

Pharmacologic Strategies for Pain Management

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Albert Schweitzer once said that “*pain is a greater lord of mankind than even death itself*”.

The treatment of pain and suffering is rewarding and truly a privilege for care givers. Appropriate pain management can only be rewarding to the care giver if care is well founded on good scientific and clinical principals. The appropriate management of pain depends on a thorough understanding, by the physician, of the neurobiological mechanisms underlying the patient's pain and the varying painful syndromes that are seen in the clinic. Not all pain is the same and the successful treatment of pain depends on this understanding. Some pains respond to opioid management and some pains do not; some pains may respond to destruction of the sympathetic nervous system (the sympathetic nervous system is part of the involuntary nervous system of the body controlling bodily functions such as blood flow, heart rate, sexual function, respiration, digestion, etc.), while others do not; some pains may respond to anti-depressant medications or anti-convulsant medications, again, while others do not, and so on.

It is the purpose of this presentation to enhance the understanding by the reader of sound principles of drug prescribing by pain physicians. This presentation should not serve the reader as a bible of understanding. Rather, it should clarify why we do what we do. Also, the clinical practice of medicine is more of an art than a science and not all artists

create in the same manner. What one physician prescribes, another may not and vice versa. Also the reader should understand that this discussion may not be complete and some drugs that the reader may have heard of might be omitted.

Myths and Barriers that Prevent Adequate Pain Management

Before undertaking the task of discussing what are appropriate pharmacologic strategies for pain management, it is important to understand that there are myths and barriers that prevent people, suffering from pain, getting the appropriate therapy that they need. These barriers, here-to-fore, have been successful in preventing good pain management, however, pain and its adequate control are ideas whose time have come. Patients are recognizing that there are means to good pain control and they are learning to demand the best that is available to them. Most importantly there has been a new awareness in the medical and biomedical communities that there are neurobiologic causes for persistent pain and new strategies for treatment of this pain have been developed. **See our web discussion on the neurobiology of pain.** Because of this growth in information regarding pain and its appropriate therapy, government regulators all over the country are now listening with new ears as to what are appropriate regulations governing the medical dispensing of analgesics.

These various barriers to effective pain control come from many areas of our society. They include the beliefs and mores of patients, care givers, and government alike and misinformation surrounding the analgesics that are needed for pain management. Clinician factors may include **uncertainty** about the role of opioid therapy for patients with non-malignant or cancer related pain. Many physicians feel that opioids are not appropriate for patients with non-terminal disease or that they might make addicts of their patients if they treat with opioids. In cancer patients, physicians might be uncertain about the role of opioids for patients with early cancer related disease, slow growing metastatic disease, or treatment-related disease. Another important clinician factor, resulting in ineffective pain management, is **under treatment** of the patient's pain caused by deficiencies of knowledge of opioid therapy, failure to adequately assess patient's pain or

pain complaints, overestimation of the risks of addiction, overconcern by physicians of side effects of the drugs prescribed, or fears of government regulatory scrutiny and loss of license. Patient related barriers to effective pain management may include insufficient pain reporting, erroneous fears of addiction to the opioids prescribed, beliefs that these drugs are harmful, or inadequate understanding of dosing guidelines.

What ever the cause for creating these myths and barriers, it is important that the physician participating in pain care understand what is and what is not appropriate for their patients. It is very important for you, the reader to also understand what is correct and what is not. The one single belief or myth of patients and care-givers alike that prevents the rational use of opioid medications for pain of non-malignant origin or even cancer related pain more than any other myth or belief is the fear that opioids invariable lead to addiction and loss of control in patients given opioids for medical reasons.

OPIOIDS ARE MEDICATIONS THAT CONTROL PAIN. ANOTHER WORD FOR OPIOID IS NARCOTIC. WE PREFER TO USE THE WORD OPIOID, RATHER THAN NARCOTIC, BECAUSE THE WORD NARCOTIC ASSUMES THAT PATIENTS WILL BE NARCOTIZED (MADE SLEEPY) BY THE DRUG USED, WHICH IS CERTAINLY NOT ALWAYS THE CASE. OPIOIDS EITHER COME FROM THE OPIUM POPPY AS IN MORPHINE OR CODEINE OR THEY ARE MADE BY PHARMACEUTICAL COMPANIES AS IN DEMEROL OR FENTANYL.

Opioid therapy for non-cancer related pain remains a controversial issue today, with many professionals in the health care field as well as government regulators alike still believing that the use of opioids are contraindicated and counterproductive in these patients. They fear that the use of opioids in this population of patients invariably will lead to **tolerance**, drug abuse and **addiction**.

