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Managing Noncancer-related Chronic Pain Without Opioids

Chronic Pain Background

Managing chronic pain is a challenge for patients and clinicians alike, with 52% of chronic pain patients being treated solely by their primary care physician.[1] Chronic myofascial pain affects 116 million American adults, which is more than heart disease, cancer, and diabetes combined.[2] In 2010, an estimated $635 billion was spent on medical treatments and lost work productivity due to chronic pain.[3] In 2005, the American Pain Foundation released a comprehensive report that estimated 9% of the U.S. adult population suffered from moderate-to-severe pain, with two-thirds of pain sufferers having had pain for more than 5 years. According to this report, more than 68% of all surveyed full-time employees — more than 80 million people — suffer from pain-related conditions, of which 18% is work-related. Meanwhile, more than half of full-time surveyed employees suffer from pain that is not due to work-related injuries. Fourteen percent of all full-time employees — more than 17 million people — took sick days in 1995 due to pain conditions, resulting in more than 50 million workdays.[4] According to a cross-sectional study published in the *Journal of the American Medical Association*, more than half (52.7%) of the workforce surveyed reported having headache, back pain, arthritis, or other musculoskeletal pain in the previous 2 weeks, and 12.7% of all workforce lost productive time in a 2-week period due to pain.[5] More recently, 76.5 million Americans reported that they experienced pain that persisted for more than 24 hours in the past month.[6] However, the actual prevalence of myofascial pain syndromes varies, mostly based on variable diagnostic criteria and terminology. For example, differentiating myofascial pain from fibromyalgia clinically can be challenging, if not impossible, given the extensive overlap of comorbid and coexisting conditions such as fatigue, sleep disturbance, mood disorders, and other common disorders, including migraine headache and irritable bowel syndrome (IBS), that fall under the larger classification of central sensitization syndrome.[7,8] Nonetheless, myofascial pain is widely considered the leading cause of musculoskeletal pain, and is the most widely used and general term that encompasses many different forms and types of chronic pain conditions. It has been found to affect up to 85% of the general population at some point in their lives.[9] Women and the elderly (older than 65 years of age) appear to be more affected with pain syndromes in general, at 65% and 80% prevalence, respectively. This is compared to 37% prevalence in men from ages 30-60.[10,11]

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with or without actual tissue damage.[12] Predisposing factors for chronic pain can include a range of conditions such as musculoskeletal injury, sleep dysfunction, psychological and environmental stress, acute and chronic medical illnesses, prolonged immobility, lack of exercise, posture abnormalities, and nutritional or endocrine abnormalities.[13] Comorbidities often include non-restorative sleep; chronic fatigue; stiffness; IBS; temporal mandibular joint syndrome; history of sexual, emotional,

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Executive Summary

- Chronic pain affects more Americans than heart disease, cancer, and diabetes combined.
- Public attention in recent years has focused on the growing crisis of prescription drug abuse resulting in a rising incidence of death.
- Primary care physicians are well aware of the dangers of opioid prescribing and the challenge of getting patients off opioids.
- Complementary therapies for managing pain include massage therapy, manipulative therapy, acupuncture, trigger point therapy and prolotherapy, exercise, and nutrition.
- Creating a chronic pain health plan involving team-based, non-opioid approaches that combine relevant aspects of manual therapies, lifestyle changes, and mind-body therapies will require patience and persistence.

or physical abuse; and various mood disorders including depression, anxiety, and post-traumatic stress disorder (PTSD).[14]

The actual mechanisms leading to chronic pain syndromes are incompletely understood. Although chronic pain is a multifactorial condition with significant psychological and emotional influences, it is primarily a problem of central and peripheral somatosensory dysfunction. Investigators in the field of chronic pain generally agree that increases in pain sensitivity in myofascial pain syndromes such as fibromyalgia are the result of central nervous system augmentation of sensory input, as well as diminished central nervous system inhibitory pain function.[15,16] Physiologically, chronic myofascial pain is related to sensitization of the motor-end-plate, which then sensitizes the mechanosensitive afferent nerves and their connection at the dorsal horn at the spinal cord. Once established, this pain process can have cortical effects such as thalamic asymmetry leading to spontaneous or stimuli-generated tissue hypersensitivity called central sensitization. As a result, patients with chronic myofascial pain may exhibit symptoms such as allodynia and hyperalgesia.[17] In addition, many neuroendocrine and immune function alterations are often present. For example, cerebrospinal fluid levels of substance P can be elevated, which results in exacerbated pain sensation.[18] Further dysfunction is present in the regulation of cortisol, adrenergic, serotonin, and growth hormone.[19] There also appear to be increases in inflammatory cytokines, such as interleukin-2, with impaired lymphocyte and T cell function.[20,21]

Clinicians who work with patients with chronic pain often are aware of the sensitive temperament connection with pain symptoms in this patient population. Although there are likely genetic predispositions toward pain syndromes and hyperalgesia (for example, NMDA receptor variations), further research is needed. Nonetheless, familial and environmental factors do influence pain sensation, and research has shown that stressful life events are correlated with the development of chronic pain syndromes. For example, PTSD and other similar stressful life events and various other forms of trauma often are present as comorbidities. Careful history taking by the clinician often will reveal stress-related triggers, including an accident, illness, abuse history, relationship strain, environmental stress such as overwork, or negative emotional events such as the loss of a loved one.[22,23] As a result, perceptions of pain are influenced by social, cultural, and psychological factors that produce variable nociceptive sensations in different people. The variable location and degree of pain symptoms is influenced by one's genetic predispositions, which is a risk factor for chronic pain as seen in family medical histories, as many patients exhibit higher than normal sensitivities to environmental factors as already mentioned. These personality traits often include being overly empathetic, having a high degree of self-criticism and judgment, having a strong personal drive with self-expectations that are perfectionistic, having a heightened desire to please and take care of others, and being hypersensitive to emotional cues of acceptance or rejection from others.[24,25,26] Furthermore, predispositions for chronic pain often are expressed through stressful physical and emotional triggers that occur in the context of a society that places escalating expectations on increased productivity, which often comes at the expense of decreased self-care.[27]

The Opioid Dilemma

Conventionally, treatment of chronic pain has commonly involved escalating doses and dependence on opioid medications. In the 1980s, wider use of opioids for noncancer chronic pain increased significantly, which resulted in large quantities of opioids being diverted for nonmedical and inappropriate use.[28] In 2003-2004, 23% of all emergency room visits resulted in an opioid prescription. Between 1988-1994 and 1999-2002, the age-adjusted percentage of women reporting prescribed narcotic drug use increased by from 3.6% to 5.3%. During this period, use of narcotic medications rose by almost 75% among women 45-64 years of age and by more than

50% among women age 65 years and older.[1] A study using data from the National Ambulatory Medical Care Survey reported that opioid prescriptions in general increased from 4.1% (in 1992 and 1993) to 6.3% (1998 and 1999) of office visits to primary care providers.[29] In 2012, the CDC reported that between 1999 and 2010, overall pharmacy sales of opioid analgesics increased fourfold.[30] By 2011, hydrocodone was the most dispensed prescription medication in the United States at 131 million prescriptions.[31]

Although treating acute moderate-to-severe pain with opioid medications is efficacious and appropriate, using opioids for noncancer-related chronic pain has come into question, with increasing calls to avoid or reduce opioids for chronic noncancer pain when possible.[32,33,34] Practitioner experience and a growing body of evidence suggest that treating noncancer-related nociceptive chronic pain with opioid medications may not be helpful in improving quality of life, pain reduction, or daily activity and function. There are data to suggest that chronic opioid use can decrease the pain threshold through the development of opioid-induced hyperalgesia.[35] Prolonged opioid treatment not only results in a loss of anti-nociceptive desensitization, but also leads to activation of a pro-nociceptive sensitization known as hyperalgesia[36] and irreversible gray matter changes.[37] Another study from Denmark of more than 10,000 noncancer chronic pain patients concluded that opioid treatment of long-term/chronic noncancer pain does not fulfill any key outcome treatment goals of pain relief, improved quality of life, nor improved functional capacity.[38] Similarly, a 2009 review found that a 423% increase in spending for opioid medications to treat low back pain was not accompanied by any improvement in patient outcomes or disability rates (*See Table 1*).[33]

