

CHRONIC PAIN: TREATMENT WITH MEDICATION

Lorne K. Direnfeld, M.D., F.R.C.P. (C)

The goals of this presentation include understanding:

- The definition of pain.
- The difference between acute pain and chronic pain.
- The pharmacologic rationale for the use of various medications in the treatment of chronic pain.

This presentation will provide insight to better understand the condition of chronic nonmalignant pain and its management.

In this presentation, the following questions will be answered:

- What is pain?
- What is the relationship between tissue damage and pain?
- How are pain and suffering related?
- What are the characteristics of pain (temporal, severity, location, etc.)?
- What is the difference between acute and chronic pain?
- What are the three main mechanisms of pain?
- How does the body modulate pain?
- What kinds of medicines are used to treat pain?
- What is the role of opioids in pain management?
- What are the adverse effects of opioids?
- What is the difference between addiction and dependence?
- Is there a role for opioids in the management of chronic nonmalignant pain?
- What are some of the other drugs often used to treat chronic pain?
- What is meant by "off-label" drug use?

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What is pain?

Pain is defined as an unpleasant sensory and emotional experience which we primarily associate with tissue damage or describe in terms of such damage, or both.

The report of pain reflects both a sensory experience and a person's emotional and intellectual responses.

What is the relationship between tissue damage and pain?

The relationship between pain and tissue damage is not constant. An evaluator may infer that the pain reported is either proportionate or disproportionate to the tissue injury that is present.

Nociception is the term applied to the activity induced in nerve pathways by potentially tissue-damaging stimuli.

Pain is the conscious perception of nociception, and is only partly determined by activation of nerve pathways from the injured area. Factors other than nociception influence the perception of pain, and in some patients become the major determinants of the pain complaint.

The existence of tissue damage should not be viewed as presumptive evidence that psychological processes affecting the report of pain are absent. Similarly, the inference that psychological factors contribute to pain should not be viewed as evidence against the existence of a physical abnormality.

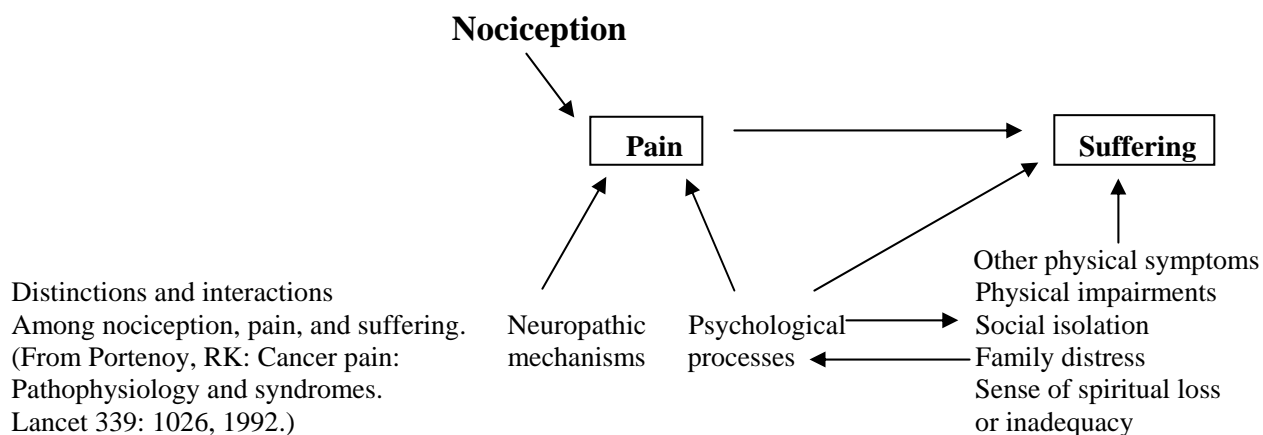
Are pain and suffering related?

Suffering is a more global construct related to the experience of pain. Like pain itself, suffering is both inherently subjective and multidimensional. Suffering may result from a variety of negative perceptions including pain, loss of physical function, social isolation, family dissolution, and financial concerns.

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Psychiatric disturbances such as depression, anxiety, and pre-existing character makeup may also contribute to suffering.



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What is the difference between acute and chronic pain, and what are the characteristics of pain?

The distinction between acute pain and chronic pain is very important. Acute pain is usually defined as pain of recent onset that ends, or is anticipated to end, in a period of days or weeks. Pain that persists or recurs frequently is considered chronic.

The management of acute pain and chronic pain is different.

Pain intensity is measured by various scales, often between zero and ten. The consistent use of a particular scale is important in the ongoing management of a patient.

Pain may be focal, multifocal, or generalized. Pain experienced at a site remote from a presumed causative lesion is termed referred pain.

Some patterns of referred pain are characteristic, such as cardiac pain radiating to the left shoulder and arm. More complex patterns are described for various muscular and skeletal structures.

DIFFERENCES BETWEEN ACUTE PAIN AND CHRONIC PAIN

	Acute Pain	Chronic Pain
Temporal features	Recent, well-defined onset; expected to end in days or weeks	Remote, ill-defined onset; duration unpredictable
Biologic function	Essential warning; impels rest and avoidance or further harm	None apparent
Intensity	Variable	Variable
Associated affect	Anxiety common when severe or cause is unknown	Irritability or depression
Associated pain-related behaviors	Pain behaviors common (such as moaning, splinting, rubbing, etc.) when severe or cause is unknown	May or may not give any indication of pain
Associated features	May have signs of sympathetic hyperactivity when severe	May have vegetative signs, such as lassitude, anorexia, weight loss, insomnia, loss of libido
Types of examples	Monophasic (such as postoperative, traumatic, and burn) Recurrent (such as headache, sickle cell anemia, hemophilia, inflammatory bowel disease)	Due to progressive medical diseases (such as Cancer or AIDS) Due to nonprogressive or slowly progressive diseases (such as osteoporosis, osteoarthritis, and many neuropathic pains) Pain determined by psychologic

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factors

What are the three main mechanisms of pain?

The main causes of pain can be broadly divided into nociceptive, neuropathic, and idiopathic categories.

Nociceptive pain can be defined as pain commensurate with a presumed degree of ongoing activation of peripheral nociceptors. The complaint of pain in this context is viewed as an appropriate response to tissue damage.

