REVIEW

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Challenges and choices in drug therapy for chronic pain

ABSTRACT

By treating chronic pain effectively, physicians can improve the quality of their patients' lives considerably. This article reviews the mechanisms and treatment of chronic pain, with emphasis on overcoming the barriers to effective analgesia.

KEY POINTS

Chronic pain can be multifactorial, and it is often hard to determine if it is nociceptive, neuropathic, idiopathic, or all of the above.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of treating many pain conditions, but they pose the risk of gastric bleeding. Cyclo-oxygenase 2 (COX-2) inhibitors pose less risk but are not necessarily more effective. Serial trials of different NSAIDs may identify the one that is most effective for an individual patient.

Although many physicians are reluctant to prescribe opioids for long-term pain relief, these drugs can be used for this purpose if the goals are clear and use is closely monitored.

Tricyclic antidepressants, anticonvulsants, and other psychopharmacologic agents have an adjuvant role in managing chronic pain, with some being considered directly analgesic and others working indirectly.

CHRONIC PAIN is different from acute pain, and its treatment poses challenges that treating acute pain does not. As our understanding of the mechanisms of pain improves, treatment for chronic pain is changing and now includes drugs that we do not normally think of as painkillers.

Chronic pain is a symptom of an essential bodily system gone wrong. Thus, pain can become a disease in and of itself. At times, treating chronic pain can bring about a remarkable reversal in nociception and an improved quality of life.

DIFFICULTIES IN TREATING CHRONIC PAIN

Pain is biopsychosocially complex, and treatment of chronic pain is often challenging and frequently requires a broad-minded approach. The approach to a patient in chronic pain is similar to that for any chronic condition that treatment may control but may not cure.

What is 'pain'?

A major problem in approaching chronic pain is the terminology. Foremost is the word "pain," which defies a concise, universally accepted definition and which manifests as an untestable hypothesis. There is no way to prove that someone's claim of pain is true or false.

Moreover, pain can be different to different people. For instance, what is the difference between the pain of a broken leg and the pain of a broken heart?

The vagaries of terminology for pain used by the patient and the physician sometimes lead us away from the true problem. "Pain" can be related to the physiologic meaning of pain,

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or it may (and often does) encompass all the facets of human suffering, including physical pain, depression, demoralizing depletion of self-image, and social suffering involving interpersonal relationships, financial concerns, and spiritual aspects of life.

Diagnosing and classifying pain

Diagnosing chronic pain accurately can be difficult, and controversy remains regarding how to classify many pain conditions such as reflex sympathetic dystrophy, sympathetically maintained pain, and complex regional pain syndrome.

Identifying the source of chronic pain can be equally challenging, as a patient may have multiple factors that could generate or potentiate pain. It is often difficult to discern whether the pain is nociceptive (generated or facilitated by a normal functioning pain alarm system), neuropathic (due to a dysfunctional nervous system), or idiopathic. All of these factors in any combination may contribute to chronic pain. Psychologic disturbances can also play a role in amplifying any of these conditions.

There is no way to prove that someone's claim of pain is true or false

Fear of addiction: A barrier to care

Unfortunately, a major concern for many physicians confronted with treating chronic pain is the potential for opening a Pandora's box of escalating treatment and dosages. Too often, clinicians do not treat pain adequately out of fear that patients will become addicted to medications without objective evidence of efficacy.

OVERVIEW OF PAIN PROCESSING

Pain is generally classified as acute (immediate) or chronic (prolonged).

Acute (immediate) pain

Immediate pain is the warning signal the brain receives that damage has been done or is imminent.

Immediate pain is subdivided into fast pain and slow pain. This is the familiar "double" pain of a stubbed toe whereby you realize that you've hurt yourself, and then you wait the split-second for the wave of pain to hit.

Fast pain. Immediately after you stub a toe, a signal travels through the neospinothalamic tract to the brain via A-delta fibers. These are myelinated fibers that conduct signals quickly. Fast pain serves mostly to tell us where the pain is and how intense it is.

Slow pain. The slower, unmyelinated paleospinothalamic tract then conducts the signal with diffuse projections through the brain, and may be responsible for appreciating the extent of injury and modulating the suffering perceived.

Chronic (prolonged) pain

Prolonged pain is the result of temporary or permanent changes in and around the peripheral and central nervous systems. Common changes are related to tissue injury, often mediated by inflammation. Tissue injury releases multiple mediators, which proliferate the pain alarm in complex cascades.

The pain of inflammation and injury is usually limited and resolves as the injury heals. However, inflammation and injury are always accompanied by changes in the peripheral and central nervous systems. Peripheral nociceptors (pain fibers) become sensitized and more readily transduce pain signals and may do so in response to a lower-intensity stimulus than before the injury. This can result in continuous spontaneous pain, as well as pain upon movement or manipulation of the injured tissues (incident pain). Adjacent uninjured tissues are recruited by neurons in the spinal cord in a phenomenon known as secondary hyperalgesia. If these changes persist after the initial inflammatory response resolves, the pain becomes chronic.