Opioid abuse and misuse, adverse effects, escalating doses, overdose, and death are concerning challenges seen with increasing widespread opioid availability. In 2008, nearly 10% of high school seniors in the United States self-reported recreational use of hydrocodone.[39] A study published a year later reported that one in five high school-aged teens abused a prescription medication at least once.[40] Furthermore, teenagers admit that obtaining prescription opioids is "very easy." Similarly in 2009, 2.6 million Americans, approximately 7000 Americans per day, used prescription medications recreationally for the first time.[41] Among chronic pain patients, a review of 67 studies found that 3% develop opioid addiction while 12% show aberrant drug-related behavior.[42] Overall, the United States Substance Abuse and Mental Health Services Administration found that 53% of people obtained their recreational narcotics from a friend or relative, and 10.6% purchased them from someone they knew.[43] In 2007, a study by the Florida Medical Examiners Commission concluded that hydrocodone and oxycodone caused more than twice as many deaths as cocaine, heroin, and methamphetamine combined. In comparison, the percentage of people admitted for alcohol abuse treatment dropped during this same time period by 5%. Similarly, admissions to hospitals and treatment programs for the treatment of cocaine abuse dropped by 16%.[44] In practical figures, in 2012, the CDC reported that for every opioid medication overdose, nine people are admitted for opioid abuse treatment, 35 are seen in emergency department visits, 161 report drug abuse or dependence, and 461 report recreational and non-medical use of opioid medications.[29]

Table 1: Ten-year Trends in Medicare Spending for Low Back Pain, Despite No Improvement in Patient Outcomes or Disability[33]

- Epidural steroid injections increased by 629%
- Opioid expenditures increased by 423%
- Lumbar MRIs increased by 307%
- Spinal fusion rate increased by 220%

In addition to becoming the fastest growing drug problem in the United States, opioid-related morbidity and mortality is now recognized as a growing epidemic, with prescription opioids accounting for 70% of all misused and diverted narotics.[45] In more general terms, total adverse drug reactions are the sixth leading cause of death in the United States, estimated at 106,000 per year.[46] Between 1997-2002, there was nearly a 100% increase in opioid-abuse related death, with oxycodone use increasing by 727%. This public health study and the Office of National Drug Control Policy have concluded that continuing dramatic increases in the availability of such opioids have made their abuse a major growing problem.[47,48] *Morbidity and Mortality Weekly Report* concluded that unintentional drug poisoning mortality rates increased substantially in the United States during 1999-2004 and can be attributed primarily to increasing numbers of deaths associated with prescription opioid analgesics such as oxycodone. In 2004, nearly 10,000 cases of unintentional opioid-related deaths were reported, which increased by 54.6% from 1999.[49] From 2003-2012, more overdose deaths have involved prescription opioid analgesics than heroin and cocaine combined.[29]

Curbing Opioid Therapy

Establishing a therapeutic relationship with chronic pain patients is the cornerstone of non-opioid based therapy. Primary care medicine is particularly well poised to address the opioid dilemma for this reason.[50] Continuity of care, integrated electronic health records, strictly managed limited-quantity

opioid prescriptions, and enhanced monitoring of opioid prescriptions by pharmacies and insurance companies are a few of the emerging safeguards that can help avoid escalating and misappropriated opioid medications.[29] Referral to detoxification (methadone) clinics for illegal or prescription narcotic abuse and addiction is necessary in appropriate cases when identified (not reviewed here). Patient education that explains opioid-related hyperalgesia, allodynia, and opioid-induced hyperalgesia in ways that are understood by the patient is essential. Often this requires several visits and taking more time to adequately address the patient's questions. It is also important to recruit support from clinical staff, colleagues, and consultants.[51] Clear communication and opioid/treatment plan contracts are helpful in this process. Specifically, it is helpful to offer three options to patients with noncancer chronic pain who are taking opioids on a daily basis:

1) Strict opioid non-escalation with limited-quantity, no-refill opioid prescriptions with frequent review of a pain contract with patients, or referral to a pain management specialist who can help manage opioid needs and offer other non-opioid therapy options;

2) Taper opioids over a predetermined period of time with clinical team support (may include opioid substitution — for example with tramadol or naltrexone) and initiate a pain treatment plan with active patient participation;

3) For the patient who is unsatisfied with these options and expresses desire to establish care with a different primary care physician, assistance should be offered to help with transition of his/her medical care (*see Figure 1*).

Through this process, it is important to repeatedly impress upon the patient that his/her pain is real, and that dependence on daily and long-term use of opioid medications will not improve quality of life or decrease long-term pain symptoms; in fact, it may result in worse pain or other side effects over time. It is important to emphasize that team-based, non-opioid approaches that combine relevant aspects of manual therapies, lifestyle changes, and mind-body therapies will take patience and persistence to yield positive results. For patients with opioid dependence, it is recommended to begin tapering doses over several weeks in a predetermined period of time. Similarly, substituting weak opioids with pharmacist or pain management specialty input as needed may be helpful. One study found that the use of tapering tramadol doses for heroin addiction for the treatment of withdrawal was superior to buprenorphine with reduced withdrawal symptoms over time, as well as a small number of side effects.[52]