Neuropathic pain is defined as pain perceived to be sustained by abnormal processing in the sensory part of the nervous system, either in the peripheral nerves, or the central nervous system.

Idiopathic pain can be defined as pain that persists in the absence of an identifiable organic substrate, or pain that is believed to be excessive for the organic process. A subgroup of patients with idiopathic pain have positive evidence of a psychological contribution to the pain. These pains are described as psychogenic, or labeled with a specific psychiatric diagnosis.

These pathophysiologic constructs have important therapeutic implications. For example, response to opioids appears to be relatively better treatment of nociceptive pain than some neuropathic pains. Non-nociceptive pains are also thought to be less responsive to techniques that isolate the painful part from the nervous system.

It is also important to keep in mind that the distinction between organic (nociceptive and neuropathic) and idiopathic or psychogenic pain is somewhat artificial, as pain by definition is an "experience." The brain and its associated psychological properties are required to have this "experience." Therefore, one must not adhere rigidly or thoughtlessly to the notion that pain is either physical or psychological. There is always a psychological component to the experience of pain.

How does the body modulate pain?

Our perception of pain is modulated in the nervous system at levels including the spinal cord and brain.

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The elucidation of pain-modulating systems was supported by the discovery of endogenous opioids known as endorphins. Endorphins are related to morphine. They are made within the body. They play a role in modulating pain on multiple levels, including the emotional response to pain.

In the nervous system, there are pathways that ascend, that is, go up from the spine toward the brain, known as spinothalamic pathways that interact with nerves at the base of the brain, in the brainstem, and other regions.

Endorphins and other pain-modulating systems interact in the spinal cord and brain.

Other descending pain-modulating systems use nerve transmitters such as serotonin and norepinephrine. There is only limited understanding of the function of these systems.

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What kinds of medicines are used to treat pain?

One of the main types of medicines to treat pain are the opioid analgesics. These compounds have been recognized since antiquity. Also, since antiquity, their clinical use has been problematic. This is due to concerns for potential adverse risks, including addiction. However, there is limited data regarding these risks when opioids are used clinically.

Opioid drugs bind to opioid receptors, including the receptors to which endorphins attach. They mimic the actions of endorphins. There are a large number of opioid-related drugs, including "natural drugs", such as morphine and codeine, and semisynthetic and synthetic opioids.

Non-opioid medicines are also used to treat pain of both acute and chronic types, but especially chronic pain. Non-opioid medicines include simple analgesics (such as acetaminophen), non-steroidal anti-inflammatories, antidepressants (of different types), and anticonvulsants, among others.

What is the role of opioids in pain management?

In general, opioids are excellent pain relievers, particularly for acute nociceptive pain, with a good side-effect profile.

What are the adverse effects of opioids?

Transient adverse effects of opioids may include dose-dependent drowsiness. Constipation is also not uncommon, and can be somewhat long lasting.

Acute administration of opioid drugs in appropriate doses is not thought to injure major organ systems, with the exception of isolated reports of pulmonary edema in extremely ill patients on high doses. Whether chronic opioid use results in significant organ pathology is controversial; however, significant irreversible changes have not been demonstrated.

Most adverse effects, including nausea, somnolence, and mental clouding diminish within

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days to weeks after the initiation of therapy.

Patients and doctors alike express concern that the long-term use of opioid drugs may produce cognitive impairment sufficient to prevent normal functioning. However, most of the currently available data suggests that long-term opioid therapy is generally compatible with normal functioning. Despite that, persistent cognitive impairment is a possible outcome, and must be assessed repeatedly during therapy. Normal cognition is the anticipated goal of therapy.

Patients who have no clinical evidence of impairment should be encouraged to engage in all routine activities.

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STANDARD DOSES OF COMMONLY USED OPIOIDS

Generic Name (Trade Name)	Analgesic Dose	Typical First Dose
Codeine		
Oral	30 mg every 3-4 hr	30 mg every 3-4 hr
Parenteral	10 mg every 3-4 hr	10 mg every 3-4 hr
Fentanyl (Duragesic)		
Patch	25- μ g-per-hr patch every 72 hr	25- μ g-per-hr patch every 72
Hydrocodone (Vicodin, Lorcet)		
Oral	NA	10 mg every 3-4 hr
Parenteral	NA	NA
Hydromorphone (Dilaudid)		
Oral	7.5 mg every 3-4 hr	2-4 mg every 3-4 hr
Parenteral	1.5 mg every 3-4 hr	1.5 mg every 3-4 hr
Levorphanol (Levo-Dromoran)		
Oral	4 mg every 6-8 hr	4 mg every 6-8 hr
Parenteral	2 mg every 6-8 hr	2 mg every 6-8 hr
Meperidine (Demerol)		
Oral	300 mg every 2-3 hr	100 mg every 3 hr
Parenteral	100 mg every 3 hr	100 mg every 3 hr
Methadone (Dolophine)		
Oral	20 mg every 6-8 hr	5 mg every 8-12 hr
Parenteral	10 mg every 6-8 hr	5 mg every 8-12 hr
Morphine		
Oral	30 mg every 3-4 hr	15 mg every 3-4 hr
Parenteral	10 mg every 3-4 hr	10 mg every 3-4 hr
Morphine SR (MSContin)		
Oral	NA	15 mg every 8-12 hr
Parenteral	NA	NA
Oxycodone (Percocet, Percodan)		
Oral	NA	5 mg every 3-4 hr
Parenteral	NA	NA
Oxycodone CR (OxyContin)		
Oral	NA	10 mg every 8-12 hr
Parenteral	NA	NA

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Challenges and Adverse Consequences of Prolonged High Dose Opioid Therapy

Studies indicate prolonged use of opioids have adverse consequences, including opioid tolerance with the need for dose escalation, and opioid-induced abnormal pain sensitivity.

Prolonged use may result in immunosuppression, especially in susceptible persons.

Prolonged opioid use may also have hormonal effects resulting in reduced fertility, libido, and drive. Prolonged use of high doses of opioids is likely to be more toxic than short-term use of low doses. Therefore, hormonal effects are most likely to occur in patients with chronic pain who receive high dose opioid therapy.