Prolonged pain can be the result of ongoing tissue injury with normal nociception or due to nerve injury with abnormal nociception (neuropathic pain). In inflammatory and neuropathic pain, reactions to mild stimuli are out of proportion to the stimuli. Such evoked stimulus-induced reactions are termed allodynia, hyperalgesia, and hyperpathia.

Allodynia is pain caused by a normally nonpainful stimulus. An example is sunburn.

Hyperalgesia is an exaggerated painful sensation caused by a normally painful mechanical or thermal stimulus. For example, a gentle pinprick is usually barely painful but can be very painful in a hyperalgesic area.

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In this condition, the threshold of firing for the dorsal horn neurons is lowered by the continuous input of spontaneously firing C-fibers. This may result in increased excitability of the central nervous system, a process that is broadly termed central sensitization. In other words, the dorsal horn neurons respond to normally painful inputs in a sensitized fashion, potentially manifesting as amplified pain sensitivity or expression. This may be seen as enlargement of the area in the periphery where a stimulus will trigger pain or sensation.

Hyperpathia is an abnormally painful and prolonged reaction to a stimulus. For example, a single pinprick may cause minimal pain, but with repetitive pinpricks patients describe the pain as explosive and worsening as time passes.

The worsening pain represents either summation or aftersensations. Summation is the perception of increasing pain or sensation to a fixed repetitive stimulus with no change in the stimulus pattern or intensity. Aftersensations are persistent painful sensations that are felt even after the stimulus is removed.

TREATING CHRONIC PAIN

Acute pain can usually be managed effectively with standard, well-established regimens that include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, mild or strong opioids, and reassurance.

But acute pain is finite and usually has an identified cause and a time-limited course. Chronic pain does not usually come in such a neat and logical package, which can lead to frustration and inadequate pain treatment.

SETTING GOALS

In treating chronic pain, you should start by setting clear and reasonable goals and expectations. Restoration of function may be the most important single goal for monitoring treatment success. No matter what goals are chosen, however, the definition of success should be discussed with the patient before treatment is started, and treatment goals should be agreed upon and continually reviewed.

Goals should be concrete and as clear as possible, since this allows cooperative measurement of success or failure. These goals should be reasonable and achievable, given the patient's baseline condition and capacity. It should be obvious when the goal is achieved, and the patient's quality of life should be better.

HOW DO ANALGESICS WORK?

Analgesia has been attributed to many different cellular mechanisms. The diversity of proposed analgesic mechanisms for all of the drugs used to treat pain indicate the complexity of pain mechanisms.

Blockade of cyclo-oxygenase (COX) reduces proliferation of inflammatory prostaglandins and prostacyclins. Willow bark, the first COX inhibitor, was used for centuries, but only recently have we learned about the selective effects of induced COX-2 and how to block constitutive COX-2 in the central nervous system.

Opioid receptor agonism remains the gold standard of pain treatment.

Blockade of other cellular channels such as sodium channels is well established in local anesthesia and in neuropathic analgesia. Recently, we have come to appreciate that antagonism of the *N*-methyl *D*-aspartate (NMDA) receptor complex (which involves a calcium channel) may be useful in treating neuropathic pain or preventing tolerance to opioids. NMDA antagonists include ketamine, dextromethorphan, methadone, and others. Blockade of specific calcium channels by SNX-111 (ziconotide) also appears to have analgesic properties.

Increasing synaptic concentrations of both norepinephrine and serotonin, as seen with use of tricyclic antidepressants (TCAs), may have a special role in neuropathic pain. However, TCAs are also membrane-stabilizing agents by virtue of sodium channel blockade, and this mechanism as well as their NMDA antagonism may independently subserve their known analgesic properties. Many of the conventional analgesics that are thought to be selective for neuropathic pain conform to the profile of the TCAs in that they have neuron membrane-stabilizing prop-

In treating chronic pain, set clear, concrete, reasonable goals

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erties. In other words, they are either antiarrhythmics or anticonvulsants. Alternatively, agonism of both gamma-aminobutyric acid A (GABA-A) and GABA-B (eg, with clonazepam and baclofen) may be effective in neuropathic pain, as can alpha-adrenergic agents (clonidine and tizanidine).

Chili pepper, in the form of capsaicin, has been found to deplete substance P from nerve terminals and may be helpful in some forms of acute and chronic pain.

As this list suggests, the spectrum of analgesics for chronic pain is broader than can be comprehensively examined in this review. However, specific analgesic groups are further described below.

NSAIDs AND ACETAMINOPHEN

NSAIDs and acetaminophen are the cornerstones of treatment for most pain conditions.

