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Chronic Pain Medications: Current Trends For Life Care Planners

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Abstract. *Chronic pain cannot be treated the same as acute pain. Many treatments that are perfectly appropriate for acute pain do not help chronic pain and may make it worse. Once pain becomes chronic, most patients require daily medication, and rational polypharmacy is the treatment approach of choice. No cure currently exists for chronic pain and the treatment focus includes lifestyle and behavioral management. This article summarizes the most useful drugs for chronic pain patients, and their common uses in a pain clinic. Most pain treatment is done "off-label," that is, without a specific approval from the Federal Drug Administration, so treatments common in a pain clinic may not appear in research literature. The goals of chronic pain management are to increase function and daily activity, and by doing so, help patients gain better pain control. Even those patients who do not gain lower pain levels gain better quality of life through increased activity. Medication regimens that support pain management goals are better than medications whose actions inhibit functional improvement.*

Introduction

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"(Merskey & Bogduk, 1994, p. 210). According to the biopsychosocial model, pain begins with input from sensory structures, which cognitive processes interpret. Next, individuals respond at a feeling level, then act on their feelings. The progression is sensory -> cognitive -> affective -> illness behavior (Waddell & Turk, 1992). Recent research from the neurosciences is leading to profound changes in the way chronic pain is conceptualized, researched, and treated. A key finding is the existence of both upgoing and downgoing pain tracks in the brain and spinal cord. The author encourages life care planners to read the excellent discussion found at http://www.medscape.com/viewprogram/2170?src=search (Schatzberg & Korn, 2002).

A second key finding is that pain processing structures in the brain and spinal cord can be molded during adulthood, a phenomenon once thought impossible (Flor, 2003). These changes appear permanent, both for musculoskeletal (nociceptive) pain patients and neuropathic (nerve) pain patients. Researchers found functional reorganization in both the somatosensory and motor systems. Behavioral interventions can modify cortical plasticity somewhat (Birbaumer, Lutzenberger, Montoya, Larbig, Unertl, Topfner, Grodd, Taub, & Flor, 1997; Wiech, Preissl & Birbaumer, 2000). Researchers seek to identify pharmacological agents that prevent or reverse maladaptive cortical reorganization.

A third key finding is that humeral (blood) changes contribute to the formation and main-

tenance of chronic pain, occurring as early as the surgeon's first incision (Reuben, 2004). New treatments are available for prevention and palliation, and research moves at a furious pace.

With so much new information, one would think that life care planners could easily address chronic pain medications. Unfortunately for life care planners, the challenge is often finding the pertinent information and identifying current pain practices. Effective treatments and new applications are not yet in print, and some may never be (Raziano, 2004a). One factor is that many pain treatments are done off-label, that is, drugs legally prescribed but not specifically approved for that use by the Food and Drug Administration. A common misconception among lawyers is that off-label uses or treatments mean physicians have breached some standard of care. Observationally, pain professionals acknowledge that at least 75% of all treatments done in a pain clinic are off-label and historically have always been so. Off-label uses and treatments are so commonly-accepted that they do not result in raging debates at professional pain meetings. Literature supporting common pain treatments can be sparse.

The purposes of this article are to discuss current trends in pain medication management, such that life care planners become more familiar with current pain therapies, and to provide brief bibliographic references. Though an extensive review of the literature is beyond the scope of this article, most articles cited here include lengthy bibliographies that readers may examine at leisure. The article will review classes of drugs, common pain treatment uses, novel approaches still being explored, and, very briefly, nonmedication strategies that can improve the efficacy of medications.

Chronic Pain Medications

Drug therapy is indicated when the pain condition is substantial enough to affect the patient's quality of life and cannot be treated adequately by physical therapy, or similar physical interventions, alone (Supernaw, 2002). Medications that work very well for acute or short-term use may not work well for chronic use, and may even serve to exacerbate or perpetuate pain complaints (Raziano, 2004a; R. Rizor, personal communication, June 10, 2004; D. Simone, personal communication, May 19, 2004). Once initiated, drug therapy is usually lifetime and can result in significant costs in a life care plan.