Often, time or resources are insufficient to offer a truly comprehensive and careful approach to complex pain problems. These sometimes become even more complex when opioid treatment is added. Paradoxically, opioid treatment may be offered in an attempt to improve pain and functioning and reduce the burden of care, but the treatment may actually increase the burden of care because the management of opioid therapy in patients with complex problems is time consuming, and difficult.

Limiting the Opioid Dose

The concept of a ceiling dose of opioids in the treatment of chronic pain is growing, yet it is difficult to define the dose that could be recommended as a ceiling. Ceiling doses probably vary among patients.

Drug Formulation

According to a consensus documents recently published by the American Society of Anesthesiologists, slow release formulations (morphine and oxycodone) are preferable to methadone for outpatient pain management because of the risk of respiratory depression due to methadone accumulation. The chief drawback of methadone is its prolonged and unpredictable half-life, which may extend beyond the average of 12-16 hours. When methadone is taken more than once a day, as is commonly the case when used for pain, the drug may accumulate, resulting in dangerously high plasma levels.

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Methadone is less likely to cause respiratory depression in patients who are already opioid tolerant, and it may be particularly useful in opioid rotation.

Failure to Control the Dose

Despite various strategies, attempts to limit the escalation of the opioid dose sometimes fail. If dose escalation is unsuccessful (in reducing pain), it is crucial to ask whether the opioid used is effective in treating the patient's chronic pain. Sometimes the only way to answer this question is to reassess the management approach after weaning the patient from the opioid.

Two to three months or longer without opioid therapy may be needed to make a true assessment. Non-opioid and non-medical treatments can be used more intensely during the period of opioid detoxifications, if necessary.

Some patients find that after they have overcome the fear of living without opioids, they prefer not to receive opioid treatment. Some even experience a reduction in pain.

For patients who do not have an improvement without opioids, therapy can be resumed, but at much lower doses of opioids than previously prescribed.

Aberrant opioid-seeking behavior may complicate the clinical picture of failed opioid therapy. Although occasionally aberrant behavior is a manifestation of inadequate analgesia, and will revert to normal behavior when pain is adequately treated, more commonly, it is a manifestation of addiction or noncompliance.

The relation between addiction and noncompliance is complex, and poorly understood. Noncompliance shares many features with addictive behavior, and may or may not indicate addiction.

In general, noncompliance should arouse the physician's concern about possible addiction or diversion, and prompt careful control and monitoring of opioid therapy. Opioid therapy should be discontinued if the behavior persists.

What is the difference between addiction and dependence?

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To answer this question, it is first necessary to consider tolerance. Tolerance refers to the process defined by the occurrence of decreasing effects at a constant dose, or the need for a higher dose to maintain an effect.

In humans, tolerance to the non-analgesic effects of opioids occurs commonly. Clinical tolerance to side-effects is beneficial, and increases the likelihood of a favorable balance between analgesic effects and side-effects. Tolerance to analgesic effects, if severe, can become a barrier to effective long-term therapy. It is a common mistake to refer to any patient who develops the need for dose escalation as tolerant, even if the pathology the medicine is treating is actually worsening.

In general, patients without progressive disease that are administered an opioid typically achieve stable dosing that extends for a prolonged period.

There is confusion about the terms "dependence" and "addiction."

Physical dependence is a physiologic phenomenon characterized by the development of an abstinence syndrome following abrupt discontinuation of therapy, substantial dose reduction, or administration of an antagonistic drug. The capacity for withdrawal, that is, physical dependence, is presumed to exist whenever repeated doses of an opioid have been administered for more than a few days.

Some people often mistakenly apply the term "addicted" to the patient who may be physically dependent on an opioid. This term has a negative connotation, and its use to describe a physiologic outcome is an error. Patients who are perceived to be at risk of withdrawal should be described only as "physically dependent."

Addiction is a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user, and continued use despite that harm.

Fundamentally, addiction is a psychological and behavioral syndrome characterized by loss of control over drug use, compulsive drug use, and continued use despite harm.

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**ABBERANT DRUG-RELATED BEHAVIORS THAT RAISE CONCERN ABOUT THE
POTENTIAL FOR ADDICTION**

Behaviors More Suggestive of an Addiction Disorder

Selling prescription drugs

Prescription forgery

Stealing or "borrowing" drugs from others

Injecting oral formulations

Obtaining prescription drugs from nonmedical sources

Concurrent abuse of alcohol or illicit drugs

Multiple dose escalations or other noncompliance with therapy despite warnings

Multiple episodes of prescription "loss"

Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber or after warning to desist

Evidence of deterioration in the ability to function at work, in the family, or socially that appear to be related to drug use

Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychologic effects from the drug

Behaviors Less Suggestive of an Addiction Disorder

Aggressive complaining about the need for more drug

Drug hoarding during periods of reduced symptoms

Requesting specific drugs

Openly acquiring similar drugs from other medical sources

Unsanctioned dose escalation or other noncompliance with therapy on one or two occasions

Unapproved use of the drug to treat another symptom

Reporting psychic effects not intended by the clinician

Resistance to a change in therapy associated with "tolerable" adverse effects, with expressions of anxiety related to the return of severe symptoms

Source: Portenoy, RK: Opioid therapy for chronic nonmalignant pain: Current status. In Fields HL, and Liebeskind JC (eds): Progress in Pain Research and Management, Vol I: Pharmacological Approaches to the Treatment of Chronic Pain: New Concepts and Critical Issues. IASP Press, Seattle, 1994, p267.

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The major risk associated with physical dependence is abstinence, which is simply prevented by avoiding abrupt dose reduction and avoiding the use of opioid antagonistic drugs. Extensive clinical experience has not confirmed that physical dependence, or fear of withdrawal due to physical dependence, complicates medically indicated dose reduction or discontinuation of opioid therapy. Although physical dependence has been postulated to drive the development of an addiction disorder in non-patient substance abusers, experience with patients indicates that physical dependence is neither necessary nor sufficient for addiction.

Iatrogenic addiction is of greater concern than the adverse effects associated with physical dependence. Concern that the medical use of opioid drugs carries a substantial risk of addiction was heightened by early surveys of addict populations. This data combined with reports of high recidivism rates among detoxified addicts stimulated concern that exposure to an opioid drug would induce addiction in previously normal patients.