But these drugs are not without risk. The cost of complications of NSAID treatment is estimated at more than $1.3 billion per year. NSAID-related gastropathy is one of the most serious complications of pharmacologic treatment in the United States.[1] An estimated 86,000 hospitalizations and 13,000 deaths per year are related to complications of NSAIDs in patients with osteoarthritis and rheumatoid arthritis.[1]

Since it is the COX-1 enzyme that is involved in gastric mucosa cytoprotection and platelet aggregation, selective COX-2 inhibitors have been developed to minimize gastric mucosa ulceration and bleeding.

NSAIDs and acetaminophen do not induce either tolerance or dependence; however, their analgesic efficacy varies widely among individual patients. By trying different NSAIDs in succession, one may find a medication with greater analgesic response for a given patient. This individual variability may relate to the variable selectivity of NSAIDs for inhibition of COX-1 and COX-2 enzymes.

Mechanism of action

Traditional wisdom teaches that NSAIDs work by blocking induction of the COX-2 enzyme in inflammatory lesions. NSAIDs may reduce inflammation by a separate process from the one by which they relieve pain, however, although the actions may be complementary.[2]

NSAIDs usually induce analgesia rapidly, whereas their anti-inflammatory effects are usually delayed. Moreover, COX-2 inhibitors are analgesic before there is peripheral induction of COX-2 by inflammatory processes. Therefore, the central nervous system actions of COX-2 may be different from the peripheral actions of inflammation mediation and may involve constitutive activity.

Much of the data on the efficacy and toxicity of NSAIDs in general are from studies of arthritis patients, or the limited treatment of postoperative pain. Thus, clinical use of NSAIDs in patients with chronic nonarthritic pain is often by extrapolation. For instance, although classically considered devoid of anti-inflammatory properties, acetaminophen has been recommended by the American College of Rheumatology as first-line therapy for osteoarthritis of the hip and knee at a dosage of up to 1 g four times a day.[3]

Are COX-2 inhibitors better?

The new, selective COX-2 inhibitors were developed to decrease the bleeding and ulcer risks associated with standard NSAIDs. As analgesics they may not be more potent than standard NSAIDs. They do have a long half-life, leading to longer activity than, say, ibuprofen.

NSAIDs have a ceiling to their efficacy

The FDA-approved dosages of the COX-2 inhibitors rofecoxib and celecoxib are twice as high for treating acute pain and primary dysmenorrhea as for treating osteoporosis. At doses effective for osteoarthritis, COX-2 inhibitors were no more effective than placebo in patients with acute pain.

Overcoming the analgesic ceiling

One of the limitations of NSAIDs is they have a ceiling effect—a top dosage beyond which efficacy does not increase. However, this ceiling may be overcome by adding synergistic medications, such as adding acetaminophen to ibuprofen[4] or acetaminophen to diclofenac.[5]

Additionally, some COX-2 isoforms may be inhibited by specific medications, but not others. For instance, acetaminophen may specifically inhibit an isoform of COX-2 that

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may be resistant to inhibition by diclofenac or aspirin.[6]

OPIOID ANALGESICS IN CHRONIC PAIN NOT DUE TO CANCER

Using opioids to treat chronic nonmalignant pain not due to cancer remains controversial. The decision to use opioids long-term is often made reluctantly, after other options have failed. Social, medical, and legal stigma contribute to the reluctance, particularly now in the wake of recent media attention to oxycodone abuse.

However, for many patients, long-term opioid therapy may offer the only way to achieve a functional lifestyle. Some need consistent amounts of opioid over time with little variation, but others have needs that are seemingly never satisfied and dosages that are frequently escalating.

Long-term opioid therapy can be a challenge because the goal of analgesic therapy is usually the patient's subjective experience of pain relief. Treatment success usually hinges on distinguishing between positive and negative impact on quality of life, which includes measuring functional gains.

For many, long-term opioid therapy may be the only way to achieve a functional lifestyle

Rational use vs the risk of abuse

The exact extent of opioid abuse is unclear. Federal guidelines indicate that abuse may be common,[7] and some studies indicate that patients who use opioids are more likely to be dishonest about their medication use than patients taking nonopioid medications.[8] However, this is not universally accepted.[9]

Rational use of opioids for treatment of chronic pain, whether due to cancer or other causes, differs significantly from opioid abuse in that it is not intended to produce euphoria. In fact, in patients with chronic pain, long-term opioid therapy may even produce side effects that are unpleasant or dysphoric.[10,11]

Since opioids are never curative, always have potential side effects, and can reduce an individual's autonomy, when they are given long-term the goal is usually to improve function, eg, to decrease disability, increase independence, or improve quality of life. In contrast, opioid addiction is intrinsically marked by dysfunction.[11,12] Therefore, effective opioid use for chronic pain improves function, whereas opioid use in opioid addiction usually does not.