These fears, now pervasive, were first created by some early 1950's studies that suggested that addicts became addicts by doctors giving them opioids for whatever reason. Unfortunately these studies were biased by the fact that only addicts were included in the studies and not other patients given the same medications for the same reasons who did not become addicted to the medications. In the last ten years, however,

many new studies, testing samples of patients given opioids for non-cancer related pain, and non-painful disorders, actually suggest an extremely low incidence of tolerance formation, few if side effects to the drug given, and a low incidence of addiction with the use of these opioids. Because of this new information suggesting the safety of using opioids for non-malignant pain, more and more pain practitioners are prescribing oral opioids for patients who continue to suffer in spite of numerous and more conservative interventions for their **intractable** pain problems. Intractable means no success of therapy inspite of multiple therapies tried.

IN THE LAST TEN YEARS, HOWEVER, MANY NEW STUDIES, TESTING SAMPLES OF PATIENTS GIVEN OPIOIDS FOR NON-CANCER RELATED PAIN, AND NON-PAINFUL DISORDERS, ACTUALLY SUGGEST AN EXTREMELY LOW INCIDENCE OF TOLERANCE FORMATION, FEW IF SIDE EFFECTS TO THE DRUG GIVEN, AND A LOW INCIDENCE OF ADDICTION WITH THE USE OF THESE OPIOIDS.

This new information regarding addiction has led to a redefining of the term. In years past, addiction was defined by the physiologic consequences of prolonged use of opioids leading to tolerance formation and physical dependence. It is now clear that addiction does not equal tolerance or physical dependence; they are separate and discreet entities.

Tolerance
and
Physical Dependence
are not the same as..
Tolerance
and
Physical Dependence
are not the same as..
Addiction

Tolerance to a given drug is a physical and cellular phenomenon where there is a greater and greater dosing need to achieve a desired or unwanted drug effect. Tolerance is heralded by a decreasing time interval for the effect of the drug to wear off.

Physical Dependence is also a cellular and physical phenomenon. Physical dependence is defined by the abstinence of the drug and the development of a drug withdrawal syndrome. Drug abstinence syndrome can be brought on by the sudden stopping of the drug after prolonged use or the introduction of an antagonist to the drug.

If tolerance and physical dependence is **not** addiction, what is it? See **figure #1**

Addiction is defined in psychologic and not in physical terms. Addiction is a psychologic dependence on a drug where the use of that drug by patients becomes the central theme of their existence. Addiction is when the patient will use a drug in spite of the harm that is knowingly caused to them. Addiction is heralded in the medical patient by use, despite harm, doctor shopping, lying to get the needed drug, and drug hoarding.

Pseudoaddiction is a new term to define what happens to the patient with poor and inadequate pain control. The signs of addiction should not be confused with the similar signs seen with patients who are under treated for the severity or intensity of their pain. These under treated patients are all too frequently seen in the pain clinic because there was some barrier to their receiving adequate pain management. These patients are now called **pseudo addicts**. Pseudo addicts are patients who look and act like addicts. They have real cause for their pain and are **not** drug seeking. These patients, like addicts, lie, cheat, and hoard drugs to get the necessary amount of drug commensurate with the level of their pain.

Pharmacologic Strategies for Acute, Chronic and Cancer Related Pain

Acute Pain

We all can easily understand the pain that people feel when they injure themselves or when they have surgery. It is difficult to understand why, when we are healed of our injuries or surgery, sometimes, pain persists and may persist for years. The pain of surgery or injury is called **acute pain**. This pain has a biologic purpose. It tells us where we are hurt so that we may protect ourselves. This pain also activates defensive fight and flight mechanisms which protect us when we are threatened by a hostile environment. The pain that lasts and lasts, in spite of the healing of injury is called **chronic pain**. This pain is not easy to understand. It has no biologic purpose. It appears that this pain is a disease in of itself.

Our bodies are made up of various tissues that serve many functions. Our skin protects us from a very hostile environment and serves to preserve our inner body temperature so that normal bodily functions can go on. Our muscles, joints and bone give us form and allows us to freely move about in our environment. Our inner organs serve many functions that are necessary for life including digestion, respiration, reproduction, etc. At the very heart of this very complex system called the body is the nervous system. The nervous system controls all of the other systems and tissues of the body. It is the central and peripheral control of the body. The nervous system is subdivided into a **voluntary nervous system**, controlling movement and sensory function, and, an **involuntary nervous system** that controls bodily functions such as heart rate and blood flow, blood pressure, breathing, digestion, sexual function, etc. The nervous system can also be subdivided into **the peripheral nervous system**, with all of the body's nerves going to our skin, muscle, bone, viscera, blood vessels, etc., and the **central nervous system** which includes the spinal cord, the midbrain, and the brain. The spinal cord lies encased

and safe within the vertebral bony spine and the brain lies protected within the bony skull. All of the nerves of the body, including motor, sensory, and involuntary nerves, connect in some way to the spinal cord and brain. The brain is where perception and awareness of pain occurs.