However, addiction is commonly perceived to be extremely rare during chronic opioid therapy for cancer pain.

Extensive clinical experience supports the argument that the risk of addiction does not reside predominantly with the drug. The risk of addiction is low in most patients with no prior history of drug abuse prescribed an opioid for a painful medical condition.

Long-term opioid administration has been considered inappropriate for the management of chronic nonmalignant pain. In the mid-1980's, a critical reappraisal of this issue began, and continues to this day.

Two sets of observations encouraged the re-evaluation of traditional thinking about the role of opioids. First, a favorable response to opioid therapy in cancer patients contradicted many commonly held beliefs. Secondly, the negative effect of regulatory policies on physician prescribing has been thought to result in under-treating pain in some patients.

Chronic pain patients are a heterogeneous group. There are likely subgroups. For some patients with chronic nonmalignant pain, opioid therapy may be appropriate, and for others it may not.

Patients referred to pain clinics, for example, have higher levels of psychosocial distress and functional impairment than patients with chronic pain surveyed in the community. It may be that the characteristics that lead to a pain clinic referral predispose these patients to problems with opioid therapy.

Patient selection is key.

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HOW TO ASSESS WHETHER AN OPIOID TRIAL IS INDICATED

1) IS THE PATIENT LIKELY TO IMPROVE?

2) IS THE PATIENT LIKELY TO ABUSE OPIOIDS OR HAVE OTHER ADVERSE OUTCOMES?

MAY IMPROVE

PROBABLY WILL NOT IMPROVE

- 1) Patient has taken opioids in the acute and subacute phases with some improvement in pain and function.
- 2) Other conservative measures have failed (NSAIDs, etc.) and opioids have not been tried.
- 3) Your pain diagnosis falls into one of the following three categories:
 - a) Nociceptive pain (for example, ischemia, tissue destruction, arthritis, cancer, arachnoiditis).
 - b) Neuropathic pain (for example, sciatica, carpal tunnel syndrome, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain).
 - c) Mixed nociceptive and neuropathic pain.

- 1) Patient has taken opioids in the acute and subacute phases with NO improvement in pain and function (assuming appropriate dosing, etc.).
- 2) The pain diagnosis falls into the category of somatoform disorder. A consultation should be considered to address the underlying problem. In particular, conversion disorder, somatization disorder, or pain disorder associated with psychological factors (DSM-IV 307.80) is associated with poor response to opioids.

The risk of abuse or adverse outcome is high if any of the following are present:

- 1) History of alcohol or other substance abuse, or a history of chronic, high dose benzodiazepine use.
- 2) Active alcohol or other substance abuse.
- 3) Borderline personality disorders.
- 4) Mood disorders (e.g., depression) or psychotic disorders.
- 5) Other disorders that are primarily depressive in nature.
- 6) Off work for more than 6 months
- 7) Poor response to opioids in past.

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Guidelines for opioid therapy in chronic nonmalignant pain have been developed.

**PROPOSED GUIDELINES FOR THE MANAGEMENT OF OPIOID THERAPY FOR CHRONIC
NONMALIGNANT PAIN**

1. Should be considered only after all other reasonable analgesic therapies have failed.
2. A history of substance abuse, severe character pathology, or chaotic home environment should be viewed as relative contraindications.
3. A single practitioner should take primary responsibility for treatment.
4. Patients should give informed consent before the start of therapy; points to be covered include:
 - (a) Recognition of the low risk of true addiction as an outcome
 - (b) Potential for cognitive impairment from the drug alone or from the combination of the drug with other centrally acting drugs
 - (c) Potential for other side effects
 - (d) Likelihood that physical dependence will occur (abstinence syndrome possible with acute discontinuation)
 - (e) Need for responsible drug-taking behavior (e.g., no unsanctioned dose escalation, no prescriptions from other physicians, and so on)
5. The use of a written contract to inform patient of his or her responsibilities should be considered, but is not mandatory.
6. Except in rare circumstances, therapy should be administered by the oral route.
7. The use of long-acting opioid (e.g., controlled-release morphine or methadone) may be preferable because of ease of administration, but is not mandatory.
8. Dosing on a fixed-schedule basis ("around the clock") is preferable if the patient experiences continuous or frequently recurring pain.
9. In addition to the daily dose determined initially, most patients should be permitted to escalate dose transiently on days of increased pain; two methods are acceptable:
 - (a) Prescription of an additional 4-6 "rescue doses" to be taken as needed during the month
 - (b) Instruction that one or two extra doses may be taken on any day, but must be followed by an equal reduction of dose on subsequent days.
10. Initially, patients must be seen and drugs prescribed at least monthly; when stable, less frequent visits may be acceptable.
11. Several weeks should be agreed upon as the period of initial dose titration; although improvement in function should be continually stressed, at least partial analgesia should be viewed as the primary goal of therapy.
12. Failure to achieve at least partial analgesia at relatively low initial doses in the patient with limited prior opioid consumption should raise questions about the potential treatability of the pain syndrome with opioids, and lead to reassessment.

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~Continued~

**PROPOSED GUIDELINES FOR THE MANAGEMENT OF OPIOID THERAPY FOR CHRONIC
NONMALIGNANT PAIN**

13. Emphasis should be given to attempts to capitalize on improved analgesia by gains in physical and psychosocial function; opioid therapy should be considered complementary to other analgesic and rehabilitative approaches.
14. Exacerbations of pain not effectively treated by transient and small increases in dose are best managed in the hospital, where dose escalation, if appropriate, can be observed closely, and return to baseline doses can be accomplished in a controlled environment.
15. Evidence of drug hoarding, acquisition of drugs from other physicians, uncontrolled dose escalation, or other aberrant behaviors must be carefully assessed. In some cases, tapering and discontinuation of opioid therapy will be necessary. Other patients may appropriately continue therapy with rigid guidelines. Consideration should be given to consultation with an addiction medicine specialist.
16. At each visit, assessment should specifically address:
 - (a) Comfort (degree of analgesia)
 - (b) Opioid-related side effects
 - (c) Functional status (physical and psychosocial)
 - (d) Existence of aberrant drug-related behaviors
17. Use of self-report instruments may be helpful in documenting pain relief and functional status, but are not mandatory.
18. Documentation is essential; the medical record should specifically address comfort, function, side effects, and the occurrence of aberrant behaviors repeatedly during the course of therapy.