Long-term opioid treatment for noncancer pain raises many controversies and concerns, including questions of efficacy, adverse effects, toxicity, addiction, tolerance, misuse, and fear of regulatory scrutiny. Other concerns that may limit opioid use in chronic pain relate to neuropsychiatric deterioration,[13] poor treatment outcome,[14] reinforcement of pain behavior,[15] and immunosuppression.[16]

Guidelines for long-term opioid use in nonmalignant pain have been proposed jointly by the American Pain Society and the American Academy of Pain Medicine **(www.ampainsoc.org/advocacy/opioids.htm).** Portenoy[10] and others[17,18] have advocated the judicious use of opioids for chronic noncancer pain, including using greater caution when patients have a history of substance abuse. However, a history of substance abuse, in and of itself, is probably not sufficient grounds for withholding long-term opioid therapy.[19]

The decision to treat chronic pain with opioids should be based on clear goals of treatment. It should come after determining whether the patient's pain is opioid-responsive, whether side effects will be tolerable, and whether substance abuse is a part of the history of present illness that requires further consideration. While substance abuse is not an absolute contraindication for chronic opioid therapy, it may imply the need for special considerations, precautions, and adjunctive treatments.

Can NMDA blockers reduce opioid resistance and tolerance?

Opioids are the gold standard for treating severe somatic and inflammatory pain. Inflammation induces de novo expression of opioid receptors on nociceptive neurons where they were not previously present.

Neuropathic pain, on the other hand, has long been considered opioid-resistant, and opioids have traditionally been avoided in patients with painful neuropathy. However, this view has been refuted by recent literature.[20]

Opioid resistance and opioid tolerance

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have been linked to a common mechanism involving the NMDA receptor. It has been suggested that opioid-resistant pain and tolerance to opioids from chronic exposure are two sides of the same coin.[21] As such, NMDA blockade should be effective in reversing tolerance and in treating neuropathic pain.

Considerable evidence is mounting to support this view, based on studies in laboratory animals, but clinical results have been conflicting, and treatment is limited by side effects such as psychotomimetic symptoms or seizures.

Clinically available NMDA blockers are dextromethorphan, amantadine, methadone, and ketamine. Low doses of dextromethorphan (90 mg/day) showed no efficacy in neuropathic pain[22]; however, dextromethorphan in high doses (400 mg/day) was analgesic in patients with diabetic neuropathy, but not with postherpetic neuralgia.[23] Both methadone and propoxyphene exert NMDA antagonism and may be useful in treating neuropathic pain. Some studies have shown that very high doses of morphine, fentanyl, and meperidine block the NMDA receptor. Perhaps this explains why high doses of opioids are often required for neuropathic pain.[24]

Along the same lines, combinations of opioids and NMDA blockers may prevent tolerance. Patients with chronic pain used less daily morphine and needed to escalate their morphine dose less when treated with morphine plus dextromethorphan compared with morphine alone.[25] New combinations of dextromethorphan and morphine may be available soon to serve just this purpose. Opioids such as methadone and propoxyphene have similar receptor activity profiles.

Assessing response to opioids

Responsiveness to opioids can only be assessed with a titration trial. Simply prescribing the medication and assuming that pain will disappear is unrealistic and poses the risk of either undershooting or overshooting the side-effect-free window of analgesia. A successful opioid trial should result in significantly less pain in the short term, and in increased function or improvement in quality of life in the long term.

Be concerned if a patient says that an opioid "takes the edge off" or something similar. Such statements may indicate a contradiction whereby the opioid is not having a substantial analgesic effect while simultaneously implying that the medication is needed. The patient may only be receiving nonanalgesic effects from the opioid such as distraction, sedation, or anxiolysis. On the other hand, an opioid trial that produces neither analgesia nor side effects possibly indicates underdosing.

Sustained-release opioids

Chronic pain that is always present should be treated with continuously acting, ie, sustained-release, medications. When short-acting narcotics are used, the pain is undertreated or untreated for a significant portion of the patient's day. Remember, the goal is to improve the patient's quality of life—and chronic clock-watching and short duration of effect are not conducive to a good quality of life. Long-term opioid therapy is therefore usually best offered with sustained-release preparations.

Sustained-release morphine (MSContin, Oramorph, others) **and oxycodone** (Oxycontin) can usually be used with twice-a-day or three-times-a-day dosing. The tablets cannot be cut or broken without compromising their prolonged action and reverting the preparation to a short-acting, fast-onset drug. Steady-state dosage increases can be achieved by increasing the milligram dose, or by decreasing the dosing interval.

Be concerned if a patient says an opioid 'takes the edge off'

Fentanyl patches have the longest dosage interval, as each patch usually lasts for 3 days. However, the weakest patch, which delivers 25 µg/hour, is roughly equivalent to 100 mg/day of oral morphine. As these patches are only manufactured in dosages of 25, 50, 75, and 100 µg/hour, titration can be difficult and the effects of too great a dose can be persistent.