Complementary Therapies

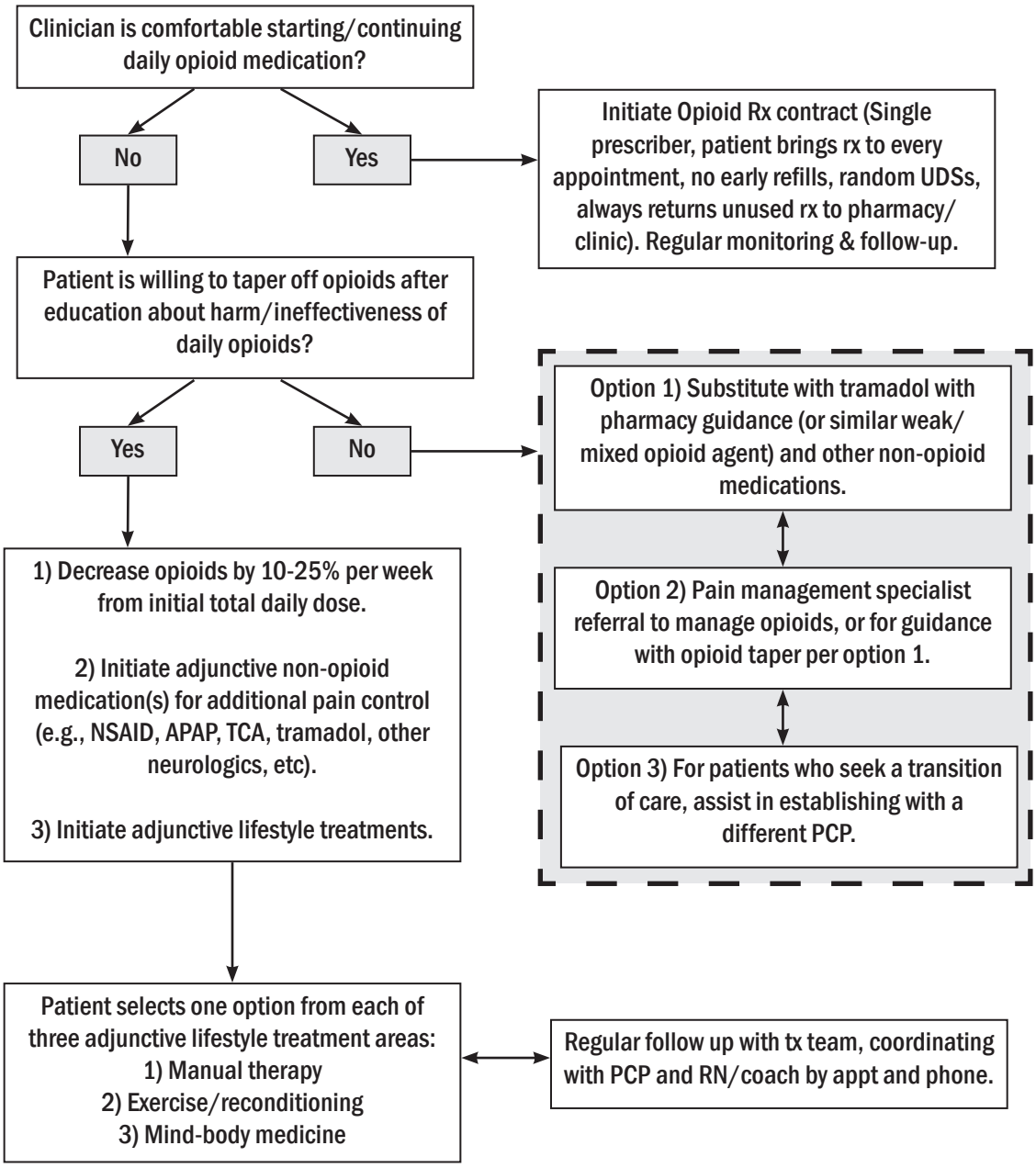
Massage Therapy

In addition to other non-opioid medications and supplements for the treatment of chronic pain (not reviewed here), increasing evidence suggests that non-pharmaceutical adjunctive therapies are widely used by patients and also should be considered by physicians for the management of pain. For example, one study of licensed complementary and alternative practitioners revealed that 20% of massage therapy sessions were made for back and neck pain alone.[53] Manual therapies such as massage can reduce myofascial pain through upregulation of oxytocin, serotonin, and dopamine along with reduction of cortisol, epinephrine, and norepinephrine through the activation of the parasympathetic nervous system with resultant myofascial release and relaxation.[54,55] Improvements in circulation, range of motion, and immune function through self or practitioner-assisted massage are other well-known benefits of various forms of massage therapy.[56] Although, in general, the research literature for massage therapy contains shortcomings in quality and rigor — particularly with reviews, which often lack a definition, description, or rationale for the technique in question — there is emerging evidence in support of efficacy and safety. A systematic review of 19 studies of massage therapy for the treatment of myofascial neck pain concluded that massage therapy was safe. This review did not find any advantage of massage therapy compared to other treatments.[57] However, a 2001 randomized controlled trial (RCT) found that the benefits of 10 massage treatments for the treatment of back pain were still significant 10 months after the last therapy session.[58] Another RCT evaluating massage therapy for chronic neck pain revealed long-term improvements in pain symptoms and function, as well as decreased medication use.[59]

Manipulative Therapy

In a review of 43 RCTs evaluating chiropractic manipulation treatment (CMT) for chronic low back pain, 30 favored manipulation therapy over conventional care, while 13 reported no significant difference. None of the trials reported inferior outcomes with manipulation.[60] A meta-analysis of RCTs using osteopathic manipulative treatment (OMT) for acute low back pain concluded that OMT significantly reduces low back pain in the short and long term.[61] However, it is important to note that the evidence is strongest for OMT in the acute pain setting with decreased use of medications and physical therapy at little additional cost.[62,63,64] Other less rigorous research suggests benefit of OMT in fibromyalgia and acute and chronic headache.[65-67] It should be noted that manipulative therapy is considered quite safe. One review found that worsening disk disease occurs in fewer than 1 in 3.7 million patients undergoing manipulative therapy. Further, the reported incidence of iatrogenic stroke or vertebral artery dissection from high-velocity manipulative techniques is as low as 1 in 5.85 million. It is important to note that most injuries are known to occur when patients are treated by an untrained professional.[68] Ideally, primary care physicians should collaborate with osteopathic colleagues and physical/occupational therapists (PT/OT)

Figure 1: Treatment Pathway for the Patient Diagnosed with Noncancer Chronic Pain



1. Awareness. Each patient begins with a long office visit with her/his primary care physician for education on chronic pain and avoiding opioid medications, which also determines which patients (options 1-3) are willing to proceed with an opioid-free treatment plan.
2. Action. In addition to utilizing non-opioid medications and supplements, the patient enrolls in a team-based therapeutic process that involves the following three foundations for health, which are patient-directed and include appointments with other members of the health team:
   a. Manual Therapy (passive): OMT/CMT manipulation, myofascial release, massage therapy, Feldenkrais, healing touch, reiki, trigger point injections, acupuncture, prolotherapy.
   b. Exercise/Nutrition (active): PT/OT/LAT directed exercise/movement training, yoga, qi gong/tai chi, other structured fitness class, individual exercise journal, nutrition consultation.
   c. Emotional and Mind-Body (internal): Meditation/ mindfulness, relaxation techniques, health-psychology, journaling, breath-work, biofeedback, education, emotional freedom technique, guided imagery, etc.
3. (Follow up) Close and regular follow up with various members of the health team (e.g., nurse/health-coach, PT, psychologist, osteopath, etc.) is important to ensure treatment adherence and to address any areas where further help is needed.

Table 2: Acupuncture vs Epidural Steroids for Low Back Pain[70-74]

	Acupuncture	Epidural Steroid
Evidence of benefit	++	+
Cost/QALY	$	$$$$
Patient cost (with insurance)	$$$	$
Potential harm	+	++
Supported by NICE guidelines?	Yes	No

Cost/Quality adjusted life year (Cost/QALY): The cost of a therapy in relation to the amount of quality life obtained from the therapy or Cost/QALY — the lower the ratio the better.

who specialize in manual therapies.

Acupuncture

Compared to conventional approaches to pain management, acupuncture generally has less risk, harm, and expense. A systematic review of the world literature on nine prospective acupuncture safety studies involving tens of thousands of treatment sessions revealed two cases of pneumothorax and no incidence of infection.[69] Comparison analyses of studies involving epidural steroid injections or acupuncture for low back pain reveal decreased cost and increased pain relief with the latter (*see Table 2*). In particular, acupuncture showed a 10-15% improvement at 12 and 24 months when compared with usual standard of care.[70,71] In comparison, epidural steroid injections showed no improvement in low back pain symptoms at 12 and 26 weeks,[72,73] despite being nearly 40 times as expensive as acupuncture in Quality Adjusted Life Year costs.[74] A cost effectiveness study that evaluated acupuncture for the treatment of headache in the United Kingdom found that acupuncture improved health-related quality of life and was relatively cost effective.[75] Similarly, in a study of 401 patients with chronic headache, compared to standard of care, on average acupuncture treatments resulted in 22 fewer headaches per year with 15% fewer medications and 26% fewer physician visits. Further, the pain-relieving effects of acupuncture were long lasting, with 34% improvement in headache symptoms at 12 months when compared to 16% in the standard of care control group.[76] Acupuncture also has demonstrated benefit for the relief of more general myofascial pain syndrome in a controlled trial of gentle, superficial Japanese-style technique.[77] Many physicians, PTs, and OTs have received training in medical acupuncture, which is becoming more widely available.

Trigger Point Therapy and Prolotherapy

Myofascial trigger point (TrP) therapy is another useful approach to pain relief that has similarities to acupuncture. One study proposed a 70% correlation between acupuncture points and conventional trigger points.[78] TrP therapies encompass several varieties, which are largely based on the original work of Simmons and Travell.[79] The simplest varieties of TrP encompass less invasive approaches such as myofascial release, low-level laser therapy, biostimulation, and thermotherapy. Often, these gentle and very safe approaches lend themselves well in combination with other therapies.[80] Dry needling technique has been shown to inactivate localized TrP areas and improve pain sensitivity of other satellite TrPs, as well improve function and range of motion.[81] Injection techniques that introduce various pharmaceutical agents into tendons, ligaments, joint spaces, and muscle are variably effective. Increased caution should be used when using corticosteroids and botulinum toxin type A due to increased harm potential.

Prolotherapy is a unique form of TrP therapy that involves injecting small amounts of irritant solutions into painful areas. The most common and safest solution contains varying mixtures of hypertonic glucose, saline, and lidocaine, which stimulate the release of growth factors and chemotactic attraction of inflammatory mediators favoring soft tissue healing.[82] It is postulated that dextrose injections target peripheral nociceptors responsible for pain and neurogenic inflammation. Irritant solutions such as dextrose have a capsaicin receptor antagonist effect, which are expressed on peptidergic C-fibers that innervate joint synovium tissue. It is now recognized that sensitization of these peptidergic C-fibers, also called sensocrine neurons, play an important role in the development of pain. Prolotherapy has a neuromodulating effect on sensitized sensocrine neurons allowing for physiological tissue repair, including chondrocytes, but further research is needed.