Medication selection for specific pain conditions is beyond the scope of this article. The author encourages life care planners to review the excellent treatment algorithm presented at http://www.medscape.com/viewarticle/441743_9 (Gallagher, 2002). Another excellent medication review article may be found at http://www.hospitalphysician.com/pdf/hp_aug02_principles.pdf (Supernaw, 2002).

To outsiders, pain treatment philosophy may seem to vacillate between no medication and high dose opioids. Neither extreme works very well. Rational polypharmacy, the strategic use of multiple medications, is often what work the best, especially for neuropathic pain (Bajwa, 2000). Agents that work especially well for chronic use with chronic pain include antidepressants, anti-inflammatories, antiseizure drugs, atypical antipsychotics, nonsedating muscle relaxers, and strategic use of opioids. This article will examine each category and its utility for life care planning.

Antidepressants

Antidepressants and pain. Antidepressants are excellent drugs for use in chronic pain and pain physicians have employed them for many years. However, until August 2004, no antide-

pressant had formal approval for any chronic pain treatment from the Food and Drug Administration (FDA). In August 2004, Cymbalta® (duloxetine) received FDA approval for painful diabetic neuropathy, but no other chronic pain conditions (Latner, 2004). Yet, the negative impact of anger, anxiety and depression on chronic pain management is well-known and widely reported in the literature (Price & Harkins, 1992) and theorists once believed pain was a variant of depression (Hendler, 1990). Although researchers have not yet shown such a unitary psychological profile (Turk & Melzack, 1992), the links between somatic (physical) symptoms and depression appear strong. Dysregulation of serotonin and norepinephrine may be the biochemical links (Greden, 2003; Montano, 2003), and dopamine may also be a culprit (Barkin & Barkin, 2001). In ways that researchers do not yet fully understand, antidepressants seem to modulate the pain signal in the brain, perhaps by acting on serotonin, dopamine, and/or norepinephrine receptors.

Current pain practice includes tricyclic antidepressants (TCAs), and the newer selective serotonin reuptake inhibitors (SSRIs) and dual serotonin-norepinephrine (SNRI) antidepressants; dopamine agents also have utility. The old monoamine oxidase inhibitors (MAOIs) are not currently used, largely because of management complexities. High side-effect profiles, and risks of drug-to-drug or drug-to-food interactions make MAOIs impractical, especially when several other good choices exist. TCAs have long been the drugs of choice for opioid-insensitive pain syndromes such as neuropathic pain.

Patients who perceive depression, anger or anxiety as pejorative labels will often try antidepressants when the drugs are presented as a pain signal modulator. Once they experience results with an antidepressant, patients usually want to continue because the perceived benefits easily overcome pejorative labels.

Seven broad classes of antidepressants are listed below, including their specific biochemical action and representative drugs:

1. Mixed and neuroreceptor antagonists plus sodium fast channel inhibitors (amitriptyline, doxepin, imipramine)
2. Norepinephrine selective reuptake inhibitors (desipramine, nortriptyline)
3. SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline)
4. Dual serotonin and norepinephrine reuptake inhibitors (venlafaxine, duloxetine)
5. Serotonin-2A (5-HT2A) receptor blockers and weak serotonin reuptake inhibitors (nefazodone)
6. Serotonin (5-HT2A and 5-HT2C) and norepinephrine alpha2-receptor blockers (mirtazapine)
7. Dopamine and norepinephrine reuptake inhibitors (bupropion) (Preskom, 1999).