Methadone

Methadone is a unique opioid. It has a relatively long plasma half-life of approximately 1 day but an intermediate length of action of about 4 to 8 hours for analgesia. Thus, it is ideal for opioid addiction maintenance, but the once-a-day dosing used to maintain opioid addiction usually cannot be used for pain control. Moreover, because it has a highly variable elimination half-life (12–140 hours), toxicity can occur rarely, especially when combined with depressants.

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TABLE 1

SAMPLE FOR ADAPTATION AND REPRODUCTION ON PHYSICIAN LETTERHEAD. PLEASE CONSULT YOUR ATTORNEY.

Sample agreement: Long-term controlled substances therapy for chronic pain. A consent form from the American Academy of Pain Medicine

The purpose of this agreement is to protect your access to controlled substances and to protect our ability to prescribe for you.

The long-term use of such substances as opioids (narcotic analgesics), benzodiazepine tranquilizers, and barbiturate sedatives is controversial because of uncertainty regarding the extent to which they provide long-term benefit. There is also the risk of an addictive disorder developing or of relapse occurring in a person with a prior addiction. The extent of this risk is not certain.

Because these drugs have potential for abuse or diversion, strict accountability is necessary when use is prolonged. For this reason the following policies are agreed to by you, the patient, as consideration for, and a condition of, the willingness of the physician whose signature appears below to consider the initial and/or continued prescription of controlled substances to treat your chronic pain.

1. All controlled substances must come from the physician whose signature appears below or, during his or her absence, by the covering physician, unless specific authorization is obtained for an exception. (Multiple sources can lead to untoward drug interactions or poor coordination of treatment.)

2. All controlled substances must be obtained at the same pharmacy, where possible. Should the need arise to change pharmacies, our office must be informed. The pharmacy that you have selected is: _____; phone: _____.

3. You are expected to inform our office of any new medications or medical conditions, and of any adverse effects you experience from any of the medications that you take.

4. The prescribing physician has permission to discuss all diagnostic and treatment details with dispensing pharmacists or other professionals who provide your health care for purposes of maintaining accountability.

5. You may not share, sell, or otherwise permit others to have access to these medications.

6. These drugs should not be stopped abruptly, as an abstinence syndrome will likely develop.

7. Unannounced urine or serum toxicology screens may be requested, and your cooperation is required. Presence of unauthorized substances may prompt referral for assessment for addictive disorder.

8. Prescriptions and bottles of these medications may be sought by other individuals with chemical dependency and should be closely safeguarded. It is expected that you will take the highest possible degree of care with your medication and prescription. They should not be left where others might see or otherwise have access to them.

9. Original containers of medications should be brought in to each office visit.

10. Since the drugs may be hazardous or lethal to a person who is not tolerant to their effects, especially a child, you must keep them out of reach of such people.

11. Medications may not be replaced if they are lost, get wet, are destroyed, are left on an airplane, etc. If your medication has been stolen and you complete a police report regarding the theft, an exception may be made.

12. Early refills will generally not be given.

13. Prescriptions may be issued early if the physician or patient will be out of town when a refill is due. These prescriptions will contain instructions to the pharmacist that they not be filled prior to the appropriate date.

14. If the responsible legal authorities have questions concerning your treatment, as might occur, for example, if you were obtaining medications at several pharmacies, all confidentiality is waived and these authorities may be given full access to our records of controlled substances administration.

15. It is understood that failure to adhere to these policies may result in cessation of therapy with controlled substance prescribing by this physician or referral for further specialty assessment.

16. Renewals are contingent on keeping scheduled appointments. Please do not phone for prescriptions after hours or on weekends.

17. It should be understood that any medical treatment is initially a trial, and that continued prescription is contingent on evidence of benefit.

18. The risks and potential benefits of these therapies are explained elsewhere (and you acknowledge that you have received such explanation).

19. You affirm that you have full right and power to sign and be bound by this agreement, and that you have read, understand, and accept all of its terms.