Nonetheless, research in prolotherapy has accelerated significantly, with improvements in methodological quality and rigor.[83] For non-specific low back pain, two RCTs reported positive results with more than 50% improvement in pain/disability scores at 6 months.[84,85] The strongest data supporting prolotherapy are for chronic tendonopathies. A RCT evaluating prolotherapy for chronic lateral epicondylosis (tennis elbow) demonstrated improvements in pain relief and strength compared to controls, with results showing stability at 52 weeks.[86] Achilles tendonopathy is another overuse injury that lends itself well to prolotherapy, according to a well-designed case series. In this study, participants reported decreased pain at rest and activity at 52 weeks.[87] In patients with osteoarthritis (OA), prolotherapy appears to benefit both pain and function at 52 weeks in patients with at least 3 months of symptomatic knee pain. In this case series, there were no reported adverse effects and overall patient satisfaction was high.[88]

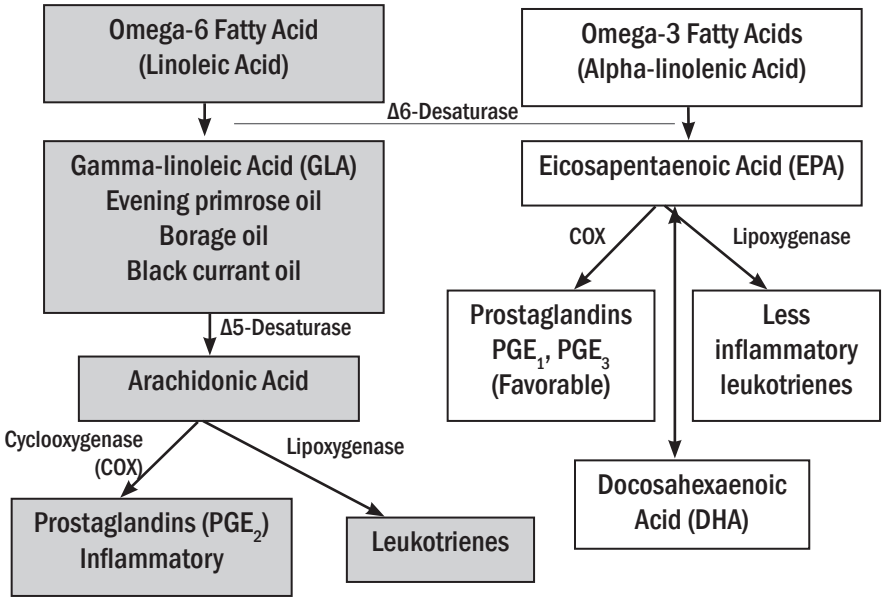
Exercise

Being sedentary with low physical activity levels is linked to progressive myofascial pain. However, research demonstrates the development of hypoalgesia after regular aerobic exercise.[89] Many meta-analyses report

exercise to have a positive effect on pain symptoms, aerobic capacity, and physical function. Although the exact mechanisms behind these effects are not completely understood, exercise is thought to improve pain symptoms through its positive effect on weight reduction, enhanced sleep, aerobic conditioning, and improved mood.[90]

Recommendations for exercise in patients with chronic pain should be a part of every treatment plan. However, it is important to introduce exercise slowly, with recommendations to begin with light intensity for short periods of time to minimize or avoid post-exercise pain flares, which is defined as having increased pain 2 or more hours after exercise compared to baseline pain levels. However, exercise counseling should be based on patient preferences and needs, with adaptations and modifications being made as needed. For example, one study demonstrated improved pain scores in patients with fibromyalgia after a period of self-selected daily physical activities.[91] For deconditioned patients, which is common with chronic pain, two exercise sessions of 10 minutes during the day can be a starting point.[92] Lower-intensity activity — such as land or water walking, or gentle tai chi or yoga — should take place over longer periods of time, such as 30-60 minutes as tolerated and titrated up over time.[93] According to a 2008 systemic review, aerobic exercise improves physical function and reduces pain symptoms in patients with fibromyalgia.[94] In particular, pool exercise should be considered for many chronic pain patients in that it provides as much physical fitness and pain reduction over time as land-based exercise. Additional benefits from pool exercise include myofascial support from the water and improved psychological symptoms.[95] In addition, tai chi and qi gong, very slow and gentle forms of martial arts, have shown benefit in improving pain and quality of life for chronic pain.[96] Similarly, gentle yoga appears to be beneficial as well.[97] One RCT involving 101 patients with chronic low back pain found that 12 weekly sessions of yoga improved symptoms and function at 26 weeks compared to exercise and self-care education. A study funded by the National Center for Complementary and Alternative Medicine using yoga for the treatment of chronic low back pain demonstrated decreased functional disability, pain, and depression at 12 and 24 weeks.[98] Further, yoga therapy was associated with decreased medication use.[99] Another RCT demonstrated significant reduction in pain scores and improved spinal flexibility for participants with chronic low back pain when compared to wait-list controls enrolled in a general physical exercise group.[100]

Figure 2: Effects of Omega-3 (Anti-inflammatory) and Omega-6 (Proinflammatory) Fatty Acids on Inflammation[104]



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Nutrition

The standard American diet (SAD) has changed dramatically for the worse during the last 50 years, with significant increases in sugar, simple carbohydrates, overall calories, and artificial additives with resultant increases in systemic inflammatory processes called meta-inflammation.[101] This term describes the chronic, low-grade, metabolically induced, inflammatory cascade that is mediated by the same molecules and markers of inflammation that results in chronic diseases such as cardiovascular disease and arthritis. It is telling that more than 90 million Americans are affected by chronic diseases related to meta-inflammation, which accounts for 70% of all deaths and 75% of medical care costs.[102] Furthermore, it is estimated that 60% of chronic disease could be prevented by eating a healthy diet.[103] Specifically with pain, research has shown that eating a vegetarian diet rich in omega-3 fatty acids (*see Figure 2*) can decrease the number of tender and swollen joints in rheumatoid arthritis, with average decreases in pain symptom scores by more than 30%.[105,106] For myofascial pain syndromes such as fibromyalgia and low back pain, eating a vegan diet can improve overall pain symptoms.[107] One correlation is that the enzyme phospholipase A2 — which is more than 20 times more active in lumbar disk tissue — is stimulated significantly by proinflammatory omega-6 fatty acids from the SAD diet, resulting in worse pain

symptoms.[108]

It is important to note here that, in the case of OA for example, abnormal physiologic and metabolic pathways — and not solely "wear and tear" and advancing age as once thought — are considered principle factors in progression of the disease. Imbalances facilitated by systemic proinflammatory cytokines, eicosanoids, prostaglandins, and many other chemical mediators appear to play a central role in susceptibility and progression of pain sensitivity. In total, the combination of a sedentary lifestyle, obesity, and a SAD diet creates a vicious cycle of disease progression and worsening pain ensues.[109,110]

Recent interest in the role of glutamate on pain activating NMDA receptors in the central nervous system has suggested that diets low in aspartame, monosodium glutamate, and other artificial food additives may be helpful in treating some forms of chronic pain, such as fibromyalgia.[111] Although further research is needed, evidence is lacking to suggest one particular diet over another for the treatment of various pain syndromes. However, an anti-inflammatory diet based on fewer overall calories, less sugar, substituting other fats with omega-3 fatty acids, and more plant-based whole foods may be most practical and helpful. Recommending a persistent and patient course of exercise and eating an anti-inflammatory or Mediterranean-type diet[112] is nevertheless essential for improved overall health and concomitant pain relief over time. Weight loss should be emphasized with regular and close follow-up for patients with a body mass index (BMI) > 30 using this same approach. One study found that a combination of moderate exercise and modest weight loss provided more improvements in pain and function than either intervention alone.[113] Partnering with patients using motivational interviewing, coaching, and collaboration with a dietician is encouraged.