Important to the discussion here is that there exist discrete nerve endings or even discrete anatomic structures called **nociceptors** that serve to receive painful information and change that information into electrical signals that are transmitted via the peripheral nervous system to the central nervous system. Painful information can be categorized as chemical, thermal, or mechanical in nature, and, therefore, there are chemical, thermal, and mechanical nociceptors. **See Table 1.** Some nociceptors may even receive and process more than one type of painful information such as nociceptors that are classified as mechanico-thermal in nature. Nociceptors have two functions. The first function is to receive painful or noxious information. The second function is to change or **transduce** this information into electrical signals so that these signals can be transmitted through the peripheral nervous system to the central nervous system. This function of changing noxious information into electrical signal is called **transduction**. The process of reception and transduction of painful information is called **nociception**. Nociceptors, also have other properties that make them quite complex. At any one time, only approximately 20% of nociceptors are activated, but, in response to tissue injury and inflammation, up to 100% of nociceptors may be activated. By virtue of the chemical changes that occur after tissue injury, nociceptors, themselves, change chemically to self regulate or modify the body's responses to injury. Nociceptors are not merely passive structures; they are quite complex.

Nociceptors

- 1. Nociceptors are found in all tissues of the body except nervous tissue.**
 - 2. Nociceptors convert noxious information into electrical information.**
 - 3. Nociceptors are either chemical, thermal, or mechanical in nature.**
 - 4. Nociceptors may have dual function as in mechanothermal nociceptors**
 - 5. At any one time, only 20% of the body's nociceptors are activated, but in response to tissue injury and inflammation, up to 100% of the body's nociceptor may be activated.**
 - 6. In response to injury, chemical changes occur within nociceptors to self regulate the body's responses to the injury.**
-

Table 1

Examples of acute pain include pain due to trauma, surgical pain, visceral pain, etc. Treatment of acute, nociceptive pain pharmacologically rests with the use of NSAIDs and opioids or combinations of the two. **See Table 2**

Nociceptive Pain

- | |
|---|
| <ol style="list-style-type: none">1. Nociceptive pain is mediated by nociceptors widely distributed in skin, bone, connective tissue, vessels, viscera, etc.2. Nociceptive pain is often described as sharp or dull, aching, throbbing, etc.3. Nociceptive pain is opioid responsive4. Examples of nociceptive pain include pain of trauma, tissue injury and surgery. |
|---|

Table 2

The Non Steroidal Anti -inflammatory drugs: NSAIDs

Because nociceptive information is the result of tissue destruction and release of peripheral "sensitizers" of pain such as the inflammatory chemicals, bradykinin, histamine, norepinephrine, and most importantly, prostaglandins, acute pain usually responds well to the non-steroidal anti-inflammatory drugs (NSAIDs).

A SENSIZOR IS AN AGENT THAT EXCITES NOCICEPTORS TO RESPOND TO A NORMAL STIMULUS IN AN EXAGGERATED MANNER. THE CHEMICALS BRADYKININ, HISTAMINE, AND PROSTAGLANDINS ARE SENSITIZORS.

Tissue destruction leads to release of arachadonic acid from the cell interior and through the arachadonic cascade to the formation of prostaglandins. Cyclo-oxygenase, an enzyme necessary for the production of prostaglandin, is inhibited by all of the NSAIDs. All of the NSAIDs are, therefore, called cyclooxygenase inhibitors. **See Figure 1.**

The rational use of the NSAIDs depends on the knowledge of each individual patient's particular response to singular inflammatory or painful disorders and a knowledge of the pharmacokinetics of the agent used. Some NSAIDs appear to act more on bone pain and some appear to act more on inflammatory disorders such as synovitis. All act the same pharmacodynamically, but not the same pharmacokinetically. Some of these numerous agents have short half-lives and some have longer half-lives.