_____	_____
Physician signature	Patient signature
_____	_____
Date	Patient name (print)

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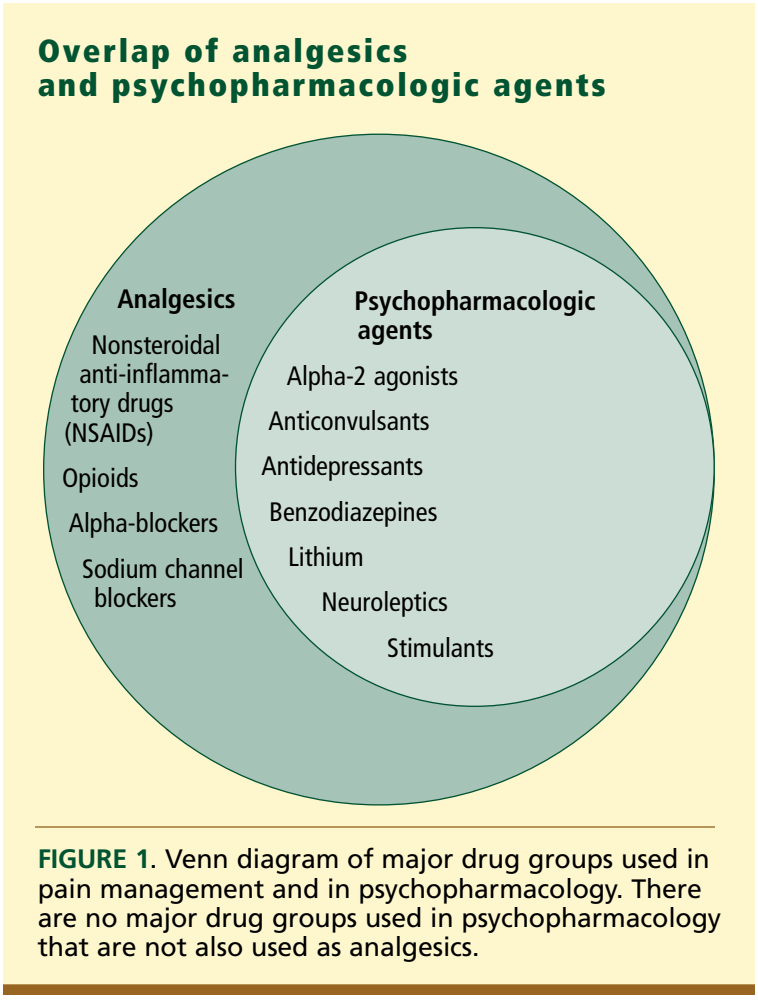

FIGURE 1. Venn diagram of major drug groups used in pain management and in psychopharmacology. There are no major drug groups used in psychopharmacology that are not also used as analgesics.

In addition to mu receptor agonism, methadone blocks NMDA receptors and inhibits serotonin and norepinephrine reuptake in a fashion similar to TCAs. Thus it has garnered the reputation as a "broad-spectrum" opioid. By extrapolation, methadone may be particularly effective in neuropathic pain.

Special care must be used in starting and titrating methadone. The exact conversion ratio for patients who are already established on high dosages of other opioids is uncertain, and thus extremely conservative estimates should be made when changing from any other opioid to methadone.

Methadone is available as an elixir, an injection, and pills, which can be divided.

Opioid agreements

It may be helpful to use an opioid agreement with patients undertaking chronic opioid therapy. This may help to define the goals and limits of treatment and establish informed consent, and may offer some protection under rare circumstances of abuse.[26]

Calling this an opioid "contract" may raise concerns that clinicians may be subjecting themselves to legal liability. Nonetheless, any mutually and formally agreed-upon plan, verbal or written, no matter whether it is titled a contract, agreement, or guideline, will hold a clinician accountable for any specific responsibilities outlined by the agreement. Clinicians must be careful to follow their own rules or subject themselves to possible ramifications.

Recently, the American Academy of Pain Medicine released a sample patient-physician agreement form for long-term controlled substances therapy for chronic pain (**TABLE 1**; **www.painmed.org/productpub/statements/sample.html**).

Distinguishing addiction from pseudoaddiction, tolerance, and dependence

Fear of addiction continues to be a significant barrier to opioid therapy. Beliefs about addiction are often founded by false assumptions or the fear that such an adverse effect, if it were to manifest, would be unmanageable. Any physician who treats chronic pain patients with opioids should have a clear understanding of the features that distinguish addiction from pseudoaddiction, tolerance, and dependence.

Drug addiction is a biopsychosocial disease in which there is compulsive use of a substance that causes dysfunction, and continued use despite that dysfunction.

Pseudoaddiction, in contrast, is medication-seeking behavior by patients whose pain is undertreated. It is an iatrogenic behavior. Pseudoaddiction differs from addiction in that adequate dosing results in improved function, whereas increased use of an addicting drug is by definition linked to dysfunction.

Tolerance is a pharmacologic state of requiring increasing amounts of a drug to achieve a desired response. Alternatively, it is the reduced effect of a fixed amount of a drug over time. Tolerance is a pharmacologic property of a drug and does not necessarily relate to or occur with addiction.