Current antidepressants commonly used in pain clinics include Lexapro® (escitalopram), Effexor® (venlafaxin) and Wellbutrin® (buproprion). Cymbalta®, a similar antidepressant to Effexor®, reports pain reductions in female patients with fibromyalgia (Arnold, Lu, Crofford, Wohlreich, Detke, Iyengar, & Goldstein, 2004). FDA approval for painful diabetic neuropathy may cause Cymbalta® to become first-line treatment for other neuropathies. Lexapro® is a subsequent-generation SSRI, and is the single isomer of the (slightly) older drug Celexa®

(citalopram). Single isomer antidepressants have a lower side-effect profile with equivalent treatment efficacy and are probably the direction of future research. Effexor® and Cymbalta® act on both serotonin and norepinephrine (SNRI); Effexor also acts on dopamine receptors at higher doses. Wellbutrin® acts on dopamine and norepinephrine receptors, with lower side-effects than older TCAs (Barkin & Barkin, 2001). Lexapro®, Effexor® and Cymbalta® may not be used simultaneously, but each can be used concurrently with Wellbutrin®. Lexapro® has faster onset and a cleaner side-effect profile; Effexor® has more research on its positive effects on somatic disturbance; Cymbalta® seems to help female, but not male, fibromyalgia patients for reasons that are not clear; and Wellbutrin® is excellent for the "weepy" chronic pain patient. Wellbutrin® also may help counteract sexual side-effects of SSRIs.

Observationally, the usual treatment strategy is to start either Lexapro® or Effexor®, titrate to maximum doses, and allow six or eight weeks for an adequate trial. If the patient gets no results in eight weeks, then switch to the other drug. If the patient gets results but not enough relief, augment the SSRI or SNRI with Wellbutrin®. Starting antidepressants several weeks before functional improvement ("work hardening") programs can dramatically improve physical outcomes.

As a practical matter, the best antidepressant is the one the patient will take. Patients who feel they are doing well with older antidepressants may not want to change drugs. Most pain patients will be on antidepressant therapy at least one year and some will require lifetime treatment. After the first year, the only sure way to tell whether a patient can discontinue antidepressants is for physicians to titrate the medications down, watch the patient carefully, and make appropriate changes.

Severely depressed patients. Treatment-refractory depression, when all else has failed, may respond to Zyprexa®, an atypical antipsychotic, or the newer combination drug Symbyax®, which combines Zyprexa® with Prozac®. Zyprexa® and Symbyax® are not first-line treatments for depression, but have tremendous utility for treatment-refractory chronic pain patients, for reasons discussed in a later section.

*Antidepressants and anxiety***.** The neurobiology of anxiety is not as well-researched as that of depression. Besides the obvious effect of lessening depression, SSRIs are also the current drugs of choice for anxiety (J. Andrews, personal communication, April 16, 2004). Although observationally, one angry anxious patient significantly improved her behavior with Effexor® and group patient education, research literature is sparse on anger and SSRIs/SNRIs. Benzodiazepines were the traditional choice for medicating acute anxiety, but these drugs are not good for chronic use because of dose escalation, inhibition of activity levels, and the potential for abuse and habituation (Raziano, 2004a; R. Rizor, personal communication, June 10, 2004; D. Simone, personal communication, May 19, 2004). Two antidepressants, Lexapro® and Effexor®, have FDA approval for Generalized Anxiety Disorder, and both may help anxious pain patients. Lexapro® works a few days faster, and with some extremely anxious patients, time can be a crucial factor. Around eight weeks, treatment results even out, and both are excellent drugs for this use.

Antidepressants and sleep. Sleep disturbance is a chronic problem for many pain patients, both sleep onset and early awakening. Sleep deprivation, by itself, can cause pain in otherwise-healthy people, and exacerbates and perpetuates chronic pain complaints. In cases of patients with chronic pain, sleep medications should be addressed in a life care plan. Benzodiazepines and hypnotic drugs may be helpful for a few days (14 days or less), but are not generally useful for chronic administration. A subset of pain patients may benefit from Ambien® or Sonata® for occasional use. Both are hypnotics with lower side-effect profiles than the older hypnotics.