Source: Portenoy, RK: Opioid therapy for chronic nonmalignant pain: Current status. In Fields HL, and Liebeskind JC (eds): Progress in Pain Research and Management, Vol I: Pharmacological Approaches to the Treatment of Chronic Pain: New Concepts and Critical Issues. IASP Press, Seattle, 1994, pp 274-275.

These guidelines emphasize the feasibility of a therapeutic opioid trial and the importance of dose adjustment and careful monitoring. This includes monitoring for pain relief, side-effects, functional status (including willingness to engage in other components of therapy), and the development of aberrant drug-related behaviors.

Patients who receive opioid therapy for chronic nonmalignant pain should be informed about the controversial nature of this approach. Some doctors use a formal written consent to document this. A sample of such a consent form is attached, along with a protocol for this treatment.

A fair therapeutic trial requires individualization of the opioid dose, which should optimize the balance between analgesia and side-effects.

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Opioid therapy is not a substitute for a comprehensive pain management approach, that also incorporates psychological and rehabilitative therapies.

If aberrant drug-related behaviors develop during treatment, it must be responded to appropriately.

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Is there a role for opioids in the management of chronic nonmalignant pain?

There are very few randomized controlled trials of chronic opioid analgesic therapy (COAT) for the management of chronic nonmalignant pain, such as problems with chronic low back pain. The current literature suggests there is a place for their use in some patients. COAT may not eliminate pain, but may make it more tolerable, allowing patients to increase activity and return to work. However, the evidence that this actually occurs is generally lacking.

It is also important to note that the majority of studies in this area have been sponsored by industry. This can sway the results toward the use of opioid medication.

There is a great need to pursue randomized clinical trials for opioid therapy.

Therefore, in answer to the question, "Is long-term use of opioid therapy for chronic back pain worth it", the medical literature suggests the answer for most patients is "yes, but only in selected patients."

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What are some of the other drugs used to treat chronic pain?

The major adjuvant or helping analgesic classes include antidepressants, anticonvulsants, some muscle relaxants, and local anesthetics.

There is strong evidence that antidepressant drugs have an analgesic effect in a variety of pain syndromes. Controlled studies have demonstrated the beneficial effect of antidepressants, such as amitriptyline (Elavil), in migraine, arthritis, chronic low back pain, diabetic neuropathy, and other chronic painful conditions.

The newer antidepressants, such as SSRIs, have also been found to have analgesic properties in some patients.

The analgesic effects of antidepressant drugs are not related to their mood-elevating properties. The dose of these drugs required for analgesia is lower than that to treat depression, and the onset of analgesia is more rapid than the onset of the antidepressant effects of these medicines. In addition, analgesia can occur without an effect on mood.

The action of antidepressant medicine in reducing pain is likely related to the effects of these medicines on the endogenous pain-modulating pathways, including the serotonin pathway.

A trial of treatment with antidepressant medication may be appropriate in the management of virtually any patient with chronic pain, or frequently recurring pain, including headache.

Serious adverse effects during antidepressant therapy are uncommon, particularly in the relatively low doses compared to those used to treat depression.

Common side-effects at moderate to higher doses include somnolence, weight gain, dry mouth, blurred vision, and constipation.

Anticonvulsant medicines are also helpful in the management of some types of chronic painful conditions, particularly pain of neuropathic origin. Pain symptoms often associated with neuropathic pain include lancinating or sharp pain, or sudden paroxysms or bouts of pain.

Some medicines in this class include carbamazepine (Tegretol), phenytoin (Dilantin), clonazepam (Klonopin), valproic acid (Depakote), gabapentin (Neurontin), and topiramate (Topamax).

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The mechanism by which these drugs relieve pain is thought to be related to their suppression of sudden discharges in nerves, and reducing the excitability of nerves.

Anticonvulsant medication should be considered early in the treatment of neuropathic pain syndromes.

What is meant by "off label" drug use?

Off label drug use is the use of a medicine for a condition other than that for which it was initially approved by the FDA. Off label drug use is a common everyday occurrence in virtually all medical practices.

Drugs are often used for "off label" indications when there is research performed after the drug was initially made available that demonstrates its efficacy for conditions other than those for which its use was initially approved.

You may not see reference to the use of antidepressants or anticonvulsants, for example, for the management of chronic painful conditions, in the Physicians' Desk Reference (PDR). However, they are commonly used in that situation.

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CASE STUDIES

Case A

Betty is a 48-year-old, married, mother and Public Health Nurse who was involved in a work-related motor vehicle accident on 7/7/03. Following that accident, Betty experienced low back pain.

Betty sought treatment from her primary care medical physician. Treatment included rest and various medications. Betty was referred for treatment with physical therapy. Symptoms persisted.

At Betty's request, her PCP referred her for trials of treatment with chiropractic manipulation and massage. These treatments provided only temporary relief of symptoms.

Betty continued to experience persistent, severe, functionally limiting low back pain.

Betty's examination is noteworthy for a decreased range of low back motion. The motor, reflex, and sensory examination in the lower extremities was normal.

An MRI scan of the lumbar spine revealed degenerative disc changes at the L4-5 and L5-S1 disc levels.

Betty's PCP initiated a trial of treatment with narcotic analgesic medication. Betty reported improvement in symptoms. The dose of narcotic analgesics was adjusted. Betty has been maintained on OxyContin 40 mg bid for the past year.

Since beginning treatment with chronic opiate analgesic therapy (COAT), Betty has returned to full-time full-duty work.

Betty continues monthly follow-up with her PCP.

RE: CHRONIC PAIN: TREATMENT WITH MEDICATION

Lorne K. Direnfeld, M.D., F.R.C.P. (C)

Case B

Bob is a 43-year-old, married, father and printing company salesman. Bob experienced a work-related injury on 5/4/02. At the time of that injury, Bob was transporting cartons of paper in the company van. As he was unloading the cartons, they began to tip. He pushed and twisted the stack of cartons to prevent them from falling over. While doing so, he reportedly heard a "pop" in the low back. Since then, he has experienced problems with severe low back pain.