Tolerance has been thought to be due to

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TABLE 2

Tricyclic antidepressants commonly used in chronic pain management

DRUG NAME	DOSAGE (MG/DAY)	METABOLISM	PROTEIN BINDING
Tertiary amines			
Amitriptyline	25–300	Hepatic	Highly bound
Doxepin	25–300	Hepatic	?
Clomipramine	25–250	Hepatic	?
Imipramine	25–300	Hepatic	Highly bound
Secondary amines			
Desipramine	25–300	Hepatic	Highly bound
Nortriptyline	25–250	Hepatic	Highly bound

DATA FROM BALDESSARINI RJ. DRUGS AND THE TREATMENT OF PSYCHIATRIC DISORDERS. DEPRESSION AND MANIA. IN: HARDMAN JG, LIMBIRD, LE, EDITORS. GOODMAN AND GILLMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 9 ED. NEW YORK, MCGRAW-HILL 1996:431–459; AND KATZUNG BG. BASIC AND CLINICAL PHARMACOLOGY 8 ED. NEW YORK, MCGRAW-HILL 2001.

up-regulation of opioid receptors; however, as mentioned previously, evidence suggests that tolerance is at least partly mediated by a mechanism coupling opioid receptors with NMDA receptors and G-proteins. Although tolerance can develop, it is not the rule and many patients can be stable for years at a given dose. Need for increasing doses, especially in cancer patients, is often due to progression of the disease.

Physical dependence is also a pharmacologic property of a drug and does not necessarily relate to or occur with addiction. It relates to a reaction to sudden cessation of a chronically administered drug, otherwise known as a withdrawal reaction. For instance, stopping clonidine suddenly poses the risk of a life-threatening withdrawal reaction; however, clonidine has no addiction potential.

Start tricyclics at low dose to minimize adverse effects

ADJUVANT MEDICATIONS AND NEUROPATHIC ANALGESICS

Adjuvant analgesics range from agents that selectively treat pain due to nerve injury to those that have synergistic effects in combination with other known analgesics.

Since pain is multifactorial and has input and modulation from systems beyond the nociceptive sensory nervous system, drugs that do not necessarily directly decrease nociception may have potent indirect effects on pain in certain settings. For instance, there is no single drug group within the field of psychopharmacology that does not also have pain-relieving properties (FIGURE 1).

Tricyclic antidepressants

Tricyclic antidepressants (TCAs, TABLE 2), probably the best known of the adjuvant group, have analgesic properties independent of their effects on depression. Their analgesic mechanism may be due to their known inhibitory effects on sodium channels (which make them potentially cardiotoxic) as well as their NMDA-blocking effects. As noted above, TCAs are independently effective in neuropathic pain.

There are more reports on the neuropathic analgesic effects of amitriptyline (Elavil) than other TCAs, so this tends to be the medication most often prescribed. Few studies have compared TCAs with newer antidepressant drugs for their analgesic effects.

Unfortunately, TCAs affect multiple receptor systems (cholinergic, histamine, alpha, others) and therefore have many side effects (TABLE 3), which may limit their use in many patients. Anticholinergic side effects such as urinary retention, dry mouth, constipation, and sedation are much more pronounced with amitriptyline than with its active metabolite nortriptyline. Desipramine also has a more favorable side effect profile than its parent compound, imipramine (TABLE 3). Other therapy-limiting side effects of TCAs include antihistamine effects (which can cause weight gain), anti-alpha effects (which can cause orthostatic hypotension in the elderly), and serotonergic effects (which can impair sexual function).

For these reasons, TCAs should be prescribed at low starting doses (10–25 mg at night) and increased as tolerated. Analgesia may be seen at dosages lower than those necessary for antidepressant effects; however, analgesia occurs in a dose-response pattern. If sedation on the morning following a dose is a problem, shifting the dose to earlier in the evening may help.

Selective serotonin reuptake inhibitors

SSRI antidepressants do not share the mem-

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TABLE 3

Common side effects of tricyclic antidepressants

Anticholinergic—Urinary retention, blurred vision, confusion, constipation, dry mouth, cycloplegia, mydriasis, increased intraocular pressure, adynamic ileus, abdominal pain or cramps, nausea and vomiting, anorexia, diarrhea, jaundice
Most effect: Amitriptyline, clomipramine, doxepin, imipramine
Moderate effect: Nortriptyline
Least effect: Desipramine

Alpha-1 receptor blockade—Orthostatic hypotension, reflex tachycardia, dizziness
Most effect: Amitriptyline, clomipramine, doxepin
Moderate effect: Desipramine, imipramine, nortriptyline

Serotonin reuptake blockade—Decreased libido, impotence, testicular swelling, ejaculation dysfunction, breast enlargement, galactorrhea (women), gynecomastia (men), alteration of glucose metabolism
Most effect: Clomipramine
Moderate effect: Amitriptyline, imipramine
Least effect: Desipramine, doxepin, nortriptyline

Antihistaminergic—Weight gain, appetite stimulation, sedation, hypotension
Most effect: Amitriptyline, doxepin
Moderate effect: Imipramine, nortriptyline
Least effect: Clomipramine, desipramine

DATA FROM RICHELSON E. PHARMACOLOGY OF ANTIDEPRESSANTS—CHARACTERISTICS OF THE IDEAL DRUG. MAYO CLIN PROC 1994; 69:1069–1081; AND FROM BALDESSARINI RJ. DRUGS AND THE TREATMENT OF PSYCHIATRIC DISORDERS. DEPRESSION AND MANIA. IN: HARDMAN JG, LIMBIRD, LE, EDITORS. GOODMAN AND GILLMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 9 ED. NEW YORK, MCGRAW-HILL 1996:431–459; AND KATZUNG BG. BASIC AND CLINICAL PHARMACOLOGY 8 ED. NEW YORK, MCGRAW-HILL 2001.