Patients should avoid SSRIs at night because they can cause insomnia if taken too late in the day or at bedtime. In contrast, the older antidepressant drugs often had limited utility as antidepressants because drowsiness was such a negative side-effect. Older antidepressants make wonderful sleeping aids for chronic use and fit life care plans very nicely. Trazadone is a serotonin agonist that works very well as a first-line sleep agent, when taken in low doses at bedtime. Trazadone is well-tolerated in low doses and can be used chronically without serious risks of abuse, accelerating doses, or habituation common to benzodiazepines and older hypnotics. Amitriptyline is a tricyclic antidepressant, another older drug, that works well in low doses for sleep; amitriptyline also has utility for reducing pain intensity in neuropathic pain. Remeron®, taken in low doses at bedtime, is a second-generation SSRI that seems to have a stronger sleep action than either trazadone or amitriptyline, and should probably be used as a second-line sleep agent after trazadone or amitriptyline have failed. In low doses, either trazadone or Remeron® can be used at night with therapeutic doses of newer SSRIs or SNRIs. Once started, a patient will probably need low dose antidepressants for sleep on a daily basis, to lifetime.

Anti-Inflammatories

Anti-inflammatories and inflammatory disease. Nonsteroidal anti-inflammatories (NSAIDs) treat any painful condition with an inflammatory component, especially arthritis or rheumatic diseases. NSAIDs also are both primary prevention drugs and acute treatment for migraine. The mechanism of action is to inhibit cyclooxygenase, a biological component of inflammation. Researchers have identified at least three COX enzymes, with evidence pointing toward more, so more NSAIDs are in research development.

NSAIDs date from the ancient Greeks and Romans, who used willow bark, a natural source of salicylic acid (aspirin). An excellent discussion and review of NSAIDs, including doses and dosing schedules can be found at http://www.hospitalphysician.com/pdf /hp_aug02_principles.pdf (Supernaw, 2002). Although both physicians and pain patients tend to overlook NSAIDs, NSAIDs have significant utility for chronic use (Raziano, 2004a).

Older NSAIDs are still useful in life care planning, especially for patients with limited funds. Used with appropriate precautions (food or milk), older NSAIDs are reasonably manageable when no other good choices exist. An excellent discussion of older NSAIDs can be found at http://www.spineuniverse.com/displayarticle.php/article1832.htm (Malanga, n.d.). Nevertheless, the optimum treatments are the newer NSAIDs, cyclo-oxygenase-2 (COX2) inhibitors. COX2s reduce incidences of gastric distress, the major side-effect of NSAIDs, though none are perfectly side-effect free. The four available COX2s are Bextra®, Celebrex®, Mobic® , and Vioxx®. Coxibs (COX2), still in the research pipeline, include parecoxib, etoricoxib, and lumaricoxib (Stichtenoth & Frolich, 2003). Once instituted for chronic pain, patients will probably use NSAIDs daily, to lifetime.

As mentioned, the primary complication of NSAIDs is gastric distress. However, a subset of patients will experience rebound pain from NSAIDs, greatly restricting NSAIDs' utility for these patients. Rebound pain occurs when the patient becomes habituated to painkillers that are not ordinarily habituating; instead of the drug treating the patient's pain, absence of the drug causes the patient's pain, often as headache. Rebound pain may occur with over-the-counter preparations such as aspirin, acetaminophen and non-prescription strength ibuprofen or naproxin. Current medical research cannot predict which patients will rebound. Once rebound pain occurs, the patient is at-risk for future rebound pain to lifetime. Some physicians

believe that the best management course for rebound patients is to provide as-needed NSAIDs for use in pain flare-ups, but no more than two weeks at a time, and weeks or months between courses of treatment. Other physicians believe that rebound precludes using any NSAIDs. After clarifying with the patient's physicians, life care planners should account for as-needed use in rebound patients but should not assume that patients successfully using daily NSAIDs will suffer rebound.

NSAIDs and preemptive analgesia. Anesthesiologists have long used ketamine, an n-methyl-d-aspartate (NMDA) -inhibitor, to prevent the brain from processing and interpreting pain signals during surgery. Without NMDA-inhibitors, surgical patients are unconscious but their brains continue to read and store pain signals, a process many researchers believe predisposes later development of chronic pain.