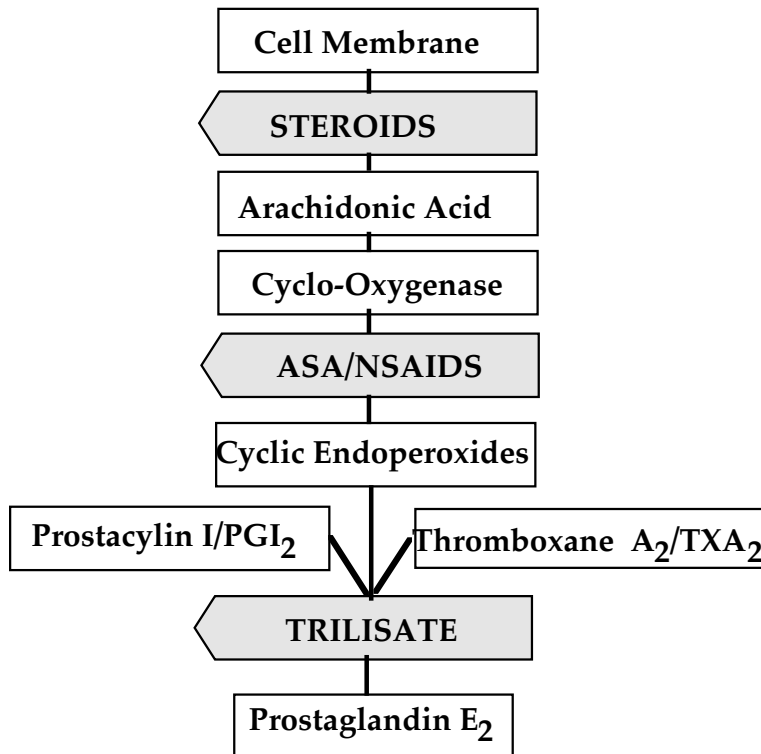


Figure 1: from the PURDUE-FREDERICK Co. With destruction of the cell, arachadonic acid is released and then in a chemical cascade, prostaglandins are released. These chemicals sensitize nociceptors to pain. The NSAIDs are cyclooxygenase inhibitors that block the formation of the sensitizing prostaglandins and therefore block pain and inflammation.

Opioids and Acute pain

Because nociceptive, acute pain is mediated and modulated by the central nervous system at pre and post synaptic enkephalinergic receptors, this type of pain is expected to be opioid responsive. The rational choice of opioids rest with a complete knowledge of the pharmacokinetics and the pharmacodynamics of these agents and will be discussed under the treatment of cancer related pain. The goal of opioid therapy for acute pain is to match the strength of the agent to the intensity of the pain and not to allow periods of uncontrolled pain. The strength of the opioid for acute pain is titrated downward over

time to meet the decreasing intensity of pain and therefore decreasing need for analgesic medications .

Cancer Pain

It has been suggested that 90-95% of cancer or AID's related pain syndromes can be well controlled using guidelines established by the World Health Organization (WHO). See **figure #4**

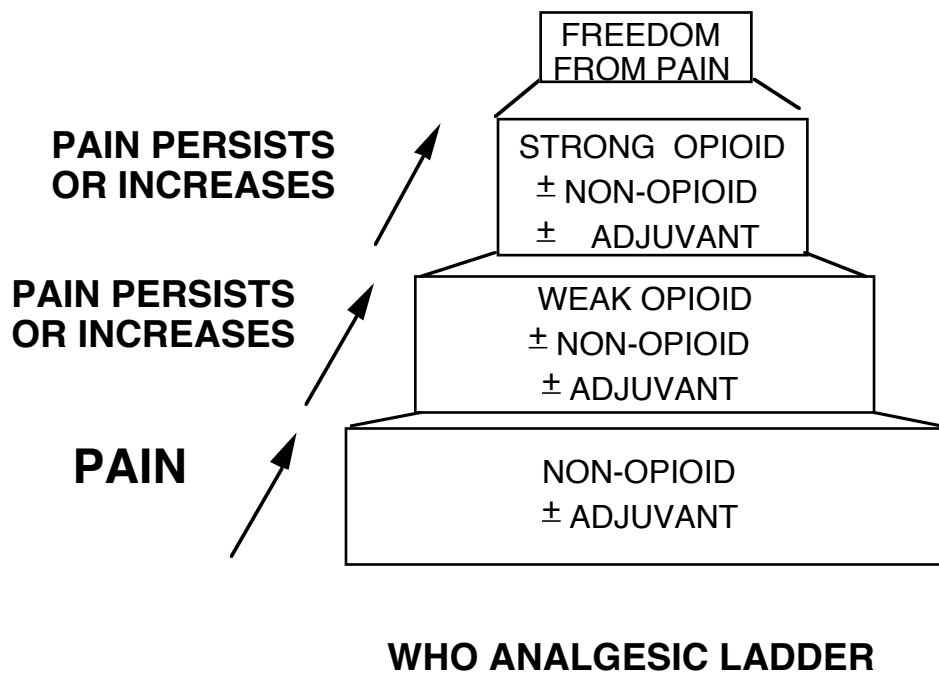


Figure 4 World Health Organization advocates pharmacologic ladder approach to the treatment of cancer pain. Recommendations are given for mild, moderate and severe pain using non-opioids, weak and strong opioids supplemented by adjuvant medications.

The pharmacologic tailoring approach of these guidelines group cancer and AID's related pain syndromes by severity and intensity into mild, moderate, and severe and suggest "tailoring" strength and potency of medications to the severity of the pain syndrome.

Non-opioid medications such as the NSAIDs and adjuvant medications are suggested for mild to moderate cancer or HIV related pain. Adjuvant medications might include heterocyclic antidepressants, anticonvulsants, steroids, Na⁺ and Ca⁺⁺ channel blocking agents, alpha-2 agonists, alpha-1 blocking agents, Beta blocking agents, and GABA agonists. Weak to moderate strength opioids such as codeine and hydrocodone along with appropriate non-opioid and adjunctive medications are suggested for moderately severe cancer pain by these guidelines. Potent

opioids such as morphine, hydromorphone, methadone, etc., together with non-opioids and adjuvant medications, are suggested for strong and severe cancer related pain. Guidelines for dose escalations, sequential drug trials, and management of medication related side effects and symptoms are also suggested by these guidelines.