Treatment of neuropathic pain is based largely on drugs with anticonvulsant or antiarrhythmic properties

brane-stabilizing properties of TCAs and thus may not have the same analgesic effects. Nonetheless, depression can magnify pain, and thus any intervention that diminishes depression can decrease concomitant pain. Anxiety and other affective states can also magnify pain, and treatment of these concomitant affective states can offer indirect pain relief.

Anticonvulsants, others

Pain due to nerve dysfunction is a complex phenomenon, with many potentially disparate causes at any point along the path of the peripheral and central nervous systems. However, at present, pharmacologic treatment is largely based on membrane-stabilizing medications such as anticonvulsants and antiarrhythmics.[27] This group includes all of the older and newer anticonvulsants (TABLE 4), as well as drugs that may seem dissimilar, such as TCAs or benzodiazepines, which also have anticonvulsant or antiarrhythmic properties.

Other medications outside of these groups that may possess neuropathic analgesic properties include baclofen, tizanidine, L-dopa, ziconotide, or even corticosteroids.

Our knowledge of how these drugs produce neuropathic analgesia is incomplete; they may work through multiple actions. Classic anticonvulsants are thought to act at the level of the voltage-dependent sodium channels, as do local anesthetics and mexiletine.

Second-generation anticonvulsants such as gabapentin[28] have multiple modes of action, low toxicity, and known efficacy in neuropathic pain. Gabapentin has taken the lead as a standard of treatment of neuropathic pain due to its safety profile—it does not undergo hepatic P450 metabolism or protein binding—rather than to any well-established advantage for efficacy (TABLE 4).

Other newer anticonvulsants show promise in treating neuropathic pain. Lamotrigine and topiramate are being used and studied. Clonazepam is a benzodiazepine thought to enhance GABA activity. It is also an anticonvulsant and is widely used as a neuropathic analgesic. Whether it is unique among benzodiazepines is not clear.

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TABLE 4

Anticonvulsants used in chronic pain management

DRUG NAME	DOSAGE (MG/DAY)	METABOLISM		PROTEIN BINDING*
		HEPATIC*	RENAL*	
First-generation				
Carbamazepine	100–800	++++	++	+
Phenytoin	30–300	+++	+	+++
Valproic acid	150–3,000	++++	++	+
Second-generation				
Gabapentin	100–4,800	0	+++	0
Topiramate	25–400	0	++	+
Lamotrigine	25–500	+++	?	++
Tiagabine	2 mg/week–64 mg/day	?	?	+++
Oxcarbazepine	150–2,400	?	?	+
Levetiracetam	250–3,000	0	+++	+
Zonisamide	100–600	?	++	++

*High = ++++, moderately high = +++, moderate = ++, minimal = +, none = 0

DATA FROM GOODMAN LS, GILLMAN A. THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 9 ED. NEW YORK, MCGRAW-HILL 1996; AND TANTUM WO, GALVEZ R, BENBADIS S, CARRAZANA E. NEW ANTIEPILEPTIC DRUGS. ARCH FAM MED 2000; 9:1135–1141.

Other medications in the realm of analgesic adjuvants may be thought of as multipurpose analgesics that do not appear to be solely targeted to specific mechanisms or specific types of pain.[29] These include non-TCA antidepressants, alpha-adrenergic agonists, and corticosteroids.

Alpha-adrenergic agonists include clonidine and tizanidine. These agents may be useful for a wide variety of pain syndromes, including headache, back pain, neuropathic pain, and cancer pain.[29]

Tramadol is an analgesic with multiple mechanisms of action including weak mu receptor agonism as well as serotonin and norepinephrine reuptake inhibition. Unfortunately, cases of tramadol abuse and dependence have been reported, tarnishing the drug's reputation. There is an increased risk of confusion in the elderly, as well as seizures or serotonin syndrome when used with monoamine oxidase inhibitors, TCAs, and SSRIs.

INTEGRATED APPROACH NEEDED

Delivering effective treatment for chronic pain often requires knowledge of comorbid nociceptive and non-nociceptive disorders, an understanding of principles of analgesic pharmacology, and experience with empiric titration and application of multidisciplinary therapies. With facility in using a few of the analgesics in each of the various groups presented here, clinicians may feel well armed in combating the therapeutic challenge of chronic pain.

There are many different analgesic options for managing chronic pain, each of which requires the clinician to pay attention to the whole person rather than just the pain and its possible origin. Thus, concomitant pharmacologic, behavioral, and social interventions may be necessary for a drug treatment to have its best chance of efficacy.

Successful drug treatment often requires concomitant nondrug interventions

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