However, protecting the brain is not enough. Preventing the humeral (blood) system from starting the inflammatory cascade is also key to preventing chronic pain. Surgeons typically tell patients to stop all NSAIDs before surgery because the older NSAIDs prevent blood clotting. However, the COX2 NSAIDs do not prevent blood clotting and may be used for preemptive analgesia of postsurgical pain. Patients who received COX2 NSAIDs within 24 hours before surgery had less pain and used fewer opioids postsurgically (Fenton, Keating & Wagstaff, 2004). Parecoxib, an injectable form of Bextra®, is in the research pipeline, and will permit administration just before surgery. Peri-operative administration of NSAIDs does not work as well because the inflammatory cascade starts with the first surgical incision (Reuben, 2004). Preemptive analgesia is a major step toward primary prevention of chronic pain, and life care planners should include these costs in any proposed surgery.

Anti-Seizure Medications

Antiseizure (neuroleptic) drugs are excellent choices for neuropathic pain, trigeminal neuralgia, migraine prevention, diabetic neuropathy, postherpetic neuralgia, nerve injuries, and other opioid-insensitive pain syndromes. Patients may report pain reductions within 48 hours. Common neuroleptic drugs are carbamazepine (Tegretol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), zonisimide (Zonogran®), topiramate (Topamax®) and tiagabinet (Gabitril®). Used less often and best reserved for use after treatment failures with other neuroleptics are phenytoin (Dilantin®) and valproic acid (Depakene®) (Supernaw, 2002).

Neuropathic pain patients tend to experience better relief with antiseizure drugs than they do with opioids. The exact mechanisms of the drugs are unknown. Observationally, pain patients either love neuroleptic drugs or they hate them because of side effects. Lower doses may not work and patients must reach peak doses before deciding that a neuroleptic drug does not help. When patients do not respond at peak doses of one neuroleptic, systematically titrate other neuroleptics to peak doses before abandoning this class of drugs. Like many treatments in pain management, drugs that work for one patient may not work for another; trial-and-error is inherent in pain management.

Atypical Antipsychotics

Older antipsychotic drugs have no utility in chronic pain management because the side-effect profile outweighs the benefit. An intriguing class of drugs for pain management are the atypical antipsychotics. While not side-effect free, atypicals are less likely to cause tardive dyskinesia, the main complication of the older antipsychotics. Use of these drugs requires

patient preparation and education. Patients (or professionals) who read these package inserts without knowing their use in pain management become justifiably confused. As the name implies, antipsychotics treat schizophrenia and other psychotic disorders. Olanzepine (Zyprexa®) and quetiapine fumarate (Seroquel®) have gained FDA-approval for bipolar mania, with fewer side-effects than the older antipsychotics. Their exact mechanisms of action are unknown, but both are dopamine and serotonin antagonists, which may play a role.

Both drugs work very well for extremely difficult to treat pain patients. These patients typically have some combination of treatment-resistant depression, bipolar disorder, and/or severe sleep disturbance. Patients whose pain medications have reached maximum doses but who continue to crave narcotics, seem to especially benefit. With the most complex pain patients, atypical antipsychotics may help when all else fails (J. Hall, personal communication, March 11, 2004). Besides psychiatric rehabilitation and chronic pain management, Zyprexa® and Seroquel® have proven useful for drug rehabilitation centers and post-traumatic stress disorder clinics. Side-effects seem to be weight gain and metabolic slowing, though a raging debate is currently ongoing about the connection between atypical antipsychotics and diabetes. The treatment gains so thoroughly outweigh the risks for intractable patients that the author would not hesitate to use atypical antipsychotics for the most difficult patients.

In contrast with SSRIs, atypical antipsychotics should be used at bedtime. Many patients experience somnolence, and this side-effect can be used to their benefit. Patients who complain of sleeping no more than two or three hours nightly gain sound sleep with atypical antipsychotics. The extra sleep when first taking the drugs is both common and beneficial, but decreases to more normal levels after the first few days. For life care plans, once treatment starts, patients can expect to use atypical antipsychotics daily, to lifetime. Life care plans should also take into account dietitian assistance due to weight gain and metabolic slowing for patients taking atypical antipsychotics.

OPIOIDS

Opioids' primary function is analgesia. Opioids useful for pain management are pure agonists of the opioid mu receptor in the brain. Examples include codeine, oxycodone, hydrocodone, fentanyl, dilaudid, and the opioid gold standard, morphine. Opioids are always federally-regulated, scheduled drugs, Schedule II or Schedule III.