Opioids

Opioids are the main stay of pharmacologic management in moderate to severe cancer, opioid responsive pain syndromes. Opioids are chemically divided into three classes of agents depending on their actions at the opioid receptors and are broadly divided into receptor agonist drugs, the pure **agonists**, receptor **agonist/ antagonists**, and the **partial agonist** drugs.

Opioid agonists are divided into the phenanthrene's, the phenylperidine's and the diphenylheptane's. All of these agents have to differing degrees similar wanted effects and unwanted side-effects. The wanted effects include analgesia and antitussive effects. The unwanted side-effects include constipation, respiratory depression, sedation, emesis and physical dependence. The **phenanthrene's** include codeine, hydrocodone, hydromorphone, levorphanol, morphine, oxycodone, and oxymorphone. The **phenylperidine's** include meperidine, fentanyl, sufentanil, and alfentanil. The **diphenylheptane's** include methadone and propoxyphene. The pharmacokinetics of narcotic agonist agents are seen in **figure #5**

The opioid agonist/antagonist agents include buprenorphine, butorphanol, dezocine, nalbuphine, and pentazocine. These agents compete with agonist agents at the mu opiate receptor. There are two types of these agents, agents that are antagonists at the mu receptor and are active at other opiate receptors like pentazocine, active at the kappa receptor or agents partially active at the mu receptor such as buprenorphine. **See figure #6**

The narcotic agonist/antagonist analgesics are potent analgesic agents thought to have a lower abuse potential than the pure agonist agents. Because of their antagonist properties they should never be given to patients who are physically dependent to the pure agonist analgesics. They will precipitate opiate withdrawal. Because of this fact, these agents are not thought of as optimal agents for the treatment of cancer related pain.

Figure 5

Pharmacokinetics of Narcotic Agonist Analgesics

Drug	Onset minutes	Peak hours	Duration hours	t 1/2 hours	equianalgesic Dose ²	
					IM mgs	Oral mgs
Alfentanil	immediat	nd	nd	1-2 ⁸	nd	na
Codeine	10-30	0.5-1	4-6	3	200	

Fentanyl	7-8	nd	1-2	1.5-6	0.1	na
Hydrocodone	nd	nd	4-8	3.3- 4.5	nd	nd
Hydromorphone	15-30	0.5-1	4-5	2-3	1.5	7.5
Levorphanol	30-90	0.5-1	6-8	12-16	2	4
Meperidine	10-45	0.5-1	2-4	3-4	75	300
Methadone	30-60	0.5-1	4-6 ⁴	15-30	10	20
Morphine	15-60	0.5-1	3-7	1.5-2	10	60
Oxycodone	15-30 ⁵	1	4-6	nd	na	30
Oxymorphone	5-10	0.5-1	3-6	nd		
					10 ³	
Propoxyphene	30-60	2-2.5	4-6	6-12		
					130 ⁶ /200 ⁷	
Sufentanil	1.3-3 ⁸	nd	nd	2.5	0.02	na

*** from Drug Facts and Comparisons 1994**

nd-no data available **na**-not applicable

¹ After IV administration, peak effects may be more pronounced but duration may be shorter. Duration may be longer with oral route.

² Based on acute, short term use. Chronic administration may alter pharmacokinetics and decrease the oral:parenteral dose ratio. the morphine oral-parenteral ratio decreases to 1.5 to 2.5 to 1

³ Rectal

⁴ Duration and half-life increase with repeated use due to cumulative effects

⁵ Data based on intrathecal or epidural administration

⁶ HCL salt

⁷ Napsylate salt

⁸ Data based on IV administration

figure #6

Narcotic Agonist-Antagonist Pharmacokinetics

Agonist/Antagonist	Onset min	Peak min	Duration hrs	t1/2 hrs	Equivalen t Dose mgs	Relative Antagonist Activity
Buprenorphine						
IM	15	60	6	2-3	0.3	Equipotent with naloxone
IV ²						
Butorphanol						30x Pentazocine or 1/40 Naloxone
IM	<60	30-60	3-4	2.5-4	2-3	
Dezocine						Greater than Pentazocine
IM	≤30	30-	2-4 ³	nd	10	
IV	<15	150		2.4 ⁴		
Nalbuphine						10x Pentazocine
IM	≤15 ⁵	60	3-6	5	10	
IV	2-3	30				
Pentazocine						Weak
IM	15-20	15-60	3	2-3	30	
IV	²	nd				
Oral	2-3	60-				
	15-30	180				

¹ Parenteral dose equivalent to 10 mg morphine.

⁴ For 10 to 20 mg dose; 1.7 hr for 5 lmg dose.

² Time to onset and peak effect shorter.

⁵ Also for subcutaneous administration

³ Dose related

nd -no data

An important property of weaker or moderately strong opioid medications is that their analgesic effects are enhanced when combined with non-narcotic analgesics including aspirin, acetaminophen, and other NSAIDs. This enhancement of analgesia by the addition of a non-opioid analgesic allows overall reduction in the daily dose requirement of the opioid and is called synergy.