Mind-Body Therapy

Mind-body interventions such as mindfulness meditation, psychology, biofeedback, and journaling can significantly reduce pain, improve physical function, and improve mood, and are considered very safe. A meta-analysis of 34 trials evaluating biofeedback for migraine headache compared to medications found similar improvements for both treatment options. Another review found that biofeedback was superior to medications in treating migraine headache in children.[114] Biofeedback also has demonstrated decreased pain symptoms in fibromyalgia when compared to standard of care.[115] In another study, 90 chronic pain patients trained in mindfulness meditation over 10 weeks showed significant reductions in pain symptoms and mood disturbance such as anxiety and depression. Use of pain medication decreased and activity levels and feelings of self-esteem increased, while a comparison group did not show significant improvement.[116] These benefits were maintained at 15 months post-meditation training.[117] Similarly, another study found that teaching affective awareness through journaling to patients with fibromyalgia significantly reduced pain symptoms at 6 weeks and 6 months.[118] Resources for meditation and emotional awareness in clinical settings are evidence-based and widely available.[119,120]

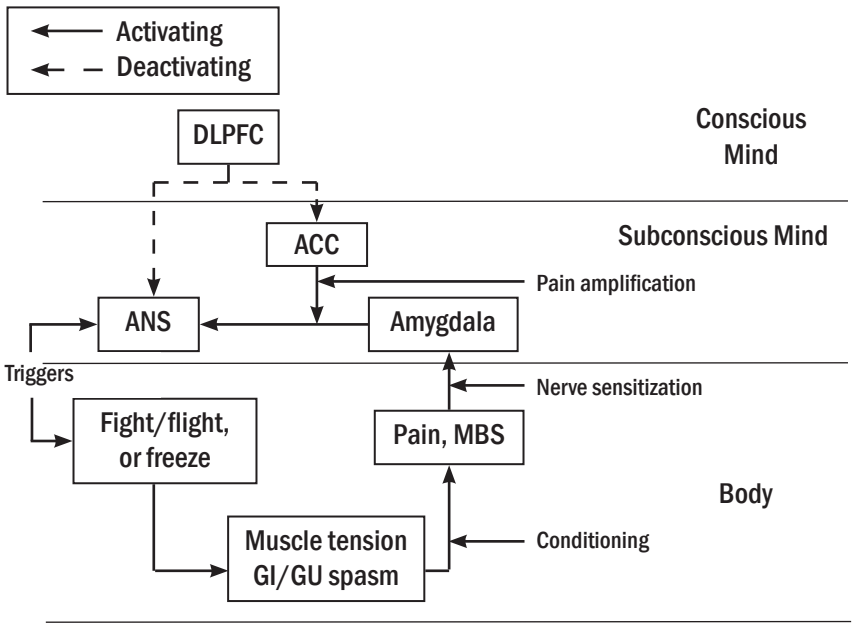
Often unrecognized, pain also has psychological and emotional components that are easily left unaddressed. For example, early childhood abuse is associated with increased chronic pain and IBS symptoms.[121] More specifically, childhood abuse is present in 54% of chronic pain patients compared to 21% of controls.[122] Not only are there complex interactions among early abuse, stressful life events, depression, and the occurrence of chronic pain,[123] but the effects of childhood abuse appear to last a lifetime.[124] Traumatic life events can result in dysregulation of the inflammatory response system that can be triggered by subsequent life stressors that result in activation of pain symptoms. One study indicates that neonates who receive more heel sticks have lower pain thresholds later in life.[125] Furthermore, 37% of patients with fibromyalgia and IBS also have a history of PTSD, and many more have subclinical symptoms.[126,127,128] Among military veterans with PTSD, 80% also report chronic pain.[129] Inversely, self-injurious patients who engage in cutting behavior have been shown to activate the dorsolateral prefrontal cortex region of the brain, which decreases pain sensations when compared to controls.[130] Another study reported that activation of the prefrontal cortex region correlated positively with symptom improvement in patients with IBS who were given a placebo.[131] Therefore, it is striking to correlate these findings with the effects of mindfulness training on negative affect — such as anxiety — and immune function. In a wait-list controlled study, participants trained in mindfulness over 8 weeks were found to have decreased negative affect, increased positive affect, increased immune response, and increased prefrontal cortex activity when compared to controls.[132] In a direct study on the effect of emotional awareness using journaling and mindfulness practices in patients with fibromyalgia, the study group had significantly lower pain severity, higher physical function, and higher tender-point threshold at 6 months compared to controls. Nearly half of participants in this study had at least a 30% reduction in pain severity compared to baseline.[118] This suggests that activation of the prefrontal cortex and other central structures can be learned over time, which may have a pain dampening effect. For example, a 5-year follow-up study of 213 patients with chronic low back pain revealed that those who participated in cognitive behavioral therapy had reduced pain, increased physical activity, improved quality of life, and overall better health. There was also a reduction in total overall medical costs and missed days of work.[133] This and other forms of health-psychology can be useful and are essential for the successful management of chronic pain.

Table 3: Key Mind-body Medicine Web Resources

PPD/TMS Peer Network: www.tmswiki.org	A participant-oriented information site on psychophysiologic disorders, including a list of practitioners who practice in this area and an active forum
RSI-Back Pain: www.rsi-backpain.co.uk	A patient-run information site for people suffering with chronic painful conditions
Chronic Pain Treatment Plan: www.fammed.wisc.edu/integrative/	A general approach for non-opioid treatments for patients with chronic low back pain (also for general myofascial pain)
Mindfulness: www.fammed.wisc.edu/mindfulness	An overview and clinical approach to patient care for clinicians that uses mindfulness as a therapeutic tool
Emotional Awareness: www.fammed.wisc.edu/integrative/modules (Detoxification: Mind/Body Awareness Writing Exercises pdf)	A seven-step writing course that addresses mind-body factors in chronic pain

Many forms of chronic pain such as fibromyalgia, myofascial low back pain, and migraine headaches have common pathophysiology involving sensitization of the central and peripheral nervous systems, with augmented neuroendocrine and immune dysregulation.[8] In other words, there are areas of the brain that are involved in processing, increasing, and decreasing pain. As in the case of phantom limb, pain can and often does originate centrally in the absence of tissue injury or disorder. Whether initiated centrally or peripherally, the pain is real. Many types of pain, such as low back pain and headache, often are started from traumatic life events, and then subsequently triggered by daily life stressors. Explaining this process to patients with chronic pain can often be helpful and therapeutic.[134] John Sarno, MD, from New York University has written widely about this process, which he calls tension myoneuronal syndrome (TMS). Through a complex interaction of the autonomic nervous system, central brain structures, such as the anterior cingulate cortex and various negative affective emotions, somatic pain symptoms become entrenched and chronic. It is important to note that although this type of pain is not associated with tissue damage, it is nonetheless real pain. According to Sarno and others, physical pain in this setting — after a comprehensive rule-out medical evaluation — is unconsciously substituted for intolerable or inescapable emotional pain (*see Figure 3*). Further, he asserts that patients who learn about this process realize a reduction or elimination of their pain. However, a certain level of self-awareness and acceptance of this explanation of the mind-body connection is required to realize pain relief. Emotional awareness therapy therefore requires screening for appropriate candidates, education and counseling, and a degree of self-motivation to engage in exercises such as journaling, reading, counseling, and meditation. In addition to pain psychology referral and collaboration, there are several effective resources that clinicians can recommend to patients (*see Table 3*).