Chronic use of opioids can be problematic, for reasons that include legal, criminal, sociocultural, and medication side-effects, detailed discussion of which are beyond the scope of this article. No topic in chronic pain management is most emotionally-loaded than discussion of opioids. To gain a clearer view of this very complex picture, the author encourages life care planners to read the position statement of the American Academy of Pain Medicine (1996) and the American Pain Society (1996), also adopted by the American Academy of Pain Management. The opioid position statement can be found at http://www.ampainsoc.org/advocacy/opioids.htm.

Unless independently qualified, life care planners do not make treatment decisions about opioids, but must be aware of the issues. Life care plans that fund opioid medications invariably raise questions about appropriateness, addiction, abuse, habituation, dose escalation, diversion, and complications. Detailed discussion could be the subject of another article.

Opioids are excellent drugs for acute pain, such as postsurgical pain, or for acute pain flares. A subset of pain patients benefits from chronic opioid management. In contrast, another subset is recovering persons with pain who should never attempt chronic opioid therapy.

Few pain patients find that opioids, alone, address their complaints, and many pain patients fare better taking drugs more suited to chronic use. Rational polypharmacy may include both opioid and non-opioid medications.

For discussion purposes of this article, opioids will be divided into short-acting, long-acting and novel delivery systems.

Short-acting opioids. Short-acting opioids have been around since the Greeks and Romans used poppy juice for pain relief. As the name implies, these drugs have fast onset and short half-life, typically four to six hours. Short-acting opioids typically cause euphoria or somnolence, and some patients mistake euphoria for pain relief. Examples include Lortabs®, Vicodin®, and Tylenol® #3. Ultram® (tramadol) and Ultracet® (tramadol and acetaminophen) are short-acting synthetic opioids useful for breakthrough pain. Tramadol's exact action is unknown, but may be a combination of affinity for the mu receptor and weakly inhibiting the reuptake of norepinephrine and serotonin. Short-acting opioids are excellent for acute pain, postsurgical pain, breakthrough pain, or similar, but are not good choices for chronic use.

Long-acting opioids. Long-acting opioids first appeared on the market in 1995 with the introduction of Oxycontin®. For patients requiring chronic opioid management, long-acting opioids are excellent choices. These drugs have slow onset, long half-life up to 72 hours, produce no significant euphoria when used correctly, and greatly improve quality of life for appropriate patients. Despite its utility, Oxycontin® has produced raging debates, even litigation, about diversion, addiction, and abuse. To address this problem, in May 2004, Oxycontin's manufacturer formed a manufacturing alliance to explore abuse-resistant technology. http://www.oxycontin.com/pressroom/news/20040510-01.pdf) (Will, 2004).

Other long-acting opioids include Avinza® (morphine), Duragesic® (fentanyl) patches, Kadian® (morphine), and MS Contin (morphine), all discussed below. Methadone is an old drug available in generic form that is useful for patients with limited funds, but is not the best opioid treatment alternative available. Blood levels can vary widely with the same dose and methadone does not provide the comfort level of the newer long-acting opioids. However, methadone is the most inexpensive alternative for nociceptive pain when other drugs have failed.

Novel delivery systems. The hot debate about diversion, abuse and criminal concerns has generated intense research for novel delivery systems that reduce diversion and abuse. Human nature being what it is, no drug delivery system is foolproof. Documented cases of entrepreneurial uses of novel drug delivery systems are already appearing. However, novel drug delivery systems may slow diversion.

Duragesic® patches are one such novel delivery system. The medication is stored in gel form in a protected reservoir, then released slowly through an absorption membrane. The patches release medication over a period of 72 hours. Medication release is so slow that patients report little euphoria.

Kadian® capsules are a second novel delivery system for long-acting morphine. Administered at 12 hours or 24 hours, time release pellets deliver oral morphine sulfate. Polymer shells enclose the pellets and break down to release the drug in the digestive tract. The opioid cannot be extracted from the polymer casing except in the digestive tract (Kaplan, Miliman, Kaplan & Collins, 2004). In theory, the polymer pellets preclude a euphoric dose if crushed.