Bob sought treatment from his primary care physician. Treatment included rest and medication. Medicines included Vicodin, Soma, and Celebrex.

Bob was referred for a trial of treatment with physical therapy. This was discontinued after three sessions due to the report of increased pain.

Bob has experienced severe functionally limiting pain.

An MRI scan of the lumbar spine performed on Bob demonstrated degenerative disc changes at the L4-5 and L5-S1 levels.

Bob's examination is noteworthy for a decreased range of low back motion due to complaints of pain. The motor, reflex, and sensory examination in the lower extremities is normal.

Bob has continued regular follow-up with his PCP. Treatment has included escalating doses of chronic opioid analgesic therapy (COAT). Currently, Bob is taking OxyContin 80 mg tablets two po tid, along with Vicodin ES one to two q4-6h prn for breakthrough pain, and Soma one tablet tid.

Bob sees his PCP for follow-up and medication renewals every two weeks. Often, Bob will come in early for medication. Bob also seeks treatment in the emergency room for flare-ups of pain. Treatment with injections of narcotic analgesics such as Demerol are provided.

Bob has remained off work since the injury date.

RE: CHRONIC PAIN: TREATMENT WITH MEDICATION

Lorne K. Direnfeld, M.D., F.R.C.P. (C)

Bob reports that because of problems with chronic pain and a big drop in his income, he has separated from his wife, and is undergoing divorce. Bob admits to problems with depression and irritability, which he attributes to chronic pain.

Although Bob states he is no better now than he was immediately following the 5/4/02 injury, he reports the need for continued treatment with opioids. Although Bob's doctor expressed concern about Bob's use of opioids, he prescribes increasingly larger doses of these medicines.

SAMPLE OPIOID TREATMENT AGREEMENT

Patient Name: _____

Date: _____

Opioid (narcotic) treatment for chronic pain is used to reduce pain and improve what you are able to do each day. Along with opioid treatment, other medical care may be prescribed to help improve your ability to do daily activities. This may include exercise, use of non-narcotic analgesics, physical therapy, psychological counseling or other therapies or treatment. Vocational counseling may be provided to assist in your return to work effort.

To the doctor: Keep signed originals in your file; give a photocopy to the patient. Renew at least every 6 months.

I, _____, understand that compliance

with the following guidelines is important in continuing pain treatment with Dr. _____.

1. I understand that I have the following responsibilities:
 - a. I will take medications only at the dose and frequency prescribed.
 - b. I will not increase or change medications.
 - c. I will actively participate in RTW efforts and in any program designed to improve function (including social, physical, psychological and daily or work activities).
 - d. I will not request opioids or any other pain medicine from physicians other than from this doctor. This doctor will approve or prescribe all other mind and mood-altering drug.
 - e. I will inform this doctor of all other medications that I am taking.
 - f. I will obtain all medications from one pharmacy, when possible known to this doctor with full consent to talk with the pharmacist given by signing this agreement.
 - g. I will protect my prescriptions and medications. Only one lost prescription or medication will be replaced in a single calendar year. I will keep all medications from children, h. I agree to participate in psychiatric or psychological assessments, if necessary.
 - h. If I have an addiction problem, I will not use illegal or street drugs or alcohol. This doctor may ask me to follow through with a program to address this issue.

Such programs may include the following:

- 12-step program and securing a sponsor
- Individual counseling
- Inpatient or outpatient treatment
- Other: _____

2. I understand that in the event of an emergency, this doctor should be contacted and the problem will be discussed with the emergency room or other treating physician. I am responsible for signing a consent to request record transfer to this doctor. No more than 3 days of medications may be prescribed by the emergency room or other physician without this doctor's approval.
3. I understand that I will consent to random drug screening. A drug screen is a laboratory test in which a sample of my urine or blood is checked to see what drugs I have been taking.
4. I will keep my scheduled appointments and/or cancel my appointment a minimum of 24 hours prior to the appointment.
5. I understand that this doctor may stop prescribing opioids or change the treatment plan if:
 - a. I do not show any improvement in pain from opioids or my physical activity has not improved. I will not increase or change medications.
 - b. My behavior is inconsistent with the responsibilities outlined in #1 above.
 - c. I give, sell or misuse the opioid medications.
 - d. I develop rapid tolerance or loss of improvement from the treatment.
 - e. I obtain opioids from other than this doctor.
 - f. I refuse to cooperate when asked to get a drug screen.
 - g. If an addiction problem is identified as a result of prescribed treatment or any other addictive substance.
 - h. If I am unable to keep follow-up appointments.

SAMPLE OPIOID TREATMENT AGREEMENT (continued)

YOUR SAFETY RISKS WHILE WORKING UNDER THE INFLUENCE OF OPIOIDS:

You should be aware of potential side effects of opioids such as decreased reaction time, clouded judgment, drowsiness and tolerance. Also, you should know about the possible danger associated with the use of opioids while operating heavy equipment or driving.

SIDE EFFECTS OF OPIOIDS:

- Confusion or other change in thinking abilities
- Nausea
- Constipation
- Vomiting
- Problems with coordination or balance that may make it unsafe to operate dangerous equipment or motor vehicles
- Sleepiness or drowsiness
- Breathing too slowly — overdose can stop your breathing and lead to death
- Aggravation of depression
- Dry mouth

THESE SIDE EFFECTS MAY BE MADE WORSE IF YOU MIX OPIOIDS WITH OTHER DRUGS, INCLUDING ALCOHOL

RISKS:

- Physical dependence. This means that abrupt stopping of the drug may lead to withdrawal symptoms characterized by one or more of the following:

Runny nose
Diarrhea
Sweating
Rapid heart rate

Difficulty sleeping for several days
Abdominal cramping
'Goose bumps'
Nervousness

- Psychological dependence. This means it is possible that stopping the drug will cause you to miss or crave it.
- Tolerance. This means you may need more and more drug to get the same effect.
- Addiction. A small percentage of patients may develop addiction problems based on genetic or other factors.
- Problems with pregnancy. If you are pregnant or contemplating pregnancy, discuss with your physician.

PAYMENT OF MEDICATIONS:

State law forbids L&I from paying for opioids once the patient reaches maximum medical improvement. You and your doctor should discuss other sources of payment for opioids when L&I can no longer pay.

