

Pain Relief Connection

The Pain Information Newsletter

Provided by MGH Cares About Pain Relief

Archived issues are available at <http://www.MassGeneral.org/PainRelief>



Volume 1, No. 12

December 19, 2002

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Clinical Focus: Pharmacologic Interventions for Pain.

NOTE: This series is intended to provide general information and context about medications for the treatment of pain. Clinical experience and judgement, individualization of treatment, and consultation with experts and standard references should guide the treatment of specific patients.

WORLD HEALTH ORGANIZATION [ANALGESIC LADDER](#): STEP 1--NONOPIOID ANALGESICS--NSAIDS, PART 1

PATHOPHYSIOLOGY OF INFLAMMATORY PAIN--A BRIEF LOOK

Step 1 of the WHO Analgesic Ladder includes both acetaminophen (see [Pain Relief Connection Vol 1 #11](#)) and nonsteroidal anti-inflammatory drugs (NSAIDs). Inflammation is a complex process fundamental to immune response and healing, and contributes to many acute and chronic pain conditions. Tissue injury results in the release of the enzyme cyclooxygenase-2 (COX-2). COX-2, in turn, "stimulates the production of prostaglandin E₂, which promotes a region of localized hypersensitivity surrounding the injury." ([The Scientist](#)) Other types of prostaglandins, stimulated by COX-1, are involved in production of the protective mucosa of the stomach, and the capacity of platelets to clump by becoming sticky. It is unclear what role COX-1 may have in pain and/or inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are thought to provide pain relief primarily by targeting COX-2 at sites of inflammation. Both efficacy and toxicity of most NSAIDs is dose dependent.

There has been a dramatic increase in scientific knowledge about NSAIDs in the past 30 years, and especially in the past 10 years. New NSAID classifications and drug selection criteria have been proposed based on the relative ability of a drug to inhibit COX-1, COX-2, or both. Some NSAIDs are also antipyretics. Most classes of NSAIDs ("nonselective NSAIDs") target both COX-1 and COX-2 to a greater or lesser degree. The newer selective COX-2 inhibitors (celecoxib, rofecoxib, and valdecoxib) will be the subject of the February "Clinical Focus."

SPECTRUM OF NSAIDS

There are a large number of NSAIDs ([Micromedex](#), in the [Partners Handbook](#), lists 64 drugs) in roughly a half-dozen subclasses. Several are available over the counter, while most are available only by prescription. All NSAIDs are available for oral administration. A few are available in liquid formulations, as chewable tablets, as topical preparations, or as rectal suppositories. One, ketorolac, is available for parenteral administration. Aspirin is found in combination with many over the counter and prescription analgesic products and cold remedies. Ibuprofen is found in certain cold remedies and in combination with the opioids hydrocodone and oxycodone.

PRINCIPLES OF NSAID THERAPY

1. When studied over large populations, no specific NSAID has been found to be more efficacious as an analgesic than the others.
 - Drug and dose should be individualized to patient characteristics, including patient-reported pain relief.
 - If pain is not sufficiently relieved with escalating doses of an NSAID over 2 weeks, trials with other NSAIDs may be attempted.
2. Assessment should include a history of what has worked in the past and what side effects were experienced.
3. For persistent pain syndromes such as arthritis, dosing should be scheduled rather than PRN.
4. Over the counter NSAIDs or acetaminophen should be considered first line treatment for mild to moderate acute or persistent pain. Note that moderate (WHO Step 2) pain may require addition of an opioid.

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5. All NSAIDs have potentially serious and even life-threatening toxicities, especially when used chronically or in high doses. The balance of benefit and risk must be considered in prescribing and managing NSAIDs.
 - Most NSAIDs are excreted by the kidneys; renal function should be considered in prescribing and dosing.
 - History of peptic ulcer, bleeding disorder, cardiac disease, or asthma requires caution and monitoring.
 - Concurrent use of anticoagulants may preclude use of some NSAIDs or require dose adjustment
 - If a surgical procedure is anticipated, NSAIDs should be stopped or the drug changed to one that does not inhibit platelet aggregation. For disabling pain conditions, temporary substitution of an opioid should be considered.
 - The prescriber should know components and doses of all prescription and non-prescription products that the patient is taking.
 - Patient education should include dose and schedule, side effects, and drug-drug interactions.
6. Safety and efficacy for most NSAIDs has not been determined in children; ibuprofen in age-appropriate doses is widely used.
7. Aspirin should not be used in children < 18 years unless specifically prescribed for a non-viral condition.