Figure 3: Chronic Pain Mind-Body Connection[134]



The Neurology of Psycho-physiologic Disorders
ACC, anterior cingulate cortex; ANS, autonomic nervous system; DLPFC, dorsolateral prefrontal cortex; GI/GU, gastrointestinal/genitourinary; MBS, mind-body syndrome; TMS, tension-myoneuronal syndrome

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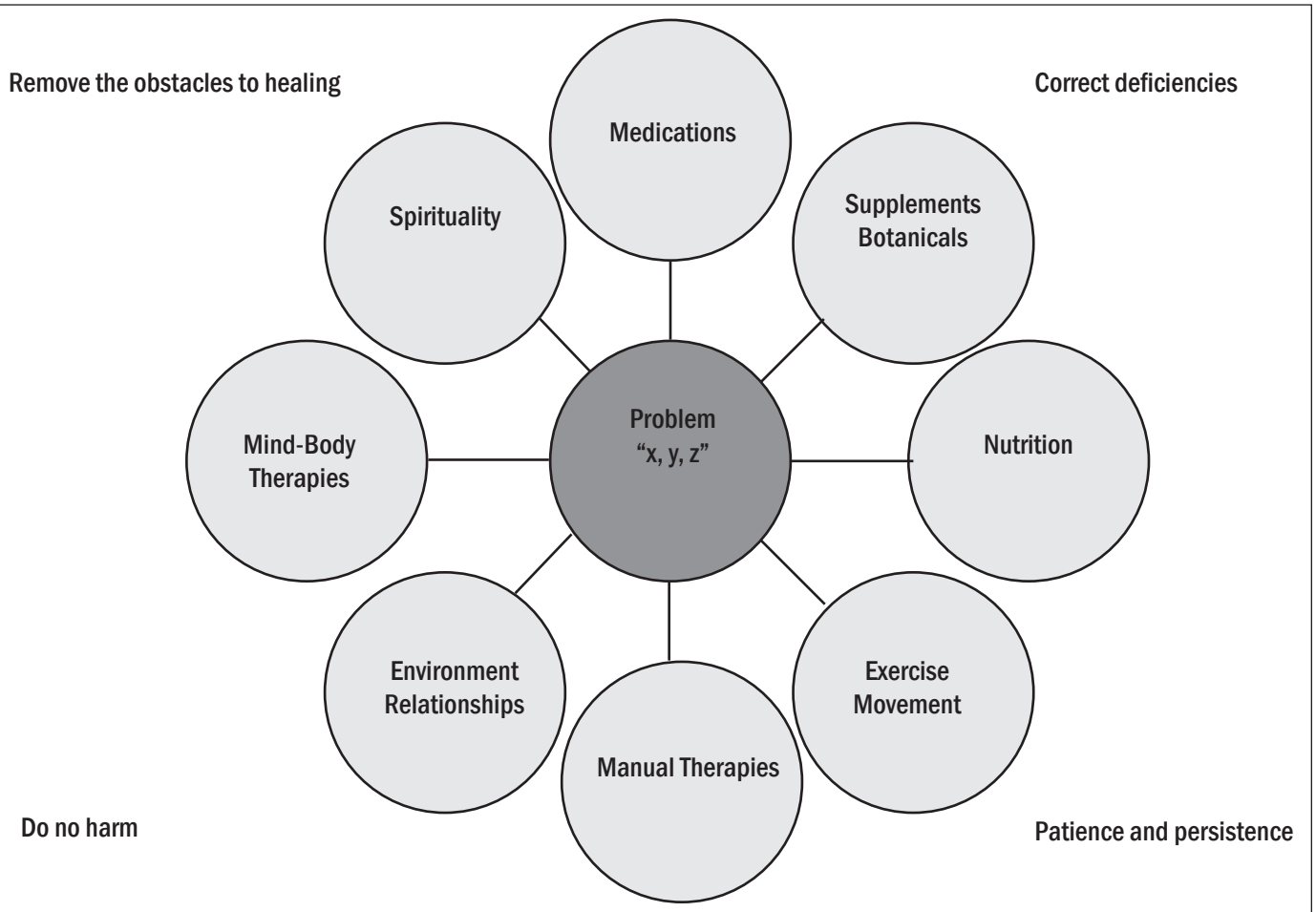
Figure 4: Integrated Eight-wheel Approach to Health and Wellness



General handout for review with patients at each visit to facilitate: 1) Awareness of the factors influencing pain, and 2) Action steps to begin reversing the symptoms of pain.

Peripheral lifestyle factors: 1) Discuss obstacles to healing such as smoking, overeating, and those factors from a patient's lifestyle that are in direct competition to his/her healing; 2) Identify and correct obvious deficiencies such as hypothyroidism, vitamin deficiencies, etc; 3) Choose therapies that are not harmful/have very low risk of iatrogenic harm; 4) Encourage the patient to be patient and persistent with lifestyle changes.

Eight integrated approaches to addressing any particular health concern (e.g., chronic pain): 1) Medications (non-opioid options for noncancer chronic pain); 2) OTC supplements/botanicals/herbs that have evidence for safety and efficacy; 3) Improved nutrition to include transition to a general healthy anti-inflammatory, whole-foods based diet; 4) Encouragement and program to increase movement, activity, and exercise in any capacity that begins gently but is progressively intensified, varied, and coached; 5) Manual therapies defined as therapies that are delivered to a patient in a receptive and passive way, which may range from surgery to gentle forms of massage; 6) Environment/relationship factors that are external to a patient but have influence on his/her health such as air pollution, abuse relationships, toxic work/home setting, etc; 7) Mind-body therapies address those factors that are internal to a patient, such as emotions, beliefs, thoughts, and memory; 8) Spirituality defined here as that which gives meaning and purpose and/or is valuable to the patient, which may or may not be religious.

Creating a Chronic Pain Health Plan

Offering patients the opportunity to play an active role in their treatment by selecting one of several complementary treatments from various options in the areas of manual therapy, exercise, and mind-body medicine can result in a synergistic effect that goes beyond the individual benefits of each modality when administered separately.[74] Specific therapies should be matched to the unique needs, culture, and beliefs of each patient based on

Table 4: Summary Goals of Non-opioid Treatment for Chronic Pain

- To empower patients to assume an active role in their care
- To decrease pain and increase function and quality of life
- To prevent chronic disability with reduced need for long-term therapies

insight obtained during an initial long-office visit. Opioid medications should be avoided, substituted, or tapered. According to the 2009 National Institute on Health and Clinical Excellence (NICE) report, pain management strategies should consider non-pharmacologic means such as exercise, biofeedback, relaxation techniques, and manual therapies including acupuncture, manipulation, and massage.[135] A multidisciplinary team-based approach can be an especially useful and effective strategy for managing chronic pain.[50] For example, an RCT involving 207 patients with fibromyalgia found that combining exercise with a facilitated self-help educational class resulted in better symptom control than either intervention alone.[136] An evidence-based estimate of number needed to treat (NNT) for the treatment of chronic low back pain using manipulation is 5.4. Moreover, the NNT is 5.1 for exercise and 3.3 when combining exercise with manipulation.[137]

Establishing a positive therapeutic relationship with the patient can result in pain reduction by as much as 28.4%, which is similar to morphine.[138] To this aim, clinicians are encouraged to guide, coach, and facilitate self-management strategies that empower patients to take control of their health and symptoms,[139] while at the same time directing patients away from dependence on opioid medications. This educational process can be facilitated by asking the patient to identify the primary "problem" or area of focus that is most important to him/her. This "central issue" or main concern can then be addressed in a comprehensive way by addressing eight main areas that directly influence both the etiology and treatment (*see Figure 4*). These areas draw from external physical factors — such as medications, supplements, nutrition, exercise, manual therapies, and environment — as well as the internal factors of belief, thoughts, emotions, and memories.[50,140] This framework — Step 1 Awareness — sets the stage where the patient begins to see and understand the various factors that influence pain severity, with particular emphasis on recruiting active patient participation in creating a health plan that draws from all aspects of the healing process. Rather than being told what to do, the patient may instead discover the obstacles to recovery for himself/herself (e.g., being sedentary, tobacco use, abusive environment). From here, the patient may choose what particular therapies — Step 2 Action — from the three areas of pain treatment (manual therapy, exercise, and mind-body medicine) to begin working with. Close and regular follow-up with various members of the health team is important to ensure treatment adherence and to address any areas where further help is needed (*see Figure 1*).