Guidelines for Appropriate use of Opioids in Pain Management

It was once said by Jerome Jaffe that "*No patient should ever wish for death because of a physician's reluctance to use adequate amounts of effective opioids.*"

As stated above, opioids are and should be the foundation of effective pain management in opioid responsive, cancer pain syndromes. These agents should be used with adjunctive medications and with NSAIDs when appropriate. The narcotic ladder suggests the use of weaker opioids or opioid combinations for moderate pain and strong opioids for stronger pain syndromes not responsive to the weaker agents.

Opioid management should be guided by sound clinical principles. Some suggested principals are as follows:

- Use a specific drug for a specific type of pain, i.e., weak opioids for low intensity pain and strong opioids for strong intensity pain

- **Know** the pharmacology of the drug prescribed
- Don't be wedded to only one agent; Use sequential drug trialing
- Adjust the route of administration to the patient's needs, but obey the **KISS** principle (**Keep it Simple Stupid**)
- Administer the agent on a timed and regular basis after initial titration to the patient's need
- Use long acting agents as the primary opioid and allow for breakthrough pain with immediate release agents.
- Use drug combinations to reduce side effects and decrease overall daily dose of opioid. Avoid combinations that increase unwanted side effects.
- Anticipate and treat side effects
- Watch for the development of tolerance
- Prevent acute withdrawal
- Anticipate and manage complications

Adjunctive Pain Medicines

Not all patients respond to opioids or may respond to opioids in higher than usual doses. Nociceptive pain, as above stated, usually responds to opioid medications, but

neuropathic pain may not. Neuropathic pain due to damage to the peripheral or central nervous system or expressed as a result in abnormal pain processing mechanisms does not, like nociceptive pain, respond normally to opioid medications, although there are some exceptions. **See figure 7**

Non-opioid agents found to be analgesic in neuropathic pain syndromes are called **adjunctive** pain medications. These agents, unlike the opioid analgesics or even the NSAIDs do not work immediately on analgesically active systems. These agents appear to work indirectly on these systems by modulating activity or neurotransmitters that act directly upon them. Also, unlike the opioids and NSAIDs, these agents usually take time to act upon these systems to produce analgesia. Tricyclic anti-depressant agents and serotonin specific reuptake inhibiting agents might act on neuromodulatory systems by blocking the reuptake of norepinephrine or serotonin at the nerve endings, thereby impacting on these systems. **See figure 8** Anticonvulsant medications and Na⁺ channel blocking agents such as the local anesthetics are membrane stabilizing agents and therefore act analgetically by stabilizing the abnormal firing patterns from active neurons in the central nervous system. **See figure 9.** Physicians should know and understand the pharmacology of these agents and their interrelationships with other drugs and agents. Care must be taken not to prescribe too many of these agents together as a poly-pharmacy since drug-drug interactions are complicated and could lead to disaster

Figure 7

Neuropathic Pain

- **Elicited by damage to or pathologic changes of the peripheral or central nervous system**
- **May be mediated by the NMDA receptor**
- **Pain often described in terms of electrical like sensations such as: burning, tingling, shooting, electrical-like, lightning-like**

- **May exhibit opioid resistance**
- **Examples include: post herpetic neuralgia, trigeminal neuralgia, peripheral neuropathies, traumatic peripheral neuropathies, plexopathies, reflex sympathetic dystrophy, etc.**

Adjunctive pain medications include:

- 1. heterocyclic antidepressants**
- 2. serotonin specific reuptake inhibitors (SSRI's)**
- 3. anti-convulsants**
- 4. GABA-b analogs**
- 5. klonopin**
- 6. alpha adrenergic blocking agents**
- 7. beta adrenergic blocking agents**
- 8. Ca⁺⁺ channel blocking agents**
- 9. Na⁺ channel blocking agents**
- 10. NSAIDs**
- 12. steroidal agents**
- 13. amphetamines**
- 14. methylphenidate**

15. calcitonin

16. phenothiazines

figure 8

Antidepressant Pharmacologic and Pharmacokinetic Parameters

0-none + - slight ++ - moderate +++ - high ++++ - very high +++++ - highest	<u>Major Side Effects</u>			Amine Uptake		t 1/2 hrs	Therape u Plasma level ng/ml	Time to Reach Plasma level days
	Anti- Ortho Cholinergic Stasis	5-HT	NE	5-HT				
3-Amines								
Amitryptaline	++++	++++	++	++	++++	31- 46	110-250 ¹	4-10
Clomipramine	+++	+++	++	+	+++++	19- 37	80-100	7-14
Doxepin	++	+++	++	++	++	8-24	100-200 ¹	2-8
Imipramine	++	++	+++	++ ²	++++	11- 25	200-350 ¹	2-5
Trimipramine	++	+++	++	+	-	7-30	180	2-6
2-Amines								
Amoxapin	+++	++	+	+++	++	8 ⁴	200-500	2-7
Desipramine	+	+	+	++++	++	12- 24	125-300	2-11
Nortryptaline	++	++	+	++	+++	18- 44	50-150	4-19
Protryptaline	+++	+	+	++++	++	67- 89	100-200	14-19
Tetracyclics								
Maprotaline	++	++	+	+++	0/+	21- 25	200-300	6-10
Triazolo- pyridine								
Trazodone	+	++	++	0	+++	4-9	800-1600	3-7
Bycyclic								
Fluoxetine	+	+/0	+	+	+++++	7-9 d	-	2-4 w