In the News

In a strong vote of confidence in MassGeneral and MGH Cares About Pain Relief, the [Mayday Fund](#) has awarded MGH a supplementary grant to continue the initiative into 2003. The grant recognizes both past performance and the hospital's commitment to improved pain management. At this writing, not only do we expect to continue with our "signature" programs (Pain Relief Champions course; Pain Pulse; the [PainRelief](#) web site; and *Pain Relief Connection*), we will also be working on JCAHO preparation and new educational initiatives. Requests for mentoring for pain projects or for pain management educational presentations can be directed to PainRelief@Partners.org or Tom Quinn at 617-726-0746.

[Last Acts](#), a national coalition to improve care and caring near the end of life, has issued a national and state-by-state [report card](#) on care of people near the end of life, "Means to a Better End: Report on Dying in America Today." Many variables were evaluated. Among those related to pain were reports on the percentage of nursing home residents in persistent pain (35 - 45% in Massachusetts); the degree to which public policy supports pain management (in Massachusetts public policy "creates barriers" to pain management); and existence of hospital-based pain and/or palliative care services and pain management education programs. Most states, including Massachusetts, scored mostly C's and D's.

Journal Watch: Acute abdominal pain update

In the "Pain Topics" column of the [November issue](#) of *Pain Relief Connection*, the controversy about the use of opioid analgesics in the acute abdomen was explored. One of the points raised was the problem of rapid diagnosis and the questionable benefit of newer diagnostic tools. An underlying theme was the historical lack of evidence to support common practice. A [small study](#) in the Dec 14 issue of [BMJ](#) suggests that early use of abdominal CT "can identify unforeseen serious abdominal conditions," and possibly reduce length of hospital stay and mortality. Note that the focus of the study was early diagnosis, not pain. Limitations: this was a prospective randomized study, but the study population was small and randomization took place after admission, not in the emergency room.

URL notes: **Hold your cursor over the link for a second to see the URL.** If you are reading this in hard copy, this month's links are:
 Center for Clinical & Professional Development course calendar: <http://tinyurl.com/23zk>
 WHO Analgesic Ladder: <http://www.mcmahonmed.com/wworks/CHARTS/3step/default.html>
 November issue of *Pain Relief Connection*: http://www.massgeneral.org/painrelief/Newsletter/prevol1_11.pdf
The Scientist, Daily News, March 26, 2001: <http://www.biomedcentral.com/news/20010326/02>
 Micromedex: <http://is.partners.org/handbook/TextJournal/pdr.asp> (available only from Partners HealthCare System computers)
 Partners Handbook: <http://is.partners.org/handbook> (available only from Partners HealthCare System computers)
 Abdominal pain and early CT diagnosis article: <http://bmj.com/cgi/content/abstract/325/7377/1387?ijkey=9ZSfG7NBPEIJK>
BMJ: <http://bmj.com> (a major peer-reviewed journal available free online)
 MGH Cares About Pain Relief web site: <http://www.massgeneral.org/painrelief>
 Last Acts: <http://www.lastacts.org>
 "Means to a Better End": http://www.lastacts.org/scripts/la_tsk01.exe?FNC=BetterEndHome_Ala_newtsk_laxlike_html
 Massachusetts report card: <http://www.lastacts.org/files/publications/Fact%20Sheet%20MA.pdf>
 Mayday Fund: <http://www.painandhealth.org/mayday/mayday-home.html>

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PAIN TOPICS

Shingles and Postherpetic Neuralgia

Anne Louise Oaklander, MD, PhD, and Julia Campeti, BS
Partners Nerve Injury Unit at MGH

Overview

Shingles (herpes zoster) is a painful, necrotizing rash caused by focal reactivation of latent varicella-zoster virus. The virus, which causes varicella (chickenpox) in naïve individuals, lies dormant in sensory ganglia long after the resolution of chickenpox.¹ The most common locations for a shingles rash are the torso and above the eye, but shingles can occur anywhere on the body.² Shingles has the highest annual incidence of any neurological illness³ and will affect 15% of Americans during their lifetime.⁴