Summary

The use of opioids for the treatment of noncancer chronic pain should be discouraged and avoided when possible. Coordinating safe and effective treatments for noncancer chronic pain that avoid opioids should draw on physical and mind-body disciplines that are efficacious and generally regarded as safe. Building a stable network of various referral partners with expertise in these areas is a necessary step in creating successful and efficient treatments that honor the individual needs of each patient, while at the same time maintaining a firm sense of patient accountability. Setting intention and being clear with patients about pain management goals up front is important. By offering an individualized health plan that emphasizes active patient participation, the clinician can achieve greater treatment adherence from the patient. Increased face-to-face time at the onset of treatment also facilitates a stronger patient-clinician relationship by allowing the patient to tell her/his personal story, which engenders a feeling of being recognized and heard, which alone has therapeutic benefit and should be supported.[141] (*See Table 4.*)

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Primary Care Reports CME Objectives

Upon completion of this activity, participants should be able to:

1. Summarize recent, significant studies related to the practice of primary care medicine;
2. Evaluate the credibility of published data and recommendations related to primary care medicine;
3. Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

CME Questions

1. Chronic pain central sensitization is a process that typically occurs with all of the following ***except***:
   a. irritable bowel syndrome.
   b. fibromyalgia.
   c. migraine headache.
   d. gout.
   e. myofascial low back pain.
2. International Association for the Study of Pain defines pain solely as an unpleasant sensory experience that occurs only in the presence of actual tissue damage.
   a. True
   b. False
3. Which of the following brain structures are associated with pain amplification?
   a. Pons
   b. Left prefrontal cortex
   c. Anterior cingulate cortex
   d. Cerebellum
4. Unintentional drug poisoning mortality is now primarily attributed to increasing prescription opioid availability.
   a. True
   b. False
5. Daily long-term use of opioid medications for noncancer chronic pain is ***not*** associated with any of the following outcomes ***except***:
   a. pain relief.
   b. improved quality of life.
   c. improved functional capacity.
   d. increased adverse effects.

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Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Secondary Prevention of Lacunar Stroke

Source: SPS3 Investigators. *N Engl J Med* 2012;367:817-825.

LACUNAR STROKES (L-CVA) ARE SMALL subcortical brain infarctions that may comprise as many as 25% of ischemic strokes. Aspirin (ASA) monotherapy is already established as appropriate treatment for secondary prevention of ischemic stroke, as is clopidogrel (CLOP) monotherapy. In the CAPRIE trial, CLOP provided a *marginal* advantage over ASA for major adverse cardiovascular events (absolute risk reduction = 0.5%) in the overall study population, leading some to advocate clopidogrel routinely over ASA. It is often underrecognized that in the CAPRIE trial, study subjects who enrolled specifically because of previous stroke did *not* experience any statistically significant stroke reduction with CLOP compared to ASA; the outcomes were the same.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial is the first published trial to compare the efficacy of ASA monotherapy vs ASA + CLOP in reference to L-CVA. The study population included more than 30% Hispanics, concordant with the observation that L-CVA is more common in Hispanics.

At the conclusion of the trial (3.4 years mean), ASA + CLOP was *not* more effective than ASA alone in preventing L-CVA. Among the study population (n = 3020 adults with prior L-CVA), most new strokes were L-CVA (71%).

Unfortunately, as has been seen in other studies of combined ASA + CLOP, bleeding risk was significantly increased compared to ASA alone, as was all-cause mortality. Two prior trials in vasculopathic populations (MATCH, CHARISMA) have arrived at similar conclusions: For persons with stable non-acute vascular disease, ASA + CLOP is not more beneficial than ASA alone, but incurs greater bleeding risk. ■

Quality-of-life Effects of PSA Screening

Source: Heijnsdijk EA, et al. *N Engl J Med* 2012;367:595-605.

THE EUROPEAN RANDOMIZED STUDY OF Screening for Prostate Cancer (ERSPC) is a clinical trial in which adult men (n = 162,243) were randomized to prostate-specific antigen (PSA) screening or no screening. While this trial did find a statistically significant reduction in prostate cancer deaths, overall mortality was not affected, supporting the current recommendations by the United States Preventive Services Task Force (USPSTF) that PSA screening be abandoned. Although the USPSTF decision was based on the "hard" data about mortality, there is likely also substantial quality-of-life (QOL) burden engendered from PSA screening, since many — indeed, the vast majority of — men diagnosed with prostate cancer through PSA screening will die with, not from, their prostate cancer. Additionally, adverse effects of intervention for (the mostly) early prostate cancer detected through screening are not uncommon, and include erectile dysfunction and incontinence. Finally, even in men who elect not to have a surgical intervention in response to prostate cancer detected as a result of PSA screening, it would take little imagination to envision substantial ongoing concerns/anxieties referable to that diagnosis.

Heijnsdijk et al report that per 1000 men screened by PSA, nine fewer prostate-cancer related deaths would occur and 73 life-years would be gained. After adjustment for overdiagnosis and overtreatment of prostate cancer subsequent to PSA screening, these benefits were reduced by almost one-fourth. In an era when PSA screening is no longer supported because of an insufficiently favorable risk:benefit ratio, recognition of the negative QOL impact of PSA screening may help clinicians (and their patients) better come to terms with the now well-recognized limitations of PSA screening. ■

PSA Elevations After Prostate Cancer Radiotherapy

Source: Crook JM, et al. *N Engl J Med* 2012;367:895-903.

SINCE PROSTATE CANCER (PCA) IS OFTEN ANdrogen-dependent, PCA recurrences after radiotherapy are often treated with androgen deprivation by means of regimens consisting of continuous luteinizing hormone-releasing hormone agonists (LHRHa) combined with antiandrogens. Unfortunately, such treatment is associated with hot flashes, decreased libido, urinary symptoms, and fatigue. Might intermittent androgen deprivation be equally effective, but less problematic as far as adverse effects?

Crook et al randomized patients who had undergone radiation treatment for PCA but had a post-treatment PSA > 3.0 ng/dL to continuous or intermittent androgen deprivation.

For overall mortality, intermittent androgen deprivation was non-inferior to continuous treatment. The time to development of castration-resistant disease (the stage at which androgen deprivation no longer represses disease progression) was significantly longer for intermittent treatment. Similarly, the adverse effects of hot flashes, libido, and urinary symptoms were all significantly fewer in the intermittent treatment group. In addition to necessitating a substantially reduced amount of medication (and of course, expense), intermittent androgen deprivation regimens are non-inferior for overall mortality, and are associated with superior quality of life. ■

Attenuated CV Benefits of Clopidogrel in Diabetes

Source: Andersson C, et al. *JAMA* 2012; 308:882-889.

There is no controversy over whether antiplatelet therapy (e.g., aspirin, clopidogrel, prasugrel) reduces cardiovascular (CV) events when used for secondary prevention (i.e., post-acute coronary syndrome, post-myocardial infarction [MI], post-stroke). It is equally apparent that risk reduction through antiplatelet therapy is not equal among all risk groups. For instance, although aspirin (ASA) consistently shows CV risk reduction in mixed populations post-MI, two clinical trials of ASA comprised solely of diabetics failed to show benefit. Diabetics are known to have greater platelet reactivity, and their platelets are relatively resistant to antiplatelet effects as measured by medication-induced platelet aggregation inhibition testing.

Comparative benefits of clopidogrel in diabetics vs non-diabetics have not been described well enough. To assess whether diabetics fare as well with clopidogrel post-MI as non-diabetics, Andersson et al reviewed data from the Danish nationwide administrative registries of patients discharged from the hospital post-MI (n = 58,851), of which 12% had diabetes.

One-year follow-up compared outcomes among all persons treated with clopidogrel. Although all groups did have CV risk reduction from clopidogrel treatment, there was a significant difference between diabetics and non-diabetics, favoring non-diabetics. For instance, the hazard ratio (HR) for all-cause mortality was more than twice as favorable for non-diabetics (HR = 0.75, a 25% reduction) than diabetics (HR = 0.89, an 11% reduction).

The obstacle of clopidogrel-resistant platelets can be overcome by dose intensification (i.e., more clopidogrel), combination therapy (i.e., clopidogrel + ASA), or consideration of another P2y12 agent (i.e., prasugrel). Unfortunately, however, each of these methods has been associated with an increased risk for bleeding. Optimization of antiplatelet therapy in diabetics remains somewhat elusive. ■

Is A1c Always the Best Game in Town to Monitor Type 2 Diabetes?

Source: Wright LAC, Hirsch IB. *Diabetes Spectrum* 2012;25:141-148.