Actiq® (fentanyl) is a transmucosal delivery system for short-acting fentanyl. The drug is released only when swabbed against the mucus membrane inside one's cheek. The transmucosal mechanism delivers a lower dose, if crushed, and in theory, delivers a subeuphoric dose.

Mixed agonist-antagonist opioids. Re-introduction of mixed agonist-antagonist opioids is a recent development in pain management. Mixed agonist-antagonist opioids are those that partially target the mu opioid receptor in the brain but also partially block it. Buprenorphine is a mixed agonist-antagonist opioid, with trade names including Nubain®, Stadol®, Buprenex®, and Subutex®. A related drug, Suboxone®, combines buprenorphine with naloxone (Narcan®), a pure opioid antagonist used to counteract overdoses. The theory behind Suboxone® is that the antagonist effect of naloxone further reduces chances for euphoria.

Occasionally, life care planners may see mixed agonist-antagonist drugs in a life care plan. As pain drugs, mixed agonist-antagonist drugs work poorly and may be most appropriate for the small subset of pain patients who were substance abusers before their pain started. Mixed agonist-antagonists provide some analgesia and are safer to use when the medical providers treat an unknown patient, as in an Emergency Room visit. Because of their mixed effect, they are harder to abuse and make diversion less likely. The best use for mixed agonist-antagonists is to cushion the detoxification process for substance abusers. Patients on chronic opioid therapy with pure agonist opioids cannot take mixed agonist-antagonists because a dose of mixed agonist-antagonist will cause them to go into withdrawal.

Novel delivery systems in the pipeline. Research continues on a miniature implanted osmotic medication pump delivering sufentanil (Sufenta®), a stronger drug than fentanyl. The osmotic mini-pump is the size of a matchstick implanted under the skin and is designed to deliver medication for 90 days (Fisher, Kellett & Lenhardt, 2003). Researchers are working on a controlled-release version of tramadol (Ultram®) (Tiwari, Murthy, Pai, Mehta, & Chowdary, 2003). Sublingual buprenorphine also is in the research pipeline (Das & Das, 2003).

Nonsedating Muscle Relaxers

Presently, Skelaxin® (metaxalone) is the only available nonsedating muscle relaxer and is, therefore, the most appropriate choice for chronic use. Older muscle relaxers are effective for acute use, but are sedating, reduce physical activity and blunt feelings, and therefore older muscle relaxers are not appropriate for chronic use.

The best plan is to identify the pain generator causing the chronic muscle spasm, so the patient may not need Skelaxin® daily. However, daily use to lifetime would be acceptable, if that is what works best for the patient.

Laboratory Tests

Beyond general cautions, none of the drugs discussed require laboratory tests except Tegretol®. Patients on long-term Tegretol® require quarterly complete blood counts (CBC) (K. Raziano, personal communication, August 12, 2004).

Nonmedication Pain Management

Detailed discussion of nonmedication pain management is beyond the scope of this article. However, optimum pain medication management greatly depends on optimum lifestyle management. Determined pain patients can successfully defeat the best pain medications, if they poorly manage behavioral factors. Immune system function is not purely biological and, to paraphrase St. Augustine, drugs act on the nature that they find. A flu shot is about as bio-

logical an intervention as there can be. Researchers from the University of Wisconsin identified that thinking about positive or negative events in one's life affected how robustly study participants produced antibodies (Fauber, 2003). Although no similar research exists for pain medications, ignoring the implications would be unwise.