Shingles destroys peripheral sensory neurons and can cause serious complications, of which the most common is postherpetic neuralgia (PHN), the persistence of pain in an area affected by shingles at least three months prior. PHN often resolves within the first six months following shingles, but for some, the pain can last for years or indefinitely. Age is the most significant risk factor for developing shingles and, independently, PHN.⁵ At least 50% of shingles patients over age 50 and 75% of those over 70 will be left with PHN.⁵ Consequently, shingles and PHN are a major health threat to the elderly. Other at-risk populations include those immunocompromised from illness or medication.

PHN causes combinations of various pain complaints. Some PHN patients will experience *mechanical allodynia*, or pain from light touch, and will go to extremes to avoid contact between their PHN-affected skin and clothing, bed sheets, or even a light breeze. Other PHN patients will be left with *hyperalgesia*, or exaggerated pain following a minimally painful stimulus. Others report sudden paroxysms of stabbing or lightening-like pain known as *lancinating pain*. Another complication of zoster is the chronic itch syndrome known as *postherpetic itch* (PHI).⁶ PHI is more common after shingles on the face or neck than torso⁷ and seems more resistant to medical treatment than PHN.

Treatment of established PHN

Immediate treatment of shingles with antiviral medications and tricyclic antidepressants is proven to lessen the likelihood and severity of PHN.⁸ Treatment of established PHN is similar to that of other neuropathic pain syndromes, with medications as the most effective therapeutic option. Efficacy and safety have been established in placebo-controlled double-blind studies for four categories of treatments:

1. topical local anesthetics
2. tricyclic antidepressants
3. anticonvulsants
4. opioids

It is difficult to predict who will be helped by which medication, so it is often necessary to try several medications before finding the optimal treatment and dose for a particular patient. As a rule, the medications most likely to be effective should be tried first, titrated to an adequate dose, and then discontinued if ineffective or poorly tolerated. Elderly patients should be treated with attention to potential cognitive side effects, hypotension, constipation, cardiac arrhythmia, and urinary retention.

1. **Topical anesthetics** in patch, cream, and other forms are a promising advance for PHN. Applied to painful skin, topical anesthetics act locally, making them ideal for many patients because of the lack of side effects and drug interactions. The Lidoderm™ patch contains 5% lidocaine and is FDA approved for PHN.⁹ Lidocaine in gel, ointment, or spray preparations can help patients with pain affecting mucous membranes, especially by allowing them to engage in specific activities (e.g., chewing). Because systemic absorption can occur when lidocaine is applied to the mucosa, serum levels should be tested. Topical creams and ointments containing capsaicin, a substance P depletor found in chili peppers, are not widely used because

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of their intolerable burning sensation upon application.¹⁰ A few small clinical trials of topical non-steroidal anti-inflammatory drugs (NSAIDs) have been conducted¹¹ with uneven results.

2. **Tricyclic antidepressants** (TCAs) are a mainstay of treatment for PHN and other types of neuropathic pain.¹²⁻¹⁴ Noradrenergically active TCAs are effective for persistent ongoing pain,¹²⁻¹⁵ lancinating pain, and allodynia as well.¹⁵ However, patients rarely obtain total relief from TCAs and are often unable to tolerate their side effects (cognitive changes, constipation, dry eyes and mouth, and orthostatic hypotension).

Desipramine, given in the morning, and nortriptyline, given at night, are the best tolerated; amitriptyline is contraindicated for patients over 65 because of side effects.¹⁵ Initial doses range from 10–25 mg daily, depending on a patient's age and risk for side effects. Elderly patients should always be started on the lowest dose. Dose escalation should proceed in 10–25 mg weekly increments as tolerated. Most patients achieve pain relief in the dosage range of 60–100 mg/day. If marked relief is not obtained at this level, other therapies should be tried. Rare patients benefit from and tolerate doses ranging from 150–250 mg/day.

