candidate.

Medications for the treatment of neuropathic pain

Antidepressants and membrane-stabilizing agents (anti-convulsants) form the mainstay of treatment of neuropathic pain. Although NSAIDs and opioids can be effective in the treatment of neuropathic pain in their role as "general" analgesics, they do not represent primary therapy for neuropathic pain. Their use is adjunctive. As patients with orthopaedic pain may have a significant neuropathic component to their pain, it is appropriate to discuss the anti-depressants and membrane-stabilizing agents in some detail.

Antidepressants

The oldest and most clinically useful of the antidepressants are referred to as *tricyclic antidepressants* (TCAs). Of course, they possess three rings. Chemical substitution occurs on the middle ring. The second group of older anti-depressants is referred to as *heterocyclics* as they do not possess three rings. The analgesic as well as antidepressant effects of these two groups of antidepressants are attributable to the blockade of presynaptic uptake of serotonin and norepinephrine. Both groups of antidepressants are excellent for the treatment of depression. The tricyclic anti-depressants are most useful with respect to analgesia, and they are the best ones studied [25].

A more modern group of antidepressants solely blocks the reuptake of serotonin. These agents are referred to as *serotonin-specific reuptake*

inhibitors (SSRIs). Although excellent antidepressants, the serotonin-specific reuptake inhibitors have a poor record as analgesics in the treatment of neuropathic pain [23]. At least in one analgesic model, venlafaxine (Effexor) has been shown to have some analgesic utility. We must wait for further research regarding the analgesic utility of the newer serotonin-specific uptake inhibitors as well as venlafaxine.

Tricyclic antidepressants exist as tertiary or secondary amines (the result of metabolism of the tertiary amine). The side effects of the secondary amines seem to be more moderate than those inherent with the use of the tertiary precursors. Amitriptyline (Elavil) is metabolized to nortriptyline (Pamelor). Imipramine (Tofranil) is metabolized to desipramine (Norpramin) [16].

With the use of tricyclic or heterocyclic antidepressants, no antidepressant effect is classically seen for 1--4 weeks after the beginning of therapy. On the other hand, analgesic effects are almost immediate, occurring within 48--72 hours. Thus, it is possible to rapidly titrate these antidepressants for the treatment of neuropathic pain [16]. However, side effects become more prominent with rapid titration.

It is important to note that serum or blood levels of the antidepressants bear no relationship to the production of significant analgesia in the treatment of neuropathic pain [35]. Because of idiosyncratic variations in clearance among patients, there is marked variability in the serum and blood levels that are obtained after oral ingestion [14]. Although therapeutic ranges for the treatment of affective disorders have been established, serum or blood levels should not be used to determine the presence of "therapeutic levels" for analgesic purposes. With respect to the treatment of neuropathic pain, serum or blood levels of antidepressants can only be relied on as measures of potential toxicity and patient compliance.

Unfortunately, side effects become dose-limiting for their use as analgesics for neuropathic pain. The common side effects for tricyclic and heterocyclic antidepressants are: (1) anticholinergic, (2) antihistaminic, (3) $alpha_1$-adrenergic receptor blockade, and (4) miscellaneous.

The anticholinergic side effects are muscarinic in nature, including dry mouth, difficulties with visual accommodation, constipation, urinary retention, and delayed gastric emptying [16]. Fortunately, patients usually accommodate to the presence of dry mouth over time. For patients with narrow-angle glaucoma, tricyclic antidepressants are contraindicated. Caution must also be exercised with the use of these agents for patients with benign prostatic hypertrophy because of the possibility of the exacerbation of urinary retention.

The antihistaminic side effects are caused by the blockade of H_1-receptors. Sedation is the most common clinical manifestation. As with dry mouth, most patients will accommodate to this side effect if they are counseled before institution of therapy.

Other side effects can occur with tricyclic and heterocyclic antidepressants. Orthostatic hypotension may occur because of $alpha_1$-adrenergic receptor blockade. However, this side effect is rare. Miscellaneous problems include weight gain, photosensitivity, and jaundice [16].