The following nonmedication strategies, many supported by published journal articles, are offered as activities that can improve efficacy of pain medication and/or reduce its need:

Ablative procedures (radiofrequency, etc.)
Acupuncture
Anesthestic blocks
Behavioral counseling
Biofeedback
Electrical stimulation technologies (TENS, Alpha-Stim®, muscle stimulators, etc.)
Exercise
Family therapy
Guided imagery
Heat
Humor
Hypnotherapy
Ice
Implanted technologies (dorsal column stimulators, pain medication pumps)
Marriage counseling
Movies
Multidisciplinary pain management
Occupational therapy
Patient education
Physical therapy
Pool therapy
Positive self-talk
Prayer and spirituality
Relaxation
Self-hypnosis
Specialty interventions (rape survivor counseling, Eye Movement Desensitization Reprogramming, etc.)
Stress management
Twelve-Step Programs
Vocational rehabilitation
Volunteer work
Work

Drugs Not Useful For Chronic Adminsitration

To this point, the article has confined discussion to drugs useful for chronic administration. Drugs that may have excellent uses acutely often have little utility for chronic use. Usual problems include tendencies to habituation or abuse, decreased activity levels, need to escalate doses, and potential for diversion. Such drugs include benzodiazepines, most muscle relaxers, short-acting opioids (except sparingly for breakthrough pain), hypnotics, and mixed agonist-antagonist opioids (except a small subset of patients). A suggested chronic pain drug formulary is included in Table 1, and classes of drugs to avoid are listed in Table 2.

TABLE 1 - RECOMMENDED DRUG FORMULARY FOR CHRONIC PAIN USE

CLASS OF DRUG	CHRONIC PAIN USE	RECOMMENDED BRANDS
Antidepressants	Anxiety Depression Modulation of pain signal Modulation of fibromyalgia pain signal (female patients)	Effexor Lexapro Wellbutrin Cymbalta
Antidepressants as sleep preparations	Improve patient sleep	Trazodone (low dose) Remeron Solutabs (low dose)
Anti-seizure drugs	Neuropathic pain Opioid-resistant pain syndromes	Gabatril Neurontin Tegretol Topamax Zonogran
Atypical antipsychotics	Borderline Personality Disorder Drug-craving patients whose meds are already at maximum doses Drug detoxification Treatment-refractory depression	Seroquel Zyprexa

Hypnotics	Short-term use, acute insomnia flares, use limited to < two weeks	Ambien Sonata
Muscle relaxer (non-sedating, only)	Relieve muscle spasms	Skelaxin
Nonsteroidal anti-inflammatories (NSAIDS) - COX2	Arthritic and rheumatic pain Relieve pain via reducing inflammation Preemptive anagesia	Bextra Celebrex Mobic Vioxx
NSAIDs - COX1	Low income patients Patients whose insurance will not approve COX2s Higher side-effect profile than COX2 but good drugs when used with precautions	All the rest
Opioids (long-acting)	Relieve musculoskeletal pain	Avinza Duragesic Kadian Oxycontin MS-Contin

TABLE 2 - DRUGS GENERALLY NOT APPROPRIATE FOR LONG-TERM USE WITH CHRONIC PAIN PATIENTS

CLASS OF DRUG
Benzodiazepines
Hypnotics
Mixed agonist-antagonist opioids, except with a small subset of patients
Most muscle relaxers
Short-acting opioids, except sparingly for breakthrough pain

Summary

Chronic pain cannot be treated the same as acute pain. Many treatments that are perfectly appropriate for acute pain do not help chronic pain and may make it worse. Once pain becomes chronic, most patients require daily medication, and rational polypharmacy is the treatment approach of choice. No cure currently exists for chronic pain and the focus includes lifestyle and behavioral management. This article summarized the drugs most likely to be useful long-term, and their common uses in a pain clinic. Discussion was given that most pain treatment is done off-label, so treatments common in a pain clinic may not appear in research literature. The goals of chronic pain management are to increase function and daily activity, and by doing so, help patients gain better pain control. Even those patients who do not gain lower pain levels gain better quality of life through increased activity. Both non-medication pain management strategies and appropriate medications support increased activities. Chronic pain can be worsened by medication regimens whose actions inhibit functional improvement, and by treatment plans that do not address improving functional activity.

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Editor's Note: Look for the next issue of the Journal to be a special issue on pain. The editors have invited a few physicians who work with various pain problems to further contribute to the education of life care planners. We anticipate this special issue to be ready by the end of the year.