RECOMMENDATIONS TO MANAGE YOUR MEDICATIONS:

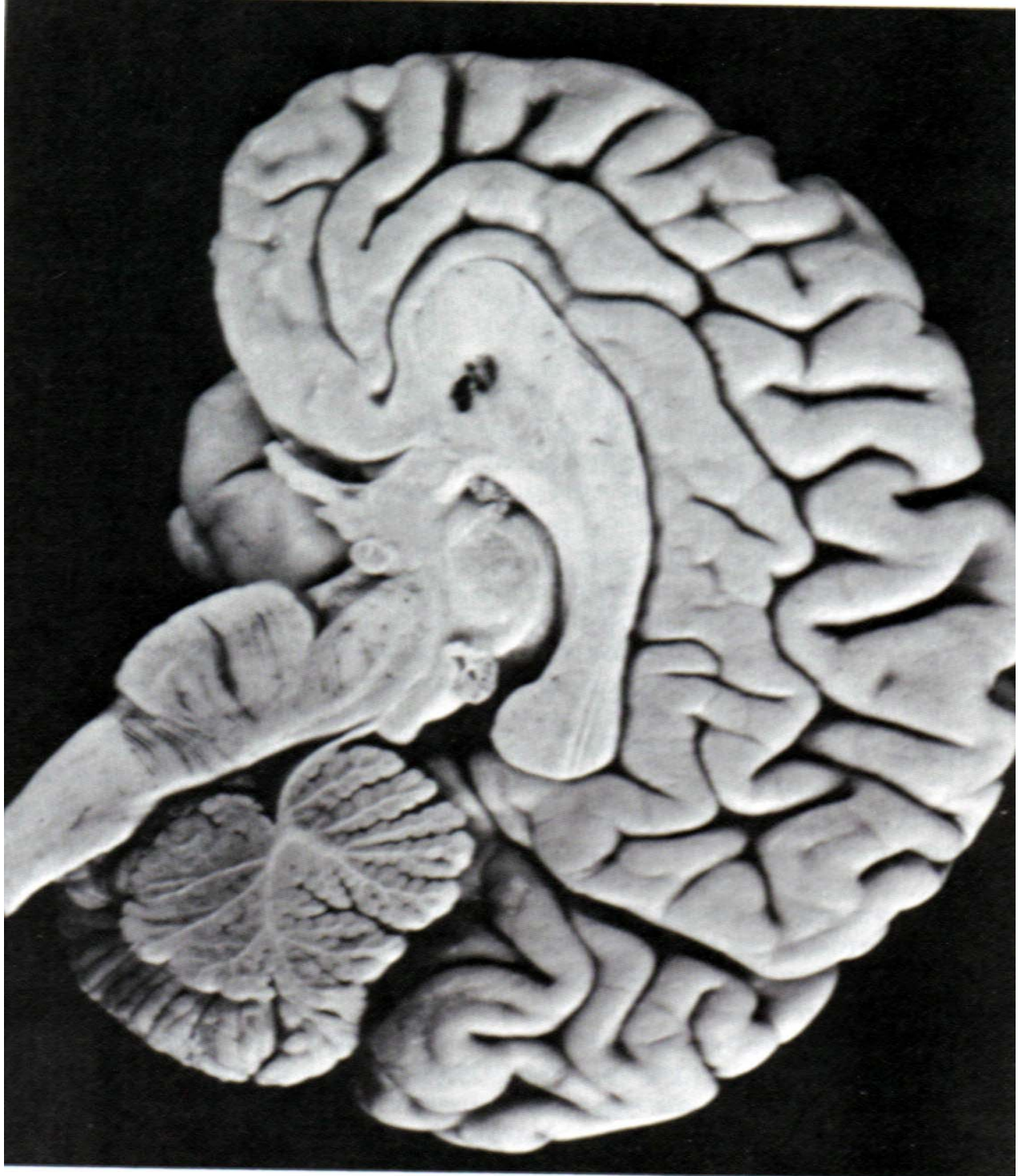
- Keep a diary of the pain medications you are taking, the medication dose, time of day you are taking them, their effectiveness and any side effects you may be having.
- Use of a medication box that you can purchase at your pharmacy that is already divided in to the days of the week and times of the day so it is easier to remember when to take your medications.
- Take along only the amount of medicine you need when leaving home so there is less risk of losing all your medications at the same time.

I have read this document, understand and have had all my questions answered satisfactorily. I consent to the use of opioids to help control my pain and I understand that my treatment with opioids will be carried out as described above.

Patient Signature: _____ **Date:** _____ **Physician Signature:** _____ **Date:** _____