Membrane-stabilizing agents

The membrane-stabilizing agents (anticonvulsants) are the other major group of drugs used for the treatment of neuropathic pain. These agents are pharmacodynamically similar to the antidepressants, and serum or blood levels are not useful in determination of analgesia [16]. Seizures can be induced with abrupt withdrawal in patients without a previous history of epilepsy. Therefore, these agents must be tapered if their use is no longer advantageous. Commonly used drugs of this class include phenytoin (Dilantin), carbamazepine (Tegretol), valproic acid (Depakene, Depakote), clonazepam (Klonopin), and gabapentin (Neurontin).

Phenytoin (Dilantin) alters sodium, calcium, and potassium ion exchange across membranes, thereby stabilizing them [16]. The use of phenytoin can be associated with hirsutism, ataxia, diplopia, confusion, nausea and vomiting, and upper gastric distress [16]. Gingival hyperplasia can be caused by stimulation of fibrocytes [40]. Vitamin K and D deficiencies as well as the anemia and neuropathy of folic acid deficiency may occur with protracted use of phenytoin [7]. Inhibition of insulin secretion and hyperglycemia are also side effects of phenytoin [16].

Similar to phenytoin, carbamazepine (Tegretol) is a sodium and potassium channel blocker. Carbamazepine bears a structural resemblance to the antidepressant imipramine (Tofranil). Except in trigeminal neuralgia, analgesia is usually not achieved with carbamazepine until a daily dosage in the range of 1.0--1.5 g is obtained. Because of the potential for significant side effects, slow titration of carbamazepine dosage is required. This limits its utility. The two major side effects are hemotologic abnormalities (thrombocytopenia, agranulocytosis, anemia and pancytopenia) and hepatic dysfunction. It is necessary to obtain blood counts as well as liver enzyme levels before therapy is instituted. These laboratory examinations should be obtained periodically to determine any decrement in cell count or elevation in enzyme levels over time. Carbamazepine therapy is also associated with ataxia, rash, sedation, nausea, and diplopia.

The mechanism of analgesia of valproic acid is unique among the membrane-stabilizing agents as it inhibits gamma-amino-butyric acid (GABA) transaminase [5]. Gastrointestinal symptoms are common but decrease over time. Liver failure is the most serious side effect [16], though sedation, ataxia, rash, alopecia, and tremor also occur.

Clonazepam (Klonopin) is a benzodiazepine. All benzodiazepines block the receptor-linked chloride channel to enhance GABA binding or activity [38]. Clonazepam is useful in the treatment of neuropathic pain because its effects can be relatively rapidly appreciated. Its side effect profile is similar to the rest of the benzodiazepines. Patients may become disinhibited, and a withdrawal syndrome may occur with abrupt cessation of therapy.

The use of Gabapentin (Neurontin), the newest of this group, is rapidly accelerating because of a benign side effect profile and apparent clinical utility for refractory pain states. Gabapentin binds to a specific receptor in the brain, blocks sodium channels, and may be associated with enhanced release or enhancement of the actions of GABA [12]. Protein binding is negligible, and there is therefore a minimal risk of drug interactions with the use of gabapentin. Gabapentin is excreted intact by the kidneys. Dosage must be reduced in patients with renal failure [33]. The side effect profile seems to be the best of all the membrane-stabilizing agents. Sedation, fatigue, gastrointestinal symptoms, and ataxia may still occur, though their

prevalence is less common [11].

Although chronic pain affects at least one in three Americans at some point in their lives, most physicians have received little formal education to prepare them to help with their care. It is important for the orthopedist to be aware of the pathophysiology involved, and the treatment options available. Consultation with or referral to a holistic, multi-disciplinary pain treatment program is appropriate for most patients with neuropathic pain and any others whose pain fails to respond to care in the appropriate time for the given pathology.

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