**Amino-
ketone**

Bupropion	++	++	+	+/0	+/0	8-24	-	1.5-5
-----------	----	----	---	-----	-----	------	---	-------

- 1** Parent compound plus active metabolite
- 2** Via desipramine, the major metabolite
- 3** Also blocks dopamine receptors
- 4** 30 hours for major metabolite 8-hydroxyamoxapine
- 5** Inhibits dopamine uptake

figure 9

Anticonvulsants Used in Pain Management

	Plasma half-life (hours)	Therapeutic plasma concentration	Dose range
Carbamazepine	10-20	4-10 ug/ml	100-600 mg bid
Phenytoin	6-24	10-15 ug/ml	200-400 q hs
Clonazepam	18-30	5-70 ng/ml	0.5-6 mg tid

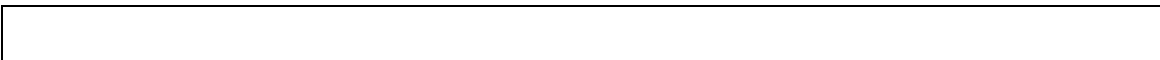
* From *Pain*, Fields, HL.

Treatment of Chronic Pain Using a Pain Treatment Continuum: Multiple Choices

Treatment of cancer related pain, requires that the pain treatment physician understand the nature of the patient's pain generation, the psychological and behavior factors operant in perpetuating the pain, and the possible treatment modalities that are appropriate for the patient's specific pain syndrome. Because chronic pain, as stated above, is almost never unidimensional, but almost always multidimensional involving neurophysiological systems as well as emotional and behavioral systems, a multidisciplinary evaluation and treatment plan is usually warranted. Once a diagnosis is made, after a thorough multidisciplinary evaluation, a parallel treatment plan addressing both the neurophysiologic process or processes operant in the patient's pain generation as well as the cognitive, emotional, and behavioral processes involved is entertained. Because there are multiple modality choices for the treatment of chronic pain, we treat chronic pain patients according to a treatment continuum listing therapies by increasing levels of intervention. According to this continuum, in an algorithmic fashion, we first choose therapies that are least invasive, and then, as lesser invasive therapies fail to provide adequate analgesia, we try therapies of increasing levels of intervention until either a single therapy or a combination of therapies is found to be efficacious. Choices for the treatment of chronic non-cancer or AID's related pain, utilizing multidisciplinary interventions, include cognitive/behavioral psychological therapies, functional rehabilitation therapies, orthopedic and neurological surgery, pharmacotherapies, anesthetic blocking techniques, neuroaugmentative procedures, and finally neurodestructive procedures. An example of a treatment continuum is found in **figure 10**

figure 10

Pain Treatment Continuum



- **OTC drugs**
- **NSAIDs**
- **Muscle relaxants**
- **Physical/occupational therapies, manipulation**
- **Rehabilitation medicine**
- **Cognitive/behavioral therapies**
- **Nerve blocks, diagnostic and therapeutic**
- **Surgery**
- **Weak opioids**
- **Strong opioids**
- **Spinal cord stimulation**
- **Intraspinaly administered opioids**
- **Destructive neuroablative procedures**

***The pain treatment continuum lists therapies for pain in increasing order of intervention and invasiveness. This therapy is to be a guide for creative thinking and not as an absolute solution to problems. Practitioners should create their own continuum based on their experiences and situation. Management of pain, however, should be dictated by an algorithm.**

The psychologic evaluation and treatment plan should address certain key issues in chronic pain patients. These issues include ferreting out psychologic causation of pain, identifying psychologic barriers to successful medical management of pain, maximizing coping strategies for pain control, and addressing loss issues.

Chronic pain in patients may involve, to various degrees, the emotional and cognitive life of the patient. At the very least, some chronic pain patients may merely lack coping skills necessary for internal, self pain modulation or some patients may derive unconscious secondary gains from having persistent pains. Some patients may have personality or neurotic barriers to successful pain management including addictive

personalities, hysteria, hypochondriasis, or depression. At the other extreme, persistent, chronic pain may represent a somatiform disorder where the patient is unable to deal with unresolved emotional pain, finding it easier to unconsciously create somatic pain. Somatic pain, in psychobehavioral terms, becomes the focus for emotional pain that is "too hot to handle." Rather than addressing the emotional conflicts directly by seeking psychiatric or psychologic help and support, this patient unconsciously seeks a "quick fix" in the form of a pill or medical intervention. These patients represent the rare extreme of pain patients, but are the hardest to treat. These patients are convinced of having a

physical, somatic illness and are focused on their body. These patients tend to deny that there are any problems in their life beside their "painful illness" and certainly deny any psychologic component to their pain. All medical interventions are doomed to fail until the patient understands, accepts, and addresses the issues causing the real underlying emotional pain. Psychological pain intervention may include long term psychotherapy, goal directed, short-term psychotherapy, "operant reconditioning," conjoint, interrelational therapies, chronic pain group therapy, biofeedback, teaching relaxation and distraction techniques, hypnosis, and self-hypnosis.