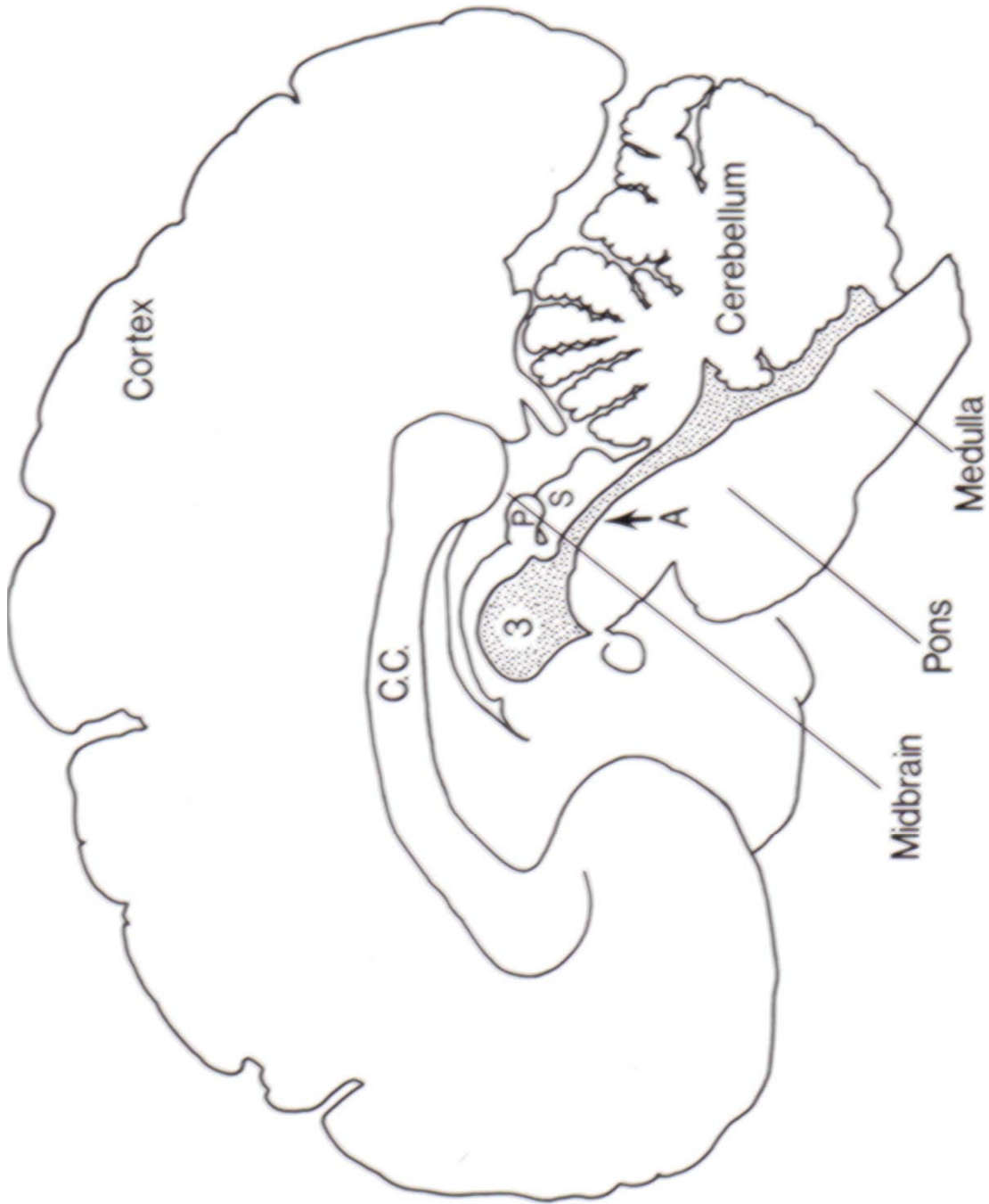
RE: CHRONIC PAIN: TREATMENT WITH MEDICATION

Lorne K. Direnfeld, M.D., F.R.C.P. (C)



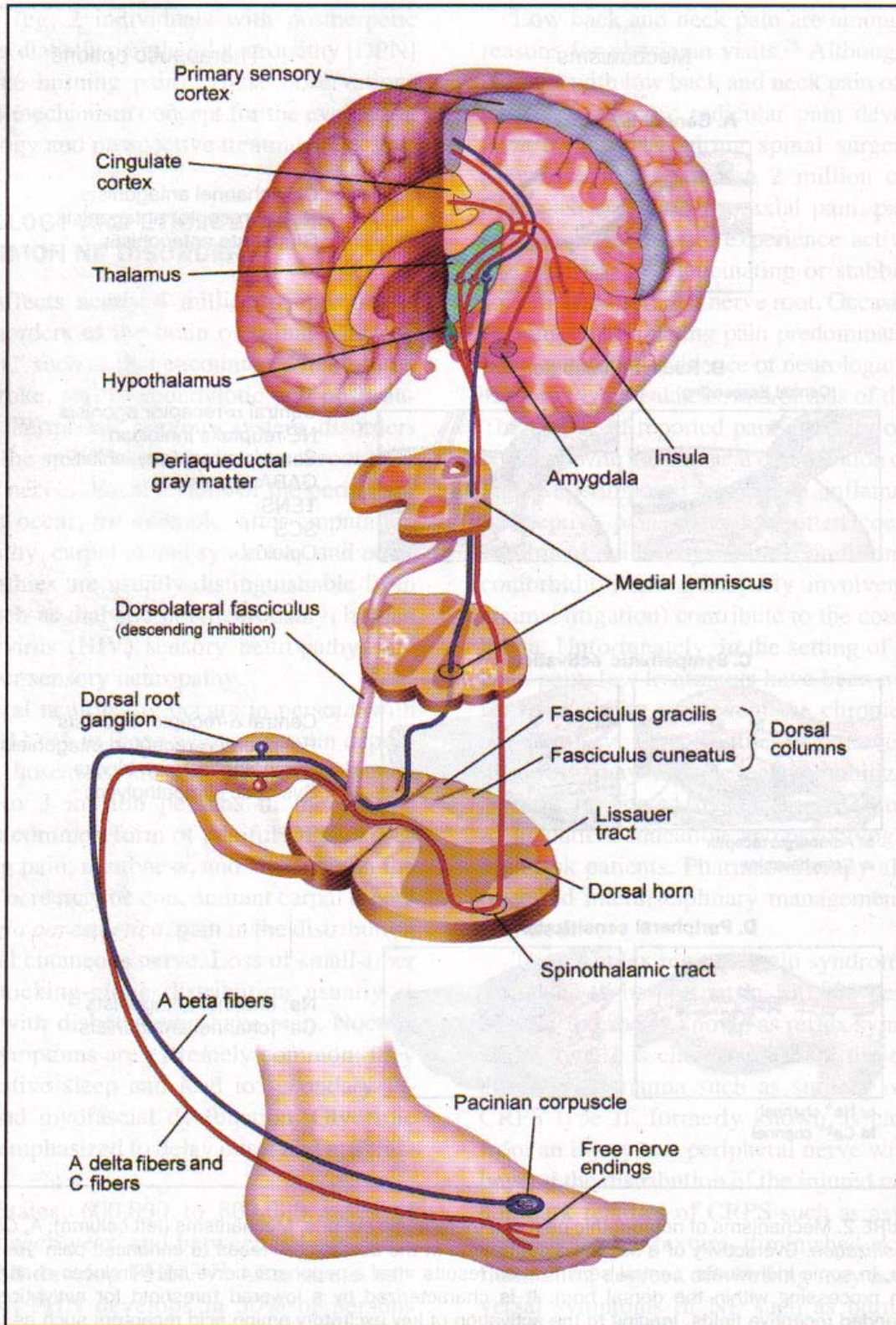
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