Even as time-honored a metric as A1c has limitations. There are, for instance, situations in which A1c can markedly mis-estimate actual sustained glucose concentrations. Since A1c measurement requires hemoglobin to be exposed to excess glucose for the entire life of a red cell (90-120 days), anything that shortens red cell life (e.g., thalassemia, Hgb C, HbS, hemolysis) will *underestimate* actual sustained glucose levels (since red cells don't live long enough to become fully glycosylated). Hemoglobin F, which is persistent in a small percentage of adults, glycosylates so rapidly that even very modest elevations of glucose can induce marked elevations of A1c (A1c 12%-17% or greater), grossly *overestimating* sustained glucose levels.

Fructosamine is a composite measure of relatively short-lived serum proteins that have become converted into irreversible ketoamines, of which glycated albumin is the primary component (approximately 90%). Since this process occurs over a few weeks, red cell life span — shortened or not — has no impact. Similarly, however, the measurement of fructosamine only provides an observation window of the sustained glucose levels in the preceding 2-3 weeks. Any condition that alters serum protein turnover (eg, thyroid dysfunction, hypopoproteinemia, nephrotic syndrome) can invalidate fructosamine measurement.

Glycated albumin, the primary protein constituent of fructosamine, has been compared with A1c and fructosamine in patients with advanced chronic kidney disease, and found to be the most accurate marker in this population, although it is subject to the same perturbations as fructosamine mentioned above.

One other serum marker not used commonly in the United States, but widely used in Japan, is 1,5 anhydroglucitol (1,5-AG), which reflects sustained glucose over a 2-14 day period. Normally, 1,5-AG is reabsorbed by renal tubules; when plasma and urine glucose are high, they compete with 1,5-AG for reabsorption, resulting in loss of 1,5-AG in the urine, with a corresponding diminution in plasma 1,5-AG. This metric has been found to be particularly useful in measurement of postprandial glucose excesses.

For the time being, A1c will remain the metric of choice for most patients. When A1c and individual glucose measurements are discordant, consideration of another metric is appropriate. ■

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Do Benzodiazepines Cause Dementia in the Elderly?

In this issue: Dementia and benzodiazepines; effectiveness of omega-3 fatty acid and *Ginkgo biloba* supplements; and FDA actions.

Benzodiazepines and dementia

Can benzodiazepines increase the risk for dementia? Researchers in France studied 1063 men and women with an average age of 78 who were free of dementia and did not start taking benzodiazepines until they had been followed for at least 3 years. During a 15-year follow-up, 253 cases of dementia were confirmed. New use of benzodiazepines occurred in 9% of the study population and was associated with an increased risk of dementia (32% benzodiazepine group vs 23%, adjusted hazard ratio 1.60, 95% confidence interval [CI] 1.08-2.38). After correcting for the existence of depressive symptoms as well as age and diabetes, the hazard ratio was unchanged. A secondary analysis looking at participants who started benzodiazepines at different times during follow-up also showed an elevated risk of dementia. Results of the complementary, nested, case-control study showed that ever use of benzodiazepines was associated with an approximate 50% increased risk of dementia compared with never users. The authors conclude that in this prospective, population-based study new use of benzodiazepines was associated with a significantly increased risk of dementia. They further conclude that "indiscriminate widespread use should be cautioned against" (*BMJ* 2012;345:e6231). The obvious criticism of the study was the presence of confounders — whether use of benzodiazepines was a marker for early onset dementia rather than a cause. While the authors feel the study was carefully controlled, selection bias cannot be completely ruled out. They further state that the research should be done on younger patients to see if starting benzodiazepines at ages younger than 65 may have deleterious effects. They also recommend that "physicians and regulatory agencies should consider the increasing evidence of potential adverse effects of this drug class for the general population." ■

Popular supplements' use questioned

Two popular supplements — omega-3 fatty acids and *Ginkgo biloba* — may be of limited value, according to two recent studies. Omega-3 fatty acids are thought to have a number of benefits, including lowering triglyceride levels, preventing arrhythmias, decreasing platelet aggregation, and lowering blood pressure. But the fish oil supplement's ability to prevent major cardiovascular events has been debated in the literature. Twenty studies of nearly 67,000 patients were included in a meta-analysis looking at the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke. After correcting for dose and comorbidities, there was no difference in the absolute or relative risk of any of the outcomes associated with omega-3 supplementation. The authors concluded that marine-derived omega-3 polyunsaturated fatty

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

acid supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (*JAMA* 2012;308:1024-1033).

Ginkgo biloba for the prevention of Alzheimer's disease (AD) was studied in a randomized, parallel group, double-blind, placebo-controlled trial of adults age 70 years or older who spontaneously reported memory complaints to their primary care physician in France. Patients were randomized to a twice per day 120 mg standardized *Ginkgo biloba* extract or matching placebo and followed for 5 years. The primary outcome was conversion to probable AD. More than 2800 patients were enrolled with about 1400 patients in each group. By 5 years, 61 participants in the ginkgo group were diagnosed with AD vs 73 in the placebo group (hazard ratio 0.84, 95% CI 0.60-1.18; $P = 0.306$). Adverse events were the same between both groups and mortality was roughly the same as well. Sixty-five participants in the ginkgo group had a stroke compared to 60 in the placebo group ($P = 0.57$). The authors conclude that long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to AD compared to placebo (*Lancet Neurology* 2012;11:851-859). ■

FDA actions

The FDA has approved teriflunomide for the treatment of relapsing forms of multiple sclerosis (MS). The approval was based on a 2-year study in which the drug reduced relapses by nearly a third compared to placebo — results that are about the same as other MS drugs and no better than Merck's popular injectable interferon beta 1a (Rebif). Side effects include diarrhea, abnormal liver function tests, nausea, and hair loss. It should not be used during pregnancy. Teriflunomide has the advantage of being a once-daily oral medication, the second oral MS medication after Novartis' fingolimod (Gilenya). Teriflunomide will be marketed by Sanofi Aventis as Aubagio. A third oral MS medication, Biogen Idec's BG-12, was recently found to reduce MS relapses by about 50% (*N Engl J Med* 2012;367:1087-1097; 1098-1107). BG-12 is not yet approved by the FDA, but a decision is expected before the end of the year.

The FDA has delayed the approval of apixaban (Eliquis) once again. Pfizer and Bristol-Myers Squibb's novel oral anticoagulant (NOAC) was expected to be approved last spring after publication of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which showed that the drug was effective in preventing strokes in patients with non-valvular atrial fibrillation — data that suggested that the drug was perhaps even more effective than the two other NOACs, dabigatran (Pradaxa) and rivaroxaban (Xarelto). In June, the FDA told the manufacturers they needed "additional information on data management and verification from the ARISTOTLE trial." Now, the agency says that the review date will be March 17, 2013. No reason was given by the FDA for the delay.

About 25% of Internet consumers have purchased prescription medications online, while at the same time, the prevalence of fraudulent Internet pharmacies has grown. The FDA has now launched a national campaign to raise public awareness called BeSafeRx – Know Your Online Pharmacy, a resource that provides patients and caregivers with a better understanding of who they are buying from, and makes sure the medication they buy matches what their doctor prescribed. The FDA recommends that patients only buy medications from online pharmacies that require a prescription, are located in the United States, have a licensed pharmacist available for consultation, and are licensed by the patient's state board of pharmacy. More information can be found at www.FDA.gov/BeSafeRx.

The FDA has approved enzalutamide to treat men with late-stage, castration-resistant prostate cancer under the agency's priority review program. The drug was approved based on a study of nearly 2000 men with metastatic prostate cancer who had been previously treated with docetaxel. Men treated with enzalutamide lived an average of 18.4 months vs 13.6 months for men treated with placebo. Enzalutamide is co-marketed by Astellas and Medivation as Xtandi.

The FDA has also approved a new agent for the treatment of advanced colorectal cancer. Regorafenib is a multi-kinase inhibitor that was also approved under the FDA's priority review program. In a study of 760 patients with previously treated metastatic colorectal cancer, regorafenib extended survival about 45 days to 6.4 months from 5 months for placebo as well as progression-free survival of 2 months vs 1.7 months for placebo. Regorafenib is marketed by Bayer as Stivarga. ■