3. **Anticonvulsant medications** decrease neuronal sodium ingress and excitability. They work against PHN as well as epilepsy because both are associated with excess central neuronal firing. First-generation anticonvulsants, such as carbamazepine, have been shown effective in relieving pain,¹⁶ but gabapentin, with fewer serious side effects, is now preferred. Because of its relatively benign side-effect profile and paucity of drug interactions, gabapentin has become a first-option treatment for neuropathic pain. Moreover, its tolerability allows for higher dosing for treating pain than necessary for epilepsy. With no need to monitor blood tests, the drug is also easy to manage. Gabapentin is effective against different pain qualities in PHN.^{17,18}

Initial dosing is 100–300 mg nightly in geriatric patients, increased by one pill (i.e., 100 mg or 300 mg) daily toward 1,800–3,600 mg daily. The most common side effects include mild sedation, dizziness, and edema of the extremities. Gabapentin is expensive, as are other new anticonvulsants (e.g., lamotrigine, topiramate) that have not yet been evaluated in clinical trials for PHN.

4. **Opioids** were once avoided in the treatment of neuropathic pain because of concerns about lack of efficacy and risk of abuse, but they have been shown effective and safe for PHN in several double-blinded placebo-controlled trials.^{19,20} Risk of abuse is particularly low among geriatric patients, unless there is a prior history.¹⁹ Raja et al.'s recent study compared opioids to TCAs for treatment of PHN and found that both provided effective pain relief but patients preferred opioids.²¹ Neither treatment significantly impaired cognitive function.²¹

These data confirm that opioids are a first-line treatment option for geriatric patients. While extended-release opioids are generally preferable for chronic pain, shorter-acting agents may lessen cognitive side effects and accumulation of metabolites in older PHN patients. Methadone is a useful option: long lasting, inexpensive, and available in minute doses adequate for treating smaller or elderly patients. Prescriptions for the opioid must be labeled with the notation “for pain” in order to be filled at most pharmacies around the country.

Other treatment options

Intrathecal steroids: A Japanese group has documented efficacy of intrathecal methylprednisolone for PHN.²² Subjects were carefully selected and followed for two years. A 90% rating of good or excellent global pain relief was reported, higher than for any other known PHN treatment. However, it is difficult to obtain approval for the intrathecal administration of methylprednisolone, and intrathecal local anesthetics in the mix can potentially cause spinal block and hypotension. Confirmation of these data is awaited.

Surgery: Although surgery be effective in some neuropathic pain conditions, it is not an option for PHN. Neurosurgical options should be considered only in rare patients with longtime pain unresponsive to all available medical options. Ablative procedures that sever pain pathways are rarely helpful and sometimes cause additional pain or neurological problems. Most experts in the surgical treatment of PHN discourage ablative procedures.²³ In rare cases, patients with limited life expectancies may be candidates for ablative techniques that can produce a pain-free interval of a few months.

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Augmentative therapies: Treatments that augment the function of remaining neurons, such as nerve or spinal cord stimulators, have proven very effective for treating other types of neuropathic pain.²⁴ Unfortunately, there are few studies in PHN patients. A recent report²⁵ supports efficacy but requires confirmation by other groups.

Comprehensive treatment

An interdisciplinary approach to caring for patients disabled by chronic pain should address psychosocial burdens and functional impact. Supportive counseling, cognitive-behavioral training, support groups, and similar normalizing interventions can help some patients and their families. These approaches may encourage safely increasing physical activity and foster reacting to pain in ways that are less negative and self-defeating. Physical and occupational therapies can address loss of strength and range of motion, and maximize function and minimize secondary problems associated with disuse.

Conclusion

PHN can be a devastating consequence of shingles, a serious and common neurologic disease. The elderly and people with immune systems weakened by disease or medication are at a higher risk of developing PHN than the population in general. Clinicians should be aware of the importance of treating zoster early and aggressively with antivirals, analgesics, and TCAs to lessen complications as well as to provide symptomatic relief. For patients with established PHN, there are four classes of medications documented in clinical trials to be effective and safe.

To learn more about treating shingles, PHN, and other zoster-related complications, please visit the websites of the [Center for Shingles and PHN at MGH](http://www.shingles.mgh.harvard.edu) and the [VZV Research Foundation](http://www.vzvfoundation.org).

Links

Center for Shingles and PHN at MGH: <http://www.shingles.mgh.harvard.edu>

VZV Research Foundation: <http://www.vzvfoundation.org>

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