Medical management of these patients should include the skills of a wide variety of health care professionals including anesthesiologists, neurologists, surgeons, physiatrists, nurses, physical therapists, occupational therapists, psychologists, psychiatrists, addictionologists, and vocational rehabilitation specialists.

Chronic pain patients, because of the inactivity brought on by their pain are generally in unfit. These patients protect their bodies to extreme, failing to use their muscles appropriately. The aim of functional rehabilitation in the treatment of chronic pain is to recondition deconditioned muscles through the skills of physical therapy, occupational therapy, and physical and rehabilitation medicine and to provide retraining for activities of daily living or the workplace through vocational rehabilitation.

Pharmacologic management of the patient with chronic pain utilizes medications that have been shown to be efficacious for either nociceptive or neuropathic pain syndromes. Nociceptive pain most often responds to NSAIDs or opioids. Non-opioid NSAIDs should be used before the use of opioids, although the long-term use of these drugs could lead to physiologic damage to the liver or renal system. There is, however, no physiologic down-side to the long-term use of strong opioid medications. If opioids are to be used, the strength of the opioid should be tailored to the intensity of the pain. Dosages should be titrated and not dependent on some fictitious "average dose." Weak opioids should be given for mild pain and strong opioids should be given for intense pain. For constant pain, opioids should be given according to a time-schedule consistent with the pharmacokinetics of the drug prescribed and not on an as-needed basis. Since some chronic pain is constant, it may also be desirable to reduce the drug-intake interval by choosing an opioid that is longer lasting over one that has a shorter duration of action. Examples of longer acting opioids include methadone, levodromiran, long-acting, slow-release morphine preparations, and trans-derm fentanyl. Also, remember that there is a ceiling effect to the NSAIDs not shared by opioid medications. Once the "ceiling" dose for a given NSAID drug is reached, adding "more" will not lead to increased analgesia, but, may only lead to an increase in undesired side-effects. Dosages of opioids can

consistently be elevated to meet the increasing requirement of the patient's pain. More, if side effects do not occur, might be better. Side effects of opioid medications include inanition, loss of appetite, nausea and vomiting, sedation, constipation, urinary retention, depression of the hypothalamic/pituitary axis, hallucinations, dry mouth, sweating, and respiratory depression. Not all patients share the same intolerances to opioids. Some patients may tolerate one or more of the opioids, but not all, some patients may not tolerate any, and some patients may tolerate all. If a patient fails to tolerate one opioid, another should be tried until one produces analgesia without undue side-effects. These **sequential drug trials** should be performed before abandoning opioid therapy.

Other non-opioid medications, beside the NSAIDs, that have shown to have some degree of analgesic efficacy for chronic pain syndromes are called, as a class, adjunctive

medications. These adjunctive medications are the same ones suggested for use in cancer pain patients and include the heterocyclic antidepressants, the non-heterocyclic, serotonin enhancing antidepressants, the anticonvulsant medications, GABA analogs, Na⁺ channel blocking, membrane stabilizing agents, Ca⁺⁺ channel blocking agents, alpha and beta blocking agents, alpha-2 analogs, substance-P depleting agents, steroids, and the psychogenic amines and their analogs. These medications, like the opioids, should be prescribed using sequential drug trialing as single agents or in combination with other active agents. Dosages of these drugs should be slowly titrated to enhance patient acceptance and their dosages should be “pushed” until efficacy or side-effects develop. If side-effects precede analgesia, differing drugs of the same class should be tried before abandoning the whole class of drugs. This trial-and-error process of finding an active, analgetic agent takes time and patients should be counseled to have patience.

As one can see from the treatment continuum, pharmacologic management of pain remains the mainstay of intervention besides cognitive behavioral interventions and functional rehabilitation. Interventional pain management, and certainly the implantable technologies for pain control should be therapies of last resort before neuroablative and neurodestructive procedures. Implantable technologies for pain control are more recent advances for the treatment of chronic pain. These therapies are invasive and relatively expensive compared to non-surgical interventions for pain control. They are to be used when more conservative, non-invasive therapies fail to provide analgesia.

Conclusion

I have presented data gleaned from years of clinical experience and from the clinic experience of others. These thoughts should guide the clinician to thinking appropriately and algorithmically in using pharmacologic strategies for the treatment of various pain syndromes. These syndromes are different and differing strategies for pain control should be used.

